EPIDEMIOLOGY OF EPILEPSY IN TASMANIA

A thesis presented in partial fulfilment of the requirements
for the degree of
Doctor of Philosophy in Epidemiology
at Massey University, Wellington, New Zealand

Wendyl Jude D'Souza

January 2008
Abstract

Background
Better understanding of the demographic distribution of epilepsy and the prevalence of ‘more specific forms of epilepsy’ in community-based settings would improve our understanding of this disorder at the population level. Although we now have good estimates of epilepsy prevalence for most countries, we still lack knowledge on its demographic distribution by age, ethnicity, region, and socioeconomic status. In addition, no studies to date have reported the prevalence of epilepsy syndromes using patient interview outside a hospital setting. This thesis provides the first community-based estimates of the prevalence of the most common clinical group of epilepsies presumed to have a genetic basis – The Idiopathic Generalised Epilepsies (IGE) - by patient and witness interview.

Methods
This thesis has involved conducting five pieces of new research: (i) a series of reviews and analyses of descriptive data on epilepsy prevalence, particularly focusing on the critical methodological issues of ascertainment, diagnosis and classification of epilepsy for epidemiological purposes; (ii) the validation of a modified diagnostic epilepsy questionnaire adapted for administration in population studies; (iii) recruitment of a community-based cohort – The Tasmanian Epilepsy Register (TER) - through the Australian national prescription database; (iv) estimation of the overall prevalence and distribution of self-reported treated epilepsy in Tasmania by imputation methods; (v)
estimation of the prevalence and distribution of IGE in Tasmania by telephone interviewing.

Results

My modified diagnostic questionnaire, administered by telephone interviewing and interpreted with standardized guidelines, demonstrated excellent agreement with an epilepsy specialist’s clinical assessment in diagnosing the presence of epilepsy (κ = 0.94), seizure-onset types (κ = 0.84), simple or complex partial seizures (κ = 0.87), any generalized non-convulsive seizure (κ = 0.82), and IGE (κ = 0.82). Although still substantial, agreement was not as close for secondarily generalized seizures (κ = 0.74), and generalized tonic-clonic seizures (κ = 0.79).

7541 patients treated with antiepileptic drugs (AEDs) in the preceding year in Tasmania were eligible for recruitment through the Australian national prescription database. After three mail contacts, 54.0% responded, with 43.6% who indicated treatment for epilepsy representing 86.0% of total possible epilepsy cases by imputation (n = 2063) in Tasmania. 1180 agreed to participate in the TER, 90.0% of participants received their AEDs either exclusively from their general practitioner (70.9%) or in combination with a medical specialist (19.1%) in the preceding twelve months. The adjusted treated epilepsy prevalence was 4.36 per 1000 (95% CI 4.34, 4.39); this was: lower in women (prevalence ratio 0.92 (95% CI 0.84, 1.00); greater with increasing age (p < 0.001); similar in the three main geographical regions; and similar by categories of socioeconomic status based on postcode of residence.
Following enrolment, 959/1083 (88.6%) eligible TER participants completed the diagnostic telephone interviewing, with partial epilepsy classified in two thirds, and generalised epilepsy in slightly more than one-fifth. IGE was observed in 20.3%, with tonic-clonic seizures (17.03%) and the absence epilepsies combined (11.01%) being the most common IGE seizure types and syndromes respectively. The estimated prevalence of IGE was 0.89 per 1000; is highest between the ages of 20-39 years and in females, but was similar between Tasmanian regions and socio-economic groups. IGE prevalence beyond childhood related to refractory childhood or adolescent disease rather than older-onset cases, and was characterised by the presence of myoclonic and tonic-clonic seizures. Generalised seizures, but not IGE, were less prevalent in southern Tasmania.

Conclusions

Utilising the design approach described in this thesis may provide an alternative to neurological assessment, and when coupled with case ascertainment through prescription data, can provide a valid estimate of the prevalence of ‘more specific forms of epilepsy’ in countries with high access to health services. The observed pattern of high elderly epilepsy prevalence, is similar to patterns in recent studies in other developed countries, and has important implications for future planning of health services in these countries. IGE represents a considerable proportion of community-treated disease with important aetiological and prognostic determinants occurring at the seizure rather than syndrome level of classification.
Acknowledgements

This work was undertaken during my tenure firstly as the inaugural Neuroepidemiology Fellow in epilepsy at St Vincent’s Hospital Melbourne, secondly as the Pfizer Epilepsy-Electrophysiology Fellow at the Alfred & St Vincent’s Hospitals Melbourne and finally as the co-joint Neuroepidemiology Fellow at St Vincent’s Hospital, the University of Melbourne and The Menzies Research Institute, the University of Tasmania. I was supported during my final tenure at St Vincent’s Hospital Melbourne from a GSK Fellowship in Neurology and at The Menzies Research Institute from an NHMRC Capacity Building Grant.

The projects in this thesis were generously supported by grants from the FRACP GSK Fellowship in Neurology, the Booth Estate Launceston, Royal Hobart Hospital Research Foundation, GSK Neurology and the Clifford Craig Medical Research Trust - North West Tasmania.

To the participants in the Tasmanian Epilepsy Register and their parents, spouses, relatives and friends who gave up their time to take part in the recruitment, validation, and prevalence studies presented in this thesis (Chapters Five, Six, Seven and Eight) my grateful thanks and heartfelt appreciation to you all.

I would like to thank Ruth Ottman for providing an electronic version of the epilepsy diagnostic interview used with modifications in this study.
I acknowledge the work of the co-investigators and research assistants who collaborated on the analyses presented in Chapters Five. These were: Nadia Farrell, Linda Seiderer, Lucas Litewka, Graeme Gonzales and Natasha Willems for conducting some of the telephone interviewing; Charlotte McKercher and Jayne Fryer, for assisting in performing the data cleaning and questionnaire mapping; Jim Stankovich who assisted in designing the study’s analytical strategy, and performing the analysis and interpretation of the results; Simon Bower, Terence O’Brien, Neil Pearce and Mark Cook who assisted in interpreting the results.

I acknowledge the work of the co-investigators and research assistants who collaborated on the analyses presented in Chapters Six and Seven. These were: Nicole Mulcahy, Leanne Barnes and Charlotte McKercher who assisted in participant liaison, data processing and management; Jayne Fryer who assisted in data cleaning, designing the study’s analytical strategy, and performing the analysis and interpretation of the results; Stephen Quinn who assisted in designing the study’s analytical strategy, performing the analysis, and interpretation of the results; Bruce Taylor, David Ficker, Terence O’Brien, Neil Pearce and Mark Cook who assisted in designing the study and interpreting the results.

I acknowledge the work of the co-investigators and research assistants who collaborated on the analyses presented in Chapter Eight. These were: Charlotte McKercher and Jayne Fryer, for assisting in performing the data cleaning and questionnaire mapping; Soo Cheng who assisted in performing the analysis of the results; Helene Roberts for
conducting a large proportion of the telephone interviewing; Jim Stankovich, Terence O’Brien, Neil Pearce and Mark Cook who assisted in interpreting the results.

To Mark Cook, thank you for your unwavering support and endless patience during the process of writing this thesis across the Tasman.

To Hilary Nuttall, thank you for your enthusiasm, industry and overwhelming commitment to get this manuscript into its final shape.

To Clyde, Fleur, Aiden, Patrick, Alwyn, Amanda, Gabriella and Kieran. For lending me your homes, bedrooms, space and support.

To my daughters Bebe Ahna and Isabella, I put this thesis on hold to parent you and then put my family on hold to complete this – I look forward to a future of being more available.

To Lee, who over the years of writing has been the foundation and inspiration to start and finish this.

To Neil Pearce, 17 years, 18 publications, and two theses - I’m still here. You are more than simply a great teacher, supervisor, employer, and mentor. I feel privileged to be marked as your student.
To my father, you always encouraged me to pursue my passions with integrity. By your example you instilled in me the importance of community – I dedicate this thesis to your ongoing presence.
Table of contents

Abstract

Acknowledgements

List of Figures

List of Tables

Abbreviations

Chapter One: Introduction ................................................................................................................... 1

1.1 Background .................................................................................................................................. 1
1.2 Objectives ..................................................................................................................................... 4
1.3 Thesis Organisation ..................................................................................................................... 5

Chapter Two: Methodological issues in measuring the prevalence of epilepsy II:

Case ascertainment ............................................................................................................................. 8

2.1 Introduction ................................................................................................................................. 9
2.2 Stigma ........................................................................................................................................... 9
2.3 Institutionalised residents ......................................................................................................... 13
2.4 Medical sources .......................................................................................................................... 20
2.5 Community sources .................................................................................................................. 37
2.6 Multiple sources ......................................................................................................................... 43
2.7 Capture-recapture methods ....................................................................................................... 43
2.8 Comparative studies ................................................................................................................... 44
2.9 Summary ....................................................................................................................................... 47

Chapter Three: Methodological issues in measuring the prevalence of epilepsy I:

Classification and diagnosis ........................................................................................................... 49

3.1 Introduction ................................................................................................................................ 49
3.2 Methodological issues in classification .................................................................................. 49
3.3 Methodological issue in diagnosis .......................................................................................... 61
3.4 Questionnaires ............................................................................................................................ 70
3.5 Summary ....................................................................................................................................... 94

Chapter Four: The prevalence of epilepsy, seizures and idiopathic generalized epilepsy – A summary of the literature ............................................................................................................ 95

4.1 Introduction ................................................................................................................................ 95
4.2 The prevalence of epilepsy ........................................................................................................... 95
4.3 The distribution of epilepsy ......................................................................................................... 99
4.4 The prevalence of seizures, epilepsy-onset type and epilepsy syndromes ................................ 108
4.5 Summary ...................................................................................................................................... 124
List of Figures

Figure 2.1: Case ascertainment methods in epilepsy prevalence studies from 1923-2007 (n=115) ........................................ 19
Figure 2.2: Studying people with seizures (disease) versus patients with diagnosed epilepsy (illness) ................................................ 30
Figure 2.3: Prevalence of epilepsy by country, region, and ethnic groups from various sources (Davenport 1923) ...................... 38
Figure 3.1: Flow diagram for classification of seizures and epilepsy in epidemiologic studies from Hauser et al 1991 .......................... 50
Figure 3.2: Frequency of generalised seizure types by age of onset (absence = 16, myoclonic = 182, tonic clonic = 93) (Senanayake 1993) ................................................................................ 67
Figure 4.1a: The lifetime prevalence of epilepsy from studies in Africa (n=19) ........................................................................... 96
Figure 4.1b: The lifetime prevalence of epilepsy from studies in Latin America (n=12) ................................................................. 97
Figure 4.1c: The lifetime prevalence of epilepsy from studies in Eastern Mediterranean (n=4) ......................................................... 97
Figure 4.1d: The lifetime prevalence of epilepsy from studies in Europe (n=23) ............................................................................. 97
Figure 4.1e: The lifetime prevalence of epilepsy from studies in North America (n=13) ................................................................. 98
Figure 4.1f: The lifetime prevalence of epilepsy from studies in Asia & Oceania (n=16) ................................................................. 98
Figure 6.1a: Map of Australia ........................................................................ 146
Figure 6.1b: Map of Tasmania .................................................................... 147
Figure 6.2: Summary of patient recruitment and participation onto the Tasmanian Epilepsy Register ............................................ 158
Figure 7.1: Prevalence of epilepsy by imputation methods ........................ 174
Figure 7.2: The prevalence of treated epilepsy in Tasmania by five-year-age-groups ............................................................. 174
Figure 8.1: The prevalence of Idiopathic Generalised epilepsy by age-group (n=175) ................................................................. 194
Figure 8.2: Idiopathic Generalised Epilepsy by age at onset (n=159) .. 194
Figure 8.3: The prevalence of IGE (n=175) and generalised seizure types by age-group (n=348) .............................................. 195
Figure 8.4: The prevalence of IGE and generalised seizure types by region .................................................................................. 195
List of Tables

Table 2.1: Case ascertainment methods in epilepsy prevalence studies from English-language publications from 1923-2007 (n=115) ........... 14
Table 3.1: Definitions for epilepsy used in prevalence studies: 1923-2007 (n=115) ................................................................. 53
Table 3.2: Definitions of ‘active’ epilepsy used in prevalence studies: 1923-2007 (n=115) ................................................................. 54
Table 3.3: Proportion of unclassifiable seizures in epilepsy prevalence studies from 1923-2007 (n=115) ............................................. 64
Table 3.4: Main validated epidemiological protocols for epilepsy prevalence studies ................................................................. 72
Table 3.5: Validity of screening questionnaires used in epilepsy prevalence study ................................................................. 76
Table 4.1: Frequency of seizure onset-types in epilepsy prevalence studies from 1923-2007 (n=61) ................................................................. 110
Table 4.2: The frequency of generalized seizure types in epilepsy prevalence studies from 1923-2007 ................................................................. 117
Table 4.3: The frequency of seizure and ‘syndromes’ in studies prior to The International League Against Epilepsy Syndrome 1989 Classification System ................................................................................................................................. 122
Table 4.4: The frequency of the Idiopathic Generalised Epilepsies based on the International League Against Epilepsy Syndromes Classification 2003 ................................................................................................................................. 123
Table 5.1: Demographic features and disease characteristics of study participants (n=99) ................................................................................................................................. 133
Table 5.2: Diagnostic agreement for the presence of epilepsy, seizures, seizure-onset types§, and the idiopathic generalized epilepsy syndrome from telephone interviews versus epilepsy specialists’ assessment ................................................................................................................................................................................................. 135
Table 5.3: Sensitivity, specificity, positive predictive value, negative predictive value and Youden’s Index (YI) for the presence of epilepsy, seizures, seizure-onset type§, and idiopathic generalized epilepsy from telephone interviews versus epilepsy specialists’ assessment ................................................................................................................................................................................................. 137
Table 6.1: “Reportable” anticonvulsant medications* supplied in Tasmania between 1st July 2001 and 30th June 2002 ................................................................. 150
Table 6.2: Comparison of HIC sample versus Register participants for anticonvulsant provider type in Tasmania between July 1st 2001 and June 30th 2002 ................................................................................................................................................................................................. 159
Table 6.3: Demographic features by age, gender, region and socio-economic status of the Tasmanian population, Register participants, responders and non-responders ................................................................................................................................................................................................. 160
Table 7.1: Response to the Health Insurance Commission mail invitations ................................................................................................................................................................................................. 177
Table 7.2: The effect on prevalence estimates of different disease disclosure among non-responders between crude and imputed prevalence estimates .......................................................... 177

Table 7.3: Estimated prevalence of treated epilepsy in Tasmania by age-group, gender, region and SEIFA .......................................................... 178

Table 7.4: Observed percentage and estimated prevalence of epilepsy treated with concurrent antiepileptic drug medications in Tasmania between July 1st 2001 and June 30th 2002 .................................................. 179

Table 8.1: Demographic features by age, gender, region and SES of the Tasmanian Epilepsy Register and diagnostic telephone interviewing respondents .......................................................... 191

Table 8.2: Frequency of broad epilepsy syndromes by diagnostic telephone interviewing of Tasmanian Epilepsy Register participants (n=955) .......................................................... 192

Table 8.3: Frequency of Idiopathic Generalised Epilepsy Syndromes and generalised seizures by diagnostic telephone interviewing of Tasmanian Epilepsy Register participants (n=955) .................................................. 192

Table 8.4: Estimated prevalence and distribution of Idiopathic Generalised Epilepsy by age, gender, region and SES in Tasmania, Australia .......................................................... 196

Table 8.5.1: Estimated prevalence and distribution of absence seizures by age, gender, region and SES in Tasmania, Australia .................... 197

Table 8.5.2: Estimated prevalence and distribution of myoclonic seizures by age, gender region and SES in Tasmania, Australia .................... 198

Table 8.5.3: Estimated prevalence and distribution of tonic-clonic seizures by age, gender, region and SEIFA in Tasmania, Australia .................... 199
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AED</td>
<td>Anti-epileptic drug</td>
</tr>
<tr>
<td>BMEI</td>
<td>Benign Myoclonic Epilepsy of Infancy</td>
</tr>
<tr>
<td>CAE</td>
<td>Childhood Absence Epilepsy</td>
</tr>
<tr>
<td>CATI</td>
<td>Computer-assisted-telephone-interviewing</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
</tr>
<tr>
<td>CTB</td>
<td>Computed Tomography of the Brain</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>EMA</td>
<td>Epilepsy with Myoclonic Absences</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Fluoro-deoxyribose glucose positron emission testing</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computerized tomography</td>
</tr>
<tr>
<td>FRACP</td>
<td>Fellow of the Royal Australasian College of Physicians</td>
</tr>
<tr>
<td>GEFS+</td>
<td>Generalised Epilepsy with Febrile Seizures Plus</td>
</tr>
<tr>
<td>GPRD</td>
<td>The General Practice Research Database</td>
</tr>
<tr>
<td>GTCS</td>
<td>Generalised tonic clonic seizures</td>
</tr>
<tr>
<td>HIC</td>
<td>Health Insurance Commission</td>
</tr>
<tr>
<td>ICEBERG</td>
<td>The International Community-based Research Group</td>
</tr>
<tr>
<td>IGE</td>
<td>Idiopathic Generalised Epilepsy</td>
</tr>
<tr>
<td>IGEU</td>
<td>Idiopathic Generalised Epilepsy not otherwise specified</td>
</tr>
<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
</tr>
<tr>
<td>JAE</td>
<td>Juvenile Absence Epilepsy</td>
</tr>
<tr>
<td>JS</td>
<td>Jeavon's Syndrome</td>
</tr>
<tr>
<td>JME</td>
<td>Juvenile Myoclonic Epilepsy</td>
</tr>
<tr>
<td>MAE</td>
<td>Epilepsy with Myoclonic Astatic seizures</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MRIB</td>
<td>Magnetic resonance imaging of the brain</td>
</tr>
<tr>
<td>NGPSE</td>
<td>National General Practice Study on Epilepsy</td>
</tr>
<tr>
<td>NHIS</td>
<td>National Health Interview Survey</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council (Australia)</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NHSCR</td>
<td>National Health Service Central Register</td>
</tr>
<tr>
<td>NHNN-GPLS</td>
<td>The National Hospital for Neurology and Neurosurgery General Practice Linkage Scheme</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
</tr>
<tr>
<td>OREp</td>
<td>Osservatorio Regionale per l'Epilessia</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>SSCI</td>
<td>Semi-structured seizure classification interview</td>
</tr>
<tr>
<td>SEIFA</td>
<td>Socio-economic status index for postcode area</td>
</tr>
<tr>
<td>SENS</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>SNES</td>
<td>The Sicilian Neuroepidemiology Study</td>
</tr>
<tr>
<td>SPEC</td>
<td>Specificity</td>
</tr>
<tr>
<td>TER</td>
<td>Tasmanian Epilepsy Register</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>YI</td>
<td>Youden's Index</td>
</tr>
</tbody>
</table>