

Review

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Review

Therapeutic Strategies in Children with Epilepsy— From the Point of View of QOL-Related Factors

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Abstract: Children with epilepsy are affected by several factors, including clinical and social variables, which can lead to reductions in quality of life (QOL). Among these variables, factors relating to seizure severity such as frequent seizures and status epilepticus (SE) have been identified as important predictors of QOL. In addition, frequency of interictal epileptiform discharges (IEDs) on the electroencephalogram (EEG) may also lead to cognitive declines and behavioral disturbances. Moreover, frequent seizures and/or IEDs may play a role in emotional mediators such as stigma and fatigue in childhood epilepsy. Seizure severity and/or IEDs are thus important QOL-related factors in childhood epilepsy. Frontal lobe dysfunctions such as cognitive decline and behavioral disturbances can result in reduced QOL for both the child and their family. Frontal and prefrontal lobe growth disturbances can be present during active-phase epilepsy in some children with neuropsychological impairments. Recovery from prefrontal lobe growth disturbance may depend on the active seizure period. Disturbance of prefrontal lobe growth can recover more rapidly in children with a shorter active seizure period. In contrast, recovery may be delayed in children with a longer active seizure period. Accordingly, severe seizures can lead to neuropsychological impairments in association with prefrontal lobe growth disturbance in children with epilepsy. Moreover, frequent seizures can lead to having seizure-associated headache, perception of self-stigma and parental stigma, and fatigue. In addition, IEDs on EEG, representing persistent pathological neuronal discharges, may be associated with several pathological aspects. Frontal IEDs can be a risk factor for recurrent seizures, cognitive decline, and behavioral disturbances and may also play a role as an emotional mediator similar to stigma. In addition, behavioral disturbances may result in the presence of secondary bilateral synchrony (SBS) on EEG. Behavioral disturbances can be improved in association with reduction of IEDs in children with frontal IED and SBS. Seizure severity and IEDs on EEG may thus be associated with neuropsychological impairments, leading to QOL reduction. Therapeutic management may be desirable to remit seizures and EEG abnormalities such as frontal IED and SBS as soon as possible to improve QOL in children with epilepsy.

Keywords: frontal; prefrontal; behavior; stigma; seizure severity; interictal epileptiform discharge (IED); quality of life (QOL)

1. Introduction

Quality of life (QOL) in children with epilepsy seems to be influenced by various factors, including clinical and social variables. Among these, seizure frequency and presence of status epilepticus (SE) are regarded as the main QOL-related factors. In addition, electroencephalogram (EEG) findings such as frequency of interictal epileptiform discharges (IEDs) may also be related to cognitive decline and behavioral disturbances. Moreover, epileptic activities such as frequent seizures and IEDs may mediate emotional states including stigma and fatigue in children with epilepsy. These findings suggest that epileptic activities including frequent seizures/presence of SE and IEDs on EEG can lead to reduced QOL in children with epilepsy.

Neuropsychological impairments such as cognitive decline and behavioral disturbances in children with epilepsy can be caused by several factors. Frontal lobe lesions may lead to cognitive

decline and behavioral disturbances in consonance with lesion location. However, children with no lesions can also present with these disturbances. A previous study showed a negative correlation between frequency of IEDs on EEG and cognitive functions in self-limited epilepsy with centrotemporal spike (SeLECTS) [1]. These impairments may thus relate to the topography and epileptic activities.

On the other hand, stigma is regarded to be an important QOL-related factor in epilepsy. Perception of stigma related to the epileptic condition may be very severe and is often under-recognized by clinicians. Stigma has a marked negative impact for not only children, but also their families. Reducing perceptions of stigma is thus necessary for the clinical management of childhood epilepsy.

In addition, fatigue is associated with reduced QOL in patients with epilepsy. Fatigue in patients with epilepsy may correlate with psychosocial factors, including anxiety, depression, and sleep problems [2]. Fatigue is considered to be associated with several issues in epilepsy. A previous study showed that frequent seizures can lead to increased fatigue [3]. Fatigue may also relate to epileptic activities.

The frontal lobes mature over a long period and so is easily damaged by various factors. Damage to the frontal regions during childhood interferes with maturational and organizational processes, which can lead to neuropsychological impairments [4]. Results from previous investigations have suggested that severe seizures as reflected by statuses such as frequent seizures and SE can impair the developing brain [4–6]. In combination with these studies, seizure severity and IED on EEG may lead to cognitive, behavioral, and psychological disturbances. Epileptic activities such as seizure severity and/or IEDs are important QOL-related factors in childhood epilepsy.

2. Can seizure severity lead to reduced QOL in childhood epilepsy?

2.1. Seizure severity and cognitive/behavioral disturbances; are they related?

Neuropsychological impairments such as cognitive decline and behavioral disturbances will reduce QOL in childhood epilepsy. Cognitive declines and behavioral deterioration may be induced by frontal lobe dysfunction. In addition, QOL reduction in children can also reduce QOL in the family. Frontal lobe dysfunction can thus result in reduced QOL for both the child and their family.

The frontal lobes are the largest cortical regions of the brain, comprising approximately 40% of the cerebral cortex. Among these regions, the prefrontal regions involve wide networks [7]. Because of these connections, the prefrontal cortex can receive abundant information from all parts of the cerebrum, and can affect information processing in those parts. Prefrontal lobe neurons and glial cells are readily influenced by various factors, so prefrontal lobe functions are regarded as vulnerable for a long period [8]. Accordingly, severe seizures, such as with frequent or prolonged seizures, more easily results in negative effects on prefrontal lobe functions than other cortical regions [7,8]. Considering these findings, epilepsy associated with prefrontal regions in children may be associated with several neuropsychological impairments in comparison with healthy subjects [9].

2.1.1. Prefrontal lobe growth in frontal lobe epilepsy

Understanding how frontal lobe epilepsy (FLE) impacts the life of the patient seems important. In a serial 3-dimensional (3D)-magnetic resonance imaging (MRI) volumetric study, growth of the frontal and prefrontal lobes in children with drug-responsive FLE without neuropsychological impairments was similar to that in healthy subjects [8]. In contrast, frontal and prefrontal lobe growth disturbances were present during the active epileptic phase in refractory FLE patients with cognitive declines and behavioral disturbances. However, a difference in association with the active seizure period was present. The active seizure period was short in children with prompt growth recovery. In children with a longer active seizure period, the growth disturbance was more severe and growth recovery required a long time [8] (Table 1). Frequent seizures in children with FLE may thus induce prefrontal lobe growth disturbance, which can lead to neuropsychological impairments.

2.1.2. Prefrontal lobe growth in SeLECTS

SeLECTS is considered a condition free of neurological and psychological impairments. However, children with SeLECTS sometimes present with severe aggravation of epileptic manifestations and cognitive decline/behavioral disturbances. Frontal and prefrontal lobe volumes and the prefrontal-to-frontal lobe volume ratio in particular showed growth disturbances during the active seizure period in patients presenting with atypical evolution [7]. However, differences in association with active seizure period were present. Active seizure period was short in the patient with prompt growth recovery. In the patient with a longer active seizure period, the growth disturbance was more severe, and growth recovery required a long time [7] (Table 1). Seizure severity in SeLECTS may thus be associated with prefrontal lobe growth disturbance, which can lead to neuropsychological impairments.

2.1.3. Prefrontal lobe growth in self-limited epilepsy with autonomic seizures

Self-limited epilepsy with autonomic seizures (SeLEAS), which represents Panayiotopoulos syndrome, is generally accepted to lack neuropsychological impairments. However, cognitive declines and behavioral disturbances may be present in at least some children with SeLEAS. SE can induce cerebral damage to various degrees. In SeLEAS patients, the seizure tends to be prolonged, with subsequent focal or focal to bilateral tonic-clonic SE [10]. A sequential study by 3D-MRI volumetry showed that frontal and prefrontal lobe growth disturbances were present after episodes of SE in SeLEAS patients presenting with behavioral disturbances. In a patient with only one episode of SE, growth disturbance soon recovered. Conversely, recovery of growth ratios was delayed in patients with several episodes of SE [11] (Table 1). Moreover, cognitive scores as measured using the Wechsler intelligence scale for children dropped after SE episodes [11]. The presence of SE in children with SeLEAS may thus induce growth disturbance of prefrontal lobe, which can lead to neuropsychological impairments.

Table 1. Association between seizure severities and prefrontal lobe growth disturbances.

Epileptic syndrome	Findings
Frontal lobe epilepsy (FLE)	<ul style="list-style-type: none"> # Frontal/prefrontal lobe volumes and the prefrontal -to-frontal lobe volume ratio increased serially in drug -responsive FLE patients without cognitive decline/behavioral disturbances and children without epilepsy. # Frontal and prefrontal lobe growth disturbances were present during the active seizure period in refractory FLE patients with cognitive decline and behavioral disturbances. # Active seizure period was short in children with prompt growth recovery . # Growth disturbance was more severe and growth recovery required a long time in children with a longer active seizure period.
Self-limited epilepsy with centrottemporal spikes (SeLECTS)	<ul style="list-style-type: none"> # Frontal and prefrontal lobe growth disturbances were present during the active seizure period in patients presenting with atypical evolution. # Growth disturbance was more severe and growth recovery required a long time in the patient with a longer active seizure period.
Self-limited epilepsy with autonomic seizures (SeLEAS)	<ul style="list-style-type: none"> # Frontal and prefrontal lobe growth disturbances were present after episodes of SE in SeLEAS patients presenting with behavioral disturbances . # In a patient with only one episode of SE, growth disturbance soon recovered. # Conversely, recovery of growth ratios was delayed in patients with several episodes of SE.

SE, status epilepticus.

2.2. QOL-related factors; headache

Epilepsy and migraine are a heterogeneous family of neurological disorders [12]. The prevalence of headache is extremely high, so concomitant headache can be present in many patients with epilepsy. Approximately 35% of epileptic children experienced headaches in association with

seizures in our previous study [13]. The frequency of seizures in children with and without seizure-associated headache was 4.1 and 1.3 times per year, respectively [13] (Table 2). Thus, seizure recurrence may induce headaches in association with seizures, which lead to reduced QOL in children with epilepsy.

2.3. QOL-related factors; fatigue

Fatigue has a negative impact on QOL in patients with various chronic diseases, including epilepsy [14–16]. Our previous study showed that mean Fatigue Severity Scale scores in epileptic children were significantly higher than those in non-epileptic children [17]. Frequency of seizures was identified as the only significant clinical manifestation in association with fatigue by multiple linear regression analysis. Moreover, children with frequent seizures presented with more severe fatigue [17] (Table 2). Accordingly, frequent seizures can lead to the presence of fatigue in children with epilepsy.

2.4. QOL-related factors; perception of stigma by children

Perception of stigma among epilepsy patients is a negative psychological issue associated with reduction of QOL. Stigma has a negative effect on self-esteem and social status and thus can lead to poor prognosis, including isolation and delayed initiation of treatment for epilepsy patients [18]. Frequent seizures could lead to psychosocial impairments in children. Our previous study using the Child Stigma Scale showed that perceptions of stigma were severe in association with seizure frequency (Table 2) [19]. Thus, stigma has negative effects on social identity in children with epilepsy experiencing frequent seizures.

2.5. QOL-related factors; perception of stigma by parents

Epilepsy in children can be a risk factor for stress in their parents [20–23]. Parents of children with intractable epilepsy tend to experience severe anxiety in relation to recurrent seizures, and this parental state of anxiety can lead to poor adaptive function in children [24]. Frequent seizures are thus an important issue with respect to parenting stress [25]. Parents of children with epilepsy showed higher scores on the Parent Stigma Scale than parents of healthy children [26]. Moreover, greater perceptions of stigma by parents correlated with higher seizure frequency [26] (Table 2). Accordingly, frequent seizures in children with epilepsy can lead to greater perceptions of stigma by parents.

Table 2. Association between seizure severities and QOL-related factors.

QOL-related factors	Findings
Headache	# Frequency of seizures was 4.1 times per year in children with seizure -associated headache. # Frequency of seizures was 1.3 times per year in children with non -seizure-associated headache. # Frequent seizures may be associated with seizure -associated headache.
Fatigue	# Mean Fatigue Severity Scale scores were significantly higher in children with epilepsy than in those without it. # Frequency of seizures was the sole clinical manifestation significantly associated with fatigue. # Higher frequency of seizures was associated with more severe fatigue.
Perception of stigma by children	# Children with frequent seizures presented with greater psychosocial impairment than in children in seizure remission. # Greater perceptions of stigma were associated with greater seizure frequency.
Perception of stigma by parents	# Parents of children with epilepsy showed significantly higher questionnaire scores than parents of children without epilepsy. # Greater perceptions of stigma were associated with seizure frequency.

QOL, quality of life.

3. Can EEG abnormalities lead to QOL reduction in children with epilepsy?

3.1. Association between IEDs on EEG and seizure recurrence

EEG abnormalities such as IEDs can be conceptualized as pathological neuronal discharges [27]. This can lead to the fact that IEDs on EEG are associated with seizure recurrence. In SeLECTS, recurrent seizures and prolonged periods of frequent IEDs were correlated [28]. This finding suggests that the occurrence of frequent IEDs and the prolongation of this state may lead to recurrent seizures in SeLECTS. In addition, seizure recurrence may be associated with the location of EEG foci. Our study showed that frontal IED induced recurrent seizures after a first unprovoked seizure more often than other EEG foci [29] (Table 3). Thus, frequency of IED and frontal IEDs may be associated with recurrent seizures.

3.2. Association between IEDs on EEG and cognitive/behavioral disturbances

Neuropsychological impairments such as cognitive decline and behavioral disturbances are seen more often in children with more severe EEG abnormalities [30–32]. Children can exhibit behavioral disturbances in association with IEDs on EEG without clinical seizures [33,34]. Cognitive decline and behavioral disturbances were present in relation to a prolonged period of frequent IEDs in SeLECTS [35]. Moreover, these disturbances were also associated with a prolongation of the frontal EEG focus [35] (Table 3). Cognitive function can deteriorate in children with frequent IEDs. In addition, neuropsychological functioning can recover with the normalization of EEG findings [36]. Thus, neuropsychological impairments may be associated with IEDs on EEG in SeLECTS (Table 3). Tassinari et al. reported that neurophysiological impairments associated with the negative myoclonus or inhibitory seizures seen in atypical SeLECTS suggest involvement of the frontal cortex, either primarily or secondarily [37]. Moreover, frontal and prefrontal lobe growth disturbances persisted even after seizure disappearance in atypical SeLECTS [7]. These findings suggest that clinical features in atypical SeLECTS may be associated with frontal lobe dysfunctions, which can lead to neuropsychological impairments. In combination with these findings, frontal IED can lead to cognitive declines and behavioral disturbances.

Frontal IED is considered to show various pathogeneses. In children with attention deficit hyperactivity disorder (ADHD) presenting with IED, frequency of IEDs was significantly correlated with ADHD-rating scale (ADHD-RS) score in frontal IED group, but not in Rolandic discharge (RD) group [38] (Table 3). In addition, the same study also showed reductions in IED frequency were significantly correlated with ADHD-RS score reductions due to antiseizure medication (ASM) treatment in the frontal IED group, but not in the RD group [38] (Table 3). These findings suggest that frontal IED can exacerbate behavioral disturbances in children with ADHD.

IED in children with autism spectrum disorder (ASD) is frequently located in the frontal region [39]. ASD children with epilepsy with frontal IEDs presented behavioral improvement (reductions in score according to the Japanese manuals for the Aberrant Behavior Checklist (ABC-J)) in association with EEG improvement (reductions in IED frequency) after ASM treatment [40] (Table 3). This finding suggests that behavioral disturbances can be associated with frequency of IED on EEG, and ASM treatment can lead to both reduced IED frequency and problems of behavior in ASD children with epilepsy with frontal IEDs [40]. Thus, frontal IEDs can lead to exacerbation of behavioral disturbances.

In addition, secondary bilateral synchrony (SBS) on EEG may be associated with cognitive decline and behavioral disturbances. The majority of children with epileptic encephalopathy with continuous spikes and waves during slow sleep (EECSWS), as a representative epileptic syndrome of SBS, present neuropsychological impairments. Our previous study showed that the volumes of frontal and prefrontal lobes were small in EECSWS children compared with healthy children [41] (Table 3). Moreover, prefrontal lobe growth disturbance was prolonged in children with longer CSWS periods in comparison with those with shorter CSWS periods [41] (Table 3). These findings suggest that persistent severe abnormalities on EEG may induce prefrontal lobe growth disturbance, which can lead to neuropsychological impairments.

From a therapeutic perspective, the association between reduction of IED frequency and behavioral improvement after ASM treatment has been evaluated in epilepsy patients presenting with SBS [42]. Scores for behavioral disturbances measured using the ABC-J were decreased in both EEG responders and EEG non-responders following ASM treatment. Moreover, reductions in ABC-J scores were significantly better in EEG responders than in non-responders. These findings suggest that EEG findings such as SBS can lead to behavioral disturbances, and that behavioral improvements may be achievable in association with EEG improvement [42] (Table 3).

3.3. Association between EEG abnormalities and stigma

The emotional state can be influenced by various epileptic activities, including EEG abnormalities. A previous study showed that frontal EEG abnormalities might affect neuropsychological functions [43]. Our previous study indicated an association between EEG abnormalities and perceived stigma [44]. Children with frontal IED had higher scores on the Child Stigma Scale than those with IED in other regions. This finding suggests that frontal IED may be associated with a greater perception of stigma. Thus, frontal IED may play a role as an emotional mediator such as stigma [44] (Table 3).

Table 3. Association between QOL-related factors and IED on EEG.

IED on EEG as QOL-related factors	Findings
Seizure recurrence and IED frequency	# Seizure recurrence and extended periods of high-frequency IEDs were significantly correlated in SeLECTS.
Seizure recurrence and frontal IED	# Children with frontal IED were at significantly higher risk of seizure recurrence than those with IEDs in other regions of EEG foci.
Cognitive decline/behavioral disturbances and IED frequency	# Cognitive decline and behavioral disturbances correlated significantly with a prolonged period of high-frequency IEDs in SeLECTS.
Cognitive decline/behavioral disturbances and frontal IED	# Cognitive decline and behavioral disturbances correlated significantly with a prolonged period of frontal EEG focus. # A significant correlation was evident between IED frequency and ADHRS in children with frontal IED. # A significant correlation was seen between decreased IED frequency and reduced ADHRS scores after ASM treatments in children with frontal IED. # The IED was most commonly located in the frontal region in ASD. # A correlation between decreased IED frequency and Japanese manuals for ABCJ score after treatment was evident in children with ASD with frontal IEDs.
Cognitive decline/behavioral disturbances and SBS	# Frontal and prefrontal lobe volumes revealed growth disturbances in all EECWS patients. # Prefrontal-to-frontal lobe volume ratios were decreased in all EECWS patients. # In patients with shorter CSWS periods, ratios were soon restored to normal values. # Prefrontal lobe growth disturbances were persistent in patients with longer CSWS periods. # Behavioral scores were significantly reduced in EEG responders compared to nonresponders.
Perception of stigma by children and frontal IED	# Scores on all questions were higher in children with frontal IED. # Children presenting with frontal IED perceived greater stigma than those with nonfrontal IED.

QOL, quality of life; IED, interictal epileptiform discharge; EEG, electroencephalogram; SeLECTS, self-limited epilepsy with centrotemporal spike; ADHD-RS, attention deficit/hyperactivity disorder-rating scale; ASM, antiseizure medication; ASD, autism spectrum disorder; ABC-J, Japanese manuals for the Aberrant Behavior Checklist; SBS, secondary bilateral synchrony; EECWS, epileptic encephalopathy with continuous spikes and waves during slow sleep.

4. How do we manage the treatment of epilepsy in children?

4.1. Is urgent suppression of clinical seizures needed?

As mentioned above, the presence of frequent seizures and SE can induce growth disturbance of prefrontal lobe, leading to neuropsychological impairments [8,11] (Figure 1). In addition, recovery from prefrontal lobe growth disturbance may depend on the active seizure period. Disturbance of prefrontal lobe growth can recover more rapidly in children with a shorter active seizure period. However, such recovery may be delayed in children with a longer active seizure period [8]. These findings support the hypothesized relationship between seizure activities and behavioral disturbances of “seizure activity per se disrupts behavior” as suggested by Austin et al. [45]. In addition, SE in children can lead to prefrontal lobe growth disruption. In our volumetric study, more frequent SE episodes could lead to poorer outcomes [11]. Accordingly, SE can lead to neuropsychological impairments in association with prefrontal lobe growth disruptions (Figure 1). Another study indicated that damage to the frontal regions during childhood can cause deteriorations in neurobehavioral development [46].

Based on these findings, the therapeutic strategy for childhood epilepsy may require remission of seizures as soon as possible to prevent neuropsychological impairments.

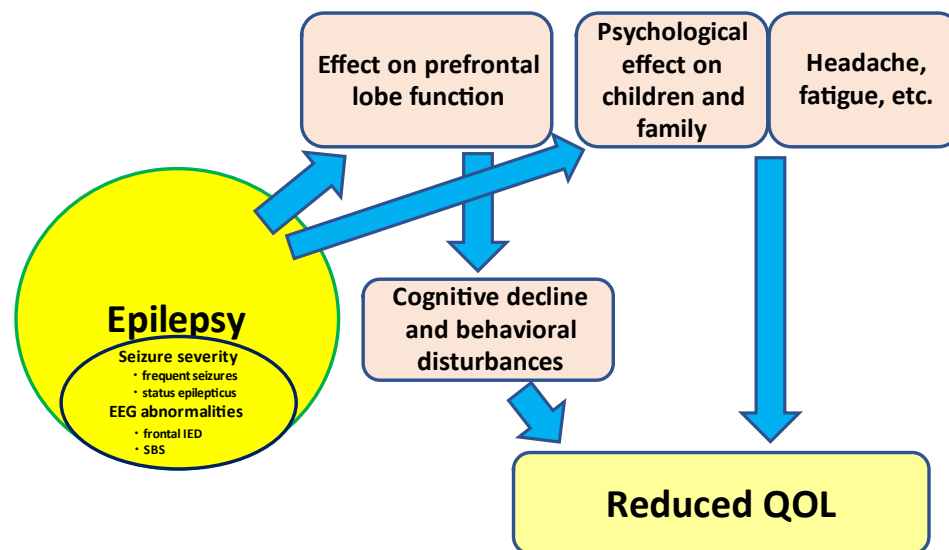
4.2. Is urgent suppression of IED on EEG needed?

As inferred from various studies, frequent IEDs and frontal IED can lead to neuropsychological impairments [35] (Figure 1). Reductions in IEDs on EEG may be related to behavioral improvements in children with ADHD/ASD with frontal IED with or without clinical seizures [38,40,47]. Accordingly, frontal IED can lead to neurodevelopmental deterioration in ADHD/ASD, and ASM treatment may affect both IED reduction and behavioral improvement in children with ADHD/ASD with frontal IED.

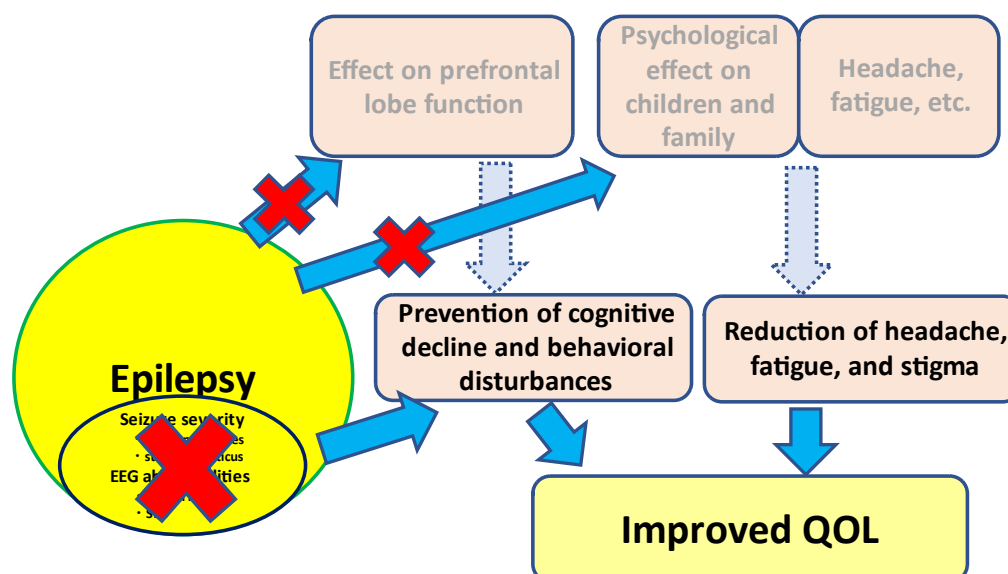
With respect to EECWS-related neurodevelopmental deterioration, previous studies have underlined the parallel course of EECWS and neuropsychological impairments [48].

Neuropsychological impairments may appear concurrent with the appearance of EEG abnormalities [49] (Figure 1). Moreover, these impairments may improve concurrent with the disappearance of EEG abnormalities rather than clinical seizures. In children with SBS, behavioral improvements can be associated with EEG improvement [42]. These findings suggest that the active phase of “epilepsy”, not only “clinical seizures”, can be a prognostic factor, and the urgent suppression of IEDs such as SBS may thus be warranted to prevent neurodevelopmental deteriorations in children presenting with SBS [50].

Based on these findings, urgent suppression of EEG abnormalities such as frontal IED and SBS may be required to prevent neuropsychological impairments.



a) Epileptic activities including severe seizures (such as frequent seizures and SE) and EEG abnormalities (such as frontal IED and SBS) can lead to neuropsychological impairments.



b) Early remission of seizures and EEG abnormalities can lead to prevention of cognitive decline/behavioral disturbances and reduction of headache, fatigue, and stigma, resulting in improvement of QOL.

Figure 1. Association between epileptic activities and reduction of QOL.

EEG, electroencephalogram; IED, interictal epileptiform discharge; SBS, secondary bilateral synchrony; QOL, quality of life.

5. Future Perspectives

As observed in these studies, epileptic activities, including seizure severity such as frequent seizures and SE and EEG abnormalities such as frontal IED and SBS, can lead to reduced QOL in children with epilepsy. Better control of seizures and remission of EEG abnormalities may improve QOL in children with epilepsy. However, caution must be taken when generalizing the results to children with epilepsy. Early remission of seizures and EEG abnormalities can lead to improvements in behavioral impairments. However, improvement or reduction of other aspects such as headache, fatigue, and stigma by ASM treatment have not yet been identified. Studies with a larger sample size are needed to evaluate the correlation between remission of seizures/EEG abnormalities and improvement of these aspects in children with epilepsy.

6. Conclusion

Cognitive declines and behavioral disturbances are not always evident in children with epilepsy. However, severe seizures, such as frequent seizures and SE, and some forms of IEDs can lead to neuropsychological impairments. To prevent these impairments, physicians should focus on controlling seizures and suppressing EEG abnormalities as early as possible. Based on the findings from various studies, therapeutic management may be desirable to achieve seizure remission and EEG abnormalities such as frontal IED and SBS as soon as possible to improve QOL in children with epilepsy.

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