CASE REPORT

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SPORADIC CREUTZFELDT–JAKOB DISEASE

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Abstract: *Sporadic Creutzfeldt–Jakob disease is a rare and fatal human prion disease characterized by a rapidly progressive dementia, myoclonus, cerebellar, pyramidal, extrapyramidal, visual, and psychiatric symptoms. These findings are all non-specific and making diagnosis is often difficult at the symptoms onset, especially in case of atypical clinical and radiological presentation. This case report describes a woman in her 60s, who presented with rapid cognitive decline, confusion, ataxia and electroencephalographic changes compatible with nonconvulsive status epilepticus. Her symptoms progressively worsened and she died 8 weeks after the onset. The two cerebrospinal fluid analyses were normal and no 14-3-3 protein was detected. The brain MRIs revealed areas of cortical restricted diffusion involving the right frontal and parietal lobe. The electroencephalographic findings of continuous periodic generalized bi-triphasic complexes, typical for sporadic Creutzfeldt–Jakob disease, were detected 1 month after the onset. Sporadic Creutzfeldt–Jakob disease was neuropathologically confirmed. Although sporadic Creutzfeldt–Jakob disease is a rare neurodegenerative disease, it should be considered in the differential diagnosis of all cases with unexplained and rapid cognitive decline and confusion, along with ataxia, pyramidal/extrapyramidal signs, myoclonus and dysphagia.*

Key words: *sporadic Creutzfeldt–Jakob disease, prion disease, brain autopsy, electroencephalogram*

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INTRODUCTION

Human prion diseases are rare, fatal and occur in idiopathic, genetically-determined and acquired forms. Sporadic Creutzfeldt–Jakob disease (sCJD) is the most common form with a worldwide incidence of 1-2 cases per 1 million people per year [1,2]. The disease was first described by Hans Gerhard Creutzfeldt (1920) and Alfons Maria Jakob (1921) [3, 4]. It is caused by the conversion of the normal cellular prion protein (PrPC) into an abnormal form of the prion protein (PrPSc, Sc stands for scrapie), which is markedly hydrophobic with a clear tendency towards aggregation, subsequent oligomerization, and formation of amyloid fibrils [5, 6]. In sCJD, age of onset shows a peak between 55 and 75 years with a median age of 67 years and a median survival time of 5-6 months [1]. Sporadic Creutzfeldt–

Jakob disease can be categorized into six subgroups (MM1, MM2, MV1, MV2, VV1 and VV2) based on the combinations of the Methionine/Valine polymorphism at codon 129 of the prion protein gene and the molecular mass of PrPSc (glycotype 1 and 2) [1, 7, 8]. The sCJD subgroups show differences regarding the clinical symptoms, neuroimaging and neuropathological findings [7, 9, 10].

The sCJD-patients usually present with a rapidly progressive dementia, ataxia, visual disturbances, pyramidal and extrapyramidal symptoms (myoclonus, dystonia, choreoathetosis, tremors, parkinsonian syndrome) and behavioral changes with agitation, depression, or confusion [2, 5]. The late stage is characterized by akinetic mutism and eventually death. Atypical manifestations have been reported in the literature, including dynamic aphasia [11], nonconvulsive status epilepticus, amyotrophy, hallucinations, vertigo [12, 13]. Diagnosis of sCJD is based on the presence of typical clinical symptoms and evidence from additional investigations including characteristic magnetic resonance imaging (MRI) patterns of restricted diffusion on DWI and hyperintensities in FLAIR images in the basal ganglia and/or cortex, electroencephalography (EEG) showing typical periodic sharp wave complexes, elevated levels of 14-3-3 protein in cerebrospinal fluid (CSF) and the detection of PrPsc in CSF using real-time quaking-induced conversion (RT-QuIC) [14]. Typical neuropathologic features of sCJD include spongiform change, neuronal loss, gliosis, and deposition of PrPSc [7, 15, 16]. Clinically, the diagnosis is based on the European Creutzfeldt–Jakob Disease Surveillance Network criteria [17]. Diagnosing possible sCJD requires clinical signs only, and exclusion of distinct etiologies, i.e., tumor, cerebrovascular lesions, autoimmune disorders, neuroinfection, neurodegenerative dementia, etc. A diagnosis of probable Creutzfeldt–Jakob disease is made if the patients have clinical signs required to diagnose probable sCJD plus positive protein 14-3-3 in CSF, magnetic resonance imaging (MRI) [18], EEG [19] with indicated sensitivity 67% and specificity 86%, and positive RT-QuIC in CSF or other tissues [17]. Further diagnostics (e.g. body CT, PET, specific CSF analyses) can be necessary depending on suspected differential diagnoses. CSF t-Tau and the p-Tau/t-tau (or t-Tau/p-Tau) ratio are valuable supportive biomarkers according to the biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. A definite Creutzfeldt–Jakob disease diagnosis requires neuropathological or genetic conformation [17].

Treatment of sCJD remains supportive. No specific therapy has been shown to stop the progression of the disease. The disease usually lasts for a few months, generally less than one year [20, 21].

We present a patient with sCJD whose initial manifestation were confusion and alternation of mental status and the electroencephalographic features resembled nonconvulsive status epilepticus.

CASE PRESENTATION

The patient was a woman in her 60s, who was referred to our clinic with a one-month history of gait unsteadiness, cognitive decline and behavioral changes. She was both physically and mentally well prior to the onset of the symptoms. She had a 5-year medical history of well-controlled arterial hypertension. No family history of dementia or other neurological diseases was reported. One and a half months before the onset of disease she went abroad. One evening she felt dizzy and disorientated. In the morning she was confused. She managed to come back to Bulgaria where she was seen by a neurologist and a brain CT was performed – no brain abnormalities were found. The next two weeks the gait impairment continued to progress and she was not able to walk without support. She had increased somnolence and problems with short memory and daily care activities. On the initial assessment at our clinic she appeared confused and was not able to perform more complex tasks. She had hypomimia and rigidly increased muscle tone in the left limbs. She was unable to walk independently due to a severe cerebellar ataxia. She also had dysmetria and intentional tremor of both hands (left greater than right). Her deep tendon reflexes were bilaterally exaggerated but there were no Babinski reflexes.

INVESTIGATIONS

Routine laboratory investigations including full blood count, blood sugar level, liver and renal panels, electrolytes and vitamin B12 level were normal. Thyroid function test, inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were also normal. The autoimmune screen (antinuclear antibodies and anti-neutrophil cytoplasmic antibodies), serology for HIV and syphilis were negative. Chest radiography, electrocardiogram, and abdomino-pelvic ultrasound were otherwise unremarkable. Paraneoplastic panel (including anti-Hu, anti-Jo, VGKC antibodies) and tumor markers CEA, CA 15-3, CA 19-9 were negative. The serum neuron-specific enolase concentration was elevated – 17.9 μg/l (normal range up to 16.3 μg/l).

We performed two lumbar punctures for cerebrospinal fluid (CSF) evaluation on day 1 and day 10 after the admission – cell counts, glucose and protein were within normal limits. No oligoclonal bands were detected. Other CSF testing for bacterial (Streptococcus pneumoniae, Streptococcus agalactiae, H. influenzae, Escherichia coli K1, Listeria monocytogenes, Neisseria meningitides) fungal (Candida, Cryptococcus neoformans) and viral encephalitis (Herpes Simplex virus 1 and 2, Varicella-Zoster virus, Human herpes virus 6, Epstein–Barr virus, Cytomegalovirus, Enterovirus, Human parechovirus) were negative. Autoimmune encephalitis panel (NMDA, AMPA-GluR1, AMPA-GluR2, GABA-A and GABA-B, LGl-1 and CASPR2) in serum and CSF were also found to be negative. CSF 14-3-3 protein was not detected. The two brain MRIs with gadolinium performed on day 1 and day 10 of the hospital admission revealed an area of cortical restricted diffusion involving the right frontal and parietal lobes (Fig. 1). Radiological reports suggested encephalitis.

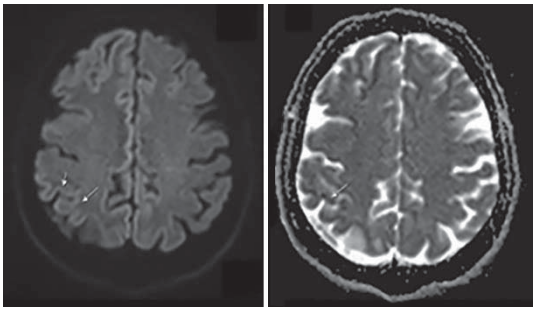

Fig. 1. MRI diffusion-weighted images showing restricted cortical diffusion (arrows) in the right parietal lobe

EEG performed on day 1 of admission showed slow sharp waves over the right hemisphere at a frequency of 2 Hz (Fig. 2).

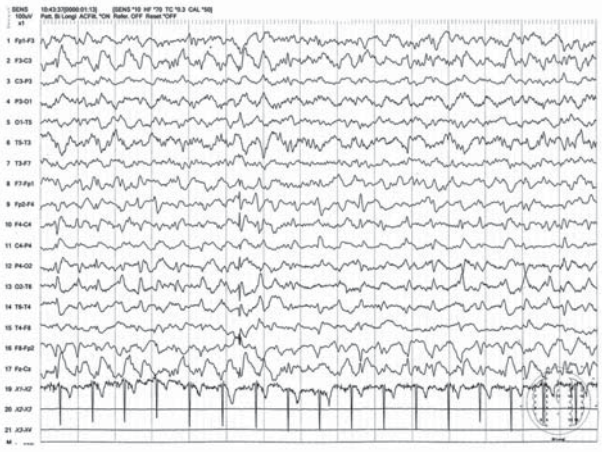

Fig. 2. Slow sharp waves over the right hemisphere at a frequency of 2 Hz

EEG at day 30 revealed a severe slowing of the background activity and periodic sharp-wave complexes with triphasic morphology (Fig. 3).

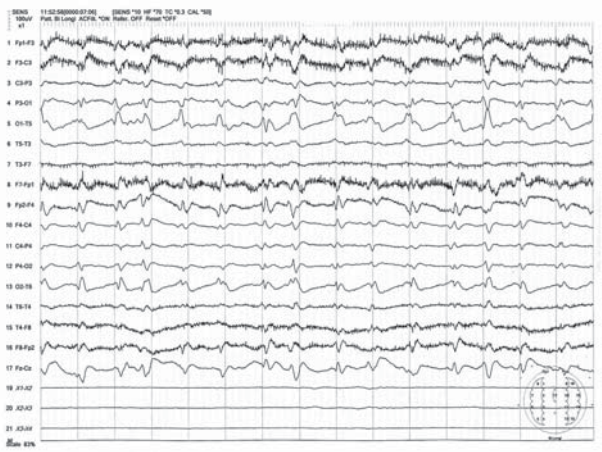

Fig. 3. The EEG performed at day 30 of the admission showed severe slowing of the background activity and periodic sharp-wave complexes with triphasic morphology

DIFFERENTIAL DIAGNOSIS

A number of differential diagnoses were considered and ruled out based on investigational results: encephalitis of viral, bacterial or fungal etiologies, autoimmune encephalitis, paraneoplastic limbic encephalopathy, metabolic encephalopathy, B12 and folate deficiency, Hashimoto encephalopathy.

Treatment

We started empirically treatment with intravenous acyclovir for viral encephalitis, which did not result in any improvement. An empirical trial of 3 days of high dosage intravenous methylprednisolone and 5 days of i*ntravenous immunoglobulin* for autoimmune encephalitis showed no clinical improvement either. Intravenous valproate and levetiracetam for the nonconvulsive status epilepticus were unsuccessful, too. We also carried out low volume plasma exchange for 3 days without benefit.

Outcome

Gradually, the patient completely lost her ability to walk, developed whole body stiffness, anarthria, aphagia, urinary and fecal incontinence. Spontaneous and stimulus sensitive myoclonic jerks were noted in all extremities. She passed away 39 days after admission due to bilateral bronchopneumonia. Postmortem brain examination revealed widespread spongiform change, neuronal loss and astrogliosis (Fig. 4).

Immunohistochemistry demonstrated granular and synaptic-like (Fig. 5), perineuronal and perivacu-

olar (Fig. 6) accumulation of abnormal prion protein (12F10-Antibody).

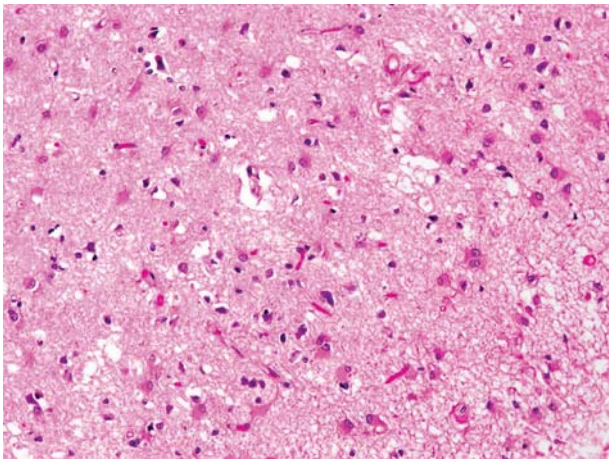

Fig. 4. Occipital cortex with astrogliosis, spongiform change and neuronal loss, H&E, Magn. x 200

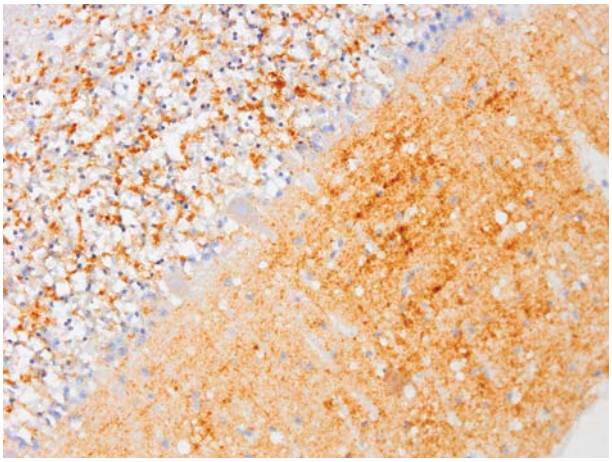

Fig. 5. Granular and synaptic-like accumulation of abnormal prion protein in the cerebellar cortex, IHC 12F10 Ab, Magn. x 200

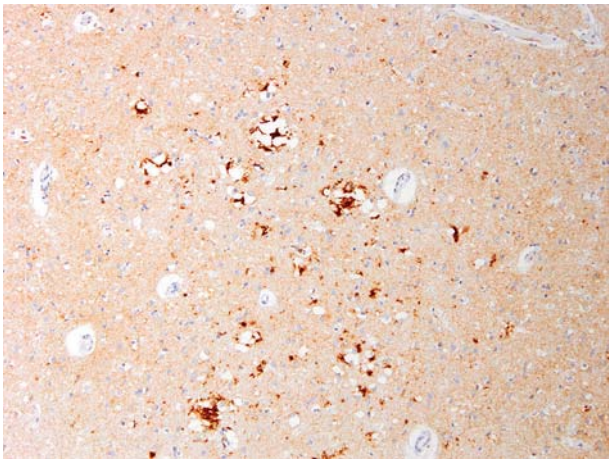

Fig. 6. Perivacuolar abnormal prion protein accumulation, parietal cortex, IHC 12F10 Ab., Magn. x 200

No plaques and plaque-like positivity was found. DNA sequencing of the PRNP gene was performed and no mutations were detected. Analysis of the codon 129 demonstrated methionine homozygosity (MM). Sporadic Creutzfeldt-Jakob disease was neuropathologically confirmed.

DISCUSSION

We describe the first Bulgarian patient with definite sCJD presented with rapid cognitive decline, confusion, ataxia and EEG changes compatible with nonconvulsive status epilepticus (NCSE). Based on the clinical symptoms, MRI and the EEG findings, our initial diagnosis was viral or autoimmune/paraneoplastic encephalitis. Because of the delayed availability of results for these etiologies on CSF, we empirically used acyclovir, steroids, plasmapheresis and intravenous immunoglobulin to treat possible encephalitis. However, the disease continued to progress and aphasia, anarthria, myoclonic jerks, and extrapyramidal signs developed. The evolution of the disease and the negative results of the laboratory tests eventually led us to the diagnosis of sporadic Creutzfeldt–Jakob disease. The MRI lesions of sCJD often appear as areas of restricted diffusion (DWI hyperintensities) and FLAIR hyperintensities in the cerebral cortex, basal ganglia, and/or thalamus bilaterally [22]. In our patient they were predominantly in the cerebral cortex of the right hemisphere and were misinterpreted as encephalitis. The CSF 14-3-3 protein was negative in our patient; its assay has a relatively low specificity and a modest sensitivity for diagnosing sCJD [23]. Status epilepticus is reported in less than 15% of patients as initial manifestation of sCJD [24]. Rees et al. (1999) [25] described two patients with Creutzfeldt-Jakob disease presenting with a rapidly progressive dementia with confusion and seizure activity on the EEG. In both patients, intravenous administration of diazepam attenuated the epileptiform activity but no clinical improvement had been observed. Fernandez-Torre at al. (2004) [26] described a follow-up study of an elderly patient with Creutzfeldt-Jakob disease and NCSE. The intravenous administration of diazepam suppressed the epileptiform activity without apparent clinical improvement. The authors conclude that dissociation between resolution of epileptiform activity on EEG and persistence of mental alteration should point toward other diagnostic possibilities including Creutzfeldt-Jakob disease instead of NCSE [26]. The initial EEG recordings in our patient were suggestive of NCSE with asymmetric discharges, but neither the EEG changes disappeared after intravenous diazepam nor any clinical change has been observed.

Nevertheless, an aggressive antiepileptic therapy was initiated but the clinical state of the patient stayed unmodified. The EEG recording performed on day 30 after the hospital admission was more characteristic of Creutzfeldt-Jakob disease, particularly as our patient had developed myoclonus. Definitive diagnosis of sCJD was established with postmortem brain autopsy and genetic analysis of PRNP gene. The brain tissue samples revealed the typical spongiform alteration, gliosis and neuronal loss. Analysis of the codon 129 demonstrated methionine homozygosity (MM). The typical clinical findings of MM subtypes (MM1~45-68% and MM2~10% of the cases) include rapidly progressive dementia, myoclonus and/or visual disturbance, dysphagia and ataxia [1, 27]. All these symptoms, except visual disturbance, were present in our patient.

CONCLUSION

In conclusion, although Creutzfeldt-Jakob disease is a rare disease, it should be considered in differential diagnosis in all cases of unexplained and rapid cognitive decline and confusion, along with ataxia, pyramidal/extrapyramidal signs, myoclonus and dysphagia. Diffuse epileptiform discharge – NCSE, on EEG in such cases also might be a presentation of sCJD [24]. Potential treatable causes of rapidly progressive dementia such as autoimmune, infectious, and toxic-metabolic etiologies should be excluded before making the final diagnosis of prion disease.

Disclosure summary: *The authors have nothing to disclose.*

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