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Seizures, epilepsy and infectious diseases of the nervous system

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ABSTRACT – The recent onset of partial epileptic seizures, secondary generalized partial seizures, or tonic-clonic generalized seizures are often diagnostic indicators of central nervous system infections (meningitis, encephalitis, single or multiple abscesses, sub-dural empyema). The occurrence of status epilepticus (SE) from an infection is a serious factor to be considered in therapeutic management. Brain CT-scan or MRI examinations are used to establish its parasitic, mycotic, bacterial or viral etiology. These studies also serve to confirm or modify the clinical diagnosis and the topographical origin of the infection. Nevertheless normal morphological examinations do not rule out a recent infection as a causative factor in epileptic seizures. This is especially true for meningitis in all age groups but particularly in children. Indeed, epileptic seizure onset in patients with meningitis is an indication of the presence of a cerebral abscess. In the acute phase, antiepileptic treatments are the rule of thumb. Their indication in the follow up phase with the purpose of preventing further seizures will depend upon the nature of the infection and availability of access to antiinfectious treatments. The risk of subsequent epileptic seizures is most common in patients with encephalitis and cerebral abscesses. In cases of trauma, infections affecting the central nervous system increase the risk of posttraumatic epileptic seizures.

Keywords: seizures, epilepsy, infectious diseases, nervous system

Epileptic seizures constitute one of the most common presenting events of central nervous system infections. In infectious etiologies overall, onset by an epileptic seizure is seen in 70% of cases of encephalitis, 40% of cerebral abscesses and 20% of cases of meningitis (Lahar and Harden, 1997). The occurrence of initial or early status epilepticus is also a vital indication of immediate severity of the disease, and serves to establish functional and cognitive prognosis (Vespignani *et al.*, 1995). At the same time, infection is one of the most common etiologies of symptomatic epileptic seizures regardless of age (15%), and particularly in children: 37% up to age 4 years, 40% between 5 and 14 years. A second frequency peak occurs in the elderly (Annegers *et al.*, 1995).

In the setting of seizures as the first presenting symptom, many diagnostic and therapeutical issues should be considered:

- envisage and look for an infectious origin in cases of epileptic seizure or status epilepticus as the presenting symptom of the clinical picture;
- know the most common infectious aetiologies, in order to choose suitable anti-infectious treatment;

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• in the acute phase, determine the appropriate antiepileptic drug and the duration of treatment;
• determine whether or not chronic antiepileptic treatment is indicated to limit the risk of subsequent epileptic seizures and, accordingly define the criteria for choice of antiepileptic drugs.

Infections also constitute a frequent etiological factor in symptomatic epilepsies, at all ages. Knowing that 40% of epilepsies are symptomatic, infectious aetiologies (viral encephalitis, cerebral abscess, AIDS, neurocysticerosis) represent 3% of all epilepsies (Annegers *et al.*, 1988). This percentage is about the same as that for traumatic causes. Although the percentage varies considerably depending on age, it seems to be most dependent on geographic region. In many countries (Latin America, Asia, Africa), neurocysticerosis (NCC) represents over half of the etiologies of initial seizures in adults (Medina *et al.*, 1990).

In the presence of symptomatic epilepsy, manifesting in repeated spontaneous epileptic seizures, the objectives pursued are:

• to link the epileptic events to a more or less remote infectious cause. Today, this problem has been solved in large part by morphologic brain imaging; keeping in mind, however, that if an infectious etiology is suspected, a normal MRI does not necessarily exclude this possibility;
• to determine criteria for choosing the most appropriate antiepileptic drugs and specify subsequent prognostic elements in cases at risk to progress towards a drug resistant epilepsy.

In order to attain these objectives, we will examine successively parasitic, viral, fungal and bacterial etiologies, specifying for each one the involved pathophysiological mechanism, as well as clinical and paraclinical diagnostic elements.

Parasitic etiologies

Neurocysticerosis (NCC)

Neurocysticerosis is the most common parasitic disease in Central and South America. After paludism, it is the most common parasitosis; it should be considered in subjects who lived in Latin America, in black Africa or in Asia. NCC represents 10% of etiologies of neurologic emergency cases. Epilepsy is the most common symptom, occurring in two thirds of patients (Del Brutto *et al.*, 1992).

In Mexico, NCC is the most common cause of adult onset epilepsy, representing half of all cases (Medina *et al.*, 1990). In Europe, foci have been observed in the Mediterranean region, particularly in Sicily. In France, few cases have been seen, although diagnosis is easy, given that neuroradiologic images are characteristic (Planque *et al.*, 1990). NCC is due to infection of a human (final host) by *Taenia Solium*, whose intermediary host is the pig. Pigs are contaminated by eating eggs found in human feces. It is possible for humans to absorb these eggs, which are particularly resistant and remain infectious for a very long time in pork. These eggs produce embryos that are encysted in different parts of the body, under the skin or, most particularly, in the muscles, as well as in the brain or in the bone marrow. Encystment in the meninges produces hydrocephalus in addition to arteritic changes at the base of the skull and secondary vascular complications.

Cerebral location of cysts is responsible for epileptic seizures, 72% of which are partial, according to Medina (Medina *et al.*, 1990), and associated with a normal neurological exam in 80% of patients. Paraclinical diagnosis is easy to be made. The scan shows a number of small cysts, rounded and covered with calcifications. Solitary brain lesions have been observed; they consist of a large hypodense or isodense cyst surrounded by perilesional edema. Cyst evolution is described in four stages: stage 1 (thin-walled cyst), 2 (cyst with thicker walls, with or without scolex), 3 (poorly limited cystic degeneration), 4 (presence of calcifications).

The presence of myalgia can lead to identification of characteristic muscular calcifications.

An antiparasitic drug (albendazole), is more specifically indicated in forms without calcifications. Long-term prognosis of epilepsy is uncertain, given the subsequent risk of seizure recurrence observed after ending treatment in over half the cases during the first three months, among 40 patients studied by Del Brutto (Del Brutto *et al.*, 1992), despite a 2-year, seizure-free period. The choice of antiepileptic therapy must take into account the possibility of reduced praziquantel blood levels due to the enzyme-inducing effect of antiepileptic drugs (Bittencourt, 1992).

Paludism

Paludism is the most common fatal parasitic disease in the world. 80% of patients die of cerebral complications. In Nigeria, where paludism is endemic, one third of epileptic seizures with fever in children are caused by this disease (Asindi *et al.*, 1993). The agent responsible, a hematozoon protozoa - of the most common *falciparum* type, the most serious, or more rarely, of the *vivax* type, *ovale*, *malariae*, transmitted by female Anopheles in Asia, Africa and Latin America – multiplies in the liver before invading red blood cells, where successive cycles provoke febrile attacks concomitant with antigen release. Changes in the central nervous system correspond to multiple necrotic and hemorrhagic foci produced by contact with fine thrombosed capillaries rich in parasites.

The characteristic symptom is an attack of paludism. Cerebral malaria is the serious, mortal form of the attack.

It must be remembered that cerebral malaria never takes the form of meningitis or meningoencephalitis, but appears instead as a very serious encephalopathy, without CSF changes, with convulsive seizures and with consciousness and tonus problems. Although euphoria is the usual mode of presentation, hyperalgic forms do also exist (Dumas, 1997). This diagnosis should be systematically

considered in travelers returning from black Africa, from Central and South America, from South-East Asia. EEG recordings are not helpful. But we must be aware of the forms of the disease characterized by periodic activity, since they could suggest a false diagnosis of necrotizing encephalitis. It is urgent to look for *Plasmodium falcifarum* by performing a blood smear or by microscopic observation, knowing that the parasite will not always be found. When in doubt, it is best to treat with quinine IV. Paludism can be prevented by taking an antimalarial drug 10 days before leaving, throughout the duration of stay in these regions, and for three months after return. Antimalarials, such as mefloquine (Lariam®) can lower convulsive threshold and reduce sodium valproate blood levels by 30 to 40%.
Therefore, it is useful to check, and if need be to change, the sodium valproate dosages of epileptics traveling in endemic regions.

Toxoplasmosis

Toxoplasma gondii, an intracellular protozoon, is transmitted in food contaminated with oocysts from cat feces, since the cat is the only known definitive host. Transmission can also take place by ingestion of undercooked meat of bovines or ovines infected with cysts. After passing through the digestive system, the parasite invades the body through the hematopoietic system, and spreads to a multitude of cells. The infection can remain quiescent, existing in a microcystic intracellular form that is virtually asymptomatic. The advent of immunosuppression may reactivate the cysts. Nervous system complications include encephalitis, large brain lesions in the course of AIDS and, rarely, myelitis, polyradiculoneuritis and polymyositis. In a pregnant woman, infection during the first two trimesters of pregnancy can result in a massive injury to the fetal encephalon, producing brain malformations, encephalopathies, psychomotor delay and chorioretinitis. Children can subsequently develop epilepsy, whose origin will be revealed rapidly by the presence of characteristic calcifications on a brain CT scan, or even a simple x-ray.
There has been renewed interest in this infection among AIDS patients, because toxoplasmosis is a complication in about 30% of cases, representing half of all neurological diseases associated with AIDS (Porter and Sande, 1992). Thus, toxoplasmosis is the most common neurological complication of AIDS, appearing at a late stage of this disease.
Epileptic seizures may be the initial manifestation in 18 to 29% of cases of toxoplasmosis complicating AIDS (Porter and Sande, 1992, Ragnaud *et al.*, 1993). The CT scan is very suggestive as it shows multiple ring-enhancing cysts surrounded by perilesional edema. This very characteristic image in the case of immunocompromised hosts justifies the institution of specific antiparasitic therapy. Diagnosis is confirmed by resolution of clinical signs and brain lesions in response to treatment.
Diagnosis is more difficult when the CT scan shows a single image suggestive of abscess, or when normal. toxoplasma serology contributes little to the diagnosis. Exceptionally, IgMs are found; more often, traces of IgG are found. Lumbar puncture, whose usefulness should be decided based on location and size of cysts, as well as on the presence of intracranial hypertension, may show moderate cellular reaction, with low CSF proteins. The MRI detects multiple T2 hypersignals with mass effect.
Brain biopsy, performed less often nowadays, shows areas of necrosis with parasitic infestation. A very important argument favoring the diagnosis is the effectiveness of the specific treatment (Malocide®, Adiazine®, Lederfoline®), resulting in clinical and imaging resolution in over 80% of cases (Lahar and Harden, 1997). Onset of epileptic seizures motivates the choice of non enzyme-inducing antiepileptics.

Other parasitoses

Helminthiasis worms include nematodes (non-segmented, cylindrical), cestodes (flat, segmented) and trematodes (flat, non-segmented).
Nematodes that infect humans are for the most part intestinal parasites: ascaris, oxyuris, trichocephalus, ankylostomas, and strongyloid threadworm. They can cause headaches, irritability, apathy, insomnia and, exceptionally, confusion of non-epileptic origin. In general, their role in neuropsychiatric disorders is ambiguous. It is not possible to assert that a parasitic origin of this type is responsible for epilepsy in a child with oxyuris or ascaris, unless the infection is massive, and there are predisposing factors.
The cause-effect relationship is very different in cases of *filaria* and *trichiuria*, which can cause neurological complications through larval migration. Filaria infections are ubiquitous in tropical regions. Nervous complications like meningoencephalitis or epileptic seizures are very rare (Dumas *et al.*, 1986).
Trichinosis exists world-wide. Short epidemics have occurred in France. The infection is transmitted through the ingestion of undercooked boar or horse meat that contains *Trichina spiralis* larvae; it causes systemic illness with hypereosinophilia and myositis, including cardiac myositis (Fourestié *et al.*, 1993). Nervous complications arise very suddenly, a few days after ingestion of the contaminated meal; they manifest as diffuse headache with or without epileptic seizures, with paralysis of variable intensity and location. CSF is normal or shows only a high protein level. The CT scan reveals the presence of numerous small and diffuse, "contrast enhancing" hypodensities, in the white matter or the cortex. Treatment consists of a combination of benzymidazoles and corticoids. Prognosis depends on the extent of cardiac involvement. Chronic antiepileptic therapy is not indicated beyond the acute phase.
Other nematode parasitoses exist in the Far East and in the Pacific. One is particularly frequent in Thailand: gnathos-

tomiasis caused by *Gnathostoma spinigeruna*, a parasite of the cat, and of rats infesting uncooked fish and shellfish meals. The disease manifests with sudden, intense pain whose location is variable, painful paralyses and convulsions, in a context of often fatal encephalitis.
Cestoda are taenias. *Taenia saginata*, the most common, particularly in France, does not cause neurologic complications, except at the stage of general complications. *Taenia solium* is the agent responsible for cryptococcosis. *Taenia ecchinococcus*, which causes hydatid cysts (hydatidosis) exists world-wide and advances along with sheep farming (intermediary host). Adult taenias live in the intestines of dogs. Humans are contaminated by ingesting eggs shed with *taenia* rings. Cerebral localization of taenias causes the development of a large, hypodense cystic lesion, as evident on CT scan imaging. The lesion may result in intracranial hypertension and symptomatic epileptic seizures. Treatment is surgical. Subsequently, chronic antiepileptic treatment must be maintained for several months, even two years.
Alveolar echinococcosis (*Echinococcus multilocularis*) is a particular form of echinococcosis; this infection is ubiquitous, also seen in France, especially in the East (Weber *et al.*, 1988). The echinococcus lives in the intestines of foxes; humans are contaminated by eating wild berries. Larvae are encysted as poly lobar nodules that appear as bunches of grapes in the meningeal spaces and sometimes in the cerebral parenchyma, particularly in the temporal region. Epileptic seizures can be the initial symptoms. Differential diagnosis is largely based on CT scan findings, and includes metastases or glioblastomas, mostly in the presence of a unique lesion. Blood hypereosinophilia should attract attention toward parasitic origin.
As far as trematodes are concerned, neuropsychic complications involve Distoma and Schistosoma. Among Distoma parasites, *Fasciola hepatica*, responsible for hepatic distomatosis, is the most likely to cause meningeal syndromes with CSF eosinophilia. Epileptic seizures are unusual.
Paragonimiases are of interest because of the neurologic manifestations seen in 30 to 50% of patients, with predominance of encephalitis and secondary epileptic seizures. In addition, the "soap bubble" appearance of scan images is particularly characteristic. This Far East parasite causes pneumopathy responsible for purulent bloody sputum containing parasite eggs. The clinical picture presents as tuberculosis, but the diagnosis can be corrected rapidly by a systematic search for eggs in the sputum.

Protozoans

Intestinal telluric protozoa responsible for amebiasis, and sanguineous protozoa causing paludism and trypanosomiasis belong to the category of protozoa with neurological tropism.
Epileptic seizures can be symptomatic of cerebral amebiasis. The clinical picture varies depending on the type of amoeba. *Entamoeba histolytica*, the agent of amebic dysentery, can cause cerebral abscess, usually single and very large. This diagnosis is suggested by intestinal symptoms. *Entamoeba naegleria* causes a very serious purulent meningoencephalitis, due to penetration by the amoeba into the olfactory tract of swimmers in the lukewarm or warm stagnant waters of lakes, ponds or even poorly maintained swimming pools.
Diagnosis is made upon discovery of the amoeba at direct phase-contrast microscopy, or after culture. Evolution is often extremely rapid. *Entamoeba acanthamoelva* is responsible for subacute meningoencephalitis that can include epileptic seizures in immunocompromised patients.
The main sanguineous protozoon is the agent of paludism.
Trypanosomiasis is also secondary to infestation by a sanguineous protozoan; Trypanosomiasis is transmitted by the tsetse fly (Glossina), only in intertropical black Africa. This parasite, presently in full recrudescence, causes meningoencephalitis with altered consciousness, which is quickly fatal if untreated (melarsoprol is the therapy of choice). The clinical picture presents subacute or chronic meningoencephalitis, with epileptic seizures in rare cases, more often with altered consciousness, extrapyramidal rigidity, hyperkinesias and psychic problems. The CSF is quite characteristic, with increased levels of gamma globulin and IgM, as shown by using immunofluorescence (Dumas, 1997).
In summary, epileptic seizures can be responsible for the discovery of intracranial parasitosis, or can complicate a chronic infestation. Epileptic events are always partial seizures or tonic-clonic seizures generalized from the outset. They can occur together to constitute status epilepticus.
When an epileptic seizure is isolated and constitutes an initial event, diagnosis depends on geographical of origin and CT scan findings:
- single cyst in France: hydatidosis,
- multiple small cysts in Latin America, black Africa, Asia, Southern Europe: cysticercosis,
- multiple or single cysts in France: alveolar echinococcosis, toxoplasmosis,
- multiple, "soap bubble" cysts in South-East Asia, black Africa: paragonimiasis,
- single cyst in North Africa: amebiasis,
- encephalopathies: pernicious paludism,
- meningoencephalitis: filariasis, trichinosis, toxoplasmosis.

From the therapeutic perspective, antiparasitic treatments act as diagnostic tests (toxoplasmosis, paludism) and are generally very active if the diagnosis is made early enough. Onset of early epileptic seizures requires antiepileptic therapy at the acute phase (benzodiazepines). Surgical treatment could be indicated in cases of single localization of large, accessible cyst. Follow-up with chronic antiepileptic therapy is necessary in case of single or multiple localization of sequel cyst, with or without calci-

fication. The drugs of choice are non-enzyme-inducing antiepileptics which do not interfere with antiparasitic treatment.

Mycotic etiologies

Central nervous system mycoses are rare but one of them, cryptococcosis, has attracted attention because of its frequent association with AIDS. Cryptococcosis caused by yeasts (*Cryptococcus neoformans*) represents about 10% of neurological affections associated with AIDS (Belec and Gray, 1990). Clinically they may present as a subacute meningeal syndrome, meningoencephalitis with cranial nerve involvement; and sometimes as pseudo tumoral syndromes. The clinical picture may consist only of moderate fever or persistent headaches, due to meningitis.
Epileptic seizures may complicate evolution. MRI is very suggestive and may show symmetrical hypersignal nodular lesions, in the Virchow Robin spaces of the basal ganglia. A systematic search for *Cryptococcus neoformans* (direct India ink CSF staining, culture, antigen identification) is essential.
The hypothesis of a mycotic origin must be considered in every case of subacute or chronic meningitis, meningoencephalitis or single, or more often multiple, abscesses in a patient with lowered defenses (immunocompromised, with serious chronic infection) after catheterization or placement of prosthesis (nosocomial infection). It also should be considered in the differential diagnosis of central nervous system tuberculosis and cacinomatous meningitis. The responsible agents are cryptococci, Aspergillus (aspergillosis), Candida (candidiasis), more rarely histoplasmosis or coccidi-oidiomycosis in cases of meningitis. Diagnosis is based largely on neuroradiological findings. Presence of one or several abscesses can be the consequence of dermatomycosis (single, blackish abcess,), nocardiosis (ubiquitous distribution), and blastomycosis (endemic in the United States).
In the acute phase, antiepileptic treatment with benzodiazepines can be necessary, followed by chronic antiepileptics to avoid the high risk of seizures relapse. Drugs to drugs interactions and the patient general status may interfere with the choice of anti epileptic drugs.

Viral etiologies

Epileptic seizures are a common symptom of viral encephalitis. They can be generalized tonic-clonic, but also, very characteristically, frequently recurrent, recent onset partial seizures. Serial seizures, and even initial status epilepticus, are not unusual. In general, a diagnosis of acute encephalitis should be considered in the presence of epileptic seizures in a context of recent altered alertness and impaired consciousness, in the course of a recent state of confusion, with or without fever. Absence of fever should not eliminate the suspicion of encephalitis. In the same way, absence of a clinical meningeal syndrome is almost universal.
However, these signs are obviously highly indicative of a diagnosis of encephalitis, in the presence of recent-onset epileptic seizures, if infection is present, if skin irritation is noted, or if there are highly suggestive epidemiological data.

The herpes virus

Necrotizing encephalitis caused by herpes virus (HSV1) is the most common, one of the most serious in the absence of specific treatment (over 70% death rate, high incidence of serious sequelae among survivors), and especially the most important to recognize early because of the therapeutic possibilities that have completely altered the prognosis of this very serious entity.
The herpes virus invades preferentially the temporal lobe and the orbito-frontal cortex, bilaterally, probably through olfactory fibers. It rapidly causes inflammation accompanied by edema responsible for rapid and massive destruction of the cerebral cortex. This preferred localisation accounts for early onset of epileptic seizures, for possible phasic problems, and for the rapid appearance of mental confusion and diminished alertness. Epileptic seizures are both early and numerous, which explains the frequency of indicative status epilepticus.
Characteristically, the possibility of herpes encephalitis should be considered first in the presence of seizures appearing to be of temporal origin, very recent and numerous from the outset, in a subfebrile or altered alertness context. Perioral herpetic lesions are observed in less than 5% of cases.
The diagnostic procedure should take the following facts into account:
- antiherpetics are more effective if administered early;
- the value of presumptive treatment combining antiherpetics with wide spectrum antibiotics (antiherpetic, anti listeria, antituberculosis) has been proven;
- for the purposes of early diagnosis, a CT scan is not as useful as a brain MRI, which shows, as early as the second day, a T2 hypersignal at both temporal lobes, keeping in mind that the MRI can be normal prior to this (in practice, this can only be done when access to MRI is easy in an emergency);
- diagnostic proof is provided by a CSF study (presence of viral DNA and levels of alpha interferon). Results for viral DNA can be obtained relatively early, within 24 to 48 hours, but a negative PCR does not exclude this diagnosis (Jambon, 2001).

Interferon-alpha levels indicate the presence of a virus, and results can be obtained in about 8 days. As for an emergency CSF test, the classic traps must be kept in mind: normal results in 10% of cases; reaction with polymorpho-

nuclear predominance that could orient the diagnosis toward other etiologies, particularly bacterial.

For all these reasons, the EEG is useful, although neuroradiologic investigations are now given priority. The EEG is useful when an MRI cannot be performed, when MRI images are not clearly indicative or are ambiguous, when lesions are unilateral, signs are atypical, or there is absence of biological concordance.

The EEG is even more important in cases of misleading clinical forms (apyretic forms, psychiatric forms), or in cases where the CSF is normal (10%) or atypical (polynucleated cells in over 40% of cases, hemorrhagic forms).

The characteristic EEG in an indicative clinical context shows localized short period periodic activity. Periodic activity is a regularly repeated paroxysmal activity occurring in stereotypical fashion for a long period, usually lasting several minutes. When the period, that is, the time between the start of each complex, is less than 4 seconds, the activity is classified as short; it is classified as long when it exceeds 4 seconds. In herpetic encephalitis, periodic activity is short and localized in temporal or frontotemporal regions. Becoming visible, in general, between the second and the fifteenth day, this activity can be labile and, at first, can consist of a few fragments that are repeated over a few dozen seconds, and that should be looked for in an indicative context (Vespignani *et al.*, 2002). This uniform or bilateral periodic activity appears over a slow background which is proportional to impaired consciousness. The periodic activity is interrupted by focal or rapidly generalized epileptic seizures. We must keep in mind that spontaneous evolution takes place through the gradual replacement of all periodic activity by a low voltage activity, which indicates necrosis and irreversible lesions.

The usefulness of the EEG for diagnosis has been illustrated in a series of 18 cases of herpes encephalitis, and in 31 cases of presumed viral, but not herpetic, encephalitis. In the herpetic encephalitis group, the EEG is normal less often than in the non herpetic group (8% *versus* 23%) and temporal abnormalities are more frequent (75% *versus* 19%). Periodic activity is only found in less than 3% of cases of non herpetic encephalitis, and can exist in spite of normal MRI (Clinque *et al.*, 1996). However, it is not constant, since the same series only shows it in 28% of cases, and remarks on its transient, labile character, and on the need to repeat the EEG in case of suspicion of herpetic encephalitis.

Differential diagnosis is only considered, in practice, after institution of presumptive treatment based on MRI clinical data. In this situation, the EEG is important once again in order to detect:

- pathologies other than encephalitis, particularly cerebral thrombophlebitis whose clinical profile can be similar, with generalized tonic-clonic epileptic seizures, apparently from the outset or, more often, partial and secondarily generalized; partial motor seizures rather than partial complex seizures. In addition, at EEG, periodic lateralized epileptiform discharges (PLED) can resemble periodic activity, adding to the difficulty;
- other viral encephalitis: diagnostic errors in favor of herpetic encephalitis are not harmful, since the other viral etiologies do not respond to treatment. The diagnosis is corrected by performing viral biologic investigations, because these clinical and neuroradiologic profiles can be similar;
- non viral encephalitis, particularly acute disseminated encephalomyelitis, where epileptic seizures are exceptional and lesions manifest through white matter anomalies revealed by MRI; paraneoplastic limbic encephalitis, called Corsellis encephalitis (Ducrocq *et al.*, 1992); or transient limbic encephalitis of dysimmune origin, associated with antibodies to cortical voltage-gated potassium channels (Thieben *et al.*, 2004). Acute onset, without fever, in a context of altered consciousness, behavioral problems, or cognitive deficit, with temporal lobe epileptic seizures rapidly becoming numerous, may point toward herpetic encephalitis, but there is no periodic activity and focal epileptic seizures are often in alternating locations on the same EEG tracing or on different tracings. MRI shows bi-temporal T2 signal abnormalities, predominating or appearing exclusively in the hippocampus.

In practice, it is only when performing a brain MRI is impossible, and when the MRI is normal or MRI images are unclear, that differential diagnosis is considered, but without delaying presumptive therapy that combines an antiherpetic (aciclovir IV, 30 to 45 mg per kg and per day for ten days), an anti-listeria (amoxicillin + aminoside or cotrimoxazole alone), an antituberculous (isoniazide-rifampicine) if there are clinical indications of tuberculosis.

Subsequent evolution will lead to stopping antituberculous treatment if clinical improvement is rapid (a few days), to stopping antiherpetics if the herpes PCR is negative and the interferon alpha is normal.

As for antiepileptic treatment, the choice is between an intravenous benzodiazepine (clonazepam) or IV sodium valproate; the latter might be preferred in order to better monitor consciousness and alertness. In case of status epilepticus resistant to this therapy, fosphenytoine (Dilantin®) is useful. The risk of epileptic sequelae is 16 times higher than that in the general population, and this risk persists for almost 15 years (Annegers *et al.*, 1988). Risk of epilepsy in encephalitis patients with early epileptic seizures is 10% in the first five years, and 22% during the 20 years after the initial infectious episode.

For patients with encephalitis without early epileptic seizures, the cumulative risk over 20 years is 10%. For patients with bacterial meningitis with or without early epileptic seizures, the cumulative risk over 20 years is 13 and 2% respectively (Annegers *et al.*, 1995).

Other herpes viruses

The cytomegalovirus (CMV) is transmitted through the blood, particularly during surgery with extracorporeal circulation. The CMV also plays a pathogenic role in many neurological syndromes, and in the late stages of AIDS, where it is ubiquitous. Apart from retinal lesions, it can cause subacute encephalitis close to "AIDS dementia", and is responsible for partial or generalized tonic-clonic epileptic seizures. MRI is suggestive, showing an abnormal T2 hypersignal lining the ventricular walls (Gastaut, 1997). In exceptional cases, the Epstein-Barr virus is responsible for acute encephalitis that can bear a clinical resemblance to herpetic encephalitis (Bale, 1993).

The other viruses

Arboviroses are transmitted by mosquitoes or ticks and belong, for the most part, to intertropical pathology. Central nervous system injury occurs most often during a second febrile episode. Seizures can occur in a very variable clinical context, depending on the agent involved. A few cases among natives have been documented. Encephalitis caused by ticks is generally associated with peripheral paralysis. Epileptic seizures are unusual (Garcia-Monco and Benach, 1995).

Rabies

In France, rabies is an imported pathology, since the disease is virtually eradicated in animals. But it is present in neighboring regions as in Central Europe and North Africa. It is responsible for encephalitis that is rapidly fatal. Epileptic seizures, usually generalized tonic-clonic and convulsive are part of an indicative clinical picture that includes hydrophobia (Dupont and Earle 1966).

Bacterial etiologies

Acute meningitis

Onset of epileptic seizures in the course of bacterial meningitis should alert to the possibility of an abscess or the development of cerebral thrombophlebitis. These hypotheses must be eliminated before a physiopathology of "irritative" meningeal inflammation, or release of epileptogenic bacterial toxins can be considered. This rule should motivate a brain CT scan and, if need be, an MRI, in the event of seizures in the context of bacterial meningitis.

Seizures are common, observed in nearly 30% of cases of bacterial meningitis, with no visible cerebral lesions (Durand *et al.*, 1993). They are more frequent in young children, being often the presenting clinical sign of meningitis, in febrile children (Green *et al.*, 1993). The agent responsible is mainly *Haemophilus influenzae*, but the bacterium varies depending on the child's age: Streptococcus B, *escherichia coli* and *Listeria monocytogenes* in the neonatal period; *Haemophilius influenzae, Neisseria meningitidis* and *Streptococcus pneumonia* after the age of six years.

Tuberculous meningitis should be considered separately because seizures are very common in the course of its evolution. This pathology is seen more often in adults and in the elderly. The typical form is subacute meningeal syndrome, with lymphocytic-type cellular reactions, low cerebrospinal fluid glucose and high proteins. Alertness problems appear early, as do EEG abnormalities related to diffuse and often significant slowing of background rhythm. Life threatening forms are not rare; they are characterized by subfebrile confusion, persistent headaches, generalized tonic-clonic or partial seizures, in a cephalalgic and subfebrile context. Tuberculous meningitis is associated with epileptic seizures in 10 to 15% of cases. The seizures are secondary to severe CSF inflammation, and associated vasculitis. Tuberculoma, a late-developing cerebral abscess is not discovered at this stage.

In the acute phase of acute bacterial meningitis, seizure onset requires urgent antiepileptic therapy with benzodiazepines or sodium valproate IV, depending on the state of consciousness; follow-up with a chronic antiepileptic treatment should be decided based on the risk of subsequent epileptic sequelae to the acute meningeal episode. Epidemiologic data on this point has been clearly established, as witnessed by the historical Rochester series (Annegers *et al.*, 1995), which documents increased risk of epilepsy. This risk is independent of age at the time of infection, but varies considerably depending on type of infection and on the presence of early seizures.

Patients with aseptic meningitis do not have added risk of subsequent epilepsy. Patients with bacterial meningitis have a five times higher risk compared to the general population, with particularly highest risk during the first two years following infection. This risk contributes to risk factors for possible head trauma, causative or associated, corresponding to a supplementary risk factor for post-traumatic epilepsy.

Cerebral abscess

Diagnostic and therapeutic procedures related to cerebral abscess have been considerably modified by the advent of the brain CT scan, keeping in mind that cerebral abscess incidence was greatly reduced with the introduction of antibiotics (Nielsen *et al.*, 1983). As is the case for all infectious pathologies, prognosis depends primarily on early diagnosis. Initial or early partial or partial secondarily generalized seizures occur in nearly one third of cases. Symptomatology is directly related to the location of single or multiple cerebral abscesses.

Although considerable progress has been made in terms of diagnostic techniques, the physiopathologic mechanisms of cerebral abscesses are still unknown. The point of entry of the infection is otic (chronic otitis, more rarely sinusitis),

either through a hematogenous pathway originating in a locus of chronic pulmonary suppuration, or by means of a congenital cardiopathy with right-to-left shunt. The shunt can be responsible for infection through venous blood contaminated by infected teeth or tonsils. Similarly, the clinical picture is classic in patients with Rendu-Osler disease, vascular dysplasia with telangiectasias, sometimes associated with pulmonary angiomas, causing suppurative emboli. It is not known why the cerebral infection is sometimes diffuse (meningeal type) and at other times localized; or why the localized form is sometimes intracerebral (cerebral abscess) and sometimes located in the subdural space (subdural empyema). In 10 to 20% of cases, an exact point of entry is not found. The organisms involved are very diverse, aerobic and anaerobic. They cause intracellular suppuration, with pus collection surrounded by a zone of inflammation, itself surrounded by edema. Abscess evolution results in the creation of a fibrous shell.

The clinical picture reflects a tumoral syndrome possibly associated with deficits and/or intracranial hypertension. When seizures are the exposing event, they can be either isolated or part of the tumoral picture. The important element to keep in mind is that the infectious syndrome with fever, and blood inflammatory syndrome, is not constant and can be discrete. Moreover, discovery of a possible source of infection is definitely not the rule, at least not during the initial diagnostic procedures. Therefore, it is the brain CT scan that makes it possible to identify a single or multiple abscesses.

Diagnostic difficulties are of two types. Erring on the side of caution, that is, diagnosing an abscess too quickly and instituting wide spectrum antibiotic treatment, has no serious consequences, and the diagnosis is rapidly corrected by the evolution of clinical signs and by scan results. By contrast, erring by default is serious because it delays treatment. A diagnosis of meningitis can be maintained when meningeal signs are predominant and the neurological deficit is discrete. As a rule, the occurrence of any seizures in the course of a meningeal syndrome is reason for performing a brain scan. The scan images can lead to making a diagnosis of brain tumor: glioblastoma or single or multiple metastases in case of subacute evolution and discrete infectious syndrome. Treatment is medical and/or surgical, by puncture and institution of local antibiotic therapy, combined with systemic antibiotic therapy.

Occurrence of initial or early epileptic seizures requires antiepileptic treatment with benzodiazepin or sodium valproate; partial or generalized status epilepticus is not rare and can require prescribing fosphenytoine (Dilantin®). Follow-up with a chronic antiepileptic treatment is obligatory in all cases. Risk of subsequent seizures is almost constant (Legg *et al.*, 1973).

This risk is greater in the context of possible post-traumatic origin. Brain abscess is an additional risk factor for the occurrence of post-traumatic epilepsy (Vespignani *et al.*, 1995). Residual risk of epileptic sequelae is high and leads to the prescription of antiepileptic therapy over several years. It is only after 5 to 10 years that ending therapy can be considered, keeping in mind that even a long time after the initial episode the risk of seizure recurrence remains significant.

Tuberculoma is a rare and particular form of brain abscess. It consists of a solid mass representing a granuloma made of epithelioid cells and caseum. At CT scan, the tuberculoma resembles a pyogenic abscess. It usually originates along vasculitic lesions and almost always it follows mastoiditis. Scanographic findings are non-specific. Treatment consists of evacuating the abscess (aspiration or craniotomy) and administering prolonged antituberculous chimotherapy. Antiepileptic treatment is required in the acute phase and follow-up with an antiepileptic drug is indicated, at least for the duration of the antituberculous treatment (12 to 18 months or more, depending on scanographic evolution). Choice of medication must take into account possible drug interactions and the possibility of enzyme induction, particularly when the drug prescribed is isoniazide (INH). □

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