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Sporadic CJD in a patient with relapsing-remitting multiple sclerosis on an immunomodulatory treatment

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Abstract

Creutzfeld-Jacob disease (CJD) is a degenerative, invariably fatal brain disorder. Multiple sclerosis (MS) is a chronic, potentially disabling, immune-mediated inflammatory demyelinating disease of the central nervous system. Here, we report a 50-year-old woman who, two years after the diagnosis of relapsing remitting MS, developed altered consciousness, dystonic posture of the left hand and myoclonic jerks. Repeated brain MRI showed hyperintensities on T2 sequences in basal ganglia bilaterally and diffusion restriction in these areas, and, since typical EEG and CSF features were present, the diagnosis of CJD was made. To the best of our knowledge, this is the first report of a glatiramer acetate-treated MS patient who developed sporadic CJD. This combination is interesting in the light of recent data suggesting that CJD and MS may share similar mechanisms of "molecular mimicry" and autoimmunity. This case also emphasizes the importance of critically assessing every new symptom even in a patient with an established diagnosis of MS.

Key words: Multiple sclerosis; relapse; CJD.

Introduction

Creutzfeld-Jacob disease (CJD) is a degenerative, invariably fatal brain disorder. It affects one to two persons per million population per year worldwide. Multiple sclerosis (MS) is a chronic, potentially disabling, immune-mediated inflammatory demyelinating disease of the central nervous system (CNS). Both MS and CJD show some similarities in the phenotypic features, disease course, histopathological and cerebrospinal fluid (CSF) findings. Multiple sclerosis can have a rapid progressive course like CJD, myelin can be affected in both diseases (while it is a defining feature of MS it has been shown that myelin can be affected in panencephalopathic CJD), and inflammatory cells and molecules appear to accumulate at the pathological sites of patients with MS as well as in patients with CJD (1, 2, 3). Here, we report the first case of patient with coexisting multiple sclerosis and sporadic CJD (sCJD).

Case report

A 50-year-old female developed decreased visual acuity (20/200) on the left eye associated with pain on left eye movement. Neurological examination, except decreased visual acuity on the left eye was normal, there was no evidence of cognitive decline. She was diagnosed with left optic neuritis. Initial brain MRI showed multiple demyelinating lesions located subcorticaly and periventriculary. Periventricular lesions were already confluent indicating chronicity. Cerebrospinal fluid analysis showed positive oligoclonal bands (OCBs). She was treated with corticosteroids and fully recovered. Follow-up MRI was performed 6 months later (Fig. 1) and revealed one new active lesion. The diagnosis of a relapsing-remitting form of MS was made according to the revised McDonald's criteria. Treatment with glatiramer acetate was introduced and she remained symptom-free and without new MRI lesions for the next two years. After this period she developed slurred speech and left-sided weakness. Three days after treatment with corticosteroids, she developed altered consciousness, dystonic posture of the left hand and myoclonic jerks. In the next days she became unresponsive to any stimuli, she rarely opened her eyes, and had severe myoclonic jerks. Repeated brain MRI (Fig. 2) showed hyperintensities on T2 sequences in basal ganglia bilaterally and diffusion restriction in these areas. Diffusion was also restricted in right parietal and temporal lobe.

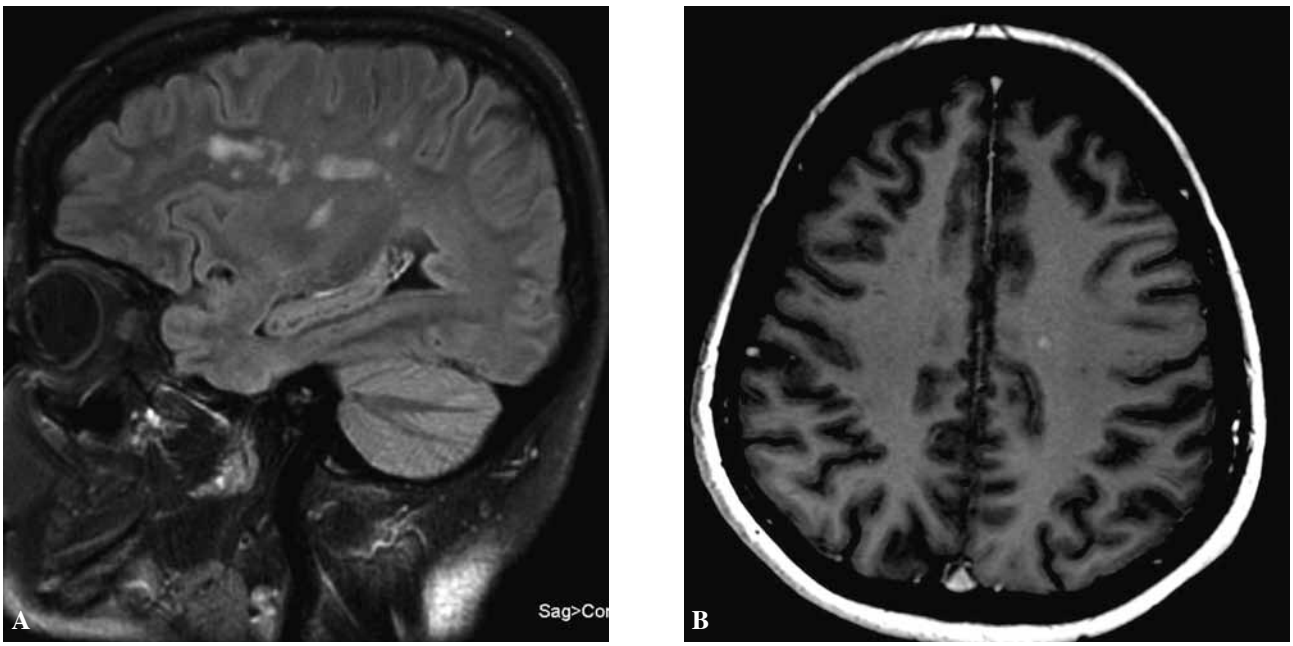

FIG. 1. — Brain MRI (left) flair coronal sequence showing lesions perpendicular to corpus callosum; (right) T1 postcontrast transversal sequence showing one enhancing lesion.

Since clinical picture and MRI findings were consistent with CJD we repeated CSF analysis. Oligoclonal bands were again positive and additionally protein 14-3-3 was detected. EEG showed periodic paroxysms of sharp waves and spikes on a slow background. Genetic test revealed that the patient was homozygous for methionine at codon 129 of the prion protein gene and the most common mutations (at codon 200, 210, 178, 105, and 102) were excluded). The diagnosis of clinically probable CJD was made.

Discussion

This case describes a patient with the diagnosis of MS and severe relapse, which proved to be an independent disease, CJD. Heterogeneity in sporadic CJD correlates with the codon 129 genotype of the prion protein gene (*PRNP*) in combination with the existence of two distinct types of pathological prion protein (PrPSc 1 or 2) (4). Heterozygosity at either of these codons is associated with resistance to sporadic CJD (5, 6). Based on these variables, six sCJD subtypes (MM1, MM2, MV1, MV2, VV1, and VV2) have been defined, and variations in the sensitivities of diagnostic tests for the different subtypes have been reported (7, 8).

Slurred speach, ataxia and pyramidal signs such as hemiparesis are common simptoms of multiple sclerosis relapse, but they are also core clinical features of CJD. Creutzfeld-Jacob disease can present with a clearly neurological symptoms that follow very rapidly progressive course, unlike variant CJD in which the initial presentation is often with psychiatric or behavioural symptoms and it may not be clear that the individual has neurological illness until several months after the onset (9).

Characteristic MRI lesion patterns may correspond to a specific CJD subtype. Our patient had MRI findings consistent with MM1 subtype. Basal ganglia and cortical hyperintensities are the most frequent MRI finding in CJD and are most typically found in MM1 subjects with a rapid disease course, but also in MV1 individuals.

Both diseases have a huge overlap in clinical presentation such as occurrence of signs of cognitive and intellectual deficits, signs of brain-stem and cerebellar involvements, and features of Parkinson's disease as well as dementia and ataxia (10). Additional investigations such as brain imaging might be helpful to diagnose the disease. It is also interesting that animal models of both MS (experimental autoimmune encephalomyelitis) and CJD suffer from similar clinical symptoms, namely lower limb ataxia. The presence of clinical and histopathological similarities in these diseases suggests a common pathology (11). CJD animals and patients suffering from MS have been found to have elevated levels of

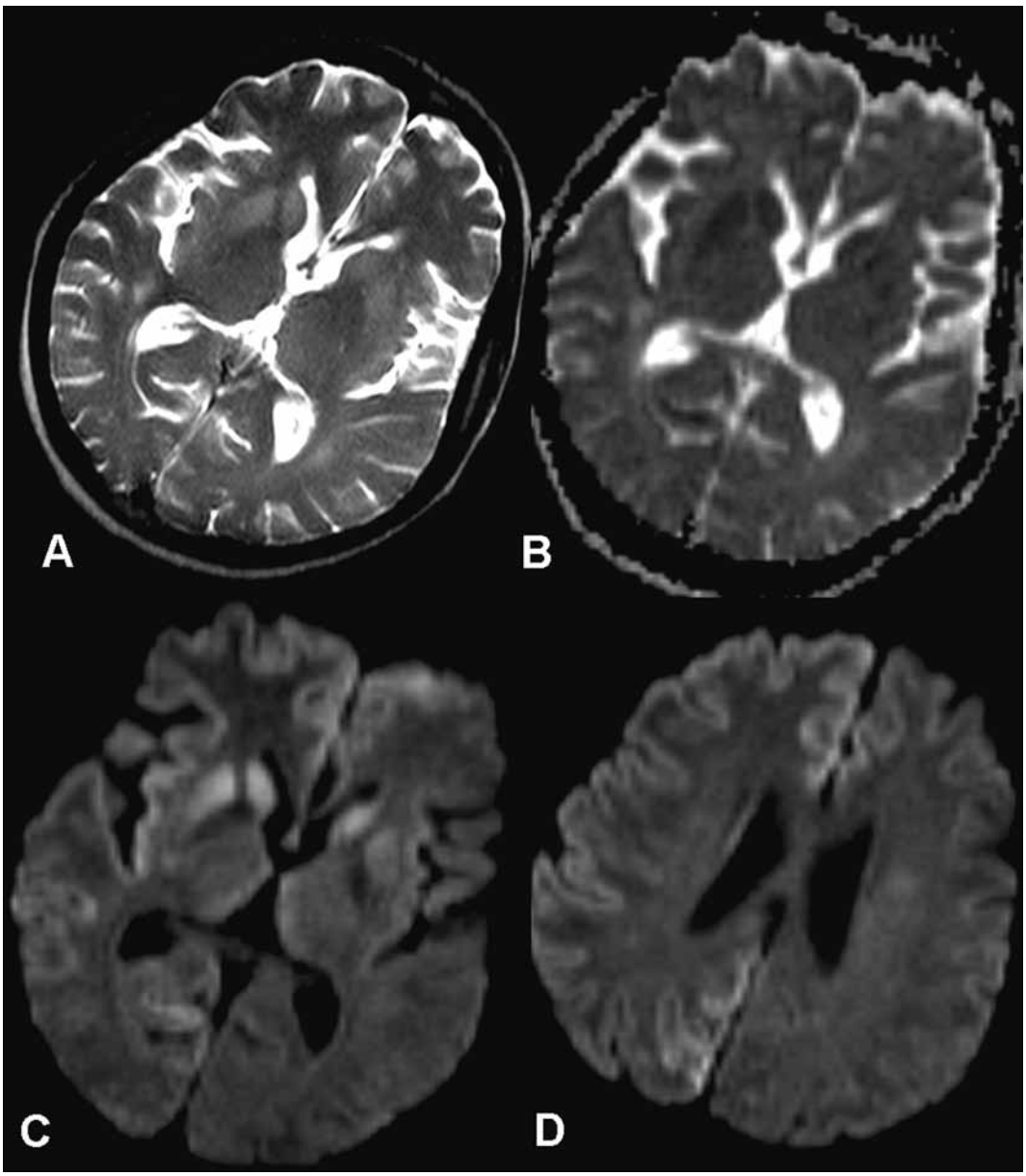

FIG. 2. — Magnetic resonance images in axial plane. A: T2-weighted image shows bilateral hyperintensities in caudate nuclei and putamina, corresponding to areas of low apparent diffusion coefficient on ADC map, shown in B. C, D: Diffusion-weighted images show additional hyperintensities in right insular, occipital and parietal cortex, indicating restricted diffusion.

antibodies to both Acinetobacter and Pseudomonas bacteria, as well as autoantibodies to both white and gray matter brain components (11). The hypothesis was proposed that Acinetobacter/Pseudomonas bacteria may favour both CJD and MS through the mechanism of "molecular mimicry" and autoimmunity (11).

Another interesting observation is that our patient was on immunomodulatory treatment with glatiramer acetate when symptoms of CJD occurred, raising the question of a possible causal relationship. Animal studies, however, suggest that glatiramer acetate has rather a protective effect against prion infection. When it was mixed with the initial prion inoculum or administered to hamsters weekly from the day of infection, both disease onset and death were delayed by 30 days (12).

This case finally emphasizes the importance of critically assessing every new symptom even in a patient with an already established diagnosis of MS. Ataxia and slurred speech are common symptoms of MS relapse which is why initially we started the

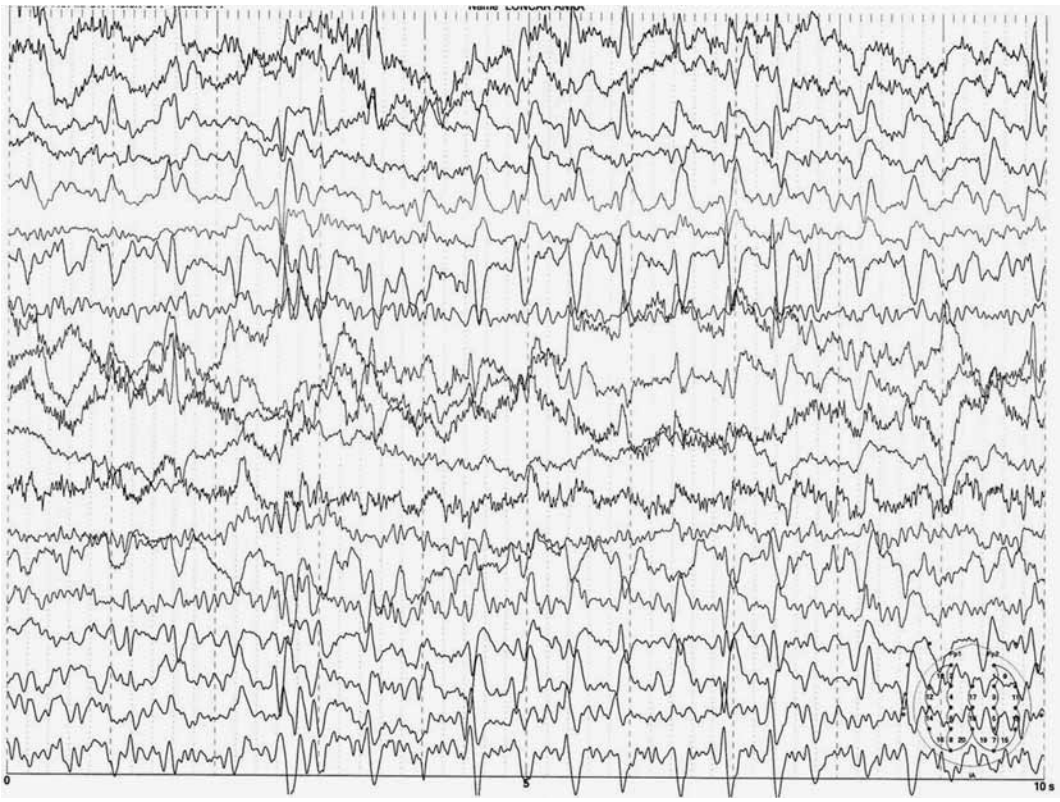

FIG. 3. — EEG showing periodic paroxysms of sharp waves and spikes on a slow background

corticosteroid therapy. However, rapidly progressing dementia symptoms, dystonia and myoclonic jerks prompted us to reevaluate the patient's clinical presentation and diagnosis.

Authors' contributions

Study concept and design: Gabelić, Habek, and Brinar. Acquisition of data: Gabelić, Habek, Zerr, Gawinecka and Brinar. Analysis and interpretation of data: Gabelić, Habek, Zerr, Gawinecka and Brinar. Drafting of the manuscript: Gabelić and Habek. Critical revision of the manuscript for important intellectual content: Gabelić, Habek, Zerr, Gawinecka and Brinar. Administrative, technical, and material support: Gabelić, Habek, Zerr, Gawinecka and Brinar.

Conflict of interest statement: There is no conflict of interest.

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