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Case Report

N-Methyl-D-Aspartate Receptor Encephalitis Masking Creutzfeldt-Jakob Disease

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Abstract

Introduction: N-Methyl-D-aspartate receptor antibody encephalitis is an autoimmune disorder presenting with psychiatric symptoms, dementia, orofacial dyskinesia, myoclonus, epileptic seizures, and central alveolar hypoventilation. The co-occurrence of N-methyl-D-aspartate receptor antibodies with Creutzfeldt-Jakob disease has been described, but the mechanism and significance of their presence is unclear.

Our Case: We present a 63-year-old woman with cognitive decline, orofacial dyskinesia, ataxia and central hypoventilation, leading to death in 13 months. She had plasma anti-N-methyl-D-aspartate receptor antibodies, and transitorily improved after plasmapheresis. Brain-autopsy did not find inflammation but spongiform changes with kuru-type amyloid plaques compatible with sporadic Creutzfeldt-Jakob disease MV-2 subtype.

Discussion: The diagnosis of autoimmune encephalitis needs careful check-up for underlying conditions. In our case N-methyl-D-aspartate receptor antibody encephalitis masked the underlying Creutzfeldt-Jakob disease calling attention to the need of careful diagnostic interpretation in such cases. In addition to onconeuronal antigens, autoantibodies might emerge against receptors released from the neurons damaged by a prion disease as well; the longer the neuronal damage exists, the more likely the development of autoantibodies.

Keywords: *NMDAR-Ab; Encephalitis; Creutzfeldt-Jakob Disease; MV Type 2; Plasmapheresis*

Introduction

N-methyl-D-aspartate receptor antibodies (NMDAR-Abs) may cause autoimmune encephalitis characterized by a spectrum of clinical signs, including acute psychosis at onset, anxiety, agitation, bizarre behaviour, hallucinations, short-term memory disturbance and disorientation; oro-facial dyskinesia, choreiform movements, myoclonus and dystonic posturing; epileptic seizures, oculomotor disorders and autonomic disturbances including central respiratory disturbances and hypoventilation (CH) [1].

Sporadic Creutzfeldt-Jakob disease (CJD) is the most frequent form of human prion disease. Based on the codon 129 polymorphism and the Western blot pattern of protease-resistant prion protein (PrP) at least six molecular subtypes have been identified [2]. The presence of NMDAR-Abs in CJD has been described [3,4], however, the significance of autoantibodies in the course in CJD is unclear. We present a patient with apparently "genuine" autoimmune NMDAR-Abs encephalitis responding initially well to immunotherapy. However, autopsy proved CJD, but its clinical diagnosis was obviously hindered by the symptoms of autoimmune encephalitis.

Case Report

We admitted a 63-year-old woman with unremarkable medical history in September 2011. Five months prior to her hospitalisation, she had noticed gait disturbance. At admission, she had central facial palsy and pyramidal signs on the right side, hypaesthesia on her legs, limb ataxia and staccato speech. We noticed her cognitive decline affecting mostly the prefrontal and the fronto-parietal functions (Addenbrooke's Cognitive Scale score: 82/100, MMS score: 25/30). Magnetic resonance imaging (MRI) of the brain and the spinal cord were normal. Nerve conduction studies, electroencephalography (EEG) and routine cerebrospinal fluid (CSF) tests were normal as well. Genetic testing excluded spinocerebellar ataxia type 1,2,3,6 and 7. Her chest CT was unremarkable and the ultrasound tests revealed a large intraabdominal mass, which after biopsy proved to be a lipoma. Since we suspected paraneoplastic syndrome, whole body fluoro-deoxy glucose positron emission tomography-CT (FDG-PET-CT) was performed with normal results. Her serum anti-Hu, -Yo, -Ri,-Ma-1, -TA and recoverin antibodies were negative.

Her ataxia and gait disturbance deteriorated quickly. Also her behaviour-abnormality and memory-impairment progressed to such an extent that she could not cooperate with dementia tests. She had visual hallucinations, orofacial dyskinesia and severe mood-depression. Her EEG progressed to moderate diffuse slowing of the background activity. During sleep, we noticed episodes of central hypoventilation with tachypnoea, finally necessitating tracheal intubation and assisted ventilation. The clinical presentation suggested NMDAR-Ab encephalitis; therefore, we initiated a series of plasmapheresis treatment. After the 4th plasma exchange session, her ventilation had normalised.

A follow up MRI brain scan 4 months later showed high signal abnormalities in the caudate nucleus and in the frontal cortex on diffusion-weighted imaging as well as on fluid inversion recovery sequences, compatible with CJD [5]. However, the improvement after plasma-exchange therapy and the relatively long duration (nearly a year) of her condition, supported the diagnosis of an autoimmune encephalitis. Although her respiration had remained normal after the last plasmapheresis she progressively deteriorated to akinetic mutism. There was significant diffuse slowing of the background activity on her EEG. More than a year after the first clinical signs, we received her positive NMDAR-Ab serum test result (immunofluorescence method), while autoantibodies to GABAB-R, AMPA-1, LGI1, AMPA2, CASPR2 were absent and her routine laboratory checks were normal. At this point our clinical diagnosis of NMDAR-Ab encephalitis appeared to be confirmed, and we initiated methylprednisolone/azathioprine treatment. Despite all therapeutic efforts, she died in pneumonia 13 months after the first clinical symptoms.

The autopsy did not find any malignant tumour. The systematic neuropathology examination (Figure 1) excluded inflammatory cell infiltration in the amygdala and hippocampus, which is the hallmark of limbic encephalitis. Surprisingly, prominent spongiform changes were seen in the basal ganglia, thalamus and neocortical areas. In addition, kuru-type amyloid plaques were found in several regions, most prominently in the cerebellum. Immunostaining for disease-associated PrP revealed synaptic, perineuronal and plaque ("kuru-type") pattern. Genetic analysis of the prion protein gene excluded any mutation, while the codon 129 polymorphism was methionine/valine (MV). These findings were compatible with sporadic CJD MV-2 subtype [6].

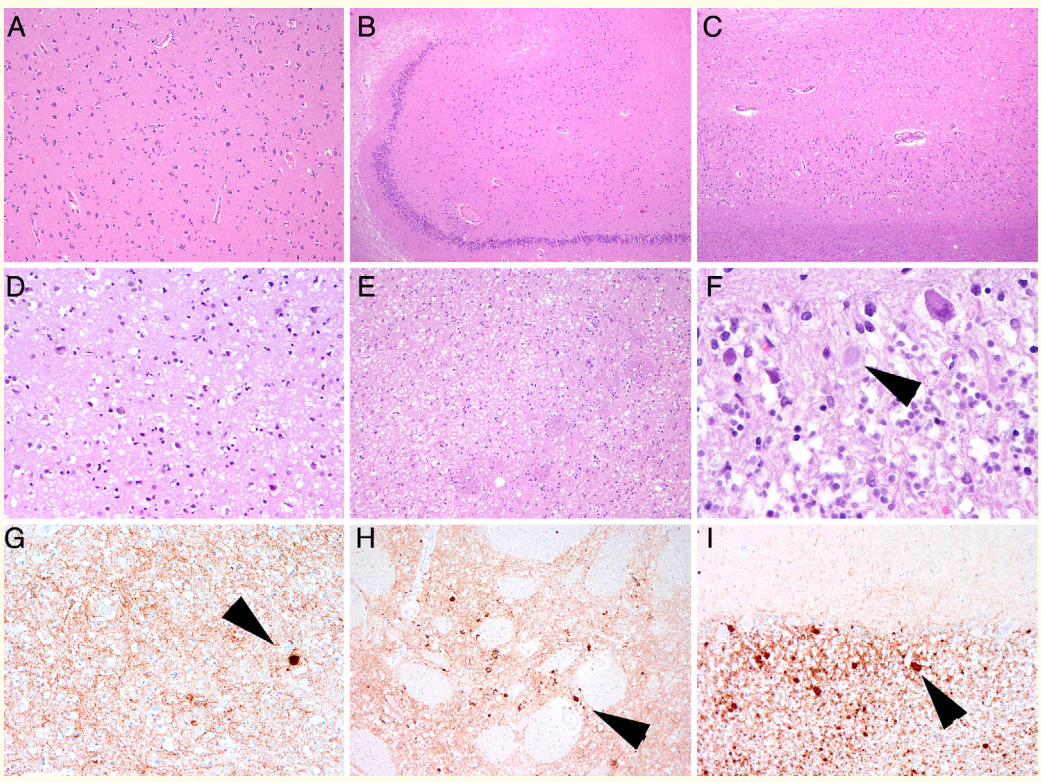

Figure 1: *Neuropathological alterations detected in the patient presented in our study. Hematoxylin and eosin (H&E) staining of the amygdala (A) and CA4 subregion of the hippocampus (B) shows lack of inflammatory cell infiltration or spongiform change, while microcystic vacuolation is noted in hippocampal CA1 subregion (C). Prominent spongiform change is observed in the frontal cortex (D) and caudate nucleus (D), whereas kuru type amyloid plaques (a representative one indicated by the arrowhead) are seen in the granular layer of the cerebellum (E). Immunostaining for the prion protein reveals synaptic pattern in the frontal cortex (G), basal ganglia (H) and cerebellum (I), along with plaque like deposits (indicated by arrowheads).*

Discussion

We present a case with kuru-plaque subtype (MV type 2) of sporadic CJD, proved by post mortem histopathology. This rare subtype of CJD is characterized by duration of several months, progressive dementia and ataxia; less consistent presence of the typical MRI findings and periodic sharp wave complexes on the EEG [3,7,8]. Her presentation, especially the orofacial dyskinesia and central hypoventilation led us to the clinical diagnosis of NMDAR-Ab encephalitis which was supported by serology and by the transitory improvement after plasma exchange therapy.

The coexistence of CJD and neuronal autoantibodies is not unprecedented [9]. Six cases with neuropathologically verified, clinically typical sporadic CJD patients progressing to akinetic mutism in 3 to 9 months were tested for serum NMDAR-Abs in the UK National CJD surveillance unit. Two of them carried the NMDA antibodies [3]. Another case, described in the literature [4] was similar to our patient. This 68-year-old male, presented with rapid personality change, insomnia, myokimias, myotonia, ataxia, apraxia and diffuse background slowing of the EEG suggesting Morvan's syndrome which was confirmed by voltage-gated K-channel (VGKC)-complex antibodies. He died in 9 months and unexpected spongiform changes, neuronal depletion, extensive gliosis was found with synaptic type of PrP immune-reactivity.

The 75-year-old patient of Zuhorn and colleagues was admitted because of disorientation, cognitive decline, aphasia, and visual disturbances as well as right parietal lobe dysfunction. The first suspicion was autoimmune encephalitis supported by the presence of thyroperoxidase and CASPR2-antibodies. Despite immune-modifying and immunoadsorption treatments, she clinically deteriorated and died a year after her first symptoms. The follow up MRI and EEG changes, the presence of 14-3-3 protein in her CSF, finally the brain autopsy result confirmed the diagnosis of CJD [10].

The history of our patient and the cases of the literature suggest that the coexistence of neuronal autoantibodies and CJD is probably not a mere coincidence. Indeed, in neurons PrP^{Sc} activates the NMDA-receptor channel resulting in a rise of intracellular Ca^{2+} level and ultimate cell death [11]. It is possible that the production of autoantibodies is an immune response against receptors released from the neurons damaged by prion disease. The presence of an altered cell surface receptor in the serum may result in an immune response with presentation of autoantibodies [3,4].

However, neuronal antibodies are not always present in CJD [3-4,9]. In a review of 256 cases of sporadic Creutzfeldt-Jakob disease, 82 of serum samples were investigated for autoantibodies (anti-NMDA, -VGKC, -GlyR, -LGI1 and -CASPR2). Two had antibodies against VGKC-, one had against CASPR2- and Gly-, and one had against Gly- and NMDA-receptors, all at low levels. This result indicates that < 5% of sporadic Creutzfeldt-Jakob cases may develop serum antibodies against neuronal surface, usually only at low titers [9]. This might suggest that autoantibodies appear only in specific subtypes of sporadic CJD. It is also possible, that the expression of autoantibodies depends on the duration of CJD: the longer the neuronal damage lasts, the more likely is the production of autoantibodies. This hypothesis would explain why the characteristic symptoms of NMDAR-Ab-encephalitis appeared several months after the disease onset in our patient, and why NMDAR-Ab-encephalitis developed just in those CJD cases where the disease duration was longer than in the classic form [3,9].

There are few data on the mechanism of antibody-production in prion diseases. Cellular prion protein (PrP^{c}) is expressed on almost every human leukocyte having multiple roles in the normal immune mechanism [12]. Based on the literature, PrP^{c} is an important factor in neuroprotection attenuating the T-cell dependent neuro-inflammation and apoptosis-induced microglia activation [13,14]. Thus, it is not surprising that the loss of PrP^{c} leads to neurodegeneration and altered immune function including production of unexpected autoantibodies [15]. The occurrence of scrapie isoform PrP^{sc} leads to the same cytokine profile as reported for macrophages in the activity of phagocytosis of apoptotic cells [16]. Elevated levels of IL-1, IL-2, IL-17 and IFNγ have been reported [17,18] creating an appropriate background for the increased production of Ig1G and Ig4G antibodies [19,20]. These molecular findings are in line with the clinical experience; in CJD patients autoantibodies with prominent Ig1G and Ig4G subtypes are more frequent including antibodies against NMDA,

VGKC receptors, axonal neurofilaments, aquaporin-4 as well as the classic antibodies of Hashimoto thyreoiditis [21]. A study from Fujita revealed that each one out of his 13 examined CJD patients carried NMDAR-Abs. In our patient and in the cases of the literature as well, the impact of these antibodies on the NMDA encephalitis-like clinical presentation and the progression of CJD remains unclear [22].

From a clinical viewpoint, it is important that autoantibody-mediated disorders could mimic the clinical presentation of different CJD types. NMDAR- and VGKCR-Ab encephalitis are often presented as rapid cognitive decline with motor symptoms [23]; anti-aquaporin-4 antibody mediated optic neuro-myelitis may present as an acute encephalopathy without affecting the vision or the spinal cord [24]; and Hodgkin-lymphoma associated anti-Tr antibodies may lead to subacute cerebellar syndrome mimicking the specific VV or MV phenotype of CJD [25]. It is important to recognise the treatable conditions and to avoid a rash diagnosis of CJD. Our case illustrates that serologically proven autoimmune encephalitis may hide an underlying CJD [9].

Conclusion

We conclude that patients with typical clinical symptoms of NMDAR-Ab encephalitis need to be followed and tested for CJD, especially in cases where a transient immunotherapy-associated improvement turns into a progressive decline. On the other hand, CSF antineuronal antibody analysis should be included in the diagnostic workup of patients with rapidly progressive central nervous system syndromes, particularly when they do not fulfil the diagnostic criteria of probable or possible CJD [22].

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