タイトル	Professor Special Lecture 75th Annual Meeting of the Medical Society of Toho University QOL-Related Factors in Childhood Epilepsy
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公開者	The Medical Society of Toho University
発行日	2022.06.01
ISSN	21891990
掲載情報	Toho Journal of Medicine. 8(2). p.52-60.
資料種別	学術雑誌論文
内容記述	Review Article
著者版フラグ	publisher
JaLCDOI	info:doi/10.14994/tohojmed.2022-008
メタデータのＵＲＬ	https://mylibrary.toho-u.ac.jp/webopac/TD00565777

Professor Special Lecture: 75th Annual Meeting of the Medical Society of Toho University

Review Article

QOL-Related Factors in Childhood Epilepsy

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ABSTRACT: Quality of life (QOL) in childhood epilepsy is associated with clinical and social variables. Among these variables, seizure frequency has been identified as the important predictor of QOL. Additionally, frequency of interictal epileptiform discharges (IEDs) on electroencephalogram (EEG) may accompany transient cognitive/behavioral impairments. Moreover, seizure frequency and/or IEDs may play a role as a mediator of emotional responses including stigma and fatigue in childhood epilepsy. Hence, seizure frequency and/or IEDs are one of the important QOL-related factors in childhood epilepsy. Frontal lobe dysfunctions such as cognitive and behavioral problems can be associated with the reduction in QOL for both child himself and his/her family. Serial three-dimensional MRI studies revealed the frontal/prefrontal lobe growth disturbance during the active phase of epilepsy in some children with neuropsychological problems. Moreover, prefrontal lobe growth showed rapid recovery in epilepsy patients with a shorter active seizure period. These findings suggest that frequent seizures may lead to prefrontal lobe growth disturbance, which relates to neuropsychological problems in children with epilepsy. Furthermore, frequent seizures may be associated with seizure-associated headaches, stigma, parental stigma, and fatigue. Additionally, among IEDs on EEG, which may correlate with persistent pathological neuronal discharges, frontal IEDs may be at risk for seizure recurrence and cognitive/behavioral impairments and may play a role as a mediator of emotional responses including stigma. Moreover, behavioral problems may be associated with secondary bilateral synchrony (SBS) on EEG. There may be a possibility that behavioral impairments will be improved in association with EEG improvement in patients presenting with frontal IED and SBS. Hence, seizure severities and IEDs on EEG may be associated with neuropsychological problems, which relates to the reduction in QOL. The preferable treatment strategy may be required to remit seizures and EEG abnormalities as soon as possible to accomplish the most favorable prognosis for children with epilepsy.

Toho J Med 8 (2): 52–60, 2022

KEYWORDS: frontal, behavior, stigma, seizure severity, interictal epileptiform discharge (IED)

1. Introduction

The quality of life (QOL) in childhood epilepsy is associated with clinical and social variables. Among these variables, seizure frequency has been identified as the important predictor of QOL. Moreover, frequency of

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DOI: 10.14994/tohojmed.2022-008

Received Mar. 15, 2022
Toho Journal of Medicine 8 (2), June. 1, 2022
ISSN 2189–1990, CODEN: TJMOA2

interictal epileptiform discharges (IEDs) on electroencephalogram (EEG) may accompany transient cognitive/behavioral impairments. Furthermore, seizure frequency and/or IEDs may play a role as a mediator of emotional responses including stigma and fatigue in childhood epilepsy. Hencec, seizure frequency and IEDs are one of the important QOL-related factors in childhood epilepsy.

Neuropsychological impairments including cognitive/behavioral problems in children with epilepsy can be induced by various causes. Patients with identifiable frontal lobe lesions may exhibit cognitive or behavioral impairments in agreement with lesion location. Nevertheless, children without obvious lesions can also exhibit the same impairments. In Rolandic epilepsy (RE), a negative correlation has been evident between the IED frequency and performance on cognitive functions.[1)]

Stigma is a major issue associated with epilepsy, with great negative effects on patients and their families. Reducing negative issues including stigma in childhood epilepsy is one of the most important aims of clinical management.

Fatigue has been associated with the reduction in the QOL of epilepsy patients. Fatigue is correlated with anxiety, depression, and sleep problems in epilepsy patients.[2)] A previous study showed a tendency for increased fatigue in accordance with frequent seizures.[3)]

The processes for maturation of the frontal lobes are regarded to be protracted. Damage to the frontal regions during childhood can obstruct usual processes for maturation and organization, resulting in neuropsychological impairments.[4)] Several studies have concluded that frequent seizures impair the developing brain.[4)-6)] Frequent/severe seizures and EEG abnormalities may lead to cognitive, behavioral, and psychological impairments.

2. Correlation between Seizure Severities and Reduction in QOL

2.1. Correlation between seizure severities and cognitive/behavioral impairments

Cognitive and behavioral deterioration can lead to a reduction in QOL in children with epilepsy. This cognitive/behavioral problem may be related to frontal lobe dysfunction. Therefore, frontal lobe dysfunctions can be associated with a reduction in QOL for both child himself and his/her family.

The prefrontal parts comprised an extensive network that links the cerebral motor, perceptual, and limbic regions.[7)] This pervasive system of connections makes it possible for the prefrontal cortex to receive information from practically all parts of the cerebral regions, as well as to affect the information processing in those parts. Prefrontal lobe functions can show vulnerability for a long period, in which neurons and glial cells are easily influenced by various factors.[8)] Therefore, the prefrontal lobe seems to be more highly vulnerable to frequent and prolonged seizures than other cortical regions.[7,8)] Epileptic children associated with frontal lobe have several neuropsychological problems relative to normative standards.[9)]

2.1.1. Frontal lobe epilepsy

It is important to understand the influence of frontal lobe epilepsy (FLE) on the life of affected patients. Serial three-dimensional MRI volumetric study in FLE patients showed that frontal/prefrontal lobe volumes and the prefrontal-to-frontal lobe volume ratio increased serially in the tractable FLE patients without neuropsychological problems and healthy participants.[8)] By contrast, frontal/prefrontal lobe volumes revealed no apparent growth during the active seizure period in intractable FLE patients with cognitive/behavioral impairments. Children with a shorter active seizure period soon achieved a restored growth ratio. By contrast, the growth ratio was stagnated in patients with a longer active seizure period[8)] (Table 1). Accordingly, the occurrence of frequent seizures in FLE patients may be associated with prefrontal lobe growth retardation, which relates to neuropsychological impairments.

2.1.2. Panayiotopoulos syndrome

In general, Panayiotopoulos syndrome (PS) is not associated with neuropsychological problems. Nevertheless, cognitive/behavioral impairments may be present in at least some of the PS patients. Some degrees of neuronal damage due to status epilepticus (SE) may occur in the brain. In approximately 40% of PS patients, the seizure duration is more than 30 min, subsequent to a focal or secondarily generalized SE.[10)] In a serial volumetric study, growth of the frontal and prefrontal lobes was slightly decreased after SE episodes in PS patients. Moreover, the scores on the cognitive measurement were decreased in the SE patients[11)] (Table 1). Therefore, the occurrence of SE in PS patients may be associated with prefrontal lobe growth disturbance, which relates to neuropsychological impairments.

2.2. Headache

Migraine and epilepsy belong to a heterogeneous fam-

Table 1 Findings for seizure severities as QOL-related factors

Seizure severities as QOL-related factors	Findings
Cognitive/behavioral impairments in frontal lobe epilepsy [8]	#Frontal/prefrontal lobe volumes and the prefrontal-to-frontal lobe volume ratio increased serially in the tractable FLE patients without cognitive/behavioral impairments and healthy controls. #Frontal/prefrontal lobe volumes showed no obvious growth during the active seizure period in the intractable FLE patients with cognitive/behavioral impairments. #Children with a shorter active seizure period soon achieved a restored growth ratio. #The growth ratio was delayed in patients with a longer active seizure period.
Cognitive/behavioral impairments in Panayiotopoulos syndrome [11]	#Growth of the frontal and prefrontal lobes was slightly decreased for some time after SE episodes in PS patients. #The scores on the neuropsychological tests were decreased in the SE patients.
Headache [13]	#The seizure frequency was 4.1 times per year in patients with seizure-associated headache. # The seizure frequency was 1.3 times per year in those with nonseizure-associated headache.
Stigma in children [16]	#Children with frequent seizures showed significant impairment of psychosocial functioning compared to seizure-free children ($p<0.01$). #Greater perceptions of stigma were associated with greater seizure frequency in accordance with the Child Stigma Scale ($p<0.01$).
Stigma in parents [23]	#Parents of children with epilepsy showed significantly higher scores on the questionnaire than those of healthy children ($p<0.0001$). #Greater perceptions of stigma were associated with a seizure frequency of more than one per month ($p=0.0036$).
Fatigue [27]	#The mean FSS scores of the children with epilepsy were significantly higher than those of the healthy group ($p<0.0001$). #Multiple linear regression analysis showed that seizure frequency was the only characteristic significantly associated with fatigue ($p<0.0001$). #A higher seizure frequency was associated with more severe fatigue ($p<0.0001$).

QOL, quality of life; FLE, frontal lobe epilepsy; PS, Panayiotopoulos syndrome; SE, status epilepticus; FSS, Fatigue Severity Scale.

ily of neurological disorders.[12] Headache, because of its higher prevalence, is common in epilepsy patients. Our previous study showed that 34 of 98 children presented with seizure-associated headaches. The seizure frequency was 4.1 times per year in patients with seizure-associated headaches and 1.3 times per year in those with nonseizure-associated headaches[13] (Table 1). This result indicates that frequent seizures may be associated with seizure-associated headaches, which relates to the reduction in QOL.

2.3. Stigma in children

Stigma is a major issue for epilepsy patients. Stigma erodes the self-esteem and social status of the individual, all of which contribute to poor prognosis including isolation and delays in seeking treatment.[14] Conversely, adolescence is the transitional stage of mental and physical development. During this unstable stage of life, epilepsy can stigmatize persons and impair their independence, social abilities, peer relations, self-esteem, and mood, because adolescents can be mentally and emotionally fragile.[15] Therefore, there can be negative effects on social identity in children with epilepsy because of the stigma associated with having epilepsy.

In our study, children with frequent seizures showed psychosocial impairments in comparison with seizure-free children. Moreover, greater perceptions of stigma were associated with greater seizure frequency according to the Child Stigma Scale[16] (Table 1). Children with frequent seizures perceived themselves as significantly more stigmatized in comparison with seizure-free children.

2.4. Stigma in parents

Childhood epilepsy is a risk factor for parenting stress.[17-20] Parents of children with drug-resistant epilepsy may experience high levels of anxiety about recurrent seizures, and this heightened anxiety may deploy their children at greater risk for poor adaptive functioning.[21] Accordingly, frequent seizures appear to be a significant factor for parenting stress.[22] In a study using the Parent Stigma Scale, parents of children with epilepsy presented significantly higher scores on the question-

naire than those of healthy controls. Additionally, greater perceptions of stigma were associated with a higher seizure frequency[23] (Table 1). Therefore, frequent seizures may be associated with greater perceptions of stigma in parents.

2.5. Fatigue in children with epilepsy

Fatigue has been demonstrated to negatively impact the QOL of patients with chronic disorders including epilepsy.[24)-26)] A previous study using the Fatigue Severity Scale showed that the mean scores of the children with epilepsy were significantly higher than those of the healthy children.[27)] Multiple linear regression analysis showed that seizure frequency was the sole clinical manifestation significantly associated with fatigue. Additionally, a higher seizure frequency was associated with more severe fatigue[27)] (Table 1). Thus, frequent seizures may be also associated with fatigue in children with epilepsy.

3. EEG Abnormalities as QOL-Related Factors

3.1. Correlation between EEG abnormalities and seizure recurrence

IEDs on EEG are regarded as correlated with pathological neuronal discharges.[28)] A previous study showed that seizure recurrence and prolonged periods of high-frequency IEDs were significantly correlated in RE.[29)] Accordingly, a combination of IED frequency and prolonged periods of high-frequency IEDs may predict seizure recurrence in RE. Moreover, patients with frontal IED may have a higher risk of seizure recurrence after a first unprovoked seizure than those with IEDs in other regions of EEG foci[30)] (Table 2). Therefore, high-frequency IEDs and frontal IEDs may be associated with seizure recurrence.

3.2. Correlation between EEG abnormalities and cognitive/behavioral impairments

Cognitive and behavioral problems are more common in children with atypical EEG manifestations.[31)-33)] Some children present transient behavioral impairments that are correlated with IEDs without clinical seizures.[34, 35)] Our previous study showed that cognitive and behavioral impairments were significantly correlated with a prolonged period of high-frequency IEDs in RE.[36)] Moreover, these impairments were significantly correlated with a prolonged period of frontal EEG focus.[36)] Performances in the cognitive measurements may be especially weakened in individuals with frequent IEDs. Additionally, neuropsychological functioning can improve with the normalization of the EEG.[37)] Thus, IEDs may contribute to the neuropsychological problems in RE. Neurophysiological findings associated with the inhibitory seizures or negative myoclonus presented in the atypical RE suggest primary or secondary involvement of the frontal cortex.[38)] Furthermore, frontal/prefrontal lobe growth disturbances were evident even after remission of clinical seizures in atypical RE.[7)] Thus, atypical RE may be associated with frontal lobe dysfunction resulting in neuropsychological impairments. Accordingly, frontal IED may be associated with cognitive/behavioral problems.

Frontal IED has pathogenesis considerably. We investigated the relationship between neuropsychological impairments, IED, and treatment with antiseizure medication (ASM) in children with both attention-deficit hyperactivity disorder (ADHD) and IED.[39)] This study showed that a significant correlation was evident between IED frequency and ADHD rating scale (ADHD-RS) in the frontal IED group but not in the RD group. Moreover, a significant correlation was seen between decreased IED frequency and reduced scores of ADHD-RS after ASM treatment in the frontal IED group but not in the RD group.[39)] Therefore, frontal IED may have a strong correlation with behavioral impairments.

In another study, the IED location was most frequently in the frontal region in children with autism spectrum disorder (ASD).[40)] Additionally, a correlation between decreased IED frequency and the Japanese manuals for the Aberrant Behavior Checklist (ABC-J) score after treatment was evident in frontal IEDs but not in nonfrontal IEDs. In the presence of frontal IEDs, behavioral impairments correlated with IED frequency, and ASM treatment showed efficacy in both reduction of IED frequency and behavioral improvement in ASD patients presenting with frontal IEDs.[41)] Hence, frontal IEDs in ASD children may be associated with behavioral problems.

Conversely, among several atypical EEG manifestations, secondary bilateral synchrony (SBS) appears to be associated with neuropsychological impairments. Many children with epileptic encephalopathy with continuous spikes and waves during slow sleep (EECSWS), as a representative epileptic syndrome of SBS, present severe cognitive and behavioral impairments. In a volumetric study, frontal and prefrontal lobe volumes revealed growth retardation in all EECSWS patients in comparison with those of controls.[42)] Additionally, prefrontal to frontal

Table 2 Findings for IED on EEG as QOL-related factors

IED on EEG as QOL-related factors	Findings
Seizure recurrence and frequency of IED [29]	#Seizure recurrence and extended periods of high-frequency IEDs were significantly correlated in RE ($p<0.001$).
Seizure recurrence and frontal IED [30]	#Patients with frontal IED may have a significantly higher risk of developing epilepsy after a first unprovoked seizure than those with IEDs in other regions of EEG foci ($p<0.05$).
Cognitive/behavioral impairments and frequency of IED [36]	#Cognitive and behavioral impairments were significantly correlated with a prolonged period of high-frequency IEDs in RE ($p<0.01$).
Cognitive/behavioral impairments and frontal IED [36, 39-41]	#Cognitive and behavioral impairments were also significantly correlated with a prolonged period of frontal EEG focus in RE ($p<0.003$). #A significant correlation was evident between IED frequency and ADHD-RS in the frontal IED group, but not in the RD group ($p<0.03$). #A significant correlation was seen between decreased IED frequency and reduced scores of ADHD-RS after ASM treatments in the frontal IED group, but not in the RD group ($p<0.001$). #The location of IED was most commonly in the frontal region in children with ASD. #A correlation between decreased IED frequency and the Japanese manuals for the ABC-J score after treatment was evident in frontal IEDs, but not in non-frontal IEDs in ASD patients ($p=0.023$).
Cognitive/behavioral impairments and SBS [42, 43]	#Frontal and prefrontal lobe volumes revealed growth disturbance in all EECSWS patients compared with those of controls. #Prefrontal to frontal lobe volume ratios increased serially in control participants, whereas the ratios decreased in all EECSWS patients. # In the patients with shorter CSWS periods, the ratios were soon restored to normal values. # Growth disturbances of the prefrontal lobes were persistent in the patients with longer CSWS periods. #The degree of decrease of ABC-J score by ASM treatment was larger in EEG responders than in EEG nonresponders in patients presenting with SBS ($p<0.01$).
Stigma in children and frontal IED [45]	#The scores of all questions were higher in the frontal group than those in other regions ($p<0.01$). #Children presenting with frontal IED perceived a greater stigma than those with nonfrontal IED ($p<0.01$).

IED, interictal epileptiform discharge; EEG, electroencephalogram; QOL, quality of life; RE, Rolandic epilepsy; ADHD-RS, attention-deficit/hyperactivity disorder rating scale; ASM, antiseizure medication; RD, Rolandic discharge; ASD, autism spectrum disorder; ABC-J, Aberrant Behavior Checklist; SBS, secondary bilateral synchrony; EECSWS, epileptic encephalopathy with continuous spikes and waves during slow sleep.

lobe volume ratios increased serially in controls, whereas the ratios decreased in all EECSWS patients. Moreover, in the patients with shorter CSWS periods, the ratios were soon recovered to normal values, whereas the prefrontal lobe growth retardation was persistent in the patients with longer CSWS periods.[42] Based on these observations, the duration of severe EEG abnormalities may be associated with prefrontal lobe growth disturbance, which relates to neuropsychological impairments.

Moreover, we evaluated the relationship between IED/seizure frequency and neuropsychological impairments after ASM treatment in epilepsy adolescents with SBS.[43] The degree of decrease by ASM treatment was greater in EEG responders than in EEG nonresponders. This finding suggests that behavioral problems may be associated with SBS on EEG[43] (Table 2).

3.3. Correlation between EEG abnormalities and stigma

The relationship between emotions and abnormalities in EEG activity has been examined. Frontal EEG abnormalities may affect neuropsychological functions.[44] In our previous study, the relationship between localized IED and the perception of stigma was evaluated to elucidate EEG factors associated with perceived stigma in children with epilepsy.[45] This study showed that the scores of the Child Stigma Scale were higher in the frontal group than those in other regions. Children presenting with frontal IED perceived a greater stigma than those with nonfrontal IED. Thus, frontal IED may function as a mediator of emotional responses such as stigma[45] (Table 2).

4. Strategy of Treatment for Childhood Epilepsy

4.1. Urgent suppression of clinical seizures

As described before, the occurrence of frequent seizures and SE may induce prefrontal lobe growth retardation, which provokes neuropsychological impairments.[8,11] Additionally, prefrontal growth may reveal more rapid recovery in patients with shorter active seizure periods.[8] The findings in previous studies may support the possible explanations for the relationship between frequent seizures and neuropsychological impairments as "seizure activity per se disrupts behavior" speculated by Austin et al.[46] Moreover, PS patients presenting with SE showed disrupted prefrontal growth in our previous study.[11] Furthermore, poorer outcomes were evident in patients with more frequent SE episodes.[11] Thus, SE can induce disruptions in prefrontal growth in the immature brain. Damage to the frontal regions during childhood can result in impairments to neurobehavioral development.[47]

Based on these findings, management of treatment may be required to remit seizures as soon as possible to achieve optimal prognosis with cognitive or behavioral involvement in childhood epilepsy.

4.2. Urgent suppression of EEG abnormalities

As suggested by several studies, high-frequency IEDs and frontal IEDs may be associated with neuropsychological impairments.[36] As described before, EEG improvement via ASM treatment may be associated with behavioral improvements in children with ADHD/ASD presenting with frontal IED.[39,41] Thus, frontal IED may be associated with behavioral impairments in ADHD/ASD, and treatment with ASM may be effective both in the reduction of IED and in the improvement of behavioral impairments in the ADHD/ASD patients with frontal IED.

Additionally, concerning the EECSWS-related neuropsychological impairments, several authors have underlined the parallel course of EECSWS and cognitive/behavioral abnormalities.[48] The manifestation of neuropsychological impairments coincided with the onset and disappearance of EEG abnormalities rather than with the outcome of clinical seizures.[49] As described before, behavioral improvement was evident in association with EEG improvement in patients presenting with SBS.[43] The duration of "epilepsy," not only "clinical seizure," seems to be a prognostic factor, and thus, the urgent suppression of SBS may be necessary to prevent the progression of neuropsychological impairments.[50]

Based on these findings, the urgent suppression of frontal IED and SBS may be necessary to prevent the progression of neuropsychological impairments and to improve the QOL of children with epilepsy.

5. Conclusion

Children with epilepsy do not always exhibit neuropsychological problems. Nevertheless, seizure severities and IEDs on EEG may be associated with neuropsychological impairments. To prevent these disturbances, we should appropriately treat patients to suppress seizures and EEG abnormalities as early as possible. Based on the results of several studies, the preferable treatment options may be required to remit seizures and EEG abnormalities such as frontal IED and SBS as soon as possible to achieve the most favorable prognosis for children with epilepsy.

Conflicts of interest: Dr. Hideaki Kanemura has received speaker's fees from Eisai Co., Ltd.

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Dr. Kanemura has received his PhD at University of Yamanashi in 2003. Presently, he is working as a professor in the Department of Pediatrics, Toho University Medical Center Sakura Hospital. His research has included pediatric neurology, epilepsy, and neurodevelopmental disorders. He is serving as an editorial member of several reputed journals like Brain & Development. He has authored epilepsy and pediatric neurological clinical research articles/books. He is a director of the Japanese Epilepsy Society and Japanese Society of Clinical Neurophysiology and a delegate of Japan Pediatric Society, Japanese Society of Child Neurology, and Japanese Society of Cognitive Neuroscience.