

Review Article

Cognitive Outcome of Status Epilepticus in Children

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Epileptic encephalopathy encompasses conditions in which cognitive, motor, or sensory deficits result as a consequence of epileptic activity defining certain syndromes. It therefore represents a more severe subset of epilepsy, which can be generally characterized as frequent or severe seizures leading to cerebral dysfunction. This disturbance in cerebral functioning can in turn hinder, somewhat dramatically, cognitive development and further impact the future lives of patients. In this paper, we describe the cognitive consequences of status epilepticus in children and in adults in the context of plasticity theories. Recent studies maintain that consequences of SE may be severe cognitive sequelae, especially in early life. Since the residual consequences of SE in adulthood seem less detrimental and long-lasting, we argue that early life insults, such as those created by SE, during a rapid period of development and functional specialization, result in specific cognitive deficits dependent on the sensitive period at which SE occurred.

1. Introduction

Epileptic encephalopathy encompasses conditions in which cognitive, motor, or sensory deficits result as a consequence of epileptic activity defining certain syndromes [1]. It therefore represents a more severe subset of epilepsy, which can be generally characterized as frequent or severe seizures leading to cerebral dysfunction. This disturbance in cerebral functioning can in turn hinder, somewhat dramatically, cognitive development and further impact the future lives of patients. In this paper, we consider status epilepticus as an epileptic encephalopathy owing to its impact on cognitive development in early life.

2. Status Epilepticus (SE)

Status Epilepticus (SE) is a medical epileptic emergency characterized by either rapidly repeating seizures without recovery or regain of consciousness between episodes, or prolonged continuous epileptic activity, both creating a fixed or lasting condition [2, 3]. It is an event rather than a syndrome. It is accepted that the duration of an episode of SE is 30 minutes or more, period after which cerebral functioning is highly probable of being affected and immediate medical

attention is needed [4]. Recently, the notions of impending SE and established SE have been introduced [5] in order to provide the best possible care for patients presenting with SE. In adults, patients presenting a seizure lasting more than five minutes can be designated as impending SE. In children, impending seizures are considered when seizures last between 5 and 10 minutes [5].

The prevalence of SE varies. Three epidemiologic studies suggest 17 to 108/100000 as being the prevalence of SE [6–8]. Although SE can occur at any age, it is most often encountered in infancy and childhood, 40% of all cases occurring prior to 2 years of age, a period in which the brain is in rapid development [9]. Such prevalence is argued to be present in early life owing to the exceeding amount of neurons and excitatory connections prior to functional specialization while undergoing neuronal pruning, which increases the vulnerability of the developing brain to SE [10]. In affected children, an imbalance between inhibitory and excitatory neurotransmissions is argued to lead to anomalies in neuronal impulses leading to prolonged seizures [11]. In fact, the pathophysiology of SE seems to involve a loss of inhibitory mechanisms, which result in a deficiency of the neuronal metabolism, which is unable to keep up with the demands of the continuous epileptic activity [12]. The seizures are most

frequently generalized, but may also be partial and either convulsive or nonconvulsive [13]. SE is further classified in accordance with its respective etiology [14]. Idiopathic SE occurs in otherwise healthy individuals without metabolic dysfunction nor an acute insult to the Central Nervous System (CNS). Furthermore, remote symptomatic SE occurs in patients with a history of insult to the CNS without acute provocation such as in mental retardation. Febrile SE, the most common etiology in children [15], occurs when the only provocation of the CNS is a high fever, usually higher than 38,4 degrees Celsius. In this population, 86% of children demonstrate normal prior development [16]. Acute symptomatic SE occurs during an acute illness with a known insult to the CNS such as in meningitis. Although there has been debate on the long-term effects of SE on cerebral functioning, recent research investigating more accurately the cognitive sequelae related to SE demonstrate that cognitive functions under development are exposed to being altered and damaged in children presenting with SE, owing to its high incidence in infancy, a period of marked and rapid cognitive development.

3. Plasticity versus Vulnerability in the Developing Brain

In considering the impact of an early insult on cerebral and cognitive development, two opposing theories are contradictory in their predictions. The plasticity theory posits that the young brain is flexible and therefore capable of recovery after insult. As such, since there is less functional specialization in early life, functions that would depend on a damaged area would simply reorganize to functionally cope with the insult [17, 18]. As such, this theory predicts that early brain damage is the most biologically manageable, resulting in less vulnerability to the impact of damage as opposed to an older brain. In contrast, the vulnerability theory posits that the young brain is the most fragile and therefore vulnerable to early insult. It argues that owing to the lack of functional specialization, the brain will attempt to recover endangered functions, but will do so aberrantly creating faulty connections in early life [19]. As such, a crowding effect will take place such that healthy tissue will take over the damaged tissue in attempt to recover the cognitive function at hand, but consequently limiting the tissue's quantitative and qualitative resources [20]. This effect was first demonstrated in the context of hemispheric dominance following left hemisphere damage in early life such that an insult to the left hemisphere prior to one year of age resulted in the proper development of language but faulty development of nonverbal skills; owing to brain plasticity, the emerging language functions took over neurons dedicated to nonverbal skills. The reverse effect was observed when the insult occurred after one year of age [20, 21]. As such, healthy tissue, although already specialized for a certain function will forgo that specialization for the proper development of the function underlying the insult, creating a "crowding" of cognitive functions for that particular tissue. Therefore, the vulnerability perspective of the developing brain predicts that early life insults are the most difficult to recover from.

In further investigating the opposing predictions of both theories of the impact of early insult on the developing brain, the vulnerability theory has been the most supported [22–25]. It has been found that young neurons more readily grow to make new connections, which following an insult, may facilitate aberrant connections [26]. As such, the developing brain is the most vulnerable to insult resulting in subsequent damage post-SE potentially persisting in later life. Furthermore, findings demonstrate that not only is the severity of the sequelae following SE predicted by the extent and location of the insult, but the nature of the sequelae itself is determined by the timing of the SE episode [27]. As such, the developmental period at which the insult occurs is argued to predict which cognitive functions will be most affected and therefore predict the general outcome of the patient.

4. A Model of Human Development

In concordance with the vulnerability theory, early insults to the brain have the most detrimental impact on cerebral and cognitive development persisting in later life. As such, faulty neuronal connections following an early life insult during a critical period of development will hinder the normal development of brain functions, for which the sequelae will persist in later life [28]. However, already developed functions at the time of the insult will be spared. The notion of critical periods during infancy through adolescence is widespread and generally accepted [29]. Critical periods allow for a logical hierarchy in development such that windows of opportunity allow for the specialization of functions. Furthermore, certain structures and their underlying function must be well specialized prior to others. As such, sensing pathways such as those involved in vision and hearing must develop prior to language pathways, which in turn must develop prior to higher cognitive functioning, including executive functions [29]. Critical periods, consequently, expose certain functions as more vulnerable than others in particular and specific periods during development. The vulnerability of different cognitive functions therefore varies with the developmental process itself. In the presence of an early insult to the brain, the function under development will be hindered, affecting not only that particular function, but also the development of subsequent functions dependent on the hindered one. Healthy development of cognitive functions depends on the integrity of the structure the function underlies. As such, following an early life insult, the integrity of a particular structure is compromised, further compromising the cognitive function that structure is responsible for.

5. Physiological Alterations Resulting from SE

Prolonged and frequent seizures, such as those involved in SE consistently show physiological brain damage. In fact, the physiological properties of cells have been shown to be altered following an SE event [30, 31]. The most vulnerable structure to the seizures is the hippocampus, which is involved in learning and memory. Hippocampal edema, cell loss particularly in the Sommer sector, and abnormalities

have consistently been detected within this structure following SE [10, 32]. Also in human, other structures have been demonstrated to show necrosis following events of epileptic attacks such as the amygdala, dorsomedial thalamic nucleus, medial layers of the neocortex, cerebellum, the piriforme and entorhinal cortices [30–33]. Neuronal degeneration and loss in these areas have been shown to occur rapidly after a SE event [30, 34]. Cerebral atrophy has also been demonstrated following SE [35]. Animal studies have further supported these physiological alterations. The work of Meldrum involving induced SE in baboons has demonstrated similar neuronal necrosis involving the neocortex, hippocampus, amygdala, thalamus, and cerebellum [35]. In a long-term followup, different SE animal models have found structural changes [36–38]. For example, smaller volumes of the hippocampus, thalamus, putamen, and perirhinal cortex have been found [38]. Interestingly, severity of hippocampal volume loss correlated with severity in spatial learning impairments. Of note, animal data describing the consequences of an induced single episode of SE tend to show greater deleterious consequences in immature rat brains in comparison to adult rat brains [39]. Although physiological alterations following SE have been shown specifically and consistently, the cognitive sequelae resulting from these abnormalities is not as clear and widespread.

6. Cognitive Sequelae of Status Epilepticus in Animal Models

Cognitive sequelae following SE were first studied using animal models in which animals showed a normal development until seizure onset. Following induced SE in rat pups, impairment in emotional behavior was observed, characterized by an increase in anxiety and fear [40, 41]. Furthermore, increased hyperactivity and spontaneous exploratory behavior was shown with a similar experimental design [40, 42]. Also, owing to the vulnerability of certain structures involved in the limbic system such as the hippocampus and amygdala, learning and memory impairments are consistently marked. Learning deficits, usually demonstrated by decreased habituation and reduced adaptations to novelty, are observed following SE, and these deficits persist into later life in rodents [40, 41, 43]. Also owing to acquired anomalies in these limbic structures, spatial and emotional learning and memory are impaired shortly after SE [41, 42, 44]. Memory impairments were thus marked in these models [44]. Whether these findings can generalize to the impact of early SE on the development of these cognitive functions to humans is a matter of debate. However, recent research has argued for cognitive sequelae resulting from SE in early life.

7. Cognitive Sequelae of Status Epilepticus in Humans

7.1. Children. Cognitive sequelae resulting from SE in early life have been demonstrated. In general, studies demonstrate progressive structural and functional alterations following SE, generally reporting broad cognitive consequences of SE.

Even so, deficits in verbal and nonverbal intellectual ability have been identified following SE [45–47]. Furthermore, global IQ deficits are demonstrated in early onset seizures [26, 46]. Several landmark studies have well demonstrated the presence of cognitive deficits following SE in early life. Aicardi & Chevrie [48] retrospectively studied 239 children having undergone one episode of SE lasting one hour or more, under the age of 15. Fifty-seven percent (57%) of the cohort presented with mental or neurological sequelae. More specifically, 20% of the cohort developed motor delays and 33% presented IQs lower than 80, all in children whose development was unremarkable prior to the SE event. Furthermore, 48% presented with mental retardation following the episode, the majority of affected children again demonstrating normal development prior to SE. Furthermore, Yager et al. [49] followed 52 children over 18 months following an episode of SE. Twenty-eight percent (28%) of otherwise healthy children developed neurological sequelae following SE, and 25% of children who were predisposed to pathologies including previous epileptic activity deteriorated further following SE. Lacroix et al. [50] also longitudinally followed 147 children following an episode of SE. Thirty percent (30%) showed a neurological deficit following SE at discharge, and 68% of these children still demonstrated these deficits one year after. Taken together, these data demonstrate marked cognitive and neurological dysfunction following SE, supporting the vulnerability theory of insult to the developing brain. However, even though dysfunctions are shown, the specific nature of the deficit remains unclear. The lack of appropriate and specific methods in evaluating the deficits makes conclusions general and nonspecific. Neuropsychological testing is however a good tool in evaluating the specific cognitive functions potentially affected as opposed to the assessment of level of functioning as a whole. Neuropsychological testing is advantageous since it can easily be adaptable to the hospital setting, however it should be noted that in infants, the age at testing poses a certain constraint on the sophistication of the assessment.

In taking these limitations into consideration, a recent study by Roy et al. [51] further assessed the vulnerability theory by studying the effect of a single episode of febrile SE on the developing brain in otherwise healthy children. They specifically examined psychomotor function as well as executive functions in these children. Executive functions, mainly involved in regulation of behavior, begin rapid development in early life, continuing through to adolescence [52–54] and are the underlying functions of the frontal lobes. Since executive skills are developed in different trajectories over a longer timeframe during development, comparing the impact of an insult at different times during this development can shed light onto its potential differing consequences. Following the hierarchy in the development of the brain, the frontal lobes depend on the structural and functional integrity of other structures as they encompass higher cognitive functions. An early insult to the brain would therefore hinder executive functions. Roy et al. [51] compared younger and older children in differing critical periods using neuropsychological testing to evaluate the prediction that the function under development would be the most vulnerable

to an insult. This is precisely what they found. In younger children (prior to 11 months of age) presenting with a febrile SE, hand-eye coordination and motor ability were most affected but were spared in older children. In contrast, older children presenting a febrile SE demonstrated personal and social deficits. Similarly, Anderson et al. [27] had previously demonstrated, with a larger age range of children and of insults, that consequence of early brain insult on executive functions was dependent on which critical period the episode occurred. As such, an insult prior to 2 years of age demonstrated deficits in goal-setting, a skill spared in children whose onset was in middle or late childhood. Furthermore, an insult prior to 3 years of age was associated with deficits in cognitive flexibility and working memory, these skills being spared in those for which SE episode occurred after the age of 10. It is important to note however that Anderson et al. [27] did not investigate the impact of an episode of SE per se, but rather the impact of early brain insult in general and as such, did not take the underlying etiologies into consideration. Indeed, studies in school age children presenting with SE are lacking. Roy et al. [51] however, investigated children affected precisely by Febrile SE and not only used healthy matched controls, but also included a control group composed of children affected by a simple Febrile Seizure (FS). Simple FS are brief (less than 15 minutes) and are argued to be unremarkable in their effects on the developing brain. As such, prolonged (SE) seizures were compared to brief (FS) seizures allowing to isolate the impact of fever and brief seizures themselves. Taken together, this particular study alone gives important insight into the presence and specific cognitive impairments observed following a single febrile SE episode in otherwise healthy children.

7.2. Adults. Patterns of cognitive sequelae following SE in adulthood seem to differ than those seen in infancy and childhood. In a prospective study of SE occurring in adults (mean age was 40) with no underlying pathology, Adachi et al. [55] did not demonstrate intellectual deficits following the episode as evaluated by neuropsychological testing (WAIS-R), but rather both the experimental and control group of matched healthy individuals could not be differentiated. This finding was also previously demonstrated [56]. In fact, resolution of long-lasting SE cognitive sequelae in adults have been demonstrated 6 to 24 months post-SE episode, and resolution of acute sequelae have been shown to resolve within 1 to 4 weeks, suggesting a reversible effect of the residual consequences of SE. Also demonstrating this effect was a case report of a 25-year-old woman with a history of epilepsy starting at age 14, hospitalized after an SE episode [57]. Neuropsychological testing demonstrated severe memory and executive function deficits at the time of the insult. However, one year after the insult and following unremarkable antiepileptic treatment, the cognitive deficits were reversed, and the woman returned to her Master's studies. These data of the impact of SE in adulthood suggest that its effects are less severe than in childhood, such that not only do studies show unremarkable intellectual deficits following SE, but also show reversible effects of the deficits. It should

be noted however that the SE described above were idiopathic. Symptomatic epilepsies in contrast involve greater presence and severity of cognitive impairments. However, even though the case study presented was symptomatic and still demonstrated reversible effects, etiology, and potentially other aspects underlying the SE episode, must be taken into account when considering its impact on cognition.

8. Other Aspects Potentially Underlying Cognitive Decline in SE

Whether an episode of SE results in cognitive deficits seems to not only rely on the onset of SE (infant versus adult) but rather on a web of interweaving aspects related to epilepsy and SE. Certain risk factors have been shown to affect prognosis following such an episode.

8.1. Etiology. The origin of the SE is an important risk factor. As there are several possible etiologies, the cause of SE can interplay with the actual seizures with regards to outcome. Idiopathic SE tends to have a more favorable prognosis than symptomatic SE [46, 49, 58]. Furthermore, a typical pattern of development prior to the episode is related to better outcome [50]. In contrast, the risk of developing epilepsy increases to more than 50% in convulsive symptomatic SE. In addition, more than 20% of children with acute symptomatic SE show new cognitive impairments compared to less than 10% in other types of SE [59]. The risk for SE is increased in neurologically deficient children [48] and children with a history of seizures are at higher risk for neurological sequelae [60]. Additionally, younger children tend to have more severe etiologies, as a decrease of acute symptomatic cases is observed after the first year of life [9]. However, 75% of children under 2 years of age demonstrated normal development until the insult [9]. In general, the presence of an organic etiology is related to poorer prognosis [46]. It should be noted however, that cognitive effects of the seizure itself without an underlying pathology have been reported [61, 62]. Taking etiology into account, if not cautious with the methodology used, the cause of the potential observed deficiency (etiology versus SE) can be confounded [4].

8.2. Duration and Frequency of Seizures. Longer durations of an SE episode are related to increased risk for deficits [58, 63]. In fact, it has been demonstrated that episodes lasting less than one hour result in neuronal injury, and episodes lasting more than one hour result in neuronal death [64], supporting the previous argument. Duration of SE is also related to etiology such that prolonged episodes typically accompany more severe etiologies [65].

Recurrent seizures are more persistent in individuals with prior neurological abnormalities [66]. Controversies exist as to the impact of recurrent seizures on cognition. It has been proposed that recurrent seizures lead to cognitive impairment, specifically, intellectual and memory deficits [44, 66]. Also, it has been shown that a long history of seizures is associated with mental deficits [67]. Furthermore, it has been demonstrated that early life seizures result in long-term

deficits [68], further supported by an animal model demonstrating deficits in learning and memory following recurrent SE [68]. In contrast, it has also been proposed that recurrence of seizures itself does not pose a risk for cognitive development [66, 69]. As demonstrated in SE, some epileptic models do not always demonstrate aggravated consequences of recurrence of seizures [70]. Following this perspective, in epileptic patients, it is suggested that the predisposed brain develops somewhat of a tolerance to the impact of seizures therefore producing less damage, whereas the naive brain is more vulnerable to one insult [71]. This perspective is however very delicate and must be debated.

8.3. Age of Onset. The risk involved in the age of onset of SE has been covered in this review such that, thus far it has been shown that SE onset in early life, a period at which individuals are more prone to SE, has a greater impact on cognitive functioning than in later life, in which even reversible effects are observed. As discussed under the related effects of etiology, SE presents greater severity in children as they more often show a symptomatic etiology than in adults [9, 48]. Furthermore, adults presenting with SE tend to have a history of seizures [9]. As such, consideration must be taken of the underlying etiology in the younger SE population on interference with development. In adults however, age of onset and duration of the SE episode has not been related to prognosis [53].

8.4. SE as Cause of Injury. In animal models, brain injuries following SE have been repetitively revealed. In children, SE can cause hippocampal lesions, at least in the acute phase [34]. Further studies are needed to investigate if long-term hippocampal MRI volume loss are due to reduced edema or to a loss of neuronal tissue. Furthermore, more human studies are needed to establish the link between hippocampal lesions following SE and cognitive impairments. This could be facilitated with the recommended use of MRI in cases of SE [72]. Investigating the link between these lesions in the limbic system and behavioral impairments could also be interesting and perhaps shed even more light on patient outcome following SE.

8.5. Other. With respect to gender, males have a higher propensity of developing symptomatic SE in contrast to females, which demonstrate a higher propensity of developing idiopathic SE [48]. However, gender itself does not have an impact on prognosis following an SE episode. It has also been suggested that an enriched environment can aid in memory decline such that enriched environments facilitate hippocampal plasticity, which in turn leads to bettered formation of long-term potentiation [73]. In contrast, race does not influence this prognosis [47, 74].

Taken together, several marked risk factors must be taken into consideration in evaluating the impact of SE on cognition such that several confounding variables are possible. However, awareness and caution in the methodologies and analyses used can shield from the confounding effect of these risk factors.

9. Impact of Antiepileptic Treatment (AED) on Cognition

Antiepileptic drugs (AED) have various effects between patients as well as between seizures and epilepsy types. The success of AED is usually measured as a reduction in the number of seizures, not necessarily as its impact on cognition following epilepsy [75]. As such, evaluation of cognitive ability following treatment poses more difficulty. In fact, some AED themselves have been shown to induce cognitive deficits such as mild memory, attention, and psychomotor problems [76]. Even though no comparative studies have been performed to investigate the side effects of more recent AED, it has been argued that Topiramate is involved in attention, concentration, and memory problems [77]. Taken together however, it is suggested that use of AED is not the major factor causing cognitive comorbidity in epileptic encephalopathies [78]. In SE, it has been demonstrated that cognitive outcome following SE depends on the time between the episode and the initiation of treatment [48, 58]. AED administered during an SE episode, in contrast to those administered in most epileptic conditions, are usually termed “aggressive treatment” since they are meant to be administered very rapidly and withdrawn within the following 24 hours [79]. Its purpose is to shorten the episode in hopes to protect against neuronal damage and therefore to potentially protect against the cognitive sequelae related to prolonged episodes [58, 79]. As such, AED have been shown to reduce cognitive sequelae following an episode [48, 58]. This was also observed in animal models [80]. More specifically, the use of AED in children presenting with SE has demonstrated a control of the seizures that resulted in a prevention of further cognitive deterioration [79]. Although AED stopped further cognitive sequelae, they did not allow recovering maladapted functions. Since AED did not allow recovering of anomalies in cognitive functions since SE onset, our argument that an insult to the developing brain at particular sensitive periods is detrimental to cognitive development is further supported.

10. Controversies

Even though we are arguing that SE has an unforgiving impact on cognitive development, as in any body of literature, results can be controversial. Firstly, a poor prognosis in early life SE has not always been reported [65, 81]. Also, it has been reported that the underlying causal factor of SE is related to outcome as opposed to age of onset [59, 82]. However, there are certain methodological considerations in these and other studies. Lack of standard categorization of underlying etiologies, as well as lack of consideration for type and frequency of seizures between testing could impact results. Furthermore, heterogeneous groups are often compared relative to age of onset, duration and frequency of seizures, etiology, treatment, and genetic factors also creating potential confounds [83]. Furthermore, it has been observed that retrospective studies tend to show greater intellectual deficit following SE than prospective studies [55].

In addition, measures of cognitive ability are often lacking accuracy and specificity such that deficits in specific skills are overlooked when simply assessing global IQ. IQ itself is not an appropriate measure for cognitive dysfunction. As such, more specific tests should be used in attempt to measure the cognitive skills of interest, such as would allow neuropsychological assessments. Again, this type of assessment is advantageous such that tests can be selectively chosen for each patient or each group of patients, categorized by site of lesion for example, in order to better comprehend the precise pervading deficits as opposed to a simple level of intelligence.

11. Discussion

In spite of these controversies and methodological issues, we maintain that consequences of SE may be severe cognitive sequelae, especially in early life. More recent studies more readily take these methodological issues into account creating a better experimental design. Also, they use more specific tests and aim and specific cognitive functions. As such, these recent results better demonstrate the presence and severity of the cognitive sequelae resulting from SE in infancy. Since the residual consequences of SE in adulthood seem less detrimental and long-lasting, we argue that early life insults, such as those created by SE, during a rapid period of development and functional specialization, result in specific cognitive deficits dependent of the sensitive period at which occurred SE. These deficits can potentially lead to deficits in later childhood expressed as such as learning disabilities, the residua of which may persist into later life. Further investigations involving the long-term effects and impacts of early life SE on later development and later life functioning are needed. Although adult-onset SE seems to spare the cognitive integrity of affected patients, it is still unknown whether early-onset SE has detrimental impacts in later life.

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