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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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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], [2] and [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], [5], [6], [7], [8], [9], [10], [11], [12] and [13] and other epilepsies [5], [6], [7], [10], [11] and [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], [11], [12], [13] and [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] and [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 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 significantly from the DQ of infants without MCD (average DQ = 0.39 and 0.37, respectively). No other significant associations were found between seizure frequency, total lifetime number of seizures, presence of MCD, and presence of spasms.

4. Discussion

We describe neuropsychological outcome in infants <3 years of age with epilepsy in relation to age at onset, duration and frequency of seizures, presence or absence of infantile spasms, and underlying etiology of seizures. Lower DQ is associated with earlier onset of epilepsy or with having epilepsy for a greater portion of one's lifetime. Because of the large degree of colinearity between the two predictors, a larger data set is needed to clarify further interrelations between these two factors.

Infants with longer duration of epilepsy and with earlier onset of epilepsy performed worse on developmental neuropsychological testing during the first 3 years of life. Several studies have observed that children with epilepsy who have progressive cognitive deterioration are those affected by poorly controlled epilepsy and/or earlier onset of seizures [1] and [2]. Of those factors, early age at epilepsy onset has been found to be the best predictor of poor prognosis [1].

Other studies have attempted to demonstrate that most cognitive change takes place early in the course of epilepsy based on a critical period of learning and development as well as greater plasticity. Meinardi et al. [3] described a cascadic model of deterioration, in which irreversible developmental regression occurs shortly after the onset of seizures while later intellectual function plateaus, and no changes may be reported on cognitive testing. These findings could explain previous longitudinal studies that have somehow challenged the notion of intellectual deterioration in epilepsy by showing that epilepsy is associated with an early impaired intellectual function but little further deterioration [1], [2], [19] and [20]. Neyens et al. [21] have shown that children between the ages of 6 and 12 with the longest duration of epilepsy had smaller gains in IQ scores when compared with age-matched controls, and those who had epilepsy for no more than 2 years showed an even more modest gain in IQ, supporting the hypothesis that intellectual deterioration likely occurs early in the course of epilepsy. Another consideration is that epilepsy may lead to decreased plasticity.

Longitudinal studies assessing mental development in infants (children <3 years of age) with epilepsy are lacking (Table 1). Few available reports have evaluated the intellectual outcome in infants who have undergone epilepsy surgery [4], [11], [13] and [14]. According to results presented by Daniel et al., neuropsychological performance after surgery was best for

children who underwent surgery at a younger age. Furthermore, increase in DQ after surgery was most prominent in patients undergoing surgery before 12 months of age [11]. The benefit of earlier surgical intervention may be explained by the interruption of intellectual deterioration, improvement in epileptic encephalopathy, and possibly related increased plasticity.

In our series of patients, infantile spasms were associated with developmental delay. Others have shown that control of infantile spasms is associated with better development during infancy and childhood [4], [6], [10], [12], [22], [23], [24] and [25]. In a previous report [11], more frequent spasms in children undergoing early surgical intervention were documented. Infantile spasms usually occur during initial stages of epilepsy and, therefore, may be, at that stage, an indicator of severe future developmental compromise. Our results indicate that the presence of infantile spasms at presentation should urge prompt medical and perhaps surgical intervention. To this effect, Asarnow et al. [4] demonstrated that the 2-year postsurgical developmental outcomes of infants were best for the infants who underwent surgery when they were relatively young and who had the highest level of developmental performance presurgically, again supporting the idea that earlier intervention may halt epileptogenesis-related developmental deterioration.

We found no correlation between developmental outcome and underlying pathology, indicating that intellectual decline may not depend on the presence of specific underlying etiological factors, but may be the result of epilepsy itself. This contrasts with past follow-up and retrospective studies that have shown a subnormal IQ performance at entry into the study and no deterioration of IQ during the following years of epilepsy [1], [2], [19], [20] and [26]. Although the results of these other studies have been interpreted as suggesting that the underlying brain pathology is responsible for the cognitive deterioration associated with epilepsy, all of these

studies started assessing patients several years after the onset of epilepsy. Therefore, as suggested by Neyens [11], the absence of significant IQ loss during follow-up could be due to the fact that these studies evaluated patients during the stable phase after epilepsy onset, while the critical period might have been the years immediately subsequent to epilepsy onset [3].

The results of our study are limited by our one-time point assessment. No longitudinal observations were included. To discern whether epilepsy itself and not the underlying pathology, such as MCD, is the major cause of developmental deterioration, a larger prospective control group with children with MCD without epilepsy would be needed. Thus, a recognized limitation of studies similar to ours is the lack of an appropriate control group. On the basis of our data, we cannot definitively determine whether the developmental delay is based on duration of epilepsy, age at epilepsy onset, underlying pathology, or an additional not-assessed factor. Data acquisition was purely retrospective and may not be representative of the general population of infants with epilepsy because we reviewed only data available at tertiary epilepsy centers with referral and ascertainment biases. As pediatric patients with epilepsy are not routinely provided neuropsychological evaluations, most of the patients included in this study were candidates for epilepsy surgery who received neuropsychological assessment as part of a routine presurgical evaluation. Rather, other young patients with epilepsy were referred for neurodevelopment assessment because of concerns about developmental delay, behavioral difficulties, specific cognitive problems, changes in developmental course, or altered neurobehavioral presentation. Of note, neuropsychological testing remains a source of limited availability and, at times, of limited demand. Thus, the main limitation of this study is related to the fact that patients with epilepsy and typical developmental progression often were not referred for evaluation and likely are not represented in our retrospective sample. In addition, test scores were incomplete for about

50% of patients initially included in the series, possibly further biasing the sample and leaving a small sample size that limits regression model analysis, a method of determining association that should not be confused with causal inference. As in our and others' previous studies [9], [10], [11], [13] and [14], we used the hypothetical construct of the DQ to compare neuropsychological outcomes and relative duration of epilepsy in lifetime percent to compare infants of different ages with one another. Performance on the Bayley Scales of Infant and Toddler Development is essentially a sample of behavior under controlled conditions. As such, there is error involved in this type of behavioral measurement, and children with physical limitations may perform more poorly on the cognitive scale of the Bayley as motor output is often necessary for correct responding. Although a future prospective trial may deliver more precise results, a large number of patients would be necessary to compare different onset times of epilepsy as this variable cannot be controlled in human trials. Furthermore, recruitment of an appropriate control group may be quite challenging in this very young age group.

Taken together, these results suggest that earlier onset of epilepsy and longer relative duration of epilepsy lead to worse developmental outcome during infancy. These results are in line with the notion that early and aggressive intervention may lead to improved developmental outcome. However, our retrospective data set does not allow conclusions on possible direct effects of epilepsy and epileptogenesis on infant development. Further prospective, longitudinal and controlled evaluations are needed to evaluate whether early onset and long-standing epilepsy are detrimental to infantile brain development.

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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, hydro-cortisone, 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
Loddenkemper et 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.

Table 2.

Clinical characteristics of the 33 infants included in the study.

ID	Sex	Age at epilepsy onset (months)	Age at testing (months)	DQ	Epilepsy duration (months)	Epilepsy duration (% lifetime)	Pathology (MCD)[a]	Type of seizure (epileptic spasms)
1	M	0.9	4	0.5	3.07	77.32	+	+
2	M	2	22	0.58	20	90.90	−	−
3	M	0.1	3	0	2.9	96.66	+	+
4	M	1.5	3	0.32	1.53	50.49	+	+
5	M	3.5	19	0.57	15.47	81.54	−	−
6	M	0	3	0	3.53	100	−	+
7	M	1.5	16	0	14.37	90.54	−	+
8	M	0	18	0.43	18.4	100	+	+
9	M	12	32	0.54	20.87	63.49	+	−
10	F	4	8	0.35	4.37	52.21	+	+
11	M	1.5	18	0.39	16.4	91.62	−	−
12	F	1.5	4	0.66	3.07	67.17	−	−
13	F	0	3	0	3.1	100	+	+
14	M	15	18	0.92	3.27	17.89	+	−
15	F	6	19	0.56	13.2	68.75	−	−
16	M	0.15	12	0.23	12.52	98.81	+	+
17	M	1.5	13	0.45	11.47	88.43	+	−
18	F	0	8	0	8.1	100	−	−
19	M	0	5	0.34	5.77	100	+	+
20	M	0	9	0.54	9.03	100	+	−
21	F	10	25	0.87	15	60	+	−
22	M	0.1	10	0.09	10.57	99.06	+	−
23	M	0	7	0	7.6	100	−	−
24	M	0	4	0	4.27	100	−	+
25	M	5	18	0.27	13	72.22	+	+
26	F	12	26	0.66	14	53.84	−	−
27	M	5	29	0.27	24	82.75	+	−
28	M	18	22	1	4	18.18	+	−
29	F	0	29	0	29	100	+	+
30	F	9	31	0.5	22	70.96	−	−
31	F	6	30	0.33	24	80	−	−
32	F	12	28	0.66	16	57.14	+	−
33	F	0.1	9	0.22	8.9	98.88	+	−

a

+, MCD; −, pathology other than MCD.

Table 3.

Regression model with developmental outcome predictors.

Predictor	Coefficient estimate	Confidence interval	*P* value
Age at epilepsy onset	0.04	(0.026, 0.054)	<0.0001
Percentage of life with epilepsy	−0.09	(−0.007,−0.010)	<0.0001

Note. The model with age at epilepsy onset as the only predictor of DQ was highly significant ($P < 0.0001$), as was the model with percentage of life with epilepsy as the sole predictor ($P < 0.0001$).

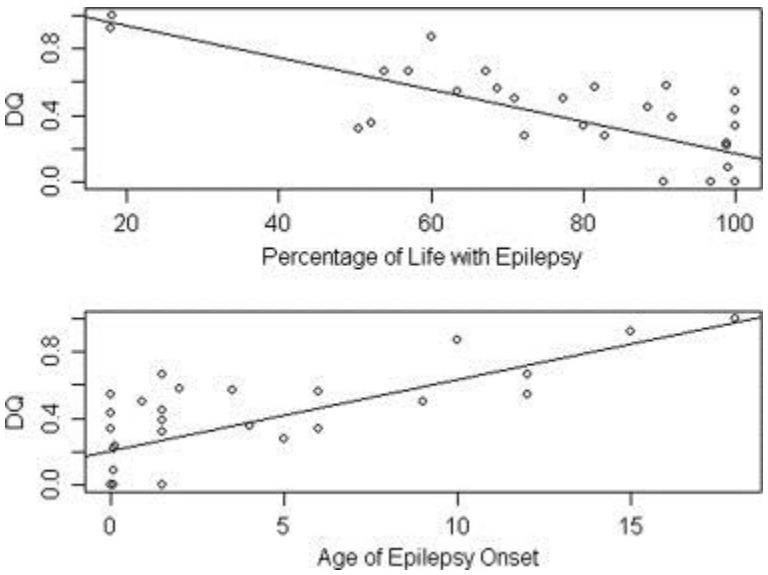

Fig. 1. Regression analysis coefficients for DQ and percentage of life with epilepsy and age at epilepsy onset. The direction of the regression coefficient indicates that the DQ rises with increasing age at epilepsy onset and decreasing percentage life with epilepsy.