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Anxiety symptoms ten years after diagnosis of childhood-onset epilepsy: Prevalence and Correlates

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Abstract

This study described anxiety symptoms in Adolescents and Young Adults (AYA) 10 years after epilepsy diagnosis and assessed the association between family characteristics and long-term anxiety symptoms controlling for parent, clinical and child demographic characteristics. Data were from a multi-centre prospective study of children with new-onset epilepsy. Ten years after diagnosis, 33% scored above the cut-off for clinically significant anxiety symptoms. The mean anxiety z-score was similar to previously reported in the US population of the same age and sex. Multiple linear regression analyses showed that family characteristics at the 10-year follow-up and at diagnosis were not independently associated with long term anxiety symptoms. Five-year seizure freedom was independently associated with long-term anxiety symptoms. These findings suggest that the long-term outcome for childhood-onset epilepsy in terms of anxiety symptoms is similar to normative population data and there is a subset of AYA experiencing anxiety symptoms that are worthy of attention.

Keywords: childhood epilepsy, anxiety symptoms, adolescents, young adults, family environment, longitudinal

Summary for Lay Audience

Anxiety symptoms are among the most common mental health symptoms experienced by children with epilepsy and contribute to poorer health-related quality of life. Current literature provides evidence that the family environment plays an important role in mitigating psychiatric symptoms such as anxiety symptoms in children and adolescents with epilepsy. Little is known, however, about the prevalence of anxiety in the long-term as those with childhood-onset epilepsy become adolescents and young adults (AYA). The aims of this thesis were: 1) To describe anxiety symptoms in AYA 10 years after epilepsy diagnosis and 2) to assess the association between family characteristics and anxiety symptoms 10 years after epilepsy diagnosis to identify potentially modifiable family characteristics early in the course of epilepsy. Data for this thesis were from a multicenter prospective cohort study that followed children with newly diagnosed epilepsy and their families for 10 years after diagnosis. The majority of AYA in our study did not experience elevated anxiety symptoms, but about one third reported experiencing anxiety symptoms 10 years after epilepsy diagnosis. AYA who had not been seizure-free for at least five years, were significantly more likely to experience elevated anxiety symptoms. These findings suggest that the long-term outcome for childhood-onset epilepsy in terms of anxiety symptoms is generally positive overall but a subgroup of these AYA with clinically significant anxiety symptoms warrant attention.

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List of Abbreviations

AYA- Adolescents and Young Adults

ASM- Antiseizure Medications

BECRS- Benign epilepsy of childhood with Rolandic spikes

BDI-Beck Depression Inventory

CDI- Children's Depression Inventory

CES-D- Center for Epidemiological Studies Depression Scale

CWE- Children with Epilepsy

Family APGAR- Family Adaptability, Partnership, Growth, Affection and Resolve

FIRM-Family Inventory of Resources for Management

GASE-Global Assessment of Severity of Epilepsy

HRQoL- Health-Related Quality of Life

HADS- Hospital Anxiety and Depression Scale

HERQULES- Health-Related Quality of Life in Children with Epilepsy Study

ILAE- International League Against Epilepsy

PWE- People with Epilepsy

QOLIE- Quality of Life in Epilepsy Inventory

STAI- Spielberger State-Trait Anxiety Inventory

Chapter 1

Introduction

This chapter provides the rationale and details regarding the study purpose and outlines the specific objectives for this thesis.

1.1 Statement of the Problem

Epilepsy is one of the most common chronic and disabling neurological diseases and it is often complicated and exacerbated by neuro-behavioural comorbidities[1][2]. There is a compelling body of evidence showing that people with epilepsy (PWE) report poorer health-related quality of life compared to people without epilepsy[3]. It is also known that epilepsy is a heterogenous medical condition and can be experienced differently by those who suffer from it[2]. Psychiatric comorbidities, particularly depression and anxiety, are prevalent among people with epilepsy and add to overall disease burden[4].

Anxiety symptoms are one of the most common psychiatric comorbid conditions reported to occur in PWE [5]. Research on psychiatric comorbidities experienced by PWE has often focused on depression[6]. However, there has been growing emphasis in the literature on the importance of identifying and treating anxiety symptoms as early as possible in the course of epilepsy[7]. Although it is known from previous studies in the literature that anxiety symptoms are experienced by PWE in the short-term, it is unknown if these symptoms persist in the long-term.

The family environment has increasingly been recognized as important to consider in delineating long-term outcomes in individuals who are diagnosed with pediatric chronic

diseases[8]. Particularly of interest is the view that the family environment is more malleable i.e. easier to change and/or modify compared to epilepsy-related clinical characteristics. A few studies have provided some evidence for the important role the family environment plays in other long-term outcomes such as health-related quality of life in people with epilepsy[9]. However, to the best of our knowledge, there are no studies investigating the potentially important role of the family environment in the experience of anxiety symptoms in the long term for individuals diagnosed with childhood epilepsy.

This thesis aims to bridge this gap by describing long-term outcomes of adolescents and young adults (AYA), focusing on anxiety symptoms, which are one of the common psychiatric comorbidities experienced by AYA diagnosed with epilepsy. It also describes the characteristics of those AYA experiencing anxiety symptoms in the long term with a novel focus on the extent to which family characteristics may be associated with anxiety symptoms many years after the diagnosis of epilepsy. Examining the association between family environment and anxiety symptoms could foster better understanding of potentially malleable factors as targets for interventions aimed at lowering the risk of anxiety symptoms in AYA.

1.2 Study Objectives

There are two primary objectives for this thesis:

1) To describe anxiety symptoms in adolescents and young adults with childhood onset epilepsy ten years after their epilepsy diagnosis.
2) To assess the association between family characteristics and anxiety symptoms in adolescents and young adults ten years after epilepsy diagnosis, controlling for parent and child clinical and demographic characteristics, at both the:

a) 10-year follow-up and

b) time of epilepsy diagnosis.

The first objective aims to describe long-term anxiety symptoms among AYA with childhood-onset epilepsy, in terms of the proportion of AYA experiencing clinically significant anxiety symptoms and also in comparison to the general population of AYA as a way of offering a relative context within which to interpret the experience of AYA living with epilepsy. The second objective, exploring the characteristics associated with anxiety symptoms in AYA with epilepsy 10 years after diagnosis, primarily focuses on family, parent, and child clinical and demographic characteristics at the 10-year follow-up given their temporal proximity to the assessment of anxiety symptoms. Secondarily, assessing the association of these characteristics at diagnosis with anxiety symptoms in the long-term could identify potentially malleable family and other parent and clinical characteristics present early in the course of childhood onset epilepsy. This could foster early identification of children who may be at risk of anxiety symptoms and, in the longer term, inform preventive interventions.

Chapter 2

Background and Literature Review

This chapter provides a summary of the literature on several topics relevant to the objectives of this thesis. Section 2.1 provides an overview of epilepsy as a disorder. Section 2.2 provides an overview of the literature on anxiety in PWE. Section 2.3 provides a review of the literature on the family environment. Section 2.4 reviews the literature regarding associations of anxiety symptoms in childhood onset epilepsy with two key categories of factors: clinical characteristics of epilepsy and demographic characteristics.

Multiple databases were searched to conduct this literature review. Through Western University library database selector, PsycINFO (ProQuest), MEDLINE(OVID), and SCOPUS(PubMed) were chosen as the three primary databases to search for relevant publications. Search results were screened for review based on the title of the articles and then the abstracts. Publications were reviewed and included if their objectives were in line with the purpose of the current literature review. In addition, the ancestry method, which involves finding additional articles through the reference lists of studies already found, was used to locate relevant studies. Publications obtained through occasional email notifications from Mendeley were also reviewed and included if appropriate.

2.1 Overview of Epilepsy

The International League Against Epilepsy(ILAE) defines epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and the psychosocial, cognitive and neurobiological consequences that arise as a result of epileptic

seizures[10]. Criteria for an epilepsy diagnosis are: (i) at least two uncontrolled seizures, also known as reflex seizures, occurring >24-hour period; (ii) one unprovoked seizure with a high probability (i.e. >60%) of further seizures occurring over the next 10 years; or (iii) a diagnosis of epilepsy syndrome[10].

Seizures associated with the diagnosis of epilepsy are categorized mainly by type of onset[11]. Focal seizures, formerly known as partial seizures, are seizures originating in and limited to the neuronal networks of parts of one hemisphere[11][1]. Focal seizures may be localized to that hemisphere or spread across both hemispheres [11]. Generalized seizures are seizures that originate within the bilateral neuronal network in the cerebral hemisphere[11][1]. Seizures can start as a focal seizure and then later become generalized and can originate cortically and subcortically[1]. Awareness, defined as knowledge of self and immediate environment, is a further optional categorization of focal epilepsy[11]. Focal seizures may be awareness-impaired (i.e., lack of consciousness during some portion of a seizure event described as “focal unaware” seizures) or may be “focal aware” which refers to the retention of consciousness for the duration of a seizure event[11][1]. Awareness impairment is not used to categorize seizures of generalized onset, as these are almost always characterized by loss of awareness[11]. Generalized seizures are further classified based on motor activity during a seizure event. Epilepsy of generalized onset may involve the presence of bilateral motor activity during the seizure event, known as generalized motor seizure, or may be characterized by the absence of motor activity during a seizure event, known as generalized absence seizures[11][1].

There is currently no cure for epilepsy, whereby people are considered “cured” if they no longer have a particular disease and have no greater risk for future diagnosis of that disease,

relative to those who have been unaffected. After having had a diagnosis of epilepsy, having the same risk as unaffected individuals is rarely possible[10]. Epilepsy can be considered resolved, however, for two types of individuals: those whose epilepsy syndrome was age-dependent and who have developed past such age, and for those who have not had any seizure events in the last 10 years and have been off medication for the last 5 years[10][11].

According to the National Population Health Survey (NHPS), the prevalence of epilepsy in Canada is 5.2 per 1000 and similarly 5.6 per 1000 based on the estimates from the Canadian Community Health Survey (CCHS)[12]. Most provinces in Canada have similar prevalence of epilepsy, with the exception of British Columbia where prevalence is 30% lower than in the rest of Canada[12]. There is no evidence of differences in the prevalence of epilepsy by gender in the Canadian population[12][13]. The prevalence of childhood epilepsy in Canada is reported at 5.2 per 1000 for children ages 0-15, which is markedly similar to the adult population; however, there is a gender difference among children, with prevalence of epilepsy being slightly higher in males than females (M:F 6.5:4.0 per 1000 children)[14][2]. Approximately 50% of people with epilepsy are diagnosed before the age of 5, and approximately 75% are diagnosed before the age of 20, which may be a reflection of the brain's susceptibility to seizures in the course of development[1][15].

The desired outcome in epilepsy treatment is the complete cessation of seizures without further treatment (i.e., anti-seizure medication which is known as remission)[16]. However, outcomes are usually complex and there may be instances of repeated remission and relapses over many years[16]. One study investigating seizure remission and relapse reported that out of 625 participants, 328 achieved remission. However, 23 participants relapsed after

remission with the highest rates of relapse occurring in the first 5 years following initial remission[16]. Most studies investigating seizure outcomes report that about 60% to 70% of individuals with childhood onset epilepsy report complete remission[17][18]. Seizure remission is usually associated with better outcomes overall for individuals who suffer from epilepsy. One study reported that remission was associated with significantly better odds of completing college, being either employed or pursuing a degree and driving[19].

2.2 Anxiety in People with Epilepsy

The etiology of psychopathology in PWE is assumed to be neurological dysfunction. This assumption is confirmed by evidence that individuals with epilepsy, especially children, suffer from higher rates of psychopathology than those with chronic non-neurological disease[20]. Psychopathology may present as both internalizing and externalizing behaviours. Internalizing behaviours highlight the emotional and psychological state of the child[21] and they include anxiety, depression, suicidal ideation and somatic complaints[21]. Externalizing behaviours emphasize a child's outward behaviour and negative reaction with external environment[22]. Externalizing behaviours include aggressive, disruptive and hyperactive behaviours[22].

The Diagnostic Statistical Manual of Mental Disorders, 5^{TH} Edition, Text Revision(DSM-5) categorizes anxiety disorders into several groups, the most common being generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder(PD), social phobia disorder and a subgroup of childhood psychiatric disorders known as separation anxiety disorder(SAD)[6][5]. Symptoms of GAD include persistent, uncontrolled thoughts with various themes for a period of 6 months or more[6]. PD is defined by periods of intense fear that occur suddenly and last minutes or longer, accompanied by physiological responses such as sweating,

breathing difficulty and a prominent fear of imminent and grave danger, such as loss of control and death[6][23]. In some cases, there might be difficulty differentiating between Panic attacks and epileptic seizures, especially focal epilepsy, due to overlap in symptoms[23]. Panic attacks usually lasts between a few minutes to a few hours, characterised by preserved consciousness with no confusion after the episode and no secondary spread or generalization to other brain regions, whereas focal epileptic seizures last seconds to a few minutes, and are typically characterized by loss of consciousness and post-episode confusion[23]. The symptoms of OCD include recurrent intrusive thoughts and impulses that are often unpleasant and characterized by behavioural or mental compulsions impulses[6][23]. These disorders are identified in both child and adolescent populations with slight variation in diagnostic criteria[6].

Most studies investigating anxiety in PWE do not specify the type of anxiety disorder under investigation. This is most likely due to the complexity of epilepsy and the nature of anxiety disorders which can make it particularly difficult to determine whether certain clusters of symptoms meet the criteria for a single group of anxiety disorder based on the DSM-5 classification[6][24]. For instance, in paediatric populations, fear of seizures or accidents related to seizures may be a symptom of agoraphobia and/or separation anxiety associated with having seizures outside of the home, or social phobia associated with fear of embarrassment if seizures occur in public places[6].

2.2.1 Differentiating between Anxiety and Anxiety Symptoms

It is important to note the distinction between anxiety disorders and anxiety symptoms. Anxiety disorders are formal clinical diagnoses made by psychiatrists or other licensed mental health professionals based on the DSM-5 criteria[25]. Anxiety symptoms, on the other hand,

encompass subclinical levels of anxiety that may not meet criteria for a formal diagnosis of a "disorder", but may nonetheless cause substantial impairment to the lives of individuals who experience these symptoms[26]. Assessment of anxiety symptoms is important, as subclinical levels of anxiety cause significant distress that may require clinical attention, and these anxiety symptoms are often a precursor to the diagnosis of anxiety disorder[26][27].

Anxiety symptoms can be assessed for research purposes in epidemiological studies using symptom checklists, as they can be easily administered on a larger scale to determine the prevalence and nature of clinical and subclinical levels of anxiety within different demographic groups[26][28]. However, in the published literature the distinction between anxiety disorder and anxiety symptoms may be blurred at times. Often, researchers will incorrectly refer to the assessment of anxiety symptoms using symptom checklists as if anxiety disorder was the outcome measured. This leads to inconsistencies in the literature and a lack of consensus on the prevalence and nature of anxiety symptoms in various populations[25]. Although most symptom checklists are created based on the DSM criteria for diagnosing anxiety disorders, and some have a cut-off point or threshold score that may be indicative of an anxiety disorder, they do not provide official diagnosis of a "disorder"[26]. The outcome being assessed in this thesis is anxiety symptoms, rather than anxiety disorder. There are references made to studies on anxiety disorder, however, given the similarity to anxiety symptoms and relevance.

2.2.2 Prevalence of Anxiety Symptoms in Adolescents and Young Adults with Epilepsy

Several psychiatric and neuropsychiatric symptoms have been found to occur at a higher frequency in youth with epilepsy, relative to the general population[15][24]. The Isle of Wight

study investigated a wide range of psychiatric factors in relation to behavioural outcomes and reported that 28.6% of children with the diagnosis of uncomplicated epilepsy experienced psychiatric disturbances, including anxiety symptoms compared to only 6.6% of the general population[29]. Anxiety symptoms are among the more common psychiatric symptoms experienced by AYA with epilepsy and often cause impediments in their daily lives[30]. One study found state and trait anxiety symptoms to be more common in young adults with epilepsy compared to a control group of healthy individuals of the same age group[31]. Another study reported that 28.6% of young male adults and 43.8% young female adults with epilepsy had developed anxiety symptoms, compared to 10.0% and 12.5% respectively in the hospital based control group[32].

Although most studies have reported a higher prevalence of anxiety symptoms in AYA with epilepsy than in the general population, a few studies have reported no difference in prevalence in anxiety symptoms between AYA with epilepsy and general population. A Turkish study reported no statistically significant difference in anxiety symptom scores between children with epilepsy and their mothers and a control group of children without epilepsy and their mothers[33]. Differences in the prevalence of anxiety symptoms across published studies may be due to the use of different anxiety symptoms checklists, the characteristics of the study participants based on inclusion and exclusion criteria used, as well as the cultural contexts of the studies.

Although depression has been the most common focus of studies investigating psychopathology in AYA with epilepsy, recent studies investigating both depression and anxiety have reported that anxiety symptoms are more common in this population[23]. A population-

based study from the US found that 17% of children and adolescents with active epilepsy experienced anxiety symptoms, whereas 8% experienced depression[34]. A Jordanian study carried out using an interviewer-administered questionnaire also reported that anxiety symptoms were more prevalent in AYA 14 to 24 years of age with epilepsy (48.5%) compared to depressive symptoms (22.8%)[27].

2.2.3 Bidirectional Relationship Between Anxiety and Epilepsy

Evidence from the literature suggests the potential of a bidirectional relationship between the initial diagnosis of epilepsy and anxiety whereby elevated anxiety symptoms or anxiety disorders may contribute to seizures, and conversely epilepsy may lead to elevated anxiety symptoms[35].

Some studies show evidence that anxiety symptoms or anxiety disorders may cause or at least contribute to epilepsy. One of such study, a Swedish population-based case control study investigated hospitalization for anxiety disorders before and after the onset of epilepsy, and reported that individuals diagnosed with epilepsy had almost three times higher odds of prior hospitalization for an anxiety disorder compared with a control group without epilepsy (CI:1.6-4.8)[36]. One study examining children right after the diagnosis of epilepsy to assess timing and development of psychopathology found that children with new onset epilepsy had higher rates of anxiety, depression, and hyperactivity before diagnosis than a control group of their first cousins[37][38]. A greater number of studies show evidence of epilepsy causing elevated anxiety symptoms. One such study reported that individuals with epilepsy had

significantly higher incidence of elevated anxiety symptoms following epilepsy diagnosis compared to a control group without epilepsy[31].

A few studies show evidence of a bidirectional relationship. A cohort study that investigated the incidence of anxiety symptoms three years prior to and after the onset of epilepsy found that the incidence rate for elevated anxiety symptoms was significantly higher in each of the three years prior to the diagnosis of epilepsy, compared to a matched control group without epilepsy (IRR: 1.5-15.7)[39]. In this same study, incidence rates for anxiety symptoms were also significantly higher after the onset of epilepsy, compared to the control group (IRR: 2.2-10.9).

Other studies have suggested the possibility that a single region of the brain may be implicated in both epilepsy and anxiety symptomology[23]. One study reported that compared with the normative data for the Revised Children's Manifest Anxiety Scale, children presenting with first seizures (i.e., at diagnosis of epilepsy) reported "significantly greater" total anxiety symptoms (RCMAS)[40]. It appears that some PWE develop anxiety prior to the onset of epilepsy whereas others develop anxiety after the onset of epilepsy. One factor that contributes to the challenge of determining the temporal relationship between seizures and anxiety is knowing whether seizures occur before they are first reported. Researchers have put forward a hypothesis that seizures may occur during sleep or even during waking hours without being noticed as seizures initially[24][23]. More research is needed to determine the temporal relationship between seizures and anxiety in PWE. It remains important, however, to continue investigating the possibility of a reciprocal relationship between epilepsy and anxiety whenever possible.

2.3 Impact of Family Environment and Parent Characteristics on Childhood Epilepsy

The family is widely considered central to epilepsy research particularly in reference to child psychopathology[41][15]. The diagnosis of epilepsy especially in children brings consequences not only for the person affected but also for their families[41]. Parents have reported feeling the loss of a perfect child and having to come to terms with the realization of their child's difference compared to other "healthy" children[41]. Parents have also reported feelings of vulnerability, anger, sadness, guilt and to be searching for the cause of epilepsy[41]. In many cases, feelings of stigma may be felt in the family as parents often fear other people's reactions and feelings about their child's epilepsy, which can extend beyond the child to other family members including siblings[41].

In dealing with the unpredictable nature of seizures, families often have to make adjustments and reorganize the existing family structure and routines to adapt to the demands of the illness[15], [42]. Current research shows that families of children with epilepsy differ from families with children without epilepsy on distinct family factors such as family functioning, family resources and family demands[15][8]. These family factors underscore important aspects of the family such as satisfaction with family relationships, family stressors, and resources available to families for coping with the demands and stressors of life events[8].

Studies have examined one or more of these family factors and their association with psychopathology in children and adolescents with epilepsy. One study reported family stress, family mastery and social support were strongly associated with total behaviour problems[43]. Another study found that poorer family functioning was significantly associated with poorer psychosocial functioning in children and adolescents with epilepsy[44]. In this study, the

authors reported that family functioning mediated the effect of other chronic illnesses on anxiety symptoms among CWE. One other study also found family functioning to be strongly predictive of child depressive symptoms which often overlaps with anxiety symptom[45]. Another study exploring predictors of behaviour problems in CWE found that family stress was a significant contributor [46].

Other than the family factors highlighted above, there are certain parent characteristics such as parental depression, family structure and family income that also impact development and mental health outcome in CWE[47]. Parental depression, specifically maternal depression, has been shown to impact psychopathology and mental health outcomes in children and adolescents with epilepsy[42], [48]. Studies have reported that CWE are at increased risk of internalizing as well as externalizing behavioural problems when their mothers suffer from depression compared to CWE whose mothers do not suffer from depression or psychiatric morbidity[47]. One study found that maternal depression was strongly correlated with internalizing child behaviours[49]. This study also found mothers' worries about epilepsy and mothers' perceived stigma correlated with total child behaviour problems. Parental depression was also found to be the strongest predictor of children's internalizing and externalizing behaviours[50]. Another study found that caregiver psychopathology was a significant independent predictor of anxiety symptoms experienced by CWE[51]. Yet another study exploring effects of parent characteristics on anxiety symptoms in paediatric epilepsy reported a statistically significant effect of parent history on anxiety symptoms experienced by CWE with controlled seizures and uncontrolled seizures[52]. The results of this study showed a three-fold increase in anxiety symptoms experienced by CWE in the presence of parental psychiatric

history regardless of whether seizures were controlled or not. There are, however, a few studies that report no association between parental depression or psychiatric disturbances and psychopathology in CWE. A study examining symptoms of anxiety and depression in adolescents with epilepsy showed no significant association with maternal depression and child psychopathology[53]. Another study investigating anxiety and depression in CWE and their mothers found no correlation between maternal psychopathology (anxiety and depression) and anxiety and depression in CWE[33].

Family structure (i.e., single parent families or two-parent families), and family socioeconomic status[8] also play a role in explaining mental health outcomes in CWE. Living with a chronic disease such as epilepsy requires a considerable amount of support from the family[8]. Research has shown that there is usually more support in two-parent households than single-parent households as the burden of the disease on a child may be shared and more easily managed by two parents[42]. There is also evidence that two-parent households are better off socioeconomically than single-parent household[49]. Families that are better off socioeconomically are at an advantage to provide better support for a child with a chronic disease like epilepsy[8]. Families and households with lower income struggle more with the burden of dealing with an illness like epilepsy and this may adversely impact parental well-being[49]. Few studies have explored such parent characteristics (i.e., family structure and family income) and how they contribute to mental health outcomes in people with epilepsy. It is common in these studies for marital status of parents and caregivers to be used as a general indicator of family structure i.e., single parent households (separated, divorced, widowed and never married) or two-parent household(married)[8]. One study reported that disrupted

parental marital relationship was significantly associated with internalizing behaviour problems in adolescents with epilepsy[54].

In summary, most studies examining family environment and psychopathology in children and adolescents with epilepsy indicate that the family factors and parent characteristics play vital roles in the development of psychopathology in CWE[41] and for this reason, it is important to investigate the association between family environment and the experience of anxiety symptoms in this population.

2.4 Association Between Child Clinical and Demographic Characteristics and Anxiety Symptoms among Adolescents and Young Adults with Epilepsy

This section consists of an overview of studies that explored the association of key child clinical and demographic characteristics in epilepsy with anxiety symptoms. These characteristics are: severity of seizures and control seizures, seizure frequency and freedom, anti-seizure medication, type of seizure, child's sex and child's age

2.4.1 Severity of Seizures and Control of Seizures

Seizure severity is determined by a combination of seizure components across studies. Most common components that determine seizure severity include pre and post seizure events, length of time a seizure event lasts, automatisms, incontinence, functional impairments, degree of altered consciousness and severity of injuries if any that occur during a seizure event[55]. There are scales that take some or all of these components into account to determine seizure severity[55]. Seizures that are uncontrolled are more severe than seizures that are controlled.

Prior evidence suggests that the severity of seizures is a significant predictor of anxiety experienced by PWE[23]. A study that investigated anxiety symptoms among adolescents with controlled and uncontrolled seizures found that a higher proportion of adolescents with uncontrolled seizures experienced anxiety symptoms compared to adolescents with controlled seizures[27]. A Korean study reported significantly higher rates of anxiety symptoms in AYA with uncontrolled seizures than those with well controlled seizures and in healthy controls[56]. Even the perception of seizure control, regardless of whether the seizures are clinically controlled or not, appears to have a significant impact on the risk of experiencing anxiety symptoms for PWE. One study investigating the psychosocial aspects of anxiety in epilepsy reported that perception of seizure control was significantly associated with the experience of anxiety symptoms in PWE such that participants who perceived that their seizures were controlled, even if they were not, had lower risk of experiencing anxiety symptoms than those who had no perception of seizure control[32].

2.4.2 Seizure Frequency and Freedom

Studies discuss the occurrence of seizures in two ways. Some studies categorize participants based on the frequency of their seizures (i.e., daily, weekly, monthly, and even yearly). Other studies categorize participants based on the period of time participants have been seizure free (i.e., one-year seizure free, two-year seizure and five-year seizure free). Regarding frequency of seizures, the literature on the association of seizure frequency with anxiety symptoms presents mixed results. Most studies are cross-sectional in nature; hence, it is difficult to ascertain whether frequency of seizures is associated with anxiety symptoms in AYA with epilepsy. Several studies have found a significant association. One study investigating

the prevalence and factors associated with the experience of anxiety and depression in a group of Nigerian youth found that a higher frequency of seizures in the month before the study began was strongly associated with youth anxiety disorders[57]. A similar study of Turkish adolescents found that higher frequency of seizures in adolescents was significantly associated with higher mean scores on the State-Trait Anxiety Inventory(STAI*)* indicating higher levels of anxiety symptoms[58].

Other studies have examined the association of seizure freedom (i.e., period without seizures rather than seizure frequency) with anxiety symptoms[30]. Few studies have examined the association of seizure freedom and remission with anxiety symptoms in AYA, finding mixed results[30][59]. One study found that 73.5% of study participants with active seizures had anxiety symptoms whereas only 26.5% of participants without seizures had anxiety symptoms when assessed using the Hospital Anxiety Depression Scale (HADS) measure[30]. Another study found no significant relationship between seizure freedom or any other epilepsy-related factors and psychiatric symptoms in adolescents with epilepsy[59]. As with frequency of seizures, the inconsistency in findings across studies might be partly explained by the varying criteria for the period of seizure-control which makes comparison among studies difficult.

2.4.3 Anti-seizure Medications

Anti-seizure medications (ASM) are important and effective psychotropic drugs used for seizure control by PWE[60]. A few studies have reported evidence that polytherapy with ASM, compared to monotherapy, increases the risk of anxiety disorders in PWE[6]. This increased risk could be attributed to direct adverse effects from specific medications including behavioural and cognitive toxicity and/or complications from withdrawal[60][5]. ASM can have either

positive or negative psychotropic effects[60][61]. Behavioural responses to specific ASM are dependent on the neurological disease, drug interaction, environmental and also genetic factors[60]. A Nigerian study designed to determine factors associated with clinically significant anxiety and depression in AYA with epilepsy using the HADS-A found polytherapy was the only factor significantly associated with anxiety[62]. Another study found the amount of ASM contributed "robustly" to the risk of elevated anxiety symptoms experienced by AYA with epilepsy[57]. A study of children and adolescents ages 6-16 years investigating anxiety symptoms and factors associated with its occurrence using the Revised Children's Manifest Scale (RCMAS) found amount of ASM to be significantly associated with anxiety symptoms in children and adolescents[63]. A study designed to investigate the magnitude of depression and anxiety symptoms among people living with epilepsy in Ethiopia using the HADS found side effects of ASM to be one of three factors significantly associated with the experience of elevated anxiety symptoms.

It is important to note that whether the relationship between polytherapy and anxiety symptoms in PWE may be causal is still unclear[24]. PWE are more likely to be on polytherapy if they suffer from uncontrolled or poorly controlled seizures; hence, it is possible that the higher risk of anxiety symptoms reported by PWE on polytherapy versus those on monotherapy might be due to an indirect effect of poor seizure control rather than a direct effect of polytherapy[6].

2.4.4 Type of Seizure

Most studies examining psychopathology and epilepsy in youth also investigated an independent effect of type of seizure. Several studies have reported a significant association between type of seizure and anxiety symptoms, particularly focal onset seizures[5]. In a study

investigating the independent association of clinical features of epilepsy with anxiety symptoms using the Symptom Checklist-90R (SCL-90R), participants with focal seizures had nearly triple the odds of experiencing a high level of anxiety symptoms, compared to participants with generalized seizures[64]. Other studies have reported contrasting results such as a population-based study examining symptoms of anxiety and depression in school-aged children using the Spence Anxiety Scale for Children (SASC), which found that participants (child-report only) with generalized seizures reported elevated levels of anxiety symptoms compared to those with focal seizures[65]. Another study reported higher rates of anxiety symptoms in participants with childhood absence epilepsy (generalized seizures) compared to participants with complex partial seizures (focal seizures)[66].

2.4.5 Child's Sex

It is well established in the literature that women are more likely than men to suffer from an anxiety disorder in the general population[67]. However, for PWE, the findings are mixed and inconclusive. Some studies investigating the association between sex and anxiety symptoms among PWE found no relationship[37][57][33][68]. There are a few studies that found an association, and the results of these studies are usually consistent with the gender differences observed in the general population. A Brazilian study investigating the frequency of psychiatric symptoms in AYA with epilepsy using the HADS found that being female was significantly associated with the elevated anxiety symptoms (95% CI:1.2-5.2)[69]. Another study suggests that females have elevated anxiety symptoms in AYA with epilepsy (95% CI:0.30–5.21][51]. One study investigating gender differences in psychopathology in PWE reported no differences in risk of anxiety symptoms between men and women[70]. However, men in this

study were significantly older, had later age of onset, were more likely to have focal epilepsy and were treated more frequently with ASM compared to women[70]. These differences in clinical characteristics, with men suffering from more severe epilepsy, may have resulted in anxiety levels among men being elevated to match that of women in the study, which may explain why no significant difference between the sexes was found in this study[70].

2.4.6 Child's Age

Most studies have found that anxiety symptoms in PWE do not appear to vary by age [71][33][59][28][69], although there have been few studies reporting a significant association. One study found that older children (ages 8 to 15 years) with epilepsy reported more symptoms of anxiety on the Spence Children's Anxiety Scale (SCAS) compared to younger children (<7yrs) at the time of the study[65]. In contrast, another study reported that participants with anxiety symptoms tended to be younger children[66]. A few other studies that have investigated association between anxiety symptoms and duration of epilepsy have reported that age may be an effect modifier in the relationship. One study reported that symptoms of anxiety differed by length of time since diagnosis, but only for older participants[58]. This study found that anxiety scores on the STAI were significantly higher in participants ages 12 to 18 years with epilepsy duration of 3 years or more, compared to those with epilepsy duration under 3 years[58]. In this study however, there was no significant difference in anxiety scores based on epilepsy duration for participants ages 9-11 years[58].

For studies that have found an association between age and anxiety symptoms, the differences between adolescents and younger children may be indicative of older children's more advanced cognition that allows an understanding of the disease and increases awareness

of the unpredictability of seizures. This awareness may in turn increase the likelihood of anxiety in older children[6]. Another explanation for these discrepancies in age groups might be that anxiety exhibits differently in different age groups. Some aspects, such as autonomic and agitation syndrome which involves pronounced physical symptoms like palpitations, increased blood pressure and reports of “feeling sick” [72]are typically exhibited by younger children whereas older children exhibit cognitive and avoidant syndrome which involves feelings of apprehension, inadequacy and deficiency compared to others [6][73] . More research is still needed in this area.

2.5 Limitations of Previous Studies

Previous studies have several limitations. First, there are inconsistencies in how anxiety is evaluated, with some studies focused on anxiety disorders (ascertained through clinical interventions and meeting diagnostic criteria) and anxiety symptoms (ascertained through questionnaires). Second, most studies, especially studies examining the impact of the family environment on childhood epilepsy, have not investigated anxiety symptoms independently. These studies usually investigate anxiety symptoms as part of investigating the broader set psychopathology which includes psychiatric comorbidities other than anxiety symptoms. This causes difficulty when attempting to draw conclusions from the literature about the impact of the family environment on anxiety symptoms. This thesis addresses this limitation by focusing on anxiety symptoms independent from other psychiatric symptoms. Third, previous studies have often focused on cross-sectional data assessing the relationship between family characteristics and psychopathology including anxiety symptoms in AYA with epilepsy. It is unknown whether the association between family and parent characteristics and anxiety

symptoms hold over the longer term. This thesis addresses this limitation by examining the relationship between early family, parent and clinical characteristics and long-term anxiety symptoms.

Chapter 3

Methods

This chapter describes the methodology employed in this thesis. Section 3.1 presents details on the source of the data, followed by descriptions of measures used in this thesis in sections 3.2, 3.3, and 3.4. This chapter closes with a description of the statistical methods in section 3.5.

3.1 Data Source and Sample

Data for this thesis come from the Health-Related Quality of Life in children with Epilepsy Study (HERQULES,). HERQULES was a Canada-wide prospective cohort study that followed families i.e. parents and their children newly diagnosed with epilepsy over a 10-year period with follow-up at 6 months, 1 year, 2 years, 8 years and 10 years. A two stage-clustered sampling strategy was used to recruit parents of children with epilepsy. The first sampling stage began in 2004 and involved inviting all neurologists who were members of the Canadian Association of Child Neurology (*n = 72*). Of the practicing neurologists invited, 74% agreed to participate in the study (*n = 53*). In the second stage of the sampling, the participating neurologists were asked to approach parents of all their respective patients who met the inclusion criteria and inform them about the study. The neurologists received consent from parents of eligible patients to provide their contact information to the study team for the purposes of sending a letter of information about the study.

Patients were included in the study if they met the following eligibility criteria:

1) Patients were seen for the first time by a paediatric neurologist participating in the study;

2) Diagnosis of epilepsy occurred between the ages of 4 and 12 years;
3) Parent participating in the study had been the child's caregiver for at least 6 months and expected to continue to be their caregiver for the duration of the study.

Ineligibility for participating in the study was based on the following exclusion criteria:

1) Previous diagnosis of epilepsy by another physician;
2) Diagnosis of progressive and degenerative neurological disorder;
3) Diagnosis of any other major non-neurological disorder that may impact quality of life;
4) Parents had insufficient English language skills to complete questionnaires.

Data collection occurred in two phases. The first phase consisted of following patients and their families for two years and collecting data at baseline, 6 months, 1 year and 2 years. Families were mailed questionnaires to complete and return at these four time points. The parent questionnaires took approximately 45 to 60 minutes to complete and asked about their child's HRQoL and the family environment. Parents were asked to give their consent for their child's neurologist to complete an assessment form providing clinical information, such as severity and type of epilepsy, medication, and side effects, as well as cognitive and behavioural problems. These assessment forms took about 7 minutes to complete and were faxed to the HERQULES office. A total of 373 parents of the 455 eligible children were successfully recruited into the study. Of those, 283 parents were retained at 2-year follow-up.

The second phase of the study consisted of re-inviting patients and their families for an 8-year and a 10-year follow up. A letter of information was sent to parents as well as to youth 11 years and older explaining that two self-administered questionnaires would be sent two years apart. These questionnaires could be completed and submitted online or on paper to mail back. For patients still receiving epilepsy care, informed consent was obtained from parents and

patients who were now adults (>18years) to contact their current health care provider to obtain updated clinical information. A total of 220 families were eligible to fill out the self-reported questionnaire at the start of the second phase. The Tailored Designed Method was employed to increase participation at each follow-up point. This technique has been shown to be effective in increasing response rate in survey research[74][75]. Research ethics approval was obtained for both phases of the study (see Appendix D, page 73). Approval for the first phase of the study was obtained from the each of the research ethics boards of the 17 paediatric neurology centers across Canada. Approval for the second phase of the study was obtained from the Western University Health Sciences Research Ethics Board only, given the established relationship with participating families. Funding for HERQULES was provided by two operating grants from the Canadian Institutes of Health Research.

3.2 Measures

The variables used in this thesis were selected based on availability in the HERQULES dataset and informed by existing literature showing associations between these measures and anxiety symptoms in AYA with epilepsy.

3.2.1 Outcome: Anxiety Symptoms

The State-Trait Anxiety Inventory Form Y-6 (STAI-Y6) was used to assess anxiety symptoms in AYA with epilepsy at the 10-year follow-up. The STAI-Y6 developed by Matteau and Bekker is a shortened version of the 20-item State Anxiety subscale of the State-Trait Anxiety Inventory Form Y(STAI-S) developed by Spielberg in 1983[76][77][78]. The STAI-S was developed to assess the transient state of arousal often subjectively experienced as

anxiety[78][79]. Respondents are asked to rate the frequency with which each item occurs on a 4-point Likert scale ranging from 1 (almost never) to 4 (almost always)[78]. The STAI-Y6 consists of a total of 6 items. Some items on the STAI-Y6 include: “I feel calm”, “I feel tense” (see Appendix B, page 68 for complete checklist). The total score is multiplied by 20 and divided by 6 to yield scores that range from 20-80 and are comparable to the full form STAI-S[76]. Scores greater than 40 are considered to be indicative of clinically significant anxiety symptoms[80][81]. The STAI-Y6 has demonstrated acceptable reliability and validity [76][79]. The STAI-Y6 is sensitive to cognitive, future oriented and global dimensions of anxiety[79]. The STAI-S measures more transient anxious state as opposed to the STAI-T that measures more enduring anxiety.

3.2.2 Exposure: Family Characteristics

Family Functioning.

Family Functioning is important to consider as it represents a major aspect of the family environment and family members’ satisfaction with family functioning gives an indication of how cohesive the family is[82]. The level of family functioning plays a major role in child development and overall wellbeing. Family functioning was measured using the Family Adaptability, Partnership, Growth, Affection, and Resolve (APGAR)[83]. The APGAR consists of five items scored on a five-point Likert-type scale with total score ranging from 0 to 20[82][83][84]. Parents were asked to rate the frequency of satisfaction with family functioning on the scale from 0 (hardly ever) to 2 (almost always) for each dimension on the instrument. Higher scores on the APGAR indicate higher satisfaction with family functioning[83]. The validity and reliability of the APGAR has been demonstrated in clinical and research settings[83]. Family

functioning was measured at baseline, 6-month, 1-year, 2-year, 8-year, and 10-year follow-up. In the current study, measures at baseline and 10-year-follow-up were used.

Family Resources

Family resources are an important part of the family environment because they give a snapshot of the extended family support a family has access to and the overall state of the family's well being. The construct family resources was measured using the Family Inventory for Resources and Management (FIRM)[43] which is a self-report instrument that asked parents to assess the degree to which resources are available to families to cope with stressful life events[85]. The FIRM consists of four subscales, two of which, , were used in HERQULES as there is evidence to support that these subscales are associated with familial adaptation to childhood epilepsy[43](i.e., Family Strength: Mastery and Health [20 items] and Extended Family Social Support [4 items]). The FIRM is scored on a 4-point Likert-type scale with scores ranging from 0 to 72[85]. Parents were asked to rate how well each item on the instrument describes their family situation from 0 (not at all) to 3 (very well). Higher scores indicate a family has a higher level of resources in terms of family strength and social support[85]. Adequate reliability and validity of the FIRM has been demonstrated[85]. The FIRM was used to access family resources at baseline, 6-month,1-year, 2-year, 8-year and 10-year follow-up. In the current study, measures at baseline and 10-year-follow-up were used.

Family Demands

Family demands were assessed by parent-report using the Family Inventory of Life Events and Changes (FILE) [85]. The FILE is a 71-item instrument that assesses family stress in the previous year across 9 domains[85]. The FILE considers normative and non-normative life events that families may experience. Scores on the FILE range from 0 to 71 with higher scores

indicating higher levels of family stress in the previous year[85]. The FILE has demonstrated adequate discriminant validity, test-retest validity and internal consistency[85]. The FILE was used to access family resources at baseline, 6-month,1-year, 2-year, 8-year and 10-year follow-up. In the current study, measures at baseline and 10-year follow-up were used

3.2.3 Covariates: Parent Characteristics

Parental Depression

Depressive symptoms in parents was assessed using the Center for Epidemiological Studies Depression Scale (CES-D)[86]. The CES-D is a 20-item scale developed to assess depressive symptoms in the past week in the general adult population[86]. It is a 4-point Likert scale in which respondents rate the number of days they felt a certain way from 0 (rarely or less than one day) to 3 (most or all the time/5-7). Scores on CES-D can range from 0 to 60[86]. Scores equal to or greater than 16 are indicative of being at risk for major depressive disorder. Parental depressive symptoms were measured at baseline, 6-month,1-year, 2-year, 8-year and 10-year follow-up. In the current study, measures at baseline and 10-year-follow-up were used.

Parental Marital Status

Parental marital status is included as an indication of family structure (single or two parent household). Data on marital status were recorded as: married, divorced, separated, remarried, never married. For these analyses marital status was dichotomized as: married (married and remarried) and not married (separated, divorced, never married). In the current study, measures at baseline and 10-year-follow-up were used.

Family Income

Primary caregivers reported their gross annual household income (income before taxes). Income options ranged from less than $20,000 to greater than $150,000. In the current study,

family income was treated as a continuous variable to obtain a more parsimonious model (results were similar when treated as a categorical variable). In the current study, family income was measured at the 6-month,1-year, 2-year, 8-year and 10-year follow-up. For this thesis, measures at baseline and 10-year-follow-up were used.

3.2.4: Covariates: Child Clinical and Demographic Characteristics

Key clinical characteristics of epilepsy and demographic characteristics were provided by neurologist and parents respectively. The clinical characteristics included in this thesis were: severity of epilepsy, type of seizure, five-year seizure freedom, anti-seizure medication (ASM) use and cognitive and behavioural problems. The demographic characteristics were children's age and sex.

Severity of Epilepsy

Severity of epilepsy is often used interchangeably with severity of seizures but severity of epilepsy is more encompassing than severity of seizures[87]. Clinical features such as frequency and intensity of seizures, anti-seizure medications, falls and injuries during seizures and level of daily disruption to patient's lives are all considered when determining the severity of the disease[88][87].

The Global Assessment of Severity of Epilepsy (GASE) was used to measure the overall severity of the child's epilepsy considering all aspects of how the disease affects patients[88]. The GASE is a single-item measure that was developed for use in HERQULES with severity of epilepsy assessed by participating neurologists[87] at baseline, 6-month,1-year, 2-year, 8-year and 10-year follow-up. Neurologists were asked to rate the severity of patients' overall epilepsy on a 7-point Likert-type scale ranging from extremely severe (1) to not severe at all (7). In this

study, severity of epilepsy was treated as continuous variables to obtain a more parsimonious model (results were similar when treated as a categorical variable).

Type of Seizure

Paediatric neurologists reported on the type of epilepsy syndromes and seizures based on the 1989 International League Against Epilepsy (ILAE) classification (the version that was current at the onset of HERQULES): primary generalized, absence, simple/complex partial(focal seizures), benign epilepsy of childhood with Rolandic spikes (BECRS), secondarily generalized, BECRS + secondarily generalized, or undetermined[89]. Type of seizures variable was collapsed into two categories: generalized and focal, in line with the conventional broader categorization of seizures.

Five-year Seizure Freedom

Five-year seizure freedom has clinical significance in that it is usually used as the length of time required to define remission. AYA were asked "When was your last seizure? (It is OKAY to provide your best guess)". The options were: less than 6 months ago, 6 months ago to less than 1 year ago, 1 year ago to less than 2 years ago, 2 years ago to less than 5 years ago, 5 years to less than 10 years ago, 10 years ago or more, I don't remember. This variable was collapsed into two categories based on whether 5-year seizure freedom had been attained. It was assessed at the 10-year follow-up to determine which individuals had achieved 5-year seizure freedom.

ASM Use

Use of ASM and variations in the numbers used is one of the clinical indicators of epilepsy severity. AYA reported on their current use of anti-epileptic drugs. They were asked,

"Are you currently taking any medication to treat epilepsy or seizures?". Two response options: were available to this question "yes" or "no".

Cognitive and Behavioural Problems

Cognitive and behavioural problems are important clinical considerations in epilepsy management. The presence of cognitive and behavioural problems is considered when making decisions on the clinical management of the disease. Paediatric neurologists were asked "Does the patient have cognitive problems?" and "Does the patient have behavioural problems?" with response options "no (normal)" and "yes". If the response was "yes", neurologists were asked to rate the severity of the cognitive or behavioural problems as borderline, mild, moderate or severe.

At the 10-year follow up, parents were asked to indicate "yes" or "no" if their child had ever been diagnosed with any of the following: developmental delay, learning disability, oppositional defiant disorder, attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD), conduct disorder, anxiety or depression. If "yes", parents were asked to indicate whether this diagnosis happened "before", "after" or "at the same time as" their child's diagnosis of epilepsy. In the current study, AYA were categorized as having cognitive problems if they were reported to have been diagnosed with developmental delay and or learning disability. AYA were categorized as having behavioural problems if parents reported they have been diagnosed with oppositional defiant disorder, attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD), or conduct disorder. AYA were categorized as having emotional problems if parents reported they have been diagnosed with anxiety or depression. Parents' report of emotional problems was not included in the multivariable

statistical analyses for this thesis given the likely overlap of this variable with the primary outcome of anxiety symptoms as self-reported by AYA.

Child's Age

Age at diagnosis was calculated using the date of birth of the patient and the date of the first visit with the participating paediatric neurologist during which the diagnosis of epilepsy was made**.**

Child's Sex

Child's sex was reported by parents at baseline and recorded as "Male" or "Female".

3.3 Statistical Analysis

All analyses were conducted using SAS software version 9.4[90]. Family, clinical, and demographic factors from the sample at the 10-year follow-up and the time of diagnosis (baseline) were described using frequencies and proportions for categorical variables and means and standard deviations for continuous variables.

3.3.1 Analyses to Address Objective 1

Objective #1: To describe of anxiety symptoms in adolescent and young adults with epilepsy 10 years after diagnosis.

Total scores on the STAI-Y6 range from 20 to 80, with scores greater than 40 indicative of clinically significant anxiety symptoms. The mean, standard deviation, and range of scores were reported, as well as the proportion of youth who had a score above 40. A standardized anxiety score (anxiety z-score) was calculated to compare AYA's scores with the age and sex appropriate US normative data[91]; this was calculated by subtracting AYA's scores from the mean of the normative data and dividing by the standard deviation of normative data. This

yielded a z-score, with scores of 0 indicative of anxiety symptoms that are the same as the population normative data, and a score of 1 indicative of scores that are 1 standard deviation above the population normative data. A one-sample t-test was used to evaluate whether the anxiety z-score was statistically different from 0.

3.3.2 Analyses to Address Objective 2

Objective #2: To assess the association between family characteristics and anxiety symptoms in adolescents and young adults 10 years after diagnosis, controlling for parent, child clinical and demographic characteristics. Specifically, focusing on characteristics from a) The 10-year follow-up and b) The time of diagnosis.

To assess the associations of anxiety symptoms with each family, parent, and child clinical and demographic variables at the 10-year follow-up (objective 2a), bivariate analyses were first conducted using simple linear regression, followed by a multivariable linear regression model. The primary 'exposure' variables of interest were family functioning, family resources, and family demands; these variables were forced into the multivariable model. Other family covariates (parental depression, family income, history of cognitive and behavioural problems (parent report)) and clinical and demographic covariates (seizure recency, ASM use, child age and child sex) were entered into the multivariable model if they attained a significance level of $p<0.20$[92] in the bivariable analyses. This level of significance was chosen since a lower significance level might result in excluding variables that may otherwise be important predictors[92]. The assumptions for linear regression (linearity, normality of residuals, lack of multicollinearity, autocorrelation, heteroscedasticity) were

checked. Assumptions of linearity, normality of residuals, lack of multicollinearity: variance inflation factor no greater than 10, autocorrelation and heteroscedasticity were met.

To address objective 2b, the analyses above were repeated and family, parent, clinical and child variables were assessed at the time of diagnosis. Specifically, the variables included in the model were: family functioning, family resources, family demands, parental depression, family income, severity of epilepsy, type of seizure, cognitive and behavioural problems, child age and child sex. As with analysis for objective 2a, the exposure variables (i.e., family functioning, family resources and family demand assessed at time of diagnosis) were entered into the model regardless of significance level. Other covariates assessed at time of diagnosis were entered into the model only if $p<0.2$ significance criteria was met in the bivariate models.

3.3.3 Attrition Analysis

An attrition analysis was conducted to determine whether the group of patients retained by the 10-year follow-up and those who did not participate in the 10-year follow-up differ in terms of any family, clinical and demographic factors at baseline. Specifically, the two groups patients were compared on family factors (family functioning, family resources, family demands, parental depression, family income, marital status,), demographic factors (child age at diagnosis and child sex), and clinical factors (severity of epilepsy, type of seizure, behaviour and cognitive problems, parent reported behavior, cognitive and emotional problems) using t-tests for continuous variables and chi-square tests and/or fisher's exact test for categorical variables.

3.3.4 Missing Data

Complete data were available for 74% of the sample of patients at the 10-year follow-up. Given the longitudinal nature of the data, single imputation was used when categorical data were missing. For example, if family income was reported as $50,000 to $99,999 / year at the 6-month follow-up, 1-year follow-up, and 12-month follow-up, but was missing from baseline, $50,000 to $99,999 was imputed as the family income at baseline. Values were not imputed where there was uncertainty about the value of the missing data. Of the variables that were included in the multivariable regression using variables from the 10-year follow-up and from baseline, a total of 98% and 82% of cases, respectively, had complete data after single imputation. Given the proportion of cases with complete data, listwise deletion was used to deal with missing data.

Chapter 4

Results

This chapter presents the findings of this thesis. The sample characteristics are first described in section 4.1, followed by results of the attrition analysis in section 4.2. The last section (sections 4.3) presents the results for each research objective.

4.1 Sample Characteristics

Tables 1 and 2 presents the demographic, clinical and family characteristics at baseline and the 10-year follow-up. At the 10-year follow-up, 176 AYA were sent questionnaires, and 131 returned them. The final size of the sample analyzed was 128; three participants were excluded as they did not provide data on the outcome of interest (anxiety symptoms). AYA (48% male) were on average 17.8 years of age (SD: 2.54) at 10-year follow-up. The majority of AYA (67%) had been seizure free for 5 or more years. Nearly three quarters of AYA were no longer on ASM. The majority (63%) of AYA reported that they were no longer receiving care for epilepsy or seizure management from any physician, whereas 25% reported receiving care for epilepsy from either an adult neurologist, pediatric care specialist or a family physician. In terms of parent-reported behavioural and cognitive problems, 20% had been diagnosed with behavioural problems, 34% had been diagnosed with cognitive problems, and 22% had been diagnosed with emotional problems at the 10-year follow-up.

Table 1: Family, Parent, and Child Clinical and Demographic Characteristics at 10-year Follow-up (n=128)

Variable	10-year-follow up Mean (SD) OR N (%)
Family functioning	14.6 (4.0)
Family resources	51.6 (11.8)
Family demands	8.5 (5.9)
Parental depression CES-D score ≥16, CES-D score < 16,	10.1 (8.9 26 (20%) 102 (80%)
Married	97 (82%)
Family income Less than $50,000 $50,000 - $99,999 $100,000 - $149,000 $150,000 or more Don't know	 19 (16%) 38 (32%) 28 (23%) 32 (27%) 2 (2%)
Child's age	17.8 (2.5) range 12-23 yrs
Male	61 (48%)
Parent reported diagnosis of cognitive problems Yes	 40 (34%)
Parent reported diagnosis of behavioural problems Yes	 23 (20%)
Parent reported diagnosis of emotional problems Yes	 26 (22%)
Current ASM use Yes	 34 (27%)
Had seizures in past 5 years Yes	 42 (33%)

Table 2: Family, Parent, and Child Clinical and Demographic Characteristics at Diagnosis (n=128)

Variable	At Diagnosis Mean (SD) OR N(%)
Family functioning	14.4 (3.9)
Family resources	52.8 (10.7)
Family demands	8.5 (5.6)
Parental depression CES-D score ≥ 16, CES-D score < 16,	12.5 (9.5) 91 (71.1%) 36 (28.1%)
Married	109 (85%)
Family income Less than $50,000 $50,000 - $99,999 $100,000 - $149,000 $150,000 or more Don't know	 18 (13%) 61 (50%) 7 (5%) 37 (31%) 0 (0%)
Child's age	8 (2.5) range 4-12 yrs
Male	61(48%)
Severity of epilepsy Extremely severe Very severe Quite Severe Moderately severe Somewhat severe A little severe Not at all severe	 0 (0%) 0 (0%) 4 (3%) 23 (19%) 23 (19%) 50 (40%) 24 (19%)
Type of seizure Generalized Focal	 52 (41%) 74 (59%)
Cognitive problems No	 119 (93%)
Behavioural problems No	 116 (91%)

At baseline, 41% of the sample were diagnosed with generalized seizures and 59% diagnosed with focal seizures. Only 7% of AYA were reported to have cognitive problems by a paediatric neurologist at baseline, similarly 9% of AYA were reported to have behavioural problems. Regarding epilepsy severity at baseline, only 3% of AYA epilepsy were classified as "quite severe", another 19% as "moderately severe", 19% as "somewhat severe", 40% as "little severe" and 19% as "not severe at all".

At the 10-year follow-up, 118 parents of the 128 AYA in our sample returned a completed questionnaire. These parents scored an average of 10.1 (SD=8.9) on the CES-D scale, with 20% scoring above the cut-off indicative of clinically significant depressive symptoms. Half (50%) of the families had an annual household income of $100,000 or greater. Regarding marital status, 83% of parents were married.

4.4 Results for Objective 1

Anxiety symptom scores ranged from 20 to 70 with a mean of 37.08 and standard deviation of 13.52. In our sample, 32.8% of AYA were above the cut-off indicative of clinically significant anxiety symptoms. As a group, AYA scored similarly to the US population norms of individuals of the same age and sex; the mean of anxiety z-score was -0.086 (SD: 1.3, 95% CI: -0.31, 0.14).

4.5 Results for Objective 2

For Objective 2a, the results of the bivariate analyses (Table 3) of family characteristics at the 10-year follow-up with anxiety symptoms suggest that higher family functioning

(β= -0.78, 95% CI: -1.37, -0.18) was associated with fewer anxiety symptoms. Bivariate analysis of other covariates at the 10-year follow-up suggest that parents report of cognitive problems (β=7.87, 95% CI: 3.18, 12.5), and parents report of behavioural problems (β=7.4, 95% CI: 2.03, 12.9) were both associated with anxiety symptoms in AYA with epilepsy. Regarding clinical characteristics at the 10-year follow-up, having seizures in the past 5 years (β=8.30, 95% CI: 3.32, 13.25) was associated with clinically significant anxiety symptoms. The results of the multivariable analysis of characteristics at 10-year follow-up (Table 3) indicate that only 5-year seizure freedom was a significant, independent factor associated with anxiety symptoms (β=8.97, 95% CI: 2.11, 15.8). AYA who had not achieved seizure freedom for at least 5 years were significantly more likely to experience elevated anxiety symptoms compared to AYA who had been seizure free for at least 5 years.

Table 3: Bivariate and Multivariable Analyses of Anxiety Symptoms with Family, Parent, Child Clinical and Demographic Characteristics at 10-year Follow-up (n=128)

	Bivariate Analysis		Multivariable Analysis	
Variable	Coefficient (SE)	95% CI	Coefficient (SE)	95% CI
Child's age	0.52(0.50)	-0.41, 1.45		
Male	1.53(2.40)	-6.27, 3.22		
Family functioning	-0.78(0.30)	-1.37, -0.18**	-0.64(0.40)	-1.40, 0.13
Family resources	1.67(0.10)	-0.37, 0.04*	0.04(0.17)	-0.30, 0.37
Family demands	0.01(0.21)	-0.40, 0.43	-0.08(0.29)	-0.65, 0.48
Not married	0.44(3.21)	-5.91, 6.80		
Family income	8.00(5.00)	-17.81, 1.85		
Parental Depression	1.17(3.00)	-4.73, 7.06		
Had seizures in past 5 years	8.30(2.50)	3.32, 13.25 ***	8.97(3.43)	2.11 15.8**
Taking ASM	3.67(2.74)	-1.75, 9.10*	-4.2(3.63)	-11.41, 3.02
Parent-reported cognitive problems	7.87(2.36)	3.18, 12.51 ***	4.2(2.80)	-1.30, 15.80
Parent-reported behaviour problems	7.40(2.90)	2.03, 12.90 ***	3.21(3.40)	-3.50, 9.91

*p<0.2 **p<0.05 ***p<0.01

For objective 2b, the results of bivariate analysis (Table 4) suggest that higher family functioning at time of diagnosis (β=-0.71, 95% CI: -1.31, -0.11) was significantly associated with fewer anxiety symptoms 10 years after the AYA epilepsy diagnosis. However, when controlling for other characteristics using multivariable regression, there were no significant, independent characteristics from baseline that were associated with anxiety symptoms at the 10-year follow-up (Table 4).

4.2 Attrition Analysis

Table 5 presents the demographic, clinical and family characteristics of patients who completed follow-up (n=130) and those lost to follow-up (n=243). There were no significant differences in terms of age, gender, type of seizure and severity of epilepsy at baseline. However, patients lost to follow up were more likely to have cognitive and or behavioural problems at baseline. Regarding family characteristics, families lost to follow up were not significantly different in terms of family functioning and marital status at baseline. Parents who completed follow-up were more likely to report having better family resources, fewer family demands, higher family income and fewer depressive symptoms at baseline.

Table 4: Bivariate and Multivariable Analyses of Anxiety Symptoms with Family, Parent, Child Clinical and Demographic Characteristics at Diagnosis (n=128)

	Bivariate Analysis		Multivariable Analysis	
Variable	Coefficient (SE)	95% CI	Coefficient (SE)	95% CI
Child's age at diagnosis	0.52(0.50)	-0.41, 1.45*	-0.65(0.5)	-0.35, 1.64
Male	-1.53(2.40)	-6.27, 3.22		
Family functioning	-0.71(0.30)	-1.31, -0.11**	-0.62(0.43)	-1.50, 0.22
Family resources	0.17(0.21)	-0.40, 0.05*	0.09(0.17)	-0.24, 0.43
Family demands	-0.3(0.21)	-0.14, 0.71*	0.15(0.24)	-0.34, 0.62
Not married	-6.5(3.32)	-13.1, 0.06*	5.4(3.43)	-1.42, 12.17
Family income	-0.43(1.11)	-2.63, 1.78		
Parental depression	0.16(0.13)	-0.10,0.40		
Severity of epilepsy	1.17(3.0)	-4.73, 7.06		
Focal seizures	-2.45(2.42)	-7.24, 2.33		
Cognitive problems	-0.86(4.70)	-10.13, 8.44		
Behavioural problems	4.47(4.18)	-3.80, 12.74		

*p<0.2 **p<0.05 ***p<0.01

Table 5: Attrition Analysis

Variable	Lost to follow-up (n=244) Mean (SD) OR N(%)	Completed follow-up (n=128) Mean (SD) OR N(%)	P-value
Child's age	7.9(3.4)	8(3.4)	0.63
Male	139(55%)	61(48%)	0.17
Family functioning	13.7 (3.7)	14.4(3.5)	0.11
Family resources	48.6(11.1)	52.8(10.7)	<0.001
Family demands	10(6.9)	8.5 (5.6)	0.04
Married	192(78%)	109(85%)	0.10
Family income Less than $50,000 $50,000 - $99,999 $100,000 - $149,000 $150,000 or more	 60(26%) 111(49%) 13(6%) 43(19%)	 18(15%) 61(49%) 7(6%) 34(30%)	0.025
Parental depression	15.2(10.6)	12.5(9.5)	0.015
Cognitive problems Yes	66 (93%)	9(7%)	<0.0001
Behaviour problems Yes	116(91%)	11(9%)	0.016
Severity of epilepsy	5.37(1.2)	5.54(1.1)	0.20
Seizure type Generalized Focal	 93(36%) 158(62%)	 52(41%) 74(52%)	0.70

Chapter 5

Discussion

This chapter discusses the findings of this thesis. Section 5.1 provides a summary and interpretation of the findings for each objective within the context of the previous literature. Sections 5.2 and 5.3 discuss the strengths and limitations of this thesis, respectively. Section 5.4 proposes recommendations for future research, and section 5.5 summarizes the main implications and conclusions of the study findings.

5.1 Summary of Findings

This thesis aimed to: 1) describe anxiety symptoms of AYA with epilepsy 10 years, after their diagnosis in terms of the proportion with clinically significant anxiety symptoms and relative to the US population norm for same age and sex, and 2) assess the association between family factors and anxiety symptoms, while controlling for child and parent factors. To the best of our knowledge, this study is the first to evaluate anxiety symptoms among AYA in the long-term and assess associations between long-term anxiety and a comprehensive set of factors (family, parent, clinical and child).

5.1.1 Objective#1

The first objective of this thesis was to describe anxiety symptoms in a sample of AYA with epilepsy 10 years after their diagnosis of epilepsy. We found that 33% of AYA scored above the STAI-Y6 cut-off indicative of clinically significant levels of anxiety symptoms. When anxiety scores were compared to STAI-Y6 normative data from the US population of the same sex and similar ages, the mean score on anxiety symptoms was not statistically different. This means

that, while our sample of AYA 10 years after the diagnosis of epilepsy is similar to their age and sex counterparts in the US population *on average*, about one third of AYA with epilepsy were experiencing clinically significant levels of anxiety symptoms. The similarity in the levels of anxiety symptoms between our sample and the US population norms may be attributed to the long-term follow up of participants in our study that allowed time for the clinical status of epilepsy to stabilize and for adaptation by the patients and their families. Our finding is consistent with previous studies in the literature that have found that in the long-term, AYA with epilepsy and healthy controls report similar HRQoL[93][94][95].

About one third of AYA with epilepsy in our study reported symptoms at a level considered to be clinically significant which is consistent with multiple previous studies of AYA with epilepsy. One cross-sectional study reported a prevalence of 33% among those 5-16-years old[66] as assessed by the Multidimensional Anxiety Scale for Children (MASC). Similarly, another study reported a prevalence of 33% in a sample of youth 10-18 years old[4] using the HADS-A.

Our results are not consistent with all previous studies, however. Some studies have reported lower prevalence of anxiety symptoms among AYA with epilepsy compared to our study. One was a cross sectional study that assessed anxiety symptoms using the Revised Children's Manifest Anxiety Scale (RCMAS) and reported a prevalence of 16% among those 7-18-years old. In this study, the mean time since epilepsy diagnosis was 4.4 years and majority of participants had not experienced seizures in the months preceding evaluation. Another cross-sectional study that assessed anxiety symptoms using the RCMAS reported a prevalence of 23% among those 6-16-years old recruited from an outpatient neurology clinic. In this study, the

mean time since epilepsy diagnosis was 4.8 years and 80% of participant were considered to have well controlled seizures.

Other studies have reported higher prevalence than we found. In particular, a cross-sectional study reported a much higher prevalence of anxiety (48%) in youth 14-24-years old. This study recruited participants from specialized epilepsy clinics and anxiety symptomatology was assessed by clinical interviews shortly after the diagnosis of epilepsy.

There are a few possible explanations for the differences in prevalence of elevated anxiety symptoms among AYA with epilepsy across studies. One possible explanation concerns the measures used to assess anxiety symptoms in these studies. The three most frequently used measures, the Hospital and Depression Anxiety Scale (HADS-A), Beck Anxiety Inventory (BAI), and State and Trait Anxiety Inventory (STAI) were each designed with unique specific goals: the HADS-A to measure anxiety and fear specifically in populations of medically ill patients; the BAI to capture somatic symptoms of anxiety and specifically discriminate between anxiety and depression, which often overlap; and the STAI-Y, which was used in our study, to capture the presence and severity of anxiety symptoms and propensity to be anxious for use in samples in the general population[80]. This variation in the basis for developing these measures may mean that they are not capturing exactly the same construct, which may mean that some of the differences in prevalence may be attributed to the differences in the measurement tools used rather than true differences in prevalence. The measure used in the two studies that reported the lowest prevalence of anxiety symptoms, the RCMAS, has been critiqued in the literature as measure that is sensitive to anxiety symptoms in children younger than twelve years of age but that underestimates the prevalence of anxiety symptoms in participants older

than 12 years of age[96][97]. This may explain the lower estimates of prevalence in studies that used the RCMAS.

A second potential explanation for the differences could be related to the length of time since epilepsy diagnosis when participants in the various studies were assessed. The study that reported a 16% prevalence had a mean time since epilepsy diagnosis of 4.4 years and a range of < 1-12 years[98]. Similarly, the study that reported a 23% prevalence had a mean time since epilepsy diagnosis of 4.8 years and a range of 1-15 years[63]. The study that reported a 48% prevalence assessed participants right after diagnosis, a time of great uncertainty for patients and their family as they learn to cope with the diagnosis[27]. In contrast, our study followed participants for a much longer period of time since diagnosis (participants were diagnosed about 10 years before the assessment of anxiety symptoms). The variability in the prevalence estimates for anxiety symptoms may be related to the heterogeneity in the length of time since epilepsy diagnosis of participants across studies, which in turn is likely to associated with variability in the achievement of seizure remission.

Another potential explanation for the variation in prevalence among studies concerns the sampling methods used to select participants and the studies' inclusion/exclusion criteria. The reported prevalence of psychiatric symptoms from specialized neurology clinics are often higher relative to samples from general medical practices[24]. Specialized neurology clinics tend to treat the most severe cases, hence participants selected from these clinics may be more likely to experience elevated anxiety symptoms. This aligns with the reported prevalence of anxiety symptoms described above, such that the highest prevalence (48%) focused on participants from a specialized epilepsy clinic[27]. In their study, 40% of AYA with epilepsy had

seizures in the previous 6 months compared to our study where two thirds of our sample had been seizure-free for 5 years or more. In sum, differences in prevalence may be explained by the inclusion and exclusion of study participants, measures used to assess anxiety symptoms and sampling methods.

5.1.2 Objective#2

The second objective of this thesis was to assess the association between anxiety symptoms 10-years after diagnosis with family characteristics, controlling for parent and child clinical and demographic characteristics. Specifically, it focused on characteristics at a) the 10-year follow-up and b) the time of diagnosis.

Our study found that family environment, specifically better family functioning, both at the 10-year follow-up and the time of diagnosis, was associated with fewer anxiety symptoms; however, neither of these associations remained statistically significant when controlling for parent and child characteristics. A possible explanation for this is that our sample had a generally positive family functioning both at diagnosis and the 10-year follow-up, which limited the variability in the measures of the family environment. This may have contributed to the lack of association between family functioning with anxiety symptoms. The findings also suggest that recent seizures may be a dominant factor that is associated with elevated anxiety symptoms among AYA with childhood-onset epilepsy. This finding is difficult to place in the context of what is known because past research that has evaluated the impact of family environment has focused on samples with ongoing seizures[27][51]. In contrast, the majority of AYA in our sample were seizure free. More so, previous studies that have considered the role of

family environment in contributing to psychiatric symptoms more generally, but none has focused on anxiety symptoms independently[20].

Neither of the other family factors, family resources and family demands assessed at the 10-year follow-up or at diagnosis, was associated with anxiety symptoms at the 10-year follow-up in AYA with epilepsy. A possible explanation for this is that there were significant differences in these variables at baseline between AYA lost to follow up and those who completed follow-up. Families lost to follow up had significantly fewer family resources and more family demands. Since the AYA at the 10-year follow-up were better off on these factors at baseline, this may have diluted the association that may have resulted if AYA with fewer family resources and more family demands at baseline were included in the analysis. Additionally, AYA lost to follow-up may be more likely to experience mental health problems such as anxiety symptoms and this may weaken any association found with our sample that completed follow-up.

In terms of clinical characteristics, our study found AYA who had been seizure-free for 5 or more years at follow-up reported fewer anxiety symptoms in the long-term, relative to AYA with continued seizures. This finding is consistent with previous studies that have investigated the association of seizure freedom with anxiety symptoms in AYA with epilepsy[56][99]. Kwon and Park found that young adults who attained seizure freedom were significantly less likely to experience anxiety symptoms compared to young adults who had not attained seizure freedom[56].

5.2 Strengths

This thesis has several strengths. To the best of our knowledge this is the first study to assess long-term anxiety symptoms in AYA with epilepsy. This study also assessed the association of anxiety symptoms in the long-term with family characteristics, controlling for parent and child clinical and demographic covariates. Data were collected prospectively at multiple time points, thereby reducing the risk of recall bias. This allowed for the opportunity to examine the clinical presentation of the epilepsy in the early stages and the family environment at diagnosis and their relationship to long-term anxiety symptoms. Data came from a population-based cohort study that included centres across Canada, providing results that are generalizable. Lastly, all measures used in this thesis are validated and reliable.

5.3 Limitations

There are some limitations to this study. Most AYA in our sample had relatively mild epilepsy; at time of diagnosis most children were rated as “little severe” (40%) or “not severe at all” (19%) (as indicated on the GASE), and at the 10-year follow-up, the majority of participants (67%) were seizure free for at least 5 years. Hence, the results may not be generalizable to AYA with more severe epilepsy. Additionally, children included in our cohort were diagnosed with epilepsy between the ages of 4 and 12 years, and the results may not generalize to children diagnosed with epilepsy earlier life, which is often associated with a more severe etiology[100]. The age range for inclusion in our study was chosen because validated measures to evaluate children’s HRQOL were not available for children younger than 4 years, and the primary objective of the HERQULES study was to evaluate children’s HRQOL over time. Another limitation concerns the significant differences in levels of family resources, family demands,

family income, and parental depressive symptoms between families that were lost to follow-up and those retained until the 10-year follow-up. Families lost to follow-up reported a poorer family environment (namely, fewer family resources, more family demands, lower family income, and greater parental depressive symptoms) at the time of diagnosis than those retained. AYA lost to follow-up also had more co-morbid problems at the time of their diagnosis of epilepsy. This means that the prevalence of anxiety problems at follow-up in our sample may be underestimated given the known associations between anxiety and these family and child characteristics.

Lastly, while the STAI-Y6 is a validated and reliable measure of anxiety symptoms, it is designed to capture transient arousal. Specifically, it assesses state anxiety symptoms, which captures transient anxiety symptoms rather than trait anxiety, which refers to longer lasting anxiety symptoms. While it may have been preferable to assess trait anxiety, it has been demonstrated that state and trait anxiety are highly correlated($r>0.90$)[77][91] so it reasonable to assert that results would likely have been similar if trait anxiety had been measured instead of state anxiety.

5.4 Recommendation for Future Research

Future studies should examine anxiety symptoms beginning at the time of epilepsy diagnosis and prospectively assess anxiety over time. This would allow researchers to observe the trajectory of anxiety symptoms in AYA with epilepsy and provide an opportunity to better determine risk and protective factors.

Future research could also consider including a more heterogeneous sample, such as including AYA with more severe epilepsy, those who have undergone surgery to manage

epilepsy, and AYA with drug resistant epilepsy. This would generate a more comprehensive description of the experience of anxiety symptoms representative of the full population of AYA with childhood onset epilepsy. Continued research on medication, treatment, and management of AYA with epilepsy with the goal of seizure control and attainment of seizure freedom should be prioritized. Lastly, future studies should continue to investigate the impact of the family environment on AYA with epilepsy using samples where there is a wider range of variation in family environmental factors such as family functioning, family resources and family demands. It is also important to consider the impact that changes in family factors over time could have on long-term outcomes in childhood-onset epilepsy.

5.5 Implications and Conclusions

The findings from this study suggest that the experience of anxiety symptoms in AYA with epilepsy in the long-term after epilepsy diagnosis is comparable on average to the same sex and age counterparts in the US population. However, there is a subset of AYA with childhood-onset epilepsy, about one-third whose anxiety symptoms are worthy of attention. Health care professionals may consider educating parents on the prevalence and likelihood of anxiety symptoms in AYA with epilepsy and provide resources on the treatment and management of anxiety symptoms should they arise. Health care providers may also consider screening for anxiety symptoms in AYA with epilepsy as part of routine care and management. Although our study did not find family factors to be independently associated with anxiety symptom about 10 years after diagnosis, this finding does not downplay the importance and role of the family environment in contributing to psychopathology in AYA diagnosed with childhood epilepsy. More research is needed to uncover the roles of various family factors and

their relationship to anxiety and other psychiatric symptoms in AYA with epilepsy. The finding that seizure freedom is associated with long-term anxiety symptoms indicates that children with persistent uncontrolled seizures are at increased risk of anxiety symptoms. Although seizure freedom should be a priority in the management of AYA with epilepsy, achieving seizure freedom does not necessarily resolve the ubiquitous comorbidities experienced by AYA with epilepsy. Comprehensive care of AYA diagnosed with childhood epilepsy, including consideration of co-morbidities is important regardless of whether seizure freedom is attained.

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Appendix A: Physician Form

Patient's Date ofBirth (dd/mm/yy):_____ Site #:_____

Please answer the following questions based on information from this patient's most recent visit and return upon completion

1. Date of patient's last visit (dd/mm/yy):_____or Date of Telephone F/U (dd/mm/yy)_____

2. Date form completed (dd/mm/yy): _____

If information for 3 thru 7 is unchanged from baseline (diagnosis) visit, please check here and proceed to 8. ☐

3. Seizure type(s): 1) _____ 2)_____

   3)_____ 4)_____

4. Epilepsy syndrome: _____

5. Convulsive status epilepticus:
   - ☐ No
   - ☐ Yes

6. Exclusive nocturnal seizures:
   - ☐ No
   - ☐ Yes

7. Age of first seizure (excluding febrile seizure):_____yrs

8. Does this patient have any family with epilepsy?
   - ☐ No
   - ☐ Yes

9. Number of AEDs currently: _____

10. Number of AEDs total: _____

11. Is this patient of school age?
    - ☐ No
    - ☐ Yes → Grade: ____ ☐ regular class ☐ regular class with resource ☐ special class

12. Does the patient have behavioural problems?
    - ☐ No (normal)
    - ☐ Yes → Please check one: ☐ mild ☐ moderate ☐ severe

    Diagnosis: _____

13. Does the patient have cognitive problems?
    - ☐ No (normal)
    - ☐ Yes → Please check one: ☐ borderline ☐ mild ☐ moderate ☐ severe

    Diagnosis: _____

14. Does this patient have motor problems?
    - ☐ No
    - ☐ Yes → Please check one: ☐ mild ☐ moderate ☐ severe

    Diagnosis: _____

15. Other neurological deficits? Please specify: _____

    _____

16. Taking into account all aspects of this patient's epilepsy, how would you rate its severity at his/her last visit? Please check one answer.

    - ☐ Extremely severe
    - ☐ Very severe
    - ☐ Quite severe
    - ☐ Moderately severe
    - ☐ Somewhat severe
    - ☐ A little severe
    - ☐ Not at all severe

17. Rate the following aspects of this patient's epilepsy at his/her last visit.

    Check one box using the following 7-point scale:
    1 = none or never
    7 = extremely frequent, severe or high

	1	2	3	4	5	6	7
Frequency of seizures							
Intensity of seizures							
Falls or injuries during seizures							
Severity of post-ictal period							
Amount of antiepileptic drugs							
Side effects of antiepileptic drugs							
Interference of epilepsy or drugs with daily activities							

Appendix B: AYA Report Measurement Tool

Spielberger State-Trait Anxiety Inventory short-form (STAI: Y-6)

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
a) I feel calm	1	2	3	4
b) I am tense	1	2	3	4
c) I feel upset	1	2	3	4
d) I am relaxed	1	2	3	4
e) I feel content	1	2	3	4
f) I am worried	1	2	3	4

Appendix C: Parent Report Measurement Tools

Family Inventory of Resources for Management (FIRM): Family Strength: Mastery and Health and Extended Family Support Subscales

The next set of questions asks about what social, psychological, community and financial resources families believe they have available to them in the management of family life. To complete this inventory you are asked to read the list of "Family Statements" one at a time. In each statement, "family" means your immediate family (mother and/or father and children.) Then ask yourself: "*How well does the statement describe our family situation?*"

Then make your decision by circling one of the following:

0 = Not At All	This statement does not describe our family situation. This does not happen in our family.
1 = Minimally	This statement describes our family situation only slightly. Our family may be like this once in a while.
2 = Moderately	This statement describes our family situation fairly well. Our family is like this some of the time.
3 = Very Well	This statement describes our family very accurately. Our family is like this most of the time.

Please read and record your decision for each of the statements below.

Family Statements:	**Not at all**	**Minimally**	**Moderately**	**Very Well**
a. Being physically tired much of the time is a problem in our family	0	1	2	3
b. We have to nag each other to get things done	0	1	2	3
c. We do not plan too far ahead because many things turn out to be a matter of good or bad luck anyway	0	1	2	3
d. Having only one person in the family earning money is (or would be) a problem in our family	0	1	2	3
e. It seems that members of our family take each other for granted	0	1	2	3
f. Sometimes we feel we don't have enough control over the direction our lives are taking	0	1	2	3
g. Certain members of our family do all the giving, while others do all the taking	0	1	2	3
h. We seem to put off making decisions	0	1	2	3
i. Our family is under a lot of emotional stress	0	1	2	3
j. Many things seem to interfere with family members being able to share concerns	0	1	2	3

k. Most of the money decisions are made by only one person in our family	0	1	2	3
l. It seems that we have more illness (colds, flu, etc.) in our family than other people do	0	1	2	3

m. In our family some members have many responsibilities while others don't have enough	0	1	2	3
n. It is upsetting to our family when things don't work out as planned	0	1	2	3
o. Being sad or "down" is a problem in our family	0	1	2	3
p. It is hard to get family members to cooperate with each other	0	1	2	3
q. Many times we feel we have little influence over the things that happen to us	0	1	2	3
r. We have the same problems over and over – we don't seem to learn from past mistakes	0	1	2	3
s. There are things at home we need to do that we don't seem to get done	0	1	2	3
t. We seem to be so involved with work and/or school activities that we don't spend enough time together as a family	0	1	2	3
u. Our relatives seem to take from us, but give little in return	0	1	2	3
v. We try to keep in touch with our relatives as much as possible	0	1	2	3
w. Our relative(s) are willing to listen to your problems	0	1	2	3
x. Our relatives do and say things that make us feel appreciated	0	1	2	3

Family Inventory of Life Events & Changes (FILE)

Over their life cycle, all families experience many changes as a result of normal growth and development of members and due to external circumstances. The following list of family life changes can happen in a family at any time. Because family members are connected to each other in some way, a life change for any one member affects all the other persons in the family to some degree.

*"**FAMILY**" means a group of two or more persons living together who are related by blood, marriage or adoption. This includes persons who live with you and to whom you have a long term commitment.*

Please read each family life change and decide whether it happened to any member of your family - **including you** - during the past 12 months and check **Yes** or **No**.

Did the change happen in your family:	During the last 12 months **Yes**	**No**	**Score**
I. Intrafamily Strains a. Increase of husband/father's time away from family			46
b. Increase of wife/mother's time away from family			51
c. A member appears to have emotional problems			58
d. A member appears to depend on alcohol or drugs			66
e. Increase in conflict between husband and wife			53
f. Increase in arguments between parent(s) and child(ren)			45
g. Increase in conflict among children in the family			48
h. Increased difficulty in managing teenage child(ren)			55
i. Increased difficulty in managing school age child(ren) (6-12 yrs)			39
j. Increased difficulty in managing preschool age child(ren) (2.5-6 yrs)			36
k. Increased difficulty in managing toddler(s) (1-2.5 yrs)			36
l. Increased difficulty in managing infant(s) (0-1 yr)			35
m. Increase in the amount of "outside activities" which the children are involved in			25
n. Increased disagreement about a member's friends or activities			35
o. Increase in the number of problems or issues which don't get resolved			45
p. Increase in the number of tasks or chores which don't get done			35
q. Increased conflict with in-laws or relatives			40
II. Marital Strains a. Spouse/parent was separated or divorced			79
b. Spouse/parent had an "affair"			68
c. Increased difficulty in resolving issues with a "former" or separated spouse			47
d. Increased difficulty with sexual relationship between husband and wife			58

Did the change happen in your family:	During the last 12 months: Yes	No	Score
III. Pregnancy and Childbearing Strains			
a. Spouse had unwanted or difficulty pregnancy			45
b. An unmarried member became pregnant			65
c. A member had an abortion			50
d. A member gave birth to or adopted a child			50
IV. Finance and Business Strains			
a. Took out a loan or refinanced a loan to cover increased expenses			29
b. Went on welfare			55
c. Change in conditions (economic, political, weather) which hurts the family investments			41
d. Change in agriculture market, stock market, or land values which hurts family investments and/or income			43
e. A member started a new business			50
f. Purchased or built a home			41
g. A member purchased a car or other major item			19
h. Increased financial debts due to over-use of credit cards			31
i. Increased strain on family "money" for medical/dental expenses			23
j. Increased strain on family "money" for food, clothing, energy, home care			21
k. Increased strain on family "money" for child(ren)'s education			22
l. Delay in receiving child support or alimony payments			41
V. Work-Family Transitions and Strains			
a. A member changed to a new job/career			40
b. A member lost or quit a job			55
c. A member retired from work			48
d. A member started or returned to work			41
e. A member stopped working for extended period (e.g., laid off, leave of absence, strike)			51
f. Decrease in satisfaction with job/career			45
g. A member had increased difficulty with people at work			32
h. A member was promoted at work or given more responsibilities			40
i. Family moved to a new home/apartment			43
j. A child/adolescent member changed to a new school			24
VI. Illness and Family "Care" Strains			
a. Parent/spouse became seriously ill or injured			44
b. Child became seriously ill or injured			35
c. Close relative or friend of the family became seriously ill			44
d. A member became physically disabled or chronically ill			73

Did the change happen in your family:	During the last 12 months Yes	 No	 Score
e. Increased difficulty in managing a chronically ill or disabled member			58
f. Member or close relative was committed to an institution or nursing home			44
g. Increased responsibility to provide direct care or financial help to husband's and/or wife's parents			47
h. Experienced difficulty in arranging for satisfactory child care			40
VII. Losses a. A parent/spouse died			98
b. A child member died			99
c. Death of husband's or wife's parent or close relative			48
d. Close friend of the family died			47
e. Married son or daughter was separated or divorced			58
f. A member "broke up" a relationship with a close friend			35
VIII. Transitions "In and Out" a. A member was married			42
b. Young adult member left home			43
c. Young adult member began college (or post high school training)			28
d. A member moved back home or a new person moved into the household			42
e. A parent/spouse started school (or training program) after being away from school for a long time			38
IX. Family Legal Violations a. A member went to jail or juvenile detention			68
b. A member was picked up by police or arrested			57
c. A member ran away from home			61
d. A member dropped out of school or was suspended from school			38

Center for Epidemiological Studies Depression Scale (CES-D)

Now we'd like to ask some questions about you. Please read these sentences that say something about how people sometimes feel and circle the number of the category on this page that best indicates how often you have felt this way in the past 7 days.

0. Rarely or none of the time (less than one day)
1. Some or a little of the time (1-2 days)
2. Occasionally or a moderate amount of time (3-4 days)
3. Most or all of the time (5-7 days)

During the past seven days:

a) I was bothered by things that usually don't bother me.	0	1	2	3
b) I did not feel like eating; my appetite was poor.	0	1	2	3
c) I felt that I could not shake off the blues even with help from my family or friends.	0	1	2	3
d) I felt that I was just as good as other people.	0	1	2	3
e) I had trouble keeping my mind on what I was doing.	0	1	2	3
f) I felt depressed.	0	1	2	3
g) I felt that everything I did was an effort.	0	1	2	3
h) I felt hopeful about the future.	0	1	2	3
i) I thought my life had been a failure.	0	1	2	3
j) I felt fearful.	0	1	2	3
k) My sleep was restless.	0	1	2	3
l) I was happy.	0	1	2	3
m) I talked less than usual.	0	1	2	3
n) I felt lonely.	0	1	2	3
o) People were unfriendly.	0	1	2	3
p) I enjoyed life.	0	1	2	3
q) I had crying spells.	0	1	2	3
r) I felt sad.	0	1	2	3
s) I felt that people dislike me.	0	1	2	3
t) I could not get "going".	0	1	2	3

Appendix D: Research Ethics Approval

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Kathy Speechley
Department & Institution: Schulich School of Medicine and Dentistry\Epidemiology & Biostatistics,Western University

Review Type: Expedited
HSREB File Number: 102819
Study Title: Health-related quality of Life in children with New-Onset Epilepsy: A Long-term Follow-up
Sponsor: Canadian Institutes of Health Research

HSREB Amendment Approval Date: September 14, 2015
HSREB Expiry Date: September 06, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Change in Study Personnel	Incoming Research Assistants (S. Brar & A. Dasiewicz)	2015/08/27
Revised Western University Protocol		2015/08/27
Other	Cover Letter: Time 6 Parent Questionnaire	2015/08/19
Instruments	Time 6 Parent Questionnaire	2015/08/27
Other	Cover Letter: Time 6 Youth 11-17 Questionnaire	2015/08/19
Instruments	Time 6 Youth 11-17 Questionnaire	2015/08/27
Other	Cover Letter: Time 6 Youth 18+ Questionnaire	2015/08/17
Instruments	Time 6 Youth 18+ Questionnaire	2015/08/27
Other	Email/Cover Letter: Time 6 Youth 18+ Questionnaire	2015/08/19
Other	Email/Cover Letter: Time 6 Youth 11-17 Questionnaire	2015/08/19

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]
Ethics Officer, on Behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information

[redacted]

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