SUDDEN NATURAL DEATH IN INFANCY
& EARLY CHILDHOOD

CHAPTER 4

INFECTIOUS CONDITIONS
INTRODUCTION

Sudden death is a well recognized sequel to infections with a wide variety of agents. The outcome of a particular infection depends on the age of the infant or child, the virulence of the organism and the immunological status of the host. For example, certain bacteria, such as *Neisseria meningitidis*, are capable of producing a fulminant septicaemia in previously healthy children with death within hours, whereas *Aspergillus sp.* is generally only of concern in children who are immunodeficient.

In spite of the possibility of a lethal outcome from many 'rare' organisms in immunocompromised hosts, this chapter tends to concentrate on more usual clinical syndromes, with only occasional reference to more obscure entities. The format reflects the sequence followed in other chapters with a discussion of infections based on particular organ systems or mechanisms rather than on specific classes of infectious agents.

In a review performed by the author of autopsy cases from the Adelaide Children's Hospital over the past 30 years the most common causes of rapid death were bacterial pneumonias, airway infections (including acute epiglottitis), meningitis, septicaemias, viral myocarditis and gastroenteritis. Table 4-1 lists possible microbiological causes of sudden death in childhood and Appendix I, Chapter 11, summarizes the types of microbiological specimens that can be taken in the workup of a septic case at autopsy.
### TABLE 4-1: TYPES OF INFECTIOUS ILLNESSES ASSOCIATED WITH SUDDEN PAEDIATRIC DEATH

<table>
<thead>
<tr>
<th>1. Cardiovascular</th>
<th>4. Haematological</th>
<th>5. Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>myocarditis</td>
<td>malaria</td>
<td>gastroenteritis</td>
</tr>
<tr>
<td>rheumatic fever</td>
<td></td>
<td>botulism</td>
</tr>
<tr>
<td>endocarditis</td>
<td></td>
<td>primary peritonitis</td>
</tr>
<tr>
<td>aortitis</td>
<td></td>
<td>hydatid disease</td>
</tr>
<tr>
<td>arteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>retropharyngeal abscess</td>
<td>pyelonephritis</td>
<td>septicaemia</td>
</tr>
<tr>
<td>posterior lingual abscess</td>
<td></td>
<td>viraemia</td>
</tr>
<tr>
<td>acute epiglottitis</td>
<td></td>
<td>endotoxaemia</td>
</tr>
<tr>
<td>acute laryngotracheobronchitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bacterial tracheitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diphtheria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute bacterial pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>interstitial pneumonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bronchiolitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CARDIOVASCULAR CONDITIONS**

**MYOCARDITIS**

Myocarditis is a well known cause of sudden and unexpected death in children of all ages and may be found in infants who present with SIDS^41,124_.

**Clinical Features**

Although some infants and children may have symptoms and signs of heart failure^40_, a significant number of cases will have nonspecific clinical features giving no indication of a primary cardiac problem prior to autopsy (vide infra)^56_. In children a history of exercise-related collapse may suggest myocardial disease and a clinical diagnosis of acute myocardial infarction may have been considered^60_. 
DEMONSTRATION OF THE ASSOCIATION BETWEEN MYOCARDITIS AND SUDDEN UNEXPECTED DEATH IN INFANCY AND CHILDHOOD

INTRODUCTION

Myocarditis is characterised histologically by an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes, not typical of the ischaemic changes associated with coronary artery disease. Clinically there may be great variability in symptomatology. To characterise further the clinicopathological features of myocarditis found at autopsy in childhood, the following study was undertaken.

MATERIALS AND METHODS

The autopsy files of the Adelaide Children's Hospital from January 1954 to July 1990 were reviewed. Data relating to age, sex, clinical presentation, macroscopic description and virological or bacteriological studies were extracted. Histological slides were reviewed and only those cases which fulfilled accepted criteria were retained. Between one and 13 blocks (mean = 3.6) were examined per case. Cases where the histological findings were more in keeping with ischaemic damage were excluded. Such findings included confluent areas of coagulative necrosis with a peripheral neutrophil infiltrate, and lesions where the subendocardial myocytes were preserved.

RESULTS

Thirty-two cases of myocarditis were found out of a total of 4969 autopsies (0.64%). Eight cases which had been called myocarditis originally were discarded as no convincing myocyte necrosis could be demonstrated. The 32 cases were separated into two groups: Group A, (16/32), where myocarditis was an isolated significant finding, and Group B, (16/32), where myocarditis was incidental to other conditions to which death was ascribed. The sex ratio in each group approached unity. No difference in age range was seen, although 8/16 of Group A were aged one year or less compared to only 3/16 in Group B (Table 4-2). The duration of symptoms was similar in each group, from 12 hours to three weeks in Group A and from one...
day to one month in Group B. In each group there were five cases of sudden death (defined as death occurring within 24 hours of the onset of symptoms).

**TABLE 4-2: CLINICAL FEATURES OF 32 PATIENTS WITH HISTOLOGICAL EVIDENCE OF MYOCARDITIS AT AUTOPSY**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>M:F</td>
<td>9:7</td>
<td>7:9</td>
</tr>
<tr>
<td>Age Range</td>
<td>8 days-9 years</td>
<td>11 days-15 years</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>12 hours-3 weeks</td>
<td>1 day-1 month</td>
</tr>
<tr>
<td>Sudden death</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Symptoms observed in Group B related to the ultimate cause of death which was bronchopneumonia in 10 (three cases with negative cultures, two cases cultures grew coliforms, two *staphylococcus*, one *Pseudomonas sp.*, one *Aspergillus terreus*, and one *streptococcus*), meningitis in two (both *Acanthamoeba*), subdural haematoma, encephalitis (culture negative), trauma (motor vehicle accident) and asphyxia (due to inhalation of foreign body) in one case each. In Group A, where myocarditis alone was diagnosed, non specific symptoms such as anorexia, vomiting, tachypnoea and pyrexia were recorded. There were three cases where signs suggestive of heart failure were observed and three where no symptoms were noted prior to death.

In Group A 3/16 hearts and in Group B 5/16 hearts were grossly unremarkable, or showed only minor changes. Combinations of pallor, dilatation, hypertrophy (wt. >95th percentile)³⁶, endocardial fibrosis, petechial haemorrhage and pericardial effusion characterised the remainder (Table 4-3). No mural thrombi were present in any case.
TABLE 4-3: MACROSCOPIC APPEARANCE OF HEARTS WITH HISTOLOGICAL EVIDENCE OF MYOCARDITIS

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or minor changes</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Dilatation only</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dilatation &amp; Pallor</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Dilatation &amp; Hypertrophy</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Pallor in any chamber</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Wt &gt;95 percentile</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Petechial haemorrhages</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Endocardial fibrosis in any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chamber, with hypertrophy</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dilatation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

(Please note that these groups are not mutually exclusive).

Histologically, neutrophils were present in 8/16 Group B, compared to 4/16 Group A hearts (Table 4-4). Conversely, 15/16 Group A and 9/16 Group B infiltrates included lymphocytes. Plasma cells and eosinophils were seen more frequently in Group A. The only statistically significant difference between the two groups was the presence of lymphocytes (two tailed testing, = 0.05, 5% level of significance).
TABLE 4-4: HISTOLOGICAL FEATURES OF ISOLATED (GROUP A) AND "INCIDENTAL" (GROUP B) MYOCARDITIS

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p Value</th>
<th>Test Applied</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocyte necrosis</td>
<td>16</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>4</td>
<td>8</td>
<td>0.27</td>
<td>*</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>15</td>
<td>9</td>
<td>0.04</td>
<td>**</td>
<td>+</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>7</td>
<td>4</td>
<td>0.46</td>
<td>*</td>
<td>NS</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>3</td>
<td>2</td>
<td>1.00</td>
<td>**</td>
<td>NS</td>
</tr>
</tbody>
</table>

Key:
*       Yates corrected Chi-square
**      Fisher exact test (2 tailed)
+       Significant at the 5% level ( = 0.05, 2 tailed test)
NS      Not significant.

Virological studies were conducted in 10/16 Group A and 6/16 Group B cases. Antibody to coxsackie B4 virus was detected in one case from Group A, and in one case from Group B (that associated with inhalation of a foreign body). Antibody to varicella was detected in one case from Group A. Coxsackie B5 and B3 were cultured from brain and CSF respectively in one case each from Group A.

There were five cases in each group where sudden death was the mode of presentation (Table 4-5). In Group A, three of these patients were less than one year of age, three of the patients had macroscopically normal hearts, one heart had dilated chambers and weighed in excess of the 95th percentile, and the remaining heart had dilated chambers only. In Group B sudden death occurred in one infant less than one year old. Only one heart in the five cases of sudden death in Group B was macroscopically unremarkable. Two hearts weighed >95th percentile, one of which showed chamber dilatation, and the remaining two of which also showed dilated chambers. Microscopic examination showed a predominantly lymphocytic infiltrate in all cases in both groups excepting one case in Group B where eosinophils predominated: other findings in this case included long standing bronchiectasis and colonizing...
aspergillosis in lung sections. A second patient in Group B died suddenly from an inhaled foreign body, and in the remaining three significant bronchopneumonia was found.

<table>
<thead>
<tr>
<th>TABLE 4-5: CASES OF SUDDEN DEATH ASSOCIATED WITH ISOLATED (GROUP A) AND INCIDENTAL (GROUP B) MYOCARDITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A n = 5</td>
</tr>
<tr>
<td>Heart grossly normal</td>
</tr>
<tr>
<td>Heart dilated</td>
</tr>
<tr>
<td>Heart weight &gt; 95th %ile</td>
</tr>
<tr>
<td>Age &lt; 12 months</td>
</tr>
</tbody>
</table>

DISCUSSION
In the early part of the 20th Century the term "myocarditis" was used to signify any chronic myocardial disease. With increased use of virological techniques it became apparent that an association existed between infection with certain viruses and myocarditis. These viruses include Coxsackie A and B, ECHO, polio, cytomegalo, rubella, mumps, Epstein Barr, influenza A and B, herpes, adeno and hepatitis viruses.

It is only recently that histologic criteria have been set out which specify that diagnosis requires myocyte necrosis, i.e. the finding of inflammatory cells alone is insufficient for the diagnosis since the presence of a normal myocardial lymphocyte population has been demonstrated. For example, studies have demonstrated 'myocarditis' (in the form of a lymphocytic infiltrate) of the conduction tracts in apparently well children who suffered sudden accidental death that was unrelated to any form of cardiac disease. Applying the most recent definition to archival material led to eight cases in which myocyte necrosis was not observed being excluded from the current series. This suggests that earlier studies may have overestimated the incidence of this disorder. The diagnosis of myocarditis depends, however, upon adequate sampling because of the often focal nature of the histological changes. It is also possible, therefore, that a number of cases have been missed in the past.
In infants and children, as in adults, the symptoms of myocarditis may be non-specific. A "flu-like" illness with pyrexia, signs of congestive heart failure and cardiomegaly and an abnormal electrocardiogram may occur. In infants, tachypnoea and intercostal recession are found. The disease may be mild and self limiting, rapidly progressive, or may present with sudden death. DeSa noted that 17 of 24 cases of isolated myocarditis presented with sudden death, 13 of whom suffered no prodromal illness. Five of 16 of our cases presented in this manner, three of whom were less than one year of age. The cause of sudden death in myocarditis is generally thought to be an arrhythmia due to involvement of the conduction system by foci of inflammation. In older children it is thought that strenuous physical exercise may predispose to sudden death by this mechanism where subclinical myocarditis is present.

Macroscopic examination of the heart in histologically proven myocarditis may demonstrate ventricular dilatation, pallor, discoloration, hypertrophy, petechial haemorrhage or endocardial fibrosis (Figure 4-1). DeSa noted one or more of these features in all of his cases of isolated myocarditis. In contrast, no macroscopic abnormality other than isolated epicardial petechial haemorrhages was observed in three out of 16 hearts in Group A. It is noteworthy that 15 out of 16 hearts in Group A compared to nine out of 16 in Group B were infiltrated predominantly by lymphocytes, as this is a characteristic of viral myocarditis. In fact, the presence of lymphocytes was the only statistically significant difference between the two groups. Other histologic features in established cases include myocyte necrosis (Figure 4-2), myocyte hypertrophy and interstitial fibrosis with scarring. Microscopically the degree of inflammation in affected hearts is variable, with some cases showing widespread myocyte necrosis with a florid interstitial inflammatory infiltrate composed of lymphocytes, eosinophils or neutrophils. In other cases the microscopic changes are more focal. Given the variable distribution of inflammation and necrosis, adequate sampling is required. However, the diagnosis is usually less of a problem with autopsy specimens than with biopsies due to the greater amount of material that is available for examination.

The extent of myocardial damage may occasionally appear out of proportion to the relatively unimpressive clinical symptoms, and myocardial inflammation with necrosis has also been an incidental finding in other autopsy series, demonstrating that myocarditis may not always be functionally significant. Scattered giant cells present in some cases arise from
Figure 4-1: Opened left ventricle of a four-month-old boy who suddenly collapsed and died revealing mottling of the myocardium due to extensive myocarditis.

Figure 4-2: Established myocarditis showing a diffuse chronic inflammatory cell infiltrate with associated myocyte necrosis (Haematoxylin & Eosin, x 280).
Figure 4-3: Giant cell myocarditis present in a 13-year-old boy who collapsed and died while at school, showing pallor and mottling of the myocardium with myocyte necrosis, chronic inflammation and characteristic giant cell formation (inset) (Haematoxylin & Eosin, x 440).

Figure 4-4: Tiny bead like valvular vegetations on the tricuspid valve in 13-year-old girl who died suddenly from acute rheumatic fever.
degenerating myocytes in so-called giant-cell or Fiedler's myocarditis. Such was the case in a 13-year-old schoolboy who collapsed and died following an apparently mild febrile illness (Figure 4-3).

Myocarditis may be caused by a variety of noninfectious agents, however, it is most commonly due to microbiological agents, in particular to coxsackie B viruses. Other viruses such as cytomegalovirus may also cause death due to cardiac involvement. Table 4-6 lists a variety of possible microbiological causes of myocardial infection.

**TABLE 4-6: INFECTIOUS CAUSES OF MYOCARDITIS**

| 2. Chlamydia | *Chlamydia psittaci* (psittacosis), *Chlamydia pneumoniae* |
| 3. Rickettsia | *Rickettsia typhi* (typhus), *Rickettsia tsutsugamushi* (scrub typhus) |
| 4. Mycoplasma | *Mycoplasma pneumoniae* |
| 5. Bacteria | diphtheria, *Salmonella*, *Brucella*, strepoccci (β-haemolytic), staphylococci, *Clostridium perfringens*, *Neisseria meningitidis*, *Borrelia burgdorferi* |
| 6. Fungi | *Aspergillus*, *Candida*, *Blastomyces*, *Cryptococci*, *Coccidioidomyces* |
| 7. Protozoa | *Trypanosoma*, *Toxoplasma* |
| 8. Metazoa | *Trichinella*, *Echinococcus* |

(Adapted from references 37,102)

In Group A, evidence of infection with coxsackie B3, B4, B5 viruses and varicella was obtained. The coxsackie viruses are commonly associated with myocarditis in children and in neonates, the latter presumably acquiring the infection in utero. Only one positive viral culture was obtained from an infant aged 11 days at death, and this was for coxsackie B3. In Group B, evidence of viral infection was only obtained from the child who inhaled a foreign body, prior to which he had appeared perfectly healthy.
The data confirm that the presentation of myocarditis in the paediatric age group may vary from an asymptomatic incidental finding, to a well defined illness of weeks duration, to sudden and unexpected death. At autopsy, gross examination of the heart may or may not suggest a myocardial abnormality and the presence of myocarditis may be apparent only after extensive histological sampling. The significance of foci of myocardial necrosis and inflammation in asymptomatic infants and children dying of unrelated disorders is difficult to determine. It is possible that these may have spontaneously resolved and remained undetected, or may have manifested subsequently as a "cardiomyopathy", had the children survived.

Due to the possibility of occult myocarditis at any age, myocarditis may be found at autopsy in infancy and childhood, even in the absence of specific antemortem symptoms and signs, or in the presence of coincident lethal disease. This is particularly so in cases of sudden and unexpected death where it is advisable to submit serum and myocardium for microbiological and DNA hybridization studies, looking particularly for evidence of coxsackie B viruses. Detection of coxsackie B virus-specific IgM may also be helpful in arriving at a diagnosis. Histologically, samples should at least include portions of both ventricles and the interventricular septum. It should be recognised, however, that there will always be a risk of under-diagnosis because of the focal and sometimes mild nature of the inflammatory changes that may occur.

SUMMARY
To characterise the clinicopathological presentation of patients with myocarditis coming to autopsy in childhood, 32 cases of histologically-proven myocarditis were obtained from the files of the Adelaide Children's Hospital. In 16 of the cases (Group A), myocarditis was the only significant finding and death was ascribed to this condition. In the remaining 16 (Group B) myocarditis was found in association with other severe disease processes. Clinical histories of the two groups showed sudden death to be a feature in five out of 16 cases in Group A, three of whom had no prodromal symptoms. Five patients in Group B also suffered sudden death, but this was associated with a variety of causes, including bronchopneumonia, and asphyxia. These cases demonstrate the variability in clinicopathological presentation of myocarditis in infancy and childhood and suggest that myocarditis should always be considered a possible diagnosis at autopsy in the pediatric age group, even in the presence of coincident lethal disease.
Figure 4-5: Typical Aschoff body of rheumatic fever composed of aggregated cells with vesicular nuclei containing a central ribbon of condensed chromatin, so-called Anitschkow cells (Haematoxylin & Eosin, x 440).

Figure 4-6: Embolized fragment of left ventricular mural thrombus in the left anterior descending coronary artery of a six-year-old girl with florid acute rheumatic fever (Haematoxylin & Eosin, x 44).
RHEUMATIC FEVER

Clinical Features

Rheumatic fever is a recurrent febrile illness of childhood characterized by subcutaneous nodules, erythema marginatum of the skin, chorea, migratory polyarthritis and carditis.

Aetiology

Rheumatic fever follows a group A streptococcal infection and is believed to be due to immunological cross reactivity between tissue and streptococcal antigens. In recent years the incidence of rheumatic fever has declined in Western countries.

Pathological Features

On gross examination, the heart is often enlarged with dilated chambers and typical vegetations along the margins of the valve leaflets (Figure 4-4). Microscopically the most characteristic lesions are Aschoff bodies, which consist of round to oval nodules with central fibrinoid degeneration and a surrounding rim of cardiac histiocytes. Anitschkow cells are also characteristic and are distinguished by oval vesicular nuclei with centrally aggregated ribbons of chromatin. They are also known as 'caterpillar' cells (Figure 4-5).

Occurrence of Sudden Death

Although sudden death is a rare complication of rheumatic fever, it has been reported from early childhood to late adolescence. For example, an 18-year-old youth with acute rheumatic valvulitis and myocarditis developed an acute myocardial infarct attributed to embolization of friable valvular vegetations and a three-year-old boy with rheumatic fever died suddenly due to involvement of his coronary arteries. A six-year-old girl with florid myocarditis due to rheumatic fever (a referral case to the Adelaide Children's Hospital) also died suddenly with an embolus into the left anterior descending coronary artery (Figure 4-6).

ENDOCARDITIS

Endocarditis is caused by infection of the endocardium or heart valves by a variety of microbiological agents resulting in vegetation formation.

Aetiology

Endocarditis in children usually occurs in those who have underlying defects such as tetralogy of Fallot, ventricular septal defect with aortic incompetence, left ventricular outflow obstructions or a ductus arteriosus, with or without corrective surgery. It also occurs in children who have
had rheumatic fever, but may also be found in children with normal hearts. Endocarditis may be associated with sepsis elsewhere or with indwelling vascular catheters. Most cases (i.e. >70%) are caused by *Staphylococcus aureus* or *Streptococcus viridans*.

**Clinical Features**

While early symptoms and signs tend to be relatively nonspecific, occasional cases may pursue a fulminant course with fever, heart failure and embolic phenomena. This is particularly so with staphylococcal endocarditis where there may be significant valvular damage, erosion of conduction tracts precipitating arrhythmias, or embolization resulting in pulmonary, cerebral or myocardial infarction. Embolisation may also occur with other types of infective endocarditis.

**Pathological Features**

At autopsy the classical lesions of endocarditis of splinter haemorrhages under the nails, subcutaneous nodules in the fingers and toes (Osler’s nodes) and haemorrhagic lesions on the palms and soles (Janeway lesions) are often not visible. Within the heart the mitral valve is most often affected. Lesions include vegetations, valve perforation, annular abscesses and rupture of the chordae.

The gross appearance of vegetations varies depending on the type of endocarditis present, however in bacterial infections they consist of friable masses of variable size adherent to the valve cusps. Microscopically, vegetations consist of aggregated cellular debris, fibrin, bacterial colonies and white blood cells.

**Occurrence of Sudden Death**

Death from embolic myocardial infarction has occasionally been reported in infants and older children with endocarditis making careful examination of the coronary arteries important in such cases. The precise mechanism of death may, however, be difficult to ascertain.

**AORTITIS**

Bacterial infection may also involve the aorta in areas of flow disturbance such as a coarctation. Symptoms of infection may be quite non-specific and sudden death can occur unexpectedly due to rupture of an eroded vessel wall. Death results from hypovolaemic shock, or from cardiac tamponade if the aortic root is involved.
Figure 4-7: Vegetations containing bacteria adherent to the thickened cusp of a dysplastic bicuspid aortic valve in an eight-year-old boy. Involvement of the right coronary artery ostium resulted in death from an acute myocardial infarct.

Figure 4-8: Rupture of the aortic arch (arrows) with focal acute inflammation in a six-year-old girl with minimal preceding symptoms. No structural abnormalities or migrated foreign bodies were present. The pulmonary outflow tract is adjacent.
An alternative mechanism of sudden death was demonstrated in an eight-year-old boy at the Adelaide Children's Hospital with a stenotic bicuspid aortic valve who developed bacterial infection of the aortic valve cusps and died of an acute myocardial infarct following occlusion of the right coronary artery ostium (Figure 4-7).

Occasionally the aetiology of the inflammation may be uncertain, as was the case of a six-year-old girl at the Adelaide Children's Hospital who died suddenly from a ruptured ascending aorta following several hours of non-specific malaise and fever (Figure 4-8). At autopsy focal acute inflammation of the aortic arch was found with abscess formation and rupture. No organisms were found on microbiological culture or within tissues on Gram and PAS staining.

ARTERITIS
Coronary artery inflammation with thrombosis, myocardial infarction and death may occur in children with rheumatic fever, syphilis or endocarditis with abscess formation.

RESPIRATORY CONDITIONS
RETROPHARYNGEAL ABSCESS
Retropharyngeal abscess may result from infection following a penetrating injury to the posterior pharyngeal wall, or in early childhood may be a sequel to pharyngitis or tonsillitis. Obstruction to the airway and even sudden death can occur if infection is severe.

POSTERIOR LINGUAL ABSCESS
Acute inflammation in the posterior portion of the tongue may also result in occlusion of the upper airway with unexpected death (see Chapter 5). These cases emphasize the importance of careful excision and examination of the upper airway in all cases of sudden infant death.

ACUTE EPIGLOTTITIS
Clinical Features
The clinical course of acute epiglottitis is often fulminant with rapid development of fever, respiratory distress, odynophagia and drooling prior to respiratory obstruction and terminal cardiovascular arrest. Occasionally symptoms may be relatively nonspecific, consisting of low grade fever and sore throat, or the infant or child may be found dead in bed. Although it is
considered to be primarily a disease of children aged between one and seven years, it does occur in younger and older individuals and has been reported in late adolescence.\textsuperscript{78}

**Occurrence of Sudden Death**

Sudden death may occur if an attempt has been made to examine the epiglottis with a tongue depressor as this may precipitate airway obstruction. The mortality rate for children in whom obstruction occurs is around 20\% even with prompt treatment.\textsuperscript{13,84} Fatal septic shock may also be a complication.

**Aetiology**

The causative organism is almost invariably *Haemophilus influenzae* type B, although some cases are due to pneumococci, staphylococci or streptococci.\textsuperscript{106}

**Pathological Features**

At autopsy the epiglottis is characteristically red, swollen and oedematous (see Figure 5-8). Microscopic examination will reveal marked submucosal oedema and acute inflammation with surface ulceration (Figure 4-9).

**Autopsy Investigation**

Blood cultures are an important part of the postmortem workup to determine the aetiologic agent and have been reported as positive in 50 to 75\% of cases.\textsuperscript{128}

**Other Epiglottal Lesions**

Due to the vulnerability of the airway to obstruction at the laryngeal inlet, any condition which causes expansion of the submucosa of the epiglottis and surrounding tissues may result in lethal airway obstruction. The case of a one-year-old girl with neuroblastoma and *Pseudomonas* septicaemia at the Adelaide Children's Hospital who developed stridor and died suddenly from marked interstitial haemorrhage around the laryngeal inlet underscores this point (see Figure 7-8).

**ACUTE LARYNGOTRACHEOBRONCHITIS**

Most cases of acute laryngotracheobronchitis occur in the form of epidemic croup due to parainfluenza and influenza viruses. The clinical course of croup is less severe than acute bacterial epiglottitis and it usually has an excellent prognosis. However, occasional cases occur where airway obstruction is severe enough to warrant endotracheal intubation.\textsuperscript{128} Respiratory arrest may also result if the child or infant is recumbent with the head tilted forward.\textsuperscript{110}
Figure 4-9: Submucosal oedema and acute inflammation in acute epiglottitis (Haematoxylin & Eosin, x 280).

Figure 4-10: Ptosis of abdominal organs caused by a tension pneumothorax complicating staphylococcal pneumonia. The diaphragm can be seen beneath the left costal margin.
Although there has been debate over the likelihood of croup causing sudden death, Segard and Koneman have concluded that 'laryngotracheo-bronchitis is a common and acceptable anatomic cause of death in children dying suddenly and unexpectedly'\textsuperscript{105}. An additional problem which may result in death due to airway obstruction in children with viral laryngotracheobronchitis is secondary infection with \textit{Staphylococcus aureus} producing thick pseudomembranes\textsuperscript{75}.

**BACTERIAL TRACHEITIS**

Acute bacterial tracheitis is most often due to staphylococci, is less acute in onset than bacterial epiglottitis and usually has a good outcome. Unfortunately some cases do occur in which acute airway obstruction results from impaction of tenacious mucopurulent membranes\textsuperscript{57}, although no deaths were recorded in this paper.

**DIPHTHERIA**

Pharyngeal infection with \textit{Corynebacterium diphtheriae} affects unvaccinated children aged between two and 15 years. The bacteria produces an exotoxin which causes epithelial inflammation and necrosis with the formation of an inflammatory pseudomembrane composed of necrotic mucosal cells and debris\textsuperscript{85}. Sudden death may occur from acute airway obstruction due to impaction of the dislodged pharyngeal pseudomembrane in the lower airway. Alternatively sudden death may result from cardiac damage due to an exotoxin (\textit{vide infra}).

**ACUTE BACTERIAL PNEUMONIA**

**Clinical Features**

Symptoms and signs of acute bacterial pneumonia in older children are similar to adults, with fever, cough and pleuritic chest pain. In infants the diagnosis may not be as obvious, with mild fever and non-specific malaise preceding the sudden onset of respiratory distress.

**Aetiology**

In children the most common serious lower respiratory tract infection is acute lobar pneumonia due to \textit{Streptococcus pneumoniae} in 90\% of cases. Fulminant respiratory infections also occur with \textit{Haemophilus influenzae} and \textit{Staphylococcus aureus}, the latter being associated with abscess formation and tension pneumothoraces (Figure 4-10).
Pathological Features

The appearance of the lungs depends on whether the underlying process is an acute lobar or lobular (broncho-) pneumonia. In acute lobar pneumonia confluent areas of pneumonic consolidation are present which appear solid and airless. In acute bronchopneumonia the lungs are mottled with scattered areas of patchy consolidation. On cut section these appear as discrete, pale and firm areas throughout both lung fields.

Microscopically alveoli are filled with neutrophils, fibrin and necrotic debris. In lobar pneumonia the stage of 'red hepatization' is marked microscopically by extravasation of red blood cells into confluent alveoli filled with pus. This progresses to the stage of grey hepatization as the inflammatory and red blood cells disintegrate. In acute bronchopneumonia the inflammatory infiltrate is bronchocentric.

Autopsy Investigation

Although tissue and blood cultures may reveal pathogenic bacteria, prior antibiotic treatment may result in sterile cultures.

Diagnostic Problems

Assessing how well established a disease has to be to result in a lethal outcome is a problem which not infrequently arises at autopsy. Unfortunately a preceding history of fever is of minimal use in establishing the diagnosis of lethal acute bronchopneumonia given the number of febrile illnesses of childhood. It is important, therefore, not to attribute death to lesions which are of doubtful significance and which would probably be overlooked except when the presentation is of sudden, unexpected death of uncertain aetiology. However, it is sometimes difficult to determine where the cut-off point lies between an infection that is relatively innocuous and one which is lethal.

In cases of sudden and unexpected death involving young children or infants it is possible to have a very non-specific history, and yet still find a marked interstitial and intra-alveolar acute inflammatory infiltrate at autopsy due to bacterial infection. In cases where there is either diffuse involvement of the majority of lung fields by the inflammatory process (Figure 4-11), or in which there is abscess formation with microbiological and histological evidence of disseminated sepsis, establishing the cause of death as infective is not difficult. Other less well established cases are not as straightforward.
Figure 4-11: Florid acute bacterial bronchopneumonia in an infant with a relatively unremarkable history of mild fever who was found unexpectedly dead one morning (Haematoxylin & Eosin, x 220).

Figure 4-12: Diffuse rash over the forehead in a young girl dying from fulminant meningococcaemia.
INTERSTITIAL PNEUMONITIS

Interstitial pneumonitis is usually caused by viruses which result in a patchy interstitial chronic inflammatory infiltrate within the alveolar septae. Although often self-limiting, a fulminant course may occur in infants or in immunocompromised children. A similar histological picture can result from a number of other organisms, including mycoplasmas, rickettsiae and chlamydiae127.

Again, the problem arises of what degree of interstitial inflammation can be accepted as significant. This is even more difficult than in cases of acute bacterial inflammation as there is a normal population of peribronchial lymphocytes present in the lungs. In the past, SIDS deaths were occasionally attributed to interstitial pneumonitis because of the presence of mildly increased numbers of peribronchial chronic inflammatory cells65. Microscopic features of interstitial pneumonitis in cases of sudden death have been described by Yip, Sein and Lung127.

BRONCHIOLITIS

The major cause of bronchiolitis in infants under six months of age is respiratory syncytial virus (RSV). Other causative agents are adeno, parainfluenza and influenza viruses, Bordetella pertussis and Mycoplasma pneumoniae. Microscopically there is a diffuse mononuclear inflammatory cell infiltrate around bronchi and bronchioles extending into the surrounding parenchyma. The airway lumina are also infiltrated by mononuclear cells and are filled with mucus and necrotic debris.

RSV infection may cause apnoeic episodes, plugging of distal bronchioles with mucus and inflammatory debris, air trapping within the lungs and sudden death3,24.

CENTRAL NERVOUS SYSTEM CONDITIONS

MENINGITIS

Bacterial infection of the meninges may result in fulminant disease and sudden death in children before symptoms are obvious or despite antibacterial therapy. Rupture of intracerebral abscesses into the subarachnoid space or ventricles is another situation which results in extensive purulent meningitis with rapid death52.

Aetiology

Causative organisms vary depending on age, with Streptococcus group B and enterobacteria being more common in neonates. In children up to 12 years of age the most common bacterial
pathogens causing meningitis are *Haemophilus influenzae* type B, *Streptococcus pneumoniae* or *Neisseria meningitidis*; after this age *Streptococcus pneumoniae* and *Neisseria meningitidis* are more significant. Fulminant bacterial meningitis may also be caused by other agents such as *Listeria monocytogenes*.

Clinical Features

Children with bacterial infection of the meninges may have several days history of nausea, vomiting and photophobia followed by alteration in conscious state and nuchal rigidity. On the other hand, infants may have minimal or non-specific symptoms and signs.

Infection with *Neisseria meningitidis* in children usually causes minimal or no inflammation at the site of entry within the upper airway. The clinical history is of a febrile illness followed by skin rash (Figure 4-12) and collapse\(^4\). Death occurs most commonly in children under the age of two years who present with a rapid course and are in coma or shock\(^9\).

Pathological Features

At autopsy, inflammation of the meninges and skin rash may not be apparent on visual inspection due to the rapid clinical course of the infection\(^6\), although this is variable (Figure 4-13). Death may also occur from septicaemia before meningitis develops\(^12\). Bilateral intra-adrenal haemorrhage, so-called 'Waterhouse-Friderichson' syndrome, may be present\(^7\) (Figure 4-14). Microscopy will reveal a polymorphonuclear cell infiltrate of the meninges (Figure 4-15) and cultures of cerebrospinal fluid should yield bacteria unless prior antibiotic therapy has occurred.

Cerebral infarction has been documented in approximately 5% of children with *Haemophilus influenzae* meningitis\(^11\) possibly due to arteritis with spasm. Necrotising cerebral vasculitis occurs with group B streptococcal, rickettsial, fungal and viral central nervous system infections\(^3\). (Viral infections include congenital rubella and herpes zoster.) Vascular stenosis following meningitis may also occur in the absence of thrombosis due to a reactive fibrointimal reparative process\(^12\).
Figure 4-13: Suppuration of the meninges in established pneumococcal meningitis.
Figure 4-14: Bilateral adrenal haemorrhages (Waterhouse-Friderichson syndrome) in a two-month-old infant with meningococcal meningitis and septicaemia.

Figure 4-15: Infiltration of the meninges by acute inflammatory cells in bacterial meningitis (Haematoxylin & Eosin, x 110).
Occurrence of Sudden Death

Lethal effects derive from septicaemia and/or meningitis, both of which may have a very fulminant course. The septicaemic shock found in cases of meningococcaemia is thought to be caused by a circulating endotoxin which also acts on the myocardium and adrenal glands\(^2\)\(^1\).

Myocarditis may be found in a significant number of cases of meningococcal sepsis, sometimes with involvement of the atrioventricular node\(^5\)\(^8\)\(^9\)\(^7\). Other lethal mechanisms involve cerebral oedema due to increased capillary permeability with brainstem herniation, vascular inflammation with thrombosis and decreased cerebral perfusion due to hypotension\(^8\)\(^9\)\(^2\).

Autopsy Investigation

Cerebrospinal fluid aspirates should be obtained aseptically prior to opening the skull, either through the fontanelle or through the posterior atlanto-occipital membrane. Swabs for microbiological assessment should also be taken from areas of meningeal congestion or suppuration. Blood cultures are routine in such cases.

As infection may spread from adjacent areas such as the middle ear, these should be carefully examined at autopsy and microbiological swabs taken if necessary. It may also be appropriate to check for skull fractures and cerebrospinal fluid leakage in cases of recurrent meningitis.

ENCEPHALITIS

Certain viruses may infect the substance of the brain resulting in inflammation, necrosis and oedema. For example, Herpes simplex virus may infect predominantly the temporal and frontal lobes in the child/adult type of encephalitis, or act more diffusely in the neonatal form. Rapid death may occur in children with these types of infections.

POLIOMYELITIS

Polioymyelitis is caused by an enterovirus which produces paralysis through infection of motor neurons. As with a number of other infections, epidemics are rare in Western countries since the introduction of immunization programs. Death in affected children may occur from respiratory paralysis which may be sudden, mimicking the presentation of SIDS. At autopsy the findings are relatively non specific, although destruction of motor neurons particularly of the anterior horns of the spinal cord may be seen on microscopy\(^45\).
HAEMATOLOGICAL CONDITIONS

SPLENIC RUPTURE

Almost any infectious cause of splenomegaly increases the risk of rupture from relatively minor trauma. In Western countries infection with Epstein-Barr virus causing infectious mononucleosis is probably the most common microbiological cause of fatal rupture\(^\text{15}\), whereas on a global scale malaria would be of greater significance.

Malaria

Malaria is an acute febrile illness caused by *Plasmodium spp.* that is transmitted by mosquito vectors. *Plasmodium falciparum* infection is the most severe form and may result in death from cerebral involvement with vascular thrombosis and localized ischaemia or less often from splenic rupture. At autopsy hepatosplenomegaly may be present with plugging of congested cerebral vessels by red blood cells in which malarial parasites can be seen on microscopy\(^\text{47}\).

SICKLE CELL DISEASE

The clinicopathological features of sickle cell disease are dealt with in Chapter 7. One of the complications of sickle cell disease is reduced splenic function which predisposes to fulminant infections particularly by encapsulated bacteria. Infectious agents include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella sp.*, *Escherichia coli* and *Staphylococcus aureus*. Affected children have a higher rate of generalized sepsis, osteomyelitis and meningitis than do normal children.

GASTROINTESTINAL INFECTIONS

GASTROENTERITIS

Fulminant viral gastroenteritis resulting in fatal dehydration is a common global problem in infants and children. Details are discussed in the following study.
STUDY #4-2

INVESTIGATION OF THE DIFFERENTIAL DIAGNOSIS AND CLINICOPATHOLOGICAL FEATURES OF UNEXPECTED DEATH DUE TO FATAL DEHYDRATION IN INFANCY AND CHILDHOOD

INTRODUCTION

Dehydration is an important cause of death in children and is often associated with gastrointestinal disorders. There are, however, other rarer associations which should be considered. Review of dehydration deaths at the Adelaide Children's Hospital was undertaken to examine autopsy findings and to ascertain specific aetiologies and causative factors.

MATERIALS AND METHODS

The autopsy records of the Adelaide Children's Hospital for a 32 year period from March 1961 to February 1993 were examined. Thirty-seven cases were found where dehydration was the primary cause of death.

RESULTS

Cases ranged in age from 2 weeks to 6½ years (mean = 11.4 months), with a male to female ratio of 1:1. The most common cause of dehydration was gastroenteritis (N = 22) with other less common associated factors including high environmental temperatures (N = 6), mental retardation (N = 3), "chronic infections with failure to thrive" (N = 2), neglect (N = 2), congenital adrenal hyperplasia (N = 1), and a single case of fatal dehydration as a first presentation of cystic fibrosis (these results are summarised in Table 4-7). Most of the cases of fatal gastroenteritis occurred in the 1960's (N = 7) and 1970's (N = 12) with only 2 cases occurring in the 1980's and 1 in the current decade. The majority of cases occurred during the autumn/winter months corresponding to outbreaks of infectious gastroenteritis. The remainder occurred within the warmer months, and in one case both high environmental temperature and gastroenteritis contributed to the lethal episode. Twelve of the 24 children with gastroenteritis died at home, eleven died within 48 hours of arrival at hospital and one died in transit.
TABLE 4-7: CLINICOPATHOLOGICAL FEATURES OF 37 CASES OF FATAL DEHYDRATION IN INFANCY AND CHILDHOOD

<table>
<thead>
<tr>
<th>CAUSE OR MAJOR ASSOCIATED FACTOR</th>
<th>NOS. OF CASES</th>
<th>AGE RANGE</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTROENTERITIS</td>
<td>22</td>
<td>2 WEEKS–20 MONTHS</td>
<td>7 MONTHS</td>
</tr>
<tr>
<td>HIGH ENVIRONMENTAL TEMPERATURE</td>
<td>6</td>
<td>3 MONTHS–26 MONTHS</td>
<td>8 MONTHS</td>
</tr>
<tr>
<td>MENTAL RETARDATION/ABNORMAL CHROMOSOMES</td>
<td>3</td>
<td>2 WEEKS–75 MONTHS</td>
<td>27 MONTHS</td>
</tr>
<tr>
<td>NEGLECT</td>
<td>2</td>
<td>6 MONTHS + 12 MONTHS</td>
<td></td>
</tr>
<tr>
<td>&quot;CHRONIC INFECTION/FAILURE TO THRIVE&quot;</td>
<td>2</td>
<td>10 MONTHS + 15 MONTHS</td>
<td></td>
</tr>
<tr>
<td>CYSTIC FIBROSIS</td>
<td>1</td>
<td>58 MONTHS</td>
<td></td>
</tr>
<tr>
<td>CONGENITAL ADRENAL HYPERPLASIA</td>
<td>1</td>
<td>8 MONTHS</td>
<td></td>
</tr>
</tbody>
</table>

Immunooassay for rotavirus performed in three of the children thought to have gastroenteritis yielded a positive result in two cases. In one case *Clostridium welchii* was cultured from bowel contents sampled at post mortem.

All cases of dehydration secondary to high environmental temperature occurred during the summer months. All six cases involved infants who were found dead at home. In three cases poor parenting appeared to play a role. Inadequate intake alone (N = 2) was an important factor contributing to dehydration when mental retardation was present.

The gross autopsy findings indicative of dehydration were sunken eyes (32 cases), sunken anterior fontanelle (N = 17), reduced tissue turgor (N = 31), flabby and wrinkled internal organs which included the liver (N = 14), kidneys (N = 12), adrenal glands (N = 5) and pancreas (N = 2) (Figures 4-16 to 4-19). In three cases the peritoneal cavity was noted to be dry. In the majority of the cases of gastroenteritis (N = 14/22) the intestines were dilated and filled with fluid faeces and in a small number of cases (6) there was an increased mononuclear infiltrate within the lamina propria of the small intestinal mucosa.
Figure 4-16: Deeply sunken eyes are evidence of marked dehydration in a two-year-old boy.

Figure 4-17: Sunken fontanelle in a five-month-old girl due to dehydration following gastroenteritis. This was associated with basal subarachnoid haemorrhage (see Figure 4-21).
Figure 4-18: Reflecting the scalp demonstrates more clearly the degree of fontanelle depression in significant dehydration. The case illustrated was a three-month-old girl with gastroenteritis.

Figure 4-19: Shrinkage of the liver capsule in a severely dehydrated six-month-old girl with gastroenteritis.
Patchy neuronal necrosis was noted in the cerebral cortex and cerebellum in two of the six cases of dehydration caused by high environmental temperatures. Generalised wasting and thymic atrophy were seen in both cases of neglect. Characteristic inspissated secretions were seen within the lungs, salivary glands, intestinal mucosa and pancreas in the case of occult cystic fibrosis (Figure 4-20). Fibrosis of the pancreas and in the portal tracts of the liver was also noted. Adrenal gland enlargement with increased cortical convolution was noted in the single case of congenital adrenal hyperplasia. Vitreous humour electrolyte analysis was available for review in six cases demonstrating an elevated sodium level in all cases examined (range 155 mmol/l to 188 mmol/l).

DISCUSSION

Dehydration from any cause may result in electrolyte imbalances with the attendant risk of sudden death. In infants and children fulminant gastroenteritis is one of the most important causes of rapid clinical deterioration if fluid balance is not maintained. Infants are at particular risk as watery diarrhoea may be mistaken for urine, leading to underestimation of the severity of the condition. Neglected children who develop gastroenteritis are also vulnerable to lethal consequences due to parental inattention and the late seeking of medical care. However, poorly educated parents may genuinely fail to appreciate the severity of a child’s illness. The effects of excessive fluid loss may also be exacerbated in areas with a hot climate, especially in the middle of summer.

Evidence of marked dehydration may be obvious at autopsy as noted in the above study, with sunken eyes, a depressed fontanelle in infants, dry mucous membranes and internal organs, and decreased skin turgor but this is not invariable. Reflection of the scalp will demonstrate a sunken fontanelle more clearly. As the clinical history may be equivocal and microbiological investigations unhelpful, Huser and Smialek have recommended that postmortem analysis of vitreous humor should be performed in all cases of unexplained infant death as this may reveal elevation in sodium and urea nitrogen levels. Knight quotes levels of vitreous humour sodium >155 mmol/L, chloride >135 mmol/L and urea >40 mmol/L as reliable markers of antemortem dehydration. This may be of particular significance if the possibility of parental neglect exists. Examination of the bowel is important, as a case of pseudomembranous colitis due to Clostridium difficile has been reported in a three-month-old boy presenting as SIDS.
The cause of sudden death in these cases may be hyperkalaemic cardiac arrhythmia, or cerebral haemorrhage, or infarction from venous thrombosis\textsuperscript{52} (Figures 4.21 & 4.22).

Occasionally sudden death may occur without dehydration as was the case in a four-month-old boy who had apparently recovered from gastroenteritis but who had \textit{Salmonella virchow} isolated from the gut, middle ear and cerebrospinal fluid, with organisms identified on immunohistochemical staining of the liver\textsuperscript{19}.

In cases of temperature-related dehydration there are no specific autopsy findings diagnostic of heat stroke, although generalised tissue anoxia may result in necrosis within many organs\textsuperscript{42} as was noted in the brain in two of our cases. A high rectal temperature after death may be found.

Mentally retarded patients are at increased risk of dehydration due to inadequate intake, although neglect may be a factor in such cases. In two of our children the cause of death was attributed to "chronic infections with failure to thrive". It is difficult from the autopsy reports to be certain, however, it is possible that these cases also represent neglect.

Death with dehydration and electrolyte disturbance on hot days is a known problem in children with cystic fibrosis\textsuperscript{1}. The mechanism involves inability to control sodium and chloride loss at times of profuse sweating. It is, therefore, important to always consider cystic fibrosis when dehydration is found at autopsy, particularly given the genetic ramifications of this diagnosis.

Another rare condition to be considered in cases of fatal dehydration in childhood is congenital adrenal hyperplasia\textsuperscript{1}. For example, one infant in our series died due to dehydration and electrolyte disturbance from the salt losing form of this condition. A history of neonatal death in previous siblings, with dehydration, should alert the pathologist to the possibility of this diagnosis.

This review demonstrates that while fatal dehydration is most often due to gastrointestinal infection, it may be a marker of occult metabolic disease. The familial basis of these disorders makes accurate identification at autopsy extremely important. Occult child abuse manifesting itself for the first time as fatal dehydration is another possibility.
Figure 4-20: Fibrosis with parenchymal loss and inspissation of secretions within pancreatic ducts in the case of cystic fibrosis that was only diagnosed at autopsy after death due to dehydration.

Figure 4-21: Spontaneous subarachnoid haemorrhage causing sudden death in a five-month-old girl with acute gastroenteritis and dehydration.
Figure 4-22: Cerebral venous thromboses with cerebral infarction in a nine-month-old boy with acute gastroenteritis and dehydration.
BOTULISM

Infantile botulism is a recognized cause of sudden death due to the actions of a potent neurotoxin which interferes with respiration\textsuperscript{76}. Further details are discussed in the section later in the chapter on toxigenic bacteria.

PRIMARY PERITONITIS

Infants may die suddenly after the development of primary peritonitis, symptoms of which are vomiting, diarrhoea and acute prostration. Causative organisms include Pneumococcus, Streptococcus and \textit{Escherichia coli}. At autopsy, purulent ascitic fluid will be identified with no demonstrable primary focus of infection.

GENITOURINARY CONDITIONS

PYELONEPHRITIS

The majority of cases of acute bacterial pyelonephritis present with fever and loin pain. Cases in which sudden death is purported to have occurred may represent examples of parental inattention or of underestimation of the severity of symptoms by attending physicians.

GENERALIZED CONDITIONS

SEPTICAEMIA

Generalized bacterial sepsis may cause sudden deterioration and death. For example, group B streptococcal infection is a major cause of sudden death within the first two months of life due to pneumonia, meningitis and generalized sepsis. Fever may not have been marked and the presentation may be of SIDS\textsuperscript{11,17}. At autopsy a focus for the infection may be discernable in some cases, although others may have no apparent source of the pathogenic agent. The mechanism of death in children who die suddenly from septicaemia is not always clear\textsuperscript{6}.

In the absence of a clear-cut history of antemortem sepsis the diagnosis of lethal septicaemia in cases of sudden death requires not only positive blood cultures, but also microscopic evidence of disseminated sepsis preferably with isolation of the same organism from multiple sites\textsuperscript{11}. Histological evidence of sepsis may include areas of localized acute inflammation such as an acute pneumonia, or haemorrhage and intravascular fibrin thrombi from disseminated intravascular coagulation\textsuperscript{117}. In the absence of these findings the possibility of external contamination, agonal sepsis or postmortem overgrowth must be considered\textsuperscript{44}.
VIRAEMIA
Disseminated infection with organisms other than bacteria may also result in sudden and unexpected cardiac arrest. Examples include adenovirus, rhinovirus and Herpes simplex virus\textsuperscript{32,116}. It has been proposed that disseminated cytomegalovirus infection may be associated with some cases of SIDS based on the finding of viral inclusions within salivary glands and brainstem microglial nodules\textsuperscript{118}, however, subsequent studies have not confirmed this\textsuperscript{109}.

ENDOTOXAEMIA
A variety of locally invasive bacteria may cause systemic effects due to the elaboration of systemically-acting potent toxins.

\textit{Staphylococcus aureus}
Toxin-producing \textit{Staphylococcus aureus} may cause sudden death in infants and children following relatively minor skin infections\textsuperscript{125}. A similar syndrome known as the 'toxic shock syndrome' has occurred in menstruating adolescent and young adult women\textsuperscript{33}, the staphylococci being present in contaminated tampons\textsuperscript{81}. Antemortem symptoms of vomiting, sore throat and skin rash may progress rapidly to shock with renal and cardiac failure\textsuperscript{86}. It has been suggested that staphylococcal enterotoxins may also be involved in some cases that have presented as SIDS\textsuperscript{74}.

\textit{Corynebacterium diphtheriae}
The exotoxin derived from \textit{Corynebacterium diphtheriae} not only causes local changes in the form of epithelial necrosis with pseudomembrane formation in the pharynx, but may also result in myocardial damage. The intensity of myocarditis varies, with 10 to over 80% of affected patients demonstrating clinical evidence of cardiac disease\textsuperscript{28,80}. Involvement of conduction tracts may lead to heart block and sudden death from arrhythmia. At autopsy fatty change within the myocardium, liver and kidneys may be observed.

\textit{Escherichia coli}
\textit{Escherichia coli} may produce an enterotoxin which is considered by some researchers to be associated with SIDS\textsuperscript{18}, although the significance of this is at present uncertain.
*Clostridium* sp.

Both *Clostridium tetani* and *Clostridium botulinum* produce potent neurotoxins which may result in sudden death. Tetanus is characterized by progressive stiffness of voluntary muscles with the development of respiratory failure or laryngeal spasm\(^1\). Occasionally the clinical course may be fulminant and death can occur rapidly, particularly in children with sickle cell disease\(^4\). Changes at autopsy are relatively nonspecific with local inflammation at the site of infection and swelling of motor neurons in the brainstem and spinal cord.

Botulism occurs in infants and children when the neurotoxin produced by *Clostridium botulinum* is ingested in food. Clinical symptoms and signs usually evolve over some time and consist of vomiting and diarrhoea progressing to respiratory paralysis. In infants botulism may present as sudden and unexpected death due to overgrowth by intestinal *Clostridium botulinum*.

**IMMUNODEFICIENCY STATES**

A heterogeneous variety of primary and secondary immunodeficiency states exist\(^2^7,9^9,1^0^0\), only some of which are associated with the occurrence of fulminant infections and death.

**PRIMARY IMMUNODEFICIENCY STATES**

i) **X-linked agammaglobulinaemia of Bruton** is one of the most common types of heritable immunodeficiencies. In severe forms it is characterized by marked reduction or absence of serum immunoglobulins resulting in recurrent pyogenic infections from an early age. Findings at autopsy include a lack of germinal centres in lymph nodes and the spleen, with rudimentary tonsils and an absence of plasma cells on microscopy.

ii) **Severe combined immunodeficiency** is a heterogeneous disorder characterized by defects in both humoral and cell mediated immunity. Death usually occurs in early life from overwhelming *Pseudomonas sp.* or viral infections. At autopsy the thymus is not found within the anterior mediastinum, but is higher up in the neck, and on microscopy is found to be devoid of lymphoid cells and Hassel's corpuscles. Affected children often lack erythrocyte and leukocyte adenosine deaminase, an enzyme which can be tested for on fresh samples.

iii) **Common variable immunodeficiency** represents the most frequent form of serious heritable immunodeficiency. This condition is characterized by reduced blood immunoglobulin levels resulting in afflicted children suffering recurrent pyogenic infections. Examination of lymph nodes reveals hyperplastic lymphoid follicles, in contrast to X-linked agammaglobulinaemia.
iv) DiGeorge syndrome results from third and fourth pharyngeal pouch anomalies such as aplasia, hypoplasia or ectopia of derived tissues, including the thymus and parathyroid glands. Sudden death in infants and children with this disorder may also occur due to associated cardiovascular abnormalities which are discussed in greater detail in Chapter 3.

v) Wiskott-Aldrich syndrome is an X-linked recessive condition characterized by eczema, thrombocytopenia and variable T and B cell defects that result in recurrent infections. Sudden death may occur due to the low number of circulating platelets, as occurred in a five-month-old boy with Wiskott-Aldrich syndrome who died rapidly at the Adelaide Children’s Hospital and was found at autopsy to have an intracranial haemorrhage.

vi) Congenital asplenia may occur on its own, or it may be part of a more extensive syndrome involving cardiovascular anomalies. The clinical presentation of cases in which there are other congenital malformations present (90%) tends to be overshadowed by cardiovascular problems in early infancy. However, in children who survive early life, there is still the ever present risk of fulminant sepsis which may result in sudden and unexpected death. Haemophilus influenzae infection and intra-adrenal haemorrhages were present in five of the six cases in these reports, all of which pursued a fulminant course with death often within 12 hours of the onset of symptoms. Familial cases of congenital hyposplenism have been reported.

If a hypoplastic or absent spleen is noted on initial examination of the abdominal cavity at autopsy, not only should complex cardiovascular abnormalities be looked for, but full microbiological examination should be conducted. This is particularly so if haemorrhagic adrenal glands are also present.

vii) Other forms of immunodeficiency syndromes include defects in the complement system and defects in macrophage/neutrophil function such as chronic granulomatous disease.

SECONDARY IMMUNODEFICIENCY STATES

Iatrogenic

Infants and children who have received chemotherapy for malignancies are at increased risk of developing fulminant infections due to opportunistic organisms. These may be multiple and result in disseminated intravascular coagulation. Sudden death due to fungal thromboembolism may occur in children infected with angio-invasive fungi such as Aspergillus sp. In these children it may be difficult to identify fungi in tissue sections unless sampling is extensive as
angio-invasion with infarction may have caused widespread tissue necrosis. As well, sampling of venous blood may be inadequate as fungal hyphae may not pass through the capillary bed\textsuperscript{28}. A proposed autopsy sampling protocol for fungi is outlined in Appendix I.

**Acquired Immunodeficiency Syndrome (AIDS)**

It could be suggested that one of the particularly unpleasant features of AIDS is the prolonged clinical course that sufferers are forced to endure. However, while sudden and unexpected death does not stand out as a particularly obvious presentation, it does occur.

In adults with AIDS, cardiac lesions have included myocarditis, endocarditis, pericardial effusions, left ventricular hypokinesia, mitral incompetence and right ventricular dilatation\textsuperscript{39,49,88}. Clinical studies of children with AIDS have also demonstrated abnormalities in left ventricular function, sometimes caused by dilated cardiomyopathy\textsuperscript{63,64} or by cytomegalovirus infection\textsuperscript{24}.

Vascular lesions found in children with AIDS may also precipitate sudden death. For example, involvement of the coronary arteries with aneurysm formation has been reported as a cause of death from myocardial infarction in a thirty-two-month-old girl with AIDS\textsuperscript{65}. Microscopically, vessels show intimal and medial fibrosis with disruption of elastin fibres and medial calcification. These fibrocalcific vascular lesions are similar to those found in idiopathic arterial calcification of infancy.

Vasculitis and perivasculitis of the cerebral vessels may be associated with intracerebral haemorrhage and ischaemic lesions in infected individuals\textsuperscript{77}. Vasculitis may result in cerebral artery aneurysm formation\textsuperscript{62} and vascular calcification has been found in the basal ganglia of infants and children with AIDS\textsuperscript{16}.

A case of sudden death following massive gastrointestinal tract haemorrhage in an eight-year-old boy with AIDS has been reported, but unfortunately further comment is not possible as permission for autopsy was not granted\textsuperscript{10}. Children with AIDS are also at much higher risk for developing a variety of other opportunistic infections, the features of which have been recently reviewed\textsuperscript{7,51,91,112}.
REFERENCES

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References Ch4-3


SUDDEN NATURAL DEATH IN INFANCY
& EARLY CHILDHOOD

CHAPTER 5

RESPIRATORY CONDITIONS
INTRODUCTION
Respiratory causes of sudden and unexpected infant and childhood death often involve acute obstruction of the airway by an impacted foreign body or by an intrinsic lesion such as an inflamed epiglottis. Other major causes of sudden respiratory death are asthma and infective conditions such as acute bronchopneumonia. These disorders are listed in Table 5-1.

TABLE 5-1: RESPIRATORY CAUSES OF SUDDEN PAEDIATRIC DEATH

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Asthma</td>
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<tr>
<td>Upper airway obstruction</td>
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<tr>
<td>Bronchopulmonary dysplasia</td>
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<tr>
<td>Acute bronchopneumonia</td>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Massive pulmonary haemorrhage</td>
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<td>Tension pneumothorax</td>
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Two studies of sudden death in children and young adults found respiratory disease as a cause of death in 10 of 31 cases (32%) and in 12 out of 78 cases (15%), respectively\(^9\). In the earlier series Molander found four cases of bronchopneumonia, three cases of asthma and three cases of acute epiglottitis\(^9\), while Siboni and Simonsen found a greater number of cases of fulminant tracheobronchitis (five out of the 12 cases of fatal respiratory disease), with four cases of acute epiglottitis, two of asthma and a final case in which death was attributed to acute tonsillitis\(^1\). Thus acute respiratory disease accounts for a significant proportion of cases of sudden natural death in childhood.

ASTHMA
Asthma is characterized by episodes of wheezy breathlessness due to paroxysmal narrowing of smaller airways, triggered by a variety of specific allergenic materials. These include pollen, dust, chemical fumes, animal products, aspirin and infectious agents such as viruses and Aspergillus sp.. Physical stimuli such as cold temperatures may also induce an attack. It is the most common chronic lung disorder of childhood in a number of countries including the United States, the United Kingdom and Australia. Although asthma is only rarely associated with a fatal outcome\(^2\), the incidence of asthma-related deaths has been reported to be
increasing. Death may occur during status asthmaticus in which severe bronchospasm persists despite medical treatment, or it may be quite sudden and unexpected. In the paediatric age range this tends to occur predominantly in older children and adolescents. For example, no children under four years of age were found in a series of 11 fatal cases taken from autopsy files at the Adelaide Children's Hospital (range = 4 to 15 years; mean = 10 years). However, the occurrence of sudden death in occasional younger asthmatic children does qualify it for inclusion in this thesis.

Clinical Features

Children with asthma have episodic wheezing, dyspnoea and hyperinflation of the chest. Individuals who are most likely to die are those with a long history of asthma who have had episodes in the past which were life-threatening or which required hospitalization. However, it must be emphasized that sudden death may still occur in individuals who have presented with only apparently mild episodes, or without particularly severe histories.

Occurrence of Sudden Death

The mechanisms of sudden death in an acute asthmatic attack are not completely understood and involve cardiac arrhythmias, hypokalaemia or asphyxia. Unfortunately it has been difficult to obtain adequate data due to the rapidity of terminal episodes and their occurrence outside hospital.

Bronchodilators have been implicated in the aetiology of sudden death possibly due to cardiac arrhythmias. Alternatively, bronchodilators may provide temporary symptomatic relief resulting in a critical delay in presentation of the patient to hospital. Delay in seeking treatment for whatever reason has been found to be a significant factor in asthma deaths. The possibility of pharyngeal irritation from inhalational agents inducing a vasovagal response and cardiac arrest has also been proposed.

Although it has been suggested that cardiac arrhythmia exacerbated by anti-asthmatic drugs is the most likely terminal event, a clinical study of ten adolescent and adult asthmatics who developed respiratory arrests before, or soon after, arrival at hospital failed to demonstrate significant disturbances of cardiac rhythm. It was concluded, therefore, that severe asphyxia rather than arrhythmia was the more important factor.
Sudden massive narrowing of the airways may cause collapse, based on observations of hospitalized asthmatic patients who were initially stable but who suddenly deteriorated and required markedly increased ventilatory pressures. The possibility of an alternative process such as pneumothorax should also be considered in this situation. This was found in two children in a series of 13 fatal cases. Pneumothorax may also be associated with fatal air embolism in status asthmaticus.

The possibility of electrolyte disturbance in fatal cases has been considered. In particular hypokalaemia due to the action of β2-agonists may potentiate the irritative effects of hypoxia, acidosis and of the β2-agonists themselves on the myocardium. It has also been proposed that hypokalaemia could induce muscle weakness, thus interfering with chest wall and respiratory muscle actions.

Occasionally the presence of other lung lesions may adversely affect the outcome of an acute attack. For example, bronchopneumonia and previous pulmonary thromboembolism were found in three of a series of 13 asthmatic children who died unexpectedly. Similarly, viral infection of the lungs may precipitate a lethal episode in predisposed children. Along with bacterial infections, this may account for the seasonal variation in incidence of lethal episodes. Pneumothoraces and drug hypersensitivity may also act as precipitating factors in a small number of cases. Children with an acute asthmatic episode often have nausea and vomiting sometimes exacerbated by medications, but gastric aspiration has not usually been considered a significant contributor to death.

A final possibility that may increase the likelihood of sudden death is adrenal insufficiency which has been demonstrated in adolescent asthmatics secondary to prolonged steroid usage.

Pathological Features

At autopsy, a history of rapidly progressive respiratory symptoms prior to collapse will enable clinicopathological correlation to be made in a child in whom fatal asthma is suspected. However the time from no apparent symptoms to death may be only seconds, and the presenting history may also be atypical in that hypoxia may have induced seizures with incontinence or impaired consciousness.
The three main components in a fatal asthmatic attack are bronchospasm, plugging of airways by tenacious secretions and oedema of the mucosa. All may contribute to worsening hypoxia resulting in cardiorespiratory arrest. Evidence of the latter two processes may be found at autopsy, with the changes in the airways occurring in response to inflammatory mediators such as histamine, leukotrienes and eosinophil cationic protein that are released by mast cells and eosinophils. Tension pneumothorax, although rare, should always be considered in these children and chest X-ray or opening of the chest under a water seal should be performed.

The lungs are usually markedly hyperinflated, often meeting in the midline and retaining their shape after evisceration (Figure 5-1). One of the most striking features on inspection of the opened airways and cut surface of the lungs is the presence of thick tenacious mucus plugs filling bronchi and bronchioles (Figure 5-2). There may also be evidence of bronchiectasis and emphysema.

Classically, the microscopic features of asthma include oedema of the bronchial walls with an increase in inflammatory cells (particularly eosinophils), thickening of the subepithelial basement membrane and hypertrophy of smooth muscle (Figure 5-3). There may also be hypertrophy of submucosal mucous glands. The increase in submucosal chronic inflammatory cells may result from a viral infection which has triggered the lethal episode. Within the bronchial lumena there may be mucous plugs which contain variable numbers of eosinophils and strands of desquamated ciliated respiratory epithelial cells forming Curshmann spirals. Charcot-Leyden crystals may be associated with eosinophils. Myocardial contraction band necrosis has also been reported in children who have died during status asthmaticus²³.

Although the histologic findings may be typical of asthma, it should be stressed that there are no pathognomonic features unique to lethal cases and that lung sections may even appear reasonably normal⁷⁶. Thus there is a need to rely on an appropriate clinical history and on the exclusion of other possibilities. As well, it should be emphasized that features may be variably distributed involving some, but not necessarily all, bronchi.
Figure 5-1: Hyperinflated lungs in a case of sudden death of a five-year-old asthmatic boy. Air trapping has caused the bulky lungs to almost completely obscure the anterior surface of the heart.

Figure 5-2: Tenacious mucous plugs filling the lower trachea and major bronchi may be found in asthma (A). Cut surface of the lung showing extruded mucus plugs (arrows) (B).
Figure 5-3: Thickening of the basement membrane and bronchiolar smooth muscle with an infiltrate of inflammatory cells containing a preponderance of eosinophils in a 10-year-old asthmatic girl who died suddenly (Haematoxylin & Eosin, x 440).
UPPER AIRWAY OBSTRUCTION

Obstruction of the airways most often occurs in children as a result of foreign body impaction, however, there are a variety of intrinsic and extrinsic lesions that may also result in acute airway occlusion, by a variety of different mechanisms\(^6,15,58,6^1\). These can be classified according to their anatomical location and are listed in Table 5-2. Although not all of these have been reported as causes of sudden death, it is reasonable to suppose that any lesion of the upper airway that causes significant dyspnoea and stridor, and that requires urgent endotracheal intubation, is also capable of causing lethal airway occlusion. While a number of congenital abnormalities, such as choanal atresia, present within the neonatal period, occasional cases with incomplete airway occlusion may not be diagnosed until later in life.

<table>
<thead>
<tr>
<th>TABLE 5-2: CONDITIONS ASSOCIATED WITH UPPER AIRWAY OBSTRUCTION AND SUDDEN DEATH IN CHILDHOOD</th>
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<td><img src="https://example.com/table5-2.png" alt="Table" /></td>
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1. Choanal atresia
2. Nasopharyngeal tumours
3. Posterior lingual masses e.g. thyroglossal duct cysts
4. Macroglossia
5. Micrognathic syndromes e.g. Pierre-Robin, Goldenhar, Treacher-Collins, Apert, Crouzon
6. Heterotopic tissues
7. Upper airway infections
8. Structural airway defects e.g. tracheomalacia, bronchomalacia
9. Tracheal stenosis
10. Vascular rings
11. Miscellaneous
STUDY #5-1

A STUDY OF MECHANISMS OF ASPHYXIAL DEATH IN INFANCY AND EARLY CHILDHOOD

MATERIALS AND METHODS

Records of the Adelaide Children's Hospital Histopathology Department were reviewed for cases of asphyxial deaths in childhood and infancy. Twenty-seven cases were found and were analysed with respect to age, sex and the circumstances of death.

RESULTS

The median age at death was 15 months (Range = 6 weeks to 7 years) and the male to female ratio was approximately 2:1. Deaths occurred from upper and lower airway obstruction, suffocation and hanging. In 15 of 27 cases death resulted from choking. In four cases the airways were obstructed by food which included peanuts (N=1), a carrot (N=1) and mincemeat (N=2). One child vomited and aspirated while travelling restrained in a car. Foreign bodies found included a toy ball, a woodscrew, a plastic chess piece, and in two cases tablets. Two cases involved airway obstruction from without by material in the oesophagus. In one case an intraoesophageal bolus (sausage) was found and in another, a one cent coin wedged in the oesophagus was associated with tracheal compression. Accidental choking due to fine granular material was found in three young boys - one died in a sand pit, another at a fertilizer works and another in a field storage bin containing wheat. Of the remaining 12 cases, three cases of wedging between the cot and a mattress or another piece of furniture was identified. Plastic bags over a pillow or mattress asphyxiated two children and another infant died when she fell between the back of the couch and the soft pillows of the seat. Five cases of strangulation/hanging were identified in which there was constriction of the neck by clothing, a curtain cord in one case and the seat belt of a baby car seat in another.

CONCLUSION

These cases demonstrate the range of asphyxial deaths that can occur in infancy and early childhood. The absence of pathognomic findings at autopsy, particularly in cases involving wedging or plastic bags may lead to a mistaken diagnosis of SIDS in infants if an adequate death scene investigation has not been conducted.

* * *
CHOANAL ATRESIA

Obstruction to the airway at the level of the choanae may be unilateral and partial, or bilateral and complete. When it is complete, either due to membranous or bony obstruction, symptoms of respiratory distress occur immediately after birth and may result in death\textsuperscript{19}. In incomplete cases infants may survive longer with signs of airway obstruction developing only during feeding\textsuperscript{30}. The cause of airway obstruction in these infants is similar to infants with Pierre-Robin anomaly and involves posterior displacement of the tongue\textsuperscript{22}.

In some cases there may be functional nasal obstruction in the absence of definite choanal atresia, so-called congenital nasal stenosis\textsuperscript{47}. The symptoms are similar to choanal atresia, suggesting that choanal atresia and congenital nasal stenosis represent different manifestations of the same disorder. Variable combinations of stenosis of the entire nasal cavity, the anterior portion of the nose or the choanae characterize the latter entity\textsuperscript{53}. A point to remember in congenital nasal stenosis is that functional airway obstruction may still have occurred even if it is possible to pass a probe from the nostrils into the nasopharynx.

NASOPHARYNGEAL TUMOURS

A variety of tumours and developmental anomalies such as teratomas and encephaloceles may impinge on the upper aerodigestive tract and cause obstruction\textsuperscript{73}. As well, hypertrophy of the adenoids and tonsils may result in upper airway blockage, respiratory distress and apnoea, with some infants developing pulmonary hypertension and cor pulmonale\textsuperscript{13,56}.

LINGUAL THYROGLOSSAL DUCT CYSTS

Characteristic features are described below.

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STUDY #5-2

DEMONSTRATION OF THE ASSOCIATION BETWEEN LINGUAL THYROGLOSSAL DUCT REMNANTS AND SUDDEN UNEXPECTED DEATH IN INFANCY

INTRODUCTION

Thyroglossal duct lesions usually present in childhood as cystic midline cervical swellings. Although they are most often found near the hyoid bone, cysts can potentially be found anywhere along the course of the duct, which runs from the foramen caecum of the tongue to the thyroid isthmus. Occasionally remnants can be found at unusual sites such as the
suprasternal notch, within the tongue or in more lateral locations. Presenting complaints most often relate to recurrent local inflammation and infection\(^\text{77}\). Thyroglossal duct remnants located at the base of the tongue may present with more serious problems due to their critical position in the upper airway\(^\text{35,55,63}\); for example, fatal airway obstruction is a complication that has been recognised for a number of years\(^\text{12}\). The following cases of sudden and unexpected death due to airway obstruction by lingual thyroglossal duct cysts in two previously well three-month-old infants, with minimal antemortem symptoms, are presented to demonstrate the clinicopathologic features of this entity and its association with sudden death\(^\text{16}\).

**CASE REPORTS**

**Case 1:** A three-month-old boy who was last fed at 0400 hours was found dead in his cot four hours later. His past history included premature delivery with a birth weight of 1,690g. Postnatally his course was complicated by possible sepsis and a mildly elevated serum bilirubin which was successfully treated with phototherapy. He was discharged from hospital at the end of one month with a weight of 2,430g. Following discharge he remained well with a 1 kilogram weight gain over the following month. The only unusual feature was occasional irregular, "rasping" respiration. On the day before his death he was noted to have a mild upper respiratory tract infection.

At autopsy the body was that of a well nourished male infant of three months weighing 3,825g and measuring 53cm (crown-heel). There were no dysmorphic features or signs of trauma. Abdominal and thoracic cavities and organs were unremarkable except for scattered petechial haemorrhages on the surface of the thymus and visceral pleura. The major finding was in the oropharynx where a large midline cyst measuring 13mm in maximum diameter was located at the base of the tongue obstructing the glottis. The airway above and below the obstructive lesion was normal, as were the surrounding soft tissues of the neck. Sectioning showed the cyst to be unilocular and fluid-filled (Figure 5-4). Microscopic examination revealed a mixed lining of ciliated pseudostratified columnar and non-keratinising squamous epithelium surrounded by a dense fibro-connective tissue capsule that was infiltrated by occasional chronic inflammatory cells. No other significant pathological findings were present. Death was attributed to asphyxia from obstruction of the upper airway by a previously unsuspected lingual thyroglossal duct cyst.
Figure 5-4: A sagittal section of the thyroglossal duct cyst and adjacent base of the tongue demonstrating the downward displacement of the epiglottis (open arrow) with compromise of the upper airway (Case 1). (Haematoxylin and eosin, x8)

Figure 5-5: A sagittal section of the tongue and epiglottis showing a cyst in the region of the foramen caecum. Note that the tongue and cyst have been displaced anteriorly in this photograph (Case 2).
Case 2: A previously well three-month-old boy, who was last fed at 1930 hours and checked at 0100 hours, was found dead in his cot at 0600 hours. He was found lying on his back with a crocheted quilt across his face. His past history is unremarkable with no record of antenatal or perinatal problems. He had been taken to his local doctor two weeks before death with a mild upper respiratory tract infection which settled spontaneously. He had been quite well on the day prior to his death.

At autopsy the body was that of a well nourished male infant of three months. There were no dysmorphic features or signs of trauma. The mouth contained fine white froth. The abdominal and thoracic cavities were unremarkable except for multiple petechial haemorrhages on the surface of the thymus with occasional petechiae on the visceral pleura. The major finding was in the oropharynx where an 8mm diameter midline cyst was found in the region of the foramen caecum in the posterior tongue (Figure 5-5). The airway above and below the lesion was normal as were the surrounding soft tissues of the neck. Sectioning showed a unilocular cyst containing clear fluid. Microscopic examination demonstrated a flattened squamous epithelial lining with several smaller irregular adjacent tracts lined by a similar type of epithelium. A surrounding layer of loose fibro-connective tissue was present. No other significant pathological findings were present. Death was attributed to asphyxia from obstruction of the upper airway by a previously unsuspected lingual thyroglossal duct cyst.

Note, in both cases the possibility of SIDS could not be completely excluded due to the age, history and other post mortem findings, although it was felt that the presence of lesions of a size considered sufficient to obstruct the upper airway precluded this diagnosis.

DISCUSSION

In the literature materials causing fatal airway compromise have been extremely diverse, although parts of toys and food products feature quite prominently\textsuperscript{27}. Infectious causes of airway obstruction such as acute epiglottis or tumours such as subglottic haemangiomas are also not uncommon. Less usual causes include choanal atresias, tracheo- and laryngomalacia, retropharyngeal abscesses, and vascular rings\textsuperscript{90,106}. Thyroglossal duct remnants very rarely compromise the airway\textsuperscript{68} and are usually not included in the list of common causes of airway obstruction in infants and children.
The thyroglossal duct develops embryologically from canalisation of an epithelial remnant that connects the caudally migrating thyroid gland to the foramen caecum of the tongue. After the thyroid gland reaches its final position in the anterior neck at around seven weeks of fetal age the duct regresses and has usually disappeared within two to three weeks. If remnants remain, however, mucus secretion with no drainage results in cyst formation. This usually occurs in midline remnants lying immediately beneath the hyoid bone. Tracts are lined by either respiratory or squamous epithelium and tend to be multiple with branching and arborisation\textsuperscript{85,86}. Subsequent infection is a complication that may lead to medical attention.

Thyroglossal duct remnants located at the base of the tongue tend to present quite differently from other sites because of their critical position in the upper aerodigestive tract. As well, this usually occurs at a younger age than the more common anterior neck remnants. Review of reported cases shows that airway obstruction manifested by positional stridor, neonatal asphyxia, or even sudden death due to complete airway occlusion, are possible modes of presentation. Other problems may include feeding difficulties or merely a mass effect at the base of the tongue\textsuperscript{35,55,63,68,77}. The differential diagnosis in this case includes ectopic thyroid tissue, haemangioma or dermoid cyst\textsuperscript{91}. The most significant side effect, that of sudden death, emphasizes the need for early diagnosis with surgical treatment if this is to be avoided.

An important antemortem clue to the diagnosis is positional improvement in dyspnoea and stridor when the infant is placed in a prone position on his abdomen as this relieves the pressure of the cyst on the glottis. Of note, the second infant was found dead in a supine position, which is the most vulnerable position for airway obstruction in patients with these posterior lingual lesions.

Obstruction of the airway is reasonably obvious in Case 1 due to the larger size of the cyst and closer proximity to the epiglottis (Figure 5-4). It is also thought to be the most probable cause of death in Case 2, particularly with the supine position of the body which would have maximised the possibility of glottic obstruction from the remnant.

An adequate paediatric postmortem examination requires careful dissection of the upper aerodigestive tract with complete excision of the soft palate, Waldeyer’s ring and tongue, so that these lesions will be adequately demonstrated and not overlooked. Failure to find the
Figure 5-6: *En bloc* dissection of the tongue and upper airway in an infant with mandibular hypoplasia and recurrent cyanotic episodes clearly demonstrating the effects on the laryngeal inlet of backward displacement of the tongue.

Figure 5-7: A three-month-old boy who was found dead in his bed showing the typical facial profile of Pierre-Robin anomaly.
thyroglossal remnant may lead to diagnostic confusion with SIDS, particularly given the presence of petechial haemorrhages that occur secondary to the terminal asphyxial event.

SUMMARY
Two infants discovered dead in their cots (one in the supine position) were found at autopsy to have died from asphyxia due to obstruction of their upper airways by lingual thyroglossal duct cysts.

MACROGLOSSIA
An interesting case at the Adelaide Children's Hospital concerned a six-month-old girl with stigmata of congenital hypothyroidism who choked and died suddenly while being bottle fed. No evidence of milk inhalation could be found, however the infant's tongue was of considerable size protruding from her mouth and causing the floor of the mouth to bulge inferiorly. It was considered likely that this had contributed to upper airway obstruction and death.

MICROGNATHISM & ASSOCIATED SYNDROMES
Infants suffering from a variety of syndromes that are characterized by micro/retrognathia are at risk of acute airway obstruction due to posterior displacement of the tongue. The anatomical effect of this arrangement on the upper airway is well demonstrated in Figure 5-6 which shows an en-bloc dissection of the mandible and tongue in an infant with Pierre-Robin anomaly in which there is complete occlusion of the glottis by the tongue. Occasionally there may also be an intrinsic abnormality of the epiglottis which may exacerbate the tendency to airway obstruction.

Pierre-Robin anomaly is characterized by micrognathia and glossoptosis, with or without cleft palate (Figure 5-7). Anomalies of the limbs are also common and congenital cardiac defects occur. Many infants with the Pierre-Robin complex also have an underlying syndrome such as Stickler, Mobius, Joubert, Brachman de Lange and Marden-Walker syndromes, features of which should be checked for at autopsy.

Sudden and unexpected death may occur even while the micrognathic infant is in hospital and, although the cause may initially appear uncertain, upper airway obstruction is most likely. Typical histories of choking, cyanosis and difficulty swallowing are supportive of
this as the lethal mechanism. Infants with Pierre-Robin anomaly are also known to suffer central apnoeic episodes during sleep which may contribute to the terminal episode\textsuperscript{33}.

A review of autopsy files at the Adelaide Children's Hospital identified several cases of Pierre-Robin anomaly with sudden death attributable to upper airway obstruction. Other conditions with fatal outcomes associated with micrognathia were Treacher-Collins and Goldenhar syndromes. Acute airway obstruction may also occur in infants with other types of facial skeletal abnormalities such as maxillary hypoplasia in Crouzon and Apert syndromes.

**HETEROTOPIC TISSUES**

Choristomas are aggregates of histologically-unremarkable tissues found in heterotopic sites. These may be of minimal significance unless there is compromise of function due to critical location of the tissue such as within the upper airway. Examples include thymus tissue within the trachea, thyroid tissue within the tongue and gastric mucosa within the hypopharynx\textsuperscript{45,50,57}.

**UPPER AIRWAY INFECTIONS**

Examination of the epiglottis is a mandatory part of every paediatric autopsy. In cases of acute epiglottitis the epiglottis is red and swollen and may completely occlude the laryngeal inlet (Figure 5-8). Microscopic examination shows a florid neutrophil infiltrate, sometimes with bacterial colonies. Throat and blood cultures are an essential part of the autopsy and most often reveal *Hemophilus influenzae* type B. Acute haemorrhage into the soft tissues around the base of the epiglottis from other causes may also occlude the airway (see Fig 7-8).

Although much less common than fatal acute epiglottitis, other acute infections of the upper airway may cause sudden death due to airway occlusion. These include tonsillitis, peritonsillar abscess, retropharyngeal abscess, lingual tonsillitis and posterior lingual abscess\textsuperscript{18} (*vide infra*). The relatively nonspecific symptoms and signs that may be present in infants with these conditions makes careful examination of the upper airway essential at autopsy.
Figure 5-8: Fatal acute epiglottitis demonstrating complete airway occlusion

Figure 5-9: Separation of muscle bundles in the posterior portion of the tongue by an extensive acute inflammatory infiltrate, (Haematoxylin & Eosin, x 110).
DEMONSTRATION OF THE ASSOCIATION BETWEEN POSTERIOR LINGUAL ABSCESS AND SUDDEN UNEXPECTED DEATH IN INFANCY

CASE REPORT

A five-month-old boy was found unresponsive one afternoon in his cot, having been last seen alive approximately two hours before. Resuscitation was attempted, but was unsuccessful and he was declared dead on arrival at hospital. The pregnancy, delivery and postnatal growth had all been normal and the only significant past medical history had been of an upper respiratory infection two days prior to death for which he had been prescribed codeine. There had been no stridor or dyspnoea noted.

At autopsy fluid blood, petechial haemorrhages of the thymus and visceral pleural surfaces, and pulmonary congestion and oedema were consistent with a diagnosis of SIDS. There was no evidence of trauma. A small focus of acute bronchopneumonia in the lower lobe of the right lung was not considered to have played a significant role in the cause of death and a postmortem blood culture was sterile. Of note, an area of extensive acute inflammation with neutrophil aggregation and interstitial expansion was found at the base of the tongue in the midline adjacent to deeply placed mixed minor salivary glands and ducts and closely apposed to, but not involving, the epiglottis (Figure 5-9). No cultures were taken from the lesion and Gram staining for micro-organisms was uninformative.

Due to the presence of a relatively large inflammatory mass in the upper airway that could have caused or initiated obstruction and asphyxia, death could not be attributed to SIDS, but was labelled more generally as "sudden unexpected death in an infant with acute posterior lingual inflammation".

DISCUSSION

As already noted, the possibility of intrinsic obstructive lesions within the airway must always be considered in cases of sudden death. This is of particular importance in infancy as it has been demonstrated that the infant airway is very susceptible to obstruction due to its relative narrowness. In the case described, sudden death occurred in association with an inflammatory lesion at the base of the tongue that was only detected at autopsy once careful
examination of the upper aerodigestive tract had been performed. Histological examination confirmed the diagnosis of extensive acute inflammation. The presence of very focal bronchopneumonia would be in keeping with the clinical history of infection, but was not in itself sufficient to have caused death. This was supported by the lack of organism growth on blood cultures.

The underlying cause of the posterior lingual inflammation in the reported case remains unclear. While it is possible that it represented an infected thyroglossal duct remnant, the absence of lining epithelium and the relatively diffuse nature of the infiltrate makes this unlikely. Another possibility that could not be confirmed due to the extensive acute inflammatory infiltrate was of an infected retention mucocoele with deeply placed minor salivary glands and ducts providing a basis for this. The more significant feature, however, was that interstitial inflammation and oedema had occurred at a critical point in the upper airway.

Although it is impossible in this case to definitely exclude the pathophysiologic mechanisms that are responsible for SIDS, the presence of a lesion that could have contributed to, or even caused, death precludes this diagnosis. It is interesting to note that a recent report has proposed that infants who die of SIDS have significantly larger tongues than age-matched controls. Given other studies which have suggested that the upper airway in infants dying of SIDS may be narrower than normal, the presence of any space-occupying process within the airway would, therefore, have an even greater potential for obstruction in this population. If this is the case, then it would seem appropriate to pay particular attention to the assessment of the upper aerodigestive tract in infants who are in the high risk group for SIDS.

**SUMMARY**

A case is described of sudden and unexpected death in a five-month-old boy who was found to have acute inflammation with multifocal abscess formation at the base of his tongue adjacent to the epiglottis. The case demonstrates the vulnerability of the upper aerodigestive tract in infancy to possible anatomic or functional obstruction from intrinsic lesions and draws attention to the potentially lethal effects of critically-placed posterior lingual inflammation.
TRACHEOMALACIA/BRONCHOMALACIA

These entities are grouped together as they represent conditions in which loss of structural integrity of the upper airway at various levels results in airway collapse and obstruction.

Tracheomalacia may be primary or it may develop secondarily in infants with tracheo-oesophageal fistulas and vascular rings, congenital chondromalacia, polychondritis, Ehlers-Danlos and Larsen syndromes\textsuperscript{11,108}, or as a result of prolonged artificial ventilation (for example in infants with bronchopulmonary dysplasia). It is characterized by a deficiency in tracheal cartilagenous rings and although it is generally benign and undergoes spontaneous resolution, it may result in unexpected death in infancy due to airway compromise\textsuperscript{24,43}.

Bronchomalacia may occur spontaneously, or as part of a familial syndrome. It is characterized by incomplete development of cartilage resulting in weakening and collapse of the walls of the lower airways. The presentation may be of respiratory distress soon after birth\textsuperscript{2}, or rarely as sudden infant death\textsuperscript{9}.

TRACHEAL STENOSIS

Tracheal stenosis may predispose to sudden airway occlusion due to increased vulnerability to mucus plugging or to other conditions which may exacerbate lumenal narrowing.

VASCULAR RINGS

Respiratory distress has been described in infants with aberrant vessels compressing the upper airway\textsuperscript{43,90} and also in acyanotic congenital cardiac disease due to bronchial compression by hypertensive pulmonary arteries. Occasionally a massively enlarged heart may also compress the lungs\textsuperscript{88}. Vascular rings are discussed further in Chapter 3.

MISCELLANEOUS

As well as external compression from aberrant vessels, the trachea may be compromised by food or objects within the oesophagus, or from neck and mediastinal masses\textsuperscript{17,73,92}. Tracheal compression resulting in stridor in a seven and a half-year-old boy due to achalasia has also been reported\textsuperscript{20}.

Acute upper airway obstruction is a feature of a variety of other entities. Although they are either exceedingly rare, manifest in the neonatal period or are not usually associated with fatal airway compromise, they have been mentioned here for completeness\textsuperscript{39,46}. It must be
remembered that any lesion which narrows the airways increases the risk of acute obstruction when more common coincident inflammatory conditions occur.

**Vocal cord paralysis** may be unilateral or bilateral, the latter more often associated with cerebral problems such as Arnold-Chiari malformation. Although sudden death is not a feature of reports in the literature, airway obstruction may occur necessitating tracheostomy.73

**Rheumatoid arthritis** involving the cricoarytenoid joint is rarely found in childhood, although occasional case reports have documented it as a cause of acute airway occlusion.30

**Ligneous conjunctivitis** is a rare, possibly familial condition, of uncertain aetiology in which recurrent pseudomembranes form on the conjunctivae and within the nasopharynx, larynx, trachea and bronchi.5 Girls under the age of three years are most often affected and significant airway obstruction may result. Histologically there is pseudomembrane formation with chronic inflammation and neovascularization.21

**Congenital subglottic stenosis** is characterized by narrowing of the subglottic area producing stridor and respiratory distress. There is an association with other congenital lesions and with Down syndrome. Acute airway obstruction may occur with minimal laryngeal inflammation, causing a significant percentage of affected infants to require tracheostomy in an earlier series.40, although the risk of sudden death remains even if tracheostomy has been performed. Histopathologically the stenosis may be caused by either soft tissue or cartilagenous narrowing of the subglottic space.94

**Laryngomalacia** is characterized by collapse of the epiglottis and adjacent airway. Although the possibility of laryngomalacia causing infantile apnoea has been the subject of debate, Sivan, Ben-Ari and Schonfeld.83 have documented a series of six infants with recurrent apnoea of infancy who were found on fibre-optic endoscopy to have airway obstruction at the laryngeal orifice due to laryngeal collapse.

**Laryngeal webs and atresias** are lesions which also cause airway obstruction but which usually present at, or soon after birth.73

**Subglottic haemangiomas** are benign vascular lesions which may result in respiratory compromise due to their critical position (Figure 5-10). As with haemangiomas in other parts of the body in early childhood, spontaneous resolution may occur.54 Other lesions such as
Figure 5-10: Marked obstruction of the airway can be seen in this transverse section of the trachea due to an intraluminal haemangioma.

Figure 5-11: Narrowing of the laryngeal inlet due to an extensively infiltrating cystic hygroma.
extensive cystic hygromas may also compromise the upper airway if the epiglottis is involved (Figure 5-11).

Laryngeal cysts which fill with fluid and cause airway blockage occur in neonates and young infants. Oedema and haemorrhage associated with endoscopy in these cases may precipitate complete airway occlusion and sudden death.

Marshall-Smith syndrome is another exceedingly rare condition in which there is micrognathia, choanal atresia, laryngomalacia and pulmonary hypertension, all of which may contribute to sudden death.

Harpey and Renault have postulated that an excessively long uvula may result in sudden infant death, however confirmatory data are lacking.

Certain subtypes of epidermolysis bullosa produce blistering within the upper aerodigestive tract. It is conceivable that detachment of an inflammatory pseudomembrane could cause acute airway obstruction.

FOREIGN BODY IMPACTION/MIGRATION

Given the possibility of sudden and unexpected infant death being caused by an occult foreign body, it is worthwhile briefly considering the range of clinicopathological features that may occur. In the literature the peak age range for choking on foreign bodies is two to three years, with 90% of cases occurring in children under five years. Round foods (hot dogs, carrots, candy, nuts, and grapes) are the most frequently aspirated foreign objects causing death, although a variety of objects may impact in the upper airway. Symptoms, which include choking, gagging, coughing, or wheezing, may subside when the foreign body moves into the bronchi. A significant problem may occur in infancy due to eruption of incisor several months before molar teeth, as this enables portions of firm food to be bitten off, but not chewed. The diagnosis may be delayed in 30% of cases and only 80% will have a positive history for aspiration. The chest X-ray may be normal and foreign material aspirated into the trachea may cause delayed death. If there has been medical attention, the foreign object may have been removed and thus the autopsy may not reveal the cause of death. In such cases, reading the medical record should provide appropriate documentation. Optimally the foreign body can be retrieved by the pathologist for examination and photographic documentation.
Foreign bodies causing acute upper airway obstruction in children usually lodge in the pharynx or within the tracheobronchial tree. In addition, foreign material may pass into the oesophagus and compromise the upper airway, even in very young infants.

In infants a foreign body may lodge within the upper oesophagus without causing significant immediate symptoms. Over time, compression of the trachea combined with local inflammation may cause acute airway blockage. Such was the case in a four-month-old infant who presented as probable SIDS, the details of which are described below.17

STUDY #5-4

DEMONSTRATION OF THE ASSOCIATION BETWEEN OCCULT INTRA- OESOPHAGEAL FOREIGN BODY AND SUDDEN UNEXPECTED DEATH IN INFANCY

INTRODUCTION

A case is presented which illustrates the potentially lethal complication of delayed airway obstruction by a foreign body that has by-passed the larynx and lodged in the adjacent oesophagus.

CASE REPORT

A previously well four-month-old boy was last fed at midnight and put to bed at 0100 hours on the morning of his death. He was heard snoring at 0400 hours and found dead at 0930 hours lying prone and face down in bed. The deceased’s past medical history included a normal pregnancy and vaginal delivery with a birth weight of 3.5kg. In the ten days preceding death he had been diagnosed as having a mild upper respiratory tract infection which was treated with a decongestant mixture. He seemed to be improving on this regime. It was noted that he had always snored intermittently during sleep. The clinical impression was of SIDS.

At autopsy the body was that of a normally formed four-month-old boy. There were no external dysmorphic features. The pleural and peritoneal cavities were unremarkable and the thoracic and abdominal organs were normally situated. Several petechial haemorrhages were present on the thymus. In the oesophagus a 1 cent piece (diameter approximately 17mm) was found lodged 35mm above the level of the carina. At the site of the impaction the mucosa was eroded bilaterally by the edge of the coin. A small amount of white exudate was present covering the mucosal defects (Figure 5-12A). There was no evidence of haemorrhage into the
Figure 5-12: A one cent coin firmly wedged in the upper oesophagus in a four-month-old boy who was initially considered to have died of SIDS (A). Histologic cross-section after removal of the coin revealed ulceration on either side of the oesophagus with compression of the adjacent trachea which contained mucopurulent debris (B) (Haematoxylin & Eosin, X 6).
tissues around the oesophagus. There were no diverticulae or fistulae. The trachea contained a plug of pale mucopurulent material within the lumen extending into each of the major bronchi. The lungs were slightly atelectatic. All other organ systems were normal.

Microscopic examination of the oesophagus at the level of the coin showed two foci of mucosal ulceration where the lateral edges of the coin had eroded into the wall, with prominent underlying necrosis of the muscularis propria and replacement by granulation and fibrous tissue (Figure 5-12B). A marked mixed inflammatory infiltrate extended into the surrounding tissue involving the adjacent trachea, which showed thickening of the submucosa with squamous metaplasia of the mucosa anteriorly and posteriorly. There was a large amount of mucopurulent material within the lumen of the trachea extending to involve the main bronchi. The trachea above the level of the coin showed moderate mucosal congestion with a mixed inflammatory cell infiltrate, associated with moderate amounts of mucopurulent material within the lumen. Other sections of the oesophagus were unremarkable. Special staining for micro-organisms failed to demonstrate bacteria or fungi. Post-mortem viral and bacterial cultures showed no significant growth.

Death in this four-month-old boy was attributed to acute tracheobronchial obstruction due to chronic mucopurulent tracheobronchitis and external compression associated with an adjacent intra-oesophageal foreign body. On specific questioning, no history of ingestion could be obtained from the parents, although they thought that a two-year-old sibling, who often played with the deceased, may have provided him with the coin.

DISCUSSION

Serious complications of intra-oesophageal foreign bodies in infancy and childhood are rare, tending to occur in cases with prolonged impaction, and include oesophageal perforation with abscess formation, aorto-oesophageal fistula formation, mediastinitis and para-oesophageal abscess. Tracheobronchial occlusion occurring once an ingested foreign body has passed the larynx and entered the oesophagus is an unusual phenomenon that may, however, be responsible for symptoms of respiratory obstruction. In addition to coins and sharp objects, button batteries may be particularly hazardous as leakage of contents may hasten perforation. In a series of 2394 patients with intra-oesophageal foreign bodies, the youngest
was aged seven months. Infants under six months of age who aspirate usually have been
given the foreign body by an older sibling, as was suspected in this case.

The case reported illustrates the potential danger at a very young age of delayed airway
obstruction from a foreign body that has impacted in the oesophagus. The patient is unusual in
that only signs of a minor upper respiratory tract infection were exhibited, rather than the more
usual acute onset of voice change, increase in salivation, odynophagia, dysphagia, dyspnoea and
wheezing. Focal ulceration of the oesophagus due to pressure necrosis was associated
with inflammation which extended through to the underlying trachea, resulting in
tracheobronchitis with thickening of the submucosa and formation of a mucopurulent exudate.
Sudden death from tracheobronchial occlusion occurred due to a combination of tenacious
mucopurulent material present within the lumen of an inflamed trachea already narrowed by
external compression from the coin. The presence of chronic inflammatory cells and fibrosis
within the underlying oesophageal wall and an increase in minor salivary glands within the
trachea, with squamous metaplasia of the overlying mucosa, indicates that the process had
some chronicity. Of note, acquired tracheo-oesophageal fistulae due to impacted intra-
oesophageal coins has occurred by a similar process of localised pressure necrosis and
inflammation.

Although most foreign bodies that pass through the oesophagus are not associated with
a serious outcome, occasional cases may occur in which there is perforation of a viscus and
occasionally there may even be unexpected death due either to associated vessel perforation or
to sepsis.

SUMMARY
Acute upper airway obstruction in a four-month-old boy presenting as SIDS is described. At
autopsy external tracheal compression and tracheobronchitis with plugging of the trachea and
bronchi by an abundant mucopurulent exudate were found. The source of the inflammation was
the adjacent oesophagus where previous impaction of a coin had caused pressure necrosis with
mucosal erosion and transmural granulation tissue formation. Intra-oesophageal foreign bodies
that have not been aspirated into the tracheobronchial tree must therefore be considered in
cases of sudden asphyxia due to airway compromise in early infancy.

* * *
Figure 5-13: Irregular scarring and uneven expansion of the lungs in bronchopulmonary dysplasia.

Figure 5-14: Prominant septal fibrosis due to bronchopulmonary dysplasia in a six-month old boy dying unexpectedly. There was a history of prolonged ventilation following delivery at 26 weeks (Haematoxylin & Eosin, x 170).
**BRONCHOPULMONARY DYSPLASIA**

Bronchopulmonary dysplasia refers to a chronic lung disease that was first reported in 1967 in infants with severe respiratory distress syndrome who had been treated with artificial ventilation and oxygen therapy\(^6\). Subsequent studies have demonstrated a variety of contributing aetiological agents including nutritional deficiencies and pulmonary oedema\(^6\).

**Frequency**

The frequency of bronchopulmonary dysplasia in ventilated infants varies from a little over 4% to as high as 70% in infants ventilated for more than two weeks\(^7,31\).

**Occurrence of Sudden Death**

Infants who have pulmonary changes of bronchopulmonary dysplasia are known to be at increased risk of sudden death, and this has led to diagnostic confusion with sudden infant death syndrome\(^7\). The risk of sudden death has been estimated as seven times that of other infants in the population\(^9\). Sudden and unexpected death has also been reported in hospitalized infants with bronchopulmonary dysplasia in spite of close cardiorespiratory monitoring\(^1\).

**Pathological Features**

Pathologically there are three distinct phases in the development of bronchopulmonary dysplasia: acute, reparative and chronic stages\(^3\). On gross examination, the lungs are initially smooth surfaced, bulky and increased in weight, but progressively develop scarring so that the final stage is characterized by marked fissuring (Figure 5-13). There may also be evidence of cardiac hypertrophy in the later stages involving both right and left ventricles\(^8,9\).

Microscopically, damage occurs from the trachea down to the alveoli, with the earliest changes being necrosis of the lining epithelial cells with ulceration. In particularly severe cases, necrosis may involve the tracheal cartilage resulting in subsequent tracheomalacia. As repair occurs, there may be squamous metaplasia, epithelial dysplasia, submucosal fibrosis and muscular hypertrophy of smaller airways. In healed cases, evidence of damage may be patchy, with relatively normal appearing hyper-expanded alveoli abutting alveoli that show prominent septal fibrosis with fibrous obliteration of distal airspaces. Alveolar septal fibrosis has been cited as the hallmark of healed bronchopulmonary dysplasia\(^8,9\) (Figure 5-14). Pulmonary arteries may show changes compatible with grade I to II hypertension, and within the heart there may be secondary hypertrophy of cardiac myocytes and interstitial fibrosis.
Pathophysiology

Infants who survive with moderate to severe bronchopulmonary dysplasia manifest a variety of abnormalities including reduced head growth, general growth delay, pulmonary hypertension, increased airway resistance, reduced lung compliance, bronchial hyper-reactivity, marked maldistribution of ventilation, carbon dioxide retention, hypochloraemia with metabolic alkylosis, hypoxaemia, sleep-related arterial oxygen desaturation and neurodevelopmental deficits. Given the presence of these features, and abnormal lungs on pathological examination, the diagnosis of SIDS in these infants cannot be sustained.

ACUTE BRONCHOPNEUMONIA

Acute bacterial infection of the lungs and distal airways may cause sudden and unexpected death in children with relatively nonspecific symptoms and signs. Diagnostic difficulties are discussed further in Chapter 4.

CYSTIC FIBROSIS

Cystic fibrosis is described in detail in Chapter 8. While the respiratory manifestations tend to be chronic, sudden death can occur in children due to electrolyte imbalances or to septic or gastrointestinal complications. Although the lungs in advanced cases may show extensive scarring with mucus plugging of bronchiectatic airways, this is not always the case in children who die early from the above complications. For example, a four-month-old boy who was brought to the Adelaide Children’s Hospital after being discovered dead in his cot was found at autopsy to have undiagnosed cystic fibrosis with marked atrophy and fibrosis of the pancreas which contained residual ducts distended with typical inspissated eosinophilic secretions. The lungs were only mildly inflamed.
Figure 5-15: Microscopic section from the lungs of an 11-day-old girl who died from massive pulmonary haemorrhage demonstrating filling of the alveoli with red blood cells (Haematoxylin & Eosin, x 170).

Figure 5-16: Bulging of the diaphragm inferiorly due to massive bilateral tension pneumothoraces.
MASSIVE PULMONARY HAEMORRHAGE

Massive pulmonary haemorrhage of uncertain aetiology may be responsible for sudden and unexpected death in severely growth retarded infants (Figure 5-15). Risk factors include intra-uterine growth retardation, prematurity, birth asphyxia, breech or caesarian delivery, multiple births, the presence of a patent ductus arteriosus and hyaline membrane disease84. However, cases may occur in which none of these features are present. In older children hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu disease) may also result in death due to massive intrapulmonary haemorrhage72.

TENSION PNEUMOTHORAX

Tension pneumothorax occurs in a number of conditions such as asthma or staphylococcal pneumonia when there is air trapping with forcing of pressurized air into the pleural cavity. Sudden death results from compression of the lungs and shifting of the mediastinum. At autopsy the most obvious initial finding may be ptosis of the abdominal organs and bulging of the diaphragmatic domes into the peritoneal cavity (Figure 5-16).
REFERENCES


References Ch5-2

References Ch5-3


102. Wilson, J.D., Sutherland, D.C. & Thomas, A.C. (1981). Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? The Lancet, 1, 1235-7.


SUDDEN NATURAL DEATH IN INFANCY
& EARLY CHILDHOOD

CHAPTER 6

NEUROLOGICAL CONDITIONS
INTRODUCTION

This chapter deals with causes of sudden natural death in infancy and early childhood involving the nervous system, a large number of which are due to vascular or infective disorders. It should be stressed, however, that trauma should be suspected if intracranial haemorrhage is found at autopsy. Detailed review of the presenting history should then be undertaken with a complete radiological survey of the body. If a traumatic aetiology can be excluded, other conditions such as cerebrovascular disease may then be looked for. Although fatal cerebrovascular disease in the paediatric age group is not common it is possible that any of the causes of occlusive vascular disease that result in childhood stroke can also result in sudden death. Possible causes of sudden death and stroke in infancy and childhood can be found in Tables 6-1 & 6-2 (Adapted from references 10,69,128,139,142,144).

<table>
<thead>
<tr>
<th>TABLE 6-1: CONDITIONS ASSOCIATED WITH CENTRAL NERVOUS SYSTEM CAUSES OF SUDDEN PAEDIATRIC DEATH</th>
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<tbody>
<tr>
<td>1. Haematologic</td>
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<tr>
<td>Bleeding diatheses</td>
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<tr>
<td>Haemoglobinopathies</td>
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<tr>
<td>2. Cardiovascular</td>
</tr>
<tr>
<td>Thromboembolism</td>
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<tr>
<td>Vascular malformations</td>
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<tr>
<td>Aneurysm rupture</td>
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<tr>
<td>Connective tissue disorders</td>
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<tr>
<td>Moyamoya disease</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
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<tr>
<td>Vasculitides</td>
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<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>3. Tumours</td>
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<tr>
<td>4. Epilepsy</td>
</tr>
<tr>
<td>5. Metabolic Disorders</td>
</tr>
<tr>
<td>6. Infections</td>
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<tr>
<td>Meningitis</td>
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<tr>
<td>Encephalitis</td>
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<tr>
<td>Poliomyelitis</td>
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<tr>
<td>7. Structural Abnormalities</td>
</tr>
<tr>
<td>8. Friedreich Ataxia</td>
</tr>
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<td>9. Tuberous Sclerosis</td>
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<td>10. Von Recklinghausen disease</td>
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<tr>
<td>11. Guillain-Barré syndrome</td>
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</tbody>
</table>
### TABLE 6-2: CONDITIONS ASSOCIATED WITH CEREBROVASCULAR ACCIDENTS IN INFANCY AND CHILDHOOD

<table>
<thead>
<tr>
<th>1. Haematologic</th>
<th>5. Microbiologic</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>A. Local infection</td>
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<tr>
<td>Thrombocytosis</td>
<td>ENT pyogenic infections</td>
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<tr>
<td>Polycythaemia</td>
<td>Cavernous sinus thrombophlebitis</td>
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<tr>
<td>Leukaemia</td>
<td>Mucormycosis</td>
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<tr>
<td>Coagulation disorders</td>
<td>Meningitis</td>
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<tr>
<td>Lupus anticoagulant</td>
<td>Malaria</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
<td>Herpes ophthalmicum</td>
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<tr>
<td>Haemoglobinopathies</td>
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<tr>
<td>Marked anaemia</td>
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<td>Haemolytic uraemic syndrome</td>
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<tr>
<th>2. Cardiac</th>
<th>6. Traumatic</th>
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<tr>
<td>Cyanotic congenital heart disease</td>
<td>Closed head injury</td>
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<tr>
<td>Infective endocarditis</td>
<td>Neck or intraoral injury</td>
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<td>Myocarditis</td>
<td>Foreign body embolism</td>
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<td>Rheumatic fever</td>
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<td>Myxomas</td>
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<td>Prosthetic valves</td>
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<td>Rhythm disorders</td>
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<td>Cardiomyopathy</td>
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<td>Myocardial infarction</td>
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<td>Mitral valve prolapse</td>
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<td>Vascular malformations</td>
<td>Arterial spasm</td>
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<td>Arterial aneurysms</td>
<td>Necrotising vasculitis</td>
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<td>Moyamoya disease</td>
<td>Septic emboli</td>
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<td>Fibromuscular dysplasia</td>
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<td>Collagen vascular diseases</td>
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<td>Connective tissue disorders</td>
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<td>Takayasu disease</td>
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<td>Hypertension</td>
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<td>Acute hypotension</td>
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<td>Thromboembolism</td>
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<td>Hereditary haemorrhagic telangiectasia</td>
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<td>Neurocutaneous syndromes</td>
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<td>Arterial kinking</td>
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<td>Migraine</td>
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<td>External compression</td>
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<td>Superior vena cava syndrome</td>
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<td>Arterial agenesis or hypoplasia</td>
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<td>Inflammatory bowel disease</td>
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<th>4. Metabolic</th>
<th>8. Skeletal</th>
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<td>Diabetes mellitus</td>
<td>Klippel-Feil anomaly</td>
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<td>Homocystinuria</td>
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<td>Hyperlipidaemia</td>
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<td>Fabry disease</td>
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<td>Congenital adrenal hyperplasia</td>
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<td>Scurvy</td>
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<td>Vitamin K deficiency</td>
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<td>Liver disease</td>
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<td>Congenital C2 deficiency</td>
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|                                | 9. Iatrogenic                 |
|                                | Angiography                   |
|                                | Radiotherapy                  |

|                                | 10. Idiopathic                |
|                                |                               |
HAEMATOLOGIC CONDITIONS

Due to the relative rigidity of the skull and the plasticity of cerebral tissue, areas of significant haemorrhage develop at the expense of the surrounding brain. Death may therefore occur rapidly from resultant cerebral oedema and brainstem herniation through the foramen magnum. Once occult trauma has been excluded there are a number of aetiologically unrelated disorders with very different pathophysiology responsible for intracranial haemorrhage in infants and children.

BLEEDING DIATHESSES

Bleeding diatheses are dealt with in greater detail in Chapter 7, however many conditions which predispose to spontaneous haemorrhage in other areas of the body may also cause major problems with intracranial bleeding. One of the most common clinical scenarios resulting in sudden death in this situation involves a child who has an acute leukaemia with thrombocytopenia either due to marrow infiltration by malignant cells or secondary to chemotherapy (see Figure 7-6). Spontaneous intracranial haemorrhage may also occur in other disorders where there is reduction in the number of circulating platelets such as in aplastic anaemia or in Wiskott-Aldrich syndrome.

Intracranial haemorrhage may follow relatively minor trauma in children with coagulation disorders such as Haemophilia A where there is a reduction in the amount of functional circulating factor VIII\(^5\) (see Figure 7-7).

While intracranial haemorrhage may result from disseminated intravascular coagulation, bleeding tends to be more widespread and not necessarily unexpected, occurring in patients who are already seriously ill from severe trauma or infection.

HAEMOGLOBINOPATHIES

Ischaemic cerebral events are a known complication of sickle cell disease due to vascular obstruction by sickled red blood cells. This may lead to intracerebral and subarachnoid haemorrhage\(^67,137\) or to infarction\(^109\) with sudden death. Cerebral vascular occlusion occurs in as many as 17% of children with sickle cell disease and may be exacerbated by the hypercoagulable state in these patients secondary to plasminogen deficiency\(^62\). Stroke in children with sickle cell disease has also been reported in association with fibrointimal proliferation of the carotid arteries\(^156,184\). The extent of cerebral ischaemia may be significantly
worsened by the anaemia that is present, as anaemia on its own has been associated with symptomatic hypoxic episodes in children\textsuperscript{184}.

**CARDIOVASCULAR CONDITIONS**

**THROMBOEMBOLISM**

Thrombosis of the cerebral veins or sinuses with stroke may occur in children with polycythæmia and/or thrombocytosis secondary to cyanotic congenital heart disease\textsuperscript{143}. More rarely venous thrombosis is due to hypercoagulable states which may be familial or result from sepsis (Figures 6-1 & 6-2)\textsuperscript{15,88}. Dehydration and anaemia may be exacerbating factors, the former playing a major role in cases of cerebral venous sinus thrombosis in infants with profound gastroenteritis.

Local sepsis involving the middle ear or sinuses can erode the skull and extend into the adjacent cranial cavity resulting in meningitis and venous sinus thrombosis\textsuperscript{76}. In addition it may also cause an arteritis with subsequent occlusive thrombosis and stroke\textsuperscript{159}. Although viral upper respiratory tract infection has been associated with cerebral arterial thrombosis\textsuperscript{16,46} its role in causing vascular occlusion is ill understood\textsuperscript{74}. On occasion no apparent cause for spontaneous intracranial vessel thrombosis will be found in spite of careful pathological examination\textsuperscript{56}.

Intracranial embolism either derives from a left-sided intracardiac source or from paradoxical embolism. Bacterial endocarditis associated with congenital cardiac defects or prosthetic materials may result in cerebral embolism. Other lesions within the left atrium and ventricle which have led to cerebral ischaemic events are those associated with rheumatic fever, myxomas\textsuperscript{10}, hydatid cysts,\textsuperscript{23} marantic endocarditis, cardiomyopathy\textsuperscript{82}, and disorders associated with arrhythmias or infarction, including cardiac transplantation\textsuperscript{2}. Although the latter series included children, it is not certain whether any of them suffered cerebral events.

Theoretically any venous source of embolic material can lead to paradoxical embolism if there is a communication with the left side of the heart, such as an atrial or ventricular septal defect. Embolized material may be thrombus, air or even tumour, as was the case in an eight-year-old boy who suffered extensive cerebral infarction due to occlusion of his left internal carotid artery by Wilms tumour fragments that had passed through a ventricular septal defect during surgery\textsuperscript{112} (see Figure 8-19). Pulmonary disorders such as hereditary haemorrhagic
Figure 6-1: Basilar artery thrombosis with occipital lobe and cerebellar infarction in a one-year-old boy with viral pneumonia.

Figure 6-2: Cerebral infarction following cerebral venous thrombosis in a one-month-old boy with cyanotic congenital heart disease.
Figure 6-3: The first indication of the presence of extensive intracerebral haemorrhage due to a vascular malformation may be limited basal subarachnoid haemorrhage.
Figure 64: Haemorrhage from an arteriovenous malformation within the parieto-occipital lobes of the right cerebral hemisphere in a three-year-old boy with minimal subarachnoid extension (A) and a large amount of subdural clot (B).
Figure 6-5: Subarachnoid haemorrhage visible on external examination of the brain (A) of a nine-year-old girl who was found dead in bed. The subarachnoid haemorrhage was in continuity with an area of extensive intracerebellar haemorrhage (B), however, the only residual vessels found were dilated but otherwise normal meningeal vessels (C).
Figure 6-6: Typical dilated and abnormal vessels with interposed cerebral tissue characteristic of an arteriovenous malformation (Haematoxylin & Eosin, x 280).
telangiectasia and arteriovenous fistulas may lead to paradoxical cerebral embolism\textsuperscript{129} (See Table 6-2).

**VASCULAR MALFORMATIONS**

In a review of ten autopsy cases of sudden death involving non-traumatic intracranial haemorrhage from clinically unsuspected cerebral lesions in children the most common findings were vascular malformations and tumours\textsuperscript{24}. The youngest case was a two and a half-year-old boy.

**Clinical Features**

It is generally considered that children bleeding from an intracranial vascular malformation tend not to die suddenly, the usual presentation being with symptoms and signs of raised intracranial pressure, focal neurological deficits or fitting\textsuperscript{115}. Sudden and unexpected death may, however, be the presenting feature.

**Pathological Features**

The first indication of a possible vascular malformation may be the presence of cerebral oedema associated with localized subarachnoid haemorrhage around the base of the brain (Figure 6-3). A point worth emphasizing is that significant subdural haemorrhage can occur in these patients in association with intracranial haemorrhage without any apparent subarachnoid extension. Figure 6-4 demonstrates such a phenomenon in a three-year-old boy who died following haemorrhage from an intracerebral arteriovenous malformation.

One of the major problems in trying to provide confirmatory histologic evidence at autopsy of a suspected vascular malformation is that the lesions may be destroyed when haemorrhage occurs (Figure 6-5). For example, it has been estimated that diagnostic material will be found in only 70 to 80\% of cases\textsuperscript{41}. It is important, therefore, to carefully sample as much of the loose and adherent blood clot as possible as remnants of abnormal vessels may still be present within this material.

Vascular malformations can take a number of different histological forms, with the most common being a tangle of disordered arterioles and venules. Histologically, a typical arteriovenous malformation can be recognized by the presence of abnormally dilated and shaped vascular channels composed of an intimate admixture of arterioles, venules and capillaries, often with residual cerebral tissue interspersed between the vessels\textsuperscript{106} (Figure 6-6). Haemosiderin
deposition, calcification, demyelination, neuronal loss and gliosis adjacent to vascular malformations occur when cases have had a more prolonged time course¹⁶⁷. Osseous metaplasia has also been described¹⁰⁷.

**Occurrence of Sudden Death**

Byard, Bourne and Hanieh found that nearly one half of their cases of probable bleeding cerebral vascular malformations presented acutely, with one patient surviving the onset of symptoms for less than one and a half hours, and another being found dead in bed having been apparently well the night before²⁴. Other authors have described similar cases of sudden death¹⁵⁰. It has been suggested that lesions that are within the posterior fossa or near the base of the brain are more likely to be associated with sudden death⁴² (Figure 6-7) although this is not necessarily always the case (Figure 6-8). However, children with vascular malformations of the medulla may die very quickly if haemorrhage occurs. Occasionally sudden death occurs in children from bleeding vascular malformations of the choroid plexus¹⁷³.

**ANEURYSM RUPTURE**

Death due to haemorrhage from a ruptured intracranial aneurysm is usually a condition of adults, however, sudden collapse and death may also rarely occur in children with this anomaly²⁴,¹⁵³. As there is an association between intracranial aneurysms and cystic renal disease, both the kidneys and liver should be carefully examined and sampled at autopsy, although this applies more to adult patients¹⁷⁴. There is also an increase in the incidence of intracranial aneurysms in children with coarctation of the aorta, collagen vascular disease, Marfan syndrome, Ehlers-Danlos syndrome, tuberous sclerosis, Moyamoya disease, fibromuscular dysplasia and syphilis³³. Familial cases rarely involving children have been described⁶⁶,¹⁰⁸ and occasionally dissecting aneurysms of the cerebral arteries will be found at autopsy with no apparent predisposing disease¹⁰⁵.

The so-called aneurysm of the vein of Galen is caused by direct shunting of branches of the internal carotid or posterior cerebral arteries into the vein of Galen. Although the presentation may be of high output cardiac failure or hydrocephalus in early life, older children and adolescents may present with subarachnoid haemorrhage.
Figure 6-7: Massive intracerebellar haemorrhage due to a probable vascular malformation resulting in sudden death of an eight-year-old girl.

Figure 6-8: Sudden death due to intraparenchymal haemorrhage within the occipital lobe of a three-year-old boy caused by an arteriovenous malformation (AVM).
CONNECTIVE TISSUE DISORDERS

Although rare, disorders of connective tissue should be considered in the differential diagnosis of cerebral haemorrhage at any age. These can be separated into primary and secondary groups, represented by disorders such as Ehlers-Danlos syndrome and scurvy, respectively. While patients with Ehlers-Danlos syndrome type IV often show general fragility of connective tissues with easy bruisability\(^{73,123}\), this is not always the case, and fatal intracranial haemorrhage may be the first manifestation of the disorder\(^{25}\) (see Figure 10-3). It may, therefore, be appropriate to take fresh and frozen tissue (e.g. skin and aorta) to facilitate subsequent collagen analysis and cell culture studies in cases of intracranial haemorrhage where the cause of the bleeding is not immediately apparent at autopsy, particularly if there is evidence of haemorrhage within other organs. For example, lack of type III collagen in analyses from a five-month-old girl enabled the diagnosis of type IV Ehlers-Danlos syndrome to be made, thus explaining the subarachnoid and multifocal visceral haemorrhages that had been found at autopsy\(^{25}\).

MOYAMOYA DISEASE

In Moyamoya disease a proliferative arterial lesion causes occlusion of the intracranial arteries with the development of a web-like net of vessels at the base of the brain. This creates the characteristic angiographic appearance of Moyamoya, 'something hazy just like a puff of cigarette smoke drifting in the air'\(^{166}\). Although originally described in Japan, it is now apparent that the condition has a world-wide distribution\(^{114,151}\).

Clinical Features

There are two clinical variants, one which affects older children and causes subarachnoid haemorrhage, and the other which affects younger children and causes exercise-related ischaemia. The angiographic appearances are quite characteristic\(^{165}\) and usually allow the diagnosis to be established prior to death. The incidence of Moyamoya disease as a cause of childhood stroke varies with different series from four to as high as 50%. Massive intracranial haemorrhage from collateral arteries\(^{119}\) or multiple dissecting aneurysms may also be found in affected children. The finding of a familial incidence of greater than 12%\(^{86}\) increases the importance of confirming the diagnosis at autopsy.
Pathological Features

The major arteries that are affected are the internal carotid, anterior and middle cerebral, the posterior communicating and the anterior choroidal, all of which should be sampled at autopsy. Microscopically, affected vessels show splitting and reduplication of the internal elastic lamina with eccentric intimal proliferation resulting in luminal narrowing. Vessels with microaneurysm formation show attenuation of the wall with focal fibrin deposition. Rarely there may be an associated intracranial saccular aneurysm, although this is distinctly uncommon and tends to occur in older adolescents and adults.

Differential Diagnosis

To establish the diagnosis of Moyamoya disease there has to be bilateral involvement of the cerebral vessels. If there is evidence of only unilateral disease the differential diagnosis would include the possibility of trauma, cerebral tumour, tuberculosis, von Recklinghausen disease, radiation effect or fibromuscular dysplasia (although these may also have bilateral involvement). Moyamoya has also been associated with renovascular hypertension.

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia is an uncommon condition which may involve the carotid arteries resulting in vascular occlusion and ischaemic cerebral events. Angiographically, single or multiple stenoses as well as aneurysms are seen, giving the artery a beaded appearance. Microscopically there is marked hyperplasia of the arterial media with disruption of the elastic laminae and adventitial fibrosis. Although generally a disorder of older age groups, cases in children have been reported involving both the carotid and vertebral artery systems. Affected children have had cerebral and cerebellar infarctions.

VASCULITIDES

INFECTIOUS

Involvement of cerebral vessels in bacterial meningitis may result in ischaemic episodes as detailed in Chapter 4. Vasculitis and perivasculitis have also been found in children with AIDS in association with cerebral haemorrhage and stroke. Other viral infections such as herpes zoster may also be associated with vasculitis and stroke.
INFLAMMATORY

Although inflammatory vasculopathies of the cerebral circulation are exceedingly rare in the paediatric age range, a number have been described which may have neurological sequelae. These include systemic lupus erythematosus, lupus anticoagulant syndrome and granulomatous arteritis\textsuperscript{83,146,183}. Kawasaki disease occasionally has been described as a cause of neurological problems but this is most likely due to thromboembolism rather than direct involvement of the cerebral vessels\textsuperscript{92,96}. Takayasu aortitis may rarely give rise to stroke in infancy\textsuperscript{87}. The neurological complications of the vasculitides have been described in detail by Moore and Cupps\textsuperscript{113}.

MISCELLANEOUS

ARTERIAL KINKING

One controversial clinicoradiological entity that has been described in association with cerebral infarction in children is arterial kinking. It has been proposed that coiling of the internal carotid artery in certain children predisposes to temporary lumenal occlusion with resultant cerebral ischaemia/infarction\textsuperscript{53,127,147}. However, other investigators have either not commented on kinking in their series of children with strokes\textsuperscript{71} or have found carotid artery elongation in a high percentage of children with no evidence of cerebral ischaemia\textsuperscript{131}. Given the difficulties encountered at autopsy in examining portions of the internal carotid artery, it is unlikely that pathological examination can contribute to this debate except to exclude other aetiologies.

MIGRAINE

On very rare occasions migraine has been reported as a cause of cerebral or cerebellar infarction in children\textsuperscript{11,31,43,44,75} sometimes resulting in death\textsuperscript{21}. There is also an association between migraine and epilepsy\textsuperscript{12}.

STURGE-WEBER SYNDROME

Sturge-Weber syndrome is one of the neurocutaneous disorders characterized by cutaneous and leptomeningeal angiomatosis. Although the vast majority of cases present with epilepsy, subarachnoid haemorrhage has been reported as a presenting complaint in an adult\textsuperscript{5}.

MITRAL VALVE PROLAPSE

A family has been reported in which there was an apparent association between mitral valve prolapse and embolic stroke at a young age. The two youngest members to manifest
hemiplegias were aged six months and ten years respectively\(^{140}\). Other reports have also documented the association of thromboembolic stroke in adolescence with mitral valve prolapse\(^{170}\).

**CARDIAC ARRHYTHMIAS**

Cardiac arrhythmias may also rarely be responsible for the development of acute hemiplegia in children, most likely on an embolic basis\(^8\).

**DRUG OVERDOSE**

The occurrence of haemorrhagic stroke in an adolescent due to phenylpropanolamine overdose\(^{55}\) suggests that drug screening at autopsy may be appropriate in some cases of childhood stroke of uncertain aetiology.

**Other Factors**

Other less common causes of haemorrhagic or ischaemic cerebrovascular accidents in childhood include hypertension, acute hypotension and collagen vascular diseases\(^{10,65}\). Finally, it should be noted that no cause will be found in a percentage of ischaemic strokes in children in spite of detailed investigation\(^{13}\).

**TUMOURS**

Generally tumours of the brain and cranial contents produce symptoms and signs of raised intracranial pressure with headache and alteration of conscious state. Occasionally the presentation is more dramatic due to an acute disturbance in blood or cerebrospinal fluid flow\(^1\). As well, direct pressure on brainstem respiratory centres may cause sudden death in children with neoplasms located within the medulla\(^{117}\).

Metastatic tumours may also result in cerebrovascular accidents in children, particularly in the case of neuroblastoma. Other malignancy-related complications include intracranial haemorrhage/thrombosis due to disseminated intravascular coagulation or to chemotherapy with L-asparaginase\(^{124}\).

**Haemorrhage**

Haemorrhage has initiated the presentation of between three and 10% of reported brain tumours in different series in the literature\(^{95,126}\) and has a documented association with sudden death in both infancy and childhood\(^7,136\).
Figure 6-9: Marked cerebral oedema in a two and a half-year-old boy with recent haemorrhage into a fourth ventricular ependymoma showing flattening of gyri (A) and herniation of the cerebellar tonsils through the foramen magnum (arrow) (B).
Figure 6-10: Cross section of the cerebellum, in a two and a half-year-old boy showing extensive haemorrhage into a clinically undiagnosed ependymoma.
Pathophysiology

Haemorrhage into a neoplasm may result in rapid expansion in size with compression of the surrounding cerebral parenchyma. This is usually a complication of tumours such as medulloblastoma, malignant astrocytoma, ependymoma or oligodendroglioma, which have infiltrated and eroded a vessel wall, or bled from rupture of delicate tumour neovasculature.

Pathological Features

At autopsy the presence of markedly increased intracranial pressure may be obvious as soon as the calvarium and dura are removed as this will reveal prominent flattening of cerebral gyri. Other indicators of cerebral oedema such as uncal grooving and herniation of the cerebellar tonsils may also be present (Figure 6-9).

A variety of tumour types may result in massive intracranial haemorrhage, having variable locations which include both infra- and supratentorial compartments, and minimal or often non-specific antemortem symptoms. Figure 6-10 illustrates an ependymoma of the fourth ventricle in a two and a half-year-old boy. It is also apparent that not only high grade neoplasms are associated with haemorrhage.

Cerebrospinal Fluid Obstruction

Other rare cerebral lesions which may cause sudden death in childhood are tumours which cause obstruction to cerebrospinal fluid flow such as colloid cyst of the third ventricle. Reported cases have not, however, involved infants.

Miscellaneous

Peripheral neural tumours may also cause rapid deterioration due to interstitial haemorrhage as was the case in a previously well three and a half-month-old girl who developed 'colic' one evening. Her condition rapidly deteriorated and she died within seven hours due to massive intraperitoneal haemorrhage caused by metastatic neuroblastoma infiltrating the liver. Autopsy was performed at the Adelaide Children's Hospital.

EPILEPSY

It is now well recognized that infants and children with epilepsy have a higher mortality rate than unaffected individuals, although this proposal has not always been accepted. Death may occur due to an accident resulting from a seizure, a prime example of which would be drowning, to an associated disease process such as tuberous sclerosis, to status epilepticus,
or it may occur suddenly and unexpectedly for reasons that are not immediately obvious\(^\text{169}\). The final group is the most enigmatic as the underlying mechanisms responsible for death are far from clear. For example, no mechanism of death could be determined at autopsy in four to 30\% of reported cases reviewed by Terrence, Wisotzkey and Perper\(^\text{169}\). The rarity of unexpected death during febrile convulsions in otherwise normal children also suggests that other mechanisms are operating in children with epilepsy who die suddenly. A certain percentage of children who have febrile convulsions will, however, later develop epilepsy\(^\text{78}\).

Unfortunately the problem of sudden death in epileptics has not been extensively addressed in the literature\(^\text{39}\). When it has been reviewed the patient populations studied have tended to be adult and include a large number of alcohol abusers\(^\text{99}\). As well, other authors have specifically excluded younger children from their analyses because of the occurrence of a wide variety of epileptogenic disorders that are associated with neurological deficits\(^\text{72}\). Conclusions based on this material are not, therefore, completely applicable to paediatric cases.

**Frequency**

The estimated frequency of sudden and unexpected death in children with epilepsy is unknown, however in general epileptic populations it has ranged from one in 200 to one in 680 patients\(^\text{77}\). Reported figures show that sudden and unexpected death accounts for between 10 and 30\% of all epileptic deaths and that sudden epileptic death represents from 1 to 1.5\% of all natural deaths, and from 8 to 12\% of all sudden unexpected deaths\(^\text{97}\). (These latter data are derived from predominantly adult cases.) The typical case of unexpected death encountered in paediatric autopsy practice is of an epileptic child, often with mental retardation, who is found dead in bed with minimal external or internal findings.

**Pathophysiology of Sudden Death**

The association of sudden death with sleep is noteworthy and most likely relates to reduction in seizure threshold that occurs with an increase in epileptic discharges\(^\text{72,155}\). For example, up to 79\% of cases of sudden epileptic death have been found either in bed or in a bedroom\(^\text{155}\).

A variety of theories have been proposed to explain the occurrence of sudden death in epilepsy (Table 6-3) including suffocation from bedding, asphyxia, pulmonary oedema and cardiac dysrhythmia. Suffocation and aspiration of food or foreign material are considered unlikely in most cases\(^\text{72}\). Although supportive evidence for any of the categories is not great,
Leestma has grouped the currently favoured possibilities into: i) sympathetic induced cardiac arrhythmia, ii) parasympathetic induced bradycardia/asystole, iii) apnoea/respiratory failure, iv) a combination of arrhythmia and apnoea, and v) neurogenic pulmonary oedema with cardiac failure\(^7\).

**TABLE 6-3: POSTULATED CAUSES OF SUDDEN DEATH IN EPILEPSY**

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<td>Asphyxia</td>
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<td>4.</td>
<td>Cardiac arrhythmia (sympathetically mediated)</td>
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<td>5.</td>
<td>Bradycardia/asystole (parasympathetically mediated)</td>
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<td>6.</td>
<td>Apnoea/respiratory failure</td>
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<td>7.</td>
<td>Neurogenic pulmonary oedema</td>
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The most popular theory to explain why apparently stable epileptic children are at increased risk of sudden death involves autonomic nervous system instability with abnormal cardiac rhythms during seizure activity. This is supported by experimental data which show synchronization of vagal and sympathetic activity with cortical discharges in epileptic cats\(^{94,152}\). It is proposed that an increase in predominantly sympathetic activity can result in tachycardias, ventricular arrhythmias and asystole\(^8\). Of interest, overt muscle contractions were not necessary for this synchronization to occur. Vagally-induced cardiac asystole or bradycardias are considered to be much less common than sympathetically-induced arrhythmias\(^7\). The effects of this increased neural activity on the cardiac conduction system may also be exacerbated by coexistent hypoxia, and it is possible that laryngospasm, which has been documented in temporal lobe epilepsy\(^138\), may also increase ictal hypoxia. However, it should be noted that there are very few cases of sudden death or cardiac arrest due to epilepsy in which an arrhythmia has actually been recorded\(^{40,101,120}\). Most reported clinical and experimental cases of arrhythmias associated with cerebral events have not been fatal\(^{39,85}\). As well, Keilson and colleagues in monitoring 338 epileptic patients found no increase in cardiac arrhythmias compared to the general population, with only 5% of patients showing high-risk patterns\(^{80,81}\). There may also be a reverse association of cardiac arrhythmias with seizures, as
there has been an increased incidence of epilepsy reported in patients with hereditary prolongation of the QT interval\(^{20}\). It is hypothesized that the seizures in this situation result from cerebral hypoxia secondary to ventricular tachycardia.

Determining the role of apnoea in the terminal event is difficult, with some authors suggesting that seizures may be directly responsible for delayed respiratory arrest\(^{45}\). This contrasts with the proposal that apnoea plays only a secondary role during the tonic phase of the seizure\(^{97}\). As in other situations where complex pathophysiological processes are acting it may be that the end result is produced by integration of a number of predisposing factors, rather than the effect of one element in isolation.

**Autopsy Findings**

The absence of death scene and autopsy findings of disturbed bedding, urinary or faecal incontinence, bite marks on the tongue and foam in the mouth or trachea, does not mean that an epileptic episode did not occur, as these features have been absent in fatal episodes that have been witnessed\(^{58}\). As any type of fit may precede sudden death, not just generalized tonic/clonic convulsions\(^{39}\), this could explain fewer external findings. In spite of this, bite marks on the tongue should always be looked for.

Autopsy investigation may show pre-existing chronic brain damage, developmental malformations, evidence of previous surgery or neuronal depopulation and gliosis of the hippocampus secondary to past hypoxic episodes, usually with no evidence of an acute lesion. Relating these findings to autopsy data in the literature is complicated by the older age and previous alcohol intake of reported cases\(^{58}\). For example, residual traumatic lesions, subdural haematomas and Wernicke’s disease characterized the neuropathological findings in the series of Leestma *et al.*,\(^{98}\). Similarly, the significance of cardiomegally and interstitial and intra-arterial fibrosis within the heart\(^{51,99}\) is difficult to determine given the medical histories and ages of the reported patients. It has, however, been suggested that prolonged sympathetic stimulation of the heart may result in similar lesions\(^{39}\).

The presence of neurogenic pulmonary oedema likely represents a secondary phenomenon rather than the cause of death and may imply that death is not instantaneous since oedema takes some time to become established\(^{168}\).
It is important at autopsy to take serum for anticonvulsant drug levels, as poor compliance with medication has been noted by several authors\textsuperscript{99,169}. Therapeutic levels of anticonvulsants in 44\% of Schwender and Troncoso’s cases suggests that this does not preclude the occurrence of sudden death, however\textsuperscript{155}.

Associated Features
A feature of paediatric cases of sudden death in epileptics is the number of infants and children who have an associated severe neurological handicap. Whether this takes the form of profound mental retardation or merely motor difficulties, the most significant feature is that there is seizure activity present which may predispose to sudden death with minimal acute pathological findings. Examples of this occur in infants and children with cerebral palsy\textsuperscript{49}. Unfortunately, as there are usually no specific pathological findings in cases of non-accidental asphyxia in young infants this possibility should also be borne in mind in cases within that age group.

Conclusion
In summary, there is no doubt that infants and children with epilepsy from any cause are at increased risk of sudden death. This often occurs during sleep, and the pathologist will quite often find no major, or acute lesions at autopsy. The absence of seizure-related phenomena such as disturbed bedding, incontinence and tongue biting does not exclude an epileptic attack, and the most likely terminal event is lethal cardiac arrhythmia, although it must be admitted that evidence for this in the literature is incomplete and that most studies have involved adults rather than children. Given the absence of positive findings at autopsy, the diagnosis often becomes one of exclusion that relies on clinicopathological correlation, supported to a large degree by the past history of epilepsy.

**METABOLIC DISORDERS**
A variety of acquired and familial metabolic disorders have been associated with strokes in children including diabetes mellitus, homocystinuria, congenital adrenal hyperplasia, Menkes kinky hair syndrome, familial hyperlipidaemias and Fabry disease.

Any condition which interferes with the adequate availability of vitamins necessary for haematopoiesis or in the maintainence of normal vascular integrity may also result in fatal haemorrhage. Examples include intrinsic liver disease resulting in deficient absorption of vitamin K or dietary deficiency of vitamin C causing scurvy.
SCURVY

Infants with scurvy tend to be irritable with multiple mucosal and cutaneous petechial haemorrhages and pseudoparalysis due to bone pain. Although not seen as often today, scurvy still occurs in impoverished communities. Spontaneous intracranial haemorrhage may be a rare complication which results in sudden death from subdural or intracerebral collections. The underlying problem is a deficiency in dietary intake of vitamin C with interference in the normal process of hydroxylation of collagen, with resultant vessel fragility. Figure 6-11 demonstrates such a case, showing a coronal section of brain from a 10-month-old scorbutic child who died due to massive haemorrhage into the right parietal lobe. Other findings at autopsy which may point to vitamin C deficiency are swollen bleeding gums and swollen joints with widening of the costochondral joints producing the so-called scorbutic 'rosary'.

HOMOCYSTINURIA

Homocystinuria is a heterogeneous metabolic disorder that may be caused by a deficiency in cystathionine synthetase. Patients with this disorder have variable mental retardation and cardiovascular disease with a high rate of thromboembolism. The basis for the repeated thromboembolism is believed to be endothelial shedding with exposure of subepithelial collagen, as well as a reactive fibrointimal proliferation which may also contribute to reduction in blood flow and peripheral organ ischaemia. Abnormalities in blood clotting have also been documented and cerebral thromboses and fatal cerebral infarcts are well recognized complications.

FABRY DISEASE

Fabry disease, also known as angiokeratoma corporis diffusum universale, is an X-linked recessive inborn error of metabolism caused by a deficiency of lysosomal alpha-galactosidase A. While cardiovascular involvement is a major feature of the disorder, death due to acute myocardial infarction appears to occur only in adults. On the other hand, ischaemic events involving the brain have been reported in childhood in this condition.

LEIGH DISEASE

Leigh disease, or subacute necrotising encephalomyelopathy is a heterogeneous, heritable, and progressive degenerative disorder of the brain characterized by capillary and glial proliferation within the medulla and thalamus with neuronal degeneration. The aetiology involves
Figure 6-11: Intracerebral haemorrhage in a 10-month-old girl with scurvy.

Figure 6-12: Sagittal section of an Arnold-Chiari malformation demonstrating elongation of the medulla and cerebellar tonsils.
disordered thiamine metabolism. While affected infants and children generally have a steadily downhill course, the presence of an associated hypertrophic cardiomyopathy occasionally results in sudden death.

MISCELLANEOUS

Children with diabetes mellitus or with congenital adrenal hyperplasia have been reported with acute cerebrovascular accidents\(^8,34\). Ischaemic cerebral events may also complicate familial hyperlipidaemias due to premature atherosclerotic vascular occlusion\(^37,84\).

INFECTIONS

A number of infectious agents which may cause sudden and unexpected death in children due to meningitis, encephalitis or spinal cord involvement are dealt with in Chapter 4. One of the most common agents in Western communities causing fulminant meningitis often resulting in death is *Neisseria meningitidis*. Death in these cases may be due to brainstem herniation due to massive cerebral oedema associated with adrenal apoplexy in the form of Waterhouse-Friderichsen syndrome.

STRUCTURAL ABNORMALITIES

It is often difficult to determine the mechanism of death in infants and children who die suddenly and who are found to have structural defects of the brain such as microcephaly, hydrocephalus, pachygyria or holoprosencephaly\(^162\). Patients with abnormalities, such as the Arnold-Chiari malformation where there is chronic tonsillar herniation, are known to have an increased incidence of sleep apnoea\(^145\) and to be at risk of sudden death from brainstem compression\(^58,172\) (Figure 6-12). Other problems which may be responsible for sudden death in children with Arnold-Chiari malformation are laryngeal obstruction due to recurrent laryngeal nerve paralysis and acute shunt blockage. In developmentally retarded children, epilepsy, aspiration or bacterial pneumonia are not infrequent\(^118\). It is also quite possible that there has been defective autonomic control predisposing to cardiorespiratory arrest in such cases.

In a study of 146 patients with hydrocephalic spina bifida, 12 died suddenly (8%), due to either pulmonary embolism associated with ventriculovascular shunts, or to shunt blockage\(^163\). Patency of the shunt on subsequent examination does not exclude previous malfunction\(^157\).
FRIDREICH ATAXIA

This rare hereditary spinocerebellar degenerative disorder, which usually manifests itself before adolescence with limb incoordination, dysarthria, scoliosis, pes cavus, and nystagmus, has a strong association with cardiac problems and an increased risk of sudden death.

Inheritance is autosomal recessive and the aetiology of the condition is unknown. Rhythm disturbances, subaortic stenosis, and dilated or hypertrophic cardiomyopathies are found in children with this disorder. Microscopic changes in the heart are non-specific with fibrointimal proliferation of the coronary arteries, diffuse myocardial fibrosis and fatty change.

There is a high incidence of diabetes mellitus in affected individuals with its associated risk of ketoacidosis. Other documented causes of death are intracranial thromboembolism and haemorrhage.

TUBEROUS SCLEROSIS (BOURNEVILLE DISEASE)

Clinical Features

Tuberous sclerosis, or Bourneville disease, is an autosomal dominant condition characterized by mental retardation, epilepsy and facial angiofibromas (so called 'adenoma sebaceum'). It has quite variable penetrance with differing clinical manifestations. Convulsions result from the presence of central nervous system lesions such as cortical tubers, however, cardiac rhabdomyomas are a more important finding in cases of sudden and unexpected death in childhood.

Aetiology

The gene locus for tuberous sclerosis has been assigned to 9q34, with linkage to the ABO blood group, although there is evidence of heterogeneity with another locus reported on chromosome 11.

Pathological Features

At autopsy a wide variety of lesions may be observed, ranging from hypopigmented skin patches and facial angiofibromas to periungual and gingival fibromas, renal cysts and angiomyolipomas. Cerebral findings consist of ventricular dilatation, central demyelination, cortical tubers composed of aggregates of large bizarre cells interspersed with more normal appearing neurons and astrocytes, and subependymal nodules, sometimes with giant cell astrocytomases (Figures 6-13 & 6-14).
Figure 6-13: The arrowheads indicate two cortical tubers in a child with unsuspected tuberous sclerosis, demonstrating how subtle an appearance they may have.

Figure 6-14: Large abnormal cells in a cortical tuber from a 13-month-old boy with tuberous sclerosis (Haematoxylin & Eosin, x 280).
Rhabdomyomas are composed of markedly enlarged myocytes that are packed with glycogen. Leaching out of the glycogen during processing leaving strands of cytoplasmic material results in the characteristic 'spider' cells (see Figure 2-14).

Occurrence of Sudden Death

Cardiac rhabdomyomas may be a 'forme fruste' of tuberous sclerosis when multiple, and may either be completely occult representing an incidental finding at autopsy in early childhood, or be responsible for sudden death. Rhabdomyomas in these cases may cause outflow obstruction, obstruct coronary artery flow, or may involve conduction pathways resulting in arrhythmias. These lesions may also lead to cerebral embolization with resultant focal ischaemia. Aortic rupture is another unusual cause of sudden death in young children with tuberous sclerosis although the exact reason for this association is unclear.

Autopsy Investigation

The importance of accurately diagnosing cases at autopsy lies in the inherited nature of some cases. Although as many as 80% of cases have negative family histories and are assumed to represent new mutations, thorough clinical, echocardiographic and radiological examination may reveal abnormalities compatible with tuberous sclerosis in apparently normal siblings or parents. While not all studies have demonstrated this association, awareness of this possibility enables extra tissues to be taken for further investigation if needed. For example, cultured fibroblasts from affected patients have demonstrated consistent karyotypic variations. Given this finding and identification of the gene locus, it may be important at autopsy to remove sterile skin for fibroblast culture and to obtain fresh tissue for DNA studies.

VON RECKLINGHAUSEN DISEASE (NEUROFIBROMATOSIS)

This autosomal dominant condition characterized by pigmented skin patches ('cafe-au-lait spots'), neurofibromas and a variety of other malformations has not been associated with sudden death in infancy or early childhood. However, an unusual case of unexpected death due to haemorrhage into the substance of a massive intrathoracic neurofibroma in a 15-year-old male with neurofibromatosis has been described. Other potentially-lethal abnormalities that have been reported in children with von Recklinghausen disease include fibromuscular dysplasia of the intracranial vessels, hypertensive stroke, hypertrophic cardiomyopathy, and right
ventricular outflow obstruction. Cases of gangrene have been reported in infants and children with neurofibromatosis and fibromuscular dysplasia. Hypertension may also occur in affected children due to fibromuscular dysplasia of the renal arteries.

**GUILLAIN-BARRÉ SYNDROME**

Guillain-Barré syndrome is an acute or subacute illness characterized by motor weakness. The aetiology is not clear although there is an association with preceding gastrointestinal or respiratory infection, immunization or surgery. The clinical course varies from days to weeks, however, sudden death may occur in rare cases. This was the case in a two and a half-year-old boy autopsied at the Adelaide Children's Hospital who suffered an unexpected respiratory arrest following two days of leg weakness. On the day of his death the weakness had progressed to involve his arms and he had experienced difficulty in swallowing.

**SUDDEN INFANT DEATH SYNDROME**

A much more detailed review of possible mechanisms responsible for causing the sudden infant death syndrome (SIDS) is provided in Chapter 13. A number of investigators believe that SIDS is due to subtle abnormalities of cerebral and neural biochemical and physiological function. It is postulated that there is a defect in the brain and/or autonomic receptors and pathways that puts these infants at risk of sudden death during a particularly vulnerable period of their lives (between two and four months). Whether the morphologic finding of increased brainstem gliosis has any relationship to this postulated malfunction awaits clarification.
REFERENCES


References Ch6-2


References Ch6-5


References Ch6-6


SUDDEN NATURAL DEATH IN INFANCY
& EARLY CHILDHOOD

CHAPTER 7

HAEMATOLOGICAL CONDITIONS
INTRODUCTION

Haematologic disorders are not often considered in the differential diagnosis of unexpected death in infancy although most physicians would be aware of sudden death as a potential complication of sickle cell anaemia. While the mechanism of sudden death in sickle cell disease relates most often to splenic sequestration crisis, other complications may also result in quite rapid demise. Similarly, the range of lethal mechanisms in other forms of haematological disorders may be more diverse than initial observations would suggest and include massive haemorrhage, thromboses, stroke, overwhelming infection, airway obstruction and cardiac arrhythmia. A listing of haematological conditions that may result in sudden paediatric death is provided in Table 7-1.

TABLE 7-1: HAEMATOLOGIC CONDITIONS ASSOCIATED WITH SUDDEN PAEDIATRIC DEATH

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Haemoglobinopathies</td>
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<tr>
<td>Haematologic malignancies</td>
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<tr>
<td>Disorders of coagulation</td>
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<tr>
<td>Platelet disorders</td>
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<tr>
<td>Anaemia</td>
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<tr>
<td>Haemolytic-Uraemic syndrome</td>
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<tr>
<td>Polycythaemia</td>
</tr>
<tr>
<td>Splenic disorders</td>
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</tbody>
</table>

HAEMOGLOBINOPATHIES

SICKLE CELL ANAEMIA

Of all the disorders caused by structural defects in the haemoglobin molecule, sickle cell disease is the most significant in terms of sudden death. Sickle cell anaemia, which results from the replacement of glutamic acid by valine in the sixth position on the β chain of the haemoglobin molecule, is characterized by decreased plasticity of red blood cells resulting in elongation and 'sickling'. The sickled cells are no longer able to traverse the normal vascular channels due to their altered configuration, and as such are more susceptible to damage and more likely to obstruct blood vessels.
Clinical Features

Homozygous patients develop a severe and chronic haemolytic anaemia which is marked by episodic clinical deterioration in the form of 'crises', several of which are potentially lethal. Sickle cell disease and trait are much more common in black populations than in white, possibly related to the partial protective effect that sickle cell trait has against malaria.

Although heterozygous patients generally have a more benign clinical course than homozygotes, under certain circumstances they nevertheless appear to have an increased risk of sudden death compared to the general population. For example, sickle cell trait has been associated with an estimated 28 to 40 times increased risk of sudden death in black American military recruits during exercise. This phenomenon is of more concern in young adults rather than infants. It is considered that exercise predisposes to acidosis and venous hypoxia, and that these factors in combination with dehydration and hypotension cause sickling. These factors may, however, also precipitate sickling in infants with sickle cell trait and have been associated with sudden death in heterozygous children following general anaesthesia.

Coagulopathy and exercise-induced rhabdomyolysis associated with unexpected death, as well as sequestration crisis, occur in heterozygous adults.

Vaso-occlusive crisis

Vaso-occlusive, or painful, crises which occur relatively frequently in homozygous patients are often precipitated by infection and may be lethal in children. The underlying problem is of small vessel occlusion by the deformed erythrocytes resulting in peripheral ischaemia and infarction. The extremities are most often involved (so-called hand-foot syndrome or sickle cell dactylitis) with infarction of the small bones of the hands and feet causing very characteristic changes on X-ray. Cerebral involvement is a more sinister potential complication occurring in approximately 7% of homozygous children which may result in intracerebral haemorrhage, subarachnoid haemorrhage and infarction with sudden death. Cases have also been reported of fatal cranial sinus thromboses in children.
Figure 7-1: Markedly enlarged spleen in a 21-month-old Jamaican boy who died from a sickle cell acute splenic sequestration crisis while sleeping in his mother's arms.

Figure 7-2: Engorgement of the splenic parenchyma by sickled red blood cells protruding into the lumen of a sinusoid in the boy described in Figure 7-1 (Haematoxylin & Eosin, x 440).
 aplastic Crisis
In aplastic crises there is temporary cessation of red blood cell production resulting in a marked fall in haemoglobin levels which may be idiopathic or precipitated by infection, folic acid deficiency or exposure to certain drugs.\(^4\)

Haemolytic Crisis
Haemolytic crises may be induced by infection or may be precipitated by antioxidant drugs when there is an additional haematologic abnormality present such as glucose-6-phosphate dehydrogenase deficiency. Haemolytic crisis may acutely exacerbate the effects of an already established haemolytic anaemia.

Splenic Sequestration Crisis
One of the most feared complications of sickle cell disease is splenic sequestration crisis.\(^5\) When this occurs there is marked pooling of blood within the spleen and a danger that the patient may die very quickly of circulatory collapse.\(^13\) Figure 7-1 illustrates the massive splenic enlargement that may occur. Figure 7-2 shows a tangled array of erythrocytes clogging the splenic vascular channels taken from a Jamaican boy who was not known to have sickle cell disease\(^6\) (vide infra).

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STUDY #9-1
DEMONSTRATION OF THE ASSOCIATION BETWEEN UNSUSPECTED SICKLE CELL DISEASE AND SUDDEN UNEXPECTED DEATH IN INFANCY

CASE REPORT
A previously well 21-month-old black male had a convulsion while sleeping in his mother’s lap. This was followed by abnormal breathing and cardiac arrest which failed to respond to resuscitation. The only past history was of a mild febrile illness on the day before death which responded to antipyretics. His mother was not aware of any sickle cell disease in the family.

At autopsy the conjunctivae were pale, as were all of the internal organs except for the spleen. The spleen was markedly enlarged (Figure 7-1) (wt. 256g, normal for age = 32g) with prominent congestion of the red pulp which was almost completely effaced by masses of tightly packed sickled red blood cells (Figure 7-2). Post-mortem blood examination showed occasional
sickled red cells with a haemoglobin of 18g/l. The sickle test was positive and haemoglobin electrophoresis revealed HbS (86.6%), HbF (10.9%), and HbA2 (2.5%). The heart was enlarged (wt. 114g, normal for age = 56g) and the bone marrow was hypercellular with increased erythropoiesis.

The cause of death was cardiovascular collapse due to splenic sequestration crisis associated with previously unsuspected sickle cell disease.

CONCLUSION

This case demonstrates the occurrence of sudden death in early childhood in a boy with clinically-occult sickle cell disease. Of interest, the presence of cardiomegaly with erythroid hyperplasia of the bone marrow suggested that significant anaemia with a physiological response had been present for some time, in spite of his apparently normal health status and growth parameters.

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The diagnosis of acute splenic sequestration should be suspected at autopsy when the spleen is markedly enlarged and has a purplish congested appearance due to engorgement with irreversibly sickled red blood cells. The remainder of the organs are unusually pale, giving the brain in particular a 'porcelain-like' appearance (Figure 7-3). Although the detection of sickled erythrocytes on microscopy does not necessarily imply that sickling was an antemortem phenomenon, extensive sickling in acute sequestration should be readily demonstrable. Other autopsy findings in cases of fatal sickle cell disease include purulent meningitis, cerebral infarction, cardiomegaly, splenic infarction and hyperplasia of bone marrow.

Splenial sequestration crisis is a particularly common presenting feature in infants and children under the age of two years, accounting for a third of cases in one series. In this report other presentations of sickle cell disease included pneumococcal sepsis and cerebrovascular accident. Twenty-four percent of their patients who died did so on first presentation, including 15% who were dead on arrival at hospital. The fact that sudden death may occur due to splenic sequestration with either no known history of sickle cell disease, or with only minimal
Figure 7-3: Marked pallor producing a 'porcelain brain' appearance in acute sickle cell sequestration.

Figure 7-4: Fibrointimal proliferation in a minor pulmonary artery in a nine-year-old girl who died suddenly with sickle cell disease/thalassaemia (Haematoxylin & Eosin, x 280).
symptoms as noted above, may make the autopsy examination crucial in the establishment of the diagnosis.

**Cardiovascular Complications**

Proliferative lesions of the walls of the carotid arteries that are associated with childhood stroke and death in patients with sickle cell disease may be similar to arterial lesions of Moyamoya disease. Thus, at autopsy it is appropriate to sample the carotid arteries in cases of childhood stroke in sickle cell disease, as the brain pathology may not be due solely to local sickling and stasis.

Sudden death from coronary occlusion with acute myocardial infarction is a rare occurrence in childhood sickle cell disease, but has been reported in young adults. Cardiomegaly is a reasonably common finding in older children with sickle cell disease, associated with chronic anaemia and high output cardiac failure. In cases of sudden death in which cardiomegaly is found at autopsy, it is possible that the underlying mechanism is ischaemic arrhythmia, rather than acute sequestration. However, the proposal that thrombotic occlusion of intramural coronary arteries in patients with sickle cell disease results in ischaemic left ventricular dysfunction and cardiomyopathy has not been supported by later studies. The latter authors found no evidence of coronary occlusion or of ischaemic myocardial damage in a series of 52 patients at autopsy. They concluded that there is no evidence for a specific 'sickle cell cardiomyopathy' and that changes observed resulted from the effects of chronic anaemia exacerbated by acute complications of the disease. Sudden death from pulmonary thromboembolism, possibly preceded by manifestations of 'acute chest syndrome', appears to be a phenomenon that occurs predominantly in affected adults, although pulmonary vascular changes may be found at earlier ages (Figure 7-4).

**Infectious Complications**

Infections in infants and children with sickle cell disease may be fulminant and may also result in sudden death. For example there is a significantly increased risk of pneumococcal septicaemia and meningitis particularly in early childhood. This is thought to be due to a combination of: reduced splenic function associated with repeated episodes of infarction which ultimately result in functional asplenia, a defect in the alternative pathway of complement activation, altered
neutrophil activity, reduced serum opsonizing activity for pneumococcus, and reticuloendothelial
dysfunction due to chronic haemolysis\textsuperscript{26,43-45,76}.

**Autopsy Investigations**

Sickle cell disease should be suspected in any infant who suddenly collapses and dies, particularly if there is African heritage. Investigations at the time of autopsy include a full septic workup with cerebrospinal fluid and blood cultures, haematocrit, haemoglobin and haemoglobin electrophoresis (if possible). Given the possibility of sudden and unexpected death from a variety of mechanisms in asymptomatic infants with sickle cell disease, it would not seem appropriate to make the diagnosis of sudden infant death syndrome (SIDS) in this group, although it has been claimed that the incidence of SIDS is higher in these infants\textsuperscript{76}.

**OTHER HAEMOGLOBINOPATHIES**

The association of sudden death and the other haemoglobinopathies is not as well recognized in the literature, although sudden death in childhood may occur with haemoglobin CS\textsuperscript{73}, or in sickle cell disease-\& thalassaemia. The presence of the latter combination in populations around the Mediterranean means that the presence of a white skin does not exclude the possibility of acute splenic sequestration at autopsy (Figure 7-5). Intractable cardiac failure with arrhythmias due to iron overload may occur in children with thalassaemia, however the terminal episode usually extends over one to two days\textsuperscript{39}.

**HAEMATOLOGIC MALIGNANCIES**

**LYMPHOMAS**

The clinical course of infants or children with haematologic malignancies that fail to respond to therapy is usually relatively protracted, with death being neither sudden nor unexpected. When unexpected death does occur a common cause is fungal thromboembolism following immunosuppressive therapy. A clinical history of prolonged fever, antibiotic and corticosteroid administration and profound neutropaenia may be clues to the presence of fungal sepsis prior to performance of the autopsy. Overwhelming bacterial sepsis and haemorrhage are also potentially lethal complications which may result in rapid demise.

A less common cause of death may, however, be upper airway compromise due to a local mass effect from mediastinal lymphoma. A case such as this occurred in a two-year-old
Figure 7-5: Marked enlargement of the spleen due to acute splenic sequestration in an eight-year-old boy with a Southern European background and combined sickle cell disease-ß thalassaemia.

Figure 7-6: Sudden death in a three-year-old girl due to haemorrhage into the brainstem with compression of adjacent vital centres. Clinically unsuspected acute myeloid leukaemia was also found at autopsy.
mentally retarded girl thought to have asthma, who was found at autopsy at the Adelaide Children's Hospital to have a clinically-unsuspected anterior mediastinal large cell lymphoma compressing her airways. In this case other medical problems had made accurate clinical assessment difficult. Airway obstruction in children with mediastinal tumours may also occur following the induction of anaesthesia and children with this problem are also at risk of sudden death from cardiac compression, or from compression of the pulmonary artery in the supine position.

Another potential cause of sudden death in lymphoma is marked metabolic disturbance. This may occur following chemotherapy in sensitive tumours resulting in rapid tumour lysis with marked hyperkalaemia and hypocalcaemia. Rarely, rupture of the spleen resulting in rapid death may be the first presentation of lymphoma. This usually involves older children, rather than infants, and was reported in a 15-year-old girl who died soon after the onset of abdominal pain. Hodgkin's disease was discovered at autopsy.

LEUKAEMIAS
In the author's experience the usual cause of sudden death in children with leukaemia is intracranial haemorrhage due to primary or secondary thrombocytopaenia. Children with acute promyelocytic leukaemia are particularly prone to developing haemorrhagic complications. Other mechanisms may involve local cerebral leukaemic infiltration, or hyperviscosity and leukostasis in acute disease. Fungal disease may also result in occlusive thromboemboli, and certain types of chemotherapy, such as asparaginase and methotrexate can cause thromboses and haemorrhage.

A three-year-old girl who had been treated with antibiotics for cervical lymphadenopathy and an upper respiratory tract infection, collapsed and died suddenly. At autopsy at the Adelaide Children's Hospital massive intrapontine haemorrhage was found in association with an acute myeloid leukaemia (Figure 7-6). Thus death may occur rapidly in young patients with leukaemia sometimes even before the clinical diagnosis has been established.

DISORDERS OF COAGULATION
Disorders of the coagulation pathways may be inherited, such as deficiencies of Factors VIII and IX, or acquired, due to liver disease or to inadequate dietary intake of vitamin K resulting in low
levels of factors II, VII, IX and X. Independent of the underlying aetiology, patients with any of these conditions are at risk of significant haemorrhage, either spontaneously or following minimal trauma.

**PRIMARY DEFICIENCIES**

Inherited disorders of coagulation usually involve Factor VIII, Factor IX or von Willebrand factor, although a number of other less common deficiencies have been described, haematological details of which have been reviewed elsewhere.36

While patients with either of the first two deficiencies (haemophilia A or B) tend to bleed spontaneously into the soft tissues and joints, intracranial haemorrhage remains the major cause of premature mortality and has been reported in 2.2 to 7.8% of affected individuals accounting for 25 to 30% of deaths overall. There are also significantly increased risks associated with surgical and dental procedures, and with minor trauma. Damage to the posterior pharynx, as may occur in a child who falls with an object in the mouth, is a feature of older, ambulatory children, which may result in massive retropharyngeal space haemorrhage with life-threatening upper airway obstruction. Although intracranial haemorrhage is much less common in von Willebrand disease it remains a potentially fatal complication.

The following case of a 14-year-old boy with known haemophilia A illustrates how insidious the haemorrhage in these children may be. The boy had suffered mild concussion with no loss of consciousness following a fall from his bicycle. Skull X-ray revealed no evidence of fractures, however, in view of his underlying coagulopathy he was admitted to the Adelaide Children’s Hospital and observed for three days. At the end of that time he appeared quite well and so was sent home, only to appear at the end of the first week with an acute onset of reduced consciousness, hemiparesis, and death within 24 hours. There had been no additional trauma. At autopsy extensive haemorrhage into his left frontal lobe with intraventricular extension was found (Figure 7-7). Other coagulation disorders such as congenital afibrinogenaemia and factor VII and XIII deficiencies may result in intracranial bleeding in childhood, while antithrombin III and protein C deficiencies predispose to thrombotic events in adolescence.
Figure 7-7: Intracerebral haemorrhage resulting in the sudden onset of a reduced conscious state followed by death within 24 hours in a 14-year-old boy with haemophilia A. This occurred one week after apparently minor head trauma.

Figure 7-8: Obstruction to the laryngeal inlet due to interstitial haemorrhage resulted in sudden onset of inspiratory stridor, cyanosis and death in a one-year-old girl with neuroblastoma, Pseudomonas sepsis and chemotherapy-induced thrombocytopenia.
SECONDARY DEFICIENCIES

There are a variety of acquired disorders of coagulation, the most common being disseminated intravascular coagulation associated with sepsis, malignancy or trauma. In most of these conditions, however, the patient is in a critical state, and thus haemorrhage is often terminal, multifocal and associated with a range of haemodynamic and metabolic disruptions. Death is, therefore, usually not all that sudden or unexpected.

THROMBOTIC CONDITIONS

Familial hypercoagulable syndromes in which there are repeated episodes of spontaneous thrombosis are documented in the literature. These have been associated with a variety of abnormalities including reduced levels of anti-thrombin III and increased amounts of factor V\(^{18}\). Their rarity makes them only potential causes of sudden paediatric death.

PLATELET DISORDERS

Thrombocytopenia from any cause may result in spontaneous haemorrhage. A list of possible causes of thrombocytopenia is given in Table 7-2.

TABLE 7-2: CAUSES OF THROMBOCYTOPAENIA

1. Decreased production
   i) Decreased megakaryopoiesis - e.g. aplastic anaemia, drugs, chemicals, marrow replacement from leukaemia/lymphoma, solid tumours such as neuroblastoma, osteopetrosis and storage disorders.
   ii) Ineffective thrombopoiesis - e.g. megaloblastic anaemia, hereditary thrombocytopenias

2. Abnormal distribution or dilution
   i) Pooling in cases of splenomegaly
   ii) After stored blood transfusion

3. Increased destruction
   i) Immunological - e.g. idiopathic thrombocytopenic purpura
   ii) Non-immunological - e.g. thrombotic thrombocytopenia, disseminated intravascular coagulation, haemolytic uraemic syndrome, cardiac prostheses.
Occurrence of Sudden Death

Sudden death may occur in children with any of these entities if bleeding occurs in a vital location, such as within the cranial cavity. Rarely, haemorrhage into soft tissues around the laryngeal inlet may also result in death from airway obstruction. Figure 7-8 illustrates such a case in a one-year-old girl with treated neuroblastoma, *Pseudomonas* sepsis and marrow aplasia who suffered airway compromise from spontaneous pharyngeal haemorrhage.

The usual conditions associated with sudden lethal intracranial haemorrhage in childhood in this collection of disorders are the acute leukaemias. This is because of replacement of marrow haematopoietic cells by malignant cells, or treatment-induced marrow aplasia with reduction in circulating platelet numbers.

In a number of childhood malignancies there may be several contributing factors to spontaneous haemorrhage as well as thrombocytopenia. These include reduced clotting factors from an inadequate diet associated with the underlying malignancy and chemotherapy, or disseminated intravascular coagulation due to concurrent sepsis.

**INHERITED PLATELET ABNORMALITIES**

Inherited disorders of platelets involving abnormal function or reduced numbers are less common than acquired disorders but may also result in lethal haemorrhage at an early age. Miller has separated these conditions into five main groups: i) defects of the platelet surface membrane, ii) platelet-type von Willebrand disease, iii) granule defects, e.g. Wiskott-Aldrich syndrome (X-linked thrombocytopenia with eczema), iv) defective arachidonic metabolism, and v) a miscellaneous group which is quite heterogeneous, including platelet abnormalities associated with congenital heart disease, Down syndrome and metabolic disorders.37

An example of sudden death in one of these conditions occurred in a five-month-old boy with Wiskott-Aldrich syndrome who was in the Adelaide Children's Hospital for a platelet transfusion when he suffered sudden deterioration and death. Intracerebellar and diffuse basal subarachnoid haemorrhage were found at autopsy.

**IDIOPATHIC THROMBOCYTOPENIC PURPURA**

Idiopathic thrombocytopenic purpura is the most common childhood thrombocytopenic purpura and is characterized by decreased circulating platelets, increased marrow megakaryocytes, and
Figure 7-9: Large cavernous haemangioma of the upper thigh causing Kasabach-Merritt syndrome with thrombocytopenia and resultant fatal subarachnoid haemorrhage.

Figure 7-10: Massive cardiomegaly with chamber dilatation in a seven-year-old boy with thalassaemia.
Figure 7-11: 'Thrush breast' dappling of the heart due to marked fatty change in an anaemic nine-year-old boy with acute lymphoblastic leukaemia in relapse.

Figure 7-12: Multiple dense hyperchromic microspherocytes typical of hereditary spherocytosis (Giemsa, x 1100).
mucocutaneous bleeding. The underlying aetiology is believed to be an autoimmune response to platelets, often triggered by a preceding viral infection. Although mucosal bleeding may be quite profound, intracranial haemorrhage occurs in only one to two percent of cases.46

**KASABACH-MERRITT SYNDROME**

Kasabach-Merritt syndrome is characterized by a consumption coagulopathy with reduction in platelet numbers due to trapping and destruction of platelets within large vascular neoplasms that are most often haemangiomas. While most infants and children with this condition survive, this is not always the case as demonstrated in Figure 7-9. This shows a large cavernous haemangioma of the leg in a four-day-old infant that was associated with thrombocytopaenia and unexpected death from subarachnoid haemorrhage. Hyperkalaemia secondary to excessive red blood cell destruction in Kasabach-Merritt syndrome has also been reported as a rare cause of potentially fatal cardiac arrhythmias in this age group.74

**ANAEMIA**

Unless there is postmortem evidence of previous high output cardiac failure with marked cardiomegaly (Figure 7-10) and erythroid hyperplasia of the bone marrow, it may be difficult to determine the significance of an antemortem diagnosis of anaemia. However, if these findings are present it is reasonable to suggest that anaemia of whatever aetiology may have contributed to sudden death, given the known association of cardiac arrhythmias with hypoxia and cardiomegaly. Other cardiac findings in cases of severe anaemia include chamber dilatation, myocardial infarction/ischaemia and fatty infiltration with a 'thrush breast' pattern to the myocardium.6,15 (Figure 7-11). Certainly it would be difficult to support a diagnosis of sudden infant death syndrome in infants who are found to have these changes, no matter how typical a history. The case of a four-month-old boy with hereditary spherocytosis (Figure 7-12) who was initially thought to have succumbed to SIDS illustrates this point. He had required blood transfusions because of ongoing haemolysis and at autopsy was found to have marked cardiomegaly and marrow erythroid hyperplasia thus precluding the diagnosis of SIDS. An additional reason for clearly separating infants who die with anaemia from infants who die of SIDS is the known association of acute life-threatening events (ALTE) with anaemia in infancy.68
Other possible mechanisms relating anaemia and sudden death are those of cerebral ischaemia\(^7\) and increased cyanotic breath-holding episodes\(^4\). As well, while anaemia may not be solely responsible for the lethal event it may serve to exacerbate pre-existing conditions. An example of this was a 13-month-old boy who had a cardiac arrest and was found to have both severe anaemia and a solitary coronary artery\(^2\).

Anaemia may also be associated with reduction in platelet numbers, as in aplastic and megaloblastic anaemias, which may result in death due to spontaneous haemorrhage\(^1\). This was the case in a 10-year-old boy with a past history of intracranial haemorrhage, who was known to have aplastic anaemia. He presented to the Adelaide Children's Hospital dead on arrival following the acute onset of headache which had rapidly progressed to coma. At autopsy, extensive intracerebral haemorrhage was found involving the left parietotemporal lobes with extension into the subarachnoid space (Figure 7-13).

HAEMOLYTIC-URAEMIC SYNDROME
The aetiology of this disorder, which is characterized by the sudden onset of haemolytic anaemia, thrombocytopenia and uraemia, is not understood, although the major feature is endothelial damage. Clinically, about one third of patients have neurological complications with coma, seizures and hemiparesis\(^6\) resulting from thrombosis of the microvasculature, metabolic abnormalities or systemic hypertension\(^7\). Intracranial haemorrhage\(^1\) and status epilepticus\(^4\) are two manifestations that have a known association with sudden death.

POLYCYTHAEMIA
The most common forms of polycythaemia in children are secondary to cyanotic congenital heart disease and chronic pulmonary disease. Primary polycythaemia occurs much less often. Other disorders such as cystic renal disease, cerebellar haemangioblastomas and the Pickwickian syndrome may also result in marked polycythaemia\(^5\),\(^2\), all of which may predispose to lethal thrombotic cerebral events.

SPLENIC DISORDERS
CONGENITAL ASPLENA
Congenital absence of the spleen may be associated with both cardiovascular abnormalities and with an increased risk of fulminant sepsis. The most common associated cardiac anomalies are
Figure 7-13: Spontaneous fatal intracerebral haemorrhage in a ten-year-old boy with aplastic anaemia.

Figure 7-14: Traumatic rupture of the spleen resulting in sudden death in an adolescent girl with splenomegaly due to infectious mononucleosis.
transposition of the great vessels, pulmonary stenosis or atresia and total anomalous pulmonary venous drainage. Details of vascular and infectious complications are dealt with in Chapters 3 and 4, respectively.

**SPLENIC RUPTURE**

Although often related to haematologic disorders, splenomegaly from any cause may be associated with rupture and sudden death due to exsanguination. While malaria would be a more frequent cause of splenomegaly on a global scale, infectious mononucleosis and leukaemias are more common causes of splenic enlargement in Western countries. Even relatively mild trauma may cause rupture when the spleen is significantly enlarged. This was the case in an adolescent girl with infectious mononucleosis (Figure 7-14) who died quite suddenly due to massive intraperitoneal haemorrhage with no history of trauma. Trauma resulting in splenic rupture in individuals with infectious mononucleosis may be minimal; for example, straining at stool, vomiting, coughing, exercise and medical examination have all been cited as causes. Rupture of the spleen as the initial presentation of Hodgkin's disease has also been reported in adolescence. Haemangiomas, cysts and Ehlers-Danlos syndrome are other extremely rare causes of spontaneous splenic rupture.

* * * *
REFERENCES

References Ch7-3


SUDDEN NATURAL DEATH IN INFANCY
& EARLY CHILDHOOD

CHAPTER 8

GASTROINTESTINAL AND GENITOURINARY CONDITIONS
INTRODUCTION

Gastrointestinal causes of sudden and unexpected death in infancy such as intussusception, volvulus and small intestinal obstruction\(^24\) (Table 8-1) are uncommon. As the clinical presentation of these disorders may be relatively non-specific the diagnosis may not have been established prior to autopsy. However, the cause of death usually becomes obvious once the peritoneal cavity has been opened.

**TABLE 8-1: GASTROINTESTINAL CAUSES OF SUDDEN PAEDIATRIC DEATH.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
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<tbody>
<tr>
<td>Gastroenteritis</td>
<td>Gastro-oesophageal reflux/aspiration</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Late-presenting congenital diaphragmatic hernia</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>Volvulus</td>
<td>Cystic fibrosis</td>
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<tr>
<td>Intestinal perforation</td>
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**GASTROENTERITIS**

Gastroenteritis resulting in dehydration and electrolyte imbalance may cause sudden death particularly in early life. The causative agents are often viral infections and the effects of fluid depletion may be exacerbated by hot weather or parental inattention. Further discussion on the role of gastroenteritis in sudden death may be found in Chapter 4.

**INTESTINAL OBSTRUCTION**

Acute intestinal obstruction in infants and young children may be caused by intussusception and volvulus, with rare lethal episodes resulting from electrolyte imbalance or intestinal perforation with sepsis. As obstruction causes a characteristic clinical picture of colicky abdominal pain and vomiting over some time, it is usually not considered a cause of unexpected death. However, occasional cases of bowel obstruction presenting in a fulminant manner have been reported\(^34,36\). As well, cases are occasionally encountered in which either delay by parents in seeking treatment, or inadequate medical treatment, have resulted in early death. For example, two cases have been encountered at the Adelaide Children’s Hospital in which death occurred during or shortly after transfer from rural centres. In the first case a 17-month-old boy suddenly
collapsed and died from peritonitis associated with ischaemic necrosis of the small intestine due to obstruction from a congenital band (Figure 8-1). In the second, a five-year-old girl died suddenly from dehydration due to small bowel obstruction caused by postsurgical adhesions. A change in management strategies may have altered the outcome in both cases.

INTUSSUSCEPTION

Intussusception refers to telescoping of a proximal segment of bowel into the adjacent distal bowel (Figure 8-2). Males are affected more often than females, with most cases occurring in infancy. Intussusception is a common cause of intestinal obstruction in childhood, but is rarely fatal. The presenting features are usually abdominal pain, vomiting, rectal bleeding or an abdominal mass. Most cases are ileocolic, with ileo-ileal, jejuno-jejunal and colocolic occurring less often. Lesions that may be found at the leading edge of an intussusception include hyperplastic Peyer's patches, Meckel's diverticulum, duplication cysts, or lesions of Henoch-Schönlein purpura. If the presenting symptoms are relatively non-specific there is a possibility that the intussusception will remain undetected allowing progression to bowel infarction due to vascular compromise. In these rare cases there may be precipitate clinical deterioration with unexpected death secondary to the development of septicaemia. Two fatal cases of ileocolic and ileo-ileal intussusception are illustrated in Figures 8-3 & 4, in infants aged five and six months respectively, both of whom presented with sudden collapse and death following non-specific symptoms and signs which were incorrectly attributed to minor upper respiratory tract infections.

Agonal intussusception is an unrelated and incidental finding at autopsy in infants that should be clearly distinguished from the above situation. In these cases there is no evidence of vascular obstruction or of infarction, and the bowel appears quite viable (Figure 8-5).

VOLVULUS

Volvulus is a rare event in infancy which may involve any portion of the gastrointestinal tract from the stomach to the sigmoid colon. Infants and children with gastric or small intestinal volvulus may present with bilious vomiting, however, clinical symptoms may be non-specific with volvulus of the large intestine leading to a delay in treatment. In most cases the
Figure 8-1: Intestinal band that had caused bowel obstruction on several occasions before death in a three-month-old boy.

Figure 8-2: A typical case of intussusception in which the bowel has been opened to reveal distension and mottling of the distal bowel (the intussusceptum) that has enveloped the invaginated portion of proximal bowel (the intussusceptum).
Figure 8-3: Opening of the abdomen in this five-month-old girl who suddenly developed respiratory distress revealed a necrotic segment of distal ileum associated with an ileo-ileal intussusception.

Figure 8-4: Marked intestinal dilatation with distal necrosis of the ileum was the first indication of an ileocolic intussusception in this six-month-old girl who died suddenly en route to hospital after blood was noted in her diaper.
Figure 8-5: Agonal intussusception in an infant unrelated to the cause of death.

Figure 8-6: Colonic dilatation due to a right sided volvulus in a seven-week-old boy who had appeared quite well prior to being put to bed. Blood, CSF and lung cultures all grew *Clostridium perfringens*. 
underlying predisposing factors are unknown although unusually long loops of colon and chronic constipation have been reported\textsuperscript{10}. Volvulus may also complicate meconium ileus in infants with cystic fibrosis. Death may occur very rapidly in an infant with a volvulus\textsuperscript{46} due to vascular compromise of the twisted bowel with ischaemic necrosis and resultant septicemia.

Figure 8-6 demonstrates a dilated and dusky-appearing colon caused by a right sided colonic volvulus in a seven-week-old boy who had appeared quite well several hours before he was found moribund in his cot. His only significant past history was of minimal episodic vomiting after feeding in the preceding two weeks of life. Blood, cerebrospinal fluid and lung cultures all grew \textit{Clostridium perfringens}.

\textbf{INTESTINAL PERFORATION}

Non-traumatic perforation of the intestine may result from ischaemic necrosis due to mechanical obstruction or from localized inflammation associated with acute appendicitis\textsuperscript{4}. Alternatively, traumatic perforation may occur from intraluminal objects.

Perforation with fulminant sepsis may also occur in children with distension of the bowel from impacted material. Untreated Hirschsprung disease (Figure 8-7) or the trichobezoars found in the Rapunzel syndrome\textsuperscript{45} are illustrative of this phenomenon. Trichobezoars (hair balls) may extend from the stomach or proximal small intestine into the colon in older children. Perforation is believed to result from pressure necrosis on the distended bowel wall from the impacted material. Unexpected cardiac arrest and death due to duodenal perforation during medical treatment has been reported in a 14-year-old girl with a trichobezoar that extended from the stomach into the transverse colon\textsuperscript{13}.

Other causes of intestinal perforation in infancy and childhood include undiagnosed necrotizing enterocolitis, dermatomyositis, Ehlers-Danlos syndrome and congenital absence of small intestinal musculature.

\textbf{GASTRO-OEOSOPHAGEAL REFLUX/ASPIRATION}

Mechanisms by which gastro-oesophageal reflux might cause sudden death in infancy, such as reflex apnoea, bradycardia and anaphylaxis, have been discussed in Chapter 1.

The contribution of gastric aspiration to sudden death in other cases is often difficult to determine as reflux of stomach contents has been produced experimentally within cadavers\textsuperscript{17}.
and may also occur as an agonal event in a variety of disorders\textsuperscript{27}. While large amounts of food within the major airways extending into the smaller air passages are compatible with a lethal episode of airway obstruction due to gastric aspiration, clinicopathological correlation is required before this can be accepted as a cause of death\textsuperscript{4}. For example, histories of sudden collapse while vomiting, of swallowing incoordination in cerebral palsy, or of mental retardation, may lend weight to the possibility of genuine aspiration\textsuperscript{15}. Gastric aspiration becomes more plausible if other causes of death have been excluded, although it is often difficult to accept it as the cause of death in previously apparently healthy infants with no known neurological impairment.

Occasionally a bolus of solid food may be found lodged within the airway or oesophagus in cases of sudden childhood death. The large portion of sausage (Figure 8-8) retrieved from the oesophagus of a 19-month-old child who suddenly collapsed while eating his lunch at a child care centre demonstrates this phenomenon.

**LATE-PRESENTING CONGENITAL DIAPHRAGMATIC HERNIA**

Infants with congenital diaphragmatic hernias usually show symptoms and signs of marked respiratory distress due to lung compression and pulmonary hypoplasia, exacerbated by persistent fetal circulation\textsuperscript{12}. These infants often have a scaphoid abdomen. However, occasional infants do not present classically, either because a membrane covers the defect preventing intestinal herniation, or because the defect has been plugged by one of the abdominal organs such as the spleen\textsuperscript{29}.

It is usually considered that infants with diaphragmatic herniae presenting after the neonatal period have an excellent prognosis, responding well to surgical repair\textsuperscript{22,44}. While this is generally true, it should be emphasized that rare infants and children may suffer a precipitate clinical deterioration with sudden death\textsuperscript{6,8,9}. Clinical symptoms and signs in the late-presenting group tend to be relatively nonspecific often resulting in misdiagnosis. Presenting problems include failure to thrive, recurrent chest infections, episodic dyspnoea, diarrhoea, constipation, vomiting, dysphagia and colicky upper abdominal pain. On occasion thoracentesis has been performed due to a mistaken clinical diagnosis of pneumothorax\textsuperscript{5}. 
Figure 8-7: Markedly dilated descending colon with distal perforation in a fatal case of untreated Hirschprung disease.

Figure 8-8: A large portion of partially-chewed sausage retrieved from the oesophagus of a 19-month-old boy who collapsed and died while eating.
Figure 8-9: Herniation of the abdominal contents through a small left sided diaphragmatic hernia in a four-month-old boy resulting in sudden death (Case 3 in Table 8-2).

Figure 8-10: The relatively small size of the diaphragmatic defects in late-presenting cases can be appreciated when the diaphragms have been removed as in Cases 1 & 3 in Table 8-2 (A & B respectively).
Thus, although rare, congenital diaphragmatic hernias which do not present at birth have the potential to cause sudden and unexpected death (Figure 8-9). This under-recognized phenomenon is clearly demonstrated in the following studies8,9.

STUDY #8-1

DEMONSTRATION OF THE ASSOCIATION BETWEEN LATE-PRESENTING CONGENITAL DIAPHRAGMATIC HERNIAS AND SUDDEN UNEXPECTED DEATH IN INFANCY AND CHILDHOOD

INTRODUCTION

Congenital posterolateral diaphragmatic hernias (foramen of Bochdalek) usually present as a surgical emergency within hours or days of birth40. Respiratory distress due to pulmonary hypoplasia resulting from incomplete development and expansion of the lung during gestation is worsened as the herniated bowel fills with swallowed air. The treatment of choice is surgical repair once the neonate has been stabilized19.

Occasionally, diaphragmatic hernias present in later life with mild gastrointestinal or respiratory problems43. The prognosis in this latter group is thought to be generally better than in patients who present earlier with respiratory difficulties19,40. However, the following three cases taken from the files of the Hospital for Sick Children (HSC), Toronto, Canada over a 37-year period from 1952 to 1989 demonstrate that undiagnosed diaphragmatic hernias in infancy and early childhood may have lethal consequences with sudden collapse and death occurring due to massive intestinal herniation.

CASE REPORTS

Case 1: A previously well two-month-old boy had an episode of crying prior to being put to bed. This settled and two hours later he was noted by his parents to be groaning in his sleep. This was followed by cardiorespiratory arrest that was unresponsive to resuscitation. The clinical diagnosis was SIDS. His only past history was of occasional "colic" for which a sedative medication had been prescribed.

At autopsy, a two cm diameter defect in the posterolateral portion of the left side of the diaphragm was found with herniation of most of the small and large intestine into the left pleural
cavity (Figures 8-10 & 8-11). No hernial sac was present. The proximal part of the small intestine, measuring 180 cm in length, was dusky in colour due to ischaemic necrosis. The mediastinum was displaced to the right with hypoplasia of the left lung. The lung weighed 24 g with a volume displacement of 60 mL compared with the right lung, which weighed 43 g and displaced 130 mL.

Case 2: A previously well two-year-old girl suffered an unexpected cardiorespiratory arrest following one day's history of a "flu-like" illness with vomiting. Brain death was noted after resuscitation at a local hospital. Chest x-ray showed a left-sided diaphragmatic hernia with a markedly dilated stomach, which was located in the thorax causing a shift of the mediastinum to the right. Death occurred the following day after transfer to HSC. Consent for autopsy was refused.

Case 3: A previously well four-month-old boy suffered a cardiopulmonary arrest after sudden onset of irritability and seizures. The only recent past history had been of an upper respiratory tract infection for several weeks prior to presentation. Minimal neurological function was noted subsequent to resuscitation at a local hospital. On transfer to HSC brain death was confirmed. Four additional cardiac arrests were followed by death the next day.

At autopsy, the most significant gross finding was a three cm-diameter defect in the posterolateral portion of the left diaphragm. Approximately 15 cm of dusky, congested distal ascending, transverse, and proximal descending colon along with two thirds of the jejunum and ileum were present above the diaphragm occupying the left pleural cavity (Figure 8-9). The heart and lungs were displaced to the right side of the chest. There was no evidence of pulmonary hypoplasia or intestinal malrotation. No hernial sac was present. Microscopic examination showed focal transmural infarction of the herniated portions of the small intestine with mural infarction of the involved portions of large intestine. Cerebral oedema with extensive neuronal hypoxic-ischaemic damage secondary to prolonged anoxia following the numerous cardiac arrests was also present.

Death in all cases was due to cardiovascular and respiratory compromise caused by compression of the heart, lungs, and great vessels by abdominal viscera that had herniated into the thoracic cavity through previously unsuspected diaphragmatic hernias.
Figure 8-11: Marked dilatation of the stomach may be found in cases of late presenting diaphragmatic hernias which exacerbate respiratory difficulties (Case 1 in Table 8-2).
DISCUSSION

Congenital posterolateral diaphragmatic hernias develop during early fetal life when the pleuroperitoneal folds that grow laterally from the developing central portion of the diaphragm fail to close the defect between the pleural and peritoneal cavities\textsuperscript{26,43}. If there has been failure of closure there exists a potential passage for abdominal contents to herniate into the thorax. When the defect is large, the bulk of the abdominal organs may find their way into the chest, causing pulmonary hypoplasia with the typical picture of respiratory distress at birth. In cases of smaller defects there may be no respiratory compromise and so the condition initially remains undiagnosed\textsuperscript{18,40,43}. Although in some series in the literature as many as 13\% to 28\% of patients have been diagnosed after the neonatal period\textsuperscript{32}, the usual incidence is around 5\%\textsuperscript{33}. Late presentation of paediatric post-traumatic diaphragmatic hernias has also been reported\textsuperscript{14}.

Intermittent intestinal obstruction may be the only clue to the presence of a late-presenting diaphragmatic hernia\textsuperscript{33}, which may remain undetected well into adult life. The small size of the defect with protective "plugging" of the gap by the spleen or liver is believed to delay intestinal herniation\textsuperscript{23}. In some cases there may also be a confining sac that prevents visceral herniation until rupture occurs.

The cases described demonstrate that not all late-presenting diaphragmatic hernias have a favorable prognosis, as has been previously reported\textsuperscript{19,23,40}. On the contrary, they can be associated with a rapidly downhill clinical course with a lethal outcome. In Case 1, death had occurred during sleep, thus causing clinical confusion with sudden infant death syndrome. In the other two cases brain death followed the initial sudden cardiac arrests. The proximity of local hospitals enabled partial resuscitation of these two patients, although it soon became obvious that survival was unlikely.

Case 1 is unusual in having asymptomatic pulmonary hypoplasia, in that patients diagnosed after the first weeks of life, as in Case 3, usually have lungs of normal weight and volume\textsuperscript{32}. Whether the episodes of "colic" that occurred in the second patient were related to intermittent bowel obstruction is difficult to determine, particularly in the absence of vomiting at any stage. Both Cases 2 and 3 had mild respiratory and gastrointestinal symptoms preceding their unexpected arrests, which may explain the timing of the fatal herniations. Coughing and
vomiting raise intra-abdominal pressure, thus increasing local pressure on any defects present in the diaphragm, making visceral herniation more likely. A similar process may have occurred in Case 1 following the episode of crying. On the other hand, it is also possible that the herniations may have initiated these symptoms.

SUMMARY
Three previously well patients (aged 2, 4, and 24 months) are described who suffered unexpected cardiorespiratory arrests due to unsuspected congenital diaphragmatic defects with intestinal herniation. Deaths resulted from cardiovascular and respiratory compromise due to visceral herniation that caused mediastinal and pulmonary compression.

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STUDY #8-2

DEMONSTRATION OF THE OCCURRENCE OF FATAL GASTRIC PERFORATION AS A CAUSE OF SUDDEN AND UNEXPECTED DEATH IN CHILDHOOD ASSOCIATED WITH LATE-PRESENTING CONGENITAL DIAPHRAGMATIC HERNIA

CASE REPORT
A previously-well four-year-old boy complained of left upper quadrant pain associated with vomiting of white mucus one evening. The following day he was noted to be rather listless and was not interested in eating. He remained lethargic and anorexic and the next day was taken to the local medical officer who diagnosed an otitis media and prescribed oral antibiotics and ear drops. His condition worsened later that day and he suffered an unexpected cardiorespiratory arrest. Resuscitation attempts were unsuccessful and he was certified dead on arrival at the Adelaide Children's Hospital, approximately 48 hours after the onset of symptoms. His past history included occasional abdominal discomfort with one or two transient episodes of vomiting which were not felt to be particularly serious at the time. A chest X-ray, which had been taken
Figure 8-12: Perforation of the stomach that had herniated through a small left sided diaphragmatic hernia resulted in fulminat sepsis in a four-year-old boy (Case 5 in Table 8.2).
two years before death during investigations for a functional cardiac murmur, was completely normal.

At autopsy the body was that of a well nourished boy of around four years of age. There were no external signs of trauma or dysmorphism and both eyes were slightly sunken. The major findings were in the left pleural cavity which contained the stomach, spleen, splenic flexure of the transverse colon, tip of the pancreas and the bulk of the greater omentum, which had plugged a 50 x 40 mm oval defect in the posterior part of the left diaphragm (Figure 8-12). The rest of the diaphragm was unremarkable and there was no evidence of a hernial sac. The anterior surface of the stomach was discoloured and thinned with two 10mm diameter perforations in the mid portion of the greater curvature. The adjacent wall showed numerous smaller ulcers covered only by serosa. Both pleural cavities contained a large amount of greenish-grey gastric fluid. The left lung was collapsed and the mediastinum was shifted to the right. The heart was unremarkable and the remainder of the small and large intestines, except for the splenic flexure of the colon, were normally situated. Microscopy confirmed the presence of widespread ischaemic necrosis of the anterior gastric wall with perforation. Postmortem blood and tissue cultures grew mixed bacterial and fungal organisms.

Death was attributed to gastric perforation due to ischaemia that had resulted from herniation of the stomach into the left pleural cavity through a previously unsuspected congenital diaphragmatic defect. This was associated with compression of the left lung and shifting of the mediastinum to the right.

DISCUSSION

In the case reported, delay in diagnosis due to the non-specific, and apparently relatively-benign, nature of the presenting symptoms resulted in perforation of the stomach which had herniated into the left pleural cavity. While gastric dilatation has been demonstrated in children with delayed presentation of their diaphragmatic hernias, fatal perforation is an exceedingly rare complication. This may partly be due to the intra-abdominal location of the stomach in 40-51% of cases. The patient did not have any of the other congenital conditions that have been associated with congenital diaphragmatic hernias such as Down syndrome, congenital heart defects or midline fusion defects.
This case demonstrates, therefore, that late-presenting congenital diaphragmatic hernias in childhood may have dire consequences if treatment is delayed. The diagnosis should be entertained in any child who presents with lower chest signs in association with gastrointestinal symptoms and an unusual chest X-ray, particularly if these occur on the left side. It should also be noted that previous chest X-rays may be completely normal, as it was in this case, and so this finding does not exclude the diagnosis as has been previously suggested. If herniation is suspected, urgent surgical repair is indicated.

**SUMMARY**

A previously-well four-year-old boy presented with a two day history of listlessness, anorexia, left upper quadrant pain and vomiting, followed by sudden cardiorespiratory arrest and death. At autopsy a 50mm diameter congenital defect in the posterolateral part of the left diaphragm was discovered associated with herniation of the stomach, spleen, greater omentum and portions of the transverse colon and pancreas into the chest cavity. Perforation of the anterior wall of the stomach had filled the pleural cavity with gastric contents. This case demonstrates a rare lethal mechanism that has not been reported before as a cause of unexpected death in late presenting congenital diaphragmatic hernias in early childhood. Serious, even fatal, consequences may occur with delayed presentation in childhood quite soon after the onset of symptoms.

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Table 8-2 lists the clinicopathological features of six children, three of whom were infants, who suffered unexpected cardiac arrests caused by gut herniation through unsuspected diaphragmatic hernias. These cases (four of whom have been described in greater detail in the above case reports) demonstrate the diversity of presenting symptoms, signs and clinical diagnoses, the latter including croup, otitis media and SIDS. In four children the diagnosis was not suspected until autopsy, a feature that has been noted in other series.
TABLE 8-2: SUMMARY OF CLINICOPATHOLOGICAL FEATURES OF 6 CASES OF LATE-PRESENTING CONGENITAL DIAPHRAGMATIC HERNIAS WITH SUDDEN DEATH

<table>
<thead>
<tr>
<th>NO.</th>
<th>AGE</th>
<th>SEX</th>
<th>INITIAL CLINICAL DIAGNOSIS</th>
<th>PRESENTATION</th>
<th>AUTOPSY FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2Mo</td>
<td>M</td>
<td>'colic' SIDS</td>
<td>vomiting</td>
<td>2cm defect in L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diaphragm</td>
</tr>
<tr>
<td>2.</td>
<td>3Mo</td>
<td>M</td>
<td>vomiting croup</td>
<td></td>
<td>3cm defect in L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diaphragm</td>
</tr>
<tr>
<td>3.</td>
<td>4Mo</td>
<td>M</td>
<td>irritability cardiac arrest</td>
<td></td>
<td>3cm defect in L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diaphragm</td>
</tr>
<tr>
<td>4.</td>
<td>2Y</td>
<td>F</td>
<td>'flu' with vomiting, 1D</td>
<td></td>
<td>no autopsy, CXR -hernia L. diaphragm</td>
</tr>
<tr>
<td>5.</td>
<td>4Y</td>
<td>M</td>
<td>lethargy, vomiting, media abdominal pain, 2D</td>
<td>otitis</td>
<td>4cm defect in L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diaphragm</td>
</tr>
<tr>
<td>6.</td>
<td>13Y</td>
<td>F</td>
<td>abdominal pain, 1wk vomiting 1D</td>
<td>gastro-enteritis</td>
<td>postsurgical hernia repair L. diaphragm</td>
</tr>
</tbody>
</table>

D = day; wk = week; Mo = month; Y = year; L = left; M = male; F = female
Summary of Pathological Features

At autopsy the usual finding is of small and large intestinal herniation into the chest cavity (Figure 8-9) through relatively small diaphragmatic defects (Figure 8-10). This causes considerable mediastinal shift, usually to the right, as can be seen in the chest X-ray from the 13-year-old girl described in Table 8-2 (Figure 8-13). Atelectasis of the ipsilateral lung occurs, and a complicating factor may be massive gastric dilatation (Figure 8-11).

Pathophysiology

While the usual mechanism of death is similar to that of untreated tension pneumothorax, cases with a more prolonged course may develop ischaemic necrosis of the herniated segments of intestine with perforation and sepsis (Figure 8-12).

GASTROINTESTINAL HAEMORRHAGE

Massive haemorrhage from the gastrointestinal tract during childhood may result from systemic disease or from localized lesions. For example, terminal haemorrhage into the bowel is occasionally seen in malignant disease, particularly in leukaemias or lymphomas, but is usually the final manifestation of a generalized decline.

Brisk haemorrhage may result from upper gastrointestinal peptic ulcer disease in children who may require emergency surgery. In contrast, the bleeding associated with ulcers due to heterotopic gastric mucosa in Meckel's diverticulae tends to be less spectacular. Both haemorrhage from, and perforation of, peptic ulcers may result in death in childhood. Oesophageal varices may cause fatal haemorrhage in children with portal hypertension but are not described as a cause of sudden death in infants. Profuse gastrointestinal haemorrhage may also complicate arteriovenous malformations such as those found in Osler-Weber-Rendu syndrome and angiodysplasia.

CYSTIC FIBROSIS

Cystic fibrosis is an autosomal recessive disorder caused by a defect in the cystic fibrosis transmembrane conductance regulator gene located on the long arm of chromosome 7. This defect results in increased viscosity of exocrine secretions with particularly severe effects noted in the pancreas, liver, gastrointestinal tract and lungs. The major pulmonary problems are
Figure 8-13: Marked mediastinal deviation to the right in a 13-year-old girl who presented with relatively non-specific symptoms prior to terminal collapse from a late-presenting diaphragmatic hernia (Case 6 in Table 8-2).
Figure 8-14: Inspissated mucous within duodenal crypts suggestive of cystic fibrosis (Haematoxylin & Eosin, x 110).

Figure 8-15: Intestinal infarction following a small intestinal volvulus in an infant with cystic fibrosis and meconium ileus.
caused by recurrent and persistent bacterial and fungal infections which result in progressive bronchiectasis and destruction of lung parenchyma.

Occurrence of Sudden Death

Sudden and unexpected death can occur in the neonatal period due to intestinal volvulus, infarction and perforation from meconium ileus, or later in life due to electrolyte imbalance and dehydration. Affected infants are particularly vulnerable to dehydration during hot weather as they lose excessive amounts of sodium in their sweat. Occasional infants may present with collapse in hot weather before the diagnosis has been established clinically. Thus the presence of inspissated secretions within the intestinal mucosal, pancreatic and salivary glands at autopsy may be the first indication of the diagnosis (Figure 8-14).

Figure 8-15 shows an 11-day-old infant who died unexpectedly following a short history of vomiting and drawing up of the knees. The autopsy findings were of small intestinal volvulus with infarction associated with meconium ileus and inspissation of secretions within the remainder of the bowel, pancreas and submandibular gland, characteristic of cystic fibrosis.

2. GENITO-URINARY CONDITIONS

Genitourinary causes of sudden death in infants and children are rare. Table 8-3 summarizes some of the entities that have been reported as causes of unexpected paediatric death.

<table>
<thead>
<tr>
<th>TABLE 8-3: GENITOURINARY CAUSES OF SUDDEN PEDIATRIC DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary renal disease</td>
</tr>
<tr>
<td>pyelonephritis</td>
</tr>
<tr>
<td>glomerulonephritis</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

PRIMARY RENAL DISEASE

Although diseases of the urinary tract in children have been cited as causes of sudden death, detailed clinicopathological information on affected children is generally not available. However, the author has one case, that of a six-year-old girl who presented to the Adelaide Children’s Hospital with a one day history of vomiting, who died of acute renal failure within
hours. At autopsy the kidneys were pale, and microscopy revealed hypercellular glomeruli typical of acute proliferative glomerulonephritis. Rarely sudden death may also result from a hypertensive crisis in children with chronic renal insufficiency. Sudden death reported in apparently stable children with nephrotic syndrome is believed to be due to marked hyponatraemia resulting from a combination of salt-restriction, vomiting and hot weather\textsuperscript{21}. Vitreous humour electrolyte levels are mandatory in such cases.

**URINARY TRACT OBSTRUCTION**

Untreated urinary tract obstruction usually results in progressive loss of renal function with associated symptoms and signs of chronic renal failure. However, occasional cases may have the diagnosis made at autopsy following a supposed precipitate clinical deterioration. Male infants with posterior urethral valves may present in this manner (Figure 8-16).

**WILMS TUMOUR**

Wilms tumour may result in sudden and unexpected death due to secondary haemorrhage or to tumour embolism. For example, massive haemorrhage from a Wilms tumour may occur into the parenchyma of the tumour itself or into the adjacent retroperitoneal tissues and abdominal cavity. Hypovolaemic shock may ensue followed by death if fluid replacement and urgent surgery are not undertaken. Figure 8-17 illustrates a Wilms tumour with extensive intraparenchymal haemorrhage in an infant who died of shock. Haemorrhage may result from erosion of the tumour into vessels, and may be exacerbated by an accompanying consumption coagulopathy secondary to disseminated intravascular coagulation.

Embolization of tumour fragments is a particular problem in Wilms tumour due to its angio-invasive qualities\textsuperscript{47}. Figure 8-18 shows a sectioned Wilms tumour which had invaded the adjacent inferior vena cava and embolized to the main pulmonary trunk in a three-year-old girl. Portions of necrotic tumour may lodge more distally in branches of the pulmonary arteries and paradoxical embolization may occur if there is communication between the right and left sides of the heart. Figure 8-19 illustrates cerebral infarction in an eight-year-old boy due to a paradoxical tumour embolus that had passed through a ventricular septal defect\textsuperscript{30}.
Figure 8-16: Hypertrophied bladder with bilateral hydroureteronephroses due to posterior urethral valves in a four-month-old boy. His final presentation was of fulminant metabolic acidosis with death within 12 hours attributed before autopsy to meningitis.
Figure 8-17: Extensive intraparenchymal hemorrhage into a cystic congenital Wilms tumour resulted in sudden death.
Figure 8-18: Wilms tumour extending along the renal vein into the inferior vena cava (A), with sudden death in a three-year-old girl due to a saddle tumour embolism blocking the pulmonary outflow tract (B).
Figure 8-19: Base of the brain in an eight-year-old boy who died postoperatively following an attempted resection of a large Wilms tumour. A portion of tumour that paradoxically embolized through a ventricular septal defect can be seen protruding from the left middle cerebral artery (arrow) (A). Coronal section of the brain revealing recent infarcts in the areas of the left middle cerebral and right anterior cerebral arteries due to Wilms tumour emboli (B).
HAEMOLYTIC URAEMIC SYNDROME
The haemolytic uraemic syndrome is characterized by the acute onset of a microangiopathic haemolytic anaemia, thrombocytopenia and renal insufficiency. It often follows an infectious illness such as gastrointestinal infection with vero-toxin producing *Escherichia coli* and has been linked with immunization, although this association is speculative. Children under the age of five years are at particular risk. The aetiology remains obscure, although endotoxaemia has been proposed as the initiating event.

Most patients recover, although a small percentage develop chronic renal disease or relapse. Central nervous system manifestations such as respiratory deregulation, seizures and coma may result from vascular thrombosis, systemic hypertension or metabolic derangements such as hypocalcaemia and hyponatraemia. However, despite the serious hematologic and vascular complications, sudden death is not generally found.

OVARIAN TORSION
Torsion and infarction of ovaries has been associated with sudden death in neonates and infants, sometimes associated with massive haemorrhage into cystic ovarian tissue or with intraoperative rupture. It has also been suggested that pain in the absense of rupture might precipitate reflex apnoea or bradycardia with lethal consequences.
REFERENCES

SUDDEN NATURAL DEATH IN INFANCY
& EARLY CHILDHOOD

CHAPTER 9

METABOLIC AND ENDOCRINE CONDITIONS
INTRODUCTION
A variety of inborn errors of metabolism listed in Table 9-1 may cause unexpected death in infancy. Clinical presentations include failure to thrive, hypotonia, psychomotor delay, seizures, unusual odours, vomiting or diarrhoea, and there may be a family history of an inherited metabolic disorder. Only the more 'common' conditions are dealt with in detail in the text, which also includes acquired metabolic disorders. As the diagnosis of a metabolic disorder is more likely to be known in older children than in infants the autopsy may assume particular importance in establishing the diagnosis in very early life.

TABLE 9-1: INBORN ERRORS OF METABOLISM THAT HAVE BEEN ASSOCIATED WITH SUDDEN OR UNEXPECTED DEATHS IN INFANCY AND EARLY CHILDHOOD. (Taken from references 20,36,91)

FATTY ACID OXIDATION DISORDERS
Acyl-CoA dehydrogenase deficiencies (MCAD, LCAD)
Carnitine palmitoyltransferase deficiency
Long chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
Systemic carnitine deficiency

CARBOHYDRATE DISORDERS
Fructose-1,6-diphosphatase deficiency
Galactosaemia
Glycogen storage diseases
Hereditary fructose intolerance
Mitochondrial phosphoenolpyruvate carboxykinase deficiency

AMINO ACID DISORDERS
Homocystinuria
Isovaleric acidaemia
Lysinuric protein intolerance
Maple syrup urine disease
Non-ketotic hyperglycaemia
Tyrosinaemia

UREA CYCLE DISORDERS
Argininosuccinate lyase deficiency
Argininosuccinate synthetase deficiency
Carbamylphosphate synthetase deficiency
Ornithine carbamoyltransferase deficiency
ORGANIC ACID DISORDERS

Glutaric aciduria type 2
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
Propionic acidaemia
Lactate dehydrogenase complex defects
3-Methylcrotonyl-CoA carboxylase deficiency
Methylmalonic acidaemia

MISCELLANEOUS

Biotinidase deficiency
Cytochrome oxidase deficiency
Electron transfer flavoprotein deficiency
Electron transfer flavoprotein dehydrogenase deficiency
Glycerol kinase deficiency
GM1 Gangliosidosis
Holocarboxylase synthetase deficiency
Mucopolysaccharidoses
Niemann-Pick disease type C
Phosphoenolpyruvate carboxykinase deficiency

Pathological features

The findings at autopsy are quite variable because of the disparate nature of these disorders. However, in infancy certain features should suggest an underlying metabolic defect. These are summarized in Table 9-2 and include cardiomegaly and fatty change in the liver, heart, smooth and skeletal muscle, and renal tubules (Figures 9-1 & 9-2). Unfortunately autopsy findings are often not specific. For example, cerebral oedema is found in many conditions ranging from trauma to SIDS. Additionally, fatty change within the myocardium has also been found in a wide range of disorders including infections and congenital malformations. Hypertrophic or dilated cardiomyopathies occur but are not specific to any particular metabolic disorder (Table 9-3).

TABLE 9-2: AUTOPSY FINDINGS THAT MAY INDICATE AN INBORN ERROR OF METABOLISM

| Family history of similar sudden death, particularly in siblings |
| Dysmorphic features |
| Enlargement of liver, spleen, heart |
| Pallor of liver, heart, muscles |
| Cerebral oedema |
| Fatty change in liver, heart, smooth muscle |
Figure 9-1: Mixed macro- and microvesicular steatosis of the liver indicating the possibility of an underlying metabolic disorder in an infant who died suddenly and unexpectedly (Haematoxylin & Eosin, x 440).

Figure 9-2: Oil-red O staining of a frozen section of the heart demonstrating extensive lipid deposition (x 440).
### TABLE 9-3: INBORN ERRORS OF METABOLISM ASSOCIATED WITH CARDIOMYOPATHY IN INFANTS (Modified from reference 66)

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STORAGE DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>a) Hypertrophic cardiomyopathy</td>
<td>Ethanolaminosis</td>
</tr>
<tr>
<td></td>
<td>Glycogen storage diseases (types II &amp; III)</td>
</tr>
<tr>
<td></td>
<td>Lysosomal glycogenosis without acid maltase deficiency</td>
</tr>
<tr>
<td></td>
<td>Mucopolysaccharidoses (types I &amp; VII)</td>
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<td>b) Dilated cardiomyopathy</td>
<td>Cardiac phosphorylase kinase deficiency</td>
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<td>Gangliosidoses (GM1 &amp; GM2)</td>
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<tr>
<td>c) Uncharacterized</td>
<td>Familial steatosis of heart, liver and kidneys</td>
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<td><strong>MITOCHONDRIAL DISORDERS</strong></td>
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<td>a) Hypertrophic cardiomyopathy</td>
<td>Hereditary hypertrophic cardiomyopathy with mitochondrial myopathy</td>
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<td>Respiratory chain disorders (cytochrome-c-oxidase deficiency, cytochrome-3-oxidase deficiency, cytochrome-c-reductase coenzyme deficiency)</td>
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<td>Leigh disease</td>
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<td>b) Dilated cardiomyopathy</td>
<td>X-linked cardiomyopathy</td>
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<td><strong>MISCELLANEOUS</strong></td>
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<tr>
<td>a) Dilated/Hypertrophic cardiomyopathy</td>
<td>Carnitine deficiency</td>
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<td>b) Uncharacterized</td>
<td>Amino acid disorders</td>
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<td>Organic acid disorders</td>
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**Autopsy sampling**

The specimens that need to be taken at autopsy in cases of suspected metabolic conditions are listed in Appendix II, along with appropriate sampling methods. Further details of the laboratory diagnosis of these disorders have been reviewed by Applegarth, Dimmick and Toone.5

**Frequency**

The estimated frequency of metabolic disease has been controversial, with some authors claiming that between 5 and 20% of cases of sudden death in infancy result from metabolic defects. These high figures do not appear to reflect general experience. For example, no examples of medium acyl CoA dehydrogenase (MCAD) deficiency were identified on fibroblast culture in one study of 70 cases of SIDS, and no abnormal organic acid metabolites...
were found on examination of urine, CSF and vitreous humour from 88 SIDS cases in the same report\textsuperscript{56}. Similarly, another study of 47 cases of SIDS also failed to identify any evidence of organic acidemias\textsuperscript{30}. Miller \textit{et al.} did not find any infants homozygous for the common G-985 mutation of medium chain acyl-CoA dehydrogenase (MCAD) deficiency in a retrospective examination of DNA taken from 67 SIDS infants\textsuperscript{84}. Thus it seems likely that the number of cases of sudden infant death caused by metabolic disease is closer to 1\% or less, although the possibility of underdiagnosis must be considered in centres that do not test for these conditions.

**FATTY ACID OXIDATION DISORDERS**

**ACYL-CoA DEHYDROGENASE DEFICIENCIES**

Metabolic defects involving fat oxidation have received particular attention due to the possibility of sudden and unexpected death in infancy producing an identical clinical picture to SIDS. The enzymes concerned are dehydrogenases involved in the progressive mitochondrial \(\beta\)-oxidation of long chain fatty acids mobilized from adipose tissue stores\textsuperscript{69}. Hypoglycaemia results when glycogen stores are depleted, as the deficiency of acyl-CoA dehydrogenases hinders gluconeogenesis from fat stores\textsuperscript{57}.

**MEDIUM CHAIN ACYL CoA DEHYDROGENASE (MCAD) DEFICIENCY**

The most common defect is medium chain acyl CoA dehydrogenase (MCAD) deficiency which may cause lethargy, vomiting and seizures. Findings of hepatomegaly, encephalopathy and marked hepatic steatosis may lead to confusion with Reye syndrome. Alternatively, in some infants sudden and unexpected death may be the first manifestation, thus leading to confusion with SIDS\textsuperscript{103}.

**Frequency**

MCAD deficiency is one of the most common inborn metabolic errors and has an estimated frequency of one per 20,000 newborns\textsuperscript{115}.

**Aetiology**

Inheritance of the acyl CoA dehydrogenase deficiencies is autosomal recessive and the gene for MCAD has been fully characterized on the short arm of chromosome 1\textsuperscript{80}. The most common mutation, found in nearly 85\% of patients, involves an A to G nucleotide replacement at position...
985 resulting in a substitution of glutamate for lysine at position 329 of the MCAD precursor protein.

Pathophysiology
Metabolic crises are often precipitated by viral infection or fasting, and result in hypoglycaemia and hypoketonuria, sometimes with a metabolic acidosis. This may occur after immunization and may be heralded by episodic diarrhoea and vomiting. The first episode of metabolic decompensation usually occurs in the second year of life, although it may occur much earlier. For example, a four-day-old infant who presented in a 'Reye-like' manner to the Blodgett Memorial Medical Center (Michigan, USA) was subsequently proven to have MCAD deficiency on postmortem blood and liver DNA analysis (Dr. S.D. Cohle, personal communication).

Pathological Features
The autopsy findings in the acyl CoA dehydrogenase deficiencies are variable, and although lipid accumulation within hepatocytes and cardiac myocytes is characteristic, it cannot be relied upon. For example, Carter and Variend found fatty change within the heart in only one of three cases with proven MCAD deficiency. Similarly, while diffuse hepatic steatosis has been accepted as a marker for β oxidative defects, it may not be present even in fatal cases. On the other hand, fatty change in the liver may be found in so many children dying of non-metabolic conditions that Bonnel and Beckwith describe it as 'ubiquitous', and consider that it is a nonspecific finding of little use in isolation. Thus diagnosis of the acyl-CoA dehydrogenase deficiencies depends on other investigations.

Diagnosis
Traditionally the diagnosis of acyl-CoA dehydrogenase deficiencies is made by identifying urinary dicarboxylic acids on gas chromatography-mass spectrometry or by measuring enzyme activity in cultured skin fibroblasts. However for most cases of MCAD, molecular analysis of DNA can be performed on DNA extracted from either frozen blood following polymerase chain reaction amplification, from liver extract, from paraffin embedded formalin-fixed material, or from stored Guthrie blood cards.
LONG AND SHORT CHAIN ACYL CoA DEHYDROGENASE DEFICIENCIES

Long chain acyl CoA dehydrogenase (LCAD) deficiency occurs less frequently than MCAD deficiency, but may also result in a 'SIDS-like' picture. Other manifestations include neonatal hypoglycaemia, hypotonia, cardiomyopathy and encephalopathy\(^{32,118}\) although these may not always be present\(^{33}\). Short chain acyl CoA dehydrogenase (SCAD) deficiency is extremely rare and affected infants have not been reported presenting with sudden infant death.

CARNITINE DEFICIENCY

Carnitine deficiency is a disorder of fatty acid metabolism in which there is defective fatty acid transport across mitochondrial membranes. It may be myopathic or systemic\(^{12}\).

Clinical Features

The clinical presentation of systemic carnitine deficiency may mimic Reye syndrome with an acute encephalopathy\(^{19}\) or there may be evidence of cardiac involvement with cardiomegaly\(^{58}\), heart failure and endocardial fibroelastosis. Sudden death may occur following prolonged illness\(^{72,119}\).

Pathological Features

At autopsy there may be biventricular cardiomegaly with lipid accumulation within myocytes on microscopy\(^{41}\), although on occasion the myocardium may apparently be spared\(^{63}\).

CARBOHYDRATE DISORDERS

GLYCOGEN STORAGE DISEASES

Sudden and unexpected death has been reported in both types Ic and II glycogen storage disease, with SIDS being a differential diagnosis in infancy\(^{10,56}\). Although in one series of 38 infants diagnosed as having died of SIDS, eight were reported to have glucose-6-phosphatase deficiency (type Ia glycogen storage disease) with two having transport protein T2 deficiency (type Ic glycogen storage disease)\(^{15}\), doubts have been raised as to the reliability of these results\(^{99}\).

Type II glycogen storage (Pompe) disease is an autosomal recessive disorder caused by acid maltase deficiency. The clinical expression is varied with both infantile and adolescent/adult types being recognized. In the classic infantile form (type IIa), affected infants are profoundly hypotonic with cardiomegaly and usually die within the first year of life\(^{82}\) (Figure 9-3). This
Figure 9-3: Cross-section of the heart in a five-month-old girl with Pompe disease demonstrating massive cardiomegaly.

Figure 9-4: Microscopy of the heart in Pompe disease showing extensive vacuolation of myocytes due to leaching out of glycogen during processing (Haematoxylin & Eosin, x 280).
contrasts with the more benign muscular form which is associated with longer survival. Sudden death is a known complication of type IIa\textsuperscript{10}, most likely due to metabolic or cardiac sequelae\textsuperscript{14,18}. A family has been reported in which unexpected death occurred in two siblings with acid maltase deficiency due to rupture of basilar artery aneurysms\textsuperscript{76}, although the relationship between the vascular abnormalities and the metabolic disorder is unclear.

Clinical Features

The characteristic finding in this disorder is of failure to thrive with skeletal muscle involvement, hepatomegaly and cardiomegaly, the latter being profound enough to cause outflow obstruction. Within skeletal and cardiac muscle there is an increase in membrane bound intracytoplasmic glycogen, as well as an increase in free cytoplasmic glycogen within cardiac myocytes (Figure 9-4).

Diagnosis

As increased cellular glycogen stores are not always present, biochemical testing of tissue for specific enzyme deficiencies is required for diagnosis\textsuperscript{39}.

**AMINOACID DISORDERS**

**HOMOCYSTINURIA**

Homocystinuria may be caused by any one of several enzyme defects, including cystathionine synthetase deficiency. This autosomal recessive defect results in increased levels of serum and urine homocystine\textsuperscript{17} and is characterized by a similar phenotype to Marfan syndrome. Features which separate homocystinuria from Marfan syndrome are the finding of homocystine in plasma and urine, variable mental retardation, generalized osteoporosis, malar flushing and different vascular complications\textsuperscript{106}.

**Occurrence of Sudden Death**

Myocardial infarction, cerebrovascular accident and pulmonary thromboembolism are complications of homozygous homocystinuria which may result in premature death in childhood and adolescence, but are not usual in infancy. However, up to 50\% of affected patients have died before the age of twenty years in some series\textsuperscript{46,61,106}. 
Pathophysiology

The cause of the thromboembolic phenomenon in homocystinuria is an increase in fragility of endothelial cells\textsuperscript{4} with desquamation and exposure of subendothelial connective tissue. Cerebral arteries, veins and sinuses are all at increased risk of thrombosis. Similar changes have been produced in experimental animals exposed to increased levels of homocystine\textsuperscript{49,81}. Blood coagulation abnormalities have also been reported which may contribute to the thrombotic tendency\textsuperscript{93}. As well, there is fibromuscular thickening of the intima of vessels with premature atherosclerosis and endocardial fibroelastosis of the heart\textsuperscript{40}. Premature atherosclerosis has been found in heterozygous adults, but does not appear to be a major problem in infants or children\textsuperscript{97}.

**MAPLE SYRUP URINE DISEASE**

While the usual presentation of maple syrup urine disease is with anorexia, vomiting and convulsions during the neonatal period, a late onset form is recognized. It is possible for apparently healthy infants with this condition to present with unexpected cardiorespiratory arrest\textsuperscript{47}.

**OTHER INBORN ERRORS OF METABOLISM**

**BIOTINIDASE DEFICIENCY**

Biotinidase deficiency is the major defect in children with late-onset multiple carboxylase deficiency. Features include convulsions, developmental delay, hypotonia, hearing loss, alopecia, ataxia and skin rashes\textsuperscript{125}, however, the clinical presentation may be variable. Metabolic acidosis may occur in undiagnosed cases resulting in sudden and unexpected death\textsuperscript{16}.

**GANGLIOSIDOSES**

These disorders are characterized by abnormalities in the metabolic handling of complex sugar-containing cerebrosides. While a chronic clinical course is more typical, with progressive dementia from cerebral storage, sudden death due to cardiac arrhythmia may occur in GM\textsubscript{1} gangliosidosis\textsuperscript{95}. 
Figure 9-5: Thickening of the aortic valve in a case of Hurler syndrome.

Figure 9-6: Typical axial twisting of a hair shaft with pili torti of Menkes syndrome.
MUCOPOLYSACCHARIDOSES

This heterogeneous collection of lysosomal enzyme disorders are characterized by abnormal accumulation of acid mucopolysaccharides within a variety of tissues. Six main types have been identified, the features of which have been well described elsewhere\(^2\). Hurler, Sanfilippo, Morquio, Scheie and Maratoux-Lamy syndromes are inherited on an autosomal recessive basis, whereas Hunter syndrome is inherited as a sex-linked recessive trait.

As the most severe cardiovascular abnormalities are found in Hurler syndrome, which is due to a deficiency of alpha-L-iduronidase, the following discussion will concentrate predominantly on infants and children with this variant, although similar changes may be found in the other types of mucopolysaccharidoses\(^3\).

Pathological Features

At autopsy, lesions may be found within the coronary arteries, elastic arteries, endocardium, myocardium and within the heart valves (Figure 9-5), all of which show infiltration by large vacuolated cells with surrounding fibrosis. For example, the coronary arteries, which may be prominent on gross examination, show marked diffuse luminal narrowing due to concentric thickening of the intima which contains numerous clear cells, collagen fibres and increased amounts of acid mucopolysaccharide\(^1\). The media may also be involved and some of the intramural arteries may be similarly affected. The absence of cholesterol deposits and the concentric nature of the luminal narrowing help to differentiate the arterial lesions from those seen in premature atherosclerosis\(^2\). The degree of narrowing is marked, with 71% of arteries in one study showing 76 to 100% stenosis on cross-sectional study\(^1\). Very occasional calcification occurs within coronary arteries and focal intimal changes have also been reported in both the aorta and pulmonary artery\(^6\).

Although the heart weight may not necessarily be increased in these disorders there is diffuse thickening of the endocardium resulting in a lack of compliance in the ventricular walls, particularly within the left ventricle. Microscopic examination reveals typical storage cells and collagen deposition within the ventricular myocardium\(^1\)

Valvular lesions result from the same underlying process and involve particularly the mitral valve\(^4\). All of the cardiac valves may be involved and mitral stenosis, aortic stenosis and
incompetence have all been reported. Visual inspection of the cardiac valves may reveal thickened leaflets and shortening of the chordae tendinae.

Occurrence of Sudden Death

Although recognized more for severe mental retardation, hepatosplenomegaly and skeletal abnormalities, the presence of cardiovascular disease and upper airway narrowing may predispose affected children to sudden death. For example, ten out of 87 deaths (12%) in children with Hunter-Hurler syndrome were sudden, although the pathophysiology was often not clear. The age of the children who died suddenly is not specified in the latter report, and so it is not certain whether any infants were involved.

Pathophysiology

The cause of sudden death might at first seem relatively straightforward given the degree of coronary arterial narrowing that occurs, however, affected infants and children usually do not show evidence of myocardial ischaemia. This may be partly due to somatic death occurring prior to the development of histologic changes within the myocardium, although it is felt that other factors such as valve disease, aortic narrowing, myocardial infiltration by storage cells, systemic hypertension, respiratory insufficiency and nutritional anaemia all contribute to myocardial instability with its attendant risk of sudden death. Pulmonary hypertension has also been described in these children, in one case associated with acute postoperative death.

Upper airway narrowing is another risk factor which may cause particular difficulties during intubation for general anaesthesia, and which also results in sleep apnoea. Krovetz and Schiebler describe two children out of a total of 87 who died during anaesthetic induction due to this problem.

HYPERLIPIDAEMIAS

The hyperlipidaemias can be inherited or acquired and are divided into five categories according to the Frederickson classification, each of which is biochemically and aetiologically heterogeneous. Sudden death may occur in early childhood in Types I and II. As well, ischaemic cerebrovascular strokes in infants and children have been associated with low levels of high-density lipoprotein cholesterol, sometimes occurring with high levels of triglycerides.
TYPE I

This is the rarest of the inherited hyperlipidaemias and is believed to be due to a defect in extrahepatic lipoprotein lipase or its activator, apoprotein C-II, resulting in delayed clearance of chylomicrons from the blood. While patients with this condition do not have accelerated atherosclerosis, cerebral infarction has been reported in a six-year-old\textsuperscript{9}, and in a two-month-old infant who died suddenly\textsuperscript{98}. The cause of death in the latter case was cerebral infarction due to excessive blood viscosity associated with marked chylomicronaemia. Subsequent investigation of other family members demonstrated occult lipid abnormalities compatible with lipoprotein lipase deficiency.

TYPE II

Familial hypercholesterolaemia is characterized by elevated low density lipoproteins and cholesterol due to a deficiency of low density lipoprotein receptors. It has an autosomal dominant inheritance pattern. The homozygous form is clinically the most severe with manifestations of accelerated atherosclerosis developing in childhood (not infancy) which can result in death from myocardial infarction at an early age\textsuperscript{75,109}. In some cases death may be sudden and unexpected\textsuperscript{124}.

At autopsy the ascending aorta shows more severe atherosclerosis than the abdominal aorta. This may be sufficiently florid to produce an angiographic appearance of supravalvular stenosis. Involvement of the coronary ostia\textsuperscript{2} may precipitate myocardial infarction, even in the absence of coronary artery disease although the coronary arteries usually show diffuse involvement with atherosclerotic narrowing. Involvement of the aortic and mitral valves with significant stenosis is also characteristic, along with atherosclerotic deposits in the pulmonary artery. Microscopically the atherosclerotic plaques are similar to the more usual atheromas that occur with aging.

Clues to the presence of familial hypercholesterolaemia prior to the commencement of autopsy include orange-yellow cutaneous xanthomas which may develop in early childhood or tendon xanthomas and arcus senilis which are more common in older adolescents.
TYPES III-V
Type III and Type IV hyperlipoproteinaemias are characterized by abnormal β-very low density lipoproteins and elevated very low density lipoproteins, respectively. Although both are associated with a high incidence of atherosclerosis, sudden death in infancy or childhood does not appear to be a feature of these disorders. Similarly, sudden infant death has not been found in Type V hyperlipoproteinaemia in which there is elevation of plasma very low density lipoproteins and chylomicrons.

MISCELLANEOUS
Premature atherosclerosis is a feature of Cockayne, Hutchinson-Gilford (progeria) and Werner syndromes.

MENKES KINKY HAIR SYNDROME
Menkes Kinky Hair syndrome is an X-linked recessive disorder characterized by mental and growth retardation, abnormal hair growth producing the characteristic 'pili torti' (Figure 9-6), and progressive neurological deterioration with death within one or two years. Other features include hypothermia, convulsions, aneurysms, arterial stenoses and thromboses. Sudden death may occur, however, and was present in two of six cases reported by Danks et al.

The underlying defect in this syndrome is defective copper absorption with low serum copper and caeruloplasmin levels. Vascular changes are common and superficial vessels may be aneurysmally dilated and tortuous. Microscopically there is fibromuscular intimal proliferation with fragmentation of the internal elastic lamina and decreased numbers of medial smooth muscle cells in a variety of vessels, including the coronary arteries. Veins as well as arteries are affected with arterial changes resulting in obliteration of vessel lumina.

REYE SYNDROME
Reye syndrome is a metabolic disorder of infancy and early childhood characterized by an acute onset of encephalopathy often associated with hypoglycaemia and/or hyperammonaemia, liver dysfunction and fatty change in the viscera associated with mitochondrial malfunction. The clinical presentation has been confused with a wide range of other metabolic disorders including defects in ketogenesis, amino acid metabolism and the urea cycle, as well as hereditary fructose intolerance, cystic fibrosis and systemic carnitine deficiency. It has been proposed, therefore,
Figure 9-7: Cut surface of the liver in a six year girl who died from Reye syndrome showing diffuse mottling from lipid accumulation.

Figure 9-8: Marked cerebral oedema with flattening of gyri is a nonspecific finding but may be found in cases of metabolic encephalopathy.
Figure 9-9: Section from the kidney in the previous case (Fig. 9-8) showing marked lipid accumulation within renal tubular epithelial cells (Haematoxylin & Eosin, x 110).
that the diagnosis of Reye syndrome cannot be made in a child under three years of age unless these disorders have been excluded\textsuperscript{70}.

**Clinical Features**

The clinical course of this syndrome may be fulminant, usually occurring in children under ten years of age. It often follows a viral illness, particularly influenza A and chicken pox, although occasionally sudden death may occur with relatively nonspecific symptoms and signs which were not thought to be significant at the time\textsuperscript{126}. Features of vomiting, lethargy, irritability, delirium and coma have raised the possibility of a toxic aetiology. Aspirin is the chief suspect as it is recognized that children who are on salicylate medication for other diseases have an increased risk of Reye syndrome\textsuperscript{48,83,100,110}. Additionally, the incidence of the syndrome has declined markedly with declining aspirin use.

In reviewing the clinical presentation, the diagnosis of Reye syndrome may be less likely in younger children who have had previous episodes of hypoglycaemia or acidosis precipitated by minor illness or fasting. An inherited metabolic disorder is also more probable if there has been a similar sibling death.

**Pathological Features**

At autopsy the liver may be enlarged and on cut section will show yellowish colouration (Figure 9-7). There may be quite marked cerebral oedema noted when the calvarium is removed (Figure 9-8). Microscopically the pattern of hepatic steatosis may be relatively unhelpful as a number of conditions may result in microvesicular lipid deposition. However, Reye syndrome can be differentiated on electron microscopy if tissue preservation is adequate. Unfortunately, evidence of swelling of mitochondria, with accumulation of flocculent matrix material and loss of intramitochondrial dense bodies\textsuperscript{94} may be more discernable in biopsy than autopsy material. In contrast, these features are not present in livers of children with MCAD or LCAD deficiencies\textsuperscript{117}. Lipid deposits may be found in other organs such as the heart or within the renal tubules (Figure 9-9).
Occurrence of Sudden Death

Sudden death in fulminant cases may lead to confusion with acyl CoA dehydrogenase deficiencies or with SIDS. However, a history of progressive neurological deterioration can usually be elicited.

Autopsy Investigation

Meier, Baron and Greenberg, recommended that postmortem levels of serum transaminases, creatinine kinase, blood ammonia and prothrombin time should be measured in suspected cases as they are elevated, whereas serum alkaline phosphatase, gamma glutamyl transpeptidase and bilirubin are within the normal range. Further investigative protocols for Reye syndrome and metabolic disorders with similar presentations have been outlined by Green and Hall.

MISCELLANEous DISORDERS

Mitochondrial encephalomyelopathies are a diverse group of conditions in which there are structurally abnormal mitochondria with defects in mitochondrial aerobic oxidative metabolism. While the clinical course is usually chronic with hypotonia, the association with cardiomyopathies (Table 9-3), convulsions and stroke-like episodes raises the possibility of rapid terminal decline.

Although cardiomyopathy or cardiac involvement may be present in a range of other inherited metabolic disorders (Table 9-3) such as Fabry disease (angiokeratoma corporis diffusum universale), Leigh disease (subacute necrotising encephalomyelopathy), Refsum disease (phytanic acid alpha-hydroxylase deficiency), Cori-Forbes disease (Type III glycogen storage disease, amylo-1,6-glycosidase deficiency) and primary oxalosis, the clinical courses tend to be relatively chronic, the cardiac lesions are of secondary importance, or sudden death usually does not occur in infancy or early childhood.

ENDOCRINE DISORDERS

Endocrine disorders are not usually considered in the differential diagnosis of sudden and unexpected deaths in infants as the clinical courses are often prolonged, occurring in children with well established diagnoses. Very occasionally, however, death can occur unexpectedly at the time of the first presentation, or when coincidental stresses result in a fulminant and fatal episode in a child who was felt to be clinically stable.
INSULIN DEPENDENT DIABETES MELLITUS

The occurrence of sudden death in insulin dependent diabetes mellitus is not a reported problem in infancy. Although children may die on their initial presentation with insulin dependent diabetes mellitus reports of sudden death in previously undiagnosed individuals due to ketoacidosis have occurred mainly in adults. Sudden death has, however, been occasionally reported in undiagnosed children. Unexpected death has also been described in diabetic children who were thought to be responding appropriately to treatment for ketoacidosis. The mechanisms for this are not well understood but may involve cerebral oedema from excessive rehydration, or hypokalaemia with cardiac arrhythmia. Although blood glucose levels are unreliable at autopsy, analysis of vitreous humour provides a reasonably reliable estimate of glucose levels in cases of possible hyperglycaemic ketoacidosis. Cerebrospinal fluid glucose levels may be of use if taken within several hours of death and interpreted in conjunction with vitreous humour glucose levels. Vascular complications may infrequently occur in childhood resulting in myocardial or cerebral infarction.

ADRENAL HYPOPLASIA

Hypoplasia or atrophy of the adrenal glands may result in sudden and unexpected death in infants and children due to Addisonian crisis. This may mimic SIDS.

Two types of congenital adrenal hypoplasia have been identified. In the first the adrenal gland is morphologically similar to the adult adrenal but is considerably reduced in size. This type may be associated with pituitary hypoplasia and anencephaly and may be inherited in an autosomal recessive manner. The second type shows remnants of the fetal cortex in the form of cytomegaly, is associated with a much longer survival and may be inherited in an X-linked recessive manner. There is, however, considerable variation in clinical expression and there may be a degree of histological overlap between the two types.

Addison disease in later life may be asymptomatic until exertion precipitates sudden collapse and death. Careful clinical investigation may reveal a history of weakness, lethargy and diarrhoea prior to death. An association with Duchenne muscular dystrophy has been reported in the X-linked variant.
ADRENAL HYPERPLASIA

There are a group of enzymatic defects in the cortisol synthetic pathway which result in congenital adrenal hyperplasia due to increased stimulation of the adrenal gland by elevated levels of adrenocorticotropic hormone (ACTH). These inborn errors of metabolism are autosomal recessively-inherited with the most common defect involving a deficiency in 21-hydroxylase. This results in excessive loss of sodium due to aldosterone deficiency which may lead to rapidly developing shock and death.

Clinical Features

Female infants are usually diagnosed at a younger age than males because of virilization with variable clitoral enlargement and fusion of the labioscrotal folds. Males may remain undiagnosed until a fatal episode occurs, although in retrospect there may have been a history of anorexia, failure to thrive or vomiting. Cardiac tachyarrhythmias may have been noted prior to collapse. Hypertension, a feature of 11ß-hydroxylase deficiency, may be associated with stroke at an early age.

Pathological Features

At autopsy infants and children may be dehydrated with female infants showing evidence of masculinization, sometimes with polycystic ovaries. The internal genitalia are normal in appearance. Male infants may have undescended testes and hypospadius, and boys may show signs of sexual precocity. The adrenal glands are enlarged with a nodular or diffuse cortical hyperplasia. Histologically the cortex appears homogeneous with loss of distinction between the zona fasciculata and reticularis.

NESIDIOLASTOSIS

Nesidioblastosis complex, also known as islet cell dysmaturational syndrome, refers to the range of histologic changes that may be found in the pancreas in association with hyperinsulinaemic hypoglycaemia. Histologic findings in infants with infantile hyperinsulinaemic hypoglycaemia are variable, consisting of apparently normal pancreatic morphology, hyperplasia, adenoma or nesidioblastosis. The latter entity is a proliferation of islet cells from small ducts and acini, with scattering of endocrine cells throughout the pancreatic parenchyma (Figure 9-11).
Figure 9-10: Virulization with clitoral enlargement in an infant with congenital adrenal hyperplasia.

Figure 9-11: Immunoperoxidase staining of the pancreas for insulin, demonstrating diffuse dispersion of endocrine cells throughout the pancreatic parenchyma in three-month-old boy with recurrent hypoglycaemia (x 110).
While nesidioblastosis was once claimed to be a factor in certain infant deaths ascribed to SIDS\textsuperscript{55} it is now apparent that 'disorganization' of islet cells is probably a normal phenomenon related to maturation\textsuperscript{60}. Certainly a number of infants examined by the author with otherwise typical features of SIDS, have had this finding (see Figure 1-27). It has been suggested therefore, that this finding is only of significance if hyperinsulinaemia and hypoglycaemia can be demonstrated. Nesidioblastosis has also been associated with the development of hypertrophic cardiomyopathy but this is of uncertain physiological significance in terms of the potential for sudden death\textsuperscript{52}.

THYROID DISEASE

Fatal upper airway obstruction may rarely occur in infants with congenital hypothyroidism and macroglossia. It is possible that hyperthyroidism may induce fatal arrhythmias.

CONCLUSION

Endocrine disorders may, therefore, be responsible for sudden death at all ages, associated with a variety of different mechanisms including marked electrolyte disturbance, cardiac arrhythmia, hypoglycaemia and mechanical airway obstruction.
REFERENCES


References Ch9-4


Sudden Natural Death in Infancy
& Early Childhood

Chapter 10

Miscellaneous Conditions
INTRODUCTION
This eclectic chapter summarizes a variety of unrelated conditions that have not been specifically dealt with elsewhere. For convenience these disorders have been grouped into the following categories: connective tissue, skeletal, dermatological, muscular, chromosomal and immunological. An overview of the range of anomalies which should be looked for at the time of autopsy in infants with these conditions is provided.

CONNECTIVE TISSUE DISORDERS

MARFAN SYNDROME

Overview

a) Characteristic Features
The characteristic features of Marfan syndrome that are usually manifested outside infancy include long arms and legs (dolichostenomelia), long fingers (arachnodactyly), pectus excavatum or carinatum, kyphoscoliosis, high arched palate, cutaneous striae, ectopia lentis, dilatation of the ascending aorta and dural ectasia. There is microscopic fragmentation of arterial collagen and elastin with accumulation of acid mucopolysaccharides.

b) Possible Mechanisms of Death
Possible mechanisms of death include arterial dissection, aortic aneurysm rupture and cardiac arrhythmia.

c) Other Potentially Significant Features
Associated features include mitral valve prolapse, aortic incompetence and coronary artery aneurysms.

Clinical Features
Marfan syndrome is characterized by cardiovascular, ocular and skeletal abnormalities which have quite variable degrees of clinical expression. Patients may have a history of joint hyperextensibility, recurrent joint dislocations, spontaneous pneumothoraces and ocular abnormalities such as lens dislocation and retinal detachment. Cardiac arrhythmias may be a complication of the syndrome and there may be arterial dissection or rupture.
Aetiology
While most cases of Marfan syndrome are inherited in an autosomal dominant manner, 15% of cases are sporadic. The genetic defect has been recently mapped to the fibrillin gene on the long arm of chromosome 15.\textsuperscript{27,51}

Pathological Findings
At autopsy, affected infants may be morphologically unremarkable, although older children are often readily identifiable due to their increased height and excessive thinness, associated with reduced amounts of subcutaneous fat. The arms and legs may be long due to a disproportionate increase in the length of the distal long bones and typically the arm span exceeds the height.

The major internal findings involve the cardiovascular system which may show dissection of the ascending aorta and/or ectasia of the aortic root and valve with saccular aneurysm formation. There may be aneurysmal dilatation of the sinuses of Valsalva, coronary artery aneurysms and dilatation of the mitral and tricuspid valve rings.\textsuperscript{12,13,24,80} There is an increased incidence of mitral valve prolapse due to an increase in size of the valve leaflets, an increase in length of the chordae and dilatation of the valve annulus.\textsuperscript{81,86} Occasionally subpleural pulmonary cysts give rise to spontaneous pneumothoraces.\textsuperscript{81}

Microscopically, involved vessels demonstrate cystic medial necrosis with degeneration of elastin fibres, fragmentation of collagen and accumulation of acid mucopolysaccharides\textsuperscript{101} (Figure 10-1). Affected cardiac valves also show interstitial mucopolysaccharide aggregation.\textsuperscript{16} It has been suggested that the aggregated material results from attempted repair of tissues that contain defectively cross-linked collagen following exposure to the stress of hemodynamic pressures.\textsuperscript{89} Fibrointimal and medial hyperplasia of intramural coronary arteries and of arteries supplying the sinoatrial and atrioventricular nodes have been described.\textsuperscript{49}

Occurrence of Sudden Death
Individuals with Marfan syndrome are at increased risk of death at all ages due to major arterial dissection, aneurysm rupture,\textsuperscript{23} heart failure or myocardial infarction.\textsuperscript{60} While the average age of death in one series was 32 years, a significant number of children have died within the first decade of life.\textsuperscript{60} Sudden and unexpected death in infancy may occur prior to establishment of
Figure 10-1: Typical features of cystic medial necrosis in the aorta characteristic of Marfan syndrome, with fragmentation of elastic lamina and accumulation of interstitial mucopolysaccharide (Movat pentachrome, x 280).

Figure 10-2: Massive intrathoracic haemorrhage from dissection and rupture of a patent ductus arteriosus as the presenting feature of Marfan syndrome resulted in sudden and unexpected death in a two-month-old girl.
the diagnosis\textsuperscript{16}. For example, fatal rupture of a dissecting aneurysm of a patent ductus arteriosus has been reported as the presenting feature in a two-month-old girl\textsuperscript{35} (\textit{vide infra}). Dissecting aneurysms and arterial rupture have also been reported in the aorta and pulmonary artery in children\textsuperscript{74,102}.

**STUDY #10-1**

**DEMONSTRATION OF THE ASSOCIATION BETWEEN MARFAN SYNDROME AND SUDDEN INFANT DEATH**

**CASE REPORT**

A two-month-old white girl who was the product of a normal pregnancy and delivery suddenly collapsed while waiting for a CT scan of her head for suspected hydrocephalus. Cardiac arrest occurred that was not responsive to resuscitation. Although her developmental milestones had been normal and there had been no illnesses, multiple minor congenital abnormalities had prompted investigation. Specifically, she was noted to have an abnormally shaped head, a cleft palate, arachnodactyly with bilateral metatarsus adductus, finger contractures and a patent ductus arteriosus. Marfan syndrome was suspected although other family members were morphologically normal.

At autopsy, external examination revealed a female infant with a long body (crown-heel = 67 cm, 97th percentile) and long fingers and toes. There was frontal bossing. Internally, a false aneurysm of the ductus arteriosus was found. The ductus was patent at both the aortic and pulmonary ends. The surrounding tissue was friable (Figure 10-2) and there was a massive bilateral haemothorax (50ml), haemopericardium (10ml) and haemomediastinum. The aortic arch, pulmonary trunk and heart valves were all significantly dilated. There were several intimal tears at the junction of the ductus and aorta suggesting dissection as the cause of the false aneurysm.

Microscopic examination of the aortic arch showed disruption of elastin fibres with an increased amount of surrounding mucoid ground substance. Increased mucoid ground substance with cystic change was also present within the heart valves. The unusually shaped head had resulted from premature fusion of the lambdoid suture. There was no hydrocephalus.
The cause of death was cardiac arrest due to rupture of a dissecting aneurysm of a patent ductus arteriosus with massive haemothorax and haemopericardium associated with Marfan's syndrome.

SUMMARY

A two-month-old girl with suspected Marfan syndrome, died from a ruptured dissecting aneurysm of a patent ductus arteriosus. This case represents the youngest reported patient to present with lethal Marfan syndrome.

***

Associated Features

Rarely, patent ductus arteriosus, pulmonary stenosis, tetralogy of Fallot, and atrial or ventricular septal defects have been reported in patients with Marfan syndrome\(^7\). However, it has been claimed that the presence of septal defects is coincidental\(^3\). Very occasionally supravalvular aortic stenosis may be present\(^15,36\).

EHLERS-DANLOS SYNDROME TYPE IV

Overview

Ehlers-Danlos syndrome is a heterogeneous group of at least 11 subgroups which have different clinical manifestations, biochemical defects and inheritance patterns\(^9\). While the majority of cases belong to types I, II and III, sudden and unexpected death is generally only a feature of type IV, the so-called 'arterial-ecchymotic' variant. The following discussion will deal mainly with this subtype.

a) Characteristic Features

The characteristic features of Ehlers-Danlos type IV include easy bruisability, herniae, colonic diverticula and thin facies. There is variable fragmentation of arterial elastin on microscopy.

b) Possible Mechanisms of Death

Possible mechanisms of death include arterial rupture and dissection, left ventricular, uterine, colonic or splenic rupture.
c) Other Potentially Significant Features

Associated features include a variety of possibly coincidental congenital cardiac defects, saccular arterial aneurysms and pneumothoraces.

Clinical Features

Individuals with Ehlers-Danlos type IV have thin, translucent skin, with premature aging over the hands and feet (acrogeria). In later childhood the face is characteristically thin due to a lack of subcutaneous fat. Unlike the other subtypes, skin and large joint joint hyperextensibility are not a feature of type IV. Further manifestations of Ehlers-Danlos syndrome in general are rectal prolapse in young children, multiple bruises and dermal scars\(^{44,85}\). In children the skin manifestations may be so pronounced that nonaccidental injury has been suspected on more than one occasion\(^{71,85}\). Carotid-cavernous fistulae have been documented\(^{31}\) and very rarely saccular aneurysms of the coronary arteries occur\(^{29}\).

Aetiology

Ehlers-Danlos type IV is dominantly inherited, with approximately half of the cases representing new mutations. The phenotype has been shown by linkage analysis to cosegregate with the COL3A1 locus\(^{85}\).

Pathological Findings

The most significant complications of Ehlers-Danlos syndrome are spontaneous rupture of large arteries, aortic dissection, left ventricular rupture, and splenic and intestinal rupture\(^{8,41,105}\). The most common cause of death is rupture of branches of the abdominal aorta. Rupture of the gravid uterus and pneumothorax are additional serious complications in later life\(^{48,103}\).

The microscopic findings are variable, and cannot be relied upon to establish the diagnosis as there may be no abnormal features discernable even in the presence of typical morphologic and biochemical features\(^{17}\). Some cases may show decreased or absent, fragmented and disorganized elastin fibres within large arteries\(^{21,93}\), thinning of the vessel wall and an increase in interstitial acid mucopolysaccharide\(^{29}\). Other cases have not shown marked difference from controls\(^{53,99}\). Electron microscopy may reveal reduction in collagen fibre diameter\(^{34}\) and prominent dilatation of endoplasmic reticulum, but this also is not invariable\(^{19}\).
Occurrence of Sudden Death

Although the average age of death in Ehlers-Danlos type IV is between 35 and 40 years affected individuals may die suddenly and unexpectedly in infancy from arterial rupture and dissections, as detailed below. An important point is that fatal arterial rupture may be the only morphologic feature of Ehlers-Danlos syndrome present.

STUDY #10-2

DEMONSTRATION OF THE ASSOCIATION OF TYPE IV EHLERS-DANLOS SYNDROME WITH SUDDEN INFANT DEATH

INTRODUCTION

A unique case of sudden death is described due to spontaneous subarachnoid haemorrhage in a five-month-old infant girl with previously unsuspected type IV Ehlers-Danlos syndrome (EDS).

CASE REPORT

A female infant was born at term by lower segment caesarean section to a 25-year-old primigravida mother. The pregnancy had been uncomplicated until breech presentation necessitated surgical intervention. The infant was quite healthy with normal developmental milestones. She remained well until the day before death at the age of five months, when she was noted to be transiently febrile and anorexic. This was attributed to teething. On the day of death, she was put to bed by a baby sitter, who subsequently found her unresponsive. Resuscitation was attempted unsuccessfully by the baby sitter and at the local hospital.

Family History

Both parents, who were originally from South America, were 25 years of age and were quite healthy. There was no parental consanguinity. The paternal grandparents were in good health, as were three paternal uncles, two aunts, and five cousins. An uncle had died at two days of age of uncertain causes. The maternal grandfather had died at age 54 years of a myocardial infarct; the maternal grandmother and four uncles were all alive and well. Specifically, there was no history of joint laxity, skin hyperextensibility, friable tissues, scarring, bruising, or spontaneous haemorrhages.
Autopsy Findings

Postmortem examination revealed an externally normal female infant weighing 6.6kg. On reflection of the scalp, three bruises ranging in size from 1 to 2 cm in maximum diameter were present. There also was diffuse subarachnoid haemorrhage over the frontal, parietal, and occipital lobes (Figure 10-3) with small intraventricular haemorrhages in the anterior horn of the left lateral ventricle and in the fourth ventricle. The remainder of the gross examination was unremarkable. Specifically, there were no arterial aneurysms or arteriovenous malformations present. Features of Menkes' syndrome, which also may present with arterial rupture in childhood, were absent. There were no skin petechiae or adrenal haemorrhages, and microbiological cultures were negative for meningococcus. Despite careful dissection, the precise origin of the haemorrhage could not be localized.

Microscopic examination demonstrated the subarachnoid haemorrhages, as well as focal periarterial haemorrhages in both kidneys, within the submucosa and lamina propria of the small intestine, and within the lung parenchyma. The other organs were normal. No specific abnormalities of connective tissue, such as variable amounts of elastin or increased ground substance, were noted.

Biochemical Analysis

Pepsin-solubilized collagen was prepared from the patient's skin and aortic tissue according to methods described previously\(^4\). The ratios of alpha 1-to-alpha 2 chains of type I collagen and of type III-to-type I collagen (alpha 1 chains) were determined by polyacrylamide gel electrophoresis\(^1\). Analysis of the skin demonstrated that there was <5% Type III collagen present, compared to the expected amount of approximately 15-20%. In addition, there was a reversal in the usual 2:1 ratio of alpha 1:alpha 2 chains of type I collagen, with a predominance of alpha 2 chains. Analysis of the aortic tissue also showed a low level of type III collagen, which constituted approximately 4% of the total, rather than the expected value of 20-30%. Again there was a low alpha 1:alpha 2 ratio in type I collagen. Two sets of controls also were analyzed, the first set consisting of aortic and skin tissue from an age-matched control patient with no evidence of connective tissue disease (P), and the second consisting of standard preparations of type I collagen from rat tail tendon and type III collagen from neonatal sheep skin.
Densitometric scans of the gel separations from the patient and controls are shown in Figure 10-4. Table 10-1 shows the percentage composition of the collagen subtypes. Fibroblast cultures were not performed.

**TABLE 10-1: COMPOSITION OF COLLAGEN SUBTYPES IN THE PATIENT, CONTROL PATIENT (P) AND STANDARD CONTROLS (S)**

<table>
<thead>
<tr>
<th>Sample</th>
<th>% Type III Collagen</th>
<th>Ratio $a_1/a_2$ Type I Collagen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient aorta</td>
<td>&lt;5</td>
<td>0.48</td>
</tr>
<tr>
<td>2. Patient skin</td>
<td>&lt;5</td>
<td>0.53</td>
</tr>
<tr>
<td>3. Control (patient) (P) aorta</td>
<td>22</td>
<td>1.62</td>
</tr>
<tr>
<td>4. Control (patient) (P) skin</td>
<td>21</td>
<td>1.65</td>
</tr>
<tr>
<td>5. Control (standard) (S) type I</td>
<td>0</td>
<td>1.50</td>
</tr>
<tr>
<td>6. Control (standard) (S) types I</td>
<td>23</td>
<td>1.68</td>
</tr>
</tbody>
</table>

**Cause of Death**

Death was attributed to massive subarachnoid haemorrhage with associated minor renal, gut wall, and intrapulmonary haemorrhages in an infant with type IV Ehlers-Danlos Syndrome.

**Further Family Analysis**

The parents were reluctant to submit to further investigation; however, later examination of a maternal skin biopsy showed a normal ratio of type III:type I collagen. A second child born one year later was alive and well at a year of age with no stigmata of Ehlers-Danlos syndrome.

**DISCUSSION**

The reported patient is of interest because of the fatal outcome at an unusually early age associated with the lack of an antemortem diagnosis. In the literature, complications in females tend to occur at an older age, usually in young adult life after the diagnosis has been established4. In retrospect, there had been no features of Ehlers-Danlos syndrome noted, presumably because the relative immobility of the 5-month-old infant had protected her from much of the trauma that would have led to bruising.
Figure 10-3: Marked subarachnoid haemorrhage present diffusely over most of the brain surface in a case of fatal Ehlers-Danlos syndrome in a five-month-old girl.
Figure 10-4: Densitometric scans of gel separations of pepsin-solubilized collagen from skin and aortic tissue taken from the patient (1 and 2), an age-matched control P (3 and 4), and standard controls S (5 and 6).
Confirmation of the diagnosis was made by the demonstration of negligible (<5%) amounts of Type III collagen in the skin and aortic tissue. The reversal of the alpha chain ratio in type I collagen that was found in this case is an unusual feature in type IV Ehlers-Danlos syndrome. Whether this influenced the clinical presentation is difficult to ascertain, however. Although no specific light microscope abnormalities of connective tissue were noted, this may have been due to variable expressivity because a wide spectrum of histologic features have been reported. Finally, the unremarkable family history and normal levels of Type III collagen in a maternal skin sample suggest either an autosomal recessive mode of inheritance or a spontaneous mutation.

While there is no doubt that death was caused by intracranial haemorrhage, the exact site of vascular rupture remains uncertain, although arteriovenous malformation and aneurysm were excluded after meticulous gross and microscopic examination. This is not at all unusual in children, however, as up to 20-30% of cases of subarachnoid haemorrhage do not have the precise source of bleeding identified. The concurrent presence of multifocal interstitial haemorrhages in the lungs, small intestine, and kidneys is consistent with a generalized weakness in blood vessel walls due to the demonstrated lack of Type III collagen, as spontaneous haemorrhaging from blood vessels of varying sizes is a well-recognized complication of type IV Ehlers-Danlos syndrome.

Although the possibility of resuscitation-induced injury was considered, tissues most likely to have been traumatized during the procedure (anterior chest wall, heart and liver) showed no evidence of haemorrhage, so this was not thought to be a significant contributor to the pathological changes present. Most probably, intracranial haemorrhage was the primary event, followed by widespread interstitial haemorrhage from hypoxically damaged structurally defective vessels.

**SUMMARY**

A previously healthy five-month-old female infant presented with sudden death due to spontaneous subarachnoid haemorrhage associated with minor multifocal visceral haemorrhages. The clinical diagnosis had been of SIDS. Although the family history was noncontributory and other features of type IV Ehlers-Danlos syndrome were absent, the pattern of haemorrhage was
consistent with this type of connective tissue disorder. The diagnosis was confirmed after postmortem analysis of skin and aorta showed <5% type III collagen (normal: >15%). Extensive literature review failed to find any other reported cases of sudden death in infancy due to intracranial haemorrhage in patients with previously unsuspected type IV Ehlers-Danlos syndrome. Collagen analysis should be performed in cases of unexplained multifocal spontaneous haemorrhage in infancy so that this rare diagnosis will not be missed. This case represents the youngest reported patient to present with lethal Ehlers-Danlos syndrome type IV.

** Diagnosis

Arterial and visceral rupture are caused by reduced amounts of type III collagen\(^1\),\(^7\). Standard diagnosis depends on analysis of connective tissue for type III collagen, as above, and on demonstration of decreased production of type III procollagen by cultured fibroblasts\(^8\).

** Autopsy Investigation

Localized haemorrhage in patients at autopsy, particularly if it is multifocal with no obvious reason for a bleeding diathesis, should prompt consideration of underlying occult Ehlers-Danlos syndrome type IV\(^7\). Even in the absence of external morphologic evidence of Ehlers-Danlos syndrome\(^7\) fresh and frozen skin and aorta should be taken from all cases of unexplained spontaneous haemorrhage so that collagen studies can be performed if indicated. Blood or tissue for linkage analysis should also be taken.

** Associated Features

Mitral valve prolapse occurs in children with type IV Ehlers-Danlos syndrome\(^4\). Congenital cardiovascular anomalies which have been reported in the other subtypes such as bicuspid aortic valve and tetralogy of Fallot\(^4,5,56,57,107\) may be coincidental\(^5\).
PSEUDOXANTHOMA ELASTICUM

Overview

a) Characteristic Features

The characteristic features of pseudoxanthoma elasticum include yellow-orange papular skin lesions with calcification of skin and peripheral arteries.

b) Possible Mechanisms of Death

Possible mechanisms of death involve myocardial ischaemia and spontaneous gastrointestinal haemorrhage.

c) Other Potentially Significant Features

Associated features include systemic hypertension and mitral valve prolapse

Clinical Features

Skin and ocular changes include drooping skin folds, linear or aggregated yellow cutaneous papules, and angioid streaks of the retina. Vascular manifestations are quite variable and result from ischaemia due to vessel narrowing\(^9,11\) which may cause spontaneous haemorrhage, particularly from the gastrointestinal tract.

Aetiology

The underlying problem is believed to be an enzyme defect which results in calcification of elastic fibres within the walls of muscular arteries\(^5\). Similar changes may also be present within the endocardium\(^64\). The inheritance pattern is varied with both autosomal recessive (90% of cases) and dominant forms reported\(^76,106\).

Pathological Features

At autopsy, 'cobblestone' skin lesions, acute myocardial infarction, myocardial scarring, calcified endocardial plaques and gastrointestinal or intracranial haemorrhage may be found.

Elastic fibres in the retina, skin and vasculature are fragmented, disorganized and calcified\(^24\) although cutaneous lesions may not always be visible\(^55\). Affected arteries show calcification of the intima and media\(^69\). Rarely cardiac conduction tracts may be surrounded by fibrous scar tissue resulting in sudden unexpected death in adult life\(^46\).
Occurrence of Sudden Death

Sudden death is rare, but may occur in adolescence in association with strenuous exercise\textsuperscript{108}. Acute myocardial infarction has been reported in a six-week-old infant with arterial calcification and a maternal history of pseudoxanthoma elasticum\textsuperscript{39}, and significant vascular disease in other children has also been documented\textsuperscript{80}. Affected patients may also have systemic hypertension, gastrointestinal bleeding and mitral valve prolapse\textsuperscript{1,61} which may lead to sudden death. Restrictive cardiomyopathy with pulmonary oedema was reported in one young adult due to calcified endocardial bands\textsuperscript{20}. Rarely in adults there may be symptoms and signs from cerebral ischaemia or haemorrhage from vessel rupture\textsuperscript{47}.

SKELETAL DISORDERS

ACHONDROPLASIA

Overview

a) Characteristic Features

The characteristic features of achondroplasia include rhizomelic dwarfism, enlargement of the head, trident-shaped hands, an exaggerated lumbar lordosis and thoracic kyphosis. There is microscopic disorganisation of the growth plate with loss of the normal orderly columns of chondrocytes and irregular metaphyseal ossification.

b) Possible Mechanisms of Death

Possible mechanisms of death involve brainstem and upper spinal cord compression.

c) Other Potentially Significant Features

Associated features include thoracic cage abnormalities and upper airway obstruction.

Clinical Features

Affected infants are characterized by shortening of the proximal limbs (rhizomelic dwarfism) with enlargement of the head and a relatively normal thoracic cage. The cranial vault has a characteristic shape due to compensatory overgrowth of the membranous calvarial bones, with prominent frontal bones, maxillary hypoplasia and mandibular prognathism. The foramen magnum and spinal canal are reduced in size due to failure of growth of the cartilagenous bones at the base of the skull, and there is hydrocephalus possibly due to obstruction of venous return at the jugular foramina\textsuperscript{76}. Radiological features have been described in detail elsewhere\textsuperscript{54}.
Aetiology
The genetic defect in this dominantly inherited condition has not been identified.

Occurrence of Sudden Death
Achondroplastic infants are at increased risk of sudden death due to lower brainstem and upper spinal cord compression\(^{45,72}\). For example, a study of 13 achondroplastic infants who manifested significant apnoeic episodes and sudden death demonstrated compression of the brainstem and upper cervical cord within the narrowed foramen magnum and spinal canal\(^{73}\) (Figure 10-5). Other authors have also reported sudden death in apparently well achondroplastic infants\(^{10,62}\), possibly associated with this type of compression of respiratory control centres\(^{32,70,110}\). An exacerbating factor in these children may be arterial hypoxia caused by thoracic cage abnormalities and sleep-related upper airway obstruction\(^{86}\).

It is difficult to estimate the exact increase in risk of sudden death of these infants however, the risk of dying suddenly in the first year of life was 7.5% in the study by Hecht et al.\(^{42}\). These investigators also found that nine of the 13 children dying before five years of age died suddenly, and that compression of the brainstem was found in three of the four children who had autopsies. It is, therefore, important to examine the cervical cord and brainstem in detail in these cases.

CRANIOSYNOSTOTIC SYNDROMES
Overview
Premature fusion of cranial sutures, craniosynostosis, occurs in a number of inherited conditions and has been associated with sudden death\(^{82}\). Possible mechanisms of death are uncertain but may involve upper airway obstruction due to hypoplasia of the facial skeleton and prolonged central apnoeas during sleep\(^{38}\). Associated features include cerebral compression and possibly coincidental congenital cardiac defects.
DERMATOLOGICAL DISORDERS

HYPOHIDROTIC ECTODERMAL DYSPLASIA

Overview

a) Characteristic Features
The characteristic features of hypohidrotic ectodermal dysplasia include decreased sweating, anomalies of dentition, sparse hair and characteristic facies with frontal bossing and malar hypoplasia.

b) Possible Mechanisms of Death
Death is caused by uncontrolled hyperthermia.

Clinical Features
This unusual condition is characterized by hypohidrosis, hypodontia and hypotrichosis. Affected infants show frontal bossing, low set ears, malar hypoplasia and flattened nasal bridges. One of the major clinical problems related to the absence or hypoplasia of eccrine glands is a reduced capacity to tolerate heat.

Aetiology
Hypohidrotic ectodermal dysplasia is inherited in an X-linked manner.

Occurrence of Sudden Death
Although not usually life-threatening, affected infants must be protected from high temperatures, as uncontrolled hyperthermia may result in sudden unexpected death.

EPIDERMOLYSIS BULLOSA
Airway obstruction due to involvement of the upper airway in this condition is described in Chapter 5.

MUSCULAR DISORDERS

MALIGNANT HYPERTHERMIA

Clinical Features
This rare condition is characterized by a marked increase in muscle metabolism triggered by anaesthesia. Classically this results in tachycardia, hyperthermia and acidosis.
Figure 10-5: MRI scan in an achondroplastic boy demonstrating reduction in the size of the foramen magnum with narrowing of the upper cervical spinal cord (arrow).

Figure 10-6: Marked oedema of the upper airway may be the only finding in fatal cases of anaphylaxis (Haematoxylin & Eosin, x 45).
Aetiology

It is proposed that the gene for this autosomal dominant condition is localized to the ryanodine receptor locus on chromosome 19\textsuperscript{59,63}.

Occurrence of Sudden Death

A number of cases have now been reported with atypical presentations which include sudden and unexpected death in the absence of anesthetic exposure\textsuperscript{109}. This has occurred in families who were not known to have this disorder\textsuperscript{83} and has mimicked the clinical presentation of SIDS\textsuperscript{26}.

Pathological Features

Autopsy findings are uninformative and further information may need to be derived from halothane- or caffeine-induced contraction tests performed on skeletal muscle biopsy material from other family members.

**CHROMOSOMAL ABNORMALITIES**

**THE TRISOMIC SYNDROMES**

Overview

Infants with any one of the three common trisomies, 21, 18 and 13, may have congenital cardiac defects which may be lead to early death. It is reasonably clear, however, that death in trisomies 18 and 13 is usually not particularly sudden, and is certainly not unexpected, as it is assumed that most infants will succumb within the first few months of life. Infants with Down syndrome are different in that they usually survive into later childhood and adolescence. In Down syndrome 'unexpected' death may result from a number of different causes.

Occurrence of Sudden Death

Sudden death in Down syndrome infants can occur from a variety of mechanisms including those associated with congenital cardiac defects. Structural cardiac defects are found in 40 to 60\% of cases and consist predominantly of endocardial cushion defects resulting in hypoxia and cardiomegaly from left to right shunting\textsuperscript{104}. A full listing of the types of congenital cardiac defects that may be found in infants with chromosomal abnormalities may be found in a review by Ferrans and Boyce\textsuperscript{29}. 
Pulmonary hypertension may be an added problem in these infants, related to cardiac shunting that occurs through endocardial cushion defects, and also to sleep apnoea. Systemic hypertension due to diffuse fibrointimal hyperplasia has also been reported in Down syndrome.

Down syndrome infants are at risk of haemorrhagic complications due to an increased incidence of leukaemia, and of hyperviscosity problems because of neonatal polycythaemia. Death may also occur because of spinal cord compression from atlanto-occipital instability.

FRAGILE X SYNDROME

Clinical Features
Fragile X syndrome represents the most common heritable type of mental retardation as well as being one of the most frequently encountered genetic syndromes. It is characterized by variable mental retardation and a typical morphology which includes prominent jaw and forehead, dysmorphic ears, macro-orchidism, hyperextensible joints and other connective tissue abnormalities such as kyphoscoliosis and pectus excavatum. The fragile site on the X chromosome is in band q27.3 which disrupts the FMR1 gene. The clinical and genetic features have been recently summarized by Sutherland and Richards. Occurrence of Sudden Death
Six out of a total of 68 liveborn children (9%) died suddenly after one year of age in a study of eight families who had retarded members with fragile X syndrome. In a follow-up study of the progeny of 86 normal obligate carriers, the mortality rate before the age of 18 months in males was 17/219 (8%), and in females was 6/169 (4%). Unfortunately, meaningful pathological interpretation of this data is not possible because of the absence of autopsy information in all but one case.

These cases do not, therefore, fulfil the criteria for the diagnosis of SIDS, given the age, lack of autopsy investigation, possibility of hypothalamic-pituitary abnormalities and occurrence of transiently raised intracerebral pressure in affected children. They do, however, indicate a significantly increased risk of sudden death in infants with this syndrome.
TURNER SYNDROME

Clinical Features
Turner syndrome has a characteristic phenotype of short stature, webbing of the neck, broad chest, and delayed sexual maturation.

Aetiology
A 45X0 chromosome complement has been found in 50 to 60% of individuals with the Turner phenotype.

Occurrence of Sudden Death
As well as the above features, infants with Turner syndrome have a variety of cardiovascular anomalies that may result in sudden and unexpected death. These include aortic coarctation, bicuspid aortic valve, aortic stenosis and anomalous pulmonary venous drainage. Rarely rupture of a dissecting aortic aneurysm may occur.

IMMUNOLOGICAL CONDITIONS

IMMUNOLOGICAL DEFICIENCY
Although immunological under-reactivity has been proposed as a cause of SIDS, research has not supported this contention. Infants with immunological deficiencies are, however, at increased risk of developing overwhelming sepsis which may result in rapid death (see Chapter 4). Often, but not invariably, the diagnosis has been established prior to death. As a number of these conditions have a heritable basis the autopsy may assume a vital role in directing family counselling.

ANAPHYLAXIS
Anaphylaxis refers to a serious, potentially-fatal reaction that is most often due to IgE mediated sensitivity to a foreign substance. It is less common in children than in adults and is usually associated with drugs such as penicillin or bee or wasp stings. In the latter cases death may also result from asphyxia if there has been a sting involving the upper airways. Occasionally angioneurotic oedema may also cause critical epiglottal swelling.

Fatal anaphylactic reactions to food in infants are poorly characterized in the literature, however, these are well recognized entities most often involving the ingestion of nuts, eggs or milk. Very rarely fatal anaphylaxis may follow rupture of an echinococcal cyst.
Pathological Features

Autopsy findings are relatively nonspecific and unhelpful, although occasional cases have demonstrated glottal oedema (Figure 10-6) or high levels of allergen-specific IgE in postmortem sera. Diagnosis relies on a history of exposure to a particular agent followed by dyspnoea and collapse. The autopsy may exclude other causes of death.

MYASTHENIA GRAVIS

Myasthenia gravis is a disorder of the neuromuscular junction caused by an autoantibody to acetylcholine receptors. Although uncommon in infancy and childhood, sudden and unexpected death has been reported in young children following respiratory arrest, with minimal clinical evidence of the disorder preceding the terminal lethal event. In older children life-threatening myasthenic crises may follow infections. Some of these cases have a familial distribution.
REFERENCES


References Ch10-2:


References Ch10-3


References Ch10-4


References Ch10-5


SUDDEN NATURAL DEATH IN INFANCY
& EARLY CHILDHOOD

CHAPTER 11

APPENDIX
APPENDIX I: AUTOPSIES INVOLVING POSSIBLE SEPSIS

1) SPECIMENS THAT MAY BE TAKEN

a) Blood: venous and arterial
b) Cerebrospinal fluid
c) Trachea swab/tissue
d) Lung swab/tissue
e) Liver swab/tissue
f) Spleen swab/tissue
g) Any other obviously infected/necrotic tissue
h) Indwelling catheters/devices

(Specimens taken for viral, bacterial and fungal cultures)

2) # TABLE: AUTOPSY SAMPLING PROTOCOL FOR SUSPECTED FUNGAL SEPSIS

? DISSEMINATED FUNGAL DISEASE

CENTRE

MIDDLE

EDGE

LESION SAMPLE

FLUID SAMPLE

BLOOD SAMPLE

FORMALIN

FROZEN

FRESH

FUNGUS CULTURE

VENOUS

ARTERIAL

STAINING

SPARE TISSUE

WET MOUNT
APPENDIX II: AUTOPSIES INVOLVING POSSIBLE METABOLIC DISORDERS

Biochemical studies will be directed by histologic and electron microscopic examinations, however, initially it is appropriate to collect as wide a range of tissues as possible. Many may not be needed, but those that are required must be retrievable in a form that can be used 2.

A) SPECIMENS TO BE TAKEN

a) Urine
b) Blood (10 mls)
   i) with EDTA
   ii) with heparin
   iii) clotted
c) Vitreous humour
d) Skin or pericardium
e) Other tissues - brain, heart, kidney, liver, skeletal muscle, adrenal gland

B) MINIMUM REQUIREMENTS

urine, blood, skin and liver

C) TIME INTERVAL

Although skin fibroblasts may still grow in tissue culture from specimens taken several days after death, accurate tissue enzyme analysis requires specimens to be taken as soon after death as is practicable i.e. within several hours of death. However, both MCAD and LCAD enzymes within liver tissue have been found to be stable for up to 100 hours if the body is refrigerated, and for at least five years if tissues are maintained at -70°1.

D) METHOD OF TAKING AND STORING SPECIMENS

a) Urine:

Withdrawn from the bladder by syringe after the abdominal cavity has been opened.

If no urine can be obtained in this manner, the bladder can be opened, the renal pelvis can be
aspirated or urine may be squeezed from the diaper, if this is otherwise clean. Storage is at -80°C in 1ml aliquots for amino and organic acid analysis.

b) Blood:

Blood with EDTA stored as whole blood. Heparinised blood promptly centrifuged to enable separate storage of packed cells and plasma in 1ml aliquots. Stored at -80°C if possible, or at -20°C if not.

c) Vitreous humour:

Withdrawn from the eye by syringe and sent for electrolyte and glucose analysis.

d) Skin or pericardium:

Skin cleaned with alcohol and a 3.0 x 3.0 mm piece placed in sterile tissue transport media for fibroblast culture. Storage is possible at -70°C if culture facilities are not immediately available.

e) Other Tissues:

i) 1mm cubes placed in 4% glutaraldehyde for electron microscopy.

ii) 10 x 1cm² blocks snap frozen in liquid nitrogen and stored at -80°C for biochemical assay/DNA analysis.

iii) 1mm cubes snap frozen in liquid nitrogen and stored at -80°C for enzyme histochemistry.

iv) 1cm blocks of heart, liver, brain, muscle, adrenal gland and kidney snap frozen in liquid nitrogen and stored at -80°C for fat staining with Oil Red O.

v) 5gms of spleen fresh or stored at -80°C for DNA analysis.

REFERENCES


APPENDIX III: AUTOPSIES INVOLVING POSSIBLE NON-ACCIDENTAL INJURY

SPECIFIC REQUIREMENTS

a) Complete body X-ray
b) Examination of mouth, eyes, palms, soles, genitalia, anus
c) Photography of all suspicious lesions
d) Shaving of hair and examination of underlying skin
e) Semen and microbiological swabs
f) Incision of livid areas
g) Representative sampling of wounds/bruises/fractures for histology
h) Excision of some wounds in toto
i) X-ray of excised rib cage in infants and children
j) Removal of eyes in infants and young children
k) Toxicology

APPENDIX IV): AUTOPSIES INVOLVING POSSIBLE POISONING

SPECIMENS TO BE TAKEN

Blood: cardiac & peripheral  Kidney
Gastric contents  Skeletal muscle
Urine  Brain
Vitreous humour  Liver
Gall bladder contents  Hair & nails

APPENDIX V: AUTOPSY INFORMATION PAMPHLET

Many of the deaths due to disorders in this thesis will be the subject of a medicolegal enquiry due to their sudden and unexpected nature and so parental permission may not be required for the performance of an autopsy. However, where permission is required, the following information pamphlet, which was written by the author and is currently in use at the Adelaide
Children's Hospital, may be of use in explaining the process and purpose of an autopsy to parents and guardians.

THE AUTOPSY - AN EXPLANATION

The Hospital staff would like to extend their deepest sympathy to you and your family. The death of a child is one of the most terrible tragedies that can affect a family, and it is often hard to make decisions during this time of grief. A request for an autopsy examination may, therefore, seem intrusive and unnecessary.

Because of this, we have prepared this pamphlet to provide you with information about the autopsy and why doctors feel that it is so important. We hope it will provide answers to some of your questions and help you to make your decision.

Be assured that, with the exception of unexpected deaths from the sudden infant death syndrome and those involving car accidents and drownings etc, which come under the jurisdiction of the State Coroner, the right to decide what is to happen is entirely yours. The staff will always be guided by this and will be supportive of your decision.

WHAT IS AN AUTOPSY?

An autopsy is a systematic examination of the body of a person who has died, performed by a doctor who is a specialist in pathology in consultation with the doctors who were looking after the person during life. It begins with a full external examination followed by an examination of individual organs inside the body. The techniques are similar to those found in the operating theatre, except that every part of the body is examined. A number of special investigations are also performed which include looking for infections, as well as looking at tissue under a microscope for the presence or absence of particular diseases.

Once the examination is completed, the pathologist prepares a detailed report of the findings, and a summary of the person's medical history. A copy of this is then sent to their hospital doctor and, if requested, to their local doctor.
WHY IS IT NEEDED?

Sometimes parents feel that there was something extra that they could have done to prevent their child's death. This is a normal reaction to the loss of a person you love. In our experience, autopsies may help to alleviate these feelings of guilt by clearly showing the seriousness of the disease and the inability of anyone to prevent the final outcome.

Some people also feel that once a child has died an autopsy can be of little or no help, but this is not true. Doctors are continually learning, not only about rare diseases, but also about more common ones as well. An autopsy enables a full scientific study of all of the different features of a particular illness which then helps doctors to understand better the reasons for the outcome.

Greater understanding may then help children who present with the same or a similar illness in the future. As well, performing an autopsy may be the only way that the cause of a particularly puzzling symptom can be explained. Sometimes even the exact cause of death may not be obvious until after the autopsy.

New treatments and investigations are continually being developed and used in hospitals and a complete autopsy examination may be the only way to fully assess the accuracy of new diagnostic procedures and the response of particular illnesses to new medicines or surgical techniques. By allowing an autopsy to be performed, the family enables direct feedback of this information to doctors, resulting in greater understanding of new technologies, procedures and treatments. It is only by completely understanding new developments that progress in medicine can be made.

Other advantages of an autopsy include detection of abnormalities that were not obvious during life, as these may have relevance to other family members.

WHAT IS A 'LIMITED AUTOPSY'?

Sometimes a family may not want a complete autopsy performed. In this case, although it is less satisfactory, it may be sufficient for the pathologist to examine only one area of the body. For example, a limited autopsy may be restricted to the organs inside the chest in a patient who has heart or lung disease, or to the head in a patient who has a brain tumour. This is an option that you can discuss further with your doctor if you wish.
WILL AN AUTOPSY BE DISFIGURING?

With modern autopsies there is almost no difference in the appearance of the body at the funeral, and a normal viewing can be held. Although incisions are made, they are placed so that they will not be seen. They are also very carefully closed after the procedure just as in operations. At all times the body is treated with the utmost respect.

WILL TISSUES BE REMOVED?

Often some tissues require very special examinations. This will depend on the disorder causing death and can be discussed with your doctors.

WILL AN AUTOPSY INTERFERE WITH FUNERAL ARRANGEMENTS?

Autopsies are usually completed within a day of death and so there should be no delay in making funeral preparations. Funeral directors are accustomed to working with pathologists, and can arrange any service that the family may request. Embalming is still possible after an autopsy.

WILL AN AUTOPSY BE AGAINST RELIGIOUS BELIEFS?

Families are sometimes concerned that an autopsy may be against their religious beliefs. Autopsies have been performed on people from a wide range of religions, but if you are concerned it may be best to discuss the matter with someone from your church before deciding. Hospital staff will be pleased to help you to contact the appropriate person.

We hope that this information has been of use to you in helping to show the value of the autopsy examination. If you have any further questions your doctor or the pathologist will be most willing to answer them for you.

The following explanatory note to hospital staff accompanies the autopsy pamphlet:

'It is hoped that the attached pamphlet may be of assistance to you in discussing the possibility of an autopsy examination with parents. The pamphlet is intended to supplement discussions with the parents by providing information that they can take some time to read over. It is not intended in any way to interfere with, or replace, discussions between staff and parents, as these are an essential part of obtaining permission for an autopsy'.
APPENDIX VII: PUBLICATIONS

Much of the material presented in this thesis has been previously published in peer reviewed journals, is 'in press', or has been submitted for publication. Papers incorporated into the text are listed below to acknowledge the co-authors contributions. The author of this thesis has played a major role in the production of the book (12 out of 14 chapters), and in the papers and proceedings cited, and has therefore been either first or senior/corresponding author in all of the material listed.

TEXTBOOK


PAPERS/PROCEEDINGS


