Lesion Extent Negatively Impacts Intellectual Skills in Pediatric Focal Epilepsy

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Abstract: BACKGROUND Cognitive development in children and adolescents with focal lesional epilepsy is determined by the underlying epileptogenic lesion, in addition to epilepsy itself. However, the impact of lesion-related variables on intelligence quotient (IQ) and developmental quotient (DQ) remains largely unexplored. Here, we aimed to determine the effect of lesion-related predictors and their relation with epilepsy-related predictors of intellectual functioning. METHODS We retrospectively analyzed data from children with focal lesional epilepsy who underwent standardized cognitive evaluation yielding IQ/DQ in our institution. RESULTS We included 50 consecutive patients aged 0.5 to 17.5 years (mean, 9.3; S.D., 4.9) at cognitive assessment. Epilepsy duration was 0 to 15.5 years (mean, 3.8; S.D., 4.1). Of the total cohort, 30 (60%) patients had unilobar lesions, seven (14%) multilobar, 10 (20%) hemispheric, and three (6%) bilateral. Etiology was congenital in 32 (64%) cases, acquired in 14 (28%), and progressive in four (8%). For patients with unilobar lesions, the mean IQ/DQ was 97.1 ± 15.7, for multilobar 98.9 ± 20.2, for hemispheric 76.1 ± 20.5, and for bilateral 76.3 ± 4.5. Larger lesion extent, earlier epilepsy onset, and longer epilepsy duration correlated with lower IQ/DQ in the univariate analysis, whereas only lesion extent and epilepsy duration contributed significantly to the explanatory model in the multivariable analysis. CONCLUSIONS The present study demonstrates that lesion extent and epilepsy duration are important risk factors for intellectual impairment in pediatric patients with focal lesional epilepsy. These findings are useful for family counseling and the early consideration of interventions that may limit the duration of epilepsy.

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Lesion Extent Negatively Impacts Intellectual Skills in Pediatric Focal Epilepsy

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ABSTRACT

Background: Cognitive development in children and adolescents with focal lesional epilepsy is determined by the underlying epileptogenic lesion, in addition to epilepsy itself. However, the impact of lesion-related variables on intelligence quotient (IQ) and developmental quotient (DQ) remains largely unexplored. Here, we aimed to determine the effect of lesion-related predictors and their relation with epilepsy-related predictors of intellectual functioning.
Methods: We retrospectively analyzed data from children with focal lesional epilepsy who underwent standardized cognitive evaluation yielding IQ/DQ in our institution.
Results: We included 50 consecutive patients aged 0.5 to 17.5 years (mean, 9.3; S.D., 4.9) at cognitive assessment. Epilepsy duration was 0 to 15.5 years (mean, 3.8; S.D., 4.1). Of the total cohort, 30 (60%) patients had unilobar lesions, seven (14%) multilobar, 10 (20%) hemispheric, and three (6%) bilateral. Etiology was congenital in 32 (64%) cases, acquired in 14 (28%), and progressive in four (8%). For patients with unilobar lesions, the mean IQ/DQ was 97.1 ± 15.7, for multilobar 98.9 ± 20.2, for hemispheric 76.1 ± 20.5, and for bilateral 76.3 ± 4.5. Larger lesion extent, earlier epilepsy onset, and longer epilepsy duration correlated with lower IQ/DQ in the univariate analysis, whereas only lesion extent and epilepsy duration contributed significantly to the explanatory model in the multivariable analysis.
Conclusions: The present study demonstrates that lesion extent and epilepsy duration are important risk factors for intellectual impairment in pediatric patients with focal lesional epilepsy. These findings are useful for family counseling and the early consideration of interventions that may limit the duration of epilepsy.

Introduction

Brain lesions in children and adolescents with seizures, commonly focal cortical dysplasias (FCDs), glioneuronal tumors, or perinatal ischemic lesions, correlate strongly with the onset of epilepsy, which often takes a pharmacoresistant course.[1] In addition, brain lesions correlate with impaired cognitive development, which affects the quality of life as much as the seizures themselves.[2] Developmental delay in pediatric lesional epilepsy is commonly attributed to the deleterious effect of recurrent and/or prolonged epileptic seizures and antiseizure medications (ASMs)

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on cognitive networks during sensitive windows of brain development.[3,4] Especially during critical development periods of brain maturation,[5] cognitive skills are put at particular risk by the onset of epilepsy.[3] Cognitive deficits may be noted in relation to focal lesions even in the absence of seizures and may manifest early in the disease.[2,6] Although several epilepsy-related features, such as younger age at epilepsy onset,[5,7-11] longer epilepsy duration,[12-16] higher seizure frequency,[17] and dysplastic etiology,[8,16] have been linked to cognitive impairment in pediatric cohorts, lesion-related features impacting cognitive development in pediatric focal epilepsy, such as lesion extent, lateralization, and lobar localization, remain largely unexplored.

In particular, data on the effect of lesion-related features on intellectual skills as measured with intelligence tests or developmental tests in this patient group is so far sparse and inconsistent,[5,8-10,12,17,18] in some cases stemming from historical cohorts assessed over 20 years ago.[8] Existing studies have drawn (1) on mixed pediatric and adult cohorts[5,17]; (2) on specific pediatric age groups, such as infants and toddlers[12] or preschool children[9]; (3) on specific etiologies such as cortical dysplasia[5,17] and low-grade tumors[19]; and (4) on specific lobar localizations, such as frontal lobe epilepsies,[10] thus limiting the generalizability of their findings. Furthermore, intellectual functioning in these studies has been assessed within the scope of presurgical evaluation for pharmacoresistant epilepsy, thus introducing a bias toward more severe epilepsy courses and higher cognitive impairment rates, which reach 70% in very young children.[12] Studies addressing the crucial etiologic subgroup of FCD, the most frequent substrate of pediatric epilepsy amenable to surgery,[10,13,20,21] have produced contradictory results, supporting a negative impact of widespread lesions on intellectual functioning in one study[5] and excluding such an effect of lesion extent in another.[17]

To assess the distinct impact of epilepsy-related and lesion-related features on intellectual functioning in pediatric lesional epilepsy, we retrospectively analyzed the characteristics of children and adolescents with lesional epilepsy who underwent standardized cognitive evaluation at our institution. Our study aimed to evaluate the interrelations of epilepsy-related features, such as age at epilepsy onset, epilepsy duration, and seizure frequency, and lesion-related features, such as extent, lateralization, and lobar localization, on intelligence quotient and developmental quotient (IQ/DQ) over a wide age range and across a range of underlying etiologies. We hypothesized that younger age at epilepsy onset, longer epilepsy duration, higher seizure frequency, and, most importantly, larger lesion extent correlate with lower intellectual functioning. Our precise delineation of lesion-related and epilepsy-related effects on IQ/DQ can help improve counseling and prognostication and enable the timely introduction of appropriate neuropsychologic therapeutic interventions.

Methods

Patient selection

In this single-center, retrospective cross-sectional study, we selected children and adolescents from our institutional patient registry who underwent a standardized evaluation of cognitive development according to a dedicated epilepsy protocol at the University Children's Hospital Zurich between May 1, 2013, and July 1, 2021. Patients with focal lesional epilepsy in whom standardized evaluation of cognitive functioning was impracticable due to severe developmental impairment, behavioral issues, or language problems were not entered in our institutional patient registry. Inclusion criteria for our study were (1) diagnosis of focal epilepsy; (2) presence of a structural, potentially epileptogenic cortical lesion in magnetic resonance imaging (MRI); and (3) age <18 years at the time of the standardized evaluation of cognitive development. Exclusion criteria were (1) epilepsy attributable to a pathogenic genetic variant, independent of a coexisting cortical lesion, and (2) lacking comprehensive demographic and electroclinical data. All patients underwent thorough clinical evaluation, including medical history, neurological examination, scalp video electroencephalography, and high-resolution MRI. Epilepsy duration was defined as the time passed between epilepsy manifestation and enrollment for this study. Seizure frequency was assessed by long-term video electroencephalography or seizure diaries at the time of the cognitive and developmental evaluation and categorized as "none," "daily or weekly," and "monthly or yearly" seizures. Pharmacoresistant patients had failed trials of two tolerated and appropriately chosen and used ASM schedules to achieve sustained seizure freedom,[22] whereas pharmacoresponsive patients had remained seizure-free for a year or longer. None of the patients had undergone epilepsy surgery at the time of data acquisition.

The collection of patient data and the scientific analysis were approved by and performed according to the guidelines and regulations of the local ethics committee (Kantonale Ethikkommission Zürich, KEK-ZH PB-2022-00199). All patients and their caregivers gave written informed consent.

Evaluation of lesion characteristics

3T MRI scans, including T1, T2, and fluid-attenuated inversion recovery sequences, were retrospectively reviewed by an experienced radiologist (A.G.G.) with epileptology expertise together with an experienced pediatric neurologist and epileptologist (G.R.) to define (1) the extent, lateralization, and lobar localization of the lesions; and (2) the radiologic properties supporting the etiologic classification of the lesions.[23-25] Discrepancies were resolved by consensus. Lesion extent was classified as "unilobar"; "multilobar," including lesions extending over more than one lobe in one hemisphere irrespective of the lobes involved; "hemispheric"; and "bilateral," in line with our previous work.[12] Unilobar and multilobar lesions were visually classified according to their extent into "small" or "medium-to-large" lesions. Small lesions were defined as those with a width of two or fewer gyri, including the sulcus between the two gyri, and a length of less than half of the gyri. Medium-to-large lesions included all lesions deemed larger than small lesions. Lesion lateralization was classified as "left," "right," and "bilateral." Among unilobar lesions, lobar localization was classified as "frontal," "temporal," and "posterior," including parietal and occipital lesions. Lesion etiology was defined according to radiologic diagnosis in all cases and verified by histopathology in patients who had later undergone resective epilepsy surgery ($n = 21$). Etiology was classified as "acquired," "progressive," or "congenital."

Evaluation of intellectual skills

Intellectual functioning was evaluated with standardized tests yielding full-scale intelligence quotient (FSIQ) or DQ. Intelligence tests were performed by clinical neuropsychologists, and developmental tests were administered by specialists in developmental pediatrics. We selected the appropriate test for each patient according to developmental level and chronological age. We considered a single evaluation in patients who had undergone multiple testing. To assess the FSIQ, the most current German version of the Wechsler Intelligence Scales was administered in 37 cases (Wechsler Preschool and Primary Scale of Intelligence-III[26] in two, Wechsler Preschool and Primary Scale of Intelligence-IV[27] in one, Wechsler Intelligence Scale for Children-IV[28] in 12, Wechsler

Intelligence Scale for Children-V[29] in 19, Wechsler Adult Intelligence Scale-III[30] in one, Wechsler Adult Intelligence Scale-IV[31] in two). To assess the DQ, the cognitive composite score from the Bayley Scales of Infant Development III3[32] was administered in nine cases, and the revised Snijders-Oomen Nonverbal Intelligence Test (SON-R) was administered in four cases (SON-R 2½-7[33] in two and SON-R 2-8[34] and SON-R 6-40[35] in one each) where applying the Wechsler Intelligence Scales was impracticable due to language issues. The comparability of these tests is supported by studies reporting their high correlation and validity.[36-38] We considered the FSIQ from the Wechsler Scales, the cognitive domain score from the Bayley Scales, and the SON-IQ from the SON-R test. We classified the intellectual skills of the children tested as above the average range (>115 IQ/DQ), within the average range (85 to 115 IQ/DQ), mildly impaired (70 to 84 IQ/DQ), moderately impaired (50 to 69 IQ/DQ), or severely impaired (<55 IQ/DQ).

Statistical analysis

We conducted the statistical analysis using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). We reported continuous variables by mean ± S.D. and categorical variables by absolute numbers and percentages. We set statistical significance at $P < 0.05$.

To determine the impact of lesion-related and epilepsy-related predictors on IQ/DQ, we first conducted univariate analyses investigating the association between the dependent continuous variable IQ/DQ and the independent variables of age at epilepsy onset, epilepsy duration, lesion extent, lesion lateralization, lesion localization among unilobar lesions, etiology, and seizure frequency. We investigated lesion extent as an ordered factor, assuming that multilobar is larger than unilobar, hemispheric is larger than multilobar, and bilateral is larger than hemispheric. Next, we examined the variables for collinearity using a heterogeneous correlation matrix for continuous and categorical variables with a collinearity correlation threshold of $r > 0.5$.[39] We evaluated continuous variables with Spearman correlation and categorical variables with the Wilcoxon rank-sum test for two categories and the one-way analysis of variance for more than two categories. We then applied the posthoc Tukey honest significant differences test to assess the significance of differences between pairs of group means. We controlled for multiple testing, correcting for the false discovery rate with the Benjamini-Hochberg procedure.[40,41] Finally, we conducted a multivariable analysis using a bidirectional stepwise multiple regression model, including lesion extent, epilepsy duration, age at epilepsy onset, seizure frequency, lesion lateralization, and etiology. We then selected the most meaningful, candidate-independent variables contributing to the best-fitted model according to the Akaike information criteria.[42]

Results

Medical history

Of 55 consecutive children who underwent a standardized evaluation of cognitive functioning in our institution, 50 were selected for this study and five were excluded: two due to epilepsy attributable to a pathogenic genetic variant and three due to lacking demographic or electroclinical data. Our study cohort thus consisted of 50 consecutive children and adolescents (24 female) aged 0.5 to 17.5 years (mean, 9.3; S.D., 4.9) at the evaluation of cognitive development. Age at epilepsy onset was 0 to 14.3 years (mean, 5.4; S.D., 4.2): 12 (24%) children had their first seizures in the first year of life. Epilepsy duration was 0 to 15.5 years (mean, 3.8; S.D., 4.1): 17 (34%) children had suffered epileptic seizures for less than or equal to one year. Mean epilepsy duration was the shortest in unilobar lesions (mean, 3.0 years; S.D., 3.2) and the longest in bilateral lesions (mean, 6.3 years; S.D., 4.5).

Seizure frequency per month ranged from 0 to 3000 (mean, 138; S.D., 457): 17 patients (34%) were seizure-free, 23 (46%) patients suffered daily or weekly seizures, and 10 (20%) had monthly or yearly seizures. Overall, 27 (54%) patients were pharmacoresistant, whereas 17 (34%) patients were pharmacoresponsive, two even after ASM withdrawal. Patients received zero to four ASM treatments (mean, 1.7; S.D., 0.8) at the evaluation of intellectual functioning; two patients received no ASM, 19 one, 23 two, and six more than two ASM treatments. ASM treatment regimens were highly variable among patients. Fifteen had a history of status epilepticus. None of the patients was diagnosed with spike-and-wave activation in sleep[42] or with epilepsy syndromes such as Landau-Kleffner syndrome or Lennox-Gastaut syndrome[43] at the evaluation of cognitive development. Of the 50, two (4%) had a history of West syndrome, and 21 of 50 (42%) patients in our cohort eventually underwent resective epilepsy surgery.

Lesion characteristics

Etiology was classified as (1) *congenital* in 32 (64%) cases, including 20 with malformations of cortical development (16 with FCD, three with polymicrogyria, and one with hemimegalencephaly), 10 with low-grade tumors, and two with tuberous sclerosis; (2) *acquired* in 14 (28%) cases, including seven with scars (six with perinatal ischemic stroke or hemorrhage and one with hemiconvulsion-hemiplegia syndrome), four with hippocampal sclerosis, and three with cavernomas; and (3) *progressive* in four (8%) cases, including two cases each with Sturge-Weber syndrome and Rasmussen encephalitis. Of the lesions, 30 (60%) were left-sided, 17 (34%) were right-sided, and three (6%) were bilateral. Of the patients, 30 (60%) had unilobar lesions, seven (14%) multilobar, 10 (20%) hemispheric, and three (6%) bilateral. Among unilobar lesions, 13 were frontal, 12 were temporal, and five posterior. Of 30 (90%) unilobar lesions 27 were deemed small and only three (10%) were deemed medium to large, whereas five of seven (73%) multilobar lesions were deemed medium to large and only two (27%) were deemed small (Supplementary Table 1).

Intellectual skills

Neuropsychologic and developmental evaluation revealed intellectual functioning above the average range (>115 IQ/DQ) in four (8%) children, within the average range (85 to 115 IQ/DQ) in 31 (62%) children, and below the average range (<85 IQ/DQ) in 15 (30%) children: nine were mildly impaired (70 to 84 IQ/DQ) and the remaining six were moderately or severely impaired (<70 IQ/DQ).

Figure 1 shows the IQ/DQ distribution in our cohort among the four lesion extent categories.

The mean IQ/DQ differed significantly between the four lesion extent categories (analysis of variance, $F = 5.002$, $P = 0.01$ Table). Patients with hemispheric lesions presented significantly lower mean IQ/DQ (76.1 ± 20.5) than patients with unilobar (97.1 ± 15.7; $P = 0.01$) and multilobar (98.9 ± 20.2; $P = 0.05$) lesions, whereas the mean IQ/DQ did not differ significantly between patients with unilobar and multilobar lesions (posthoc Tukey honest significant differences test, Fig 2). This analysis did not consider patients with bilateral lesions (mean IQ/DQ: 76.3 ± 4.5) due to the small (n = 3) subgroup size.

Lower IQ/DQ was related to earlier epilepsy onset (Spearman correlation, $\rho = 0.29$, $P = 0.048$, Fig 3A) and longer epilepsy duration (Spearman correlation, $\rho = -0.28$, $P = 0.048$; Fig 3B).

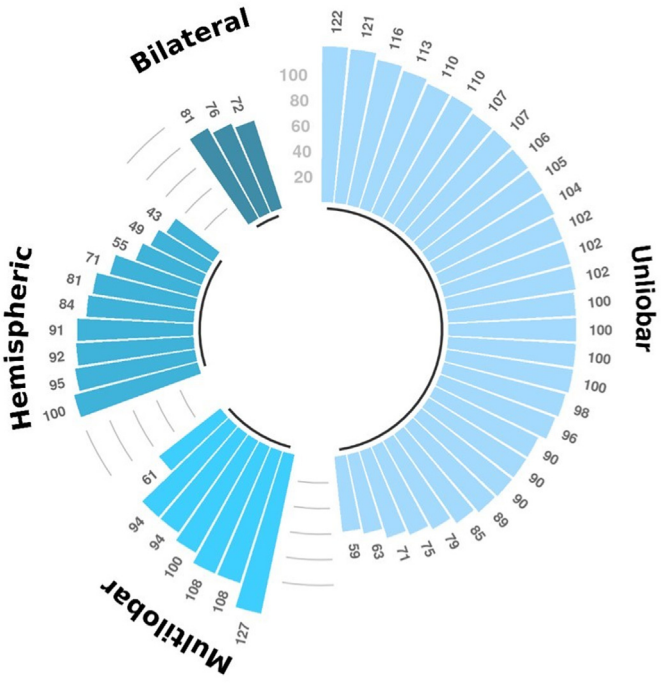

Figure 1. Intelligence quotient and developmental quotient (IQ/DQ) distribution in our cohort among the four lesion extent categories. Circular bar plot depicting the IQ/DQ for each patient as classified into the four lesion extent categories: unilobar, multilobar, hemispheric, and bilateral. The color version of this figure is available in the online edition.

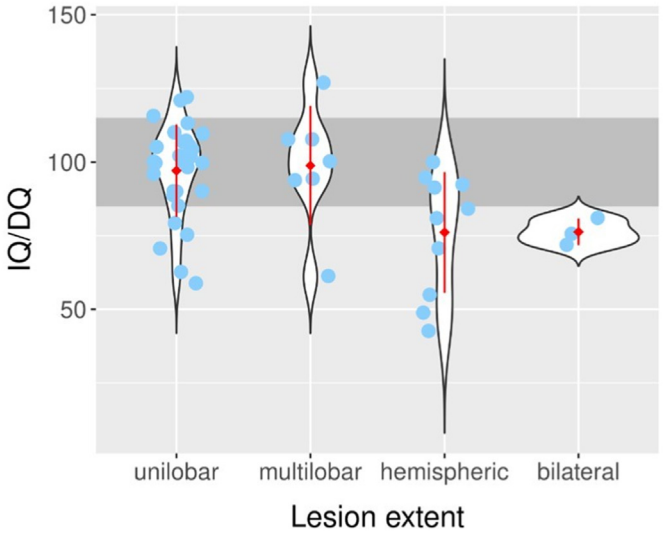

Figure 2. Lesion extent determines lower intelligence quotient and developmental quotient (IQ/DQ). Violin plot presenting the mean IQ/DQ values (red dot), the S.D. (red vertical line), and the distribution of IQ/DQ values in our cohort (blue dots) in relation to lesion extent, categorized as unilobar (N = 30), multilobar (N = 7), hemispheric (N = 10), and bilateral (N = 3). The average IQ/DQ range (85 to 115 IQ/DQ) is depicted in dark gray. Larger lesion extent determines lower IQ/DQ values (one-way analysis of variance: F = 5.002, $P = 0.01$). The posthoc Tukey honest significant differences test revealed significantly lower IQ/DQ in patients with hemispheric lesions than in unilobar ($P = 0.01$) and multilobar ($P = 0.05$) lesions. In contrast, IQ/DQ did not differ significantly between patients with unilobar and multilobar lesions. The color version of this figure is available in the online edition.

No significant effect was found of lesion lateralization, lobar localization (among unilobar lesions), seizure frequency, or etiology on IQ/DQ. The univariate analyses after correction for multiple comparisons are summarized in Table.

We refrained from analyzing the effect of ASM on intellectual functioning due to the heterogeneity in the type and number of ASM treatments among our patients and the relatively small size of our cohort.

Among the variables investigated in the multivariable analysis, which comprised lesion extent, epilepsy duration, age at epilepsy onset, seizure frequency, lesion lateralization, and etiology, the bidirectional stepwise multiple regression model selected lesion extent and epilepsy duration as the variables contributing to the best-fitted model according to the Akaike information criteria (F = 4.623, $P = 0.003$), with lesion extent remaining significant ($P = 0.03$), in contrast to epilepsy duration ($P = 0.10$).

Table
Impact of Clinical Features and Lesion Characteristics on IQ/DQ

Clinical Variables (n, %)	Mean IQ/DQ ± S.D. (Range)	*P* Value
Age at epilepsy onset*	–	0.048§
Epilepsy duration*	–	0.048§
Lesion extent†	91.9 ± 19.0 (43-127)	0.01§
Unilobar (30, 60%)	97.1 ± 15.7 (59-122)	
Multilobar (7, 14%)	98.9 ± 20.2 (61-127)	
Hemispheric (10, 20%)	76.1 ± 20.5 (43-100)	
Bilateral (3, 6%)	76.3 ± 4.5 (72-81)	
Lesion lateralization‡	–	0.51
Left (30, 60%)	91.2 ± 19.3 (49-127)	
Right (17, 34%)	95.9 ± 19.1 (43-122)	
Lobar localization (30, 60%)†	97.1 ± 15.7 (59-122)	0.85
Frontal (13, 26%)	96.3 ± 18.2 (63-122)	
Temporal (12, 24%)	96.3 ± 14.9 (59-116)	
Posterior (5, 10%)	100.8 ± 12.5 (79-110)	
Etiology†	–	0.62
Acquired (14, 28%)	88.4 ± 22.3 (43-122)	
Congenital (32, 64%)	94.4 ± 17.8 (55-127)	
Progressive (4, 8%)	83.5 ± 15.8 (61-95)	
Seizure frequency†	–	0.09
None (17, 34%)	93.4 ± 20.3 (49-122)	
Daily or weekly (23, 46%)	91.4 ± 15.3 (55-116)	
Monthly or yearly (10, 20%)	90.5 ± 25.7 (43-127)	

Abbreviations:
DQ = Developmental quotient
IQ = Intelligence quotient
Correction for multiple comparisons was performed by applying the Benjamini-Hochberg procedure.
* Spearman correlation.
† One-way analysis of variance.
‡ Wilcoxon rank-sum test.
§ $P < 0.05$.

Discussion

This is the largest pediatric-specific study to address the impact of both lesion-related and epilepsy-related predictors of cognitive development in focal lesional epilepsy. Our study found that a larger epileptogenic lesion and a longer epilepsy duration negatively impacted IQ/DQ. In addition to guiding prognostic counseling, our observations support guidelines promoting the timely initiation of targeted therapeutic interventions, including early epilepsy surgery in appropriate candidates.[44]

Larger lesion extent negatively impacts intellectual skills

Our study demonstrates that the severity of cognitive impairment relates to lesion extent in pediatric focal lesional epilepsy. In particular, children with larger hemispheric lesions were more likely to have lower IQ/DQ than those with unilobar or multilobar lesions. Our findings thus verify the adverse effect suggested[5,8-10,12,18] of lesion extent on intellectual functioning in

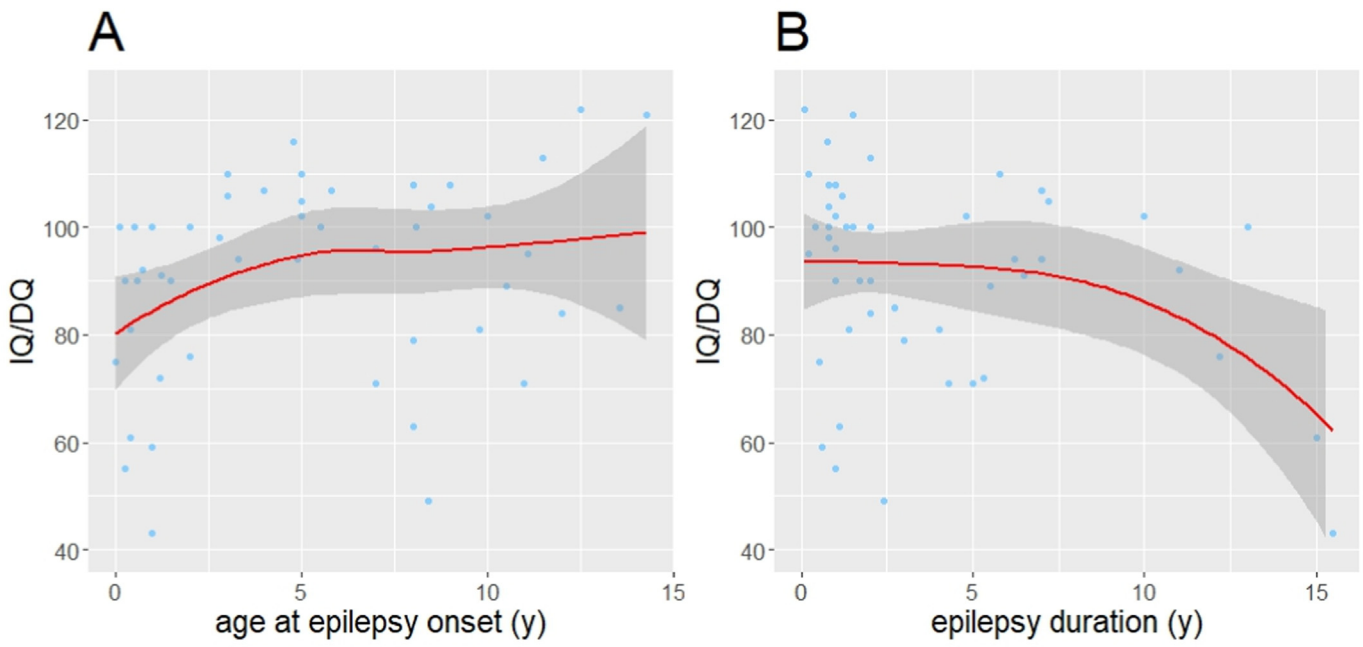

Figure 3. Earlier epilepsy onset and longer epilepsy duration determine lower IQ/DQ in the univariate analysis. (A) Scatterplot of IQ/DQ in relation to age at epilepsy onset (Spearman correlation, $\rho = 0.29$, $P = 0.048$). (B) Scatterplot of IQ/DQ in relation to epilepsy duration (Spearman correlation, $\rho = -0.28$, $P = 0.048$). The red line represents the smoothed fitted curve of the data points, and the dark gray field is its confidence interval. The color version of this figure is available in the online edition.

a purely pediatric contemporary cohort representative of (1) the pediatric age range from early life through to adolescence; (2) different underlying etiologies, including the prevailing pediatric substrates of cortical malformations and low-grade tumors in the majority of cases; and (3) variable lobar localizations and extents of affected tissue. Our observations underline the impact of lesion extent on cognitive trajectories, in contrast to a previous study reporting no effect of lesion extent on intellectual functioning.[17] However, that previous study investigated a purely adult cohort with exclusively FCD-associated epilepsy and a predominance of 91% unilobar lesions,[17] thus limiting the relevance of those findings for pediatric populations with lesional epilepsy.

Beyond corroborating previous studies, our findings extend their observations from the subset of pharmacoresistant patients undergoing presurgical evaluation[5,8-10,12] to the overall pediatric population presenting with focal lesional epilepsy over the course of their disease, including pharmacoresistant and pharmacoresponsive cases in roughly equal parts. Our study considered cases across the pediatric age range with 54% pharmacoresistence and 12% severely impaired intellectual functioning; interestingly, this negative impact of lesion extent on IQ/DQ is consistent with previous studies that evaluated infants and preschoolers with 100% pharmacoresistence and 58% to 70% severely impaired cognitive development.[9,12] The extent of affected brain tissue plays a significant role in cognitive development by limiting the available resources throughout the disease, resulting in deficits often apparent at epilepsy onset[6] even before the secondary adverse effects of seizures or ASM. Thus, the disruption of network function by extensive epileptogenic tissue will result not only in seizure generation but also in cognitive disturbance,[45] particularly during crucial stages of brain development,[3,46] suggesting a relation between widespread networks involved in epileptogenesis and basic cognitive functions.[5]

Other lesion-related variables, such as lesion lateralization, lobar localization, and etiology, had no significant impact on IQ/DQ in our pediatric lesional epilepsy cohort. Indeed, only two past studies have shown marginally lower intellectual functioning in children with left-hemispheric lesions than in those with right-hemispheric lesions,[16] with this discrepancy concerning only verbal measures in one study.[8] Furthermore, no significant variation in intellectual functioning with lobar localization has been noted in lesional epilepsy in pediatric[16] or adult cohorts.[17] In line with these studies, our results suggest that intellectual impairment in focal lesional epilepsy results from dysfunctions of the entire neural network rather than localized disruptions.[17,45,47] However, these findings are derived from global measures of cognition, such as IQ tests, rather than from tests measuring a particular cognitive domain, such as language. Domain-specific tests might have provided a more detailed insight into the impact of lesion lateralization and lobar localization on cognitive functioning. Finally, low-grade tumors have been associated with higher intellectual functioning than have FCD and other etiologies,[8,16] and acquired and progressive etiologies have been related to less severe developmental impairment than congenital etiologies.[21,48] Although intellectual functioning did not differ by etiology in our cohort, identifying etiology-specific effects requires more extensive and homogeneous datasets than the one available here.

Longer epilepsy duration negatively impacts intellectual skills

Our study demonstrates that the severity of intellectual impairment relates to longer epilepsy duration in pediatric focal lesional epilepsy. The deleterious effect of longer epilepsy duration on cognitive trajectories has been suggested for (1) specific pediatric age groups, such as infants and toddlers[12,49]; (2) specific etiologies, such as low-grade tumors[14]; and (3) specific lobar localizations, such as frontal lobe epilepsies,[10] thus limiting the generalizability of these findings. Here, we verify and extend these observations to a contemporary pediatric cohort representative of the pediatric age range, various underlying etiologies, and variable lesion characteristics. Furthermore, we broaden the applicability of our findings from the well-studied subset of pharmacoresistant patients undergoing presurgical evaluation[10,12,14] to the overall

pediatric population with focal lesional epilepsy, including pharmacoresponsive cases. The impact of longer epilepsy duration may partly be attributed to the prolonged exposure to seizures and ASMs with their detrimental effects on developmental trajectories during a particularly vulnerable period of brain development.[12,46,50]

Conversely, shorter epilepsy duration due to successful early intervention, such as epilepsy surgery, allows affected children to benefit from unobstructed learning through sensitive periods of cognitive development.[12,50] Indeed, epilepsy duration has been identified as one of the few modifiable predictors of postsurgical cognitive development,[9,10,12,14-16,51,52] highlighting the importance of early intervention for optimal cognitive outcomes. However, although timely intervention to end diffuse epileptiform activity and disabling seizures arising from a focal lesion can be essential for resuming cognitive development,[53] shorter epilepsy duration will not entirely alleviate the cognitive deficits associated with extensive cortical pathology,[5,12] as corroborated by our findings. The extent of affected brain tissue may impact the developmental trajectories by limiting the available resources and the potential for functional plasticity. Thus, a child with a large lesion extent is likely to have diminished intellectual skills regardless of the epilepsy duration, and the damage to the developing brain may not be undone even by successful early intervention with full seizure control.[53]

Finally, our study revealed a negative impact of earlier epilepsy onset on IQ/DQ in a univariate analysis, in line with previous observations in pediatric focal epilepsy.[5,7-11,49] However, this impact did not retain its significance in a multivariable analysis. This effect may be partly attributed to the comparatively late epilepsy onset in our cohort, with two-thirds of patients presenting their first seizure after age three years, in contrast to cohorts with epilepsy onset predominantly in the first year of life.[7,9,49] The network maturation processes that enable the acquisition of intellectual skills are particularly profound and widespread during early development and thus particularly vulnerable to disruption by seizures following the onset of lesional epilepsy.[3,5] Focal lesions, especially if occurring early in life, can affect networks and thus disrupt the development of adjacent and remote brain regions, affecting higher-level and later-developing cognitive skills. Although our study found that seizure frequency had no significant impact on IQ/DQ, consistent with past observations,[5,9,12] findings so far have been contradictory, with single studies indicating a deleterious effect of seizure frequency on intellectual functioning.[17] This discrepancy may be attributed to the course of epilepsy, which is characterized by fluctuations, with transient seizure-free periods typically marked by a decreased risk of intellectual impairment, even with earlier seizure onset and longer disease duration.[16,17]

Limitations

Our study has several limitations. First, it is a retrospective, single-center study with all the inherent limitations of this study design. Although some of the variables investigated did not prove significant in the multivariable analysis, the relatively small sample sizes per group, particularly of bilateral lesions, may have obscured effects to be uncovered in future multicentric studies. However, our findings derive from a large cohort extending across the pediatric age range and across various levels of cognitive development, including diverse underlying etiologies. This breadth supports the representativity of our findings for the pediatric population with lesional epilepsy. Second, we analyzed data derived from a wide range of intelligence and developmental tests selected according to patient age, cognitive abilities, and test version availability, and this test variability interfered with comparability between groups. However, in contrast to previous studies,[12] our findings are based on a standardized evaluation of cognitive development rather than a global clinical impression, with a strong correlation between the Bayley Scales of Infant Development and Wechsler test results.[36] Third, our study did not assess the potential adverse effects of ASMs on cognitive development.[54] Nevertheless, previous observations of the role of ASMs have been contradictory, with some studies indicating that ASM side effects are inconsequential compared with epilepsy-related predictors[55] and other studies finding a negative impact of ASMs on cognitive development.[56]

Conclusion

The present study demonstrates that lesion extent and epilepsy duration are important risk factors for intellectual impairment in pediatric patients with focal lesional epilepsy. Our findings are useful for the prognostic counseling of patients and their families and, most importantly, for the timely initiation not only of neuropsychologic therapeutic interventions but also of surgical treatment in selected candidates. Nonetheless, further studies in larger multicentric contemporary cohorts are needed to delineate the impact of lesion extent and other lesion-related factors as predictors of IQ/DQ in affected children and adolescents.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2023.05.005.

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