CORPUS CALLOSOTOMY

OUTCOMES IN PAEDIATRIC PATIENTS

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This dissertation is submitted for total fulfilment of the degree of Master of Philosophy in Medicine

March 2018
For Kristin, Isadora, and Oscar
Corpus Callosotomy Outcomes in Paediatric Patients

David Graham - March 2018
Perhaps no disease has been treated with more perfect empiricism on the one hand, or more rigid rationalism on the other than has epilepsy.

John Russell Reynolds, 1861
DECLARATION

This dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text. It has not been previously submitted, in part or whole, to any university of institution for any degree, diploma, or other qualification.

The work presented within this thesis has resulted in one paper that has been published in the peer-review literature:


The work has also resulted in one international conference podium presentation, one local conference podium presentation, and one international conference poster:


I have also published a systematic review of corpus callosotomy outcomes in paediatric patients. This is a separate work that was produced for my MBBS, but one that informs this present Masters thesis:

Graham D, Tisdall MM, Gill D. Corpus callosotomy outcomes in paediatric patients: a systematic review. *Epilepsia* 2016; 57(7): 1053-68

In accordance with the Sydney Medical School guidelines, this thesis is does not exceed 60,000 words, and it contains less than 150 figures.

Signed

Date: 6 March, 2017

David Graham, BSc(Hons) MBBS PhD

Sydney
SUMMARY

Corpus callosotomy is a palliative disconnective neurosurgical treatment that is typically employed for patients with medically refractory epilepsy characterised by injurious drop attacks. This thesis describes the 20 year experience with corpus callosotomy at Great Ormond Street Hospital for Children (GOSH) in London and the Children’s Hospital at Westmead (CHW) in Sydney.

Between January 1995 and December 2015, 76 patients underwent corpus callosotomy at GOSH (n=47) and CHW (n=29); 55 patients met inclusion criteria. Patient records were analysed for changes in seizure type and frequency, changes in injuries, changes in use of antiepileptic drugs, and neurological and surgical complications. Rare or no drop attacks was analysed using Kaplan–Meier event-free survival curves using right-censoring of data. Multivariable regression analysis was used to assess the effect of clinical characteristics on outcome at last follow up.

Median follow up was 36 months (interquartile range 34 months). Overall 26/55 patients (47.3%) had rare or no drop attacks at last follow up. Of the children who had drop attacks at last follow up, 26/29 of these patients (89.7%) had a return of drop attacks within 12 months of surgery. There were no significant predictors of developing drop attacks post-surgery. Neurological complications occurred in 11/55 operations (20.0%) and resolved within 6 weeks in all patients. Surgical complications occurred in 6/55 operations (10.9%), with only one major complication (hydrocephalus) and no deaths.

Corpus callosotomy was a well-tolerated palliative procedure that was effective at reducing the severity of drop attacks in this case series. In patients for whom drop attacks return, they are likely to do so within 12 months of surgery. Several other case series and systematic reviews provide evidence to support the hypothesis that corpus callosotomy is a safe and effective palliative treatment for patients with medically refractory generalised seizures that is typically characterised by
injurious drop attacks. But there is no strong evidence to demonstrate the validity of that hypothesis.

A case study is presented to highlight some of the bioethical issues of corpus callosotomy in children. Parental resistance to epilepsy surgery is a well-known barrier to access for all epilepsy surgery. While earlier intervention has demonstrable benefits on quality of life, some parents find the prospect of disconnection syndrome challenging and resist corpus callosotomy. The case study is then used to frame issues relating to consent and the best interests of children undergoing corpus callosotomy, highlighting the shortcomings of the concept of autonomy.
ACKNOWLEDGEMENTS

My very warm thanks to my supervisors, Prof Russell C Dale, Dr Deepak Gill and Mr Martin M Tisdall for your robust guidance and sound advice. I could not have completed this thesis without your expertise and mentorship.

To Ms Nicola Barns, thank you for contacting parents who had been lost to follow up from Great Ormond Street Hospital for Children, and to Dr Kavitha Kothur, thank you for your early ground work on collating some of the corpus callosotomy data at the Children’s Hospital at Westmead. My humble thanks to Prof J Helen Cross, Dr Sophia Varadkar, Mr William Harkness, Dr Mark Dexter and Mr M Zubair Tahir for your kind collaboration.

My most sincere thanks to the patients and families at GOSH and CHW, without you we could not further our knowledge of epilepsy surgery.

My beautiful wife, Kristin, thank you for your love, understanding, and undying support. My darling daughter, Isadora, thank you for your inimitable way of reminding me of the wondrous little things in life. My son, Oscar, thank you for your flips and kicks punctuating the preparation of this thesis while you were as yet unborn.
Corpus Callosotomy Outcomes in Paediatric Patients

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LIST OF ABBREVIATIONS AND ACRONYMS

ADL    activities of daily living
AED    anti-epileptic drugs
AMPA   \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATSI   Aboriginal and Torres Strait Islander
CCx    corpus callosotomy
CHW    The Children’s Hospital at Westmead
CNS    central nervous system
CP     cerebral palsy
CPS    complex partial seizures
CSF    cerebrospinal fluid
CT     computer tomography
DD     developmental delay
DQ     developmental quotient
DTI    diffusion tensor imaging
DVT/PE deep vein thrombosis/pulmonary embolism
ECG    electrocardiogram
EEG    electroencephalogram
fMRI   functional MRI
GABA   \( \gamma \)-aminobutyric acid
GTCS   generalised tonic clonic seizure
GOSH   Great Ormond Street Hospital for Children
GP     general practitioner
HHE    hemiconvulsion-hemiplegia epilepsy syndrome
HIE    hypoxic ischaemic encephalopathy
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ICF-CY</td>
<td>International Classification of Functioning, Disability and Health for Children and Youth</td>
</tr>
<tr>
<td>IED</td>
<td>interictal epileptiform discharge</td>
</tr>
<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
</tr>
<tr>
<td>IQ</td>
<td>intelligence quotient</td>
</tr>
<tr>
<td>IVIG</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>LGS</td>
<td>Lennox Gastaut Syndrome</td>
</tr>
<tr>
<td>LP</td>
<td>lumbar puncture</td>
</tr>
<tr>
<td>LSAC</td>
<td>Longitudinal Study of Australian Children</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NMDA</td>
<td>n-methyl-d-aspartic acid</td>
</tr>
<tr>
<td>QOLIE-31</td>
<td>quality of life in epilepsy inventory (short form)</td>
</tr>
<tr>
<td>SCN1A</td>
<td>sodium channel, voltage-gated, type I, alpha subunit</td>
</tr>
<tr>
<td>SMA</td>
<td>spinal muscular atrophy</td>
</tr>
<tr>
<td>SNAP-IV</td>
<td>revised version of Swanson, Nolan and Pelham questionnaire</td>
</tr>
<tr>
<td>SUDEP</td>
<td>sudden unexpected death in epilepsy</td>
</tr>
<tr>
<td>SV2A</td>
<td>synaptic vesicle glycoprotein 2A</td>
</tr>
<tr>
<td>TS</td>
<td>tuberous sclerosis</td>
</tr>
<tr>
<td>VEEG</td>
<td>video EEG</td>
</tr>
<tr>
<td>VNS</td>
<td>vagus nerve stimulator</td>
</tr>
<tr>
<td>VP shunt</td>
<td>ventricular-peritoneal shunt</td>
</tr>
<tr>
<td>WS</td>
<td>West Syndrome</td>
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1 INTRODUCTION

Epilepsy is a heterogenous disease that poses a challenge for clinicians to treat. It is estimated that approximately 50 million people globally have epilepsy\textsuperscript{1,2}. Typically 70\% of patients will undergo successful seizure remission with the use of medical treatment alone, 20\% of patients will require lifelong treatment to control seizures, and the remaining 10\% of patients will continue to have uncontrolled seizures despite medical treatment\textsuperscript{3,4}. Such refractory epilepsy is especially disabling, often progressive, and carries a significant burden to patients and their families. Treatment of refractory epilepsy requires a comprehensive and multidisciplinary approach that may involve curative or palliative epilepsy surgery depending on the nature of the seizures.

Corpus callosotomy is a palliative disconnective neurosurgical treatment for patients with either generalised or multifocal refractory epilepsy characterised by injurious drop attacks. Corpus callosotomy involves the surgical division of the corpus callosum (see Figure 1.1). It usually involves either a total division or a partial anterior division, in which the splenium is spared. Posterior corpus callosotomy on the other hand involves the division of the splenium only, but is rarely performed unless it is used to complete an anterior corpus callosotomy.
This chapter describes epilepsy, including the epidemiology, pathophysiology and the prognosis of epilepsy. The chapter then outlines the treatment of epilepsy before focusing on corpus callosotomy and its outcomes in paediatric patients. The chapter concludes with a brief discussion of difficult decision-making in epilepsy surgery to be explored in further detail in chapter 4. The systematic review by Graham, Tisdall and Gill on the outcomes of corpus callosotomy in paediatric patients established the theoretical groundwork for this thesis.
1.1 Epilepsy

1.1.1 Definition

An epileptic seizure is defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”\(^6\). This is distinguished from non-epileptic seizures, which may mimic epileptic seizures but will have no electrical disruption and instead may have psychogenic or physiological causes. Epilepsy is a condition characterised by recurrent, unprovoked epileptic seizures. An epilepsy syndrome is a group of clinical characteristics that often co-occur, such as the seizure types, EEG findings, natural history, etc.

1.1.2 Semiology

The classification of seizures has evolved over many years, with early attempts dating back to Hippocrates and Galen, which highlights the difficulty of classifying the epilepsies\(^7\). The concepts of idiopathic and symptomatic date back to 1854 when Delasiauve classified epilepsy into idiopathic (with no clear anatomical lesion), symptomatic (with a clear anatomical lesion) and sympathetic (arising secondary to other disease)\(^7\). In 1931, Jackson suggested the classification take into account the presence of anatomical lesions, physiological disturbances and pathology, thereby introducing generalised and partial seizures\(^7\). This was an important step towards the current classification, but in 1955, Symonds observed that it may be difficult to clinically distinguish between generalised and partial seizures. In order to resolve this difficulty, he recommended the use of EEG, which is now the gold standard of diagnosis\(^7\).

The International League Against Epilepsy (ILAE) first standardised the terminology in 1969, and has continued to update the classification as new technologies allow for improved diagnosis\(^8\). The current classification hierarchy is shown in Table 1.1 below, which is essentially a structured approach to describing the seizure. The approach is to determine whether the onset of the seizure is focal, generalised, unknown or unclassified. Further descriptors are then applied,
including level of awareness and secondary generalisation of a focal seizure to a bilateral tonic-clonic seizure.

**Table 1.1: Classification of epileptic seizures**

<table>
<thead>
<tr>
<th>Level in Seizure Hierarchy</th>
<th>Seizure Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Focal Seizure</td>
<td></td>
<td>Further descriptors: aware, impaired awareness, unknown awareness; to bilateral tonic-clonic</td>
</tr>
<tr>
<td>1.1 Motor</td>
<td></td>
<td>Focal motor seizures involve motor activity of parts of the body</td>
</tr>
<tr>
<td>1.1.1 Tonic</td>
<td></td>
<td>Focal tonic seizures involve a strong and rigid contraction of the muscles that fixes the limbs in a strained position that lasts for seconds to minutes. A focal tonic seizure will involve parts of the body, such as a fencer’s posture seizure in which one arm will extend while the other flexes similar to the neonatal asymmetrical tonic neck reflex</td>
</tr>
<tr>
<td>1.1.2 Atonic</td>
<td></td>
<td>Focal atonic seizures involve the loss of muscle tone. They are very brief and last for less than 2 seconds.</td>
</tr>
<tr>
<td>1.1.3 Myoclonic</td>
<td></td>
<td>A myoclonic seizure is a sudden, brief (&lt;100 ms) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal)</td>
</tr>
<tr>
<td>Level in Seizure Hierarchy</td>
<td>Seizure Type</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1.1.4</td>
<td>Clonic</td>
<td>Clonic focal seizures involve convulsions in one part of the body. The amplitude of the convulsions remains constant throughout the seizure, but the frequency reduces.</td>
</tr>
<tr>
<td>1.1.5</td>
<td>Epileptic Spasms</td>
<td>An epileptic spasm is a sudden flexion or extension (or mix) of one part of the body that lasts longer than a myoclonic jerk but shorter than a tonic seizure.</td>
</tr>
<tr>
<td>1.1.6</td>
<td>Hypermotor</td>
<td>A hypermotor seizure consists of complex movements that involve proximal muscles and the trunk. They may be confused with night terrors in young children.</td>
</tr>
<tr>
<td>1.2</td>
<td>Non-Motor</td>
<td>Focal non-motor seizures are focal seizures that do not involve motor activity</td>
</tr>
<tr>
<td>1.2.1</td>
<td>Sensory</td>
<td>A focal sensory seizure is a perceptual experience that is not caused by an external stimulus. It may include auditory, gustatory, olfactory, somatosensory, vestibular or visual semiologies</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Cognitive</td>
<td>A focal cognitive seizure is a disturbance of cognitive function, and may include aphasia, dysphasia, déjà vu, jamais vu, hallucinations, memory impairment, neglect, etc</td>
</tr>
<tr>
<td>Level in Seizure Hierarchy</td>
<td>Seizure Type</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1.2.3</td>
<td>Emotional</td>
<td>A focal emotional seizure is a disturbance of emotional or affective function, and may include agitation, fear, anxiety, crying, laughing, paranoia, pleasure, etc.</td>
</tr>
<tr>
<td>1.2.4</td>
<td>Autonomic</td>
<td>A focal autonomic seizure is a disturbance of autonomic function. It may manifest in any autonomic system, including cardiovascular (such as asystole), gastrointestinal (such as nausea and vomiting), thermoregulation, sexual, etc.</td>
</tr>
<tr>
<td>2.</td>
<td>Generalised Seizure</td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>Motor</td>
<td></td>
</tr>
<tr>
<td>2.1.1</td>
<td>Tonic-Clonic</td>
<td>Tonic-clonic seizures have two phases. The tonic phase involves patient falling unconscious, possibly falling to the ground, and extension or flexion of extremities and may be preceded by aura. The clonic phase usually consists of violent muscle contractions, shaking or vibrating. The eyes may roll back in the head, the tongue may be bitten and incontinence may occur. Post-ictal phenomena may include sleepiness, headaches, amnesia and/or confusion.</td>
</tr>
</tbody>
</table>
## Chapter 1: Introduction

<table>
<thead>
<tr>
<th>Level in Seizure Hierarchy</th>
<th>Seizure Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.2</td>
<td>Tonic</td>
<td>Tonic seizures involve a strong and rigid contraction of the muscles that fixes the limbs in a strained position that lasts for seconds to minutes. The patient’s head and eyes may deviate to one side and they may turn around. As the seizure progresses, the intensity in different parts of the body changes.</td>
</tr>
<tr>
<td>2.1.3</td>
<td>Atonic</td>
<td>Atonic seizures may involve either a head nod or complete loss of axial body tone. They are very brief and last for less than 2 seconds.</td>
</tr>
<tr>
<td>2.1.4</td>
<td>Myoclonic</td>
<td>Myoclonic seizures involve brief and shock-like jerks of a muscle or a group of muscles; awareness is usually preserved.</td>
</tr>
<tr>
<td>2.1.5</td>
<td>Myoclonic-atonic</td>
<td>Myoclonic-atonic seizures involve a myoclonic seizure followed by an atonic seizure and typically results in a rapid fall.</td>
</tr>
<tr>
<td>2.1.6</td>
<td>Clonic</td>
<td>Clonic generalised seizures involve generalised convulsions that lack the tonic phase seen in tonic-clonic seizures. The amplitude of the convulsions remains constant throughout the seizure, but the frequency reduces. They usually have a short postictal phase unlike tonic-clonic seizures.</td>
</tr>
<tr>
<td>Level in Seizure Hierarchy</td>
<td>Seizure Type</td>
<td>Description</td>
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<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>Clonic-tonic-tonic</td>
<td>Clonic-tonic-clonic seizures are a variation of tonic-clonic seizures that begin with a clonic phase.</td>
</tr>
<tr>
<td>2.1.7</td>
<td>Epileptic spasms</td>
<td>An epileptic spasm is a sudden flexion or extension (or mix) of the trunk and proximal muscles that lasts longer than a myoclonic jerk but shorter than a tonic seizure.</td>
</tr>
<tr>
<td>2.2</td>
<td>Absence</td>
<td>Absence seizures are subclassified as typical, atypical, myoclonic or eyelid myoclonia.</td>
</tr>
<tr>
<td>2.2.1</td>
<td>Typical Absence</td>
<td>Typical absence seizures involve sudden onset interruption of activities with a blank stare, and can be brought on by hyperventilation or photic stimulation. The eyes may briefly rotate upwards and the patient will be unresponsive when spoken to. The seizure usually resolves rapidly after several seconds to half a minute with rapid recovery.</td>
</tr>
<tr>
<td>2.2.2</td>
<td>Atypical Absence</td>
<td>Unlike in a typical absence seizure, the patient will be responsive and may be associated with other features such as loss of muscle tone or subtle myoclonic jerks.</td>
</tr>
</tbody>
</table>
## Chapter 1: Introduction

<table>
<thead>
<tr>
<th>Level in Seizure Hierarchy</th>
<th>Seizure Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.3</td>
<td>Myoclonic Absence</td>
<td>In addition to interruption of consciousness in a typical absence seizure, myoclonic absence seizures involve myoclonic jerks, which are typically bilateral. Automatisms may occur in which the patient may smack their lips, fumble with their clothes, or wander aimlessly.</td>
</tr>
<tr>
<td>2.2.4</td>
<td>Eyelid Myoclonia</td>
<td>Again, in addition to what is seen in a typical absence seizure, the patient will exhibit flickering of the eyes.</td>
</tr>
<tr>
<td>3.</td>
<td>Unknown Onset</td>
<td>This category allows for the initial classification of a seizure when the origin is not known. Further descriptors are the same as focal seizures: aware, impaired awareness, unknown awareness; to bilateral tonic-clonic.</td>
</tr>
<tr>
<td>3.1</td>
<td>Motor</td>
<td>As per 1.1 and 2.1</td>
</tr>
<tr>
<td>3.1.1</td>
<td>Tonic-clonic</td>
<td>As per 2.1.1</td>
</tr>
<tr>
<td>3.1.2</td>
<td>Tonic</td>
<td>As per 2.1.2</td>
</tr>
<tr>
<td>3.1.3</td>
<td>Atonic</td>
<td>As per 2.1.3</td>
</tr>
<tr>
<td>3.1.4</td>
<td>Epileptic spasms</td>
<td>As per 2.1.8</td>
</tr>
<tr>
<td>3.2</td>
<td>Non-Motor</td>
<td>As per 1.2 and 2.2</td>
</tr>
<tr>
<td>4.</td>
<td>Unclassified</td>
<td>This category includes all types of seizures that can’t be classified according to the above schema due to inadequate information or unusual clinical features</td>
</tr>
</tbody>
</table>
Astatic seizures, also known as drop attacks, can be caused by either atonic, tonic, myoclonic or myoclonic atonic seizures. Drop attacks are a particularly debilitating form of seizure as they can cause serious injuries. Lennox-Gastaut Syndrome (LGS) is the archetypical syndrome refractory to medical treatment that is associated with drop attacks. LGS accounts for over 35% of paediatric patients who have been treated with corpus callosumotomy. Other diagnostic factors associated with LGS include cognitive or behavioural impairment and diffuse slow spike-wave activity on electroencephalogram (EEG) with paroxysmal fast activity. LGS is an epileptic encephalopathy and patients will exhibit normal development until the onset of seizures, after which they will developmentally stagnate or regress. Bureau, Genton, Dravet et al provide a comprehensive description of LGS and other epilepsy syndromes.

1.1.3 Incidence and Prevalence
Methodological inadequacies make the epidemiology of epilepsy difficult to assess. It is estimated that approximately 5-10 people per 1000 have epilepsy. Generalised epilepsies and syndromes tend to be more prevalent in children 0 to 5 years of age, while focal seizures tend to be more prevalent in older children. The incidence of epilepsy is approximately 50 per 100 000 in industrialised countries, and 100-190 per 100 000 in resource poor countries. The incidence of epilepsy is strongly age dependent, with the highest incidence in the first year of life. There is some evidence that the incidence is decreasing in children, which may be due to a number of factors such as improved perinatal care, increased immunisation, and improved maternal health. Estimates of the risk of developing epilepsy after a first unprovoked seizure vary from 40-50%, but can be much higher if the aetiology is known.

Evidence is emerging that there may be social determinants of epilepsy. In their data linkage study, Pickerell et al found that the prevalence and incidence of epilepsy in Wales is strongly related to deprivation. Two possible explanations
could be proposed: 1) epilepsy negatively impacts the socioeconomic status of the family (social drift theory); or 2) socioeconomic status is a risk factor for the development of epilepsy (social cause theory). The cross-sectional design of the Pickerell et al study does not allow for a causal link to be found, but there was no significant change in socioeconomic status a decade after the diagnosis was made. This led the authors to conclude that social determination is a better explanation than social drift.15

There was a similar finding for disabled children in the Longitudinal Study of Australian Children (LSAC)16 and the Longitudinal Study for England and Wales17. Both studies used logistic regression models to show that family disadvantage in early childhood is associated with the development of a disability later in childhood17,16. While these were cohort studies that were designed to find causal linkages for disability, it is not unreasonable to infer deprivation as risk factor for a disability like epilepsy. It is worth considering that the universal healthcare model afforded by Medicare in Australia and the NHS in the UK ought to provide at least some prevention of epilepsy if social deprivation is a key risk factor. It may be the case that a universal healthcare model limits the amount of social drift, and a wider social solution is needed to support primary prevention. This raises questions about access to healthcare for children with epilepsy, which will be discussed later in the context of disability.

1.1.4 Aetiology

Until recently, the aetiology of epilepsy was classified as idiopathic, cryptogenic and symptomatic. Our understanding of the underlying aetiology of epilepsy has considerably expanded in recent years thanks to advances in modern neuroimaging and genetic testing. Epilepsies are now described more precisely by their specific underlying aetiologies, namely: genetic, structural, metabolic, immune, infectious and unknown.
CNS infections are the most common cause of epilepsy worldwide and as such infectious aetiologies of epilepsy have important public health consequences, particularly in developing countries. Infectious causes may be bacterial, viral, protozoal, parasitic and, more rarely, prion disease. Bacterial causes can include meningococcus, pneumococcus, haemophilus influenza b and tuberculosis, and may result in meningitis or encephalitis. Viral causes may include human immunodeficiency virus, herpes simplex virus 1, and other less common causes of viral encephalitis. Congenital cytomegalovirus is an important foetal cause of epilepsy and can result in malformations of cortical development. Cerebral malaria is the most common protozoal aetiology, while toxoplasmosis and neurocysticercosis are common parasitic causes. Creutzfeld-Jacob disease may present with new onset seizures. The specific cause will impact the treatment choice.

Immune aetiologies of epilepsy involve the sterile inflammation of the CNS and can involve both innate and adaptive immune systems. While antibody mediated causes are strongly supported by biochemical data such as specific neuroreceptor antibodies, other types of immune-mediated epilepsy are less clear or may be based on clinical response to the use of anti-inflammatory drugs in some infantile epilepsies. Moreover, innate immunity is hypothesised to contribute to seizures and epileptogenesis. This complex and active area of research is outside the scope of this thesis, but Granata et al provide an excellent overview of immune-mediated epilepsy 18.

Structural and metabolic conditions or diseases can be associated with a substantially increased risk of developing epilepsy. Structural lesions include acquired disorders such as stroke, trauma, and infection, but may be of genetic origin (eg. tuberous sclerosis and many malformations of cortical development). Metabolic epilepsies may be due to mitochondrial disorders, disorders of transportation of key nutrients (such as folate, glucose), disorders of synthesis of biochemicals, and disorders of metabolism and recycling of biochemicals (eg. biotin). While the metabolic epilepsies and some structural epilepsies are caused
by a genetic defect, there is a separate process interposed between the genetic defect and the epilepsy.

Genetic causes of epilepsy are therefore difficult to disentangle from other causes of epilepsy. As noted above, most metabolic disease has a genetic cause, but the genetic defect in a metabolic epilepsy is not the direct cause of the seizure. Rather the metabolic disease results in nutritional deficits or the build-up of waste products, which in turn cause seizures. Genetic epilepsy on the other hand involves a genetic defect in which seizures are the core symptom of the disorder, and the defect is not mediated from the seizure by another disease process. The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests (e.g., SCN1A for Dravet syndrome) or the evidence for a central role of a genetic component of the disease may come from appropriately designed family studies. Designation of an epilepsy as genetic does not exclude the possibility that environmental factors (outside the individual) may contribute to the expression of disease.

1.1.5 Pathophysiology

The pathophysiology of epilepsy is not fully understood but involves neuronal hyperexcitability and neuronal hypersynchronicity at the cellular level that leads to a paroxysm of discharges in the cortex or brainstem\(^\text{19}\), which may be due to changes in glutamatergic and GABA-ergic systems, and also catecholamine and opioid systems. Genetic and structural abnormalities may contribute to this hyperexcitability and hypersynchronicity. Generalised epileptic seizures rapidly engage bilaterally distributed networks that may be either cortical or subcortical\(^\text{20}\). However, the location and lateralisation of generalised seizures may not always be consistent and seizures may be asymmetric. Focal epileptic seizures on the other hand originate within networks that are limited to one hemisphere that may be focal or widely distributed\(^\text{20}\).
Advances in neuroimaging and bioinformatics are providing insights into the interactions between neurons and behaviours emerging from their connectivity. This has opened up the new field of connectomics, which is the study of maps of connections within a nervous system called connectomes. Connectomics can be studied from a structural or functional perspective, or at the local circuit level. Engel et al have recently speculated that epilepsy research could benefit from studying the connectomics of epilepsy.

There are complex connectomics associated with generalised seizures. Fast EEG rhythms and spikes can be induced by the thalamus, whereas slow rhythms are induced by inhibitory thalamic systems. Bursts of fast rhythms are characteristically cortical. Oscillations may originate in the thalamus, the cortex or involve a dysfunction of thalamo-cortical loops. Such oscillations can be synchronised by the thalamus and by the corpus callosum. This complex interplay of multiple potential sources of seizure activity and EEG abnormalities suggests that generalised seizures may involve the entire brain.

While the history of generalised seizures has long benefited from studies into the nature of neuronal circuitry, challenges do remain. More recently, complex systems theory has been used to espouse the concept of system epilepsies as a hypothesis for certain types of generalised seizures. In this theory, ictogenesis arises as an emergent property of the entire network and does not depend on a focal lesion. Avanzini et al propose absence epilepsy and juvenile myoclonic epilepsy as two examples of system epilepsies, Capovilla et al propose epileptic encephalopathies (notably LGS and West Syndrome) as another set of examples.

1.1.6 Diagnosis

A diagnosis of epilepsy depends largely on clinical evaluation (see Table 1.2). EEG however is the gold standard investigation to confirm whether the seizure is indeed epileptic, which can be conducted with video telemetry so that signs can be correlated with EEG rhythms.
### Table 1.2. Key diagnostic factors for epilepsy

<table>
<thead>
<tr>
<th>History</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>The onset is important. Is it rapid? Is there a prodrome? Are there precipitating factors?</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Careful history of the seizure, including eyewitness accounts, is important to first determine whether the event is a seizure and second to characterise the seizure as generalised or focal and its semiology.</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Variable depending on the semiology (see table 1.1)</td>
</tr>
<tr>
<td><strong>Resolution</strong></td>
<td>Ictal and post-ictal factors include incontinence, tongue biting on the lateral margins during a tonic-clonic seizure, presence of any post-ictal phenomena such as somnolence and confusion</td>
</tr>
<tr>
<td><strong>Precipitating Factors</strong></td>
<td>Precipitating factors include lack of sleep, hyperventilation, or light/noise.</td>
</tr>
<tr>
<td><strong>Associated Conditions</strong></td>
<td>Common associated conditions include attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), developmental delay, learning disability and psychiatric conditions</td>
</tr>
<tr>
<td><strong>Past Medical History</strong></td>
<td>Strong risk factors include: perinatal asphyxia, metabolic/neurodegenerative disorders, head trauma, structural abnormalities of the CNS, some neurocutaneous syndromes (Sturge-Weber syndrome, tuberous sclerosis). Weak factors include: ASD, CNS infection, some neurocutaneous syndromes (neurofibromatosis type 1), history of febrile seizures.</td>
</tr>
<tr>
<td><strong>Family and</strong></td>
<td>Family history of epilepsy is a strong risk factor.</td>
</tr>
<tr>
<td>Social History</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td><strong>Examination</strong></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>Neurocutaneous stigmata may be present.</td>
</tr>
<tr>
<td>Neurological</td>
<td>Generally a neurological examination does not provide much information unless the patient is examined during a seizure.</td>
</tr>
<tr>
<td>Developmental</td>
<td>Developmental delay is common among epilepsy syndromes, either preceding the onset of epilepsy or as the consequence of epileptic encephalopathy.</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>EEG</td>
<td>Epileptic discharges may be seen on inter-ictal recording. Abnormal rhythms are characteristic for type of syndrome, such as diffuse slow spike and waves while awake and fast rhythmic and slow polyspikes while asleep in LGS. However, diagnosis may require the provocation of seizures by titrating antiepileptic drugs (AED) down, using photic stimulation or sleep deprivation, etc.</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging (MRI) is useful when the diagnosis is in doubt or a secondary cause is suspected. MRI is becoming increasingly of clinical value, especially with refractory epilepsy and is important for planning resective surgery of refractory focal epilepsy.</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography (CT) is useful for excluding intra-cerebral bleeding or a space occupying lesion. CT may be used if MRI is not available, though CT is generally inferior to MRI in the investigation of epilepsy.</td>
</tr>
<tr>
<td>Genetic</td>
<td>Genetic panels and CGH arrays are increasingly valuable in the work up of epilepsy as they can</td>
</tr>
</tbody>
</table>
Chapter 1: Introduction

<table>
<thead>
<tr>
<th>Auto-Antibodies</th>
<th>provide important prognostic information and guide treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune screens are an important investigation in the appropriate setting as autoimmune causes may be treated with intravenous immunoglobulin (IVIG) and corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Other investigations are used to exclude non-epileptic causes:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Blood glucose to exclude hypoglycaemic cause.</td>
</tr>
<tr>
<td></td>
<td>2. Basal metabolic panel to exclude metabolic disorders or electrolyte imbalances.</td>
</tr>
<tr>
<td></td>
<td>3. FBC and cultures to exclude infection.</td>
</tr>
<tr>
<td></td>
<td>4. Lumbar puncture (LP) to exclude infection and inflammation.</td>
</tr>
<tr>
<td></td>
<td>5. Electrocardiogram (ECG) to exclude cardiac causes, especially long QT syndrome.</td>
</tr>
</tbody>
</table>

There is a wide range of differentials for epilepsy. Broadly these can be classed as: syncope, anoxic seizures, behavioural/psychological/psychiatric disorders, sleep related conditions, paroxysmal movement disorders, migraine disorders, and miscellaneous. The two most common differentials are syncope and psychogenic nonepileptic events. Table 1.3 below shows how these differentials can be differentiated from epilepsy on history and eyewitness accounts.
Table 1.3. Distinguishing between seizures and syncope and psychogenic nonepileptic events\textsuperscript{26}.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Syncope</th>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aura</td>
<td>Variable (see semiology)</td>
<td>None</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Acute</td>
<td>Acute or gradual</td>
</tr>
<tr>
<td>Duration</td>
<td>Variable (see semiology)</td>
<td>Seconds to minutes</td>
<td>Several minutes to hours</td>
</tr>
<tr>
<td>Movements</td>
<td>Variable (see semiology)</td>
<td>Loss of tone, myoclonus</td>
<td>Eye closure; asynchronous, pelvic thrusting; atypical features</td>
</tr>
<tr>
<td>Trauma due to the episode</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Rarely</td>
</tr>
<tr>
<td>Pre-ictal posture</td>
<td>No impact</td>
<td>Erect or standing</td>
<td>No impact</td>
</tr>
<tr>
<td>Can occur immediately upon waking</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Post-ictal phase</td>
<td>Confusion</td>
<td>Rapid return to baseline</td>
<td>Rapid return to baseline</td>
</tr>
</tbody>
</table>

1.1.7 Comorbidities

Population based studies have found that approximately 75% of children with epilepsy have a disability\textsuperscript{4}. Worsening seizures can occur with particular anticonvulsants, but usually occurs when an inappropriate anticonvulsant is initiated when the underlying cause is unknown or wrong. Developmental delay and intellectual disability are often associated with the underlying aetiology of epilepsy. The underlying mechanism of epilepsy can result in epileptic
encephalopathies, leading to a regression in development. These associated conditions may be exacerbated by drug toxicity and status epilepticus.

The prevalence of psychopathology is difficult to assess due to the heterogeneity of epilepsy and differing diagnostic techniques. While estimates for the entire population are wide as 20-80%, roughly 50-60% of children with epilepsy have a psychopathology, in particular mood disorders and psychosis. Multiple factors are associated with this risk, including age, underlying aetiology of epilepsy, medication effects, encephalopathy, the type of syndrome and its severity, among others. Psychiatric symptoms can occur peri-ictally and interictally; interictal symptoms may be regarded as comorbid.

Hyperhomocysteinaemia and hyperlipidaemia can occur as the result of certain anticonvulsants (carbamazepine, phenobarbital, phenytoin, valproic acid) and the presence of homozygous 5-methylenetetrahydrofolate reductase polymorphism. These conditions are associated with the development of long-term sequelae such as cardiovascular disease, which has raised concerns about the chronic use of carbamazepine, phenobarbital, phenytoin, valproic acid in children. Cross-sectional studies have found patients with epilepsy have an increased prevalence of cardiovascular risk factors compared with the general population. Renoux et al's population-based cohort study in the United Kingdom found no association between AED and ischaemic stroke. However there was a small increase in the risk of myocardial infarction with P450 inducing drugs, but valproic acid was associated with a decreased risk.

1.1.8 Prognosis

Seizure freedom is synonymous with a good prognosis, though epilepsy with onset in infancy and early childhood often runs a more severe course. There is a good prognosis in 70-80% of children with idiopathic epilepsy and late onset of seizures, and in those without associated neurological dysfunction. The remaining 20-30% of patients will continue to have epilepsy despite treatment.
Rapid response to therapy is an important predictor of lasting remission, along with age of onset, number of seizures early in the condition, response to AED, EEG characteristics such as slow spike and wave patterns, and may include normal MRI and IQ>50\textsuperscript{3,14,34}. But the most important prognostic factor is likely to be the aetiology of seizures\textsuperscript{14}.

Seizure onset in infancy is more likely to be associated with comorbidities and worse outcomes, although there are some self-limiting epilepsy syndromes of infancy. Evolution to other epilepsy syndromes may occur regardless of age or type of epilepsy. For example, West syndrome may evolve to LGS, myoclonic epilepsy of infancy may evolve to infrequent generalised tonic clonic seizures (GTCS), and childhood absence epilepsy may evolve to either juvenile absence epilepsy or juvenile myoclonic epilepsy.

Treatment with AED after the first seizure reduces the risk of seizure recurrence, but there is no evidence of a difference when treatment is started after the first versus second seizure in achieving 2-year seizure remission\textsuperscript{35,36}. Indeed, there is some epidemiological evidence to support the proposition that a significant number of patients will achieve seizure freedom with or without treatment with AED\textsuperscript{3}.

Early intervention with resective surgery reduces the progress of epileptic encephalopathy and both resective and disconnective surgery have been associated with improved lifespan\textsuperscript{37}. There is a well-documented “burden of normality” following successful epilepsy surgery, which must be managed carefully\textsuperscript{38}. Features of the “burden of normality” include\textsuperscript{38}:

1. **Psychological**: Changes in the concept of self are at the core of the burden of normality as the patient transitions to a “well self,” and is especially challenging in adolescents. Patients may feel the need to demonstrate their normality as they try to make up for lost time and may feel a sense of increased expectations to succeed. Conversely, patients may feel a sense of
grief over the loss of a disease that formed a core part of their identity, and may feel a sense of lost opportunities and a need to make up for lost time.

2. **Behavioural:** Patients may exhibit changes in activities including non-adherence to pharmacological management. Patients may take on too much as they try to demonstrate their normality, or the converse could be true if they resist new expectations.

3. **Affective:** Patients may experience changes in mood, from the euphoria of a cure, to anxiety of increased expectations, to depression, frustration and regret.

4. **Sociological:** Family dynamics may shift as the roles of patients and carers change, as well as changes in attitudes of family and friends towards the patient. New vocational and social opportunities open up, including freedoms associated with driving and the shift from the sick role.

Mortality rates are substantially higher among patients with epilepsy than the general population, even with good seizure control. The potential causes of death include injury, infection (e.g. aspiration pneumonia), suicide, status epilepticus and sudden unexpected death in epilepsy (SUDEP). Immediate treatment with AED does not reduce the risk of death in patients with a first unprovoked seizure, but the risk of death is higher in those who have refractory epilepsy.

### 1.1.9 Prevention

There is currently no primary or secondary prevention for epilepsy. Patients and their families should be comprehensively informed about possible precipitating factors that could exacerbate seizures, such as avoiding photostimulation and sleep deprivation in patients with juvenile myoclonic epilepsy. Patients who experience drop attacks can experience injuries, and so appropriate headwear may be necessary. However, precipitating factors are highly variable and will depend on the individual patient, so a comprehensive history is essential.
1.2 Treatment

Antiepileptic drugs (AED) are the mainstay of epilepsy treatment. Surgery is either palliative or curative in intent and is reserved for refractory epilepsy only, in which patients fail 2 or more well-chosen drugs with ongoing epilepsy. Other options include non-drug therapies such as a ketogenic diet and lifestyle measures (i.e., avoiding any precipitating stimuli such as sleep deprivation and alcohol consumption). Occupational therapy may be important if the seizures are severe enough to cause injury. For example helmets may be required in order to prevent craniofacial injuries resulting from drop attacks.

This section will focus on pharmacological and surgical treatment but acknowledges the importance and efficacy of ketogenic diets and lifestyle modifications. Cannabinoids are an active (and controversial) area of research for the treatment of refractory generalised seizures, but they will not be discussed here due to the limited clinical data.

1.2.1 Pharmacological Treatment

Pharmacological interventions are generally the first line treatment. The overarching principle by AED action is to reduce neuronal excitation. This is currently achieved via 7 mechanisms:

1. Target excitatory synapses:
   a. Enhance sodium channel inactivation, thereby reducing neuronal firing frequency
   b. Inhibit excitatory amino acid release by blocking calcium channels
   c. Inhibit excitatory amino acid release by blocking synaptic vesicle glycoproteins (notably SV2A (synaptic vesicle glycoprotein 2A))
   d. Antagonise AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainite receptors
   e. Antagonise NMDA (N-methyl-d-aspartic acid) receptors

2. Target inhibitory synapses:
   a. Enhance GABA (γ-aminobutyric acid) action
b. Inhibit GABA breakdown

c. Inhibit GABA uptake

Two new drugs have increased selectivity of receptors involved in the action of excitatory synapses. Levetiracetam targets the synaptic vesicle glycoprotein SV2A, thereby reducing the release of excitatory amino acids. Perampanel selectively antagonises AMPA receptors. The action of GABA analogues such as pregabalin and gabapentin however is unknown. While they do increase levels of GABA in the cerebrospinal fluid (CSF), they bind to L-type calcium channels thereby inhibiting excitatory amino acid release. Figure 1.2 below illustrates the mechanisms used by various AEDs.
In practice, the choice of AED depends on the seizure semiology and epilepsy syndrome, the use of other medications and the presence of any comorbidities, pregnancy plans and patient preferences. In principle, only one drug should be used at a time with one treating physician in charge. Doses should be titrated slowly until seizures are controlled or side-effects become intolerable, or the maximum dosage has been achieved. Some AED algorithms for different seizure semiologies are shown in Table 1.4 below and represent a general consensus, but practice is centre- and syndrome-specific. For instance, lamotrigine,
carbamazepine and phenobarbital act on SCN1A and thereby worsen Dravet syndrome\(^4^{2}\).

**Table 1.4. AED algorithms for different seizure semiologies.**

<table>
<thead>
<tr>
<th>Semiology</th>
<th>First Line</th>
<th>Second Line</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTCS</td>
<td>Sodium valproate or lamotrigine</td>
<td>Carbamazepine or topiramate</td>
<td>Levetiracetam, oxcarbazepine, clobazam</td>
</tr>
<tr>
<td>Absence</td>
<td>Sodium valproate, lamotrigine or ethosuximide</td>
<td>Topiramate</td>
<td>Levetiracetam, clobazam</td>
</tr>
<tr>
<td>Myoclonic, tonic, atonic</td>
<td>Sodium valproate or lamotrigine</td>
<td>Sodium valproate, lamotrigine, oxcarbazepine or topiramate</td>
<td>Levetiracetam, gabapentin, tiagabine, phenytoin, clobazam</td>
</tr>
<tr>
<td>Partial seizures</td>
<td>Carbamazepine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1.2.2 Surgical Treatment**

Surgical treatment is only considered for refractory epilepsy, which occurs in approximately 10% of cases, and only then when the risks associated with refractory epilepsy (eg injury, developmental delay, etc) outweigh the harms of surgery. Even still, epilepsy surgery is more often indicated in focal seizures rather than generalised seizures.

The surgical intent differs according to whether the seizures are focal or generalised. A curative intent with resective surgery is typically used in the treatment of focal seizures. A palliative intent is typically used in generalised
surgery. Options for generalised seizures include VNS and corpus callosotomy. As the focus of this thesis, corpus callosotomy will be discussed in detail below. VNS is an important alternative treatment to corpus callosotomy. VNS involves the insertion of an electrical stimulator beneath subcutaneous tissue, which is connected to the vagus nerve at the carotid sheath. The relative efficacy compared with corpus callosotomy will be discussed in section 1.3.2 below.

A number of classification systems exist for the seizure outcomes of epilepsy surgery, with some authors choosing their own classification system. The most widely used system is the Engel classification\textsuperscript{43}. The ILAE classification is also used and is consistent with the Engel classification\textsuperscript{44}. The Engel classification is shown in Table 1.5 below since it will be used to base the definition of a good outcome in this thesis.

**Table 1.5. The Engel classification system**

<table>
<thead>
<tr>
<th>Engel class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Free from disabling seizures</td>
</tr>
<tr>
<td>IA</td>
<td>Completely seizure free</td>
</tr>
<tr>
<td>IB</td>
<td>Nondisabling simple partial seizures only</td>
</tr>
<tr>
<td>IC</td>
<td>Some disabling seizures after surgery, but free from disabling seizures for ≥2 years</td>
</tr>
<tr>
<td>Class II</td>
<td>Rare disabling seizures (almost seizure free)</td>
</tr>
<tr>
<td>IIA</td>
<td>Initially free from disabling seizures but still has rare seizures</td>
</tr>
<tr>
<td>IIB</td>
<td>Rare disabling seizures</td>
</tr>
<tr>
<td>IIC</td>
<td>Occasional disabling seizures, but rare seizures for the last 2 years</td>
</tr>
<tr>
<td>IID</td>
<td>Nocturnal seizures only</td>
</tr>
<tr>
<td>Class III</td>
<td>Worthwhile improvement</td>
</tr>
<tr>
<td>IIIA</td>
<td>Worthwhile seizure reduction</td>
</tr>
<tr>
<td>Class</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>IIIB</td>
<td>Prolonged seizure free intervals amounting to &gt;50% of follow up but not &lt;2 years</td>
</tr>
<tr>
<td>Class IV</td>
<td>No worthwhile improvement</td>
</tr>
<tr>
<td>IVA</td>
<td>Significant seizure reduction</td>
</tr>
<tr>
<td>IVB</td>
<td>No appreciable change</td>
</tr>
<tr>
<td>IVC</td>
<td>Worsening of seizures</td>
</tr>
</tbody>
</table>

The choice of classification of seizure outcomes may affect the significance of outcomes. Stringent definitions of good outcome tend to detect significantly better seizure outcomes for total corpus callosotomy than anterior corpus callosotomy. Such systems include the Engel classification system, which has recently been shown to have good inter-rater reliability, but there was only 1 disconnection surgery in the series of 76 patients. A consistent and stringent classification system is important for assessing the effectiveness of corpus callosotomy and is important for reviewing the literature. The assessment of seizure outcomes is further complicated by the fact that patients usually have additional often severe neuropsychological problems. So it is worth noting that other outcomes may be more important to parents in the paediatric setting than seizure reduction and have received little attention in the literature. These will be discussed in detail below.

### 1.3 Corpus Callosotomy

#### 1.3.1 Rationale

The pathophysiological basis of the use of corpus callosotomy is the hypothesis that the corpus callosum is the most important pathway for the spread of epileptic activity between the two hemispheres of the brain. Figure 1.3 shows the anatomy of the corpus callosum is divided rostro-caudally into five parts: the rostrum, the genu, the body, the isthmus and the splenium. The genu and rostrum together account for approximately 1/3 of the entire corpus callosum, the body accounts for...
approximately 1/3 of the entire corpus calosum, and the splenium and the isthmus account for approximately 1/3 of the entire corpus calosum\textsuperscript{45}. The splenium accounts for approximately 1/5 of the entire corpus calosum, and is an important landmark for corpus callosotomy.

The corpus callosum is not the only interhemispheric connection in the human brain: the anterior, middle, habenular and posterior commissures as well as thalamic and brainstem structures provide alternate interhemispheric white matter connections.

\textbf{Figure 1.3. Anatomy of the corpus callosum (plate 715)}\textsuperscript{46}.

This hypothesis was first proposed after Van Wagenen and Herren published a case series on 10 patients with tumours of the corpus callosum\textsuperscript{47}. As the tumors progressed, generalised seizure activity reduced and became confined to a single
hemisphere. The hypothesis was later tested in monkey-models\textsuperscript{48} and the technique was employed in the first commissurotomy in humans\textsuperscript{47}.

However the postoperative morbidity of a commissurotomy can be very high\textsuperscript{49}, most notably disconnection syndrome, which was studied by Sperry in patients who had undergone commissurotomy and compared them to patients with agenesis of the corpus callosum\textsuperscript{50}. Disconnection syndrome presents with a combination of alien limb, apraxia, tactile and/or visual anoma, agraphia, neglect, dyslexia. Patients may have difficulty naming or recognising objects when they cross the midline, they may experience alien limb syndrome, find reading and writing difficult, and find speech difficult. This poses a challenge to the rehabilitation of patients.

Based on this work, corpus callosotomy was proposed by Sperry’s student Gazzaniga as an approach to reduce the likelihood of disconnection syndrome. Corpus callosotomy was subsequently demonstrated to be sufficient for reducing generalised seizures and resulted in lower postoperative morbidity than commissurotomy\textsuperscript{49}. Spencer, Spencer, Williamson et al were the first to report on the anterior division of the corpus callosum\textsuperscript{51}, which involves the sparing of the splenium with the aim to reduce the possibility of disconnection syndrome. They argued that the corpus callosotomy should only be completed if there has been an incomplete response to the anterior corpus callosotomy\textsuperscript{52}. Others have also reported on posterior division of the corpus callosum. While Pinard et al found a poor response to treatment in 3 patients\textsuperscript{53}, one recent case series of 36 patients demonstrated a good response to treatment with posterior corpus callosotomy and suggest that there are more favourable connectomics\textsuperscript{54}.

1.3.2 Paediatric Outcomes

In the first systematic review of the paediatric literature, Graham, Tisdall and Gill\textsuperscript{5} found 12 papers that reported corpus callosotomy outcomes in patients under the age of 18 at the time of surgery, and with at least 1 year median follow up\textsuperscript{53,55-65}.
They found that 88.2% of patients who underwent complete corpus callosotomy were either free or almost free of drop attacks compared with 58.6% of patients who underwent anterior corpus callosotomy. Drop attacks showed greater benefits of corpus callosotomy compared with other generalised seizures. In studies that used outcomes based on the Engel classification system, significantly more complete corpus callosotomy patients had a worthwhile reduction in drop attacks compared with partial corpus callosotomy patients\(^5\). This is reflected in the broader literature on corpus callosotomy\(^34,66\).

VNS is reported to be no better than corpus callosotomy\(^5,67\), although Cukiert et al found that corpus callosotomy was superior to VNS for drop attacks\(^55\). Nevertheless VNS is a reversible intervention with fewer complications. Cukiert et al have proposed that VNS could be offered as an initial treatment option before progressing to corpus callosotomy due to its reversible nature\(^55\), but Rathore et al have observed that VNS is more expensive than corpus callosotomy, so can be prohibitive in developing countries\(^59\).

Corpus callosotomy has not been associated with a reduction in the number of AED\(^5\). Three papers in Graham et al’s review reported formal neuropsychiatric outcomes\(^60,64,65\). 83% of patients had significantly improved behaviour following surgery\(^5,59,63-65\) and 82% of patients had improved psychomotor function\(^5,53\). Nevertheless, there was no significant change in IQ or DQ following surgery\(^5,60,64\). However if a modest reduction in seizure can be achieved, parents may rate the outcome highly\(^5,59\). Indeed, most parents report they are pleased with the outcomes and would recommend corpus callosotomy to others\(^58,59,61,64\).

Adverse outcomes after corpus callosotomy include neurological complications and surgical complications. Neurological complications include the onset of new seizures, disconnection syndrome and other neurological conditions. Surgical complications include hydrocephalus, infections, CSF leaks, deep vein thrombosis/pulmonary embolus (DVT/PE), pneumonia, haematomas and metabolic disturbances\(^5\). Up to 20% of patients will develop new onset seizures,
but they are more likely to be generalised seizures than partial seizures\textsuperscript{5}. The development of new onset seizures is equally likely regardless of extent of the callosotomy. Disconnection syndrome occurred in 7\% of all patients reviewed by Graham, Tisdall and Gill and was significantly more likely in complete corpus callosotomy compared with partial corpus callosotomy (13\% vs 0\%; p<0.05)\textsuperscript{5}. Remarkably, disconnection syndrome was always transient and usually only occurred in children with either LGS or severe intellectual disability. Other neurological complications were also transient and occurred in 13\% of patients and are equally likely regardless of extent of callosotomy\textsuperscript{5}. Surgical complications occurred in up to 6\% of patients and are equally likely regardless of extent of callosotomy and the reported mortality rate was 0.26\%\textsuperscript{5}.

Outcomes in paediatric patients are better than those reported in adult patients\textsuperscript{5}. Paediatric patients are more likely to have a reduction in seizures following surgery and less likely to develop complications. However, there is no reported correlation with age or earlier surgery in this population\textsuperscript{5}, despite the fact that earlier surgery is generally preferred in epilepsy surgery\textsuperscript{68}.

Diffusion tensor imaging (DTI) studies have been used to investigate the microstructural changes following corpus callosotomy\textsuperscript{69-71}. These studies show that the early reductions in white matter tracts are consistent with axonal degradation, while later reductions are consistent with myelin degradation\textsuperscript{71}. Such degenerations persist in the long term, though some intact fibres may remain following surgery\textsuperscript{70}. However DTI is limited to the evaluation of white matter integrity. Diffusion tensor fibre tracking (DT-FT) on the other hand allows the integrity of the white matter tracts to be evaluated, which can provide an overview of the impact of the corpus callosotomy on white matter tracts and thereby potentially support a more informed prognosis\textsuperscript{69}. From a treatment perspective, DTI combined with functional MRI (fMRI) could enable the epileptogenic brain structures to be better defined and thereby support more effective surgical treatment\textsuperscript{21}. 
Overall the quality of the evidence on outcomes from corpus callosotomy is low due to the fact that the included studies each had an inherent risk of bias in their design. The level of evidence for corpus callosotomy is appropriate for raising hypotheses regarding corpus callosotomy as a treatment for refractory generalised seizure. However authors consistently concluded that corpus callosotomy is a safe and effective treatment. Such conclusions can only be confirmed with case control or randomised trials. Dwivedi et al recently conducted an RCT of 116 patients undergoing epilepsy surgery in India. They used a similar randomisation to Wiebe et al’s landmark epilepsy surgery RCT and included 10 patients who underwent corpus callosotomy and compared them with 16 patients waiting for corpus callosotomy. However none of the corpus callosotomy patients achieved seizure freedom compared with only one of the control group. Seizure freedom is an uncommon outcome in this group of patients and may be a reflection of the need for a trial specifically designed to assess corpus callosotomy outcomes. Appendix A expands on the broad scope of an RCT for corpus callosotomy as outlined by Graham, Tisdall and Gill.

1.4 Difficult Decision-Making
The evidence suggests that corpus callosotomy is likely to be a highly effective and safe procedure. While there is a risk of neurological complications, notably disconnection syndrome, these complications usually resolve in children and earlier intervention has demonstrable benefits on quality of life. However, some parents find the prospect of disconnection syndrome challenging and resist corpus callosotomy despite the good body of evidence. This raises a number of ethical questions that are not sufficiently addressed by the evidence, such as access, consent, and best interests. Chapter 4 uses a clinical case study to frame some of these bioethical issues of corpus callosotomy.

There are multiple stakeholders involved in epilepsy surgery – the patient and their parents, the treating team, the hospital administration, federal and state health departments, and society. Each stakeholder has different and at times conflicting objectives, which is highlighted by the case in chapter 4. Moreover, the
stakeholders often have limited knowledge about the incentives considered by other stakeholders as well as their decisions. But this highly complex interplay of stakeholders rests on the surrogate consent of the parents.

The second opinion can be an invaluable technique to help parental decision-making. A second opinion offers a means to increase certainty for parents and patients as to the considerations of the treating team, as well as the likely position of the hospital and health departments. Alternative therapies to corpus callosotomy, such as VNS, may also be discussed, and opportunities to meet parents of former patients may also be beneficial. Ultimately this underlines the value of patient education in this complex decision-making process.
2 STUDY METHODS

While 88% of paediatric patients reported to achieve no or rare drop attacks following complete corpus callosotomy, this figure is based on the outcome at last follow up. Indeed, in their review of epilepsy surgery, Telléz-Zenteno et al. found sustained freedom from drop attacks diminishes significantly beyond 5 years. More recently, Stigsdotter-Broman et al’s population study of long term outcomes found that sustained benefit is possible up to 10 years. Given that it is not clear how the efficacy of corpus callosotomy changes over time, it is reasonable to investigate how the effect of corpus callosotomy on the primary seizure (drop attacks) evolves. Yet this approach has not been published in the corpus callosotomy literature.

This chapter details the methods that will be used in Chapter 3. The original data from this thesis has been published in the international peer review journal Developmental Medicine & Child Neurology, which is reproduced in Appendix B.

2.1 Ethics

Ethics approval for this study was granted by the Sydney Children’s Hospital Network Human Research Ethics Committee (HREC Reference LNR/14/SCHN/178) and the GOSH Clinical Audit Department (Registration...
The applications were to review the clinical data on all patients who had undergone corpus callosotomy at GOSH and CHW.

2.2 Aim and Objectives

The aim of this thesis is to:

1. Describe the outcomes of 20 years of experience with corpus callosotomy at GOSH and CHW.

In line with this aim, the objectives of this thesis are to:

1. **Describe the tolerability of corpus callosotomy.** This objective will be achieved by analysing the surgical and neurological complications directly attributable to the corpus callosotomy at GOSH and CHW.

2. **Describe the efficacy of corpus callosotomy.** This objective will be achieved through the analysis of the effect on the primary seizure type (namely drop attacks), the impact on injuries from drop attacks, the effect on other seizure types, and any changes in AED usage. The effect on drop attacks will be analysed for durability of outcome using a Kaplan-Meier survival analysis.

3. **Identify any clinical predictors of good drop attack outcomes.** This objective will be achieved through the use of multivariable regression analysis of a number of clinical factors that have been found to be predictors of good outcomes of drop attacks based on the study by Asadi-Pooya et al.\(^{34}\)

It should be noted that this thesis is a retrospective study and therefore can only be used for hypothesis generation rather than testing. Nevertheless, as an observational study I hope that this data will be valuable for assessing the safety of corpus callosotomy.
2.3 Search Strategy

Data for this study was sourced from an exhaustive search of all clinical records for each patient who underwent corpus callosotomy at GOSH and CHW during the period January 1995 to December 2015. The search was done in order to accurately record patient demographics, the clinical progression of seizure semiology, any complications of surgery or epilepsy, and changes in AED regime. Database searches were conducted on location at each hospital in order to maintain data security.

The databases differed slightly between sites and therefore the search strategies used at each location was different:

1. **GOSH**: Complete medical records for epilepsy surgery patients at GOSH are maintained at the departmental level. Microsoft Project was used to conduct searches for all patients who had undergone corpus callosotomy at GOSH by entering corpus callosotomy as a keyword. The Microsoft Project search results linked directly to all records stored in the GOSH database for each patient.

2. **CHW**: Medical records for patients at CHW are maintained at the hospital level. A patient list based on medical records numbers was available at the CHW department of neurology and neurosurgery. Patients were identified from these records and then cross-checked with the Department of Medical Records, who were able to conduct a complete search of Power Chart for all patients who had undergone corpus callosotomy. The Power Chart search results linked directly to all patient electronic records stored in the hospital database, however there were six patients who still had data on Microfilm. These records were reviewed in the Department of Medical Records. By doing this cross checking, it was possible to ensure that all eligible patients were captured who were eligible by complementing multiple search methods.

These database searches returned a significant amount of clinic letters and notes, correspondences, emergency admissions, imaging studies, neurophysiological
studies, neuropsychological assessments, nursing phone calls, and allied health assessments and notes. I retrieved the vast majority of data for this study from these records. I used an earlier and less detailed dataset obtained by Dr. Kavitha Kothur in order to validate my own dataset. I also developed a simple proforma of outcome data designed for a phone interview and enlisted the help of the GOSH epilepsy service clinical nurse consultant Ms. Nicola Barnes in order to attempt to contact 17 GOSH patients who were lost to follow-up.

The process of encoding this data is detailed in Section 2.7.2 below.

2.4 Definitions

2.4.1 Seizures

Seizure semiology is defined in Chapter 1 according to the 2016 ILAE Commission on Classification. Refractory epilepsy is defined as “the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to sustain seizure freedom”\(^7\). Table 1.4 provides typical AED regimes, with first and second line AEDs for a number of different seizure semiologies.

2.4.2 Corpus Callosotomy

Corpus callosotomy is defined as the surgical division of the corpus callosum. The corpus callosotomy is classified according to the planned extent of callosal section:

1. **Partial corpus callosotomy:** Any corpus callosotomy that plans to spare parts of the corpus callosum is defined as a partial corpus callosotomy:
   a. *Anterior 2/3 corpus callosotomy:* division of the corpus callosum while sparing the splenium and the isthmus.
   b. *Anterior 3/4 corpus callosotomy:* division of the corpus callosum and sparing the splenium and approximately half of the isthmus.
c. *Anterior 4/5 corpus callosotomy*: division of the corpus callosum and sparing only the splenium.

d. *Posterior corpus callosotomy*: division of the splenium and the isthmus of the corpus callosum.

2. **Complete corpus callosotomy**: Any corpus callosotomy that is planned to divide the entire corpus callosum are classified as having a complete corpus callosotomy:

   a. *Complete corpus callosotomy*: division of the entire corpus callosum until the Vein of Galen can be identified intraoperatively.

   b. *Subtotal corpus callosotomy*: division of the corpus callosum with rostral parts of the splenium remaining. The Vein of Galen was not identified intraoperatively but the surgeon has assessed the division to be sufficient to close the craniotomy. This may occur if the caudal extent of the division becomes offset.

3. **Completion of corpus callosotomy**: Patients with prior anterior corpus callosotomy undergoing further surgery for a complete corpus callosotomy were classed as having a completed corpus callosotomy. This was the only circumstance under which a posterior corpus callosotomy was performed at GOSH or CHW.

4. **Abandoned**: A procedure is defined as abandoned if the surgeon has performed a craniotomy but not proceeded with the division of the corpus callosum. One callosotomy was abandoned at GOSH due to tortuous anatomy of the bridging veins.

2.4.3 Imaging

Imaging findings were defined using the Barkovich classification system of malformations of cortical development\textsuperscript{78}. The Barkovich classification system uses a developmental and genetic approach to classify malformations of the cortex. The classification hierarchy is shown in Table 2.1.
Table 2.1. The Barkovich classification system of malformations of cortical development.

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Malformations secondary to abnormal neuronal and glial proliferation or apoptosis</td>
</tr>
<tr>
<td>Group I.A</td>
<td>Severe congenital microcephalies</td>
</tr>
<tr>
<td>Group I.B</td>
<td>Megalencephalies</td>
</tr>
<tr>
<td>Group I.C</td>
<td>Cortical dysgenesis with abnormal cell proliferation but without neoplasia, such as tuberous sclerosis and focal cortical dysplasia type II</td>
</tr>
<tr>
<td>Group I.D</td>
<td>Cortical dysgenesis with abnormal cell proliferation and with neoplasia</td>
</tr>
<tr>
<td>Group II</td>
<td>Malformations due to abnormal neuronal migration</td>
</tr>
<tr>
<td>Group II.A</td>
<td>Heterotopias, including periventricular nodular heterotropia, periventricular heterotropia, and ribbon-like heterotopia</td>
</tr>
<tr>
<td>Group II.B</td>
<td>Lissencephalies (with or without subcortical band heterotopia)</td>
</tr>
<tr>
<td>Group II.C</td>
<td>Subcortical heterotopia and sublobar dysplasias</td>
</tr>
<tr>
<td>Group II.D</td>
<td>Cobblestone malformations</td>
</tr>
<tr>
<td>Group III</td>
<td>Malformations secondary to abnormal postmigrational development</td>
</tr>
<tr>
<td>Group IIIA</td>
<td>Polymicrogyria and schizencephaly</td>
</tr>
</tbody>
</table>
Chapter 2: Study Methods

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group III.B</td>
<td>Cortical dysgenesis secondary to inborn errors of metabolism</td>
</tr>
<tr>
<td>Group III.C</td>
<td>Focal cortical dysplasias (FCD) without dysmorphic neurons, namely Type I and Type III FCD</td>
</tr>
<tr>
<td>Group III.D</td>
<td>Postmigrational developmental microcephaly, such as Rett syndrome, Angelman syndrome</td>
</tr>
</tbody>
</table>

2.4.4 Neuropsychology

Neuropsychological assessment assesses a patient’s cognitive ability in a number of areas including: memory, attention, processing speed, reasoning, judgment, problem-solving, spatial function, and language function\(^79\). Table 2.2 shows the two key assessment domains reported in epilepsy surgery patients\(^80\).

Table 2.2. Neuropsychological assessment domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay</td>
<td>Severity of developmental delay was defined as mild (IQ&lt;70), moderate (IQ&lt;50), severe (IQ&lt;30)</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Formal diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD), as well as behavioural qualifiers such as cooperative, aggressive, agitated, somnolent, etc</td>
</tr>
</tbody>
</table>
2.4.5 Neurophysiology

Ictal EEG and video EEG (VEEG) changes were defined using the classification system used by Hanson et al\textsuperscript{81}. In their study of corpus callosotomy in adults, Hanson et al noted a difference in outcome based on the ictal type, but no relationship with interictal changes\textsuperscript{81}:

1. Type I: onset of generalised slow spike-wave, electrodermal patterns, or fast activity with low amplitude;
2. Type II: build-up of generalised activity or asymmetrical onset of activity.

2.4.6 Complications

Severity of surgical and neurological complications were classified using a similar system defined by Hader et al\textsuperscript{82}, as shown in Table 2.3 below.

**Table 2.3. Severity of complications.**

<table>
<thead>
<tr>
<th>Complication Type</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>Hydrocephalus</td>
<td>CSF leak</td>
</tr>
<tr>
<td></td>
<td>Deep infections (such as intracerebral and epidural abscesses)</td>
<td>Intracranial/extracranial infection</td>
</tr>
<tr>
<td></td>
<td>requiring drainage and/or bone flap removal</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DVT/PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracranial haematomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic disturbances</td>
</tr>
</tbody>
</table>
### Complication Type

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>All neurological complications persisting beyond 3 months of surgery</td>
<td>All transient neurological complications resolving within 3 months of surgery</td>
</tr>
</tbody>
</table>

### 2.5 Corpus Callosotomy Procedure

#### 2.5.1 Patient Workup

Patients with refractory epilepsy were referred for consideration of epilepsy surgery at each unit. This involved a detailed multidisciplinary review of the patient history and examination findings, seizure semiology, neuropsychological assessment, neurophysiological studies, and imaging. Patients were considered for corpus callosotomy if they had generalised refractory epilepsy with drop attacks. The decision for partial or complete corpus callosotomy was based on neuropsychological assessment; patients with poor cognitive function, especially verbal function, were more likely to be selected for complete corpus callosotomy. Completion of corpus callosotomy was based on post-operative seizure control.

Patients were worked up for corpus callosotomy as described by Cross et al\(^8^0\):

1. **EEG**: interictal scalp EEG including natural sleep recordings, as well as VEEG for recording ictal events. These were obtained using standard techniques described by the International Federation of Clinical Neurophysiology\(^8^3\).
2. **Structural Imaging**: MRI using a specified epilepsy protocol; CT was utilised when indicated, such as calcification. Special sequences were required for infants and children under 24 months old due to their immature myelation; serial sequences were also used in this group in order to identify abnormalities.
3. Neuropsychology: age appropriate intelligence, development and behaviour tests.

While the guidelines by Cross et al were published in 2006, and so only cover a decade of the present case series, it is important to note that these guidelines were developed at GOSH and it is therefore not surprising that the work up of GOSH patients has been consistent with Cross et al’s guidelines. Moreover, there is a strong historical collaboration between CHW and GOSH, and so CHW adopted a similar work up for their patients consistent with these guidelines.

2.5.2 Surgical Approach

The surgical approach and technique in both centres involved a single craniotomy over the midline and centred on the coronal suture. Depending upon the vascular anatomy, the callosotomy was performed to the left of the falx cerebri. This defines a plane for dissection.

The dissection was taken to the planned posterior extent of the corpus callosotomy. Anterior corpus callosotomy included any callosal section that aimed to spare the splenium and all or part of the isthmus. Complete corpus callosotomy included any callosal section that aimed to divide the splenium to the Vein of Galen. The callosotomy then proceeded caudo-rostrally until the anterior cerebral arteries could be identified. The depth of the disconnection of the corpus callosum proceeded until the ependyma was identified. There are no anatomical landmarks so neuronavigation offered the best intraoperative decision tool. The loss of accuracy as the division advances was small due to the fact that the procedure was midline.
2.5.3 Follow Up

This was a retrospective study that used all available routine medical, nursing and allied health correspondences and emergency department admissions, as well as any clinically necessary imaging and neurophysiological studies and neuropsychological assessments.

All patients were followed up within 6 weeks of surgery. Ongoing follow up was recorded where available in the medical records. Owing to the severity and complexity of refractory generalised seizures, most patients were followed up regularly with formal consultant review, plus nursing staff regularly contacted patients and their families. Follow up clinics involved a detailed review of the patient history and seizure semiology and frequency. AED efficacy and side effects were also reviewed for appropriateness and titrated if necessary. Parents were also asked about any concerns that they may have and were invited to ask questions.

When a patient’s epilepsy was worsening, new seizure types were emerging, or the seizures were not improving despite treatment, further investigations were conducted. These included additional imaging or VEEG. Further neuropsychological assessments were also conducted if clinically indicated.

2.6 Patient Selection

All patients who underwent corpus callosotomy at CHW and GOSH between January 1995 and December 2015 were considered for inclusion. Patients were excluded from the study based on the following exclusion criteria:

1. **Age at Surgery:** The patient was 18 years or older at the time of surgery and therefore not considered a paediatric patient even though they underwent surgery at CHW or GOSH. This typically occurred if the patient was well-known to the paediatric epilepsy service, or if the patient had a significant
level of developmental delay and/or other comorbidities that made the patient too complex for treatment in an adult setting.

2. **Lost to Follow Up**: The patient was considered lost to follow up if they had less than 3 months follow up. This occurred if the post-surgery clinic was the only clinical record available after surgery.

3. **Additional Resection**: If the patient underwent additional resective surgery at the time of surgery, they were excluded as this could cloud the results of the corpus callosotomy outcomes.

A total of 76 patients underwent corpus callosotomy at GOSH (n=49) and CHW (n=27) over this period. This included 5 patients who had a completion of their anterior corpus callosotomy and 1 complete corpus callosotomy patient for whom the surgery was abandoned. An intention to treat principle was used to analyse these patients:

1. **Completion of Corpus Callosotomy**: The patients with previous anterior corpus callosotomy were analysed in that cohort until completion. These patients were then analysed as part of the complete corpus callosotomy cohort following completion of their corpus callosotomy.

2. **Abandoned Corpus Callosotomy**: The patient for whom a complete corpus callosotomy was abandoned was analysed in the complete corpus callosotomy cohort.

A total of 55 patients met final inclusion criteria (GOSH n=33; CHW n=22). The following exclusion criteria were met by 21 patients:

1. **Age at Surgery** (n=2): Two patients were 18 years old at the time of surgery, one at GOSH and one at CHW. Both patients were severely developmentally delayed. They were treated at CHW and GOSH due to the higher levels of ward-based experience with patients with severe developmental delay.

2. **Lost to Follow Up** (n=18): Records other than the post-surgical follow up for 3 CHW patients and 15 GOSH patients were not available:
a. **CHW**: The three CHW patients were private patients who underwent surgery at CHW due to the higher levels of ward-based experience with epilepsy surgery.

b. **GOSH**: The GOSH epilepsy service registered nurse, Ms Nicola Barnes, attempted to contact 17 GOSH patients who had been lost to follow up. She was able to make contact with 2 patients who were included in the cohort. Four patients were referred to GOSH from other UK hospitals. They were discharged back to their local hospitals for follow up. The remaining 11 GOSH patients were international patients from the Middle East (n=8), continental Europe (n=2) and the Republic of Ireland (n=1). They were treated at GOSH under a diplomatic exchange and followed up in their home countries. However there was no extended follow up beyond three months.

3. **Additional Resection** (n=1): One patient at CHW also underwent a temporal lobectomy at the time of surgery. This patient had generalised seizures secondary to a herpes simplex virus infection.

### 2.7 Data

#### 2.7.1 Data Sources

The following data sources were used:

1. Patient history and seizure semiology described in outpatient clinics letters, which were the primary source of data and provided an overarching view of the patient's post-surgical trajectory. Patients typically attended clinics every 6 months, and would attend a post-surgical clinic at 6 weeks following surgery. Seizure semiology was recorded from the clinic letters and coded using the ILAE 1989 classification of seizures described in Table 1.18. These notes also included demographic data, seizure frequency, detail on AED regimes, injuries sustained from drop attacks, and any behavioural concerns raised by parents.
2. Pre-operative neuropsychological assessments detailed patient DQ or IQ, and their behaviour and cognition. These reports also provided a rich source of patient history to complement clinic letters.

3. Imaging studies were included as part of the epilepsy surgery workup for each patient. They were used to identify structural aetiologies of epilepsy, and in 30 patients provided confirmation of the extent of corpus callosotomy.

4. Ictal and interictal scalp (or intracranial grid) EEG/VEEG studies. These studies also included a rich source of patient history to complement clinic letters.

5. Genetic studies were conducted in 21 patients. These provided another source of patient history to complement clinic letters as well as detailed data on genetic aetiologies of epilepsy.

6. Emergency department and surgical discharge summaries also provided rich detail on complications of epilepsy, comorbidities, injuries following drop attacks, and complications of surgery. However data from emergency departments was not available for all patients as both GOSH and CHW are referral centres from other hospitals where patients would present with injuries.

2.7.2 Data Collection

Data was collected from the sources described above in five phases for each of the 76 patients. Inclusion criteria were assessed on the basis of this data collection, with 21 patients being excluded from the study. The data collection phases for each patient are as follows:

1. **Pre-surgical data collection:** The pre-surgical patient history was reviewed from clinical correspondences, with emphasis placed on the letters closest to admission for surgery. This allowed the following data to be collected:
   
   a. **Patient demographics:** date of birth, epilepsy diagnosis, epilepsy aetiology, comorbidities, age at seizure onset, age at surgery, planned type of surgery.
Chapter 2: Study Methods

b. *Seizure data*: seizure semiology and seizure frequency as described in the correspondences, including any reports of injuries from drop attacks. Seizure frequency was classified as daily, weekly, monthly or occasional for each seizure type. Whenever they occurred, injuries were a cause for concern for parents and were reported within formal clinics. This was noted by the consultant and included in their correspondences.

c. *Investigation data*: imaging studies, VEEG results and genetic studies.

d. *Assessment data*: IQ/DQ test results, behavioural assessments and diagnoses.

e. *Treatment data*: previous AED drugs and doses, presence of VNS and status, history of other epilepsy surgery, trials of ketogenic diet.

f. *Other*: demographic data allowed for exclusion of patients older than 18 at the time of surgery and other resective surgery at the time of corpus callosotomy.

2. **Last follow up data collection**: The patient history at last follow up were reviewed from clinical correspondences. The following data was collected at this phase:

a. *Seizure data*: seizure semiology and seizure frequency as described in the correspondences, including any reports of injuries from drop attacks. This is described above in phase 1.

b. *Investigation data*: further imaging studies, further VEEG results and genetic studies.

c. *Assessment data*: further IQ/DQ test results, further behavioural assessments. It should be noted however that formal assessment was only conducted for 11 patients.

d. *Treatment data*: current AED drugs and doses, further surgery or VNS implantation, trials of ketogenic diet.

e. *Other*: this was an important data collection phase as patients were excluded if the last follow up was at the post-surgical clinic, which occurred within the first 6 weeks.

3. **Post-surgical data collection**: Post-surgical clinic letters were reviewed for seizure semiology, completeness of callosotomy, and complications. Where
possible the completeness of the callosotomy was reviewed on post-
surgical imaging reports.

4. **Return of drop attacks data collection**: If patients continued to have drop
attacks at last follow up, correspondences and letters were reviewed in
order to identify the time post-surgery that drop attacks had returned.
Seizure semiology and frequency as described in these correspondences, as
well as reports of injuries sustained as the result of drop attacks, were
recorded.

5. **Additional data collection**: Any additional data that was not collected in any
of the preceding 4 data gathering phases was searched for in imaging
reports, neurophysiological studies, neuropsychological assessments, and
 genetic studies.

### 2.7.3 Data Entry

Data was entered into an excel spreadsheet using the data sources described in
section 2.7.1. The data fields are shown in Table 2.4.

### Table 2.4. Data fields for capturing data from patient records

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Data Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>De-identified signifier</td>
<td>Coded number unrelated to Name, Address or medical record number</td>
</tr>
<tr>
<td>Demographics</td>
<td>Sex</td>
<td>Male or Female</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Syndrome</td>
<td>LGS, West syndrome, Ohtahara syndrome, Doose syndrome, Sturge-Weber syndrome, Dravet syndrome, myoclonic epilepsy of infancy, or any other epilepsy syndrome</td>
</tr>
</tbody>
</table>
### Data Type: Aetiology
- **Description**: Genetic, structural, metabolic, infective, inflammatory, unknown

### Data Type: Comorbidities
- **Description**: ASD, ADHD, cerebral palsy (CP), etc

### Data Type: Age at epilepsy onset
- **Description**: Age in months at epilepsy onset as described in source data

### Data Type: Age at surgery
- **Description**: Age in months at surgery

### Data Type: Age at last follow up
- **Description**: Age in months at last follow up

### Data Type: Age at return of drop attacks (if applicable)
- **Description**: Age in months based on first discussion of drop attacks in source data following surgery

### Data Type: Age at death (if applicable)
- **Description**: Age in months

### Data Type: Seizure Semiology
- **Description**: Number and types of seizures, frequency of seizures (daily, weekly, monthly, sporadic), regular injuries as a result of drop attacks

### Data Type: Surgery
- **Extent of callosotomy**: Anterior 2/3, Anterior 4/5, Subtotal, Total, Abandoned, Completed
- **Neurological complications**: Minor and major complications as defined in table 2.4
<table>
<thead>
<tr>
<th>Data Type</th>
<th>Data Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical complications</td>
<td>Minor and major complications as defined in table 2.4</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>MRI findings classified using the Barkovich classification</td>
<td></td>
</tr>
<tr>
<td>Ictal and inter-ictal EEG (pre-surgery, post-surgery, last follow up)</td>
<td>EEG findings classified using Hanson classification in table 2.3</td>
<td></td>
</tr>
<tr>
<td>Genetic studies</td>
<td>Karyotype, COL4A1, TSC2, MeCP2 duplication, etc</td>
<td></td>
</tr>
<tr>
<td>Developmental delay (pre-surgery, post-surgery, last follow up)</td>
<td>Severity level as defined in table 2.2</td>
<td></td>
</tr>
<tr>
<td>Behaviour (pre-surgery, post-surgery, last follow up)</td>
<td>Formal diagnosis as well as qualifiers as described in table 2.2</td>
<td></td>
</tr>
<tr>
<td>Diet (pre-surgery, post-surgery, last follow up)</td>
<td>Any special diets, namely ketogenic diet</td>
<td></td>
</tr>
<tr>
<td>AED (pre-surgery, post-surgery, last follow up)</td>
<td>Number of AED</td>
<td></td>
</tr>
<tr>
<td>VNS (pre-surgery, post-surgery, last follow up)</td>
<td>Presence and status of VNS (active or inactive)</td>
<td></td>
</tr>
<tr>
<td>Corpus callosotomy</td>
<td>Previous anterior corpus callosotomy, previously abandoned corpus callosotomy</td>
<td></td>
</tr>
<tr>
<td>Other epilepsy surgery</td>
<td>Resection, callosotomy</td>
<td></td>
</tr>
</tbody>
</table>
2.8 Outcomes

Seizure outcomes were based on the Engel classification, which is shown in table 1.5. A good outcome was defined as completely seizure free or almost seizure free. This definition is consistent with Tellez-Zenteno et al's systematic review of epilepsy surgery and Graham et al's systematic review of corpus callosotomy in paediatric patients, and consequently allows for ready comparison with the literature.

The primary outcome for this study was a good outcome for drop attacks. While there is some controversy over its use in disconnective surgery, the Engel classification system is clinically relevant and commonly used in clinical practice for reporting epilepsy surgery outcomes as well as the literature. Therefore the Engel classification system has been used as the basis for the definition of good outcome in this thesis; the phrase “Engel Class I-II” has not been used in order to avoid confusion as this could imply “completely or almost seizure free.” Other classification schemes have been used in the literature and may be more appropriate, but the Engel classification allows for ready comparison with the majority of the literature. Therefore a good outcome was defined as free or almost free of drop attacks.

Drop attacks were classified as tonic, atonic, or myoclonic. Data on their frequency and outcome were collected from clinic reports as described above.

The following secondary outcomes were also included:

1. **Other seizure outcomes at last follow up**: based on Engel class I-II outcome, good outcome for other seizures was defined as free or almost free of generalised seizures, partial seizures and spasms at last follow up. New onset seizures were also analysed.

2. **Injury outcomes at last follow up**: The number of patients who were reported to be sustaining injuries between clinic appointments as a result of their drop attacks at the time of surgery compared with those at last follow
up. This was noted in clinic notes for all patients as it was of significant concern to parents.

3. **Changes in the number of AED at last follow up**: The number of AED at the time of surgery compared to the number of AED at last follow up.

4. **Surgical and neurological complications**: The severity of surgical and neurological complications were classified using Table 2.4 above. Data obtained from post-surgical clinics and surgical reports was readily amenable to this classification system.

5. **Neuropsychological changes at last follow up**: Formal neuropsychological assessments at last follow up were compared with formal neuropsychological assessments conducted as part of the patient workup.

6. **Neurophysiological changes at last follow up**: Formal neurophysiological findings were classified according Hanson et al’s classification described above using a post hoc approach. The findings at last follow up were compared with the findings from patient workup.

2.9 **Statistical Analysis**

All statistical analysis were conducted using SAS version 9.4. All p-values were two-tailed and significance was defined as $p < 0.05$.

Categorical data was compared using Fisher’s exact test and interval data was compared using Mann-Whitney’s U test. Fisher’s exact test is more accurate than Pearson Chi square test when the number of patients is small, such as in this present study. The test was used to compare data in a 2x2 matrix of patients in two groups, say GOSH and CHW patients, with a given category, say female or male. The Mann-Whitney U test was used in preference to Student’s t-test as it does not require the assumption of normality of data. The test was used to compare (for instance) age distribution at GOSH and CHW. The null hypotheses that were tested with each of these tests were that there was no significant difference between the two statistics being compared.
The time while patients continued to have a good outcome for drop attacks was analysed using Kaplan–Meier event-free survival curves using right-censoring of data and the logrank test; right-censor date was 31 December 2015. Kaplan-Meier event-free survival is used to estimate the proportion of patients who remain free of events, in this case drop attacks. In this study, patients were censored when they had a shorter follow up compared to the remainder of the cohort. This means that the total survival time of those patients is not known, and so they cannot be included in the analysis beyond the time they have been censored. The logrank test is a non-parametric test that allows survival curves to be compared and is appropriate to be used when right-censoring of data.

Initial seizure free period of 12, 18 and 24 months post-surgery was also analysed using a landmark analysis. A landmark analysis separates the cohort into two groups:

1. Those who are either censored up to a chosen point in time or who fail before that point in time; and
2. Those who are censored beyond the chosen point in time or who fail after that point in time.

The landmark analysis “re-sets” the clock at the landmark time, say 12 months. For instance, if 20/50 patients are censored or do not survive the initial 12 months of a Kaplan-Meier curve, the curve for the remaining 30 patients can be compared to the curve for all 50 patients using logrank statistics.

The following clinical features have been associated with good seizure outcome in the literature and were modelled using the logrank test for statistical significance as well as multivariable logistic regression analysis:

1. Age at onset;
2. Age at surgery;
3. Tonic drop attacks;
4. Extent of callosotomy (anterior vs complete);
5. Diagnosis of LGS, West Syndrome or Ohtahara Syndrome;
6. Moderate-severe developmental delay; and
7. Abnormal MRI features.

Backward selection was used for the multivariable logistic regression model; Wald Chi square statistic was used to test for significance and Harrell's C statistic was used for goodness of fit.

2.10 Data Storage

Data was collated, de-identified and then stored on hospital encrypted password protected drives at CHW and GOSH. Data was only combined after de-identification and transferred via hospital email. Data will be stored for 5 years and destroyed using data shredding software in accordance with the approved ethics.
3 outcomes of corpus callosotomy

In the absence of any definitive evidence, there are currently no universally accepted indications for corpus callosotomy, and patient selection is centre and surgeon dependent. Therefore individual case series can highlight new discoveries about the efficacy and safety of the procedure.

A total of 55 patients met the inclusion criteria, which makes this one of the largest case series of corpus callosotomy in the paediatric population (Graham 2016, Shimizu 2005, Shimizu & Maehara 2001). However, it is not clear whether there is overlap between the other two large case series by Shimizu (2005) and Shimizu & Maehara (2001), and moreover those two case series had methodological flaws.

The results and analysis in this chapter has been published by the international peer-reviewed journal *Developmental Medicine and Child Neurology* using the methods described in Chapter 2.
3.1 Patient Demographics

Pre-surgery demographic data is shown in Table 3.1, with $p$ values for the comparison of CHW with GOSH. The median age at surgery was significantly older at CHW (147.5 months vs 111 months, $p=0.021$). All patients at both centres had drop attacks at the time of surgery, but there were significantly more patients with myoclonic-atonic drop attacks at CHW (6 vs 0, $p=0.002$). There were significantly more atonic seizures (3 vs 0, $p=0.049$) and myoclonic seizures (12 vs 6, $p=0.0075$) at CHW. A total of 11/55 patients underwent anterior corpus callosotomy, 43/55 patients underwent complete corpus callosotomy.

Table 3.1. Pre-surgery demographics.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>GOSH</th>
<th>CHW</th>
<th>All</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients ($n$)</td>
<td>33</td>
<td>22</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td>M:F ($n:n$)</td>
<td>25:8</td>
<td>11:11</td>
<td>36:19</td>
<td>0.075</td>
</tr>
<tr>
<td>Extent of callosotomy ($n$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>8/33</td>
<td>3/22</td>
<td>11/55</td>
<td>0.29</td>
</tr>
<tr>
<td>Complete</td>
<td>24/33</td>
<td>19/22</td>
<td>43/55</td>
<td>0.24</td>
</tr>
<tr>
<td>Completed</td>
<td>3/8</td>
<td>2/3</td>
<td>5/11</td>
<td>1.0</td>
</tr>
<tr>
<td>Abandoned complete</td>
<td>1/33</td>
<td>0/22</td>
<td>1/55</td>
<td>1.0</td>
</tr>
<tr>
<td>Abandoned anterior</td>
<td>0/33</td>
<td>0/22</td>
<td>0/55</td>
<td>1.0</td>
</tr>
<tr>
<td>Lennox Gastaut Syndrome, West Syndrome or Ohtahara Syndrome ($n$)</td>
<td>21/33</td>
<td>12/22</td>
<td>33/55</td>
<td>0.57</td>
</tr>
<tr>
<td>Lennox Gastaut Syndrome ($n$)</td>
<td>15/33</td>
<td>12/22</td>
<td>27/55</td>
<td>0.59</td>
</tr>
<tr>
<td>West Syndrome ($n$)</td>
<td>4/33</td>
<td>0/22</td>
<td>4/55</td>
<td>0.14</td>
</tr>
<tr>
<td>Ohtahara Syndrome ($n$)</td>
<td>2/33</td>
<td>0/22</td>
<td>2/55</td>
<td>0.51</td>
</tr>
</tbody>
</table>
### Chapter 3: Outcomes of Corpus Callosotomy

<table>
<thead>
<tr>
<th>Demographic</th>
<th>GOSH</th>
<th>CHW</th>
<th>All</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Known aetiology (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural</td>
<td>9/33</td>
<td>6/22</td>
<td>15/55</td>
<td>1.0</td>
</tr>
<tr>
<td>Genetic</td>
<td>6/33</td>
<td>2/22</td>
<td>8/55</td>
<td>0.45</td>
</tr>
<tr>
<td>Metabolic</td>
<td>0/33</td>
<td>1/22</td>
<td>1/55</td>
<td>0.40</td>
</tr>
<tr>
<td>Immune</td>
<td>0/33</td>
<td>1/22</td>
<td>1/55</td>
<td>0.40</td>
</tr>
<tr>
<td>Infectious</td>
<td>2/33</td>
<td>1/22</td>
<td>3/55</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Moderate-Severe Developmental Delay (n)</strong></td>
<td>28/33</td>
<td>21/22</td>
<td>49/55</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Other comorbidities excluding developmental delay (n)</strong></td>
<td>19/33</td>
<td>10/22</td>
<td>29/55</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Median Age (Interquartile Range; IQR) (months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy onset</td>
<td>10 (31)</td>
<td>24 (25)</td>
<td>12.5 (30)</td>
<td>0.81</td>
</tr>
<tr>
<td>Surgery</td>
<td>111 (90)</td>
<td>147.5 (52.25)</td>
<td>125 (81.5)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Investigations (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>18/33</td>
<td>12/22</td>
<td>30/55</td>
<td>0.19</td>
</tr>
<tr>
<td>Chromosome abnormality</td>
<td>1/2</td>
<td>0/2</td>
<td>1/4</td>
<td>1.0</td>
</tr>
<tr>
<td>Microdeletion/duplication</td>
<td>4/11</td>
<td>3/6</td>
<td>7/17</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Seizure semiology at the time of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drop Attacks (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>33/33</td>
<td>22/22</td>
<td>55/55</td>
<td>1.0</td>
</tr>
<tr>
<td>Tonic</td>
<td>9/33</td>
<td>7/22</td>
<td>16/55</td>
<td>1.0</td>
</tr>
<tr>
<td>Atonic</td>
<td>16/33</td>
<td>5/22</td>
<td>21/55</td>
<td>0.15</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>1/33</td>
<td>3/22</td>
<td>4/55</td>
<td>0.63</td>
</tr>
</tbody>
</table>
In total, 4/55 patients prior to surgery had only drop attacks prior to surgery, 9/55 patients had drop attacks plus one other type of seizure prior to surgery, 22/55 patients had drop attacks plus two other types of seizure prior to surgery, and 20/55 patients had drop attacks plus at least three other types of seizure prior to surgery.

All patients had some degree of developmental delay (n=55); 49 patients had moderate-severe global developmental delay. Structural brain abnormality was the most common known epilepsy aetiology (n=15). Other aetiologies included genetic (n=8), infectious (n=3) and immune mediated (n=1).
Comorbidities other than developmental delay included Cerebral Palsy (CP; n=10), Autism Spectrum Disorder (ASD; n=10), Attention Deficit Hyperactivity Disorder (ADHD; n=8) and sensorineural hearing loss (n=2). Three patients had two comorbidities other than developmental delay (CP with ASD, CP with ADHD, and ASD with sensorineural hearing loss). Known aetiologies were found in 17/28 patients with a comorbidity other than developmental delay, compared with 8/25 patients without a comorbidity other than developmental delay.

Abnormalities on MRI classified according to the Barkovich classification included Group I (tuberous sclerosis, n=2; focal cortical dysplasia, n=1), Group II (lissencephaly, n=1; subcortical band heterotopia, n=3), Group III (polymicrogyria, n=4). Other abnormalities included PVL (n=2), HIE (n=2), damage secondary to infection (HSV, n=2; abscess, n=1), loss of grey-white differentiation (n=2).

Only one GOSH patient had a chromosomal abnormality, which was a ring chromosome 20, otherwise karyotyping revealed no chromosomal abnormality. The only genetic defect found in CHW patients was MeCP2 duplication (n=3); one of these patients had a structural cause of their epilepsy, namely subcortical band heterotopia. Four distinct genetic defects were found in GOSH patients: 17q22/17q23.2 deletion (n=1), TSC2 (n=1), COL4A1 (n=1) and 1p36 deletion (n=1); the patient with TSC2 was reported as having a structural cause, namely tuberous sclerosis. There were two patients with Sturje-Weber syndrome; neither patient was formally tested, but the syndrome is known to be caused by somatic mutations in GNAQ.

3.2 Tolerability

Neurological complications occurred in 20.8% of surgeries and all resolved within 6 weeks. These included: hemiparesis (n=7), disconnection syndrome (n=2), gait ataxia (n=1) and aphasia (n=1). Disconnection syndrome occurred in one patient
with anterior corpus callosotomy and one patient with complete corpus callosotomy; there was no significant difference (p=0.37). These resolved by the time of the initial post-surgical follow up.

Minor surgical complications occurred in 11.3% of surgeries and included intracranial haematoma that did not require surgical evacuation (n=2), pyrexia (n=2) and intracranial infection (n=1). The only major complication was hydrocephalus (n=1) and there were no deaths.

There was no significant difference in complications between anterior corpus callosotomy and complete corpus callosotomy (minor neurological 1/11 vs 6/43, p=0.67; minor surgical 1/11 vs 4/43, p=1.0; major surgical 0/11 vs 1/43, p=1.0).

3.3 Primary Outcome

Median follow up post-surgery was 36 months (interquartile range (IQR) 34 months, range 7-131 months). Figure 3.1 shows the frequency of drop attacks pre-surgery and at last follow up.

![Figure 3.1 Frequency of drop attacks pre surgery and at last follow up.](image-url)
Overall, 26/55 patients achieved a good outcome for drop attacks at last follow up. Of the children with a poor outcome for drop attacks, 26/29 of these patients had a return of drop attacks within 12 months of surgery. The Kaplan-Meier survival curve of good outcome of drop attacks is shown in Figure 3.2. This shows the number of months post-callosotomy that patients had a worthwhile reduction in drop attacks.

![Kaplan-Meier survival curve of good outcome for drop attacks](image)

**Figure 3.2.** Kaplan-Meier survival curve of good outcome for drop attacks

Logrank statistics for clinical features are shown in Table 3.2. None of the clinical features reached statistical significance.
Table 3.2. Logrank statistics for clinical features associated with good outcome.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Logrank $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at epilepsy onset &lt; median age at onset</td>
<td>0.6495</td>
</tr>
<tr>
<td>Age at surgery &lt; median age at surgery</td>
<td>0.4926</td>
</tr>
<tr>
<td>Tonic drop attack</td>
<td>0.2099</td>
</tr>
<tr>
<td>Total corpus callosotomy</td>
<td>0.1564</td>
</tr>
<tr>
<td>LGS spectrum</td>
<td>0.8161</td>
</tr>
<tr>
<td>Moderate-severe developmental delay</td>
<td>0.8567</td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>0.4057</td>
</tr>
</tbody>
</table>

A landmark analysis is shown in Figure 3.3. It assesses the effect of an initial good drop attack outcome period of 12 months (the "cutoff period"). Two groups are considered with this approach: 1) all patients (ie the results of Figure 3.2); and 2) patients who are right-censored beyond the cutoff period or who have drop attacks return after that period. Kaplan-Meier survival curves of these two groups of patients are compared using logrank statistics.
Chapter 3: Outcomes of Corpus Callosotomy

Figure 3.3. Landmark analysis

The results for cutoff periods of 12, 18 and 24 months are shown in Table 3.3 including the proportion of patients who continue to have good drop attack outcomes following the cutoff period. The results are not significant when the cutoff period is 6 months (p=0.074).

Table 3.3. Logrank statistics for initial seizure free period

<table>
<thead>
<tr>
<th>Initial period of good drop attack outcome</th>
<th>Proportion of patients who continue to have Engel class I-II outcome</th>
<th>Logrank p</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>0.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>18 months</td>
<td>0.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24 months</td>
<td>0.95</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
In summary, 26/55 patients (47.3%) were either free of drop attacks or continued to have rare drop attacks at last follow up. Of the remaining 29 children, 26/29 patients (89.7%) had a return of drop attacks within 12 months of surgery.

### 3.4 Secondary Outcomes

#### 3.4.1 Injuries from Drop Attacks

There was a significant reduction in the number of patients who were sustaining injuries between clinic appointments due to their drop attacks (pre-surgery 77.4% vs last follow up 20.8%, p<0.0001). Among patients who continued to have drop attacks at the time of last follow up, there was also a significant reduction in the number of patients sustaining injuries (pre-surgery 73.1% vs last follow up 42.3%, p=0.048). This is shown in Figure 3.4.

![Figure 3.4. Proportion of patients who sustain injuries from drop attacks pre surgery and at last follow up](image)

#### 3.4.2 Other Seizures

In total, 4/55 patients prior to surgery had only drop attacks prior to surgery, 9/55 patients had drop attacks plus one other type of seizure prior to surgery, 22/55
patients had drop attacks plus two other types of seizure prior to surgery, and 20/55 patients had drop attacks plus at least three other types of seizure prior to surgery. Patients with one other seizure type were significantly more likely to achieve a good outcome for other seizures compared with patients with two other seizure types or three or more other seizure types (100.0% good outcome for other seizures vs 22.7%, p=0.0084; 100.0% vs 10.0%, p=0.0014). However, the outcome for drop attacks was not statistically significantly associated with the number of other seizure types. The overall outcome and frequency of other seizure types is shown in Figure 3.5.

![Graph showing frequency of other seizures and outcomes for other seizures stratified by number of other seizure types.](image)

Figure 3.5. Outcomes for other seizures. Panel (a) shows frequency of other seizures before surgery and at last follow up; panels (b) and (c) show good outcomes for differing pre-surgical number of other types of seizure: (a) outcomes for other seizure types stratified for number of other seizure types; (b) drop attack outcomes stratified for number of other seizure types.
3.4.3 New Seizures

A total of 7/55 patients experienced the onset of new onset partial seizures at last follow up and 3/55 patients experienced the onset of new generalised seizures at last follow up. This is shown in Table 3.4 comparing good outcome for drop attacks to patients with poor outcome for drop attacks. There were no statistically significant differences.

<table>
<thead>
<tr>
<th>Any other seizure</th>
<th>Good drop attack outcome (n=26)</th>
<th>Poor drop attack outcome (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any other seizure</td>
<td>7</td>
<td>3</td>
<td>0.16</td>
</tr>
<tr>
<td>Generalised seizures</td>
<td>2</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>Partial seizures</td>
<td>5</td>
<td>2</td>
<td>0.24</td>
</tr>
</tbody>
</table>

3.4.4 Neuropsychological changes

All 55 patients had formal neuropsychological assessment as part of the workup for epilepsy surgery. Formal neuropsychological assessment was performed in 3/55 patients, each of whom had developed anxiety (n=2) or a mood disorder (n=1). Neuropsychological changes at last follow up were therefore not included as post-operative formal assessment were only conducted if clinically indicated.

3.4.5 Neurophysiological changes

Neurophysiology findings were initially included and Hanson et al’s classification system was initially applied post-hoc. The validity of this post-hoc approach was questionable for this present retrospective study and so was abandoned. A complete review of all EEG and VEEG data would be required, rather than a review of reports only, in order for this approach to be valid. Such a review was beyond the scope of this thesis. Moreover, post-operative neurophysiological studies were
only conducted in 30/55 patients (54.5%) when clinically indicated due to changes in seizure semiology. Consequently neurophysiological findings were not included as outcomes. Including Hanson et al’s classification system would be beneficial in a prospective study, but poses challenges in a retrospective study.

3.4.6 Antiepileptic Drugs

The median number of AEDs used at last follow up was 2 AED (IQR=1). Mann-Whitney’s U test showed this was significantly fewer than the pre-surgery median number of 3 AEDs (IQR=1) (p=0.0018).

3.5 Multivariable Regression Analysis

Multivariable logistic regression analysis of good outcome for drop attacks using backward selection had a Harrell C-statistic of 0.66 and a maximum rescaled $R^2$ value of 0.14. None of the clinical features described in the method reached statistical significance as predictors of good outcome. The results of the analysis are shown in Table 3.5.

**Table 3.5. Multivariable logistic regression analysis of good drop attack outcome at last follow up.**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at epilepsy onset (years)</td>
<td>0.75</td>
</tr>
<tr>
<td>Age at surgery (years)</td>
<td>0.70</td>
</tr>
<tr>
<td>Tonic drop attack</td>
<td>0.25</td>
</tr>
<tr>
<td>Total corpus callosotomy</td>
<td>0.12</td>
</tr>
<tr>
<td>LGS spectrum</td>
<td>0.98</td>
</tr>
<tr>
<td>Moderate-severe developmental delay</td>
<td>0.51</td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>0.68</td>
</tr>
</tbody>
</table>
3.6 Discussion

Despite a wide variation in patients in this present case series on paediatric outcomes of corpus callosotomy, there were very few differences between the two centres. All patients had some degree of developmental delay, with the majority having moderate-severe developmental delay and almost half of the patients having at least one other comorbidity. Lennox-Gastaut Syndrome, West Syndrome and Ohtahara Syndrome were the most common syndromes. All patients had been investigated with MRI as part of their workup, 30/55 patients (54.5%) had a structural abnormality. Genetic causes were found in 8/55 patients (14.5%), namely Stuge-Weber syndrome (GNAQ: n=2), MeCP2 deletion (n=2), Ring chromosome 20 syndrome (n=1), 1p36 deletion syndrome (n=1), 17q22/17q23.2 deletion (n=1), COL4A1 (n=1).

3.6.1 Tolerability

Corpus callosotomy was well tolerated regardless of extent of callosotomy. The complication rate in our series was comparable to the paediatric literature\(^5\). Bjellvi et al's prospective, population-based study perhaps provides the best evidence of complications after epilepsy surgery and they use a similar classification system to ours\(^84\). They observe that the complication rate may be under-reported in the literature as most studies are retrospectively designed. Although the Bjellvi et al study is limited to a single country and only 24 corpus callosotomies were performed on paediatric patients, they found that 0/24 patients developed a minor complication and 1/24 patients developed a major (unspecified) complication\(^84\).

Notably the findings in our series for disconnection syndrome differ from the literature. While the literature suggests that approximately 12% of paediatric patients will experience a transient disconnection syndrome, which is significantly more likely in complete corpus callosotomy (p<0.0001) (Graham 2016), our series found disconnection syndrome was uncommon (only 1/55) nor was there
any significant difference in outcome for complete versus anterior corpus callosotomy (p=0.37). This may in part be due to the fact that extent of callosal section in our series was largely based on intraoperative surgeon’s report.

Transient hemiparesis is a common complication in the literature\(^5\) and it was the most common complication in our series (13%). There are two hypotheses to account for the reversible hemiparesis. The usual assumption is that it is associated with the retraction of the contralateral leg motor area during surgery. This hypothesis could be confirmed with diffusion weighted imaging. However it is also possible that the hemiparesis is due to the interruption of venous drainage relating to the division of central cortical veins in order to gain access to the interhemispheric fissure. This alternate hypothesis could be confirmed with a study that investigates any relationship between the number of veins divided during surgery and any post-operative deficits.

### 3.6.2 Drop Attacks

The outcome for drop attacks at last follow up was poorer than the paediatric literature\(^5\), which may be due to the longer follow up than the reports in the paediatric literature. This was observed by Tellez-Zenteno in their review in which they found the effect of corpus callosotomy diminishes beyond 5 years\(^74\). Our multivariable logistic regression analysis showed that there was a significant effect of at least 12 months of worthwhile benefit of corpus callosotomy on drop attacks (p<0.05). Indeed, 81% of patients who did have a return of drop attacks did so within 12 months of follow up, similar to the case series by McInerney et al\(^85\), which is a clinically valuable finding. Moreover, patients who continued to have drop attacks following surgery were less likely to sustain injuries, which supports the use of corpus callosotomy for palliation of patients with drop attacks. Stigsdotter-Broman et al’s long term population-based study found sustained benefit for 56% of patients out to 10 years post-surgery\(^75\). This may suggest that a good drop attack outcome at 12 months could be a clinically valuable post-surgical marker for sustained good drop attack outcome. Interest is also turning towards selective posterior corpus callosotomy, with Paglioli et al’s recent study finding...
30/36 patients were either free or almost free of drop attacks at last follow up\textsuperscript{54}. However, this must be contrasted with Pinard et al’s older study in which all of the patients who underwent posterior corpus had poor outcomes\textsuperscript{53}.

No clinical factors were associated with a significant effect on the outcome of drop attacks. Extent of callostotomy is the factor that is most commonly associated with seizure outcome in the literature\textsuperscript{5}, however our series found no significant effect of extent of callosotomy. This may be due to a combination of factors, such as the relatively smaller number of partial corpus callosotomy patients in our case series, and the fact that extent of callosotomy was not solely based on post-operative imaging.

To date, all studies of corpus callosotomy outcomes in paediatric patients have focused on outcome at last follow up\textsuperscript{5}. This is the first study of corpus callosotomy to investigate the temporal aspect of Engel class outcome for drop attacks. The regression analysis accounts for approximately 14\% of the variance in drop attack outcome and the explanatory power of regression models has not previously been reported in the paediatric corpus callosotomy literature\textsuperscript{5}. Finally, this is one of the largest study of corpus callosotomy in the paediatric population\textsuperscript{5,61,63}, which highlights the value of combining outcomes between centres.

### 3.6.3 Other Outcomes

There were significantly fewer AEDs used at last follow-up compared with the pre-surgery (p<0.05), which is different to the paediatric literature\textsuperscript{5}. This may reflect a strategy for optimising AED usage in order to reduce the number of side effects but it could explain the relatively poorer outcome for drop attacks compared with the literature. However the complex interplay between corpus callosotomy, optimal medical management, and AED side effects is beyond the scope of this thesis and has not been explored in the literature.
The benefit on other seizures was generally poor, and was not correlated with drop attack outcome. It is not entirely clear whether the emergence of new seizure types is a reflection of the impact of the surgery or the evolution of the epilepsy. However, patients who had only one other seizure type benefited from corpus callosotomy for both drop attacks and the other seizure type. This may be indicative of the severity of seizure semiology prior to surgery, which, if appropriately defined, could prove to be another clinically relevant prognostic marker.

3.6.4 Limitations

The key weakness of this study is its retrospective case series design. This may lead to the inaccurate reporting of some data such as the full seizure semiology, any injuries from drop attacks, and the neuropsychological impact. It is for this reason the EEG characteristics could not be included for analysis even though slow ictal and interictal spike-wave patterns and reduced synchronicity of postoperative discharges have been reported as prognostic features of a good outcome\textsuperscript{34}. While this introduces bias into the results, the study is useful as it does identify new information about the durability of seizure outcomes, and supports the hypothesis that corpus callosotomy is a safe and effective palliative treatment for paediatric patients with generalised seizures characterised by drop attacks.

There are potential centre differences in patient selection, workup and surgical approach. While both centres use ILAE recommendations for referral and evaluation\textsuperscript{80}, there may be differences prior to 2006.

3.6.5 Future Directions

As discussed elsewhere in the literature\textsuperscript{5,86}, there is a clear need for a randomised control trial (RCT) of corpus callosotomy outcomes. The design of such a trial has been outlined by Graham, Tisdall and Gill in their systematic review\textsuperscript{5} based on Wiebe et al's landmark RCT of temporal lobectomy\textsuperscript{73}. This is expanded in Appendix
A. Dwivedi et al have published the results of their RCT on epilepsy surgery, which includes a corpus callosotomy group and is discussed in section 1.3.2 above. However the study does not reflect the palliative nature of corpus callosotomy. Indeed, a good outcome in Dwivedi's study is defined as seizure freedom, which is not expected with corpus callosotomy. Moreover, there is no distinction between partial or complete corpus callosotomy.

The prognostic benefit of an initial 12 month period of worthwhile benefit on drop attacks identified in this thesis could aid the design of such a trial. A prospective design would allow for imaging to confirm the extent of the callosotomy, and could include recording the number of emergency and intensive care admissions for injuries and other complications of epilepsy. However, enrolling a sufficient number of patients will be challenged by the relative infrequency of corpus callosotomy. Moreover there may be limited enrolment given the challenges faced by parents in consenting to corpus callosotomy following extended periods of optimal medical management. Imaging studies comparing semiology of drop attacks as well as other seizures pre and post callosotomy may provide some insight into the seizure outcomes reported here and elsewhere. They have potential to provide insight into the long-term tractographic changes post-callosotomy, as well as why reported outcomes in children are generally better than those of adults.

Advances in neuroimaging and bioinformatics are providing insights into the interactions between neurons and behaviours emerging from their connectivity. This has opened up the new field of connectomics, which is the study of maps of connections within a nervous system called connectomes. This can be studied from a structural or functional perspective, or at the local circuit level. Engel et al have recently speculated that therefore epilepsy research could benefit from connectomics. While connectomics provides insight into the pathogenesis of generalised seizures, its value in epilepsy surgery is yet to be established. Callosal volumes can be explored in prospective studies, with a view towards simple prognostic biomarkers. But deeper investigations into connectomics may be of benefit. Recent work suggests a potential benefit from posterior corpus...
callosotomy based on more favourable connectomics. Yet there remains many unanswered questions, such as: why do children have only transitory neurological complications? Or, why can drop attacks return following total corpus callosotomy? A deep connectomics study could help illuminate these questions.

Psychiatric conditions and developmental delay are common in children with refractory epilepsy. Indeed, there is evidence to suggest that there may be a close relationship between psychiatric disorders and epilepsy, with multiple complex biopsychosocial factors at play. This highlights the need to use a biopsychosocial perspective on the outcomes of disconnective epilepsy surgery. The neuropsychiatric complications of epilepsy may have a greater negative impact on quality of life than seizure frequency. The neuropsychiatric outcomes of resective epilepsy surgery are well-understood, with patients experiencing some cognitive benefits. However, the neuropsychiatric outcomes of disconnective epilepsy surgery are poorly understood. This is especially important in the paediatric population as generalised epilepsies have their highest incidence in children. While formal neuropsychiatric review is an important part of the workup for epilepsy surgery, to date there have been no systematic reviews of the neuropsychiatric outcomes of disconnective epilepsy surgery in the paediatric population.

Finally, there is growing interest in the health economics of epilepsy in general, with some insights already being made into the health economics of epilepsy surgery. Powerful insights into the mechanisms behind the relationship between socioeconomic factors and disease are emerging through the use of health economic theory. But the mechanisms that underlie the relationship between socioeconomic factors and disability are unclear. Microeconomic theories of health capital such as the Grossmann model have consistently supported the disentangling of these mechanisms. In so doing, such an approach to the health economics of epilepsy surgery could improve our understanding of how best to target the costs and access of treatment. Moreover a microeconomic approach would introduce rigour to the modelling beyond cross-sectional studies, but this approach has yet to be used despite the clear need.
4 BIOETHICAL ISSUES

From a clinical standpoint, corpus callosotomy is likely to be a highly effective and safe procedure that should be conducted before adulthood. The risk of transient complications and the so-called “burden of normality” can be adequately managed in hospital and through multidisciplinary post-surgical rehabilitation as well as engagement with the family’s general practitioner. But parents are faced with the challenge of weighing up uncertain success with the possibility of disconnection syndrome and other neurological complications, however unlikely.

Any paediatric epilepsy surgery therefore raises questions about access to, and the bioethics of, corpus callosotomy in particular, and epilepsy surgery in general. Resective and disconnective epilepsy surgery conjures up a dubious history of lobotomies in the 1950s. The permanent disconnection syndromes suffered by the commissureotomy patients further charges these images, and presents a challenge to parents. But times have changed and the reality of epilepsy surgery in 2017 is vastly different.

This chapter presents a clinical case of a child with frequent drop attacks but with average intelligence. While most corpus callosotomy patients have moderate to severe developmental delay, patients with average intelligence do exist such as in Cendes et al’s case series. A patient with average intelligence has been chosen in
order to frame some issues relating to access, consent and the best interests of paediatric epilepsy surgery patients.

4.1 Case Presentation

SL is a 15 year old girl of average intelligence with generalised seizures that is characterised by weekly generalised tonic-clonic seizures and daily drop attacks, many of which cause injury. Notably, her epilepsy is refractory to medical treatment. SL is currently seen in the Epilepsy Clinic at CHW.

Her past medical history is otherwise unremarkable. She was born by an uncomplicated normal vaginal delivery. Her mother was healthy throughout the pregnancy and all antenatal screening was normal. Her immunisations are currently up to date. SL has achieved all of her developmental milestones and her neuropsychological assessments show no significant deficits, with an FSIQ of 95.

SL attends high school where she has a wide circle of friends, but she still becomes embarrassed when she has a drop attack despite her good social supports, and will often take several days off school as a result. She lives with her parents, who are first generation migrants from China, and her younger brother. There is no known family history of epilepsy, though there is significant amount of stigma from her relatives in China, so it is not clear if there are any relatives in China with epilepsy.

SL’s seizure history is shown in Table 4.1. The drop attacks have proved to be difficult to control despite a trial of Lamotrigine. SL now has daily drop attacks despite maximal doses of Sodium Valproate and Topiramate.
Table 4.1. SL’s seizure history

<table>
<thead>
<tr>
<th>Age</th>
<th>Semiology</th>
<th>Frequency</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Myoclonic jerks</td>
<td>Daily</td>
<td>Sodium Valproate</td>
<td>Controlled</td>
</tr>
<tr>
<td>6</td>
<td>GTCS</td>
<td>Infrequent, increasing to daily</td>
<td>Carbamazepine</td>
<td>Weekly</td>
</tr>
<tr>
<td>12</td>
<td>Tonic seizure and tonic drop attacks</td>
<td>Daily</td>
<td>Topiramate</td>
<td>Tonic seizures controlled, drop attacks remain daily</td>
</tr>
<tr>
<td>13</td>
<td>Tonic drop attacks</td>
<td>Daily</td>
<td>Trial of lamotrigine</td>
<td>Nil benefit</td>
</tr>
</tbody>
</table>

SL has presented to CHW emergency department every two to three months over the period 2014-2016 for injuries sustained from her drop attacks. These have mostly been head injuries, especially to the face and nose, requiring sutures. She has had two broken noses and a fractured left orbit, and has lost three teeth. This has caused SL and her family distress and is impacting her attendance at school even though she has a strong social support network.

SL’s parents were offered a total corpus callosotomy for palliative treatment of her epilepsy in 2016, but they expressed concern about the possibility of permanent neurological complications, especially disconnection syndrome. The nature and likelihood of these complications, as well as the balance of benefits of corpus callosotomy, were discussed at length with SL’s parents. The topic was broached at each of her six monthly clinics, with new evidence presented, such as Graham, Tisdall and Gill’s systematic review\(^5\), or the combined CHW and GOSH case series by Graham et al\(^7\). Indeed, her parents requested copies of the literature to
consider when they returned home to discuss at the following clinic. Despite careful communication, SL’s parents redirected the dialogue to disconnection syndrome and continue to refuse treatment.

4.2 Access

The decision to progress with a corpus callosotomy is a relatively straightforward clinical one, but SL’s case raises questions about the bioethics of corpus callosotomy in particular, and epilepsy surgery in general. Ibrahim et al argue that an ethical framework of epilepsy surgery ought to be based on access, protection of vulnerable patients, transparency, equity despite inequality, and societal benefit. As early intervention is important, access is axiomatic to the clinical ethics of epilepsy surgery. Parental resistance is a common barrier to access for epilepsy surgery, however education has been shown to mitigate this barrier.

Patients with disabilities require complex management and access a wider range of services than non-disabled patients. Making sense of these services is important for good patient outcomes. Raynor argues that it is not only important to remove barriers to understanding by using plain language, but to also remove the complexities of healthcare systems. This is especially true for patients with disability. While children with disability require more frequent access to health services, their ability to access these services may in fact be more limited than healthy normal children. Equity and access, especially in relation to education, are vital for the health of children with a disability.

The family general practitioner (GP) is important for improved outcomes for children with a disability. Nevertheless, access relies on a partnership between parents and practitioners. As a child under the age of 16, the decision to divide SL’s corpus callosum rests with her parents unless she satisfies the Gillick test. An adolescent of normal intelligence makes SL a unique corpus callosotomy patient. A typical corpus callosotomy patient will have a number of co-morbidities including cerebral palsy and autism, and are usually severely developmentally delayed. This
is not the image SL’s parents see when they think of her daughter, but despite her uniqueness in this very unique community, SL is not a mature minor. SL’s uniqueness needs to be considered in sensitively representing the clinical standpoint to her parents – discussing the outcomes seen in the corpus callosotomy patient population may not be compelling to them.

4.3 Consent

Consent is at the heart of patient-centred care. It signifies the active participation of patients in their health. In its simplest terms, consent means that a patient freely agrees to the healthcare provider to infringe upon certain rights, such as the right not to be assaulted in order to undergo surgery. The elements of a valid consent essentially include:

1. Validity: the patient must voluntarily enter a “contract” with the healthcare provider, for which competence must be tested;
2. Information: the healthcare provider must disclose the risks and benefits of the intervention, and the patient must unequivocally understand them; and
3. Enaction: the consent must be specific to the intervention and the patient must authorise the healthcare provider to carry out the treatment.

But consent is fundamentally an ethical concept with an imperfect practical application. Consequently it is often over-shadowed by legal discussions in order to make sense in the clinical setting. I believe the legal discourse reflects the ethics of consent. In the landmark case of Rogers vs Whitaker (1992) 175 CLR 479, the court focused on two key elements to consent in its judgment: self-determination and disclosure of risk. Rogers vs Whitaker requires that information be provided in a patient-focused manner rather than a clinician-focused manner. The intent is to allow the patient to exercise their self-determination to balance the personal risks with the patient’s own goals.

Clearly obtaining consent is open to question in clinical practice, highlighting the practical limitations of consent. More fundamentally, Schneider suggests that the
requirement for informed consent demands a “mandatory autonomy” rather than respects patient autonomy, which has been described by Davies and Elwyn as the “paradox of imposing choice upon patients” (as cited in Manson (2010)\textsuperscript{102}, p 834).

It is important to remember that ethics is not merely morals. Medical ethics is guided by the principles of beneficience, nonmaleficience, autonomy and justice\textsuperscript{101}. As noted above, the ethics of consent tends to assume and concern the autonomy of a patient, but the meaning of autonomy has a long history of debate\textsuperscript{103}. O’Neill observes that most contemporary accounts of autonomy reduce the concept to a discussion of independence rather than its ethical significance\textsuperscript{103}.

There is much in the philosophy of autonomy that essentially begins with Kant’s philosophy of practical reason. Kant’s philosophy of practical reason concerns our ability to use reason to freely choose our own actions\textsuperscript{104}. Kant argued that moral laws that guide our own actions can only limit our freedom if those laws are acts of our own will; autonomy is the self-imposition of the moral law. In his utilitarian philosophy, Mill elevated autonomy to something of intrinsic value in itself separate from Kant’s practical reason\textsuperscript{105}. This utilitarian conception arguably lays the foundations for the principle of autonomy in modern medical ethics.

Contemporary Kantian philosophers view autonomy as a measure of self-worth whereby one must be able to trust one’s own capacity to make a decision and accept responsibility\textsuperscript{106-108}. This is perhaps easier to digest Kant’s ideas of autonomy, but tends to dilute the essence of Kant’s autonomy. However autonomy is not universally accepted among ethicists, with Hegel and Nietzsche being notable examples who had a strong influence on 20\textsuperscript{th} century philosophy. Their critiques essentially concern the assumption of universal laws as they develop their pluralistic conceptions of meaning (see for instance Deleuze (2006)\textsuperscript{109}, Foucault (1988)\textsuperscript{110}), with Foucault famously stating that “there is no sovereign, founding subject, a universal form of subjects to be found everywhere” (Foucault (1988)\textsuperscript{110}, p50). Short of suggesting patient-centred care is philosophically flawed,
we can at least agree that if consent is founded on autonomy, then it is understandable why it is fertile ground for debate and a subject of common law.

O’Neill argues that, regardless of the meaning of patient autonomy, consent fundamentally concerns coercion and deception on the part of the clinician. This detaches the concept of informed consent from a philosophically shaky assumption and returns it to a more pragmatic setting that is reflected in the fundamental requirement by *Rogers vs Whitaker* to disclose risk to the patient. It is important to begin a reframing of consent independent of autonomy as bioethics in the 21st century shifts its emphasis from autonomy to justice. In my mind, this leaves open the way for other aspects of consent that frame it in a more humane light.

Indeed, the emphasis on autonomy is sociocultural not universal. An alternate viewpoint to autonomy is that healthcare decisions should be based on the provision of care and compassion. After all, autonomy (framed as independence) diminishes the importance of caring and interdependence, which arguably is what a vulnerable patient craves. Kopelman argues that consent can never be completely rational in the face of mortality or uncertain outcomes. It is therefore perhaps more useful to view consent as a request for help rather than an agreement to proceed with an intervention that ostensibly infringes a patient’s rights. Consent is not necessarily an exercise in rational choice, which would be a Kantian interpretation, but instead introduces the emotional quality of medical decision-making. O’Neill argues that consent is a proposition that describes the action to be performed, but that it is opaque as the logical consequences of my consent may not be transparent to the patient. This is the basis of his position that consent concerns coercion and deception, and he cites events at two hospitals in the UK.

*Rogers vs Whitaker* recognises that full disclosure is impractical, which is consistent with O’Neill’s position, but it also recognises that communication is axiomatic to the determination of what is relevant for the patient. While the details of epilepsy surgery and its complications can readily be communicated, the
neuropsychological sequelae of epilepsy surgery aren’t fully understood. So there is indeed opacity to the consent for epilepsy surgery and the circumstances, and gaps in clinical research make it difficult to fully disclose every detail that would be relevant to a particular patient.

While consent is at the heart of patient-centred care, not all patients want to take part in decision-making. Despite this, patients still wish to be informed and Manson argues that this should come as no surprise. He suggests several reasons why this is the case: patients want to make decisions, but not about treatment; patients want respect and providing information is a mark of that respect; patients want to be psychologically and emotionally prepared; patients want to know the reasons behind a certain course of action; communicating information is a marker for the trustworthiness and competence of the clinician and that they have deliberated alternatives and weighed up risks; patients want the opportunity to ask questions and seek clarification. It seems that information is necessary for the involvement in decision-making, but it is not sufficient. This is consistent with most ethical positions.

When consent becomes ethically charged, a framework for ethical reasoning can be useful. Kaldjian, Wier and Duffy propose a systematic strategy for clinical ethical reasoning that parallels clinical reasoning. They argue that their approach incorporates ethical plurality by explicitly stating a “differential diagnosis” that is used in forming an ethical assessment. In order to arrive at the “differential diagnosis,” the medical facts, medical goals, patient goals and the context are elucidated. In the context of consent, their approach essentially highlights that consent is more than patient autonomy and in the practical setting can be viewed as an evolving discourse between patient and clinician. Thus, the interpersonal and transitional nature of consent can be established in a practical setting using this type of strategy rather than remain in the domain of ethics. This is also reflected in other approaches, such as Jonsen, Siegler and Winslade’s IDEA framework (Identify the facts, Determine the relevant principles, Explore the options, Act).
Chapter 4: Bioethical issues

4.4 Best Interests

Children represent a special population for whom surrogate-decisions are made on their behalf by their parents. The medicolegal test for any paediatric intervention is based on the concept of best interests. Consider Marion’s case (ie Secretary of the Department of Health and Community Services v JWB and SMB [1992] HCA 15), which is the test case for “best interests” in Australia.\(^{101}\) The High Court of Australia found that, while parents may consent to medical treatment on behalf of a child, they must act in the best interests of their child. In Marion’s case, surgical sterilisation was not deemed to be in her best interests, but instead served the interests of her parents. On the balance of risks and benefits, a corpus callosotomy is clearly therapeutic and is likely to prevent injurious drop attacks as well as improve life expectancy. Any benefit to the parents is secondary so they can legally consent to a corpus callosotomy on behalf of their child.

Best interest decisions involve the moral principles of beneficience and nonmaleficence.\(^ {101}\) These are not universal principles, but neatly represent the moral grounds that guide the delivery of medical care. As they do represent a moral position, they can be a source of ethical conflict in themselves and are important therefore in consent. The standard of best interest decision-making is patient-centred and focused on the current needs of the patient.\(^ {117}\) But such decisions will always be entangled with the interests of others.

The autonomy of the child is deferred to the parent. The ethical difficulties with autonomy that I previously discussed are further complicated by the child’s best interests. Under common law, the decision to undergo epilepsy surgery in a child under the age of 16 rests with the parents unless the Gillick test is satisfied. As noted above, parents of corpus callosotomy patients generally report satisfaction even when outcomes have been poor.\(^ {5}\) While parental resistance can pose a health literacy challenge, parental resistance in child health is ostensibly a legal barrier.
Are SL’s best interests best served by corpus callosotomy or by continuing with the current therapy regime? Only one published paper has included details of a corpus callosotomy patient with normal intelligence like SL\textsuperscript{5,6} and it is worth considering the case in this discussion. Cendes et al describe Patient 21, a 14 year old female with normal intelligence who developed epilepsy at the age of 4\textsuperscript{6}. She underwent a two-stage total corpus callosotomy with division of the anterior commissure, which resulted in >75% reduction in all seizure types and cognitive improvement. Patient 21 returned to school following recovery and had improved performance at school at 33 months follow up\textsuperscript{6}. It seems that the atypical Patient 21 had an outcome that was typical of a good outcome of corpus callosotomy.

While this anecdotal evidence seems hopeful, doubt still remains in the minds of SL’s parents. Communicating the clinical evidence has not been sufficient to lift the barriers. If SL were to develop complications, her parents will have to live with the knowledge that they gave consent to a procedure that permanently damaged their daughter’s brain. This blunt and crude reality would be difficult to live with. Does the unlikely event of permanent disconnection syndrome or a shunt for hydrocephalus outweigh a good chance at improvement in drop attacks?

A surrogate decision made in a child’s best interests would ideally provide the maximum benefit to the child. Parents may refuse on the grounds that intervention is futile or offers uncertain benefits. In the case of SL, the uncertainty potentially lies in the tension between a 90% chance of a worthwhile improvement in drop attacks following irreversible brain surgery. To be sure, individual circumstances are important and SL’s parents may feel that preventative measures may be sufficiently effective that drop attacks do not significantly impact the quality of her life.

4.5 Health Economics

The healthcare needs of a child with a disability require significant resources that are delivered by multiple services in Australia. Disability encompasses a
heterogeneous mix of conditions that each have different aetiologies and natural histories. A broad definition of disability should align with the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY)\textsuperscript{118}. In this framework, disability includes patients with a chronic physical, developmental, behavioural or emotional condition that requires health services beyond children in general, including specialist and disability services. But consideration of the impact of the healthcare system and family relationships on the child is an important perspective that should be kept in mind\textsuperscript{119}.

Understandably, a child with a disability may therefore have needs that require additional personal resources in order to access these services. Children with a disability also rely more heavily on parents, siblings, other family members and teachers for assistance\textsuperscript{120}. Indeed a parent may need to take on full time caring responsibilities. Payments for Australian carers are less than half the median full-time income \textsuperscript{118,121}, so it is evident that there is potentially a negative impact of a child’s disability on family income in spite of the support available. Disability also impacts a child’s potential employment and education opportunities and even though disability is more prevalent in boys than girls, young women report greater limitation in ADL than young men\textsuperscript{122}.

Cross-sectional studies in Australia highlight there is no significant effect of remoteness on childhood disability in Australia, but Aboriginal and Torres Strait Islander (ATSI) children are significantly more likely to develop a disability than non-Indigenous children\textsuperscript{123}. It is not clear however whether this effect is due to higher rates of socioeconomic disadvantage in the ATSI population as data is limited.

The Longitudinal Study of Australian Children (LSAC)\textsuperscript{16} and the Longitudinal Study for England and Wales\textsuperscript{17} are the first studies that include children with a disability in their cohort design. These landmark studies used household income to test socioeconomic disadvantage and its impact on childhood disability and found that children born into the lowest income quintiles were significantly more likely to
develop a disability\textsuperscript{16,17}. Spencer and Strazdins’s analysis of LSAC found that household income was negatively impacted by the onset of disability in a child, demonstrating a bi-directional relationship between socioeconomic disadvantage and the development of disability in children\textsuperscript{16}. If socioeconomic disadvantage is also a determinant of disability, then existing disadvantage is further compounded once a child develops a disability.

This complexity poses a challenge to the healthcare system and begs the question of how can it be disentangled. Galama and van Kippersluis have argued that health economic theory can provide valuable insights into the nature of these mechanisms\textsuperscript{92}. Grossman’s model of health production in particular has yielded considerable insights into the determinants of health and the allocation of time and money into the production of health\textsuperscript{92}. Many of its predictions are supported by empirical evidence, perhaps most important is the impact that education has on health. However the model cannot explain the inverse relationship between demand for medical care and health\textsuperscript{92}. This is most certainly true of children with refractory epilepsy. In patients with refractory epilepsy, early intervention with curative surgery reduces the progress of epileptic encephalopathy, and both curative surgery and palliative surgery are associated with improved lifespan\textsuperscript{37}.

Health investment in epilepsy surgery clearly delivers a significant cost benefit to the overall healthcare system. The lived experience of caring for a unique patient like SL is radically different and carries more potent weight on her parents than the statistics that we offer.

### 4.6 Outcome

At the time of writing, SL’s parents have not given their consent for SL to undergo corpus callosotomy. They have been encouraged to seek second opinions, and have taken up this opportunity. Her epilepsy remains refractory and she continues to sustain injuries from her drop attacks. The health impact of epilepsy to SL, her family and the broader community remains high.
While VNS has not been offered, SL has however been entered on the cannabis trial; results are pending. While the treating team feel that corpus callosotomy will provide SL with the best possible outcome, they have been sensitive to her family's needs. SL is a unique patient who exemplifies the individual cases that stand out from the evidence. As her 16th birthday draws closer, her own legal right to choose corpus callosotomy becomes very real.
5 CONCLUSIONS

The case series presented in this thesis is one of the largest paediatric case series of corpus callosotomy outcomes and is the first in the corpus callosotomy literature to utilise Kaplan-Meier analysis. There were significantly fewer antiepileptic drugs used at last follow up and significantly fewer injuries from drop attacks at last follow up. It further suggests that an initial 12 month period of worthwhile reduction in drop attacks as well as fewer than two other types of seizure are prognostic of a good seizure outcome. This is new and important information that has not previously been reported in the literature.

Case series cannot provide sufficient evidence for the efficacy and safety of an intervention. The highest quality evidence of course is a systematic review and meta-analysis of RCTs. But no such evidence exists within the corpus callosotomy literature. There have been a number of calls within the literature to move beyond the hypothesis generation of corpus callosotomy case series, towards the execution of an RCT and Dwivedi et al have recently presented their randomised results. The multicentre trial design presented in Appendix A mirrors that of an already successful RCT in epilepsy surgery. However the utility of conducting such a trial is questionable. Is the body of evidence sufficient to support the use of corpus callosotomy in children with refractory epilepsy? Graham, Tisdall and Gill’s systematic review highlights significant methodological issues with the published
literature\textsuperscript{5}. Rigorously designed prospective case series that use a consistent outcome measure may be sufficient to demonstrate a clear benefit of corpus callosotomy. However there remain inconsistencies between the evidence from case series and population studies\textsuperscript{5,34,53-67,74-76} and the results for corpus callosotomy in Dwivedi et al’s paper\textsuperscript{72}.

Yet the best evidence may not be sufficient to persuade patients and parents. The ethics of corpus callosotomy is set against a backdrop of fear and misunderstanding. While there are clear health economic advantages at the epidemiological level, the singular cases are what we see in clinical practice. The trade-off between the benefit of effective palliation and the risk of iatrogenic neurological harm leans towards harm in the minds of some parents. Ultimately the clinical ethics of corpus callosotomy in a child is dominated by the decisions of the patient’s family and there are no legal grounds to challenge this barrier to treatment. The clinical standpoint must acquiesce.
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Chapter 6: References

Appendix A: Design of a Multicentre Randomised Trial

The results of the case series presented in this thesis further strengthen the hypothesis that corpus callosotomy is an effective palliative treatment and is well tolerated in paediatric patients. The need for a randomised trial has been observed elsewhere in the literature\textsuperscript{A1,A2A3}, but Graham, Tisdall and Gill’s systematic review outlines the scope of the design for an RCT of corpus callosotomy based on the work of Wiebe et al\textsuperscript{A1,A3}. Noting the limitations outlined in sections 1.3.2 and 3.6.5, Dwivedi et al has achieved this to an extent\textsuperscript{A4}.

The advantage of using these other designs is that they afford comparison between results from these trials. They however note that the challenge for studying corpus callosotomy is the infrequency of the procedure. For instance, over the 20 year period covered in Chapter 2, 73 patients underwent corpus callosotomy at GOSH and CHW but only 55 met inclusion criteria.
In Harvey et al’s 2004 survey of epilepsy surgery, corpus callosotomy accounted for 18/543 (3.1%) of all epilepsy surgery in that year\textsuperscript{5}. This is fairly consistent with published case series, Téllez-Zenteno et al’s systematic review of epilepsy surgery\textsuperscript{6}. Harvey et al included a total of 7343 patients and corpus callosotomy accounted for 99 (1.3%)\textsuperscript{5}. Corpus callosotomy is more commonly performed in children than adults owing to the poorer outcomes in adults combined with the preference for early intervention in all epilepsy surgery. While Harvey et al did not report on the proportion of paediatric patients undergoing corpus callosotomy specifically, they did find that patients under 18 accounted for 77% of all palliative surgery, which included both VNS and corpus callosotomy\textsuperscript{5}. However VNS accounted for approximately 6 times as many operations in 2004 when compared with corpus callosotomy\textsuperscript{5}, so the exact proportion of paediatric corpus callosotomy patients is not clear.

This appendix details the design of an RCT of corpus callosotomy. The aim will be to investigate whether corpus callosotomy is a safe and effective treatment of medically refractory generalised seizures that is characterised by injurious drop attacks. It would randomise patients to either corpus callosotomy plus optimised medical therapy or 12 months of delayed corpus callosotomy plus optimised medical therapy. The primary outcome would be no or rare disabling drop attacks. Secondary outcomes would include outcomes for other seizure types, QOL, disability and death. Epileptologists and neuropsychiatrists would be blinded to the treatment arm and assess the efficacy of optimal medical therapy and patient outcomes. The results of such a trial is beyond the scope of this thesis, but there is momentum gaining in the literature for the serious consideration of conducting such a trial.

### A.1 Main Objectives

As discussed, the body of evidence for the safety and efficacy of corpus callosotomy can at best be used to propose the following null hypothesis:
H0: there is no significant difference in treatment outcome between patients with corpus callosotomy compared with patients with delayed surgical treatment.

The primary objective of the trial will be to compare clinically significant reductions in drop attacks following randomisation. This differs slightly from resective surgery, as corpus callosotomy is a palliative procedure rather than a curative procedure. Even still, seizure freedom rates will still be reported.

The secondary objectives of the trial will be to:

1. Determine the frequency and severity of other seizures following randomisation;
2. Determine patient quality of life (QOL) following randomisation;
3. Determine patient disability following randomisation; and
4. Determine patient mortality following randomisation.

A.2 Methods and Design

A.2.1 Design

The trial will be a randomised, controlled trial of patients undergoing corpus callosotomy at various international centres. Where possible, its design will be similar to Wiebe et al\textsuperscript{A3} in order to facilitate robust meta-analysis.

The trial will consist of two primary groups:

1. Control group: patients assigned to 12 months ongoing optimal medical management followed by corpus callosotomy
2. Anterior corpus callosotomy group: patients assigned to anterior corpus callosotomy combined with optimal medical management
3. Total corpus callosotomy group: patients assigned to total corpus callosotomy combined with optimal medical management
Patients will be randomly assigned to either the control group or the treatment groups before inpatient clinicians will be contacted; patients will be assigned to the anterior corpus callosotomy group or the total corpus callosotomy group depending on their clinical picture. The study groups will be further stratified for sub analysis of adult versus paediatric outcomes and partial versus total corpus callosotomy outcomes. Intervention and control groups will undergo optimal medical management and assessment by epileptologists blinded to patient assignment, as well as formal assessment by neuropsychiatrists blinded to patient assignment. While epileptologists will know that patients have been selected for corpus callosotomy, the blinding that will occur will be whether the patient will undergo delayed treatment or early treatment.

Patients will be followed for 12 months in order to assess differences in outcomes between intervention and control groups. The evidence presented in Graham et al’s case series suggests that approximately 80% of patients may continue to have worthwhile reduction in drop attacks\(^7\). A follow on cohort study may be used to investigate the long term benefits of corpus callosotomy.

Ethics approval for this study will be obtained independently from the various centres. The trial will be registered on clinicaltrials.gov.

A.2.2 Participants

All patients referred to the individual epilepsy surgery centres will be selected for the trial if they satisfy the following inclusion criteria:

1. Failure of 3 or more AED
2. Seizure semiology involves generalised or multifocal epilepsy that includes drop attacks (tonic, atonic or myoclonic)
3. No previous epilepsy surgery
A.2.3 Workup and Surgical Approach

Patients will be worked up for corpus callosotomy prior to randomisation in accordance with the guidelines for epilepsy surgery described by Cross et al\textsuperscript{A8}:

1. EEG: interictal scalp EEG including natural sleep recordings, as well as VEEG for recording ictal events. These will be obtained using standard techniques described by the International Federation of Clinical Neurophysiology\textsuperscript{A9}.
2. Structural Imaging: 3T MRI using a specified epilepsy protocol; CT may be utilised in when indicated, such as calcification. Special sequences will be required for infants and children under 24 months old due to immature myelation; serial sequences will also be used in this group in order to identify abnormalities. Callosal volumes will be recorded.
3. Neuropsychiatry: age appropriate intelligence, behavioural and development tests.

The surgical approach and technique will involve a single 5x5cm craniotomy over the midline and centred on the coronal suture. Depending upon the vascular anatomy, the callosotomy will be performed to the left of the falx cerebri. Anterior corpus callosotomy will include any callosal section that spares the splenium, whereas complete corpus callosotomy will include any callosal section that includes the splenium. Patients with prior anterior corpus callosotomy undergoing further surgery for a complete corpus callosotomy will be classed as having a completed corpus callosotomy.

A.2.4 Study Variables

The outcome variables will be seizure outcome, neuropsychiatric outcomes, QOL and complications:

1. Seizure outcome: a good outcome will be defined as free or almost free of seizures.
2. Neuropsychiatric outcomes: formal age appropriate intelligence, developmental and behavioural assessments will be used to assess neuropsychiatric outcomes.
3. QOL: The SF-36 will be used to report QOL outcomes.
4. Complications: Severity of surgical and neurological complications will be classified using a similar system to Hader et al\textsuperscript{10}, as shown in Table A.1.

**Table A.1.** Severity of complications. CSF = cerebrospinal fluid; DVT/PE = deep vein thrombosis/pulmonary embolus

<table>
<thead>
<tr>
<th></th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical complications</td>
<td>Hydrocephalus</td>
<td>CSF leak</td>
</tr>
<tr>
<td></td>
<td>Deep infections (such as intracerebral and epidural abscesses)</td>
<td>Intracranial/extracranial infection</td>
</tr>
<tr>
<td></td>
<td>requiring drainage and/or bone flap removal</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td></td>
<td>All neurological complications that persisted beyond 3 months of surgery</td>
<td>DVT/PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracranial haematomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic disturbances</td>
</tr>
<tr>
<td>Neurological conditions</td>
<td>All neurological complications resolving within 3 months of surgery</td>
<td>All transient neurological complications resolving within 3 months of surgery</td>
</tr>
</tbody>
</table>

The following epidemiological data will be collected at randomisation for multivariable analysis:

1. Sex;
2. Epilepsy syndrome and seizure semiology;
3. Comorbidities;
4. Age at surgery;
5. Age at epilepsy onset;
6. Investigations:
Appendix A: Design of a Multicentre Randomised Trial

a. Barkovich classification of MRI findings\textsuperscript{A11};

b. Callosal volumes; and

c. EEG findings using Hanson et al’s classification\textsuperscript{A12}.

7. Neuropsychiatric assessments;

A.2.5 Data Collection

Data collection will be conducted by epileptologists and neuropsychiatrists blinded to randomisation. At randomisation, and at 3 month intervals post-randomisation, epileptologists will document a seizure record, QOL, comorbidities and disability. Neuropsychiatrists will conduct formal assessment of intelligence, development and behaviour at randomisation and at 6 month intervals post-randomisation.

A database will be used for entry of the data. Data fields will include the following:

1. Seizures:
   a. Semiology;
   b. Frequency; and
   c. Any injuries sustained in the previous 3 months that can be directly attributed to drop attacks.

2. QOL:
   a. SF-36 score
   b. SF-36 section scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health)

3. EEG:
   a. Hanson Type I Ictal: generalised slow spike-wave pattern, electrodermal pattern, or low amplitude, fast activity without evolution pattern
   b. Hanson Type II Ictal: other less generalised patterns, which included focal features or are more chaotic; patients with Type I and Type II patterns will be defined as Type II
c. Interictal background: symmetric or asymmetric, and with or without slow spike wave activity.

4. Imaging:
   a. Barkovich classification of structural MRI features;
   b. Callosal volumes;
   c. Extent of callosotomy, which will be confirmed on post-operative MRI.

5. Neuropsychiatric assessment:
   a. Age appropriate intelligence scales for patients aged 30 months and over: Wechsler Adult Intelligence Scale, Wechsler Intelligence Scale for Children and the Wechsler Preschool and Primary Scale of Intelligence, including their index scores and the Full Scale IQ and General Ability Index
   b. Bayley Scales of Infant and Toddler Development for patients aged between 1 and 42 months, including the subset scores (cognitive, language, and motor) as well as parental reported subsets (social-emotional role and adaptive behaviour); may be used in patients with severe developmental delay unable to complete the intelligence assessments
   c. Age appropriate behavioural assessment, including: Autism Diagnostic Interview, Autism Diagnostic Observation Schedule, and the Vanderbilt Assessment Scale (teacher and parent scales), Child Behaviour Checklist.

A.2.6 Statistical Analysis

Data will be analysed using the intention to treat principle. Significance will be defined as $p < 0.05$. Freedom from drop attacks and from other seizures will be determined using Kaplan-Meier event-free survival analysis curves using right-censoring, with differences between groups assessed using log-rank tests. Cox proportional hazards regression used to control for differences in demographics and clinical characteristics. Categorical data will be compared using Fisher’s exact test and interval data will be compared using Mann-Whitney’s U test. The following
clinical features will be modelled for the primary outcome using multivariable logistic regression analysis: age at onset; age at surgery; type of drop attack (tonic vs atonic); pre-surgical ictal EEG type; size of corpus callosum; extent of callosotomy (anterior vs complete); diagnosis of Lennox-Gastault Syndrome (LGS), West Syndrome or Ohtahara Syndrome; moderate-severe developmental delay; and abnormal MRI features.

A.2.7 Study Size

The sample size has been calculated for a Kaplan-Meier survival analysis of the primary objective; the power of the secondary objectives and sub-analyses will be calculated in a post hoc analysis. A two-tailed model with a 0.05 probability of Type I error and a power of 0.8 was used.

Tellez-Zenteno et al found that 35% of adult and paediatric patients were free of disabling drop attacks\textsuperscript{A6}. In the paediatric literature, Graham et al found that 58.6% of anterior corpus callosotomy patients and 88.2% of total corpus callosotomy patients were free or almost free of drop attacks\textsuperscript{A1}. Rolston et al used a 50% reduction in drop attacks as their cut off in adult and paediatric patients\textsuperscript{A13}, which is equivalent to Engel class I or II. Using this criteria, 85.6% of corpus callosotomy patients had at least a 50% reduction in drop attacks. Finally, up to 24% of pts with refractory epilepsy have been reported to achieve seizure remission for more than 12 months\textsuperscript{A14}, but this may be an over-estimate in this difficult to treat population.

The values that were used in the sample size calculation are shown in table A.2 below. These require a total sample of 61 patients in the control and anterior corpus callosotomy groups, and 45 patients in the total corpus callosotomy group. Assuming a retention rate of 0.8 (as in Wiebe et al’s RCT\textsuperscript{A3}), the trial will require recruitment of 210 patients for randomisation.
Table A.2. Values used to calculate sample size to achieve 80% power with <5% Type I error.

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimated effectiveness</th>
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<tbody>
<tr>
<td>Control</td>
<td>0.24</td>
</tr>
<tr>
<td>Anterior corpus callosotomy</td>
<td>0.50</td>
</tr>
<tr>
<td>Total corpus callosotomy</td>
<td>0.80</td>
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</table>

A.3 Discussion

There is a precedence to RCTs in epilepsy surgery that have demonstrated clear benefits of resective surgery to prolonged medical therapy\textsuperscript{A3,A4}, but the results for corpus callosotomy in Dwivedi et al’s paper are inconsistent with the paediatric literature\textsuperscript{A1}. This will be the first RCT that will assess the safety and efficacy of corpus callosotomy and, if successfully implemented, could set the conditions for the design and conduct of other epilepsy surgery trials. The infrequency of the procedure clearly necessitates a multicentre trial, which complicates the design and feasibility of this trial. Should a trial seek to compare total corpus callosotomy to optimal medical management alone, a fewer number of patients will be required for randomisation in a 1:1 distribution, which may be a more feasible approach.

The main strength of this trial is its blinded and randomised design. As Wiebe et al found in their pilot studies, neither patients nor clinicians accept randomisation after the patients have been worked up. Their novel approach to blinding and randomisation is a key factor in ensuring the validity of the design. They also found that only 5% of patients randomly assigned in this manner were found to be unsuitable for surgery following workup. A further strength of the design of this present trial is the fact that it modifies a previously successful design, which will support meta-analyses in the future. It is possible that the trial can support the
identification of prognostic factors that have eluded case series. This would support an enhanced evidence base for patient selection.

This trial will be limited in a number of ways. First, patients will not be blinded but this is ameliorated by using Wiebe et al's strategy of randomisation before contacting inpatient clinicians and using a strategy that delays treatment in the control group. Second, this study is not designed to test the hypothesis that sustained freedom drop attacks diminishes over time, as observed in Chapter 3 and found by Telez-Zenteno et al. However the cohort could be followed for long term follow up of outcomes. Third, the design does not include VNS in the randomisation, which is an important minimally invasive alternative to corpus callosotomy.

A.4 Conclusion

The hypothesis that corpus callosotomy is a safe and effective procedure has been well established. The RCT described in this study protocol will be the first trial to assess this hypothesis. A multicentre trial will be required in order to recruit a sufficient number of patients, which will complicate the design and feasibility of this trial. A follow-on cohort study could be used to test the important hypothesis that freedom drop attacks following corpus callosotomy diminishes over time.

A.5 References for Appendix A


Corpus Callosotomy Outcomes in Paediatric Patients


APPENDIX B: SEIZURE OUTCOME AFTER CORPUS CALLOSOTOMY IN A LARGE PAEDIATRIC SERIES

The main publication arising from this thesis is included in this appendix. The reference is:

Seizure outcome after corpus callosotomy in a large paediatric series

DAVID GRAHAM 1,2,3 | DEEPAK GILL 1,2,3 | RUSSELL C DALE 1,2,3 | MARTIN M TISDALL 4,5 | CORPUS CALLOSOTOMY OUTCOMES STUDY GROUP*

1 Faculty of Medicine, The University of Sydney, Sydney; 2 Institute of Neuroscience and Muscle Research, Kids Research Institute Children’s Hospital at Westmead, Sydney; 3 TY Nelson Department of Neurology and Neurosurgery, Children’s Hospital at Westmead, Sydney, Australia. 4 Department of Neurosurgery, Great Ormond Street Hospital for Children, London; 5 Developmental Neurosciences Programme, UCL-Institute of Child Health, London, UK.

Correspondence to David Graham at Institute for Neuroscience and Muscle Research, Kids Research Institute, The Children’s Hospital at Westmead, 178 Hawkesbury Rd, Westmead, Australia. E-mail: dgra2033@uni.sydney.edu.au

*See Appendix S1 (online supporting information) for names and affiliations of the Corpus Callosotomy Outcomes Study Group.

AIM To describe 20 years of experience with corpus callosotomy at Great Ormond Street Hospital for Children, London and the Children’s Hospital at Westmead, Sydney.

METHOD Records of patients who underwent corpus callosotomy between January 1995 and December 2015 were reviewed. Complications of surgery and changes in seizure type and frequency, injuries, and use of antiepileptic drugs were recorded. Drop attacks were analysed using Kaplan–Meier event-free survival curves. Multivariable regression analysis was used to assess the effect of clinical characteristics on outcome at last follow-up.

RESULTS Inclusion criteria were met for 55 patients younger than 18 years of age. Median follow-up length was 36 months. At the last follow-up, 26 out of 55 patients (47%) had rare or no drop attacks. In those without a good outcome at final follow-up, 26 out of 29 (90%) had drop attacks return within 12 months of surgery. There were no preoperative predictors of developing drop attacks postoperatively. The median number of antiepileptic drugs significantly reduced from three to two. Transient neurological complications were experienced by 11 out of 55 patients (20%) and 6 out of 55 patients had surgical complications (11%).

INTERPRETATION Corpus callosotomy is a well-tolerated procedure that is effective at reducing the severity of drop attacks in paediatric patients. Drop attacks that do return are likely to do so within 12 months and the number of antiepileptic drugs can be significantly reduced.

Corpus callosotomy is a palliative treatment for patients with either generalized or multifocal refractory epilepsy characterized by injurious drop attacks. There are no universally accepted indications for corpus callosotomy, and patient selection is centre- and surgeon-dependent. In a systematic review of corpus callosotomy, paediatric patients appeared to benefit from corpus callosotomy more frequently than adults, with 88% of paediatric patients achieving rare or no drop attacks after a complete callosotomy procedure.1 Téllez-Zenteno et al. found that in studies without prolonged follow-up,2 at least 65% of patients were likely to be either free or almost free of drop attacks but that sustained freedom from drop attacks diminished significantly beyond 5 years. More recently, the population study of long-term outcomes by Stigsdotter-Broman et al. found that sustained benefit is possible up to 10 years.1

Surgical and neurological complications do occur, but there are typically no enduring complications in children.1,4 Notably, disconnection syndrome, which presents with a combination of alien limb, apraxia, tactile and/or visual anoma, agraphia, neglect, and dyslexia, has been reported in 13% of children undergoing complete corpus callosotomy, which is higher than that reported in adults.1 However, unlike adults, disconnection syndrome in children appears to always resolve within 3 months. Earlier intervention is generally preferred in epilepsy surgery,2 and children who undergo successful epilepsy surgery have significantly prolonged life expectancy compared with children managed medically.6

This paper presents a retrospective case series of outcomes and complications of 20 years of corpus callosotomy experience at Great Ormond Street Hospital in London and the Children’s Hospital at Westmead in Sydney.

METHOD For this type of study formal consent is not required. Ethics approval for this study was granted by the Sydney Children’s Hospital Network Human Research Ethics
Committee (HREC Reference LNR/14/SCHN/178) and the Great Ormond Street Hospital Clinical Audit Department (Registration Number 1974).

**Patient selection**

Between January 1995 and December 2015, 76 patients underwent corpus callosotomy at Great Ormond Street Hospital and the Children’s Hospital at Westmead. Patients were excluded if they (1) were 18 years or older at the time of surgery \( n=2 \); (2) were last seen in the immediate postoperative follow-up clinic (lost to follow-up; \( n=18 \)); or (3) underwent additional resection at the time of surgery \( n=1 \).

Fifty-five patients met the inclusion criteria, five of whom subsequently underwent secondary completion of corpus callosotomy.

**Surgical work-up and approach**

All patients underwent full preoperative evaluation according to the International League Against Epilepsy recommendations for referral and evaluation. This involved evaluation by a multidisciplinary team involving neurologists and neurosurgeons and agreement upon case selection before proceeding to surgery. Patients offered callosotomy were deemed to be unlikely to benefit from resective surgery but considered likely to benefit from disconnective surgery. The decision for partial or complete corpus callosotomy was based on neuropsychological assessment; patients with poor cognitive function, especially verbal function, were selected for complete corpus callosotomy. Completion of corpus callosotomy was based on postoperative seizure control.

Surgery was performed by specialist neurosurgeons WH and MMT at Great Ormond Street Hospital and MD at the Children’s Hospital at Westmead. A standard technique was used in both centres, which reduces the possibility of variability, although variability cannot be excluded. A single craniotomy was performed over the midline and centred on the coronal suture. Depending upon the vascular anatomy, the callosotomy was performed to the left of the falx cerebri. The dissection was taken to the planned posterior extent of the corpus callosotomy and then anteriorly to the anterior cerebral arteries. Anterior corpus callosotomy included any callosal section that spared the splenium and all or part of the isthmus. Complete corpus callosotomy included any callosal section that divide the splenium. There are no anatomical landmarks so neuronavigation offers the best intraoperative decision tool. The loss of accuracy as the division advances is small owing to the fact that the procedure is midline.

**Follow-up**

All patients were followed up within 6 weeks of surgery. Owing to the severity and complexity of refractory generalized epilepsy, most patients were followed-up regularly with formal review. Further investigations were conducted when a patient’s epilepsy was worsening or new seizure types were emerging. The patient was considered lost to follow-up if they had less than 3 months of follow-up. The authors attempted to contact all patients who were lost to follow-up, but contact could only be made with two patients and they were included in the case series. A total of 18 patients were lost to follow-up.

**Data**

Data were sourced from clinical records to ascertain the clinical progression of seizure semiology. Seizure semiology was recorded using the 1989 International League Against Epilepsy classification of seizures.8 Drop attacks were classified as tonic, atonic, or myoclonic.8 The Barkovich classification system was used to classify abnormal magnetic resonance imaging (MRI) findings.9 The extent of callosotomy was confirmed on follow-up MRI for 31 patients. Confirming the extent of callosotomy on postoperative imaging was not standard practice for patients during the period of this data collection but would be valuable in a prospective study.

**Outcomes**

The primary outcome for this study was frequency of drop attacks; a good outcome was defined as free of drop attacks or rare drop attacks. While there is some controversy over the use of the Engel classification system in disconnective surgery, it is clinically relevant and commonly used in clinical practice for reporting epilepsy surgery outcomes after corpus callosotomy.1 Therefore, the Engel classification system was used as the basis for the definition of good outcome in this paper;10 the phrase ‘Engel Class I–II’ has not been used in order to avoid confusion as this could imply ‘completely or almost seizure free’. Severity of surgical and neurological complications were classified according to the same classification system as Hader et al.11 Neurological complications were assessed by the treating neurologist. The following secondary outcomes were also included: (1) other seizure outcomes at last follow-up – frequency of generalized seizures, partial seizures, and spasms at last follow-up, including new-onset seizures (a good outcome for other seizures is defined as rare or no seizures of this type after surgery, aligning with Engel class I–II); (2) injury outcomes at last follow-up – number of patients who regularly sustained injuries as a result of their drop attacks at the time of surgery compared with number at last follow-up; (3) changes in the number of antiepileptic drugs (AEDs) at last follow-up – the number of AEDs at the time of surgery compared with the number of AEDs at last follow-up.

**What this paper adds**

- Corpus callosotomy is an effective palliative treatment and well tolerated in children.
- Good outcomes for the first 12 months after surgery were likely to continue.
- The number of antiepileptic drugs can be significantly reduced after corpus callosotomy.
- Patients with fewer than three types of seizure had better outcomes.
- There were fewer injuries from drop attacks after surgery.
Neuropsychological changes at last follow-up were not included as postoperative formal assessment was not regularly conducted and this paper is a reflection of actual practice.

Statistical analysis
All statistical analysis were conducted using SAS version 9.4. Categorical data were compared using Fisher’s exact test and interval data were compared using the Mann–Whitney U test. The duration of good drop attack outcome was analysed using Kaplan–Meier event-free survival curves using right-censoring of data and the log-rank test; right-censor date was 31st December 2015. The following clinical features were modelled using the log-rank test for statistical significance, as well as multivariable logistic regression analysis: age at onset; age at surgery; tonic drop attacks; extent of callosotomy (anterior vs complete); diagnosis of Lennox–Gastaut syndrome, West syndrome, or Ohtahara syndrome; moderate-to-severe developmental delay; and abnormal MRI features. Backward selection was used for the multivariable logistic regression model; Wald $\chi^2$ statistic was used to test for significance and Harrell’s C statistic was used for goodness of fit. Initial seizure-free interval of 12 months, 18 months, and 24 months postoperatively was also analysed using a landmark analysis and the log-rank test for statistical significance. The landmark analysis assessed the effect of an initial period of 12 months of good outcome of drop attacks (the ‘cut-off period’). Two groups were considered with this approach: (1) all patients; and (2) patients who were right-censored beyond the cut-off period or who had drop attacks return after that period. Kaplan–Meier survival curves of these two groups of patients were compared using log-rank statistics. All p-values were two-tailed and significance was defined as $p<0.05$.

RESULTS

Patient demographics
Preoperative demographic data are shown in Table I. Median age at surgery was significantly greater at the Children’s Hospital at Westmead (147.5mo vs 111mo; $p=0.02$), and there were significantly more patients with myoclonic–atonic drop attacks (6 vs 0; $p<0.01$), atonic seizures (3 vs 0; $p<0.05$), and myoclonic seizures (12 vs 6; $p<0.01$) at the Children’s Hospital at Westmead. A total of 11 out of 55 patients underwent anterior corpus callosotomy, 43 out of 55 patients underwent complete corpus callosotomy.

In total, before surgery 4 out of 55 patients had only drop attacks, 9 out of 55 patients had drop attacks plus one other type of seizure, 22 out of 55 patients had drop attacks plus two other types of seizure, and 20 out of 55 patients had drop attacks plus at least three other types of seizure. All patients had some degree of developmental delay ($n=55$); in 49 patients this was moderate-to-severe. Structural brain abnormality was the most common known epilepsy aetiology ($n=15$). Other aetiologies included genetic ($n=8$), infectious ($n=3$), and immune mediated ($n=1$). Comorbidities other than developmental delay included cerebral palsy ($n=10$), autism spectrum disorder ($n=10$), attention-deficit–hyperactivity disorder (ADHD) ($n=8$), and sensorineural hearing loss ($n=2$). Three patients had two comorbidities other than developmental delay (cerebral palsy with autism spectrum disorder, cerebral palsy with ADHD, and autism spectrum disorder with sensorineural hearing loss).

**Table I: Preoperative demographics**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>GOSH</th>
<th>CHW</th>
<th>All</th>
<th>p</th>
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</thead>
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<tr>
<td>N of patients</td>
<td>33</td>
<td>22</td>
<td>55</td>
<td>–</td>
</tr>
<tr>
<td>M:F</td>
<td>25:8</td>
<td>11:11</td>
<td>36:19</td>
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<tr>
<td>Extent of callosotomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anterior</td>
<td>8/33</td>
<td>3/22</td>
<td>11/55</td>
<td>0.29</td>
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<tr>
<td>Complete</td>
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<td>19/22</td>
<td>43/55</td>
<td>0.24</td>
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<tr>
<td>Completed</td>
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<td>2/3</td>
<td>5/11</td>
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<tr>
<td>Abandoned</td>
<td>1/33</td>
<td>0/22</td>
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<td>12/22</td>
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</tr>
<tr>
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<td>0/22</td>
<td>4/55</td>
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<tr>
<td>Ohtahara syndrome</td>
<td>2/33</td>
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<td>2/55</td>
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</tr>
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<td>11/22</td>
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<td>Moderate-to-severe</td>
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<td>21/22</td>
<td>49/55</td>
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<td>developmental delay</td>
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<tr>
<td>Other</td>
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<td>29/55</td>
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</tr>
<tr>
<td>comorbidities(^a)</td>
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<td></td>
<td></td>
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<tr>
<td>Median (IQR) age (mo)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy onset Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>10/33</td>
<td>24/25</td>
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<td>Abnormal MRI</td>
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<td>1/4</td>
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<td>7/17</td>
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<td>Seizure semiology at the time of surgery</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Drop attacks</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic</td>
<td>9/33</td>
<td>7/22</td>
<td>16/55</td>
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<tr>
<td>Other generalized seizures</td>
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<td></td>
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<td>22/55</td>
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</tr>
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<td>6/55</td>
<td>0.39</td>
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<td>6/22</td>
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</tr>
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<td>3/22</td>
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<tr>
<td>Therapies at time of surgery</td>
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<tr>
<td>Median (IQR) follow-up (mo)</td>
<td>3 (1)</td>
<td>3 (2)</td>
<td>3 (1)</td>
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<td>AED</td>
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<td>2</td>
<td>0.52</td>
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<tr>
<td>Median (IQR)</td>
<td>33 (34)</td>
<td>42 (30.25)</td>
<td>36 (34)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Data are n unless otherwise indicated. *Excluding developmental delay. GOSH, Great Ormond Street Hospital; CHW, Children’s Hospital at Westmead; M, male; F, female; IQR, interquartile range; MRI, magnetic resonance imaging; AED, antiepileptic drug; VNS, vagus nerve stimulator.
**Complications**

Neurological complications occurred in 11 out of 55 (20%) surgeries and all resolved within 6 weeks. These included hemiparesis \( (n=7) \), disconnection syndrome \( (n=2) \), gait ataxia \( (n=1) \), and aphasia \( (n=1) \). Disconnection syndrome occurred in one patient with anterior corpus callosotomy and one patient with complete corpus callosotomy. Minor surgical complications occurred in 6 out of 55 (11%) surgeries and included intracranial haematoma that did not require surgical evacuation \( (n=2) \), pyrexia \( (n=2) \), and intracranial infection \( (n=1) \). The only major complication was hydrocephalus \( (n=1) \) and there were no deaths. There was no significant difference in complications between anterior corpus callosotomy and complete corpus callosotomy \( \text{median neurological 1/11 vs 6/43} \ [p=0.67]; \text{minor surgical 1/11 vs 4/43} \ [p=1.00]; \text{major surgical 0/11 vs 1/43} \ [p=1.00] \).

**Primary outcome**

Median follow-up postoperatively was 36 months (interquartile range 34mo, range 7–131mo). Figure 1 shows the frequency of drop attacks preoperatively and at last follow-up. Overall, 26 out of 55 (47%) patients achieved a good outcome for drop attacks at last follow-up. Of the children with a poor postoperative drop attack outcome, 26 out of 29 (90%) of these patients had a return of drop attacks within 12 months of surgery. The Kaplan–Meier survival curve of good outcome for drop attacks is shown in Figure 2a. This shows the number of months post-callosotomy that patients had a worthwhile reduction in drop attacks. Log-rank statistics for clinical features correlated with good outcome are shown in Table II. A landmark analysis is shown in Figure 2b. The results for cut-off periods of 12 months, 18 months, and 24 months are shown in Table III, including the proportion of patients who continue to have good outcome for drop attacks after the cut-off period. The results are not significant when the cut-off period is 6 months \( p=0.07 \).

**Secondary outcomes**

Patients with drop attacks plus one other seizure type before surgery were significantly more likely to achieve a good outcome for other seizures compared with patients with two other seizure types or three or more other seizure types \( (100\% \text{ vs } 23\% \ [p<0.01]; \text{100\% vs } 10\% \ [p<0.01]) \). The number of other seizure types were not associated with any statistically significant differences in outcome for drop attacks. The overall outcome and the frequency of other seizure types is shown in Figure 3.

There was a significant reduction in the number of patients who were regularly sustaining injuries caused by their drop attacks \( (77\% \text{ preoperatively vs } 21\% \text{ at last follow-up; } p<0.01) \). Among patients who continued to have drop attacks at the time of last follow-up, there was also a significant reduction in the number of patients sustaining injuries \( (73\% \text{ preoperatively vs } 42\% \text{ at last follow-up; } p=0.05) \) (Fig. 1).

A total of 7 out of 55 patients had developed new-onset partial seizures at last follow-up and 3 out of 55 patients had developed new-onset generalized seizures at last follow-up. There were no significant differences in new-onset seizures between patients with good outcome for drop attacks and patients with poor outcome for drop attacks \( \text{new partial seizures 5/26 patients vs 2/29 patients} \ [p=0.24]; \text{new generalized seizures 2/26 patients vs 1/29 patients} \ [p=0.60]) \).

The median number of AEDs used before surgery was three (interquartile range 1), whereas at last follow-up the median number of AEDs was two (interquartile range 1). A two-tailed paired Student’s \( t \)-test showed that there were significantly fewer AEDs used at last follow up compared with preoperatively \( (p<0.01) \).

**Multivariable regression analysis**

Multivariable logistic regression analysis of good outcome for drop attacks using backward selection had a Harrell’s C-statistic of 0.66 and a maximum rescaled \( R^2 \) value of 0.14. None of the clinical features described in the method reached statistical significance.

![Figure 1: Frequency of drop attacks and proportion of patients who suffer injuries from drop attacks pre-surgery and at last follow-up. (Colour figure can be viewed at wileyonlinelibrary.com)](image-url)
DISCUSSION

Despite the heterogeneity of patients in this case series on paediatric outcomes of corpus callosotomy, there were very few differences between the two centres. All patients had some degree of developmental delay, with the majority having moderate-to-severe developmental delay and almost half of the patients having at least one other comorbidity. Lennox–Gastaut syndrome, West syndrome, and Ohtahara syndrome were the most common syndromes. All patients had been investigated with MRI as part of their work-up; 55% had an abnormality. Genetic causes were found in 15% of patients.

In a systematic review of corpus callosotomy in paediatric patients, Graham et al. reported that 88% of total corpus callosotomy patients achieved a worthwhile reduction in drop attacks compared with 59% of patients with partial corpus callosotomy,\(^1\) which is higher than the outcomes in the present study. Our landmark analysis showed that there was a significant effect of at least 12 months of worthwhile benefit of corpus callosotomy on drop attacks (\(p<0.05\)). Indeed, 81% of patients who did have a return of drop attacks did so within 12 months of follow-up, similar to the case series by McInerney et al.\(^{12}\) However, patients who continued to have drop attacks after surgery were less likely to sustain injuries, which supports the use of corpus callosotomy for palliation. Other long-term studies have shown sustained benefit.\(^3\) This may suggest that a good drop attack outcome at 12 months could be a clinically valuable postoperative marker for sustained good drop attack outcome. Interest is also turning towards selective posterior corpus callosotomy, with the recent study by Paglioli et al. finding 30 out of 36 patients were either free or almost free of drop attacks at last follow-up.\(^{13}\) However, this must be contrasted with the older study by Pinard et al. in which the patients who underwent posterior corpus had poor outcomes.\(^{14}\)

All other clinical factors were not associated with a significant effect on the outcome of drop attacks. The extent of callosotomy is the factor that has been reported as that most commonly associated with seizure outcome;\(^1\) however, our series found no significant effect of extent. This may be owing to a combination of factors, such as the

### Table II: Log-rank statistics for clinical features as predictors of good drop attack outcome

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Log-rank</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at epilepsy onset &lt; median age at onset</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Age at surgery &lt; median age at surgery</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Tonic drop attack</td>
<td>0.21</td>
<td></td>
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<tr>
<td>Total corpus callosotomy</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>LGS spectrum</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe developmental delay</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

LGS, Lennox–Gastaut syndrome; MRI, magnetic resonance imaging.

### Table III: Landmark analysis for patients who have good drop attack outcome for an initial period of 12 months, 18 months, or 24 months compared with all patients

<table>
<thead>
<tr>
<th>Cut-off period (mo)</th>
<th>N of patients with follow-up longer than the cut-off</th>
<th>N of patients with good outcome during the cut-off period</th>
<th>Proportion of patients who continue to have good outcome after the cut-off</th>
<th>Log-rank</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>52</td>
<td>26</td>
<td>0.81</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>50</td>
<td>23</td>
<td>0.83</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>49</td>
<td>19</td>
<td>0.95</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 2:** Survival estimates for good drop attack outcome. (a) Kaplan–Meier survival curve; (b) landmark analysis comparing patients who have good drop attack outcome for an initial 12 months postoperatively compared with all patients. CCx, corpus callosotomy. [Colour figure can be viewed at wileyonlinelibrary.com]
relatively smaller number of patients with partial corpus callosotomy in our case series and the fact that determination of the extent of callosotomy was not solely based on postoperative imaging. Furthermore, these factors could explain the wide confidence interval for odds of good outcome being attributed to complete or subtotal corpus callosotomy in our logistic regression analysis.

Corpus callosotomy was well tolerated regardless of the extent of callosotomy. The complication rate in our series was comparable to the paediatric literature. The prospective, population-based study by Bjellvi et al. perhaps provides the best evidence of complications after epilepsy surgery and they used a similar classification system to ours. They observed that the complication rate may be under-reported in the literature as most studies are retrospectively designed. Although their study was limited to a single country and only 24 corpus callosotomies were performed on paediatric patients, they found that no patients developed a minor complication and only one patient developed a major (unspecified) complication.

Notably, the findings in our series for disconnection syndrome differ from the literature. While the literature suggests that approximately 12% of paediatric patients will experience a transient disconnection syndrome, which is significantly more likely in complete corpus callosotomy ($p<0.001$), our series found there was no significant likelihood of disconnection syndrome occurring nor was there any significant difference in outcome for complete versus anterior corpus callosotomy ($p=0.37$). This may be owing, in part, to the fact that the extent of callosal section in our series was largely based on the intraoperative surgeon’s (MMT, WH and MD) report.

Transient hemiparesis is a common complication in the literature, and it was the most common complication in our series (13%). There are two hypotheses to account for the reversible hemiparesis. The usual assumption is that it is associated with the retraction of the contralateral leg motor area. This hypothesis could be confirmed with diffusion-weighted imaging. However, it is also possible that the hemiparesis is caused by the interruption of venous drainage relating to the division of central cortical veins in order to gain access to the interhemispheric fissure. This alternate hypothesis could be confirmed with a study that investigates any relationship between the number of veins divided during surgery and any postoperative deficits.

There were significantly fewer AEDs used at last follow-up compared with preoperatively ($p<0.05$), which is different to the paediatric literature. This may reflect a strategy for optimizing AED usage in order to reduce the number of side effects. This could explain the relatively poorer outcome for drop attacks compared with the literature. However, the complex interplay between corpus callosotomy,
optimal medical management, and AED side effects is beyond the scope of this paper and has not been explored in the literature.

The benefit on other seizures was generally poor and was not correlated with drop attack outcome. It is not entirely clear whether the emergence of new seizure types is a reflection of the impact of the surgery or the evolution of the epilepsy. However, patients who had only one other seizure type benefited from corpus callosotomy for both drop attacks and the other seizure type. This may be indicative of the severity of seizure semiology before surgery, which, if appropriately defined, could prove to be another clinically relevant prognostic marker.

To date, all studies of corpus callosotomy outcomes in paediatric patients have focused on outcome at last follow-up. This is the first study of corpus callosotomy to investigate the temporal aspect of outcome for drop attacks. This is also one of the largest studies of corpus callosotomy in the paediatric population, which highlights the value of combining outcomes between centres.

There are several limitations to this study. The key limitation is the retrospective case series design. This may lead to the inaccurate reporting of some data, such as the full seizure semiology, any injuries from drop attacks, and the neuropsychological impact. While this introduces bias into the results, the study is useful as it does identify new information about the durability of seizure outcomes within the hypothesis that corpus callosotomy is a safe and effective palliative treatment for paediatric patients with generalized seizures characterized by drop attacks. Moreover, this paper is a reflection of actual practice, and prospective data collection was not possible. Postoperative neuropsychological assessments, postoperative electroencephalography studies, and postoperative MRI were not completed for all patients. Finally, there are potential centre differences in patient selection, work-up, and surgical approach. While both centres use International League Against Epilepsy recommendations for referral and evaluation, there may be differences before 2006.

As discussed elsewhere in the literature, there is a clear need for a randomized control trial of corpus callosotomy outcomes compared with optimal medical management. The design of such a trial was outlined by Graham et al. in their systematic review based on the landmark randomized controlled trial of Wiebe et al. of temporal lobectomy. The prognostic benefit of an initial 12-month period of worthwhile benefit on drop attacks identified in this paper could aid the design of such a trial. A prospective design would allow for imaging to confirm the extent of the callosotomy, and could include recording the number of emergency and intensive care admissions for injuries and other complications of epilepsy. However, enrolling a sufficient number of patients would be challenging given the relative infrequency of the procedure. Moreover, there may be limited enrolment given the challenges faced by parents in consenting to corpus callosotomy after extended periods of optimal medical management. Imaging studies comparing semiology of drop attacks, as well as other seizures pre- and post-callosotomy may provide some insight into the seizure outcomes reported here and elsewhere. They have the potential to provide insight into the long-term tractographic changes post-callosotomy, as well as to why reported outcomes in children are generally better than those of adults.

### Conclusion

This is one of the largest paediatric case series of corpus callosotomy outcomes, and is the first in the corpus callosotomy literature to utilize Kaplan-Meier analysis. As observed previously in the literature, the results of this present case series serve to further strengthen the hypothesis that corpus callosotomy is an effective palliative treatment and is well tolerated in paediatric patients. There were significantly fewer AEDs used at last follow-up and significantly fewer injuries from drop attacks at last follow-up. It further suggests that fewer than two other types of seizure preoperatively, and an initial 12-month period of worthwhile reduction in drop attacks, are prognostic of a good seizure outcome. Owing to the limited number of cases seen in major children’s hospitals, it is clear that a multicentre randomized trial is needed.

### Acknowledgements

The authors wish to thank the Children’s Hospital at Westmead’s biostatistician, Ms Liz Barnes, for her support and advice on the preparation of statistics for this paper. The authors wish to thank the clinicians and staff at the Children’s Hospital at Westmead and Great Ormond Street Hospital epilepsy units. The authors especially wish to thank the patients and their families. The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

### Supporting Information

The following additional material may be found online:

**Appendix S1**: Corpus Callosotomy Outcomes Study Group.

### References


CORPUS CALLOSOTOMY OUTCOMES STUDY GROUP

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