The Neuropsychological and Academic Substrate of New/Recent-Onset Epilepsies

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Objective To characterize neuropsychological and academic status in children, ages 8-18 years, with new-/recent-onset idiopathic generalized epilepsy (IGE) and idiopathic localization-related epilepsy (ILRE) compared with healthy controls.

Study design Participants underwent neuropsychological assessment, and parents were interviewed regarding their child's academic history. Cognitive scores for children with epilepsy were age- and sex-adjusted and compared with controls across both broad-band (IGE n = 41 and ILRE n = 53) and narrow-band (childhood/juvenile absence, juvenile myoclonic, benign epilepsy with centro-temporal spikes, and focal [temporal/frontal/not otherwise specified]) syndromes. Academic histories were examined, including problems antecedent to epilepsy onset and diagnosis.

Results Children with new/recent-onset epilepsies exhibit considerable cognitive abnormality at baseline, including patterns of shared abnormalities across syndromes (eg, psychomotor slowing) as well as unique syndrome-specific cognitive effects (eg, executive function in IGE and language/verbal memory in ILRE) that are observed and sometimes exacerbated in specific IGE and ILRE syndromes. Academic difficulties are evident in approximately 50% of the children with epilepsy, affecting all syndrome groups to an equal degree.

Discussion Patterns of shared and syndrome-specific cognitive abnormalities and academic problems are present early in the course of virtually all epilepsy syndromes examined here, including syndromes classically viewed as benign. This is the base upon which the effects of recurrent seizures, treatment, and psychosocial effects will be added over time. *(J Pediatr 2013;162:1047-53)*.

Community- and population-based investigations as well as reports from tertiary care centers demonstrate repeatedly that childhood epilepsy can be associated with abnormalities in cognition, academics, emotional status, and social function—complications referred to collectively as the neurobehavioral comorbidities of epilepsy.[1-4] A long-standing view of the etiology of these neurobehavioral complications is that they are due to the adverse effects of seizure frequency/severity, medications, social stigma, or stresses linked to recurrent seizures.[5] However, recent literature has demonstrated that abnormalities in cognition, social and psychiatric status can be apparent at the time of epilepsy diagnosis and may even antedate the first recognized seizure.[6-10] This effect has been reported in regard to general behavioral adjustment,[6] cognition,[7] academic achievement and school performance,[8] attention deficit hyperactivity disorder,[9] and depression.[10]

These findings would not be unanticipated in children with complicated and symptomatic epilepsies, but they have been reported in children with so-called "epilepsy-only,"[7] that is, children with average intelligence, normal neuroimaging and neurological exams, attending regular schools, with epilepsy subsyndromes perceived by many clinicians not to be worrisome and even benign (eg, benign epilepsy with centro-temporal spikes [BECTS], childhood/juvenile absence [Absence] epilepsy). Here we comprehensively examine baseline neuropsychological status in a large cohort of children with "epilepsy-only" compared with healthy controls. We have previously reported on cognitive abnormalities in a subset of this sample of children with epilepsy[11]; in the larger sample presented here, we examine the cognitive profiles of both broad syndrome groupings (idiopathic generalized epilepsy [IGE], idiopathic localization-related epilepsy [ILRE]), as well as narrow-band diagnostic subsyndromes (eg, BECTS, Absence, juvenile myoclonic epilepsy [JME], Focal). These comparisons demon-

Absence	Childhood/juvenile absence
AP	Academic problems
BECTS	Benign epilepsy with centro-temporal spikes
CCPT	Conners' Continuous Performance Test
IGE	Idiopathic generalized epilepsy
ILRE	Idiopathic localization-related epilepsy
JME	Juvenile myoclonic epilepsy

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strate patterns of shared versus unique cognitive consequences of specific epilepsy syndromes close in time to diagnosis. Through structured interviews with parents, we examine rates of academic problems (AP) both at baseline and prior to the first recognized seizure and diagnosis, as well as the neuropsychological implications of this academic history.

Methods

Study participants were aged 8-18 years, comprising 72 healthy controls and 94 with new/recent-onset epilepsy, including 53 with ILRE and 41 with IGE (Table I). All participants were followed for active epilepsy. Inclusion criteria were a diagnosis of epilepsy within the past 12 months, no other developmental disabilities or neurological disorders, normal neurologic examinations, and normal clinical imaging results. A board-certified pediatric neurologist (blinded to neuropsychological and interview data) confirmed that all patients had idiopathic epilepsies and provided independent confirmation of syndrome diagnosis. Four patients with IGE did not meet criteria for a specific syndrome diagnosis (eg, JME) and were excluded from analyses utilizing narrow-band syndrome diagnoses. Children with Focal epilepsies (temporal lobe, frontal lobe, and focal not otherwise specified) were combined in 1 "Focal" group as ictal confirmation of the localization/lateralization of seizure onset was not available for this sample. Healthy controls were age- and sex-matched first-degree cousins of epilepsy participants. Healthy controls presented with no history of seizures, early initial precipitating injuries (eg, febrile convulsions), other developmental or neurologic disease, or loss of consciousness more than 5 minutes.

Research approval was obtained from the Health Sciences Institutional Review Board at the University of Wisconsin Medical School. Written informed consent was obtained from legal guardians of participating children and adolescents, written informed consent was obtained from participants age 18 years, and written informed assent was obtained from participants age 8-17 years.

Children underwent comprehensive neuropsychological testing and magnetic resonance imaging. Parents underwent a clinical interview and completed questionnaires to characterize gestation, delivery, neurodevelopment, and seizure history. All pertinent medical records were obtained after signed release of information was obtained from the parent. Parents were questioned through a structured interview about their child's school progress and, in particular, any specific educational services provided to address AP. These services included the traditional individualized educational plan process, but also included early childhood interventions, including speech therapy, physical therapy, occupational therapy, mandatory summer school, grade retention, special tutoring services (eg, reading, math), and other specific educational services (inventory available from the authors). Also of interest was whether services were provided antecedent to the diagnosis of epilepsy as well as the first recognized seizure. This interview was conducted blinded to cognitive and behavioral results.

Neuropsychological Assessment and Analysis

All participants were administered a comprehensive test battery that included measures of intelligence, academic achievement, language, immediate and delayed verbal memory, executive function, and speeded fine motor dexterity (Table II). Regression techniques converted raw test scores to age- and gender-adjusted z-scores based on the control group.

Regression-based z-scores were submitted to a one-way MANOVA with group (IGE, ILRE, healthy controls) as the independent factor. A second MANOVA compared controls with specific epilepsy subsyndromes (BECTS, Focal, JME, Absence, healthy controls). For all analyses, post-hoc comparisons were made only following a significant omnibus P-value (<0.05). Fisher's least significant difference tests were used for multi-group post-hoc comparisons. To decrease the number of statistical comparisons (thus reducing the risk of family-wise error), post-hoc pairwise comparisons focused on the contrast of healthy controls to the epilepsy subsyndrome groups (BECTS, Focal, JME, Absence) of interest (ie, all possible combinations of subsyndrome comparisons were not evaluated).

Results

IGE and ILRE

The overall MANOVA for groups (ILRE, IGE, healthy controls) across all cognitive tests was significant; ($F[38,256\ ] = 2.49$, $P < .001$). The univariate results were significant for 13 of 18 measures, with P values ranging from

Table I. Characteristics of controls and epilepsy participants by subsyndrome (mean and SD)

Variable	Healthy controls (n = 72)	BECTS (n = 22)	Focal (n = 31)	JME (n = 26)	Absence (n = 11)
Age (y)	12.86 (3.20)	10.25 (1.40)	11.82 (2.94)	14.62 (3.06)	12.24 (3.46)
Sex (number/% female)	37 (51%)	10 (44%)	14 (45%)	14 (54%)	4 (36%)
FSIQ	107.35 (12.00)	103.00 (14.53)	98.52 (10.90)	101.62 (13.89)	98.18 (11.16)
AP(+/−)	13/58	15/8	16/15	12/14	5/6
Age of seizure onset (y)	-	9.00 (2.41)	10.51 (2.81)	13.21 (4.09)	11.20 (3.52)
Seizure frequency (<1 y, >1 y)	-	4/19	4/27	7/19	3/8
Epilepsy duration (mo)	-	7.22 (4.04)	8.26 (3.56)	8.46 (3.49)	9.73 (3.17)
Antiepileptic drugs (0/1/2+)	-	9/14/0	6/24/1	0/25/1	0/9/2

FSIQ, full scale intelligence quotient.