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Starting at the beginning: The neuropsychological status of children with new onset epilepsies

Bruce P. Hermann¹, Jana E. Jones¹, Daren C. Jackson¹, and Michael Seidenberg²

¹Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison WI

²Department of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago IL

Abstract

This review examines the neurodevelopmental contributions to the cognitive and behavioral complications of epilepsy. Following a brief review of the lifespan complications of childhood epilepsies, attention turns to cognitive, psychiatric and social correlates of childhood epilepsies reported in population-based and tertiary care studies. The focus then becomes the neurobehavioral status of children with new onset epilepsy—a point in time not confounded by the effects of years of recurrent seizures, medications, and social reactions to epilepsy. Recent research shows that abnormalities in cognition, brain structure and behavior are present at or near the time of diagnosis. Further, careful history indicates that neurobehavioral problems may be present in advance of the first seizure suggesting the potential influence of epileptogenesis, antecedent neurodevelopmental abnormalities, genetic and environmental susceptibilities, and other risk factors. This becomes the substrate upon which to characterize the effects of epilepsy and its treatment on subsequent neurodevelopment. The review concludes with suggestions for future clinical care and research.

Introduction

While defined by the presence of recurrent seizures, epilepsy can be associated with abnormalities in cognition, psychiatric status, and social-adaptive behaviors that are now referred to as *neurobehavioral comorbidities*. These complications of epilepsy have a long history. Various referred to as the *psychosocial complications* or *burden of epilepsy*, problems in cognition, emotional-behavioral status and social function were investigated empirically beginning early in the past century when people with epilepsy were often segregated in colonies or other specialized treatment facilities (Fox, 1924; Wallin, 1911), subsequently examined by epileptologists seeking to provide a more representative picture of the consequences of epilepsy in community dwelling patients (Lennox, 1960), and an ongoing concern of national commissions (DHEW, 1978), public health agencies including the Centers for Disease Control (Austin et al., 2006), and national and international health organizations including the International League Against Epilepsy and World Health Organization (WHO, 2001), Institute of Medicine (2011), and others (White House, 2000). At the NIH/NINDS Curing Epilepsy Conference (2007), preventing or reversing the comorbidities of epilepsy was identified as a new major research benchmark area, joining established research benchmarks of curing existing epilepsy and preventing epilepsy and its

Address for correspondence; Bruce P. Hermann, PhD, Matthews Neuropsychology Lab, Department of Neurology, University of Wisconsin School of Medicine and Public Health, 1685 Highland Ave., Madison, WI 537056, Phone: 608-263-5430, Fax: 608-265-0172, hermann@neurology.wisc.edu.

progression. While undeniably a critical complication of the epilepsies, the etiology and course of the neurobehavioral comorbidities remain to be fully characterized.

The focus of this paper is on children with epilepsy and what we have learned about the origin and development of neurobehavioral comorbidities, and where we need to go in order to better understand, treat, and prevent these problems. We will first briefly review several trends that have been identified regarding cognitive and other neurobehavioral comorbidities of epilepsy and their potential neurodevelopmental roots, and then move to what has been learned through studying children with epilepsy at or near the time of the onset of their epilepsy.

Childhood epilepsy matters

Given the diverse medical, social, psychiatric, cognitive, and quality of life complications of the adult epilepsies (Tellez-Zenteno et al., 2005, 2007; Kobau et al., 2008; Hinnell et al., 2010; Ottman et al., 2011; Javala & Sillanpaa, 1996) and their associated direct and indirect costs (Begley et al., 2000; Jennum et al., 2011), interest has accelerated in understanding the origin, development and trajectory of these complications. At least three sets of evidence suggest a significant neurodevelopmental contribution.

First there is the *indirect* evidence linking the risk of comorbidities to the age of onset of recurrent seizures. For example, studying *adults* with chronic epilepsy, many neuropsychological studies have shown that an earlier age of onset of recurrent seizures is associated with poorer cognitive function than later onset but still chronic epilepsy (Dikmen et al., 1975, 1977; Dodrill & Matthews, 1992; Lennox, 1960; Hermann et al., 2002; Kaaden & Helmstaedter, 2009). This same relationship has been reported in some but not all neuropsychological studies of younger patients with complex partial and other types of seizures (O'Leary et al., 1981; Schoenfeld et al., 1999; Cormack et al., 1997). Complimenting these cognitive studies are neuroimaging investigations of brain structure. This is a much more limited literature but an adverse impact of childhood compared to adulthood onset of epilepsy has been shown in reductions in whole brain volume among patients with a history of complicated febrile convulsions (Theodore et al., 2003), altered volumes of the corpus callosum, whole brain white and/or gray matter tissue, and specific disrupted patterns of white matter connectivity in individuals with childhood compared to adult onset chronic partial epilepsy (e.g., Hermann et al., 2002, 2003; Kaaden et al., 2011; Riley et al., 2010; Weber et al., 2007).

Second is the compelling evidence that childhood onset epilepsy impacts life course. An important indication of the public health significance of childhood epilepsy is its association with adverse outcomes in later youth and adulthood. This impact is reflected in an international literature published during the past 30 years with studies emanating from the UK, Canada, Finland, Japan, Australia and the Netherlands. Collectively, these reports include both uncontrolled (Lindsay et al., 1979abc; Wakamoto et al., 2000; Camfield et al., 1993; Harrison & Taylor, 1976; Micallef et al., 2010;) and controlled community and population-based investigations (Jalava et al., 1997ab; Kokkonen et al., 1997; Wirrell et al., 1997; Sillanpaa et al., 1998; Shackleton et al., 2003; Koponen et al., 2007; Geerts et al., 2011) as well as long term (adult) follow-up of national birth cohorts (Cooper, 1965; Ross et al., 1980; Britten et al., 1986; Ross & Peckham, 1983; Chin et al., 2011). Several aspects of this literature are important: 1) Groups of children with epilepsy have been followed prospectively for up to 30+ years in controlled investigations (e.g., Sillanpaa et al., 1998; Shackleton et al., 2003). 2) Problems in a diversity of major life outcomes have been reported including rates of marriage, employment, income, psychiatric status, independent living status, and other critical aspects of quality of life. 3) While it would not be surprising

that children with severe and complicated epilepsies would exhibit poor lifespan psychosocial outcomes (Lindsay, 1979abc), most but not all (e.g., Wakamoto et al., 2000) investigations report adverse lifespan outcomes in persons with intact intelligence, so-called benign epilepsies, and even persons with remitted childhood epilepsy who are no longer treated with antiepilepsy medications (Camfield et al., 1993; Wirrell et al., 1997; Sillanpaa et al., 1998; Jalava, 1997ab). 4) The causes underlying these adult outcomes and the factors associated with favorable versus unfavorable outcomes remain to be fully clarified. These poor lifespan outcomes are variably associated with clinical epilepsy features (e.g., seizure control). 5) While rarely considered as predictor variables, adverse lifespan outcomes have been found to be associated with histories of neurobehavioral comorbidities including early learning/cognitive and psychiatric problems (Lindsay, 1979c; Camfield et al., 1993; Kokkonen et al., 1997; Koponen et al., 2007) including what is now called ADHD (Lindsay et al., 1979c).

Third, an important set of background data involves the direct examination of comorbidities among children with established epilepsy (Lassonde et al., 2000; Gleissner et al., 2002; McAllister & Schaffer, 2007). This literature benefits from both population-based and careful tertiary care investigations.

Population-based investigations

In regard to psychiatric status, the pediatric psychiatric epidemiological Isle of Wight study (Rutter et al., 1970) reported that 7% of children in the general population exhibited mental health issues compared to 12% of children with non-neurological physical disorders, 29% of children with uncomplicated epilepsy, and 58% of children with complicated epilepsy (i.e., structural brain abnormalities and seizures). Almost 30 years later, as part of the British Child and Adolescent Mental Health Survey, Davies et al. (2003) reported strikingly similar results, and other controlled population-based investigations have been supportive of these findings (Alfstad et al., 2010, 2011).

In regard to cognition, population-based data have addressed the status of global intelligence (Berg et al., 2008) and specific cognitive abilities including nonverbal memory (Høie et al., 2005), executive function (Høie et al., 2006a), psychosocial problems (Høie et al., 2006b), and the combined burden of cognitive, executive and psychosocial problems (Høie et al., 2008). Defining abnormal intelligence as IQ < 80, Berg et al. (2008) reported that in the Connecticut Study of Epilepsy (n=613), cognition assessed 8–9 years after epilepsy onset was considered largely normal in 73.6% of children, with mild MR or lower in the remaining sample (26.4%). Independently predictive of level of function was age of onset < 5 years of age, symptomatic etiology, epileptic encephalopathy, remission status, and current AED status (Berg et al., 2008). In their series of papers examining a population-based cohort of children (ages 6–12) with prevalent epilepsy (n=198) and controls (n=126), severe nonverbal learning problems (<10th percentile) as assessed by the Raven Matrices were found in 43% of children with epilepsy compared to 3% of controls. These problems were especially common in children with epilepsy characterized by remote symptomatic etiology, undetermined epilepsy syndromes, myoclonic seizures, early seizure onset, high seizure frequency and polytherapy (Høie et al., 2005). Comparable investigations of executive function, school achievement, depression and other comorbidities documented the neurobehavioral burden carried by children with epilepsy (Høie et al., 2006ab, 2008) as well as pre-school children with epilepsy including those with uncomplicated epilepsies (Rantanen et al., 2010, 2011).

Investigations from specialized centers

Investigations from clinical centers examining children with established epilepsy provide complimentary information and just a few examples from this extensive literature follow below. Farwell and Dodrill (1985) examined 118 children with epilepsy (age 6–15) and 100 controls using the Wechsler Intelligence Scale for Children-Revised and the age-appropriate Halstead-Reitan battery. Various epilepsy syndromes were represented (8 with absence seizures only, 8 with absence seizures and generalized tonic-clonic seizures, 30 with generalized tonic-clonic seizures only, 31 with partial seizures only, 20 with partial seizures and generalized seizures, 15 with atypical absence seizures, and 6 with minor motor seizure). They reported that Full Scale IQ was significantly lower in the children with epilepsy and was related to seizure type. All seizure types were associated with lower intelligence compared to the healthy controls except classic absence only. Children with minor motor or atypical absence seizures had the lowest average FSIQ (70 and 74, respectively). They found a significant inverse correlation between years with seizures and intelligence. A rating of neuropsychological impairment was compiled for all children and the youths with epilepsy exhibited significantly more impairment than controls. Children with epilepsy had been placed in special education or repeated a grade in school almost twice as frequently as controls.

Nolan et al. (2003) examined intelligence in 169 children with a spectrum of epilepsy syndromes including generalized idiopathic epilepsy (n=22), generalized symptomatic epilepsy (n=25), frontal lobe epilepsy (n=34), temporal lobe epilepsy (n=40), central epilepsy (n=16), and focal epilepsy NOS (n=32). They demonstrated a pattern of mildly to moderately depressed intellectual ability after accounting for covariates (age of onset, seizure frequency, number of medications). They concluded that regardless of epilepsy syndrome, children with epilepsy suffered from reduced intellectual efficiency as measured by IQ, particularly those children with remote symptomatic generalized epilepsy.

Cormack et al. (2007) characterized a downward shift in the distribution of intelligence in a sample of 79 children with temporal lobe epilepsy compared to the normal (expected) distribution. These children were surgical candidates who underwent assessment as part of the preoperative workup. Age at onset (earlier) was the best predictor of intellectual impairment (IQ <79) which was present in 57% of the cohort. Children with epilepsy onset in the first year of life had an especially high rate of intellectual impairment (84%). In regard to specific cognitive domains, Schoenfeld et al. (1999) demonstrated that among 57 children age 7–16 years with complex partial seizures with a mean duration of 5 years, mild generalized cognitive impairment was evident across language abilities, verbal memory and motor functioning compared to 27 sibling controls.

Review of studies of cognition in children with established chronic epilepsy have shown that a number of epilepsy-related factors appear to contribute to these problems, including seizure frequency, recurrent seizures, age at seizure onset, duration of illness, antiepileptic drugs (AEDs), type of epilepsy, and EEG findings (c.f., Jones et al., 2010). However, across studies, the effects of epilepsy-related variables are not consistently replicated and often variables such as family factors, preexisting learning problems, psychopathology, and neuropsychological impairments are found to be significant factors influencing academic underachievement, cognitive and linguistic deficits, as well as behavior problems in children with epilepsy (Jones et al., 2010).

The questions that arise are when and why these abnormalities exist and how they develop over time. If cognitive abnormalities are present among children with short duration of epilepsy, an important question is whether they are apparent at epilepsy onset or develop following the onset and treatment of recurrent seizures. Further, identification of

neurobehavioral abnormalities at the onset of epilepsy would infer the presence of antecedent neurodevelopmental abnormalities or the effect of other factors. Examination of children at or near the onset of their epilepsy and following them over time would prove especially informative and it is to these issues that we turn for discussion.

Youth with new-onset epilepsy

Early investigations

Prior to approximately 2000 a small number of studies examined cognition in children with new-onset epilepsy (Bourgeois et al., 1983; Stores et al., 1992; Williams et al., 1998; Kolk et al., 2001). Several of these early papers tested children at onset in order to serve as a drug naïve baseline with which to assess subsequent treatment or comparative drug effects (Stores et al., 1992; Williams et al., 1998). Others focused solely on intelligence and were primarily interested in characterizing clinical seizure factors associated with prospective IQ changes, especially declines (e.g., Bourgeois et al., 1983). These studies examined children with epilepsy of various types, age ranges, test batteries, and clinical seizure characteristics. Comments that follow focus only on the baseline findings.

Bourgeois et al. (1982) examined intelligence in 72 children with mixed epilepsies within two weeks of diagnosis, age 18 months to 16 years (with IQ 40+), compared to 45 siblings. The mean IQ of the children with epilepsy and matched siblings was 98 and 104.4—lower but not significantly so. Children with idiopathic epilepsy had a higher IQ than symptomatic (102.5 vs. 89.1) at baseline.

Stores et al. (1991) examined 63 children (ages 7–12) with new onset epilepsy both before and after initiation of AED treatment children and 47 similarly aged healthy controls. Administered were measures of specific cognitive abilities (attention, memory, motor and psychomotor speed) and general intelligence and reading and arithmetic performance. At baseline, prior to AED initiation, the partial epilepsy group exhibited significantly poorer attention (establish and focus) and motor and psychomotor ability. Children with absence and other idiopathic generalized epilepsies exhibited fewer significant baseline cognitive abnormalities, differences limited to motor/psychomotor speed. A variety of behavioral abnormalities were detected in the partial and generalized epilepsy groups at baseline as well.

Williams et al. (1998) compared 37 children with new onset epilepsy [22 partial epilepsy and 15 primary generalized] (age 6–17) prior to initiation of AEDs and a control group of 26 children with new onset diabetes on measures of attention and concentration, memory, complex motor processing speed and behavior. The children with epilepsy performed more poorly than the diabetic children across 9 of 11 measures, but none of the group differences were statistically significant.

Kolk et al. (2001) compared 14 healthy controls, 12 children with partial seizures, and 18 with congenital hemiparesis and seizures (mean age = 6 years), the children with epilepsy said to be of normal psychometric intelligence. The NESPY was used for cognitive assessment which consisted of 37 tests falling into five cognitive domains (attention and executive function, language, sensorimotor, visuospatial, learning and memory). The children with new onset partial epilepsy showed significantly poorer performance across 4 of the 5 composite cognitive domain scores.

Later investigations

This is an area of increased interest and several recent investigations have appeared. Oostrom et al (2003) examined children (age 5–16) with newly diagnosed epilepsy (n=51)

prior to the administration of antiseizure medications (tested within 48 hours of diagnosis). The children with epilepsy had at least two unprovoked nonfebrile seizures of idiopathic or cryptogenic cause, who attended mainstream schools, without any identified neurological disease, a diagnosis of another chronic illness, or previous use of AEDs. Controls were healthy classmates invited by the child with epilepsy and/or their family (n=48). A comprehensive test battery was administered which was reduced through factor analysis to measures of attention, reaction time, intelligence, academic skills, location learning and behavior. Significantly poorer performance on the part of the children with new onset epilepsy was observed in the areas of attention, reaction time, visual memory and behavior with a trend ($p=.07$) of poorer academic achievement (Ostrom et al., 2003).

Very comparable results were subsequently reported by Hermann et al. (2006) who examined 75 children with new-onset localization related and idiopathic generalized epilepsy and 63 healthy controls, aged 8–18. Research participants underwent a comprehensive neuropsychological test battery, neuroimaging, and structured psychiatric interview. Similar to Ostrom et al. (2003), they found a pattern of mild generalized cognitive impairment evident across measures of intelligence, language, attention, executive function, and psychomotor speed. Also examined through a structured interview with the parents of the children with epilepsy and controls was the history of any educational services provided to the children for academic difficulties. Supportive educational services of interest included traditional IEPs, but also required summer school, grade retention, directed homework clubs, tutoring, and other services. History of academic problems was significantly more frequent in children with epilepsy versus controls (53% vs. 18%, $p < .001$), with no difference between children with LRE versus IGE (44% vs. 58%, $p=.16$). Further, rates of need for educational services was comparably elevated in specific syndromes of LRE (BECTS=65%, other focal=52%) and IGE (absence=45%, JME=46%). Lastly, children with recent onset epilepsy exhibited an elevated rate of lifetime-to-date Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I disorders compared to the healthy controls with significantly higher rates of depressive disorders (22.6 vs. 4%, $p=0.01$), anxiety disorders (35.8 vs 22%, $p<0.05$), and attention-deficit-hyperactivity disorder (26.4 vs 10%, $p=0.01$) with elevated but less prevalent rates of oppositional defiant and tic disorders.

Fastenau et al. (2009) examined a large community-based sample of children with first recognized seizures (n=282 children, ages 6–14 years, IQ ≥ 70) and 147 sibling controls, characterizing their neuropsychological and academic status. They found that 27% of children with a single seizure and up to 40% of those with risk factors exhibited neuropsychological deficits at or near onset. Risk factors for neuropsychological deficit included multiple seizures (OR=1.96), use of AEDs, symptomatic/cryptogenic etiology (OR = 2.15), and epileptiform activity on the initial EEG (OR=1.9). Absence epilepsy also carried increased odds for neuropsychological impairment (OR=2.0). Academic achievement appeared unaffected, suggesting an opportunity for early intervention. (see Dunn et al., 2002 and McNellis et al. 2007 et al. for additional information regarding academic achievement in both new onset and chronic cases from the Indianapolis series).

Bhise et al. (2010) examined 57 children (age 6–17) with new-onset idiopathic epilepsies using measures of new learning, memory, and attention. Seizures were classified as generalized convulsive (n=5), generalized non-convulsive (n=18), or focal (n=34). They found attention to be a particular area of weakness. Children with generalized, non-convulsive seizures performed worse than children with focal epilepsies on a measure of short-term auditory memory. All groups performed poorly on a test of visual-motor speed. The findings were viewed as suggesting intrinsic abnormalities in children with new-onset, idiopathic epilepsy at baseline.

In summary, cognitive, behavioral and academic abnormality can be identified at or shortly after the onset of childhood epilepsy, even among children with uncomplicated idiopathic epilepsies—children with “epilepsy-only” per Oostrom et al. (2003). Clinically this would imply that careful attention to neurobehavioral status would be very appropriate in children with new onset epilepsies.

“Comorbidities” before epilepsy appears—neurobehavioral status antecedent to epilepsy onset

Several interesting findings suggest that cognitive, psychiatric, and academic problems may antedate the diagnosis of epilepsy and recognition of the first seizure.

Austin and collaborators (2001) examined behavioral problems in children aged 4–14 with new-onset epilepsy (n=224) compared to 135 sibling controls. Higher than expected rates of behavior problems in the 6 months before the first recognized seizure were found in the total seizure sample, with 32.1% being in the clinical or at-risk range. Rates were highest in children who had previous events that were probably seizures, with 39.5% in the clinical or at-risk range. In a population-based investigation, Hesdorffer et al. (2004) found children with a spontaneous unprovoked seizure to be 2.5 times more likely to meet DSM-IV criteria for ADHD before the first seizure. Similar findings were subsequently reported by Jones et al. (2007) who indicated that a subset (45%) of children with epilepsy (45%) exhibited DSM-IV Axis I disorders before the first recognized seizure, including rates of ADHD, depression and anxiety antecedent to epilepsy onset.

Academic problems antedating epilepsy onset have also been reported by several groups. Examining the rate of provision of special school services of diverse types for academic difficulties, approximately 25% of children with epilepsy received these services even prior to their first recognized seizure (Berg et al., 2005, 2011; Oostrom et al., 2003; Hermann et al., 2006; McNelis et al., 2005). These psychiatric and cognitive/academic problems imply the presence of adverse antecedent effects that as of yet remain to be identified.

Family aggregation/clustering of cognitive and behavioral complications appear to be a promising path to pursue to account for some of this variance (Levav et al., 2002; Clarke et al., 2007; Iqbal et al., 2009; Wandschneider et al., 2010; Hesdorffer et al., in press; Smith et al., In press). In addition, neuroimaging investigations have demonstrated abnormalities in cortical and subcortical anatomy, white matter integrity, and ventricular volumes in children with new onset localization-related and idiopathic generalized epilepsies (Hutchinson et al., 2010; Jackson et al., 2011; Pulsipher et al., 2009; Tosun et al., 2011). These baseline anatomic abnormalities, certainly taking place prior to the onset of epilepsy, have been shown to be related to the integrity of cognition and behavior (e.g., Pulsipher et al., 2010, 2011). In addition, ongoing abnormal neurodevelopmental changes in brain structure and connectivity in the context of active epilepsy and treatment (Hermann et al., 2010; Tosun et al., 2011; Pulsipher et al., 2011) as well as syndrome-specific anatomic abnormalities (Lin et al., In press; Pulsipher et al., 2009). How these effects influence cognitive and behavioral development remains to be fully characterized.

Recommendations for advancing clinical care and research

Based on the findings reviewed, several suggestions for advancing clinical care and research were provided by the participants at the Toronto Conference (Helmsteadter et al., 2011). The suggestions for childhood cognition were as follows.

Clinical needs and directions—

1. It is clear that children with new-onset epilepsies, including those with idiopathic syndromes, exhibit cognitive and behavior problems at the time of diagnosis. While there is an understandable focus on the seizures themselves and the need for treatment, there is also a need for timely, efficient, cost effective, and clinic-friendly screening of cognitive, behavioral, and academic problems at the time of diagnosis, preferably before the initiation of medication treatment. It would be helpful if there were a core uniform battery used across epilepsy centers so that collaborative clinical and research issues could be facilitated (e.g., EpiTrack Junior [Helmsteadter et al., 2010]). In addition, a core set of clinical information should be collected across centers as well. The NIH CDE approach to developing these standard measures might prove helpful.
2. The literature pertaining to the neurobehavioral comorbidities of new-onset epilepsy is largely descriptive. A large number of problems have been identified, but there are no standard interventions to treat and prevent these complications. Such approaches could benefit from standard techniques (such as Cognitive Behavioral Therapy [CBT]) or take advantage of internet technology to provide access to treatment (e.g., CDC depression treatment) and standard sets of information.
3. A finer characterization of the developmental course of children with epilepsy is needed. The core test battery could be re-administered at standard (to be determined) intervals in order to monitor development of new neurobehavioral comorbidities and their relation to seizure variables (e.g., seizure frequency) and medications, and to track the development of abnormal trajectories.

Research needs and directions—

1. There is agreement across centers that neurobehavioral comorbidities may antedate the first recognized seizure and formal diagnosis of epilepsy. This is observed in regard to academic/educational, social, and psychiatric comorbidities. Why is this the case and what are the responsible factors and causes? Identification of biomarkers would only serve to facilitate early identification and treatment.
2. Familial aggregation of comorbidities. There is emerging evidence of family aggregation of cognitive and behavioral problems in families with a child with epilepsy. Greater clarification of this aggregation with examination of potential genetic and environmental contributions would be an important path to pursue.
3. Greater examination of the correlates of specific cognitive deficits and their structural, functional and connectivity related patterns of underlying neurobiological abnormality, and development over time, would help us understand the mechanisms of these cognitive disorders.

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