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INVITED REVIEW

Paediatric epilepsy and cognition

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Abstract

Cognitive comorbidities are more frequent in children with epilepsy than in the general population. The cognitive function of children with epilepsy should be appropriately screened, and when there is an impairment, it must be diagnosed and managed. Several factors contribute to the occurrence of this comorbidity. The underlying aetiology and epilepsy syndrome are the major risk factors. Other factors also play a role, such as seizure recurrence, antiseizure medication, and interictal abnormalities. Recent evidence also suggested that cognitive involvement is an ongoing process that interacts with the normal maturation of cognitive function in children with epilepsy. Furthermore, some patients experience rapid cognitive deterioration related to epileptic activity, resulting in epileptic encephalopathy. Further research is needed to better understand how to prevent or modify factors that affect cognitive function in children with epilepsy.

Epilepsy in children and adolescents is a heterogeneous group of disorders with a prevalence between 0.5% and 0.8%. Recurring seizures are only part of the consequences of epilepsy. Comorbidities should be considered from diagnosis to the daily management of children with epilepsy. There are many diverse psychiatric and cognitive comorbidities, which differ greatly according to the epilepsy syndrome. The occurrence of epilepsy in children affects the brain during development, with a higher risk of long-term consequences.

Cognitive impairment can be observed before diagnosis or become obvious after the diagnosis of epilepsy. In cases of epileptic encephalopathy, the epileptic activity itself contributes to severe cognitive and behavioural impairments above and beyond what could be expected from the sole underlying cause of epilepsy (e.g. cortical malformation); it usually worsens over time.[1] The encephalopathic effects of seizures and interictal epileptiform abnormalities may be associated with any form of epilepsy. The term 'epileptic encephalopathy' is often used inappropriately for all neurological disorders with severe features, such as drug-resistant seizures and severe cognitive dysfunction.[2]

Cognitive impairment in children with epilepsy should be appropriately screened, diagnosed, and managed because it can affect the academic performance and quality of life of patients and their families. Cognitive level is not the only factor that contributes to academic performance. In children with epilepsy, academic difficulties are more frequent than in the general population and might be observed in children with an IQ in the normal range.[3]

Several factors contribute to cognitive impairment in children with epilepsy. At first glance, the underlying aetiology is the main contributor to cognitive function. This is particularly the case when there are severe cortical development disorders, such as lissencephaly, or a chromosomal disorder, such as chromosome 21 trisomy. However, it is more complicated when there is no evidence of an underlying aetiology. Several factors are involved in the cognitive impairment of children with epilepsy, such as seizure recurrence, antiseizure medication (ASM), and interictal abnormalities. The concept of epileptic encephalopathy has been used to describe the cognitive and behavioural impact of seizure recurrence and/or epileptiform abnormalities beyond what might be expected from the underlying pathology. The International League Against Epilepsy defined the concept of developmental and epileptic encephalopathy (DEE) when, in addition to epileptic

Abbreviations: ASM, antiseizure medication; DEE, developmental and epileptic encephalopathy; IED, interictal epileptiform discharge.

encephalopathy, a developmental component contributes to cognitive impairment.[4] The use of these terms (epileptic encephalopathy/DEE) has an impact on treatment management because seizure control alone would not improve cognition when it is predominantly a developmental encephalopathy, whereas seizure control should be maximized when epileptic encephalopathy is predominant in cognitive impairment.

In this narrative review, the incidence and risk factors of cognitive impairment in paediatric epilepsy are described. Also, discussed are the contributions of interictal abnormalities and ASM on cognitive function. Finally, the evidence for cognitive involvement as an ongoing process in children with epilepsy, interacting with the normal maturation of cognitive function, and the possible mechanisms of cognitive deterioration in epileptic encephalopathy is assessed.

INCIDENCE OF INTELLECTUAL DISABILITY IN CHILDREN AND ADOLESCENTS WITH EPILEPSY

Few studies have evaluated the incidence of abnormal cognitive levels in children with epilepsy. Using the IQ score to evaluate the incidence of intellectual disability in paediatric patients with epilepsy, the incidence in population-based studies varies by approximately 25% in children.[5–13] This proportion of cognitive impairment has been observed in several prospective cohorts of children with epilepsy (Table 1).

What this paper adds

- Cognitive comorbidities are more frequent in children with epilepsy than in the general population.
- The risk factors for cognitive impairment are the underlying aetiology/syndrome, seizure recurrence, antiseizure medication, and interictal abnormalities.
- Advanced genetic and neuroimaging studies are useful tools to better understand cognitive impairment in children with epilepsy.

RISK FACTORS FOR COGNITIVE IMPAIRMENT IN PAEDIATRIC EPILEPSY

Intellectual disability is common in children with epilepsy. Epidemiological and case–control studies have helped identify the risk factors for cognitive impairment (Table 2).

Age at epilepsy onset is an important risk factor for intellectual disability. In a study using presurgical assessment data from children with temporal lobe epilepsy, a significant correlation was observed between age at onset and IQ, while the duration of epilepsy did not correlate with IQ, suggesting that the timing of the impact on the developing brain is more important than the disease duration.[14] Age at onset before the age of 1 year was more significantly associated with

TABLE 1 Summary of the population-based and epidemiological studies reporting the proportion of intellectual disability in children with epilepsy

Study	Children with epilepsy, *n*	Prevalence of paediatric epilepsy	Proportion with intellectual disability	Comments
Cowan et al.[7]	1159	4.7 per 1000	15% intellectual or developmental disability	
Sidenvall et al.[8]	155	4.2 per 1000	21%	Prevalence of children with epilepsy and intellectual disability: 1.7 per 1000. Mild intellectual disability: 0.3 per 1000; severe intellectual disability: 1.4 per 1000
Eriksson and Koivikko[9]	329	3.94 per 1000	33%	39% male, 25% female
Kurtz et al.[10]	124	8.4 per 1000	27% neurological impairment	
Waaler et al.[11]	198	5.1 per 1000	38.9%	Prevalence of children with epilepsy and intellectual disability: 2.0 per 1000
Camfield and Camfield[12]	692	NA	21%	
Berg et al.[5]	613	NA	26.4%	Mild intellectual disability 3.4%; severe intellectual disability 17.9%
Geerts et al.[6]	413	NA	27.1%	
Sokka et al.[13]	289	38 per 100 000 cumulative incidence	35%	Mild intellectual disability 11%; moderate intellectual disability 8%; severe intellectual disability 16%

Abbreviation: NA, not applicable.

TABLE 2 Summary of risk factors for cognitive impairment in children with epilepsy

Study	Methods	Population	Risk factors	Findings
Kolk et al.[17]	NEPSY in three groups	*n*=18 congenital hemiparesis (abnormal neuroimaging) and focal epilepsy; *n*=12 newly diagnosed focal epilepsy; *n*=14 typically developing controls	Abnormal MRI in the case of hemiparesis and epilepsy vs focal epilepsy	Children with hemiparesis and epilepsy showed more severe dysfunction than those with newly diagnosed epilepsy **Hemiparesis + epilepsy** **Epilepsy** ***p*** **Mean** **SD** **M** **SD** Auditory analysis of speech −1.78 1.21 −1.5 1.5 0.03 Digit span −1.35 1.2 0.3 0.67 0.02 Delayed recall of names −0.93 1.2 0.22 0.44 0.04
Cormack et al.[14]	Preoperative neuropsychological test (Wechsler scale) of children with unilateral TLE Association between the intellectual function and clinical variables was analysed	*n*=79 children with TLE	Age at onset Sex Duration of epilepsy Seizure frequency TLE seizure lateralization TLE pathology type	Significant correlations between age at onset and both Full-scale IQ (*n*=68, ρ=0.393, *p*=0.001) and intellectual function category (ρ=0.52, $p<0.001$) No correlation No correlation No correlation No correlation No correlation
Berg et al.[5]	Population-based study, multivariable logistic regression model	*n*=613 children enrolled prospectively	Age <5 years Remote symptomatic aetiology Epileptic encephalopathy <5 years seizure-free Current ASM treatment	**Bivariate RR (95% CI), *p*** **Adjusted RR (95% CI), *p*** 2.89 (2.14–3.90), <0.001 1.92 (1.40–2.63), <0.001 4.22 (3.30–5.40), <0.000 2.36 (1.74–3.20), <0.001 4.01 (3.26–4.93), <0.001 1.30 (1.07–1.59), 0.01 2.96 (2.16–4.07), <0.001 1.34 (0.83–2.15), 0.23 3.22 (2.40–4.32), <0.001 1.87 (1.33–2.62), <0.001
Fastenau et al.[15]	Large, prospective, community-based study at the time of first seizure compared to siblings; multivariate analysis of risk factors	*n*=282	Multiple seizures (i.e. second unprovoked seizure) Use of antiseizure medication Symptomatic/cryptogenic aetiology Epileptiform activity on the initial EEG	OR = 1.96 (95% CI 1.46–3.331) OR = 2.27 (95% CI 1.35–3.84) OR = 2.15 (95% CI 1.29–3.56) OR = 1.90 (95% CI 1.15–3.12)
Sokka et al.[13]	Population-based retrospective registry of children with epilepsy	*n*=289 with 192 with psychological assessment; cognitive impairment in 101 out of 192	Sex Epilepsy syndrome Aetiology	No difference Most frequent syndrome with cognitive impairment: West syndrome in 25 out of 101 Most frequent aetiologies with cognitive impairments: epilepsy with malformations of cortical and brain development in 16 out of 101 (+8 in the group with West syndrome); epilepsy with perinatal insult in 15 out of 101 (+3 in the group with West syndrome); chromosomal or genetic disorders in 17 out of 100 (+5 in the group with West syndrome)

Abbreviations: ASM, antiseizure medication; CI, confidence interval; EEG, electroencephalogram; MRI, magnetic resonance imaging; NEPSY, A Developmental NEuroPSYchological Assessment; OR, odds ratio; RR, relative risk; TLE, temporal lobe epilepsy.

intellectual dysfunction; age at onset after the age of 5 years had a lower risk of intellectual dysfunction compared to the study population.[14]

Several major risk factors have been identified, such as epilepsy syndrome, the underlying aetiology of epilepsy, age at disease onset, and response to ASM.[5] A multivariate analysis conducted in a community-based prospective study that included children at the time of the initial diagnosis of epilepsy allowed the identification of factors strongly associated with the involvement of cognitive function.[5] These factors include epilepsy onset before the age of 5 years, the symptomatic aetiology of epilepsy, the diagnosis of epileptic encephalopathy, and current ASM. Children with an IQ within the normal range represented 59.1% when epilepsy onset was before 5 years, 85.3% and 86.9% when epilepsy onset was 5 to 9 years, and more than 10 years respectively. Furthermore, the identified underlying aetiology had the highest relative risk (RR) of cognitive involvement at 2.36 (95% confidence interval [CI] 1.74–3.20).[5]

Another prospective, community-based study was conducted at the time of epilepsy diagnosis (within 3mo of the first seizure) in children with epilepsy compared to a typically developing sibling for four cognitive domains (language, processing speed, verbal memory and learning, and attention/executive constructional ability) using a standardized test.[15] Neuropsychological deficits were observed in 27% of children who had one seizure; this rate increased to 40% when the child had other risk factors. The identified risk factors were: seizure recurrence (i.e. diagnosis of epilepsy); underlying aetiology (identified or unknown); treatment with ASM; and presence of epileptiform discharge on the initial electroencephalogram (EEG).[15]

Underlying aetiologies: epilepsy syndrome, structural abnormalities, and genetic aetiology

A list of epilepsy syndromes has been recognized by the International League Against Epilepsy (https://epilepsydiagnosis.org/). Some of these, such as Lennox–Gastaut syndrome, occur in children with cognitive impairment. Some syndromes, such as early infantile DEE, infantile spasm syndrome, and Dravet syndrome are associated with a very high risk of cognitive consequences. However, the risk of cognitive impairment in children with epilepsy is virtually increased for any epilepsy syndrome, even in self-limited epilepsy syndromes, with approximately 5% to 15% of them showing impairment in one cognitive domain.

Several studies have also linked abnormalities on magnetic resonance imaging (MRI) and neuropsychological deficits. In a study that examined MRI abnormalities at epilepsy onset (children aged 6–14y with an MRI within 3mo after the first seizure), 34 out of 249 (14%) had a structural abnormality on MRI that could be related to epilepsy.[16] These patients had slightly lower cognitive function overall at disease onset. This cognitive involvement appeared to affect several domains equally (language, processing speed, executive/constructional ability, and verbal memory).[16] The role of abnormalities on MRI in the cognitive deficit of children with epilepsy appears to be more than simply a reduction in global cortical volume related to the structural abnormality. The volume of the structural abnormality is linked with diffuse abnormalities being more impactful than smaller focal ones. In children with cerebral palsy and unilateral brain abnormalities, children with epilepsy and cerebral palsy had stronger cognitive dysfunction than those with similar brain lesions without epilepsy.[17] In the subgroup of new-onset epilepsy, cognitive impairment included several cognitive domains such as attention, auditory perception, lexical function, speech comprehension, visuoperceptual skills, and short-term memory.[17] More recently, using neuroimaging and connectome analysis, the ENIGMA study found that areas of atrophy in patients with epilepsy were anchored to the connectivity profiles, pointing to the temporal limbic cortices in temporal lobe epilepsy and the frontocentral cortex in idiopathic generalized epilepsy.[18] This is a clear illustration that epilepsy is a network disease. The size of the network might be a key parameter in the cognitive outcome.

Genetic factors also play a role in the cognitive impairment associated with children with epilepsy. For some epilepsy syndromes, the pathogenic gene variant or chromosomal imbalance is the cause of both epilepsy and cognitive impairment. Clinical data on the tuberous sclerosis complex illustrated the range of epilepsy severity and the variety of cognitive impairment that could be observed. Sometimes it is not obvious from clinical practice whether a gene defect is involved in cognitive dysfunction or if intellectual disability is due to the severity of early-onset epilepsy, as in Dravet syndrome and *SCN1A*, as discussed later in the review. Another illustration of the interaction between genes, epilepsy, and intellectual disability is the fact that epilepsy can occur in almost any patient with intellectual disability. In this population, the prevalence of epilepsy increases by up to 22% with the level of cognitive impairment.[19] Finally, gene dysfunction has been observed in a broad spectrum of phenotypes, as with the *SCN2A* gene. *SCN2A* pathogenic variants have recently been recognized as being responsible for epilepsy, intellectual disability, or autism spectrum disorder, seen alone or combined in the same patient.[20] Finally, polygenic factors are involved in human intelligence and mild intellectual disability.[21] Epilepsy syndromes, such as idiopathic generalized epilepsy with suspected polygenic inheritance, have also been observed.[22,23] The polygenic component is probably involved in monogenic DEE as suggested by genetic electro-clinical phenotype studies. In patients with de novo *KCNQ2* pathogenic variants, there was no relationship between variant position and seizure onset or cognitive outcome; however, recurrent variants were associated with overlapping epilepsy features and cognitive outcomes.[24] In the case of *STXBP1* DEE, two main epilepsy trajectories (early seizure remission or drug-resistant epilepsy) and a wide range of neurodevelopmental outcomes have been described; however, the only phenotype variable associated with cognitive outcome was the age at seizure onset. No genetic data were linked with any outcome

variable.[25] It is most likely that polygenic factors might contribute to both epilepsy and cognitive impairment in the same patient. Advances in genetic technologies and systems biology should soon allow a better understanding of polygenic factors and the neurobiology mechanisms contributing to cognitive impairment in children with epilepsy.

ASM

Many reports have described the effects of ASM on cognition. However, studies on the cognitive effects of ASM in children are lacking in quantity and quality. ASM is started in patients with epilepsy; it would not be ethical to evaluate the cognitive impact of ASM in typically developing children. There is always an interplay between epilepsy and its aetiology, recurrent seizures, and ASM when evaluating the cognitive effect of ASM in children with epilepsy.

The cognitive impact of drug development in children with epilepsy has been evaluated. However, the screening performed in this setting had major limitations: (1) it included children with drug-resistant epilepsy already treated with several ASMs; (2) the tests conducted were usually a screening rather than a precise neuropsychological tool; and (3) the trial timeline was usually limited. Therefore, subtle changes may not be easy to identify.

Studying new-onset epilepsy minimizes the cognitive impact of recurrent seizures or polytherapy. In a prospective study conducted by Fastenau et al., the use of ASM was correlated with modifications in all neuropsychological domains tested.[15]

Another method of measuring the impact of ASM is to evaluate whether withdrawal results in an improvement. Using preoperative and postoperative assessments of children with epilepsy, it is possible to measure the effect of ASM on cognition without the role of recurrent seizures. Based on more than 300 neuropsychological assessments, the start of ASM withdrawal, the number of ASMs reduced, and complete ASM withdrawal were associated with improved postoperative IQ scores and gains in IQ, independent of other determinants of cognitive outcome.[26]

Monotherapy should be prioritized over polytherapy to minimize the risk on cognition. The risk of adverse events was significantly lower in patients receiving monotherapy than in those receiving polytherapy (RR = 0.61; 95% CI 0.47–0.79; $p<0.001$) in a prospective study conducted in children with epilepsy.[27] In this study, several behavioural and cognitive scales were used. All ASMs have some effect on cognitive function; some ASMs, such as phenobarbital, have a stronger impact than others.[28] A higher amount of ASM is also associated with a higher risk of cognitive impairment. Indeed, there is a different effect of increasing the amount of ASM on seizures and the risk of side effects. The effect on seizures reaches a plateau when the amount is increased, while the increase in side effects is exponential (Figure 1).

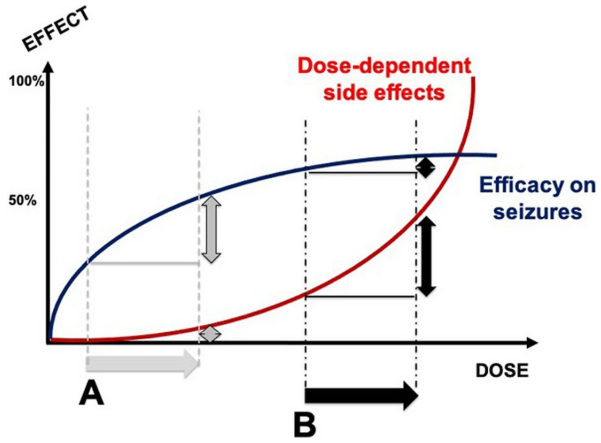

FIGURE 1 Efficacy and side effect risk of antiseizure medication (ASM). The relationship between the amount of prescribed drug and the effect of the expected efficacy (blue curve) and the expected side effect risk (red curve) are shown. An increase in the prescribed amount resulted in a change in the frequency of seizures, which then reached a plateau (blue curve). 'A' indicates an increase in the amount of ASM (grey arrow), which results in a significant increase in efficacy with a small increase in side effects (grey double arrows). 'B' indicates an increase in the amount of ASM (black arrow) that does not change efficacy but results in an important increase in side effects (black double arrows).

Interictal abnormalities

Based on daily clinical practice, it is difficult to conclude for a given patient whether the presence of interictal epileptiform activity plays a role in the cognitive outcome of children with epilepsy. Data on the incidence of EEG abnormalities do not help us draw conclusions easily. Epileptiform abnormalities are observed in typically developing children.[29] In neurodevelopmental disorders, the prevalence of epileptiform activity is higher than in the general population. This has been particularly established for attention-deficit/hyperactivity disorder[30] and autism spectrum disorder.[31] In these disorders, it is unclear whether interictal epileptiform activities play a role in the neurobiology of the disease or if they are disease biomarkers.

In new-onset paediatric epilepsy, epileptiform activity at the initial EEG was associated with slower psychomotor speed; this link was not an artefact due to ASM.[15] Experimental studies using animal models and in humans are consistent with the existence of disruption of some cognitive functions when the interictal spikes occur. For example, the occurrence of spikes in the hippocampus of epileptic rats (lithium–pilocarpine model) trained for cognitive tasks disrupted memory retrieval and increased response latency.[32] Interestingly, similar findings on memory retrieval were found in patients with epilepsy in stereoelectroencephalography investigations. The occurrence of bilateral spikes in the hippocampus during memory maintenance significantly decreased the likelihood of responding correctly to a memory task.[33]

As illustrated earlier, this seemingly simple question of the effect of interictal activities on cognition is extraordinarily complex. The problem has been addressed from very different angles without providing a definitive answer, including the potential effect of treating interictal abnormalities. On this point, interictal epileptiform discharge (IED) should not be treated with current ASM to improve cognition. There are more risks of worsening cognitive function than of restoring it with ASM. Few studies have attempted to address this issue. Only one class I study focused on this point. In this study, lamotrigine was used to reduce the IED. Lamotrigine modified the behavioural outcome but did not change cognition.[34,35] Most of the time, treating IED with current ASM is associated with a negative impact on cognition. A better understanding of the neurobiological effect of IED and its mechanisms is a good opportunity to prevent cognitive deficits in children with epilepsy that exhibit IED. The place of IED in the definition and mechanisms of epileptic encephalopathy/DEE is discussed in the 'Developmental and epileptic encephalopathies' section.

IS PAEDIATRIC EPILEPSY ASSOCIATED WITH PROGRESSIVE MATURATION CHANGES?

Cohort studies of children with epilepsy after disease onset suggested the existence of a slow progressive impact on cognition over time. In a community-based prospective study conducted by Berg et al.[5] in children with epilepsy from the time of initial diagnosis, a progressive decrease in cognitive function over time was found using the Vineland Scale. Children with epilepsy had a Vineland score below average at the time of diagnosis. Significant deterioration was observed over time, particularly in children with epileptic encephalopathy and symptomatic aetiology. In a Dutch paediatric epilepsy cohort, a progressive decrease in cognitive function was reported, with the largest decline initially and a continuous decreasing trend.[36] In late-onset epilepsy, the decline in verbal performance was attenuated. None of the other parameters of epilepsy were correlated with the course of cognitive development.[36]

There is also evidence of a change over time in epilepsy syndromes such as juvenile myoclonic epilepsy. The developmental trajectories of 19 children with juvenile myoclonic epilepsy for 2 years after diagnosis compared to typically developing controls demonstrated alterations in brain maturation. At baseline, children with juvenile myoclonic epilepsy compared to controls had similar or worse cognitive abilities, particularly executive function and processing speed. At the end of the study, children with juvenile myoclonic epilepsy did not reach the competence level of typically developing controls. Furthermore, the pattern of brain development assessed by MRI also found an alteration in trajectory, notably in the fronto-temporo-parietal regions of the brain.[37]

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

The concept of epileptic encephalopathy applies to all patients with epilepsy regardless of the syndrome and the age at which epileptic activity contributes to severe cognitive and behavioural impairments beyond what might be expected from the underlying pathology alone. This could be responsible for stagnation or regression in cognitive function.[2] In 2017, the International League Against Epilepsy introduced the concept of DEE.[4] This has added another conceptual layer to our understanding of the most severe epilepsy syndromes. The term 'developmental' was chosen to reflect the cause of the disease. In the case of a genetic aetiology, the gene defect might contribute to the developmental delay on its own; then, epileptic activity might further affect development. This concept should impact the treatment management of epileptic encephalopathy with a view to improving cognitive function, whereas treatment of the underlying cause would not change developmental impairment unless an effective personalized medical treatment is used.

In the case of Dravet syndrome, both clinical and experimental data suggest a role for the *SCN1A* pathogenic variant in cognitive impairment.[38] A study reporting the neuropsychological evaluation of 67 children with Dravet syndrome showed that cognitive involvement is an early process in this syndrome, with an IQ above 70 observed until 3 years of age, which was followed by a marked decrease (mean IQ = 48) after this age. None of the patients in this study experienced psychomotor or cognitive regression. None of the main epilepsy parameters (age, type, or duration of the first seizure, number of fever-related episodes of status epilepticus, photosensitivity at EEG recording, or treatment parameters) were correlated with cognitive outcome, while the presence of an *SCN1A* pathogenic variant was a reliable predictor of cognitive outcome.[39] This suggests a major contribution of the gene defect, with experimental studies showing that the *SCN1A* gene is involved in cognitive processes. Using a small interfering RNA approach to selectively knockdown $Na_v1.1$, the product of the *SCNA1* gene, in mice, a reduction in $Na_v1.1$ expression in the medial septum and diagonal band of Broca led to dysregulation of hippocampal oscillations in association with spatial memory deficit, although mice did not show spontaneous seizures.[40] However, a recent cohort study reported data suggesting that a higher frequency of seizures early in brain development could affect cognitive outcomes. A longer duration of worsening of ASM in the first 5 years after seizure onset was significantly associated with a worse cognitive outcome in a Dutch cohort of 164 patients with *SCN1A*-related epilepsy.[41] Dravet syndrome is consistent with the concepts of DEE.

Neuroimaging studies in epileptic encephalopathy/DEE, such as Lennox–Gastaut syndrome or epileptic encephalopathy with spike-and-wave activation in sleep, have been helpful to investigate the role of ictal and/or interictal activities on cognition. It has been suggested that IED could alter learning and memory consolidation during sleep. IED

probably interacts with cognition in several ways. Indeed, functional imaging looking at connectivity provided some insights in the mechanisms of epileptic encephalopathy/DEE. In epileptic encephalopathy with spike-and-wave activation in sleep, fluorodeoxyglucose–positron emission tomography found that increased glucose metabolism corresponded to the epileptic foci while other cortical areas were hypometabolic.[42,43] One hypothesis is that epileptic foci affect other cortical areas by surrounding inhibition when the hypometabolic area is located at the border of the hypermetabolic area or by remote inhibition when the hypometabolic area is distant from it. At remission of epileptic encephalopathy with spike-and-wave activation in sleep, both focal hypermetabolism and hypometabolism disappeared and functional connectivity between these regions returned to normal suggesting that the inhibited area might play a role in cognitive regression.[43] Data from EEG-functional MRI (fMRI) studies also support this hypothesis, showing an increase in perfusion in the epileptic focus and a decrease in perfusion in distinctive connected cortical areas.[44,45] In Lennox–Gastaut syndrome, both neuroimaging and EEG-fMRI studies showed the involvement of large networks, with the thalamus acting as synchronizer and amplifier.[46] Different brain structures are involved in the ictal and interictal abnormalities in Lennox–Gastaut syndrome, with different patterns according to the type of abnormality. EEG-fMRI studies showed that paroxysmal fast activities involve diffuse network activation including association cortices simultaneously with an activation of subcortical structures (brainstem, thalamus, and basal ganglia), while slow spike and waves involved a deactivation network including a primary cortical area and subcortical activation.[47]

For most epileptic encephalopathy/DEE, there is no evidence that treatment of the interictal abnormalities improves cognition. As mentioned with regard to the treatment of IED with ASM in other epilepsy syndromes, there are risks of worsening intellectual disability by overloading patients with ASM. The electrical status epilepticus during the slow sleep EEG pattern was seen alone in some patients, without any stagnation or regression, and should not lead to the initiation of any treatment.[2,48] Treatment should be decided based on psychomotor regression as a clinical symptom, leading to the diagnosis of epileptic encephalopathy with spike-and-wave activation in sleep; the EEG pattern should be used as a biomarker of the ongoing process. Finally, there is still an ongoing debate as to the cognitive impact that a suppressive treatment of hypsarrhythmia in the case of infantile spasm syndrome would have.[49] This remains unsolved because it is quite challenging to decipher the effect of the disappearance of epileptic spasms with the cessation of hypsarrhythmia. None of the current treatment guidelines for infantile spasm syndrome are based on hypsarrhythmia.[50,51]

CONCLUSION

Children with epilepsy are at risk for a broad range of cognitive disabilities that progress over time. This presents a risk for academic achievement and quality of life. Various factors contribute to the risk of cognitive impairment. Depending on which factors are predominant, the timing, degree, and course of cognitive impairment might differ from one patient to another. Environmental contributions to cognitive impairment are also likely. However, these are currently not well identified.

The factors for cognitive dysfunction could be divided into fixed factors, such as age at disease onset and underlying aetiology (Figure 2). Other factors, such as recurrent seizures, ASM, and interictal epileptiform activity are possibly modifiable. Currently, the most important factors in

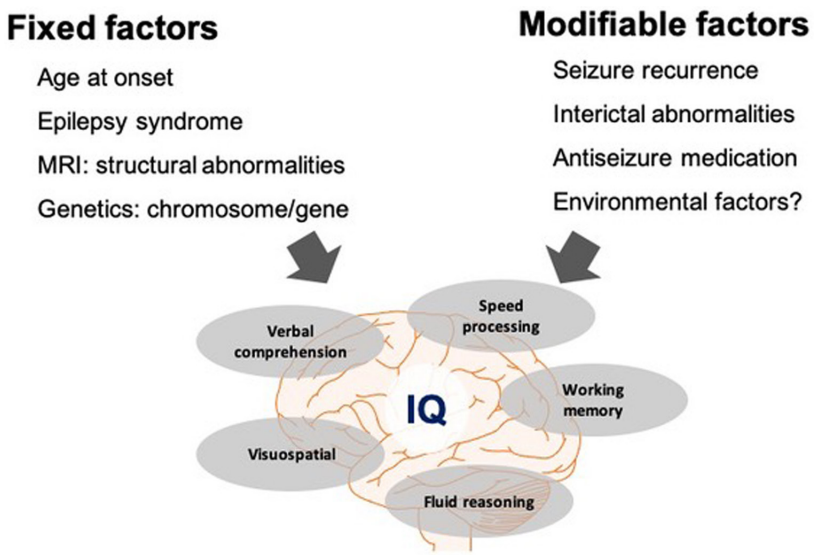

FIGURE 2 Overview of factors that contribute to cognitive impairment in children with epilepsy

lowering the cognitive impact involve looking for the best benefit–risk ratio for each child with epilepsy by avoiding possible polytherapy and using the smallest amount of ASM for efficacy. Early screening for cognitive dysfunction to propose adequate school adaptation and rehabilitation is also crucial. Unfortunately, the rate of drug-resistant epilepsy has remained stable in recent decades. For some patients, the control of seizure recurrence is not always a factor in how we act. Interictal abnormalities might be a hope for pro-cognitive intervention. Current ASM is probably more harmful than helpful except in some cases of epileptic encephalopathy/DEE. Further research is needed to better understand how to prevent or modify factors that affect cognitive function of children with epilepsy.

DATA AVAILABILITY STATEMENT

Data will be provided on request

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