

Child and Adolescent Psychiatric Late Effects of Early Herpes Simplex Virus Type 1 Encephalitis

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Abstract: The most common late sequelae of herpes simplex virus type 1 encephalitis (HSVE) include secondary epilepsy, learning, language and memory disorders, and chronic headaches. The typical pattern of HSVE leads to necrosis in the temporal and frontal lobes, thus affecting areas of the brain specifically responsible for the coordination of memory and emotion. This case report describes the course of a patient who, in addition to the typical neurological long-term sequelae, also showed severe psychiatric abnormalities and subsequently addresses the question of why there have been hardly any reports of child and adolescent psychiatric late sequelae after HSVE to date. It can be assumed that the frequency of psychiatric late sequelae is underestimated in pediatrics and in child and adolescent psychiatry and that a targeted anamnestic diagnosis is therefore too often omitted later in child and adolescent psychiatry when psychiatric symptoms appear with a long latency. The second part of the article reviews the state of research to date, revealing that there are too few data on how often and to what extent early-experienced HSVE leads to psychiatric late effects. On the basis of the case report, the specific symptoms to which particular attention should be paid and the brain structures that are typically involved in relation to a psychiatric disorder are presented. From this, it can be deduced, according to the conclusion in the third part of the article, which medications might help. Because of the typical symptomatology of emotional instability some years after HSVE, it is suggested to consider the possibility of mood-stabilizing therapy. The results from the case report presented suggest this.

Keywords: Encephalitis, Psychiatric Late Effects, Small Brain Lesions, Emotional Lability, Trauma, Borderline Personality, Mood Stabilizing Therapy

1. Introduction

If we look at the epidemiological significance of herpes simplex virus type 1 encephalitis we can summarize the following facts:

The incidence of viral encephalitis in Central and Western Europe is 1.5-7/100,000 inhabitants [5]. With a proportion of about 20% and an overall incidence of 0.2-0.4/100,000 inhabitants, encephalitis with herpes simplex virus type 1 is the most common cause of acute, sporadic CNS infection, affecting patients between 6 months and 20 years of age in 30% of cases [6-8]. The usually biphasic course of infection begins mostly nonspecifically with fever accompanied by general flu-like symptoms [1, 2]. Short-term improvement is

often followed by the acute phase, in which neurologic symptoms such as headache, impaired consciousness, and seizures may dominate. In addition to clinical chemistry and early pathogen DNA detection in CSF, diagnostic imaging such as MRI is the gold standard [3]. Therapy consists of intravenous administration of Aciclovir. In addition, immunosuppressants such as rituximab or cyclophosphamide may be required [4, 9]. Untreated, the mortality of HSVE is 70% [10, 11]. In 50-60% of HSVE survivors, neurological sequelae such as epileptic seizures or impairment of cognitive functions, learning and memory deficits or deficits of speech and motor function can be detected [12].

But what do we know about the psychological or psychiatric consequences of HSVE, which often occurs years after the acute infection?

In fact unspecific psychiatric behavioral disorders are frequently reported as a consequence of HSVE [13, 14]. Which early psychiatric symptomatology or even psychiatric disease is actually hidden behind this term can often only be guessed at. Ebaugh first described tension and emotional instability in survivors of encephalitis in 1923 [15]. Schmidt *et al.* used the geriatric depression scale to quantify the long-term psychiatric consequences of HSVE in their 2010 work [16]. In 2012, Mailles *et al.* conducted a structured interview to assess emotional health and found behavioral abnormalities, such as aggression, depression, or increased anxiety, in some of the included HSVE patients [17]. According to our research, a detailed child and adolescent psychiatric diagnosis has not been made so far. Moreover, the few papers that have dealt with the psychiatric consequences of brain injury are often found in adult psychiatry [18-20]. The problematic aspect is that the child and adolescent brain is in a process of maturation and development and is therefore particularly vulnerable to inflammatory processes, because even small injuries to the still immature neuronal networks in development can have major consequences in the long term. Although the neuroplasticity of the cortex is still very pronounced in the infantile maturation phase [21-23], in certain brain regions, such as the limbic system, postencephalitic scarring can involve irreversible neuronal losses of brain tissue that cannot be functionally replaced or compensated for by other neuronal networks (connectomes) [24]. In such brain regions, small lesions are often not so noticeable at first. Only in the course of personality development does it become apparent at some point that deep-seated brain structures such as the amygdala, which is tasked with regulating emotions, are not functioning as they should. Then, many years later, e.g. a psychiatric personality development disorder is assumed, the origin of which is not further questioned or is described as "endogenous" (genetically dispositioned) and thus remains diffuse. The connection with a somatically otherwise healed postencephalitic scarring in the neuronal network is then anything but obvious.

In the following case, we will exemplarily trace the consequences of juvenile encephalitis, which years later affected affect regulation in the corticomedullary system, as described above. We will try to relate the psychiatric abnormalities of a juvenile to a postencephalitic scarring of the neuronal tissue in order to finally ask the question whether we should provide long-term psychiatric follow-up to children and adolescents who had HSVE.

2. Child and Adolescent Psychiatric Case of Attempted Suicide Nine Years After Undergoing HSVE

A 15-year-old female patient presented to our acute psychiatric department at the Children's Hospital auf der Bult in Hannover after a suicide attempt. She had taken a potentially lethal dose of 7.5 grams of paracetamol. Nine

years earlier, the adolescent had undergone herpes simplex virus type 1 encephalitis (HSVE), which required intensive medical care with intravenous administration of aciclovir. Immediately after HSVE, at the age of 7, she had received extensive speech therapy due to a persistent speech comprehension disorder. In subsequent years, she had experienced bullying because of this. There were only a few friendships, but they were very intense. However, complex school contents had been perceived as overstraining only since about 5 months before admission. At the same time, psychiatric abnormalities had appeared for the first time in the form of a severe emotion control disorder, which led to self-injurious behavior with sharp objects on the wrists when tension arose, and atypical bulimia ("purging-eating" attacks). In addition to crying and screaming fits at school, the parents reported other unusual behaviors. Their daughter was remarkably in need of closeness and cuddling, at the same time she would hardly question rules in the household, was hardly borderline or eager to discuss, as she had been until a few months ago. In addition, some suicide notes of the patient were found. Suicidal ideation occurred, accompanied by suicidal impulses, and led to the patient finally attempting the above-mentioned suicide with paracetamol. The patient reported a feeling of release and relaxation after taking the tablets. She found the unexpected waking up the following morning with abdominal pain and nausea disappointing and highly stressful. In the first contact, the adolescent confirmed her clear intention to commit suicide and was unable to distance herself from another suicide attempt.

3. The Problem of Methods: A Question of Diagnostics

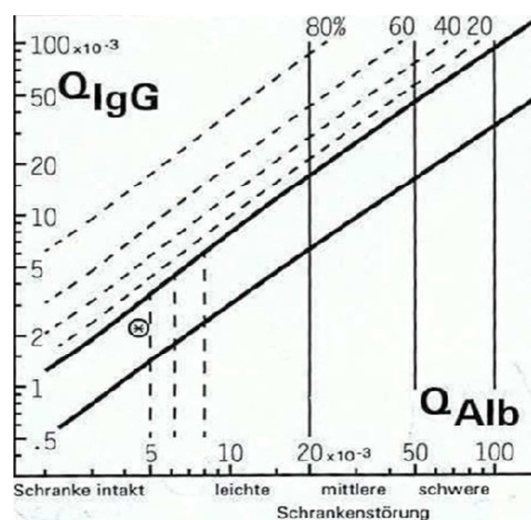


Figure 1. CSF findings according to Reiber with positive intrathecal IgG synthesis with intact blood-brain barrier.

On *physical examination*, the 56-kilogram (44th percentile), 165-cm (49th percentile) 15-year-old girl had fresh horizontal and vertical self-inflicted lacerations and cuts on both wrists. On contact, we saw a closed patient who

spoke little. She showed low affect, depression, hopelessness, and intermittent irritability; *Psychometric testing* confirmed residual language comprehension disorder. The adolescent found it particularly difficult to understand the meaning and significance of figurative language and metaphors. *EEG and ECG* showed no pathological changes. *Laboratory chemistry did not reveal any abnormalities* in the small blood count, classical organic parameters, or virological examination.

Anti-neural antibodies of the IgG type could not be detected in serum or CSF. A detailed analysis of the CSF revealed an intrathecal synthesis of IgG-type immunoglobulins in the sense of a viral encephalitis (Figure 1).

Based on the CSF findings of a postencephalitic IgG elevation in the sense of an immunologic scar, we decided to perform an MRI scan, which revealed the following findings (see Figure 2):

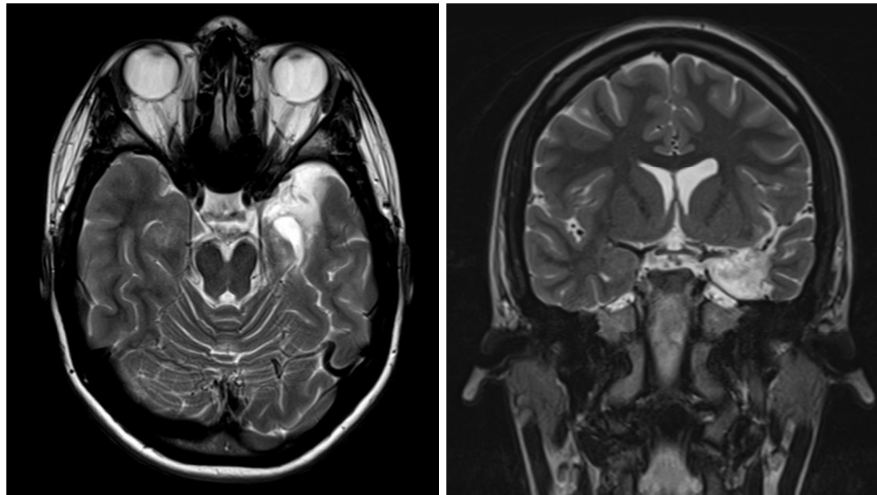


Figure 2. Current findings at KJP visit: 9 years after HSVE a corticomedullary parenchymal defect on the left temporopolar/temporomesial side with adjacent medullary bearing gliosis and resulting e-vacuo enlargement of the left temporal horn (T2 axial left) (T2 coronal right).

MRI images showed old scarring of the neural tissue corticomedullary left temporopolar/temporomesial with adjacent medullary lag gliosis, as well as dilatation of the left temporal horn. To establish a correlation of the current

parenchymal defect with the HSVE undergone nine years ago, the old MRI images were located and the findings compared (see Figure 3):

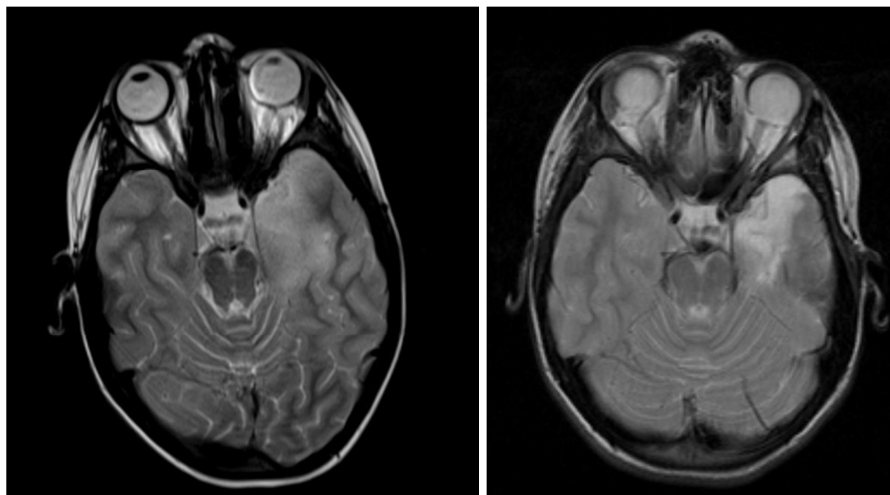


Figure 3. Left: cMRI (T2 axial) of the patient initially with areal signal enhancement of the left medial and rostral temporal lobe. Right: Control cMRI (T2 axial) three years after HSVE with residual cerebral damage of the left temporal lobe (right).

In the acute encephalitis phase, the cMRI image showed a diffuse change of the neuronal structure in the left temporal lobe medially and rostrally (Figure 3, left). In a control cMRI three years later, residual damage of the left temporal lobe could already be clearly demonstrated (Figure 3, right). The process of scarring and loss of function is already evident here. However, no mental abnormalities or expansive

behaviors have been described at this time. Apparently, the corticomedullary damage in the left hemisphere became so functionally relevant only with the development to adolescence and young adulthood that it could no longer be compensated. How this temporal latency can be explained will be discussed below. An important factor seems to be that with the onset of puberty the brain is undergoing a renewed

remodeling process in which neuronal neuronal connections that do not appear functional are completely eliminated to be replaced by new and faster neuronal connections. It is likely that the left hemispheric corticomedullary lesion of the neuronal parenchyma to cope with new developmental tasks was absent to remodel new neuronal structures, and scarring set limits to neuroplasticity in a brain region that is necessary for affect regulation and whose function cannot be compensated by other brain areas that are also undergoing pubertal remodeling with new tasks. The cMRI images shown above suggest that parts of the limbic system (amygdala, hippocampus) and its connections to more conscious cortical structures of the left temporal lobe have been affected. This finding is consistent with the psychiatric symptomatology described: The result is an affect regulation disorder, which, due to the leading symptom of emotional instability, from a child and adolescent psychiatric point of view, without further preliminary findings, initially suggests, for example, a personality disorder or a bipolar disorder.

4. Therapy and Course of Child and Adolescent Psychiatric Treatment Nine Years After HSVE

The suicide attempt was associated with severe self-reproach for the adolescent herself. Because of the marked depressive symptomatology, we started antidepressant medication (fluoxetine) combined with high-frequency cognitive behavioral therapy supplemented by elements of Dialectical Behavioral Therapy for Adolescents (DBT-A). While on the antidepressant, the patient exhibited mania-like behaviors such as increased drive, hyperactivity, and compulsive speech (logorrhea), so a reduction in the antidepressant (which itself has a drive-increasing effect) was made. The patient repeatedly decompensated after positive experiences in everyday life with exaggerated physical reactions such as severe headaches and crying or screaming fits with impulsive-self-injurious behavior. The parents reported similar reactions in the home environment since five months before admission. Such behaviors were not observed in the acute infection phase as well as in the years after HSVE. In this context, the adolescent showed severe distress in the face of the massive dissociation of everyday and emotional experience and reacted with marked suicidality in the presence of affect lability and hopelessness even after six weeks. Stress testing in the home environment led to recurrent emotional collapses. Due to the personality and behavioral changes with demonstrable damage to the brain after HSVE, we made a diagnosis of organic personality disorder. To stabilize emotions, we started a phase prophylactic treatment with carbamazepine. To prevent potential interaction, we stopped medication with fluoxetine and initially started low-dose carbamazepine 80 mg, divided into two doses daily. A reduction in symptoms was already observed with 100 mg a day. The adolescent increasingly succeeded in reacting more appropriately emotionally in

everyday situations that were difficult for her (e.g., school failures and social conflict situations) and in distancing herself from suicidal tendencies. We discharged the patient to her home environment after nine weeks of treatment with a final medication of 300 mg of carbamazepine daily and significantly increased emotion control.

Follow-up: Ten weeks after admission, the patient continued to be emotionally stable. In the meantime, she was able to solve bad school grades and disputes with friends well and appropriately. Below that, only isolated periods of tension occurred. With a carbamazepine level of 6.8 mg/l, we increased the dosage to 400 mg per day for further stabilization. Test psychology showed a significant decrease of the T-score in the DIKJ to 67, YSR and AFS were unremarkable ten weeks after discharge.

2nd Follow Up: 11 weeks after admission, after increasing medication, the adolescent continued to report emotional stability with high levels of impulse control and appropriate emotional appraisals of social interactions.

Psychometric test diagnostics during the inpatient course: The test psychology revealed conspicuous T-scores (TW) in the Depression Inventory for Children and Adolescents (DIKJ) with a TW of 80, in the Youth self-report (YSR) with particularly conspicuous scales in the areas of anxious/depressive (TW: 98) and regressive/depressive (TW:100) as well as in the Anxiety Questionnaire for Students (AFS). A performed intelligence diagnostic using the Wechsler Intelligence Scale for Children (WISC) revealed an average intelligence performance.

5. Emotional Development, Limbic System and HSVE in Childhood and Adolescence

Infection with herpes simplex virus type 1 encephalitis often results in characteristic asymmetric bilateral lesions of the temporal and frontal lobes [25]. (Figure 2). Functional abnormalities in these areas can lead to depressive symptoms, impulse control disorders, and emotional instability [26-28]. For example, some imaging studies have shown that neural correlates for the symptoms typical of the disease were present in adolescents with borderline emotionally unstable personality disorder and in adolescents who developed depression [29]. In particular, changes in amygdala and hippocampal activity were detectable [30]. While until a few years ago it was believed that the major developmental processes of the brain take place in the first six years of life, animal studies have shown that further serious remodeling processes occur with the onset of early adolescence (10-20 years of age) [31]. Especially in the limbic system, an overproduction of axons and synapses occurs during early puberty [32]. This is followed by severe synapse and dendrite reduction (pruning) with subsequent reorganization of cerebral structures, especially the amygdala, nucleus accumbens, and prefrontal cortex [33]. During the adolescent period, there is an increase in white

matter and a decrease in gray matter. In addition, experimental studies in rodents have shown changes in neurotransmitter systems [34]. The temporal process of remodeling of all cortical and cellular structures is not uniform and structured, but dynamic and asynchronous according to the principle of "use it or lose it" [35, 36]. The asynchrony of the developmental steps occurring differently in different brain regions could, among other things, be an explanation for the typical behaviors on the cognitive and emotional levels of adolescents during puberty [37]. Due to the parenchymal defect after HSVE, the reorganization of the respective central structures and the interconnection among them is disturbed during adolescence or may not occur at all [32]. If we look again at the patient's symptomatology, she did not meet the criteria for the presence of an emotionally unstable personality disorder, but she showed some typical symptoms such as impulse control disorder, changing attachment and relationship behavior, and impulsively controlled suicidality. At the same time, she described a marked depressive mood and was hopeless and lacking in perspective. In summary, this patient had an organic personality disorder, which is defined in ICD-10 as a behavioral change with impairment of affect and emotionality after brain damage has occurred [39].

Can the symptomatology be explained by the anatomically detectable lesions alone?

6. HSVE and PTSD in Childhood and Adolescence

From a child and adolescent psychiatric point of view, a type -1 HSVE can lead to considerable psychotraumatization of the affected children and their caring relatives [40, 41]. For some time, trauma research has been increasingly able to understand on a neurobiological level why early trauma correlates with neurobiological changes and has effects on endocrine, immunological, and central nervous systems. It is thus becoming understandable the direct impact that threatening life events have on changes in behavior and emotional experience [42, 43]. Trauma is now considered a confirmed risk factor for the development of almost 30% of all psychiatric disorders [43]. In international epidemiological studies, traumatized children and adolescents show significantly higher prevalences of later developing a mental disorder such as depression or borderline personality disorder [45]. The powerlessness and helplessness at the moment of a life-threatening situation can lead to a trauma sequelae disorder such as post-traumatic stress disorder (PTSD) with disturbances in emotion regulation, impulse control, and development of self and relationship schemas [40, 41, 46, 47]. Fonzo et al. (2010) found that patients with PTSD had emotionally heightened and exaggerated responses to negative and neutral stimuli. The cause of this was also in this case a hyperactivity of the amygdala [48], as it often occurs after trauma sequelae. The reason for this is a dissociation of amygdala and

hippocampus in the "freezing" moment of the situation experienced as traumatic [49-51]. A time dissociation of memory (flashbacks) occurs, which can no longer be temporally embedded (due to the dissociation of the hippocampus) in the narrative context of the remaining memories. Especially in children, this leads to additional emotional insecurity due to a profound temporal-structural disruption of their own attachment history [52]. The prevalence of PTSD following acute physical illness is approximately 12-25% [53-55]. Severe somatic illnesses such as HSVE in childhood and adolescence not only pose a great challenge to the psychological compensatory mechanisms of child and adolescent patients, but also put a strain on the entire family system [56]. Dew et al. (2004) found PTSD in 22.5% and adjustment disorder in 34.5% of relatives of seriously ill patients [57]. In 2012, Colville identified a significant association between the development of PTSD in parents and intensive care treatment of their children: 44% of parents showed symptoms of PTSD [58]. A prospective cohort study by Franck et al. (2015) detected PTSD-typical symptoms in 32.7% of parents of hospitalized children [59]. Significant parent distress may in turn impact the child's experience of illness. If the children's attachment behavior already tends to be insecure, an interaction disorder and an insecure-ambivalent, insecure-avoidant, or even disoriented attachment pattern may develop due to the additional chronic stress, which is rehearsed or reinforced by anxious or fearful behavior on the part of the parents [60]. If children are made to feel insecure in their primary attachment to their parents during their severe illness, this in turn has traumatic effects on their experience of the illness itself [61]. Children of parents with traumatic stress significantly often show early signs of attachment traumatization themselves [62]. They exhibit emotional regulation disorders and abnormalities in personality development [63]. These are exactly the symptoms that can also be caused by the HSVE itself, if (as in the present case study) the corresponding brain areas are affected.

Another aspect is that long-term neurological sequelae leading to deficits in learning and language must be seen as possible stress factors, especially in the school context. Children and adolescents who suffer from mental or physical disabilities are almost twice as likely to experience bullying compared to children and adolescents who are not impaired [64, 65]. Bullying may increase children and adolescents' risk for internalizing behavioral episodes (negative self-attributions) in particular [66, 67].

Finally, Fryers and Brugga (2013) point out another aspect that has been understudied: Inflammatory CNS diseases in childhood appear to be associated with an increased risk of later developing schizophrenia (acute psychosis) and there may also be an association with anxiety disorders and depression [68]. Nissen, et al (2019) stated that infection with herpes type 1 viruses may contribute to the development of suicidal behaviors and other psychiatric symptoms [19]. However, why such a course is significantly common remains unclear in studies. Moreover, a common feature of

all the papers mentioned here is that their studied patient population was not children or adolescents. Thus, the question remains open why HSVE has not found a special place in child and adolescent psychiatry so far and whether this case report may give reason to follow the long-term course of this particularly vulnerable group more closely in the future.

7. Conclusion for Therapy Approaches

1. Prevention and rehabilitation of the late effects of HSVE

In view of the serious neurological and psychiatric consequences of HSVE outlined above, it can be considered as a preventive measure with regard to psychiatric long-term consequences that an interdisciplinary approach is of great importance. It seems important to keep in mind the possible long-term psychiatric consequences and to continue to follow up children with neurologically rehabilitated HSVE as patients at risk for psychiatric disorders. Good follow-up diagnostics appear to be essential in this regard. Based on the cMRI images in the above-mentioned case, the neuroanatomical location of the parenchymal lesions already suggested a certain risk for an affect regulation disorder.

2. Psychotherapy of trauma and personality disorders (PSS)

In addition, it seems to be important to offer good psychological or social-psychiatric care to parents and their children affected by HSVE. The complexity of the stress factors and the effects of the disease itself on the neurobiological and psychological processes of the children and the family systems definitely indicate that a particularly high risk of the development of personality disorders is to be recognized here, which is based on an entanglement of somatic and psychological causes. A disposition due to trauma sequelae and attachment disorders provide an important background here.

3. Mood Stabilizing (Carbamazepine)

Drugs such as carbamazepine or valproate, which were originally used exclusively for epilepsy treatment, have long since arrived in psychiatry as so-called "mood stabilizers" [69-71]. Again, psychiatrically, there are insufficient studies for children and adolescents, but data are collected in adult psychiatry, which is why carbamazepine is approved in children only for epilepsy and psychiatric "mood stabilizing" is done as "off-label-use". However, there is now sufficient clinical empirical experience to say that its use in disorders such as emotionally unstable personality disorder (borderline) or bipolar affective disorder has also been successfully established in CYP [72]. The mechanism of action is not yet fully understood, but it is assumed that especially in the amygdala the membrane-stabilizing effect of carbamazepine is crucial. Dosages range from 200 to 600 mg/d in children and from 600 to 1200 mg/d in adolescents. Side effects are not insignificant: sedation (15%), therefore application starting in the evening, restlessness, tremor,

ataxia, nausea, weight gain, cycle disturbance (cave: contraception!) and visual disturbances. Allergic reactions may occur (10 - 15%), it is teratogenic and cardiac conduction disorders are described. Regular blood count checks and level determination are recommended. The use of carbamazepine in organic personality disorders is not well established in the literature. Moriwaka described successful treatment with carbamazepine of a 19-year-old man after traumatic brain injury in 2000 [73]. Muñoz also reported in 1997 a male adult who became more mood stable on carbamazepine after traumatic organic personality disorder [74].

8. Conclusion

In its initial phase, HSVE in children places the highest demands on the treating physicians. This phase is characterized by the need to ensure survival and minimize permanent brain damage. Four essential points influence the further course of the children and adolescents in the following months and years: (1) It is important to identify the typical pattern of infestation of high-vulnerable emotion centers in the child's brain. (2) The presumed consecutive maladaptive reorganization of the brain during puberty should be considered and taken into account preventively. (3) Consequential damage in the areas of language, social competence and affect regulation can lead to experiences of exclusion and frustration within the peer group. (4) The traumatization and its consequences for the affected children and their families should be recognized early and intercepted in time by social psychiatrists. HSVE represents a high risk for severe psychiatric sequelae in children and adolescents.

Illustrations

The radiological images were kindly provided by Doctor medic Oana-Roxana Funke, Radiology Department of the Children's Hospital Auf der Bult and the X-ray practice Am Marstall - Radiology and Nuclear Medicine Auf der Bult.

Conflicts of Interests

All the authors declare that they have no competing interests.

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