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Longer duration of epilepsy and earlier age at epilepsy onset correlate with impaired cognitive development in infancy

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ABSTRACT

We assessed the impact of age at onset of epilepsy and duration and frequency of seizures on cognitive development in children less than 3 years old. Retrospective analysis was conducted on clinical data and neuropsychological testing of 33 infants with epilepsy. Developmental quotients were calculated and were correlated with age at epilepsy onset, duration of epilepsy, seizure frequency, brain pathology, and types of seizures (with/without spasms) as potential predictors. Infants with longer duration and earlier onset of epilepsy performed worse on developmental neuropsychological testing. Regression analyses showed that age at epilepsy onset and percentage of life with epilepsy were both strongly associated (regression model $P < 0.0001$) with developmental quotient. There was no correlation with seizure frequency. Infants with spasms had worse developmental quotients than infants without spasms ($P < 0.001$). These results suggest that duration of epilepsy and age at onset may be the best developmental predictors during the first years of life in patients with epilepsy. Early aggressive intervention should be considered.

1. Introduction

It is well recognized that epilepsy may contribute to cognitive impairment in children and adults. Most studies have provided proof that intellectual decline during childhood epilepsy is progressive and may be related to the duration of epilepsy, overall frequency of seizures, and age at epilepsy onset [1–3].

Despite this, almost no information is available regarding cognitive development of children <3 years old in relation to duration of epilepsy and seizure burden. The limited evidence that does exist in this age group is derived from longitudinal studies assessing postinterventional neuropsychological outcome in infants with West syndrome [4–13] and other epilepsies [5–7,10,11,14] (Table 1). Most of these studies have suggested that earlier surgical or medical therapy during infancy may provide higher benefit for intellectual development of children. Seizure freedom may be associated with better mental development [4,10–14]. However, none of these studies have evaluated the effect of epilepsy in terms of duration and seizure burden on cognition during infancy. The current study expands our previous results on neuropsychological outcome in infants [11,15].

Our aim was to evaluate the impact of age at onset and duration and frequency of seizures on the cognitive development of infants (<3 years of age) and to identify the strongest predictors of developmental outcome. This article describes the experience with infancy epilepsy and neuropsychological testing at the Cleveland Clinic and Children's Hospital Boston from 1990 to 2008.

2. Methods

Among all consecutive pediatric patients with epilepsy who underwent neuropsychological testing at the Cleveland Clinic and Children's Hospital Boston between 1990 and 2008, those <3 years old were identified. Of the 59 patients identified, we conducted a retrospective analysis of clinical data and neuropsychological testing (Bayley Scales of Development) [16] of the 33 infants with complete data. Clinical evaluation included EEG monitoring and MRI. Seizures were classified according to the semiological seizure

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Table 1
Studies evaluating mental development in infants with epilepsy.

Study	*n*	Age range (months)	Time of follow-up	Seizure type	Treatment	Neuropsychological testing during infancy	Outcome
Glaze et al.[7]	64	4–12	44–51 months	Spasms and partial seizures	ACTH	Unspecified scales for IQ calculation	Poor mental outcome at follow up
Dulac et al.[6]	45	1–12	2–10 years	Spasms and partial seizures	ACTH, hydrocortisone, and valproate	French Geselladaptation[a]	Poor mental outcome at follow up in patients with persistent seizures
Guzzetta et al.[9]	31	2–18	2 years	Spasms	ACTH and multiple AEDs	Bayley and Uzgiris–Hunt scales	Variable
Asarnow et al. [4]	24	1–8	2 years	Spasms	Surgical	Vineland adaptive behavior scales	Better improvement at follow-up in younger infants
Jambaque et al. [10]	13	0.5–21	4–11 years	Spasms and partial seizures	Vigabatrin	French Gesell adaptation, Terman Merrill and calculated DQ	Improved development at follow-up
Daniel et al. [14]	2	4–9	1–3.5 years	Partial seizures	Surgical	Bartez scales and calculated DQ	Improved development at follow up
Jonas et al. [13]	55	1–50	1.6–2.2 years	Spams	Surgical	Vineland adaptive behavior scales	Improved development at follow up
Loddenkemperet al. [11]	24	3–33	10–53 months	Spasms and partial seizures	Surgical	Bayley scales	Improved development at follow up
Guzzetta et al. [8]	21	2–10	2–2.5 years	Spasms	ACTH, vigabatrin, and multiple AEDs	Griffiths' scales and general quotient (GQ)	Variable
Sharma and Vishwanthan [12]	24	4–20	2 years	Spasms	ACTH	Christian Medical College (CMC) developmental scale	Improved development at follow up
Bombardieri et al. [5]	10	2–11	3–12 years	Spasms and partial seizures	Multiple AEDs	Brunet-Lezine scale (BL) and calculated DQ[b]	Variable

[a] Development assessed only at follow-up.
[b] Development assessed only at follow-up in only one infant.

classification [17]. A developmental quotient was calculated for each case (DQ = Bayley Scales of Infant Development mental age divided by subject's biological age) as previously described [11]. Charts were reviewed retrospectively for DQ testing, age at epilepsy onset, duration of epilepsy, seizure frequency, types of seizures (with/without spasms), and etiology of seizures (with/without malformations of cortical development [MCD]). MCD included cases of focal cortical dysplasia, lissencephaly, and polymicrogyria. MCD were thought to be the cause of epilepsy in these patients as evidenced by correlation with video/EEG findings.

We used standard regression models to assess the associations between DQ and the following predictors: age at epilepsy onset, age (in months), duration of life with epilepsy (in months), percentage of life with epilepsy [18], seizure frequency, lifetime seizures, presence of MCD, and presence of spasms. All terms were initially included in the model, and decisions to reject terms as statistically extraneous were made using likelihood ratio tests and Akiake's information criterion (AIC).

3. Results

3.1. Descriptives

Thirty-three infants (21 boys) with complete data and formal neurodevelopmental evaluation were identified among 59 consecutive patients <3 years of age. Twenty-six were excluded because of incomplete data. Table 2 summarizes the demographic characteristics of the sample. Infants were 3 to 33 months old at the time of neuropsychological testing (average = 15.6, SD = 9.7). Nineteen infants presented with MCD (59.4%), and 13 had epileptic spasms (39%). The average DQ was 0.37 (SD = 0.29), and the average age at epilepsy onset was 4 months (SD = 5.12). Duration of epilepsy spanned 1.5 to 32 months (average = 11.6, SD = 7.5). Additional information on seizures and seizure frequency is outlined in Table 2.

3.2. Regression analysis

The results of the regression analysis determined that either percentage of life with epilepsy or age at epilepsy onset was associated with or predictive of DQ. All other predictors, such as seizure frequency, type of brain pathology, and type of seizures, added no additional information once age at epilepsy onset or percentage of life with epilepsy was accounted for in the model.

Highly significant associations were found in the model with age at epilepsy onset as the only predictor of DQ ($P < 0.0001$), as well as in the model with percentage of life with epilepsy as the sole predictor ($P < 0.0001$) (Table 3). In the model with both age at epilepsy onset and percentage of life with epilepsy as predictors, neither term was significant. This is explained by the high degree of colinearity between age at epilepsy onset and percentage of life with epilepsy (Pearson's correlation coefficient = −0.85). Both predictors therefore carry the same information about DQ, and the regression methods show that only one of these two variables is needed.

The direction of the regression coefficient indicates that DQ rises with increasing age at epilepsy onset and with decreasing percentage of life with epilepsy (Fig. 1). The model with age at epilepsy onset as the only predictor was a slightly better fit (as determined with Akiake's information criterion) than the model with percentage of life with epilepsy as the only predictor. Age at epilepsy onset therefore predicts developmental outcome better than percentage of life with seizures.

Infants with spasms had a significantly lower DQ (average DQ = 0.19) than infants without spasms (average DQ = 0.47) ($P = 0.01$). In contrast, the DQ of infants with MCD did not differ