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Infectious Epilepsies. Literature Review

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Summary

Infectious epilepsy can be diagnosed in patients with unprovoked seizures for which the cause is a previous limited and already healed infectious disease, suspected to have evoked changes in the brain tissue making it more susceptible to producing abnormal and excessive electrical discharges. Patients who underwent an infection have been recognized to have a higher risk of later developing epilepsy. Even as today many associated pathogens are known, the mechanisms of epileptogenesis and seizure production are still mostly undiscovered. Although we have some studies highlighting the differences of pathomechanism form other epilepsy etiologies, a lot more research hast to be done, especially regarding finding specific treatment aimed towards stopping the reorganizational changes of brain tissue after infection. Those treatments could help millions of people worldwide and decrease the burden of disease of epilepsy significantly. And while the treatment of infectious epilepsy doesn't necessarily differ from other etiologies of epilepsy, it is important to recognize the underlying etiology of acute symptomatic seizures to initiate correct treatment and reduce overall mortality and morbidity. The goal of this narrative literature review is to give an overview of acute symptomatic seizures due to infections, the subsequent development of infectious epilepsy, current understanding of epileptogenesis, and helping understand the differentiation of seizures from epilepsy for right diagnosis and treatment.

Keywords: Infectious Epilepsy; Acute Symptomatic Seizures; CNS-Infection; Encephalitis; Meningitis; Neurocysticercosis; Epileptogenesis

Introduction

Acute symptomatic seizures are one of the presentations of acute infections and acute infectious processes. While infectious epilepsy can be diagnosed if a patient has unprovoked seizures, after an infectious process is identified as the probable cause of the seizures, and other causes of seizures are excluded. Patients who underwent an acute CNS-infection or other infections of various pathogens, are known to have a higher risk of later developing epilepsy. People who had acute symptomatic seizures during the infectious period have an even higher risk of developing infectious epilepsy later in life. The etiological factors are located on a wide range of viruses, bacteria, and parasites. Infections are thought to be one of the most common causes of Epilepsy worldwide, thus being responsible for a high burden of disease and huge public health issues. Especially in low- and middle-income countries the prevalence of infectious epilepsies is more common than one would suspect. This is for various reasons, but the most prevalent are the presence and prevalence of tropic diseases, which are highly connected to epileptogenesis, as well as limited access to health care, and with it, the access to diagnostic modalities and treatment possibilities. Even though treatment does not differ in case of infectious epilepsy compared to other etiologies of epilepsy, it is important to be able to differentiate infectious causes from others, as helping understand the etiopathogenesis of the infectious genesis will help further research in this area, including preventive methods. If preventive methods of the development from acute infection to unprovoked seizures and epilepsy can be found, it may help millions of people worldwide, and decrease the burden of disease significantly. Unfortunately, studies on prevalence and epidemiology are less common than it would be required to do a comprehensive study on the association between acute symptomatic seizures and epilepsy. Present studies are barely comparable, as often times the definitions of acute symptomatic seizure and epilepsy are not provided or interchangeable used. As most infections are located in low- and middle-income countries studies would need to be primarily carried out there, but this proves difficult due to logistical and financial limitations. Even though treatment does not differ in case of infectious epilepsy compared to other etiologies of epilepsy, it is important to be able to differentiate infectious causes from others, as helping understand the etiopathogenesis of the infectious genesis will help further research in this area, including preventive methods. If preventive methods of the development from acute infection to unprovoked seizures and epilepsy can be found, it may help millions of people worldwide, and decrease the burden of disease significantly.

The goal of this narrative literature review is to give an overview over acute symptomatic seizures due to infections, the subsequent development of infectious epilepsy, current

understanding of epileptogenesis, and helping understand the differentiation of seizures from epilepsy for right diagnosis and treatment.

Literature search strategy: The literature search was conducted primarily with the PubMed search library as well as the World Health Organization Publications Platform and the Cochrane Library. Keywords used in the literature search were epilepsy, acute symptomatic seizures, epileptogenesis, pathogenesis, infection, epidemiology, and treatment. The search was conducted in September 2022 to May 2023, and no date restriction was applied. A total of 6.209 publications were identified, of which 4.203 were in English and full text. Additionally, a bibliographic search of select publications was performed. References were selected according to their relevance and comprehensiveness of the topic, which amounted to 125, of which 72 were cited in this review. The articles chosen included systematic literature reviews, clinical trials, journals, book chapters, studies, trials, and metanalysis.

Definitions

The International League Against Epilepsy (ILAE) is the leading medical professional society in everything related to epilepsy. Their goal is to improve the lives of people living with epilepsy through research (1). The ILAE published papers on the definition of epilepsy, which is the basis for almost every study, paper, and clinical diagnosis of epilepsy. According to the ILAE **epilepsy is**:

a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome (2: Table 2)

Based on this definition, we can already discern the theoretical difference between symptomatic seizures from infections and infectious epilepsy.

Symptomatic seizures due to infection: acute symptomatic seizures, or provoked seizures, are seizures which are often in close timely proximity of systemic or neurological events (3). According to the ILAE an Acute Symptomatic Seizure is occurring within 7 days of an acute infection or otherwise significant health event like trauma or stroke (4).

Infectious epilepsy: Epilepsy is diagnosed when two unprovoked seizures occur more than 24 hours apart. Unprovoked means the seizure is in no direct relation to a provoking factor, as an

immediate temporary and reversible cause of the current seizure (2). Following this definition, we might say the epilepsy is due to an infectious origin, if a seizure is occurring more than 7 days after the infection is resolved, and the infection was connected to the epileptogenesis in this patient, causing them to have unprovoked seizures later in life.

Still, not everyone who is experiencing an infection which has shown to have epileptogenic potential in other patients, is predetermined to experience seizures, and not everyone experiencing seizures during an infection, is bound to be diagnosed with epilepsy later in life. Many researchers have tried to find determining factors for the development of acute symptomatic seizures in infections and later on in epilepsy, still most epileptogenic models so far are only determined as suspected and are not necessarily proven.

One fact most researcher are consenting to, is that the main determinant of developing symptomatic seizures and epilepsy due to infections, is the causative pathogen. Whether it be viral, bacterial, or fungal. Additionally, the etiology and development of all types of seizures is hugely multifactorial, thus not only is the epidemiology of infection important in determining the risk of development, but also genetic predisposition which may be approximated by family history (4).

Epidemiology of Infectious Epilepsy

Even though there are many publications on seizures occurring during infection, it is hard to generate exact data on occurrence rates, pathogenesis, and outcomes, as most cases of infectious epilepsies are located in resource poor settings of low- and middle-income countries, in which the diagnostical tools such as continuous Electroencephalography (EEG) or Magnet Resonance Imaging (MRI) to accurately diagnose seizures and their cause, are rarer and harder to come by resulting in many cases being overlooked and missed. Due to missing diagnostic tools, there might also be an increased incidence of mislabeling febrile seizures as acute symptomatic seizures due to infections resulting in a non-accurate incidence (5,6). Additionally, most publications which are trying to indicate the incidence of epilepsy after infections, can only generate small patient cohorts, making the plausibility of correct numbers and transferability of the occurred outcomes relatively low. Another hurdle, which has to be overcome by researchers, is that the incidence of seizures due to infections differs depending on the type and etiology of infection, the patients age, a delay in starting treatment, and also possibly the type and location of cortical inflammation (5). All of these make it harder for estimating data and conducting epidemiological studies with larger patient cohorts, resulting in a gap that needs to be filled for further research of epileptogenesis.

Regardless of these hardships, some studies stipulate that, independently from the causative agent of infection, patients diagnosed with encephalitis are overall about 16 times more likely to develop unprovoked seizures later in life. Patients with acute seizures while suffering from an infectious disease are about 22 times more likely to later develop unprovoked seizures. And even patients with no acute seizures during the infectious process and period, are overall still about 10 times higher risk to develop unprovoked seizures later in life, compared to the population which has not been infected. As such, it is easy to see the possible lifelong impact such a disease has on the infected patients and overall burden of disease due to the high socioeconomic consequences, like inability to partake in road traffic and difficult access to antiepileptics, additionally to the emotional and psychological burden the patients might be objected to (5).

In the US, encephalitis is the cause for epilepsies in approximately the same number of cases as head trauma, but head trauma is about 28 time more common than encephalitis, which allows us to see the importance of the infectious etiology of epilepsy (5).

The frequency of seizures and epilepsy differs among different etiologies, as it is suspected to vary with the different anatomical location of lesions and the triggered immunological answer, which can be related to the specific pathogen causative of the lesion (7).

The etiology of the most common causes of infectious epilepsy and seizures is largely dependent on the geographical region investigated (8). For example Malaria is considered the most common cause for symptomatic seizures in sub-Saharan Africa, whereas Neurocysticercosis is the most common cause in endemic areas like Latin America, India, and China, while HSV-1 is the most common sporadic cause in Europe (9–11).

Etiology of Infectious Epilepsy

Any infection which may cause structural and inflammatory changes to the brain, can induce seizures. If those changes are long-term and do not resolve with the end of infection, they may also cause unprovoked seizures and epilepsy later in life.

Encephalitis: Encephalitis may be caused by viruses, protozoa, bacteria, parasites, but also by auto-immunological reactions. Most often viral etiologies of encephalitis are the cause of post-infectious epilepsies (5).

According to some studies, the incidence of developing epilepsy after encephalitis is between 6.1–16.4% (12,13). More importantly to note, is that the occurrence of seizures during acute infectious period with viral encephalitis changes the estimated prognosis for later developing epilepsy. A study showed that patients with acute seizures during disease developed

unprovoked seizures in 22% of cases after 20 years, while patients without early seizures only developed epilepsy in 10% of cases (14). The highest risk of developing epilepsy after encephalitis is found to be within 5 years of the acute disease (15). The incidence changes with different causative pathogens, as for example the Herpes Simplex Virus (HSV) is found to be the pathogen causing viral encephalitis with the highest incidence and severity of seizures during the infectious period, followed by the highest incidence of later developed epilepsy. In about 57% of cases across three different studies conducted in England, India, and Taiwan, patients with HSV experienced acute symptomatic seizures during infection (16–18). This compares to a study following children after having received a diagnosis of herpes simplex virus encephalitis from 1994-2005 in the Hospital for Sick Children and University of Toronto, showing that about 44% of children later presented with unprovoked seizures, and another study conducted at Auckland hospital presented that 24% of patients were diagnosed with epilepsy later in life (19,20). With HSV-1 being the most commonly recognized and diagnosed cause of viral encephalitis worldwide, we may only stipulate the amount of cases of infectious epilepsies due to the Herpes Simplex Virus (21).

Japanese encephalitis, caused by a flavivirus and transmitted by mosquitoes, is an important cause for viral encephalitis in endemic areas of Asia. It may cause seizures in 40-60% of patients, while in children the incidence of seizures may be as high as 80% (22). A Chinese study found that about 15% of children with Japanese encephalitis developed epilepsy within the follow-up period, while in total 66% of included patients experienced acute symptomatic seizures during the infectious period (23).

Meningitis: Bacterial meningitis is also a category of CNS-infections which comprises many different pathogens which are endemic all over the world. Most significant pathogens in bacterial meningitis are Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis. Like in encephalitis, the highest risk of experiencing unprovoked seizures is within 5 years after disease (24). One study conducted in the UK found that 7,3% of children who contracted bacterial meningitis later were diagnosed with epilepsy, while the control group of children who didn't have meningitis earlier in life only were diagnosed in 2,7% of cases (25). This finding is supported by other studies, as another study found 5,4% of children after meningitis to be treated with anti-seizure medication, while only 1,7% of controls were (26). One study conducted specifically to evaluate the long-term neurological sequelae after meningitis found that 31% of children included presented with acute symptomatic seizures during the acute illness. The same study included follow ups for 8 years, after which 7% of patients were diagnosed with epilepsy (27).

Neurocysticercosis: Neurocysticercosis is a helminthic disease caused by the flatworm Taenia solium after ingesting its eggs. The larvae of the parasite can reach the brain where they cause pathological changes (28).

A systematic review by Carabin et al. postulates that with 79% the most common symptom in patients presenting to the hospital are seizures (29). Neurocysticercosis has a statistically significant association to epilepsy and is suspected to be the cause of up to 30% of all epilepsies in areas where it is considered endemic, while it is diagnosed as the cause of seizures in over 2% of cases in western states of North America (30–32). The occurrence of seizures following an acute symptomatic seizure is high, but it is important to note that high occurrence is suspected to be rather connected to the presence of degenerative cysts and calcifications, even after resolution of active disease (33). A thorough systematic review conducted, calculated that about 25% of people living with epilepsy in endemic countries have lesions of neurocysticercosis in MRI or CT scans, which is backed up by previous analysis on the topic, substantiating the assumption of Neurocysticercosis being a driving factor for high incidence and burden of disease in low- and middle-income countries (34).

Malaria: Malaria is another parasitic disease endemic in low-and middle-income countries in Sub-Saharan Africa, Asia, and South America. Transmitted by mosquitos, the Plasmodium species can cause invasion into brain, causing Cerebral Malaria, which is a common cause of epilepsy in Africa and Southeast Asia. The consideration of seizures during Malaria as febrile seizures, as episodes of high fever are a main clinical symptom, is important and should be recognized, but most often seizures develop during fever-free intervals with a body temperature <38°C, meaning seizures are considered acute symptomatic. Cerebral Malaria, which is a severe complication of Malaria infection, has been found to be followed by epilepsy in 10% of surviving children, of which 80% are treatment-refractory (35). Making Malaria also one of the major driving factors of burden of disease in endemic countries.

Clinical Presentation

Seizures and subsequently epilepsy due to infections are not restricted to a specific age group and the presentation may vary with the locus of the epileptogenic center. Some diseases may have a tendency to invade specific parts of the brain, but in general it can be said that infections can cause structural change in any part of the brain, resulting in seizures.

The presentation of acute symptomatic seizures does not differ from unprovoked seizures due to epilepsy, thus differentiation can only made by concurrently occurring symptoms of infection and patient history. The clinical feature of the seizures, whether it be acute symptomatic

seizures or epileptic seizures, largely depend on the location of the seizure focus. The seizures may be generalized or focal, with clonic, tonic, myo-clonic, tonic-clonic, atonic, or partial features.

Additionally, acute symptomatic seizures are also accompanied by the features of the causative disease. If encephalitis is the underlying disease, the patients may present with a rapid onset of symptoms, fever, confusion, dizziness, and other focal neurological signs (36). In the case of neurocysticercosis the major presenting symptom is, like previously mentioned, new onset seizures. Additionally other focal neurological signs, headaches, and cognitive decline may manifest, even though most patients are asymptomatic and the diagnosis of neurocysticercosis is made by chance (29,37). In 90% of cases, patients with Malaria present with fever, and in non-endemic countries thorough history taking should be done to reveal travel history and possible exposure to Malaria (38).

The clinician is often times only presented with the patient after the seizure has already passed, thus clinical presentation should be recognized by postictal symptoms, like disorientation, drowsiness, or a bitten tongue.

Diagnostics

Seizures often present in non-medical settings and the suspicion of a passed seizure is often dependent on the description of bystanders. After a first seizure, especially in adults, it is recommended to follow diagnostic pathways, to identify the cause of such seizure and to be able to indicate the appropriate treatment.

If an acute symptomatic seizure is suspected, the patient should be admitted to the hospital and it is recommended to follow diagnostic pathways, to identify the cause of such seizure and to be able to indicate the appropriate treatment.

Before employing diagnostics, thorough history of patient has to be obtained, and standard questions of recent infection and fever should be answered. Also, previous medical history should be clarified, and recent travel anamnesis is vital. Start of the diagnostic pathway are the general blood examination, especially with regard to blood count and cellular morphology, to help differentiate between viral and non-viral infections, in case of suspected encephalitis. Additionally determining C-reactive Protein-levels or other inflammatory values might help to follow the course of disease in the long-run. Taking of blood-cultures should also be part of the general diagnostic measures in case of febrile disease. Determining levels of Creatine Kinase (CK) might be indicated if there is doubt about a psychogenic nature of reported seizure, as with myoclonic seizures CK levels rise about 8-16 times compared to normal levels (39).

When a patient presents with a first-time seizure, performing an EEG has to be part of diagnostic measures, as a diagnosis of seizure or epilepsy can also be made in the interictal phase according to the changes in the EEG. Although it is important to note that an abnormal EEG might also be present in a healthy individual, while likewise the absence of specific changes does not exclude the presence of epilepsy. Still, EEG is an important tool for early diagnostics in case of acute viral encephalitis. Neuroimaging is also required especially in regards to differential diagnostics, to display structural changes and to be able to diagnose different etiologies of seizures. If MRI is available it should be conducted with preference over CT, as it is more specific and sensitive for demonstrating abnormalities in the brain. Additionally, it allows earlier display of viral encephalitis, aiding in early diagnosis and treatment of the underlying cause of seizure (40). Still, CT is useful in restless patients by helping to obtain easy and fast imaging (41).

If an infectious etiology of seizures is suspected, a lumbar puncture with analysis of Cerebrospinal fluid (CSF) might be done. If a pathogen is detected, for example by Polymerase Chain Reaction (PCR), a more specific and targeted therapy can be initiated. A caveat is, that often within the first two days of infection a false negative PCR sample is possible, which should be known by professionals and handled accordingly. Taeniae solium, the pathogen in Neurocysticercosis, has a high detection rate in PCR detection, and is thus a good diagnostic possibility if resources allow for it (42). Generally during infection CSF can present with normal glucose level, in rare cases glucose may be decreased, and protein levels usually are >50mg/dl. The best predictor for CNS infection in CSF analysis is a leukocyte count $\geq 5 mm^3$. This value shows a high specificity for distinguishing CNS-infection from systemic infection, but unfortunately has a low sensitivity (sensitivity 46%, 95% CI 36–56%; specificity 100%, 95% CI 74–100%) (43). Still, it is a helpful indicator for locus of infection. A cell culture of CSF is unfortunately rarely useful, and only indicated in children with suspected enteroviral infection of the CNS. CSF can also be used for detection of antibodies, which helps indicating if infection is present in the CNS by presence of specific IgM, whilst the presence of several antibodies indicates the breakdown of Blood-Brain-Barrier in systemic infection (40).

The cMRI is also the best tool, possibly in combination with immunological tests, to diagnose Neurocysticercosis, based on current diagnostic criteria. It can depict active as well as calcified neurocysticercosis lesions, which may be causative of seizures or epilepsy (44).

Differential Diagnosis

Differential Diagnosis in case of acute symptomatic seizure or a first seizure is essential in choosing the right treatment method. Patient history must be obtained to exclude head trauma. Neurological evaluation of the patient if possible, or questioning witnesses for specific signs, the course, or prodromal signs previous to seizure must be done in order to quantify risk for stroke. Non-seizure diagnosis must be considered as well. Examples of those include syncope or psychiatric disorders. Blood sugar should be measured, as hypoglycemia might also present as acute symptomatic seizure, and has a fast, easy, and cheap treatment for reversal.

Another important point is, determining value of sodium in serum, especially in critical patients. It is often associated secondary to infections by various pathophysiological mechanisms and may cause seizures in severe cases. Hyponatremia, defined by serum concentration of >135mmol/l, is associated with higher mortality and morbidity in hospitalized patients. Fluid status of patient should be obtained and according to this appropriate treatment has to be initiated (45). In children between the ages of 6 months and 6 years febrile seizures have to be considered as well. Febrile seizures occur without an intracranial infection or electrolyte imbalances and are considered a common type of convulsion in fever (46).

Pathogenesis, Epileptogenesis

Acute symptomatic seizures due to infections are thought to have different disease mechanisms. The current understanding is that epileptogenesis during acute disease is based on two pillars. On one hand is the direct impact the pathogen has on the host, like invasion, CNS degeneration, or toxin production. On the other hand we can see the patient's immune systemic response, with release of inflammatory mediators which may lead to a dysregulated immune response or disruption of the blood-brain barrier, edema formation or auto-immune responses (47–49).

The progression of acute symptomatic seizures to infectious epilepsy is a poorly understood one. The current hypothesis is, that in a latent period between acute symptomatic seizures to unprovoked seizures and the subsequent diagnosis of epilepsy the brain undergoes changes which transform it from a healthy brain to one which can generate epileptogenic, spontaneous, and recurrent charges, resulting in unprovoked seizures. Unfortunately, even though research is currently conducted, this mechanism of transformation is still widely unexplored and poorly understood. The mechanism of epileptogensis is thought to be related to the pathogen, which is why some pathogens are more often associated with concurrent epilepsy, the response of the host's immune system, and the location of invasion. The hypothesis why only a small percentage of patients develop epilepsy after infection is based on the regenerative function and

- power of brain tissue. Additionally, epileptogenesis is hugely multifactorial, therefore an even smaller percentage of patients who underwent reorganization without regeneration of brain tissue are hypothesized to suffer from unprovoked seizures. The reorganizational changes the brain tissue undergoes includes hyperexcitability of neurons, change in function of receptors and ion channels, neuronal loss, or inflammation and edema (50,51). It has been shown in different studies that the pro-inflammatory cytokines IL-6 and TNF-alpha are increased in both acute symptomatic seizures and epilepsy. Both those cytokines are produced by activated macrophages and are connected to the break-down of blood-brain barrier, allowing further pro-inflammatory cytokines to enter the CNS, causing neuroinflammation and subsequently possible enhanced neuronal excitability, which facilitates epileptogenic potential generation, increased neuronal cell death, and altered regenerative abilities of brain tissue, leading to a life-long risk of faster than normal neuronal cell-death, which might be connected to a life-long increased risk of developing unprovoked seizures (52).

In case of Neurocysticercosis, seizures may be provoked based on the different stages of the larvae. The larval cyst may induce changes of the immune system and its mere presence can cause structural changes to the brain. The cyst can progress to a calcified lesion, which can cause perilesional edema and gliosis to develop, neuronal degeneration to progress, astrocytes to activate, and infiltration of blood vessels close to the cyst by lymphocytes. The calcification may be surrounded by remains of inflammation, which can cause a disruption in the blood-brain barrier. All those factors play a part in epileptogenesis and the generation of unprovoked potentials (37).

Contrary to T. solium, the Plasmodium species which causes Malaria does not invade the brain directly, but rather enters the CNS via sequestration of infected red blood cells into the intravascular space causing perivascular damage. This damage is thought to be the main culprit in epileptogenesis and seizure production, especially as perivascular damage causes reduced blood flow to affected brain tissue and subsequently localized ischemia, followed by inflammation of surrounding tissue, which is similar to epileptogenesis of neurocysticercosis. Other considerations of pathogenesis that have to be made during seizures in acute Malaria infection, are other reversible mechanisms of seizure generation due to systemic infection rather than CNS-invasion of the parasite, such as hypoglycemia, severe metabolic acidosis, and shock (35).

As previously stated, even if all those changes are present in individuals following acute symptomatic seizures or following CNS infection, not every one of them experience unprovoked seizures, which is connected to the location of tissue change, as some areas of the

brain have higher epileptogenic potential than others. The high incidence of seizures and epilepsy due to infection with HSV and Japanese encephalitis is thought to be due to exactly that. HSV's preference to settle within the highly epileptogenic zones of the frontotemporal region is thought to be primarily causative for the high incidence of seizures and epilepsy in HSV-positive patients, while the virus responsible in Japanese encephalitis is often causing inflammation in midbrain, thalamus, and basal ganglia, which are also highly epileptogenic (22,23).

Risk factors

Risk factors for developing epilepsy after experiencing an acute symptomatic seizure due to infection depend on the etiology of infection. Stratifying risk factors of developing epilepsy is important, but unfortunately not many reports have been written about them, much less quantifying the risks. In general, the major risk factor is experiencing a seizure during the active course of infection. One study found that the risk of developing late unprovoked seizures within 20-years of infection was 22% in patients who experienced an acute symptomatic seizure, compared to 10% of those who did not experience a seizure during infection (14). In addition, some risk factors have been named to be associated with late unprovoked seizures. In case of bacterial meningitis and encephalitis, some of the risk factors include developing seizures early in the period of infection, experiencing persistent neurological sequelae, excluding sensorineural hearing loss, a young age at time of infection, delayed presentation to medical care which often times equates to delayed medical treatment of infection, and the causative pathogen being Streptococcus Pneumoniae (24,25,53,54). After any form of cerebral infection, the risk of developing epilepsy is increased if the acute symptomatic seizure presented as a status epilepticus or if brain lesions remain after the infection has passed, indicating persistent reorganization of brain structure (55). Due to the multifactorial epileptogenesis, a positive family history of seizures or epilepsy is also thought to contribute to the risk factors (35,56).
But not only CNS infection is found to be a risk of developing unprovoked seizures. Infections that required contact to a health care professional, no matter the location in the body, increase the incidence of a diagnosis of epilepsy by 78%, which is a significant contribution to the epidemiology of epilepsy (57).

Treatment

Acute symptomatic seizure treatment is mainly symptomatic and based on treating the underlying pathology.

After establishing the seizure as provoked, the underlying cause must be found, and then appropriate causal treatment can be initiated. After a first symptomatic seizure has been diagnosed, anti-seizure medications (ASM) may be given to the patient to prevent long-term sequalae of prolonged seizures, as long as the causative factor or disease has not been resolved. The use of ASM during acute disease may possibly influence the occurrence of unprovoked seizures, as a study showed that animal models that did not have a seizure during Herpes Simplex Encephalitis had a much lower mortality and morbidity than controls, indicating that the use of ASM and subsequent reduced incidence of seizure has a better outcome in encephalits, but this has not been proven in humans so far (58). In the acute setting, usually intravenous, rectal or buccal available drugs are chosen as a mean to break through prolonged seizures, such as benzodiazepines, valproate, levetiracetam, and phenobarbital (59). The aim of these break-through medication is an effort to stop the seizure from converting into status epilepticus, which is associated with higher mortality and morbidity (60).

Most patients with acute symptomatic seizures during an infection are not required to receive long-term ASM (11,61). It has been under great discussion and research if long-term antiepileptic use prevents the development of epilepsy after an acute event, but so far, the consensus is that epileptogenesis is not dependent on and modifiable by current available medication, and recommendations on this topic are not evidence-based (8,55,62,63). The use of long-term ASM needs to be decided after careful consideration on a patient-to-patient basis, based on the risk of a recurrence of seizures and the side effects of the medication for the patient (64). In the same way, the use of antimicrobials outside of the treatment of the acute disease as a way to prevent infectious epilepsy has been studied incompletely, thus it is not known if aggressive treatment of infection is helpful, but like previously mentioned delayed treatment is considered a risk factor, so early treatment should be aimed for (65). On the same note, antiviral use in the prevention of epilepsy after viral encephalitis has been studied, but data is still lacking to reach a consensus and recommendation (11). In case of neurocysticercosis, symptomatic treatment is also the foundation, while later on the addition of anthelminthic therapy might be considered (32). The use of albendazole in patients who had viable cysts has been shown to marginally decrease the recurrence of generalized acute symptomatic seizures, thus after considering risk-reward ratio the treatment with anti-parasitics may be considered in appropriate patients (66,67). In calcified lesions with subsequent perilesional edema the use of corticosteroids can positively influence the occurrence of seizures, but often after reducing the dose a return of seizures is to be expected. Most often perilesional edemas which may cause seizures, resolve spontaneously, and do not need to be treated, but fortunately in those patients

where they do not resolve by themselves ASM have been observed to be quite successful. Surgery for excising cysts and calcified lesions might be considered later on in patients with treatment resistant epilepsy who are expected to profit from surgery, which can help reduce burden of disease (68).

If ASM are needed due to recurring unprovoked seizures after infection, the medication is chosen based on the clinical picture of seizures and usually the distinction of generalized and partial seizure is made. ASMs like valproic acid, levetiracetam, lamotrigine, topiramate, carbamazepine, or phenytoin are often used. Goal is the use of a single ASM achieving seizure freedom with monotherapy (69). In adults, after about 2-5 years of seizure-free interval, it can be discussed if the drug can be slowly tapered and discontinued (70).

Prevention

The burden of disease of epilepsy, especially in low-income countries, is enormous. Over 50 million people worldwide are estimated to have epilepsy. The World Health Organization is estimating that about 1/4th of cases of epilepsy could be prevented (71). A big part of this preventive efforts can be directed towards infectious epilepsy and should be directed towards primary prevention of contracting preventable infectious diseases associated with epilepsy.

In case of neurocysticercosis, efforts on education in endemic areas, about the parasite and its connection to raw, undercooked pork meat, can already have a great impact on reducing the incidence of contracting the disease. Prevention of bacterial meningitis by vaccination of the population, has been shown to greatly reduce the rate of occurrence in developed countries. Such can be achieved in low-and middle-income countries as well. For this, greater efforts must be undertaken by the governments e.g., implementing vaccination-programs (24). If a patient contracted the disease, initiating earlier treatment can reduce neurological sequelae such as infectious epilepsy (53). It is suspected that to improve the incidence of developing infectious epilepsy after viral encephalitis, earlier and more aggressive treatment in the course of disease is helpful and as such education of health care professionals is vital (72).

Unfortunately, at this point in time, we are lacking research towards secondarily preventing occurrence of epilepsy after disease has been contracted. As such greater efforts have to be put into researching the mechanisms and prevention of developing unprovoked seizures (50).

Conclusion

The clinical difference in acute symptomatic seizures due to infections and infectious epilepsy is one of definition. While the acute symptomatic seizure is directly related to a time frame of

acute infection, infectious epilepsy is diagnosed outside of this time frame if the seizure is considered unprovoked. Clinically and in appearance seizures can't be distinguished if they are provoked or unprovoked. Only additional information to the clinical picture, like markers of inflammation or symptoms associated with infection such as meningism or fever, can help clinicians distinguish underlying pathology from unprovoked seizures. This distinction is valuable in the treatment of underlying disease, which might help further along in decreasing mortality and morbidity. This makes the differentiation important, and further research into the epileptogenesis and subsequently into treatment of pathogenesis of developing unprovoked seizures is needed. This proves especially important in low- and middle-income countries, as epilepsy is a very important factor in burden of disease of countries and patients, and diagnostic modalities as well as treatment options are limited by lower socioeconomic force.

Diagnostics must be done in first seizures, to distinguish unprovoked seizures from those with a potentially curable cause, and appropriate treatment must be initiated, which can potentially prove helpful in preventing infectious epilepsies later on.

No matter the etiology of epilepsy, if seizures are expected to return, and after taking the risk-to-benefit factor for the patient into account, the first step of treatment are anti-seizure medications. If seizures are treatment refractory further diagnostics should be initiated and the possibility of anti-epilepsy surgery has to be discussed.

More work and research has to be done, to be able to actually cure epilepsy, not only to suppress seizures without taking the root of the problem into account.

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