THE ROLE OF SURGERY AND DISEASE LOAD IN REFRACTORY CHRONIC RHINOSINUSITIS

Thesis Submitted for the title of Doctor of Philosophy

June 2015

Ahmed M. A. Bassiouni

MBBCh

Department of Surgery – Otolaryngology, Head & Neck Surgery, University of Adelaide
Contents

Declaration .................................................................................................................................................. 8
Dedication ................................................................................................................................................... 9
Acknowledgements .................................................................................................................................. 10
Thesis Abstract ....................................................................................................................................... 12
Publications arising from this thesis ...................................................................................................... 14

Chapter 1  Chronic Rhinosinusitis ........................................................................................................ 15
  1.1 Overview of the chapter .................................................................................................................. 15
  1.2 CRS: Definition and Diagnosis ...................................................................................................... 15
  1.3 Epidemiology ................................................................................................................................... 17
    1.3.1 Prevalence/incidence ................................................................................................................ 17
    1.3.2 Impact on economy and public health ...................................................................................... 17
  1.4 Clinical picture ................................................................................................................................ 17
    1.4.1 Symptoms .................................................................................................................................. 17
    1.4.2 Examination (Anterior rhinoscopy +/- Nasal endoscopy) .......................................................... 18
    1.4.3 Computed Tomography (CT) ................................................................................................... 19
  1.5 Classifications .................................................................................................................................. 20
    1.5.1 CRSsNP and CRSwNP: a clinical classification ....................................................................... 20
    1.5.2 Histopathologic classification ................................................................................................... 21
    1.5.3 Allergic fungal sinusitis ............................................................................................................ 22
    1.5.4 Other syndromes causing CRS (“Other CRS”) ....................................................................... 22
    1.5.5 CRS endotyping ....................................................................................................................... 24
    1.5.6 Conclusion ................................................................................................................................ 25
  1.6 CRS Etiology .................................................................................................................................... 25
    1.6.1 First: Host factors ..................................................................................................................... 25
    1.6.2 Second: Environmental factors ................................................................................................. 28
  1.7 CRS Histopathological findings ...................................................................................................... 30
    1.7.1 Inflammatory cell infiltrate ....................................................................................................... 31
    1.7.2 Mucosal edema .......................................................................................................................... 31
    1.7.3 Epithelial injury and shedding ................................................................................................. 31
1.7.4 Goblet cell hyperplasia (Goblet cell metaplasia) ........................................... 32
1.7.5 Fibrosis/Mucosal Remodeling ........................................................................ 32
1.7.6 Osteitis/Bone remodeling ................................................................................ 33
1.7.7 Mucus ........................................................................................................... 33
1.8 CRS Pathophysiology .......................................................................................... 33
  1.8.1 Inadequate resolution of acute sinusitis ......................................................... 34
  1.8.2 Osteomeatal complex obstruction ................................................................. 34
  1.8.3 Fungal hypothesis ......................................................................................... 35
  1.8.4 Superantigen theory ..................................................................................... 36
  1.8.5 Biofilm theory ............................................................................................. 36
  1.8.6 Eicosanoid metabolism disturbance ............................................................. 37
  1.8.7 Immune barrier hypothesis .......................................................................... 37
  1.8.8 Conclusion .................................................................................................... 38
1.9 Medical Management of CRS .............................................................................. 38
  1.9.1 First: Anti-inflammatory medication .............................................................. 39
  1.9.2 Second: Anti-microbial medication .............................................................. 40
  1.9.3 Third: Saline Irrigation .................................................................................. 43
1.10 Surgical Management of CRS .......................................................................... 44
  1.10.1 Historical external approaches to the sinuses ............................................ 44
  1.10.2 Introduction of the endoscope ..................................................................... 45
  1.10.3 Functional Endoscopic Sinus Surgery (FESS) ............................................ 45
1.11 Conclusion of the chapter ................................................................................... 47

Chapter 2  Extensive surgical techniques for CRS .................................................. 48
  2.1 Full-House FESS and Extent of Surgery........................................................... 48
  2.2 Radical maxillary sinus procedures .................................................................. 48
  2.3 Draf-III/EMLP Frontal drillout procedure: the successor of the external osteoplastic flap 50
  2.4 Nasalization ..................................................................................................... 50
  2.5 Denker’s procedure ......................................................................................... 51
  2.6 Conclusion of the Chapter .............................................................................. 52

Chapter 3  Refractory CRS ...................................................................................... 53
3.1 Definition .................................................................................................................. 53
3.2 Causes of disease recalcitrance and surgical failure .................................................. 53
3.2.1 Surgery-related factors (or anatomic factors) ......................................................... 53
3.2.2 Patient-related or disease-related factors ............................................................... 55
3.3 Conclusion of the chapter ......................................................................................... 57

Chapter 4 The Eosinophil in CRS .................................................................................. 59
4.1 Definition, histology and physiology ......................................................................... 59
4.2 Life cycle of eosinophils ......................................................................................... 60
  4.2.1 Eosinophilopoiesis ............................................................................................... 60
  4.2.2 Migration from the blood stream to tissues ......................................................... 61
  4.2.3 Transendothelial migration .................................................................................. 62
  4.2.4 Role of IL-5 .......................................................................................................... 63
  4.2.5 Transepithelial migration ..................................................................................... 63
  4.2.6 End of life ............................................................................................................. 63
4.3 Pathologic roles of the eosinophil ............................................................................. 64
  4.3.1 Tissue Injury ......................................................................................................... 64
  4.3.2 Pro-inflammatory and immunomodulatory cytokines and products ..................... 64
  4.3.3 Antigen presentation ............................................................................................ 65
  4.3.4 Steroid resistance ................................................................................................. 66
  4.3.5 Role in remodeling ............................................................................................... 66
  4.3.6 Eosinophil chemotaxis and autocrine persistence ............................................... 67
4.4 Conclusion of the chapter ......................................................................................... 67

Chapter 5 Thesis ............................................................................................................ 68
5.1 Refractory CRS and questioning an exclusive role for the OMC ................................. 68
5.2 Our Research ............................................................................................................ 68
5.3 Thesis Aims ............................................................................................................... 69

Chapter 6 Clinical significance of middle turbinate lateralization post-endoscopic sinus
surgery ............................................................................................................................. 70
6.1 Statement of Authorship ............................................................................................ 70
6.2 Citation ...................................................................................................................... 71
6.3 Abstract ..................................................................................................................... 71
6.4 Introduction .................................................................................................................. 73
6.5 Methods ........................................................................................................................ 73
  6.5.1 Study design ........................................................................................................... 73
  6.5.2 Inclusion criteria .................................................................................................... 74
  6.5.3 Surgical technique ................................................................................................. 74
  6.5.4 Assessment of MTL after surgery ......................................................................... 74
  6.5.5 Outcome variables .................................................................................................. 75
  6.5.6 Statistical analysis .................................................................................................. 75
6.6 Results .......................................................................................................................... 76
  6.6.1 Baseline characteristics ......................................................................................... 76
  6.6.2 MTL and patient-reported post-operative symptoms ............................................ 77
  6.6.3 MTL and revision surgery ...................................................................................... 78
  6.6.4 Survival analysis of the need for revision .............................................................. 78
6.7 Discussion ..................................................................................................................... 79
6.8 Conclusion ..................................................................................................................... 84

Chapter 7  The inflammatory load hypothesis in refractory CRS ................................. 85
  7.1 Statement of Authorship ......................................................................................... 85
  7.2 Citation ....................................................................................................................... 86
  7.3 Abstract ..................................................................................................................... 86
  7.4 Introduction ............................................................................................................... 86
  7.5 Revisiting historical concepts: Is a restoration of sinus ventilation and mucociliary function sufficient during surgery? ......................................................... 87
  7.6 The inflammatory load and its effect on disease severity and surgical outcome .... 89
  7.7 Understanding the pathophysiologic role of the eosinophil .................................... 90
  7.8 Radical Surgery: the surgical concept of “reducing the inflammatory load” .......... 92
  7.9 Conclusion ................................................................................................................ 96

Chapter 8  Clinical significance of remodeling in refractory CRS ............................... 98
  8.1 Statement of Authorship ......................................................................................... 98
  8.2 Citation ....................................................................................................................... 99
  8.3 Abstract ..................................................................................................................... 99
  8.4 Introduction ............................................................................................................... 100
8.5 Collagen deposition and fibrosis as an irreversible end-stage of ongoing inflammation 100
8.6 The temporal component of remodeling: Does a “window of opportunity” exist? ..... 102
8.7 Surgery and irreversible mucosal changes .................................................. 103
8.8 Summary .................................................................................................... 105

Chapter 9 Role of surgery in nasal polyp recurrence ........................................ 108
9.1 Statement of Authorship ........................................................................... 108
9.2 Citation ....................................................................................................... 108
9.3 Abstract ..................................................................................................... 109
9.4 Introduction ............................................................................................... 110
9.5 Methods ..................................................................................................... 110
  9.5.1 Study design .......................................................................................... 110
  9.5.2 Study population ..................................................................................... 111
  9.5.3 Surgery .................................................................................................. 111
  9.5.4 Post-operative care and management ..................................................... 111
  9.5.5 Recording recurrence and post-operative follow-up ............................. 111
  9.5.6 Statistical analysis .................................................................................. 112
9.6 Results ........................................................................................................ 112
  9.6.1 Study cohort characteristics ................................................................. 112
  9.6.2 Incidence/frequency of recurrence ....................................................... 114
  9.6.3 Sites of recurrence ................................................................................. 114
  9.6.4 Timing of recurrence ............................................................................. 114
  9.6.5 Significant factors in determining polyp recurrence ............................ 115
  9.6.6 The role of frontal sinus surgery on polyp recurrence ....................... 118
  9.6.7 Long-term fate (need for revision surgery) ........................................... 119
9.7 Discussion ................................................................................................... 120
9.8 Conclusion .................................................................................................. 123
9.9 Acknowledgements ..................................................................................... 123

Chapter 10 Subepithelial inflammatory load and basement membrane thickening in refractory CRSwNP ....................................................................................... 124
10.1 Statement of Authorship ............................................................................ 124
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2</td>
<td>Citation</td>
<td>125</td>
</tr>
<tr>
<td>10.3</td>
<td>Abstract</td>
<td>125</td>
</tr>
<tr>
<td>10.4</td>
<td>Introduction</td>
<td>126</td>
</tr>
<tr>
<td>10.5</td>
<td>Methods</td>
<td>127</td>
</tr>
<tr>
<td>10.5.1</td>
<td>Ethics Approval</td>
<td>127</td>
</tr>
<tr>
<td>10.5.2</td>
<td>Study Design</td>
<td>127</td>
</tr>
<tr>
<td>10.5.3</td>
<td>Study Cohort inclusion criteria</td>
<td>128</td>
</tr>
<tr>
<td>10.5.4</td>
<td>Histology</td>
<td>129</td>
</tr>
<tr>
<td>10.5.5</td>
<td>Histopathological examination methodology</td>
<td>129</td>
</tr>
<tr>
<td>10.5.6</td>
<td>Statistics</td>
<td>131</td>
</tr>
<tr>
<td>10.6</td>
<td>Results</td>
<td>131</td>
</tr>
<tr>
<td>10.6.1</td>
<td>Basic characteristics of the study cohort</td>
<td>131</td>
</tr>
<tr>
<td>10.6.2</td>
<td>First substudy: Refractory group versus control group</td>
<td>132</td>
</tr>
<tr>
<td>10.6.3</td>
<td>Second substudy: Following up the refractory group – comparing results of first versus revision operations</td>
<td>134</td>
</tr>
<tr>
<td>10.7</td>
<td>Discussion</td>
<td>135</td>
</tr>
<tr>
<td>10.8</td>
<td>Conclusion</td>
<td>139</td>
</tr>
<tr>
<td>10.9</td>
<td>Acknowledgements</td>
<td>139</td>
</tr>
<tr>
<td>Chapter 11</td>
<td>Thesis Synopsis</td>
<td>140</td>
</tr>
<tr>
<td>11.1</td>
<td>Synopsis of research findings</td>
<td>140</td>
</tr>
<tr>
<td>11.2</td>
<td>Alternative views</td>
<td>141</td>
</tr>
<tr>
<td>11.3</td>
<td>Future directions</td>
<td>142</td>
</tr>
<tr>
<td>11.3.1</td>
<td>Refractory CRS and Long-term outcomes research</td>
<td>142</td>
</tr>
<tr>
<td>11.3.2</td>
<td>Origin of the Th2 response</td>
<td>142</td>
</tr>
<tr>
<td>11.3.3</td>
<td>Extent of surgery</td>
<td>143</td>
</tr>
<tr>
<td>11.3.4</td>
<td>CRS Endotypes</td>
<td>143</td>
</tr>
<tr>
<td>11.4</td>
<td>Conclusion</td>
<td>143</td>
</tr>
<tr>
<td>References</td>
<td></td>
<td>145</td>
</tr>
<tr>
<td>Appendix i: List of Abbreviations</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>Appendix ii: List of Figures</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>Appendix iii: List of Tables</td>
<td>180</td>
<td></td>
</tr>
</tbody>
</table>
**Declaration**

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Ahmed Bassiouni
This work is dedicated to all the special people in my life.
Acknowledgements

This thesis would not have seen the light without the support and contributions of lots of people. I would like to reserve this space to acknowledge everyone who has offered me their help and support.

First, I would like to thank my Prof and primary supervisor, Professor Peter-John Wormald. Prof has generously accepted me as his student, even though I arrived as a visitor from a faraway land with minimal previous research experience. Prof was never hesitant to discuss my (usually vague and inconsistent) research ideas, and helps turn them into feasible and insightful research projects. His guidance and wisdom have been quintessential for my success in the completion of this thesis and I thank him for always pushing me to do my best. I would also like to thank Prof for fostering a departmental environment rooted in team-work, camaraderie, and friendship. And it is this spirit of friendship and support from everyone in the department, what makes me delighted and excited to wake up early (or some days, not so early) to go to work, and what makes the years of my PhD some of the most memorable years of my life.

I would also like to thank my secondary PhD supervisors Dr Sarah Vreugde and Dr Steven Floreani. Dr Sarah Vreugde our chief scientist is one of the most passionate scientists I have ever met. She has taught me a lot about science and gave me inspiration to pursue science throughout my future career.

I would like to thank the University of Adelaide, in particular the support of Professor Peter-John Wormald, Professor Richard Russell and Professor Guy Maddern for waiving my study fees for the program.

I would also like to thank my thesis study coauthors and dear friends. Dr Yuresh Naidoo: Yuresh and I bounced ideas off each other in my earliest days as a research student, which helped a lot in developing my early hypotheses for this thesis. Dr Philip Chen: Phil and I worked together on multiple papers and we quickly together became a very productive team. Dr Daniel Cantero: my dear friend Daniel and I shared the same office during our PhD, and our long scientific conversations we always had together every day were, and remain, priceless. Dr Sukanya Rajiv and Dr Judy Ou have worked with me on the histopathology project and the project could not have completed without their advice, input and support.
I would also like to thank Dr Clare Cooksley, Dr Eugene Roscioli and Mr Damien Jones, who have been instrumental in introducing me to working in the laboratory and have taught me all of the lab techniques that I know today.

I would like to thank those who offered me assistance in various projects: Ms Debbie Dyer from Adelaide Pathology Partners and Dr Jim Manavis from the Henson Institute for their assistance with histopathology; Dr Thomas Sullivan from the University of Adelaide for statistical assistance; Dr Mark DeNichilo and Dr Andreas Evdokiou from the Basil Hetzel Institute Breast Cancer Research Unit for their collaborative lab work with the ENT unit.

I would also like to thank Ms Lyn Martin. Lyn has been a great friend of mine since I first arrived in the department, and I can never do without her help and support, as she knows the ins and outs of the department. She continues to take care of me, especially with her delicious recipes, which helped to keep myself alive during my PhD (and after)!

I would also like to thank my fellow ENT researchers who worked with me on various projects and whose friendship I will cherish forever: Camille Jardeleza, Sukanya Rajiv, and Daniel Cantero (forming our incredible PhD quartet!); Clare Cooksley, Amanda Drilling, Judy Ou, Dijana Miljkovic, Dong Dong, Edward Cleland, Alkis Psaltis, Eugene Roscioli, Vikram Padhye, Thanh Ha, Joseph Brunworth, Sathish Paramasivan, Zacki Malik, Neil Tan, Sakiko Oue, Jae Murphy, Mahnaz Ramezanpour, Chun Chan, Katharina Richter and David Morrissey. I also thank my dear friend Dr Alkis Psaltis for his mentoring and constant guidance since he arrived back in Australia.

Finally I would like to thank my lovely family (Dad Mokhtar, Mum Aliaa, Bro Mohamed, Sis Rana, and Grandpa Ahmed) for their endless love, support and encouragement. Mom, Dad… I love you.
Thesis Abstract

Chronic rhinosinusitis (CRS) is chronic inflammation of the sinonasal mucosa. It is a disease of significant impact on public health, one that affects about 10-15% of the population. Functional Endoscopic Sinus Surgery (FESS) is the “gold standard” surgical treatment for CRS; its original philosophy or concepts are based upon the sinonasal mucociliary clearance studies by Messerklinger and Stammberger, which emphasize the role of the osteo-meatal complex (OMC). However, although the success rate of FESS is about 90%, there is a subgroup of patients who exhibit no improvement, and thus require repeated surgeries. This subgroup of patients suffers from refractory chronic rhinosinusitis (rCRS), which is the main focus of this thesis. In this thesis the current understanding of the pathogenesis and causes of surgical failure in CRS are reviewed. This thesis presents the hypothesis that our understanding of the pathogenesis of CRS has advanced since the original concepts of FESS were put forward, and that patients who develop rCRS have other pathogenic features that cannot be addressed by these concepts. We revisit middle turbinate lateralization (MTL) as a surgery-related factor of rCRS in Chapter 6, and we pose the question: Is MTL a complication associated with worse surgical outcomes, or just a harmless sequela, of the surgical destabilization of the middle turbinate during sinus surgery? Our findings show that MTL plays a role in surgical failure and requiring revision surgery, but suggest that the clinical significance of MTL may be related to frontal sinus obstruction and not necessarily to the OMC. We then present two novel hypotheses: the inflammatory load hypothesis in Chapter 7, and the irreversible disease hypothesis in Chapter 8. In Chapter 9, we investigate nasal polyp recurrence in CRS with Nasal Polyposis (CRSwNP) as an important cause of rCRS. We study the patterns of polyp recurrence and the clinical factors associated with more aggressive recurrence. The findings show that firstly, comorbid factors such as asthma and aspirin sensitivity contribute to the disease load and rCRS; and secondly, that more aggressive surgical removal of that disease load and maximal opening of the sinuses through a frontal drillout procedure improve the surgical outcome and disease control for these rCRS patients. We then proceed to investigate the relevance of our two novel hypotheses to refractory CRSwNP through a histopathological study in Chapter 10. We also describe the evolution of the inflammatory load in patients with rCRS from first to second surgery, a topic rarely addressed in the literature. We found that a higher inflammatory load is present in patients
who fail surgery and go on to develop refractory CRS, when compared to patients who respond to surgery, with a particular significance to the eosinophilic load. In summary, our findings suggest that the inflammatory load is associated with long-term surgical outcomes. The recommendation based upon findings in this thesis is that surgery offered for CRS should be viewed as a tool for addressing and controlling disease load, and not just for the conservative clearance of disease of the OMC.
Publications arising from this thesis


