Super-refractory status epilepticus or degenerative encephalopathy with rapid progression? A case report

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Abstract

Nonconvulsive status epilepticus (NCSE) may be differentiated with difficulties from acute/subacute onset encephalopathies (metabolic, toxic, post-anoxic, spongiform), particularly in de novo cases. We report the case of a 57-year-old man, otherwise normal, who started to present brief focal seizures and behavioral changes few weeks after a febrile illness. At the onset, the clinical and EEG picture were suggestive of a de novo NCSE. However, the rapid and progressive clinical and radiological worsening, the presence of a periodic EEG pattern, the drug-resistance, led us to consider a progressive degenerative encephalopathy. We report a challenging case of de novo super-refractory NCSE, without a definite etiologic diagnosis.

KEY WORDS: non-convulsive status epilepticus, new onset refractory status epilepticus, Creutzfeldt-Jacob disease.

Introduction

Status epilepticus (SE) is a neurological life-threatening emergency. It is classically defined as “a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition” (1, 2). SE is classified in convulsive SE (CSE) and non-convulsive SE (NCSE) in relation to the presence or not of prominent motor symptoms (3). Diagnosis of NCSE may be challenging as it encompasses a wide spectrum of clinical presentations with variable degrees of alteration of consciousness, behavioural and cognitive abnormalities, autonomic abnormalities, visceral and different sensory and psychic symptoms. NCSE could be the result of a generalized or focal SE (3, 4). Diagnosis of NCSE usually involves a suggestive clinical presentation, a supportive EEG, and response to anticonvulsant medication (4, 5).

EEG recording is essential for NCSE diagnosis even if the interpretation of EEG patterns can be difficult because frequently unspecific and changing over time. Particularly, in long duration SE may prevail rhythmic and/or periodic non-epileptiform patterns that may be found in several pathological conditions and that typically show a poor response to antiepileptic treatment (3). In the last years an important effort has been done to classify EEG patterns and to highlight the crucial role of prolonged EEG monitoring in order to identify early EEG abnormalities and their space-temporal evolution, the recognition of subtle clinical ictal phenomena and the response to antiepileptic drugs (3-8).

However, NCSE, for its protean clinical and EEG presentation, is often underdiagnosed and treated with delay with possible outcome compromise. This is particularly true in cryptogenic de novo cases of super-refractory SE (SRSE), in which the etiology remains unknown and where the treatment with anaesthetics for >24 hours may fail. One of the most relevant factor that influences the prognosis and the aggressiveness of the therapeutic approach is the evaluation (and treatment) of the underlying cause of SE. NCSE may be caused by a wide spectrum of disorders ranging from “benign” conditions, such as absence status in idiopathic generalized epilepsy, to severe central nervous system’s insults (such as stroke, intoxications, encephalitis, metabolic conditions, brain tumors, neurodegenerative diseases, autoimmune disorders). In case series of NCSE, the cause of NCSE was remote symptomatic in 47%, idiopathic in 45% and remains unknown in about 48% (3, 9).
We report a case of de novo super-refractory NCSE, beginning with ictal motor phenomena, rapidly followed by a progressive consciousness impairment. The progression was rapid toward a coma condition with generalized myoclonic jerks. The etiology of this condition remains unknown and led us to consider a possible degenerative encephalopathy with a NCSE onset.

Case report

A 57-year-old man, otherwise normal, with positive family history for epilepsy, was referred to our clinic for a suspected NCSE. Few weeks after a febrile illness, he started to experience brief episodes of right head and trunk deviation with loss of consciousness, associated with progressive behavioural changes (irritability, aggressiveness), confusion and speech disturbances. After a month the clinical picture worsened and he was admitted to the hospital. The neurological examination revealed intermittent dystonia of the right hand with superimposed slight myoclonic jerks. The EEG showed a 6-7 Hz background rhythm and sporadic sequences of sharp-wave/spike-wave complexes on the left fronto-temporal regions increased by hyperventilation (Fig. 1 A, B). An MRI showed a focal diffusion restriction on diffusion weighted images (DWI) in the left fronto-temporo-parietal cortex and in the left caudate nucleus without corresponding reduction of the apparent diffusion coefficient (ADC) (Fig. 1 C).

The response to antiepileptic drugs (levetiracetam, phenytoin, phenobarbital, topiramate, valproic acid)
was negligible. Repeat cerebrospinal fluid (CSF) analysis showed only a mild proteinornioacchia and Tau protein increase; oligoclonal bands, viral PCR, paraneoplastic (neuronal nuclear cytoplasmic antibodies) and autoimmune markers (LG1, CASPR2, GluR3, NMDA, VGKC, GAD AMPA1-2, GABA1 antibodies), lactate/pyruvate, 14.3.3 protein were negative; the search for prion protein was negative on CSF and olfactory mucosa brushing (10). Total body CT scan was unremarkable and total body positron emission tomography (PET) showed a left cerebral hemisphere hypometabolism. Cutaneous and muscular biopsy were negative.

After two months from the onset the patient was clinically unresponsive and the myoclonic jerks were more evident on the right arm and mouth. The EEG showed a bilateral periodic pattern with triphasic morphology and runs of bilateral fast epileptic discharges associated with clonic jerks prevalent on the right arm and with right head deviation (Fig. 2 A); midazolam intravenous infusion showed a temporary EEG improvement and myoclonia reduction but without any other clinical improvement (Fig. 2 B, C). DWI and fluid attenuated inversion recovery (FLAIR) images showed a bilateral involvement of the basal ganglia (body of caudate nucleus and putamen), a less prominent cortical involvement, and a progressive cortical and sub-cortical atrophy (Fig. 2 D, E).

Despite the treatment with third-line anticonvulsant therapy, intravenous immunoglobulin (0.4/gr/Kg for 5 days), intravenous steroids (methylprednisolone 1 gr for 5 days) and ketogenic diet, the patient showed a progressive clinical worsening. Nine months after the onset, the patient was still in coma with widespread myoclonic jerks. The EEG showed a bilateral periodic pattern with runs of fast epileptic discharges associat-
ed with increased myoclonic activity (Fig. 3 A, B). MRI showed DWI and FLAIR hypersignal in the basal ganglia bilaterally, and a severe cortical and subcortical atrophy (Fig. 3 C, D). After one year the situation is unchanged and the etiology remains undetermined.

Discussion and conclusion

In the presently reported patient the presence at the onset of focal seizures with impairment of consciousness without recovery between the episodes and intermittent focal epileptic discharges on the EEG, fitted with a diagnosis of a new onset focal NCSE. The presence of DWI restriction at MRI in the left fronto-temporo-parietal cortex (corresponding with localization of EEG abnormalities) and in the left caudate nucleus was at least partly suggestive of the transient and heterogeneous MRI alterations described in SE-patients (11-13). In our patient, the focal cortical lesion was progressively less evident on repeat MRIs, whereas bilateral alterations in the basal ganglia and a diffuse cortical and sub-cortical atrophy were still present. Cianfoni et al. in 2013 showed that seizure or SE can induce transient MRI brain alterations that can involve cortex, subcortical structures, basal ganglia, white matter, corpus callosum and cerebellum. Recovery may be complete or partial (mainly in SE or seizures with hippocampal involvement) with residual gliosis or atrophy (11). In a case series, peri-ictal DWI restriction was found in 28% of SE-patients, with the involvement of cortex and/or sub-cortical regions (mainly pulvinar thalami). The Authors speculated that SE-patients with peri-ictal DWI hyperintensity show a more severe clinical presentation, periodic lateralized epileptiform discharges and intermittent repetitive seizure patterns with a prevalence of unilateral EEG patterns (12). Therefore, in our case the MRI pattern may be compatible with the progressive and severe impairment of consciousness and the subsequent appearance of a periodic EEG pattern.

We exhaustively searched for and failed to find any infectious, inflammatory, metabolic, neoplastic, paraneoplastic and degenerative causes. The etiology remains therefore obscure. In addition, because of preceding febrile illness, the drug-resistance, the mild CSF pleocytosis, the extensive negative workup, and the poor outcome, we hypothesized a new onset
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refractory status epilepticus (NORSE), an heterogeneous clinical entity described recently. Only few cases of NORSE has been described in limited case series. NORSE is described as a refractory or super-refractory SE that arises in otherwise normal young patients with protean clinical features, sometimes preceded by an unspesific febrile illness, more prevalent in females. The EEG shows a multifocal pattern and the brain MRI may present a temporal or leptomeningal hyperintensity. The outcome is poor and typically the underlying cause remains undiscovered (14-17).

On the other hand, because of the complete refractoriness to different treatments, the progressive clinical worsening culminating in a myoclonic status, and the EEG pattern, dominated by bilateral periodic triphasic waves, we also considered the possibility of an atypical Creutzfeldt-Jacob disease (CJD).

CJD is a rare human transmissible spongiform subacute encephalopathy. In 90% of patients it is sporadic (sCJD), in 10-15% is genetic (gCJD), inherited in autosomal dominant fashion, and in a minority of cases is acquired via iatrogenic transmission (iCJD) or exposure to the bovine spongiform encephalopathy agent (variant CJD -vCJD). sCJD has a variable and nonspecific clinical presentation, making early diagnosis very challenging. The mean age of onset is 70 years, with a survival of 3-7 months. The most common clinical manifestations include rapidly progressive dementia, behavioral changes, cerebellar dysfunctions and myoclonus. Supporting findings are an EEG pattern with periodic sharp wave complexes, a positive 14.3.3 protein in CSF assay, a MRI hyperintensity in caudate nucleus and/or putamen on DWI or FLAIR sequences. These investigations are helpful in diagnostic process in vivo, although they allow only a probable/possible CJD diagnosis. Currently, definitive diagnosis requires a positive result for pathologic prion protein (PrP) on brain tissue obtained post-mortem or via biopsy. Recently, a novel ultrasensitive method, real-time quaking-induced conversion (RT-QuIC) assay, has been used in vivo to detect prion protein on olfactory mucosa brushing and on CSF, with a sensitivity of 96% and 97% respectively and a specificity of 100%. While sCJD, gCJD and iCJD share common clinical and radiological features, vCJD shows distinctive features such as an earlier age at onset (mean age is 28 years), a longer median survival of 14 months, typical MRI findings (bilaterial pulvinar lesions), 14.3.3 protein on CSF is not a useful marker and periodic pattern on EEG may manifest only in the late stages of disease (10, 18, 19).

In our case the diagnosis remains undefined, although we suspect a case of sCJD presenting with NCSE. CJD diagnosis shows atypical features for the very long survival time (12 months), for the negativity of PrP with the use of very sensitive and specific assays (RT-QuIC) and for atypical clinical presentation (NCSE). Seizures in CJD are an uncommon findings, occurring in less than 15% patients and usually appear in late stages of disease (20). SE in CJD patients is exceedingly rare and only few cases of NCSE have been reported. Our patient shares similar features with the published cases, such as the presence of periodic pattern on EEG interrupted by very frequent electro-clinical seizures and the resolution of ictal EEG pattern without a clinical improvement after benzodiazepine infusion (21-22). The MRI characteristics reported in our patient are of non-univocal interpretation: the basal ganglia involvement is considered a hallmark of CJD, but a cortical involvement as the result of a prolonged SE may not be excluded (11-13). Furthermore, FDG-PET hypometabolism found in our patient is in line with PET studies in CJD, where on early stages may be found an hypometabolism in cortical/subcortical areas involved (24), whereas in SE patients ictal PET showed a cortical hypermetabolism (25).

In conclusion, we report a challenging case of a de novo super-refractory NCSE, in which the etiology remains elusive. Diagnosis of NCSE may be difficult because of the highly variable electro-clinical features and the heterogeneous etiologies. In these uncertain cases, a careful electro-clinical and MRI evaluation over time may allow the early recognition of a NCSE, increasing the chances of a better outcome which is, however, strongly influenced by the underlying etiology.

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Conflict of interest statement
All Authors declare that there are no conflicts of interest.

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