CREUZFELDT-JAKOB'S DISEASE – CASE REPORT

Z. Cofoian-Amet[1], B. Rusu[1], C. Mitu[1], E. Roşianu[1], B.O. Popescu[1,2,3]

[1]Department of Neurology, Colentina Clinical Hospital, Bucharest, Romania
[2]Department of Neurology, Psychiatry, Neurosurgery and Psychiatrics, School of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Laboratory of Neurosciences and Molecular Medicine, "Victor Babes" National Institute of Pathology, Bucharest, Romania

ABSTRACT

Creutzfeldt-Jakob disease is a low incidence progressive neurodegenerative disorder and, meanwhile, the most frequent human prion disease. We report here the case of a 65 years old female with a 2-month history of rapidly progressive dementia. The clinical examination identified patent cerebellar and extrapyramidal signs. Despite the absence of myoclonic jerks and pathological findings in T2 and FLAIR MRI, the presence of protein 14-3-3 in a significant amount in cerebrospinal fluid (CSF) was identified. The patient succumbed to the illness within 2 month of hospitalization.

Key words: sporadic Creutzfeldt-Jakob; rapidly progressive dementia, 14-3-3

INTRODUCTION

Prion diseases or transmissible spongiform encephalopathies (TSEs) are recently described progressive neurodegenerative disorders, with no current etiopathogenic treatment (1). Creutzfeldt-Jakob disease (CJD) is the commonest form of human prion disease, clinically being characterized by a rapidly progressive dementia and death, usually within 6 to 12 months. Sporadic Creutzfeldt-Jakob disease (sCJD) accounts for the vast majority (85%-90%) of cases, familial, iatrogenic, and variant forms being quite rare (2). The usual reported annual incidence is approximately 1 case per 1 million persons (3).

The neuropathological hallmarks of CJD are neuronal loss (mainly by apoptosis), proliferation of glial cells, low inflammatory response, and the presence of small vacuoles in brain parenchyma, which gives a spongiform appearance (4,5).

The lesions seem to be easily identifiablein the basal ganglia but the cerebral cortex and cerebellum are also commonly affected, resultinginprogressive dementia, akinesia, ataxia, and different forms of seizures, mainly myoclonus (6).

It is usually challenging to diagnose CJD premortem mainly due to a low grade of suspicion for such a rare disease. However, a rapidly progressive dementia prompts for considering the diagnosis. Additional tests which are mandatoryfor the positive and differential diagnosis are brain magnetic resonance imaging (MRI), electroencephalogram (EEG) and quantification of protein 14 - 3 - 3 in the cerebrospinal fluid (CSF) (7).

CASE REPORT

A 65 years old female presented in our clinic for investigation of a 2 month history of rapidly pro-

Author for correspondence:
Assoc. Prof. Bogdan O. Popescu, MD, PhD, Department of Neurology, Colentina Clinical Hospital, 19-21 Stefan cel Mare Road, district 2, Bucharest, Romania
e-mail: bopopescu@spitalulcolentina.ro.

gressive dementia. Initially, her symptoms were behavioral disorder associated with visual hallucinations. The patient's family first noticed emotional instability, shortly followed by depression, finally becoming apathetic.

The patient then suffered rapid progressive cognitive decline, characterized by retrograde memory loss, spatiall temporal disorientation, impaired language, and difficulty in reasoning ability and in performing usual activities.

In the past two weeks, the patient has developed gate unsteadiness with the need of bilateral support.

Her past medical history was insignificant, with no previous surgery and no family history of dementia or prion disease. Her vital signs and general exam were within normal limits without any evidence of fever.

The neurological exam revealed disorientation in time and space; she was unable to complete the Mini-Mental State Examination (MMSE) or perform other complicated tasks due to perseveration. Her gait was wide based and unsteady and also bilateral dysmetria on heel knee test and finger nose test (right > left) were present. Parkinsonian tremor (right > left) and cogwheel rigidity (left > right)appeared. Her reflexes were symmetric and there were no Babinski reflexes. During hospitalization, no myoclonic jerks were related or noticed.

Laboratory studies were within normal limits, included blood account, electrolytes, liver and renal function tests, with the exception of an urinary infection. Thyroid peroxide ase antibody, thyroid stimulating hormone, human immunodeficiency virus (HIV), Venereal Disease Research Laboratory (VDRL), Lyme antibodies, anti-neuronal nuclear antibody were negative. Cerebrospinal fluid analysis (CSF) was also performed. The result was normocytosis, excluding major inflammation, normal glucose levels and normal protein concentration.

A brain magnetic resonance imaging (MRI) showed no pathological findings, except a mild global parenchymal loss (diffuse cerebral atrophy). There were no infarcts, masses, or extra axial fluid collections. The electroencephalogram (EEG) showedslowing diffuse theta-delta waves, predominantly in frontal brain regions (Fig. 1).

In this clinical and paraclinical context, CSF was sent out for protein 14-3-3 determination. The

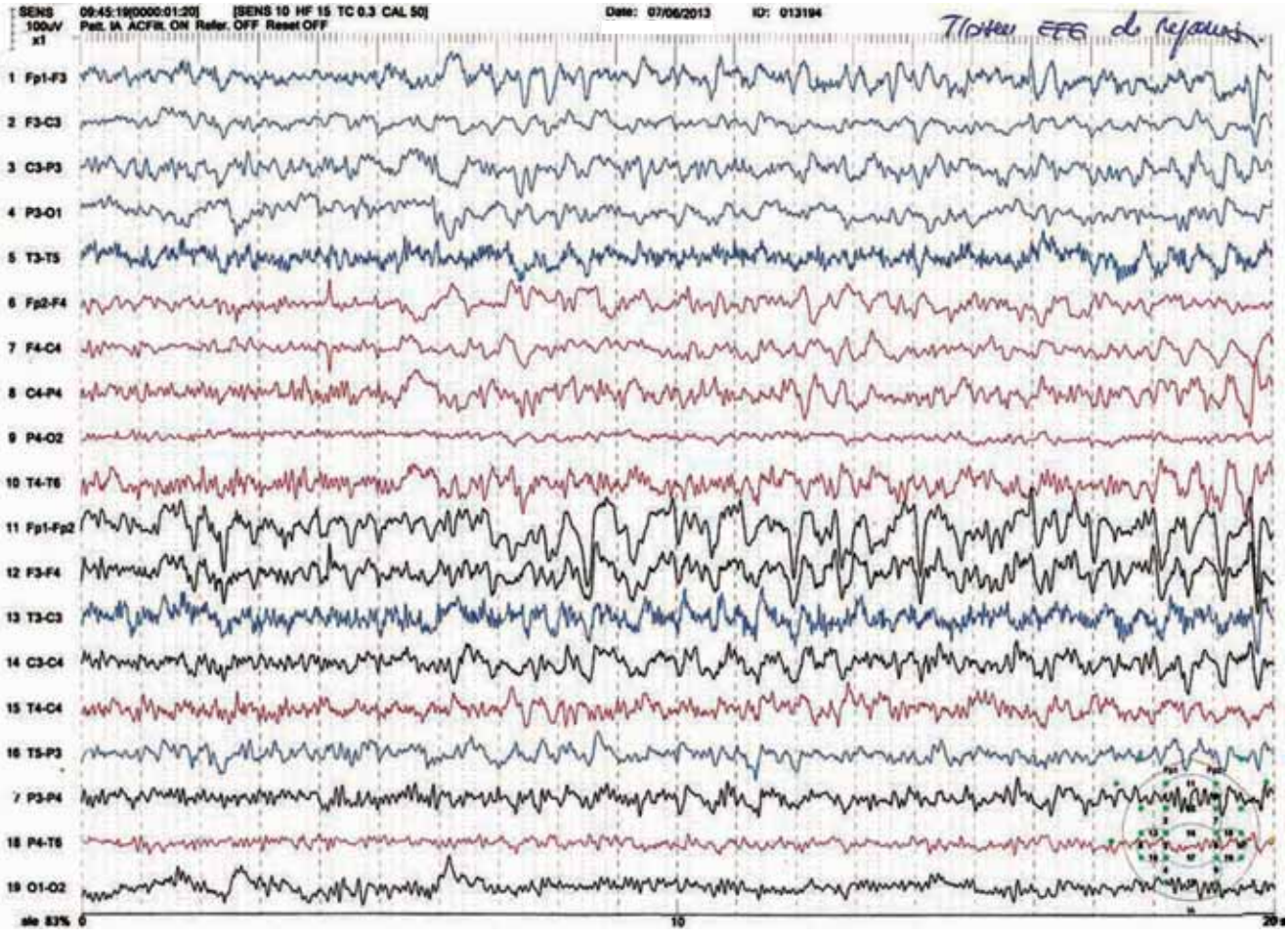

FIGURE 1.

result was positive. The patient was diagnosed with sporadic Creutzfeldt-Jakob disease and died within four months of symptom onset.

DISCUSSION

Rapidly progressive dementia is a rare clinical paradigm which usually associates decline in cognitive and behavioral function, with different degrees of motor impairment, developing in weeks or few months (8).

The differential diagnosis for rapidly progressive dementia is vast, comprising neurodegenerative, autoimmune, infectious and toxic-metabolic conditions. It is extremely important to rule out any potentially reversible conditions. CJD should always be considered in these circumstances.

Here we presented a case of rapidly progressive dementia, occurring in a 65 years old female, with no other comorbidities. In this case, shortly after the onset of rapidly progressive dementia, the cerebellar and extrapyramidal syndromes became apparent, which are commonly seen in CJD.

Given normal routine laboratory results, we ruled out reversible causes of subacute dementia like electrolyte imbalance, hepatic and uremic encephalopathy, hypothyroidism, vitamin B12 deficiency, neurosyphilis and human immunodeficiency virus encephalopathy. Cerebral MRI revealed only mild global parenchymal loss and the result of cerebrospinal fluid was non inflammatory, with normal glucose and protein levels. The absence of fever, elevated serum white count and elevated cell count or protein in CSF excluded any infectious conditions.

Various autoimune disorders may present similar clinical features to our case but no antibodies were found through our evaluation. Paraneoplastic neurological syndromes represent a group of neurological disorders, associated with systemic cancer and produced by an inflamatory response, that can affect central and peripheral nervous system. (9) Paraneoplastic/autoimmune limbic encephalitis (LE) is characterized by acute or subacute behavioral changes, complex-partial seizures, and cognitive impairment (10-12). Such neurological syndrome usually is associated with presence of anti-Hu, CV2, Ma2 and voltage-gated potassium channel antibodies (VGKC) (8). However, in our case these anti-neuronal antibodies were absent. We also ruled out Hashimoto's encephalopathy, by the absence of anti-thyroid antibodies.

Considering the absence of findings at the extensive evaluation and the presence of behavioral disorders, visual hallucinations, followed by rapidly progressive dementia and the onset of parkinsonian syndrome shortly after onset, we considered a neurodegenerative process, such as Creuzfeldt-Jacob disease or dementia with Lewy bodies. In both diseases a definite diagnosis can only be established by autopsy. However, the detection of protein 14-3-3 in CSF and the short disease course, without the presence of any clinical fluctuations lead us to the probable diagnosis of sporadic Creutzfeldt Jacob disease (13).

The protein 14-3-3 has a high specificity in distinction of other neurodegenerative (95-97%) diseases and non-neurological disorders (91-97%). Cerebrospinal fluid protein 14-3-3 detection is a signifiant test in the diagnosis of CJD, but has a loss in specifity in acute neurological events. Therefore the interpretation of a pozitive result must be made in the clinical context (14).

The World Health Organization(WHO) criteria requires that the following be acomplished for sporadic CJD:

1. Progressive dementia.
2. At least two of the following four clinicalfeatures: myoclonus, visual or cerebellar disturbence, akinetic mutism, pyramidal/extrapyramidal movements.
3. Atypical EEG during an illness of anyduration and/or positive 14-3-3 CSFassay with clinical duration to death inless than two years.
4. Routine investigation not suggestive ofan alternative diagnosis (15).

According to the above criteria, our case fullfils the conditions for possible sporadic CJD.

The peculiarity of the case consists in the absence of myoclonic jerks, with the presence of slowing diffuse theta-delta waves, predominantly frontal on the EEG, without the characteristic pattern of periodic synchronous bi or triphasic sharp wave complexes (PSWC). This PSWChas a specificity for sporadic CJD ranging from 66% to 91%. (16,17) Although the most common findings in T2 and FLAIR MRI are increased intensity in the putamen and head of caudate, in our case no patological findings have been found on cerebral MR imaging. (18)

CONCLUSIONS

In patients with rapidly progressive dementia, a positive immunoassay for the 14-3-3 brain protein in cerebrospinal fluid is a highly specific marker for CJD when used in the appropriate clinical context.

Even though myoclonic jerks are known to be predominant characteristic, the absence of them doesn't exclude CJD.

Although sCJD is currently a fatal disease and there is no generally accepted treatment currently available, an acurate differential diagnosis it is necessary in order to exclude reversible disorders that have a proper treatment.

Early diagnosis will allow families to prepare for the expected disease course, consider goals of care, and possibly have palliative care consultation if desired.

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