EPILEPSIA PARTIALIS CONTINUA ASSOCIATED WITH HASHIMOTO ENCEPHALOPATHY: MANAGEMENT DIFFICULTIES

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ABSTRACT

Both Hashimoto encephalopathy (HE) and epilepsia partialis continua (EPC) are neurological entities less encountered by the clinician. Nevertheless, they imply diagnostic and therapeutic challenges. We report the case of a 42-year old woman with HE and EPC. Difficulties of diagnosis and management of HE and EPC are discussed.

Key words: Hashimoto encephalopathy; epilepsia partialis continua; antithyroid antibodies; partial complex seizures

INTRODUCTION

Epilepsia partialis continua (EPC) is a rare form of partial status epilepticus, probably of cortical origin, manifested as a simple motor seizures usually localized to one anatomical segment and persisting for at least 60 minutes. It is highly pharmaco-resistant and implies a possible evolution to complex partial seizure but only rare generalization, being possibly followed by interictal weakness. Often it exteriorizes a permanent parenchymal lesion of any etiology but may be a manifestation of a progressive neurological disease.

Hashimoto encephalopathy (HE) is a rare, though under-diagnosed, steroid-responsive, relapsing remitting, self-limited or progressive disease with unknown pathogenesis, occurring in association with autoimmune thyroiditis independently of thyroid functional status, often in the presence of high thyroid antibodies titers (especially thyroxin-peroxidase antibodies, but also thyroglobulin and TSH receptor antibodies). It may present as stroke-like episodes, epileptic seizures (frequently myoclonic) and psychiatric syndromes and it has no typical paraclinical features (MRI, EEG or cerebrospinal fluid – CSF). EPC may be a symptom of HE.

CASE REPORT

We report the case of a 42-year-old woman, diagnosed since she was 29 with Hashimoto thyroiditis. She had persistent high titers of thyroxin-peroxidase antibodies (above 1000 times the cut-off value) and was euthyroid under levothyroxine treatment. From her medical history we point out an episode of intracranial hypertension (for which an etiology could not be demonstrated, most likely caused by venous thrombosis) accompanied by a

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right pyramidal syndrome, the latter unremitting and responsible of a persistent mild hand weakness (4/5). This was followed a year later by the acute development of persistent quasi-permanent headache compatible with chronic migraine for which she was addressed to our Deapartment. Brain MRI, angio-MRI and EEG were normal.

One and a half year since the first neurological symptoms, a few hours after she noticed sudden regain of full strength in her right hand, she developed involuntary clonic movements of the right hand that were influenced by voluntary movement, tactile and emotional stimuli. Initially the clonic movements lasted up to three hours a day (15-90 minutes per seizure) but constantly increased in persistency and frequency until a total duration of up to 8 hours a day (30 minutes to 4-5 hours per seizures, in spite of the later antiepileptic polytherapy) and evolved to partial complex seizures (lasting from 10 to 60 minutes each) up to four times a day. The clonic movements persisted during sleep and were most frequently followed by interictal weakness and somnolence. She had no generalized seizures. Though initially the atypical neurological presentation was considered functional, the presence of a constant electro-clinical correlation led to the diagnosis of epilepsia partialis continua. The antiepileptic therapy was gradually increased until she daily received 3 grams of levetiracetam, 13 milligrams of clonazepam and 200 milligrams of lamotrigine (after a non-succesfull treatment attempt with phenytoin and oxcarbamazepine). After the rapid but meticulous exclusion of other possible causes of encephalopathy (including paraneoplastic) the diagnosis of Hashimoto encephalopathy with secondary EPC was considered. Again, as previous, there were no MRI brain lesions and no CSF abnormalities (the presence of thyroid-peroxidase antibodies in the spinal fluid could not be tested). The clinical and electrical pattern of the seizures changed with time. A bipyramidal syndrome appeared causing a decrease in strength in both hands and left calf and foot (4/5). Moreover, a deterioration of the cognitive status was observed, quantified by a MMSE decline from 30 to 25.

She received corticosteroids (1 gram of methylprednisolone iv per day for 6 days followed by per os maintenance therapy). In the next seven months the evolution was satisfying with a constant but incomplete amelioration of the neurological symptoms (cessation of headache, significant decrease in seizures activity with seizures lasting up to 4 hours a day, no evolution to partial complex seizures, regain of strength in left hand, calf and foot, MMSE 29). However, even thou the seizures decreased as duration and amplitude, there is no more than 2 day-period free of critical activity.

DISCUSSION

Both HE and EPC are rare and underdiagnosed diseases. A very high clinical suspicion is essential for their diagnosis. This is not the first report in literature in which EPC appears as a symptom of HE, however this associatio is not frequent.

The diagnosis of HE is made in the presence of encephalopathy with no other proven cause in association with autoimmune thyroiditis. HE appears independently of thyroid function. It often affects women (85%), more frequently in their fourth decade, but the age of onset may vary. There are two types of HE regarding to onset: an abrupt, often stroke-like pattern, causing focal deficits and seizures and an insidious progressive one with dementia and psychiatric symptoms and no focal neurological signs,.

The evolution is self-limited, relapsing-remitting or progressive. HE may progress to coma in several weeks if untreated. The severity of HE does not correlate with the initial titer of thyroxin-peroxidase antibodies as they seem to be only a marker, an immune epiphenomenon of the disease. To the best of our knowledge no antigen for thyroxin-peroxidase antibodies was identified in the human brain. HE pathogenesis remains unknown, but is most likely immune mediated, hypothesis supported by the response to corticoids, immunosuppressants and plasmapheresis. It is considered by many to be a form of localized central nervous system small vessel vasculitis.

There is no specific diagnostic test. The brain MRI may show non specific findings or may be normal. CSF examination may show elevated protein levels, mononuclear pleocytosis or oligoclonal bands, but in 25% of the cases it remains normal. EEG is abnormal in 90% of the cases typically showing nonspecific intermittent diffuse slow wave activity. Its differential diagnosis includes encephalopathy and encephalitis of any etiology, multiple sclerosis and psychiatric disturbances. In our case the patient had acute onset of vascular headache, acute left pyramidal syndrome, cognitive deterioration, EPC, intermittent slow wave activity and epileptic focal discharges on EEG, with no brain MRI, angio-MRI and/or spinal fluid abnormalities. The presence of Hashimoto tyroiditis with very high levels of circulating thyroxin-peroxidase antibodies in the absence of any other possible cause was

leading to the diagnosis of HE. She also had a prior episode consisting of intracranial hypertension syndrome and right pyramidal syndrome that may be attributed to EH.

The diagnosis of EPC is electro-clinical. In EPC as in other epileptic partial status the epileptic activity has two essential properties: it does not spread and it self-perpetuates. Thus the epileptic focus is probably a lesion (reversible, stable or progressive) localized in the motor neocortex (structure that being designed to keep responses precisely localized has a powerful inhibitory reaction in the periphery of excitatory foci; seizures originating in the neocortex spread only if they gain access to limbic circuits) that also has properties allowing for self-perpetuation. The size of the lesion seems not to correlate with the severity and the degree of muscle groups involved. The functional brain studies usually show that the EPC focus is hypermetabolic (PET), hyperactive (MEG) and has increased blood flow (SPECT). Extrapolating the current opinion on the synaptic mechanism of status epilepticus, one can hypothesize that in EPC there is an epileptic focus of persistent stimulation of glutamate receptors and desensitized GABA receptors while the latter have their function preserved in the surroundings. This model may not explain all the situations, as there are cases of EPC described in the literature that did not respond to NMDA blockers. There is also another hypothesis in which certain autoantibodies or substances activate the excitatory circuits or block the inhibitory ones localized in or connected to the motor neocortex, thus creating synaptic disturbances that self-perpetuate the epileptic activity. In certain cases, due to the permanent activity, the epileptogenic focus degenerates (excitotoxicity, remodelation) this leading to a change in the clinical and electrical manifestations but also to possible self-limitation or augmentation of the disease. The possibility of an EPC epileptic focus with subcortical or cerebellar localization has been discussed. There are some authors which consider that EPC-like manifestation that have a non-cortical brain origin or for which a cortical etiology cannot be demonstrated should be considered separately. The differentials of EPC include involuntary localized persistent movements such as cutaneus reflex myoclonus, segmental myoclonus or certain types of tremors.

Interestingly, such as in our case most of the EPC cases reported in literature cause clonic movements localized to the right hand. Even if one can speculate in considering this possibly being expressions of the particularities of the dominant hemisphere neocortex controlling the hand that may allow for very localized responses, the presence of EPC in other muscular groups oblige to refute such a simplistic explanation as unique.

Causes of EPC are numerous: cortical dysplasias, cerebral neoplasias, infections or inflammatory diseases, arterial-venous malformations, arterial or venous infarcts, trauma, metabolic encephalopaties, hyperosmolar states (such as hyperglycemia and ketoacidotic hyperglycemic coma), toxic injury (penicillin, cefotaxime) and progressive/neurodegenerative or genetic diseases such as Rassmusen encephalitis respectively mitochondrial cytopathies. Depending on the clinical evolution, EPC was classified by Bancaud in type I and II. In type I EPC the age of onset is variable, the electro-clinical pattern remains stable, the EEG alterations are localized, there are no associated mental deterioration, psychiatric symptoms or clinical neurological findings, with the exception of a mild to moderate preexisting stable motor deficit, the cause is usually precisely identified and the prognostic is the same as the one of the underlying disease. In type II EPC, which is classically assigned to children with Rasmussen encephalitis, the age of onset is usually in the first ten years of life, the electro-clinical pattern changes, the EEG shows a long sub-clinical pattern of sharp waves with different localizations, there are usually other types of associated seizures, there is progressive motor deficit of the segment involved in the involuntary movements corresponding to an area of localized cortical atrophy on brain MRI and other neurological clinical findings. In EPC type II, there is progressive mental deterioration or psychiatric symptoms, usually followed by self-limitation (arrest of deterioration accompanied by significant decrease or cessation of the seizures). Sometimes, as in our case, the clinical presentation is not entirely compatible with either type.

The interpretation of the consecution of clinical events remains speculative. Even there is no proof to it, our patient may have had an old cortical lesion (possibly caused by a cortical venous infarct in the setting of the above mentioned intracranial hypertension syndrome) which caused mild hand weakness but no seizure activity. The EEG showed initiation of the epileptic discharge (sharp waves and spike-waves) in the frontal contra lateral leads, occasionally followed by temporal ipsilateral progression, arising from a background of intermittent slow waves. The very short regain of full strength in her right hand preceding the right hand clonic movements may suggest the loss of inhibitory influences. One can speculate and say that in this pa-

tient a relapse of HE caused a new lesion that destroyed an inhibitory circuit that prevented the old cortical lesion from causing seizures, but there is also the possibility that a humoral factor encountered in the presence of HE caused an unbalance in the synaptic activity at the site of the old lesion. The latter hypothesis may be supported by the fact that after treatment of HE with corticosteroids resulting in the cessation of headaches and improvement of overall neurological status, in parallel with a major decrease in thyroxin-peroxidase antibodies titer (from 1870 UI/ml to 75 UI/ml), the frequency and duration of the seizures also decreased (not related to adjustments in the antiepileptic therapy). After a month of persistent epileptic activity the electrical disorganization of the epileptic foci was noticed. For this euthyroid patient, the mental deterioration could be explained either as being a symptom of disease (EH and/or EPC) or less probably as being a possible side effect of antiepileptic medication.

In most of the cases HE is corticoresponsive, only rarely requiring immunosuppressant therapy. EPC is typically pharmacoresistent. There are reports that claim that corticotherapy, immunosuppressive treatment, plasmapheresis, IVIG administration and transcranian magnetic stimulation may play a role in the treatment of EPC. Also, there is a case described by Browner in which symptomatic relief was obtain by local injections of botulin toxin, of course with the undesirable loss of segmental function. In rare case the impossibility of attaining a satisfactory control leads to neurosurgical treatment.

As expected the seizures were highly resistant to antiepileptic therapy in our patient. The high dose corticoids resulted in prompt control of HE but without remission of EPC. In spite of the polimedication used we can consider the response to be at most medium, but this is often encountered in the setting of EPC.

The case reported highlights the need for considering HE in patients with encephalopathy. Nevertheless, even rare, EPC must be known and recognized by the clinical neurologist tacking into account its particular clinical and prognostic features.

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