Abstract

Central nervous system (CNS) infections are an important cause of epilepsy, especially in developing countries. They are the most frequent preventable cause of secondary epilepsy, as well. As a result of their diverse geographical distribution, the proportion of epilepsy cases due to CNS infections varies among different countries. Viral encephalitis and bacterial meningitis are the most common epileptogenic infections. Parasitic infections, mostly malaria and neurocysticercosis, HIV, tuberculosis and intracranial abscesses and empyemas are usual causes of epilepsy in endemic countries of the developing world with low healthcare level. CNS infections may cause epileptic seizures during the acute phase of the disease and this is associated in most cases with increased mortality and morbidity, including subsequent epilepsy. Subsequent epilepsy is a long-term complication and is possible to occur even 20 years after the infection. In general, the more severe the clinical manifestations of the the CNS infection during its acute phase, the more possible it is for the patients to develop epilepsy. The inflammation caused by the host immune response, as well as the cerebral damage caused by the microorganisms themselves are both blamed for the neuronal overexcitability leading to epilepsy. Despite the fact that in most infections the association is clear between them and subsequent epilepsy, further research is required for the detection of the underlying pathophysiology so as neuroprotective interventions to be developed. This could lead to more effective prevention of epilepsy because of CNS infections and significant reduction of the global incidence of the disease.

Key words: epilepsy, seizures, CNS infections, meningitis, encephalitis

1) Introduction

According to the definition proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) “epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure” 1. On the other hand, “an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” 1. This overexcitability is attributed to the imbalance of excitatory and inhibitory stimuli received by the neurons. In molecular level this is expressed as disruption in the action potentials of the membranes of the neurons, which are initiated and regulated by ion channels and imbalance of excitatory and inhibitory neurotransmitters2.

Epilepsy is one of the commonest neurological disorders, since its incidence varies from 40 to 70 new cases /100000 individuals /year in developed countries and from 100 to 190 /100000 /year in developing countries of lower socioeconomic level. Prevalence of active epilepsy is in the range of 6 to 10 cases/1000 individuals and there is a risk of around 5% for anybody to suffer non-febrile epileptic convulsion throughout their life. Although, an increased risk of premature sudden unexpected death is existent (principally in patients who do not receive medical treatment and patients with chronic epilepsy), the overall prognosis is good given the fact that almost 70% enter remission3.

The etiology of the disease seems to be multifactorial, since genetic as well as environmental factors have been implicated for its occurrence. An underlying disorder cannot be identified in 60% of the cases and epilepsy is classified as idiopathic. Secondary epilepsy in most cases is attributed to genetic, congenital or developmental disorders, cerebrovascular disease, traumatic brain injuries, brain tumors and...
CNS infections, depending on the patients' age and origin. Specifically, CNS infections are probably the commonest cause of epilepsy in low socioeconomic countries, where parasitic infections, such as cysticercosis and malaria are endemic. The incidence of these infections in developed countries is significantly lower, but epilepsy is one of the neurological sequelae of bacterial meningitis and viral encephalitis, which are frequent types of infectious diseases, especially in children.

CNS infections are possibly the only curable and preventable cause of epilepsy, among the factors mentioned above. Thus, in this literature review, an epidemiological approach of the relationship between the infectious agents implicated for epileptogenesis and the risk for epileptic seizures or subsequent epilepsy is attempted. In addition, the clinical characteristics of this relationship, the proposed underlying pathogenetic mechanisms, along with the prognosis of these patients are discussed.

2) Epilepsy as a result of CNS infections

It is important to take into account that after a CNS infection seizure disorders may be either a single phenomenon during the acute phase of the disease, or one of its chronic complications (acute symptomatic or provoked and unprovoked seizures respectively). Depending on the infectious agent, the duration of the infection and the severity of brain damage, an epileptic seizure is possible to present as an acute, sub-acute or chronic complication.

Acute symptomatic seizures usually occur in close temporal relationship with acute infections and generally during the first 7 days after infection and tend not to be recurrent; there is often an increased risk for subsequent epilepsy though. Cumulatively, 31% of CNS infections cause seizures during the acute phase and this is an independent risk factor for mortality (OR=17.6)\(^6\).

It is very difficult to come to a conclusion about the percentage of patients with epilepsy who owe their disease to infections, due to the vast geographic diversity. In a major epidemiological study in 1996 in population from USA (Rochester Epidemiology Project), 3% of newly diagnosed epilepsy cases were attributed to CNS infections\(^4\). On the contrary, in developing countries the reported percentage is much higher: indicatively, in sub-Saharan countries CNS infections are responsible for 26% of epilepsy cases\(^7\).

On the other hand, only a few studies have been carried out in order to estimate the risk for acute symptomatic epileptic seizures and subsequent epilepsy after a CNS infection because of their demanding nature. In the largest of them, all encephalitis and meningitis survivors during the period 1935-1981 were studied retrospectively and 6.8% was found to have unprovoked epileptic seizures 20 years after the infection\(^8\). The relative risk of observed to expected epilepsy cases was found to be 6.9, whereas the risk was higher for the first 5 years after the infection. Risk factor for unprovoked seizures development was found to be the occurrence of an acute symptomatic epileptic seizure during the acute infection. This danger was statistically significant for viral encephalitis and bacterial meningitis. After viral meningitis, 2.1% of the patients had subsequent seizures 20 years later and the possibility for this to happen was statistically non-significant in relation to the expected possibility in general population\(^8\).

<table>
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<tr>
<th>Infection</th>
<th>With acute symptomatic seizures</th>
<th>Without acute symptomatic seizures</th>
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<td>Viral encephalitis</td>
<td>22%</td>
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<td>Bacterial meningitis</td>
<td>13%</td>
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3) Viral infections

3.1) Viral encephalitis

As mentioned above, viral encephalitis increases 10 to 22 (cumulatively 16) times the risk for developing epilepsy, while the risk is higher compared to bacterial meningitis\(^8\). In fact, it seems to be responsible for half of epilepsy cases attributed to infections\(^9\). In a 2007 study in Taiwan, 54 out of 330 children with viral encephalitis (16.4%) developed epilepsy during a 6-years median follow-up period\(^10\).

Although viral encephalitis of any cause could lead to acute symptomatic seizures as well as long-term epilepsy, no studies have been conducted to estimate the risk for every virus separately, since the identification of the virus is not always possible. Herpes-simple virus-1 (HSV-1) is the most common cause and results in the most severe type of viral infections.
encephalitis, regarding mortality and morbidity of the survivors. The other herpesviruses (HSV-2, HSV-6, VZV, DCMV,EBV), enteroviruses (Coxsackie, Echo), the influenza virus, the measles virus and the mumps virus are other causes of viral encephalitis.

Herpesviruses are the most common sporadic cause of encephalitis: HSV-1 is the primary cause in children and adults, but HSV-2 is the most common virus in infants. Around 50% of patients with encephalitis due to HSV-1 exhibit epileptic seizures. These seizures lead to changes in patients' electroencephalogram (EEG) and although they are mostly partial, HSV-1 encephalitis is a potential cause of status epilepticus. Remote unprovoked seizures and epilepsy occur in 40-65% of infected individuals. HSV infection, status epilepticus and EEG changes have been found to be risk factors for subsequent epilepsy after viral encephalitis.

The seizures seem to be the result of HSV tendency to infest medial temporal lobe and especially hippocampus, as seen by radiologic images. This hypothesis is strengthened by an animal study, in which the inoculation of HSV-1 in the hippocampus of mice resulted in acute abnormal changes in EEG and clinical presentation of epileptic seizures. The seizures pathogenesis may be related to the virus's ability to overexcite neurons of CA3 region of hippocampus, but the cell-mediated immune response of the body's human's body through the cytokines secretion against the virus may be of significant importance, since is has been found to contribute to the pathophysiology of temporal lobe epilepsy.

Epileptic seizures are reported in 48% of EBV encephalitis in children, which is a rare manifestation of EBV infection, and up to one third of the cases has been reported to cause epilepsy development.

Cytomegalovirus as an opportunistic infection in immunosuppressed patients, mumps, measles, influenza and rarely the enteroviruses may be responsible for epilepsy cases, but the incidence of this complication is not documented. In the study mentioned above in children in Taiwan, none of this viruses was found to be associated with an increased incidence of epilepsy after the infection.

Risk factors for developing epilepsy are acute symptomatic seizures, status epilepticus as the first seizure, HSV infection, multifocal spikes in EEG, medial temporal lobe damage, as well as the clinical neurological deterioration after admission, partial neurological deficits and the failure of controlling seizures during the acute phase of the infection. As a result, early diagnosis and immediate treatment onset, especially against HSV-1, before seizure occurrence, could be of great significance for the prevention of this serious complication.

Endemic types and more rare causes of viral encephalitis

Epileptic seizures occur in 40-60% of patients with Japanese encephalitis virus, which is endemic in southeastern Asia and is responsible for up to 15000 deaths annually. These are either partial or generalized and constitute a poor prognostic factor. Many patients develop long-term neurological sequelae, especially if healthcare is not sufficient, and 20% of them develop epilepsy. The relative risk has been found to be 8.06 (95% CI 1.31 - 49.44).

West Nile virus is endemic in Africa, Mediterranean Sea, Middle East and cases are even more frequently referred in our country. CNS is insulted in 1 out of 150 cases. In a USA study in 2003, only 1 out of 8 patients with West Nile encephalitis had EEG changes compatible with sub-clinical epileptic seizure during the acute phase of the infection. After an 8 month follow-up period, the patients suffered from moving disorders, including myoclonus, but not epileptic seizures.

Nipah virus is an additional cause of encephalitis and cases are reported from Malaysia, Singapore, Bangladesh and India. Epileptic seizures are presented in around one fourth of the patients, while they are more common (50%) in the relapsing type of the disease. Epilepsy after infection's treatment was developed in 2.2% in a 137-cases study with an 8-year follow-up period, whereas the risk was higher (4%) for the relapsing encephalitis.

Both Human Herpesvirus-6 (HHV-6) and Enterovirus-71 are capable of causing encephalitis, but none of them has ever been recorded to lead to epilepsy or other neurological deficits. Nevertheless, HHV-6 infection has been correlated with febrile seizures in children. In a Greek study, 10 out of 55 (18%) children with a first mentioned febrile convulsions episode were found positive for HHV-6 infection using the PCR method. Enterovirus-71 encephalitis is presented with myoclonus in 68-86% of the cases.

Finally, 10-15% of Dengue virus infected individuals with neurological involvement clinically exhibit epileptic seizures.
3.2) Viral meningitis

Viral meningitis, due to its much better prognosis compared to bacterial meningitis and viral encephalitis, has not been thoroughly studied regarding its relation with provoked epileptic seizures and subsequent epilepsy development. Only 2 out of 282 children in Taiwan with viral meningitis by enteroviruses had acute symptomatic seizures during the infection’s acute phase, while none of them developed neurological complications, including epilepsy, after treatment. Similarly, in a Fiji Islands study, 2 out of 12 children with viral meningitis had seizures at their admission, but no neurological deficit was reported 6 months after the infection was treated. However, both of these studies had a relatively short follow-up period, which was possibly inadequate to estimate the exact danger of long-term unprovoked seizures due to viral meningitis. The major Minnesota Study (1988) found a statistically non-significant relation between viral meningitis and epilepsy. 2.1% of viral meningitis patients developed epilepsy 20 years after the infection with the odds ratio being 2.1. In conclusion, it is not clear from the up to date literature whether epilepsy could be a remote consequence of viral meningitis and more research is essential.

3.3) HIV

CNS involvement is observed in more than half of HIV seropositive patients, while this percentage is even higher in developing sub-Saharan countries (up to 75% in South Africa). The HIV infected patients proportion suffering from epileptic seizures varies between studies in the literature. In the latest of them, 831 HIV patients were studied during the period 1992-2004 in Münster, Germany. 6.1% of them (51 patients) had seizures and 67% out of them (34 patients) finally developed epilepsy in the course of their HIV infection. Two other studies report seizures in 3% and 5% respectively. On the other hand, in an Indian study in 2005, the percentage was higher enough (19.8%, 99 out of 500 HIV cases), but it is noteworthy that the sample included only patients with neurological manifestations.

Most epileptic seizures occur in an advanced stage and may be generalized, secondarily generalized or partial (simple or complex), while in all patients series status epilepticus cases are recorded. Eventually, seizures occurrence has been proposed by researchers as a poor prognostic factor.

Epileptic seizures are the result of the infestation of the CNS the virus itself or secondary due to opportunistic infections and other diseases, such as CNS lymphoma, related to HIV infection. Most of the cases seem to be attributed to underlying infections (up to 93%). Brain toxoplasmosis, cryptococcal meningitis, CNS tuberculosis, progressive multifocal leukoencephalopathy (PML), CNS lymphoma and possibly intravenous drug usage and alcohol abuse are probably the most common causes of seizures. However, in previous studied the seizures etiology was unknown in many cases and they were attributed to the encephalopathy caused by HIV itself.

4) Bacterial infections

4.1) Bacterial meningitis

Acute symptomatic epileptic seizures may complicate 27%-43% of acute bacterial meningitis cases, according to epidemiological studies, they occur until the 21st day (median 4th day) after the infection’s diagnosis and their occurrence was found to increase statistically significantly the risk for adverse complications of the infection. On the other hand, in developing countries the danger for acute symptomatic seizures may be up to 80%, which is attributed to the lower healthcare level and antibiotics deficiency. This is controversial among different studies though, since in Swaziland, South Africa, the possibility of having epileptic seizures during acute bacterial meningitis infection was found to be 18.8%. This could possibly explain the HIV infected patients susceptibility in epileptic convulsions.
an acute symptomatic epileptic seizure was present and 2.4% if not. The cumulative odds ratio was 4.2. In a nationwide study in UK, 1584 children with bacterial meningitis at their early childhood (until 5 years old) were compared to 1391 controls regarding the risk for developing subsequent epilepsy. The relative risk for epilepsy at 5-years-old-point was 2.7 (95% CI: 1.9-3.9) for survivors of the infection versus controls (7.3% vs 2.7%). A birth cohort which included children born in 1966 reports a higher risk: 8 out of 47 children with bacterial meningitis developed epilepsy (17%). In a 1993 meta-analysis, 45 perspective and retrospective population-based studies were included that studied 4418 children cumulatively in order to research neurological sequelae after bacterial meningitis. According to the 19 cohort studies conducted in developed countries, 4.2% (95% CI: 2.1-7) of children had long-term seizure disorders after meningitis, which is in agreement with the rest of the studies (non cohort and studies in developing world) that found the danger to be 5% (95% CI: 3.6-6.8).

Most children will present the fist unprovoked epileptic seizure during the first 5-year period after infection. According to Annegers et al, the incidence of epilepsy is 10.8 times higher than expected during the first 5 years (0-4) after bacterial meningitis, 3.8 times higher the next 5 years (5-9) and 5.4 times higher after the first 10 years of follow-up.

As mentioned above, seizures occurrence during the acute infection is an independent risk factor for long-term epilepsy, while the seizure type (partial or generalized) does not seem to affect the risk. Young age at infection (under 5 years old) as well as older age, log duration of infection before diagnosis and treatment start, abnormalities in EEG and brain imaging, low glucose concentration, high protein levels and abnormalities in leucocytes number in cerebrospinal fluid (CSF), in addition to decreased consciousness level and low brain blood perfusion during the acute phase, seem to increase the danger for epilepsy development. Bacterial meningitis etiology may affect the risk, since the possible infectious agents have different characteristics. Streptococcus pneumoniae is related to the highest incidence of remote neurological consequences, including epilepsy, among bacteria causing meningitis, while Neisseria meningitis to the lowest.

Unprovoked seizures are usually recurrent and partial or partial with secondary generalization. Nevertheless, generalized tonic-clonic and myoclonic seizures have been reported as well. In the Minesota Study, the risk for unprovoked partial seizures is 12 times higher after CNS infection, whereas it is only 3 times higher for unprovoked generalized seizures.

Seizures control is not sufficient. Around 1/3 of patients achieve to control seizures to less than 2 annually (3 out of 10 and 4 out of 11 patients), while in the rest of them despite the antiepileptic treatment with more than one AED, no control was possible.

According to basic research data, brain tissue damage and death of the neurons observed in acute bacterial meningitis are partly responsible for seizures occurrence, which is not just the result of bacteria’s presence and action, but the host’s immune response against bacterial products as well. This response leads to cerebral edema, increased intracranial pressure, decreased cerebral blood perfusion and changes in brain basic metabolic rate. Possibly, the risk for neurological complications development depends on the cerebral maturity, the part of the brain insulted and the damage level. Moreover, according to studies, CNS infections (encephalitis and meningitis) are related to higher incidence of medial temporal sclerosis, a finding usually observed in patients with idiopathic partial epilepsy of the temporal lobe. Thus, damage in this part of the brain by the infectious agents could be the cause of epileptogenesis because of infection.

4.2) Cerebral abscesses and empyemas

Cerebral abscesses

Cerebral abscesses, which are formatted either through extension of an adjacent inflammatory process, such as after suppurative otitis media, or hematogenously, in diseases like bacterial endocarditis, are usually clinically presented with epileptic seizures. The possibility for acute symptomatic seizures occurrence varies among studies and there are references for 26%, 13.4%, and 7% in three studies of the last decade. In one of them, that the type of the seizures is documented, the majority of the patients had generalized tonic-clonic convulsions, while partial seizures were less common (10 versus 3 patients).
Chronic neurological disorders, one of which is epilepsy, are usual complications of brain abscesses. 51 out of 70 survivors of brain abscess studied during the period 1931-1966 developed epilepsy (72%) in a follow-up period of 3 to 30 years (median 11 years)\(^61\). Epilepsy was first presented after one month to 15 years after diagnosis and the authors found no factor to be associated with the risk for its development\(^61\). A later study of 1983 comes in agreement, since 37 out of 67 patients followed for 3 to 40 years after diagnosis and treatment of brain abscess finally developed epilepsy\(^62\). Earlier studies published in the 90s record lower percentages, as only around one third of the patients reported subsequent epilepsy\(^63\)-\(^65\).

The majority of the patients report unprovoked seizures for the first time a few months after treatment. For instance, 86% of the patients who finally developed epilepsy had their first seizure during the first year after diagnosis, according to a polish study\(^63\). This latency period varies among studies though. In adults it was found that epilepsy is first manifested after 3.3 years\(^61\), while in children after 4.2 years\(^66\). Furthermore, unprovoked seizures may occur after a shorter period from diagnosis if the abscess is located in the temporal lobe and after a longer period if it is located in the frontal lobe\(^61\). These authors claim that, since epileptic seizures were observed even 15 years after brain abscess treatment, the real incidence may be sub-estimated by other studies due to the short follow-up period\(^61\).

Various parameters have been proposed and studied by researchers as potential risk factors for long-term epilepsy due to brain abscess. Large size (>4 cm) and supratentorial location of the abscess, childhood, male sex and type of the responsible microorganism are some of them proposed by various researchers, but not confirmed by all of them\(^61\)-\(^64\). Acute symptomatic epileptic seizures\(^64\) and various laboratory findings, like persistent imaging changes in CT after disease has been treated and spikes or sharp waves in EEG seem to predispose to late epilepsy development\(^67\),\(^68\). Finally, some authors refer increased risk for epilepsy in cases treated surgically compared with those treated with medication therapy with antibiotics or/and abscess aspiration\(^68\),\(^69\).

Most of the authors claim that anticonvulsant therapy should be given to all patients with brain abscess, as there is a high chance for both acute symptomatic seizures and later epilepsy. Legg et al, 1973, advocated anticonvulsant treatment for 5 years to all patients with brain abscess\(^61\), while Muzumdar et al, 2011, support that antiepileptic drugs should be continued for at least 1 year after treatment in patients treated surgically and discontinuation should be considered only if no significant epileptogenic activity is visible in the EEG\(^70\).

**Subdural empyema and epidural abscess**

Epidural and subdural empyemas (diseases more frequent in developing countries) are clinically presented with epileptic seizures and are possibly associated with subsequent epilepsy, according to various studies. The same authors studied a hospital-based series of patients with intracranial sepsis admitted in a neurosurgery clinic of South Africa during the period 1983-1997. Between them there were 699 subdural empyema cases and 76 epidural empyema cases\(^71\),\(^72\). Epileptic seizures were referred from 273 patients (39%), with 209 being partial in the first study and 9 patients (4 partial and 5 generalized seizures) in the second study\(^69\),\(^70\). 14.7% of patients with subdural empyema who were followed had epileptic seizures after surgical therapy (the duration of the follow-up period is not referred), while just 4 out of 47 patients with epidural empyema who were followed for a median period of 250 days, were in need of persistent antiepileptic treatment\(^69\),\(^70\). In a previous study of 1983, 65 survivors of subdural empyema were followed. 42% of the patients without acute symptomatic seizures reported epileptic seizures after therapy, while 71% of patients with seizures before treatment were free of seizures after surgery\(^73\). These researchers document increased incidence of unprovoked seizures in patients in the second and third decade of their lives while the median time for epilepsy to be manifested after treatment was found to be 16 months\(^73\).

**5) Tuberculosis**

In a number of patients infected by tuberculosis, it is possible that mycobacteriums penetrate the subarachnoid space and lead to the development of meningitis and cerebral tuberculomas\(^74\).

During the acute phase of tuberculous meningitis there is a risk for epileptic seizures. In a Turkish study of 2003 in 61 adult patients with tuberculosi, 16.3% of them had provoked seizures; half of them
were partial, while the other half generalized. A higher percentage (31.5%) is referred from an Indian cohort that included 54 patients. It is also possible a proportion of patients to exhibit during acute infection status epilepticus. According to two studies, 7% of patients with first reported status epilepticus were found to suffer from tuberculous meningitis, which was the cause in 6 out of 85 and 8 out of 119 cases respectively.

Regarding subsequent epilepsy after CNS insult by tuberculosis, there are no long-term perspective studies to research the risk in treated patients, probably due to the high mortality related to the disease, as well as the fact that the majority of the cases are nowadays observed in developing countries, where the long-term follow-up is more demanding.

6) Protozoal infections

6.1) Malaria

Cerebral malaria is a severe form of malaria in general, which is often associated with acute symptomatic epileptic seizures, especially in children. A study carried out in Kenya that included 65 children with cerebral malaria showed that 62% of them (40 out of 65) exhibited seizures after their admission, 28% of them (18 out of 65) had at least one episode of status epilepticus and 68% of them (44 out of 65) reported at least one seizure in their medical history before admission. In a larger study in Kenya that examined a sample of 17517 children with every kind of malaria, found that 37.5% of them, namely 6563, presented epileptic seizures.

Epilepsy was first related to malaria in 1949 by Talbot et al. Since then several epidemiological studies have strengthened this relationship. In a Kenyan hospital-based study of 2004, 9.2% of patients admitted for cerebral malaria and 11.5% of patients admitted for cerebral malaria with reported acute symptomatic seizures, finally developed epilepsy 20 to 112 months later. The odds ratios compared to general population were 4.4 (95% CI 1.4-13.7) and 6.1 (95% CI 2.0-18.3) respectively, while the risk was statistically non-significant for individuals with cerebral malaria who exhibited seizures versus those with cerebral malaria but free of seizures history (OR 1.3, 95%CI 0.6-2.7). In an equivalent study in Mali with children suffering from cerebral malaria, the relative risk (RR) for subsequent epilepsy after controlling for age and duration of follow-up period was found to be 4.3 (95% CI 1.6-132.0) and the incidence of epilepsy 17 cases/1000 individuals/year in children insulted by cerebral malaria. Finally, according to a case-control study from Gabon, patients with epilepsy are more possible to have a positive history of malaria compared to controls with no epilepsy (OR 3.9, 95% CI 1.7-8.9).

In accordance with the studies mentioned above, epilepsy is possible to present even one month after malaria has been treated, but the cumulative incidence seems to be higher the longer the follow-up period; this may indicate that it could occur after many years have passed since infection's treatment. EEG changes are observed in one third of epilepsy cases after malaria, while there are reports of patients who showed ischemia and even cortical atrophy in CT. According to results from one of the above studies, 42% of seizures recorded were generalized tonic-clonic, while the rest of them were partial or with partial onset and secondary generalization.

Plasmodium falciparum seems to cause microvascular obstruction leading to ischemic changes in cerebral cortex, which are possibly responsible for epileptogenesis in survivors of cerebral malaria. This hypothesis is strengthened by the detection of brain ischemia with MRI in a small sample of patients with epilepsy due to malaria. Genetic background could play a key role, since children with family history of epileptic seizures are more possible to exhibit acute symptomatic seizures. Analysis of CSF of patients with cerebral malaria and seizures has shown increased levels of excitotoxin quinolinic acid, denoting that excitotoxic mechanisms may contribute to their pathogenesis. Furthermore, during the acute phase of the infection, the levels of autoantibodies against voltage-gated calcium channels have been found to be high; this could be a possible explanation of how neurons lose control of their excitability leading to clinical occurrence of epileptic convulsions. Lastly, there are references from case series and case reports that antimalarial drugs are associated with increasing frequency of seizures in patients with epilepsy and precipitating seizures.

6.2) Toxoplasmosis

Besides plasmodium, the infection by Toxoplasma gondii has also been correlated with
epileptogenesis, but the literature is limited to a little number of studies. A recent large cohort of 2013 conducted in sub-Saharan Africa in which participated 1711 patients with epilepsy and 2032 controls found that seropositivity in Toxoplasma gondii is a risk factor for epilepsy in adults (OR 1.39 , 95% CI 1.05- 1.84), but not in children (OR 1.15 , 95% CI 0.85- 1.58)92. In agreement with these results, a meta-analysis of three case-control studies showed that the relative risk for epilepsy is 4.8 (95% CI 2.6- 7.8) in individuals with positive serological tests for toxoplasmosis compared to seronegative population93. Alongside the meta-analysis the same authors performed an ecological study, which evidenced a strong association of epilepsy prevalence among cities, regions and countries studied with the seropositivity of their population (and pregnant women) in T. gondii93. On the other hand, a Turkish study found no relationship, but the sample studied was relatively not of the same size (100 epilepsy cases vs 50 controls)94. Thus, it is clear that toxoplasmosis is a possible cause of cryptogenic epilepsy.

The researchers, who carried out the meta-analysis mentioned above, suggest a possible pathogenetic mechanism: the rupture of the cerebral cysts, which are created because of T.gondii infection of the brain, results in inflammation and subsequently in scar tissue formation, that has been proposed in the past as a cause of secondary epilepsy93. Furthermore, the protozoon entrance in the neurons leads to intracellular calcium levels disorder which causes both lysis of the cell resulting in microglia formation and instability of neuronal potential leading to overexcitability and epileptic seizures93.

7) Helminthic infections

7.1) Neurocysticercosis

Neurocysticercosis which is caused by CNS infestation with parasite Taenia solium larvae constitutes the most common cause of secondary epilepsy in many developing countries and is responsible for 20 million cases and 50000 deaths annually95. The helminthes form cysts in the brain parenchyma, the ventricles, the basal cisterns or the subarachnoid space (intraparenchymal and extraparenchymal neurocysticercosis)96.

Epileptic seizures are a very common symptom of neurocysticercosis, especially when referring to the intraparenchymal type. They are most likely present during the second colloidal stage of the cysts, in which the cysts degenerate causing inflammatory response, even though they have been observed during other stages as well96. Up to 94.8% of children with neurocysticercosis have been recorded to have seizures97. Despite the fact that the majority of individuals with cysticercosis living in endemic regions are asymptomatic, 30 to 50% of all epilepsy cases are seropositive for the helminth; this percentage is 2 to 3 times higher than the one observed in general population of these regions98. It is estimated that CNS cysticercosis is responsible for one third of epilepsy cases in endemic countries, but these estimations have been made using serological tests, which do not have high sensitivity and specificity for neurocysticercosis99. In extraparenchymal neurocysticercosis, epileptic seizures are quite unusual100.

The seizures are mostly partial with secondary generalization and less frequently complex partial, while their duration is short (<5 minutes)97. Seizures related to multiple and calcified cysts are prone to relapse, in contrast to those related to a solitary granuloma that after a short period of epileptic activity, they usually recede101. Specifically, 30% of patients with solitary granuloma due to neurocysticercosis exhibit relapse of the seizures and this is an indication of remanence of calcified residue101. Factors associated with epileptic seizures recurrence are the calcification remnants after the cyst has resolved, the number of calcifications and their location, the duration of seizures occurrence before the onset of treatment, the treatment selection and the compliance with AEDs, while the location and number of infestations of the brain parenchyma, inflammation surrounding a cyst and edema around a calcified lesion are correlated with subsequent epilepsy in general97,102,103.

The prognosis of patients with epilepsy due to neurocysticercosis is good after treatment with major AEDs. Although relapse of seizures after many years is a possibility, more than 50% of the patients are free of seizures after antiepileptic treatment discontinuation104.

Cysticercosis is capable of provoking seizures through various mechanisms, most of which focus on the inflammation of brain tissue. The presence of the cysts in the colloidal stage is related with inflammation, while this inflammation is possible to be expanded in adjacent vessels causing vasculitis and thromboses in these vessels, which could possibly be responsible for seizures occurrence. The seizures in patients with residual calcifications have also been
associated with surrounding edema, which could be attributed to an inflammatory response to antigens of the helminth trapped in calcified lesions. However, the seizures themselves have been proposed to be responsible for the surrounding edema formation, a hypothesis not disproved so far.

7.2) Other helminthic infections

Due to the limited geographical distribution of the rest of parasitic infections that infest CNS, there are only a few studies in international literature researching their association with epilepsy.

Onchocercosis seems to be correlated with epilepsy, according to two case-control studies, whereas a meta-analysis of 9 African studies estimated the risk for subsequent epilepsy in patients with onchocercosis to be 1.21 (95% CI 0.99-1.47). A possible relationship between Onchocerca volvulus infection and epilepsy could be explained by its penetration in the CNS, the pathogenicity of various parasite strains, immunological response of the host and cytokines secretion and sleep deprivation due to pruitus caused by onchodermitis.

Seropositivity for Toxoacara canis infection has been found to be around 2 to 4 times more possible in patients with epilepsy versus controls, while the relationship is stronger regarding partial epilepsy.

Lastly, the serological screening for antibodies against the helminth Spirometra erinacei which is the cause of sparganosis was positive in 2.5% of cumulatively 2667 patients with epilepsy, versus 1.9% of healthy population (OR 1.32, 95% CI 0.76-2.3) in a Korean study conducted in 1994.

8) Conclusions

Up-to-date literature advocates the theory that a proportion of epilepsy cases as well as epileptic seizures could securely be attributed to infectious agents, especially when referring to countries of the developing world. In some of these countries, where specific infectious diseases like malaria and cysticercosis are endemic, infections are responsible for the higher epilepsy incidence compared to Western countries and they probably are the most common cause of secondary epilepsy. In addition, infections constitute globally the most common cause of epilepsy that could be prevented through either avoidance of exposure to infectious agents (better conditions of hygiene) and development of vaccines, or timely diagnosis and onset of therapy for each infection.

Considering the above, it has been clear that CNS infections most strongly associated with epileptogenesis should receive more attention and efforts should be made in the direction of their prevention and the earliest possible therapeutic intervention for their control, especially in developing countries, since this could significantly reduce the global incidence of epilepsy. Towards this objective, more research is needed for verification of the relationship between any infectious agent that can infest CNS and the risk for subsequent epilepsy, as well as the identification of pathogenetic mechanisms of epileptogenesis underlying this phenomenon. This could result in the invention of new “antiepileptogenic” medications, which would be of great significance in the prevention of epilepsy secondary to infections, as well as other conditions like cerebrovascular disease and brain injuries.
cytes contributes to the pathophysiology of temporal lobe epilepsy. The
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