Case report

Anti-GAD antibody cerebellar ataxia mimicking Creutzfeldt–Jakob disease

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Abstract

In a patient with a rapidly progressive neurological condition with ataxia and cognitive complaints, Creutzfeldt–Jakob disease (CJD) is often high in the differential, particularly when there is an elevated CSF 14-3-3 protein level. We present a case of anti-glutamic acid decarboxylase antibody (anti-GAD65) positive cerebellar ataxia associated with cognitive complaints and elevated CSF 14-3-3 protein.

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1. Introduction

An elevated level of the 14-3-3 protein in the cerebrospinal fluid has been touted as highly sensitive and specific for the diagnosis of CJD, in the proper clinical context [1–3]. Unfortunately, other conditions that can present with features similar to, or overlapping with, CJD have also been shown to have elevated CSF 14-3-3. Many of these other conditions can mimic early CJD, especially before the CJD becomes fulminating, affecting multiple cognitive and motor domains [4–11]. Cerebellar and cognitive symptoms are typically the earliest features of CJD [12]. Here, we present a case of a 56-year-old woman with a rapidly progressive ataxia and cognitive complaints and an elevated 14-3-3 protein. The relative sparing of her cognitive function and a normal FLAIR and DWI MRI, however, made CJD less likely. Further evaluation for her ataxia revealed elevated anti-GAD65 antibodies in her serum and CSF. Anti-GAD65 cerebellar ataxia and the problems with the use of the 14-3-3 test are discussed.

2. Case report

A 56-year-old left-handed woman was referred with a diagnosis of potential CJD due to 2 months of rapidly progressive ataxia and an elevated CSF 14-3-3 protein. Her first symptom, 2 months prior, was a sensation of spinning not related to the position, resulting in mild imbalance that lasted several hours. Several days later, she noticed a decline in her fine motor skills while typing, followed by difficulty aiming her right hand towards objects, such as a coffee cup. Two weeks later, the incoordination spread to her right leg, causing frequent tripping. A fall resulted in an injured right shoulder. Over the next 2 weeks, left arm incoordination and a tremor emerged. Subsequently she developed intermittent double vision and visual disturbance.

Cognitively, she noted problems retaining what she read, and on occasion she repeated questions and misplaced objects. She complained of word finding difficulty, but this was not noted by her family. She lost 16 lb over the prior 6 months despite no change in appetite. Two months after the symptom onset, she required some assistance in dressing, transferring, and walking.

Past medical history was significant for collagenous colitis at age 46, diagnosed by biopsy, treated with prednisolone,
achieving complete remission with mercaptopurine. Other significant medical history included hypertension, a distant history of herpes zoster skin eruptions and chronic migraine. Family history was negative for neurological disease or autoimmune disease.

On examination, she was alert, oriented and cooperative providing an accurate history. She denied depression. Her mini-mental status exam (MMSE) score was 30/30 and she performed within normal limits on tests of attention, verbal memory, language, verbal and animal fluency, and executive function. Curiously, although she performed normally on most aspects of a 9-word verbal memory test, on an 18-word recognition task, although she recognized all 9 correct words, she also endorsed 4 false positives.

On neurological examination, she reported no diplopia. Her ocular pursuit was mildly jerky vertically, but was normal horizontally. She had mild decreased velocity of vertical and horizontal saccades, with normal latency and amplitude. No other abnormalities were detected on the cranial nerve examination. She had normal strength, but there was some increased arm tone with reinforcement. Deep tendon reflexes were symmetrically normal. No Babinski sign was elicited. She had severe dysmetria with right finger-to-nose and moderate dysmetria with the left arm. She had severe dysmetria with left heel-to-shin test and she was barely able to perform the task on the right. She could barely foot tap or draw a circle on the floor with her right foot but preformed these tasks slowly with her left foot. No dystonia, tremor, chorea or rigidity was noted. Gait was wide-based and required assistance. Sensation to pinprick and joint position sense were normal.

The following laboratory serological testing was normal or negative; complete blood count, fasting blood sugar, serum lactate and pyruvate, alpha-tocopherol, Vitamin A, copper, ceruloplasmin, ESR, electrolytes, anti-SSA (Ro), anti-SSB (La), rheumatoid factor, and anti-gliadin antibody. An initial serum autoimmune/paraneoplastic screen was negative for anti-Hu (ANNA-1) and anti-Ri (ANNA-2) (Focus Technologies, Inc. Cypress, CA), and anti-MaTa, CV2 (CRMP-5), Yo (PCA-1) (Quest Diagnostics-Nichols, San Juan Capistrano, CA) antibodies. An autoimmune/paraneoplastic serum screen (V. Lennon, Mayo Clinic) was additionally negative for ANNA-3, PCA-2, PCA-Tr, N- and P/Q-type calcium channel, striational, amphiphysin, and acetylcholine receptor binding antibodies. Her CSF revealed two white and five red blood cells with normal protein level (34 mg/dl) and glucose (53 mg/dl). CSF VDRL and T. Whippelli PCR were negative. CSF 14-3-3 protein was initially elevated at 4.4 ng/ml (53 mg/dl). CSF VDRL and T. Whippelli PCR were negative. Repeat CSF analysis (Mayo Medical Laboratories) 1 month after the initial positive 14-3-3, found normal levels of 14-3-3 (<0.02 ng/ml). CSF 14-3-3 protein was initially elevated at 4.4 ng/ml 9 weeks after disease onset (Mayo Medical Laboratories, Rochester, MN). CSF and serum were also screened for anti-nervous system antibodies (J. Dalmau, University of Pennsylvania) and were negative for anti-Hu, Yo, CV2, Ri, Ma1, Ma2, Zic, Amphiphysin antibodies. Additional screen of CSF (V. Lennon, Mayo Clinic) was negative for anti-Hu, Ri, ANNA-3, Yo, PCA-2, PCA-Tr, CV2, and amphiphysin.

Nine weeks after onset she had two EEGs, about 2 weeks apart. EEGs were similar and mildly abnormal, showing rare spikes arising independently from left mid-temporal and right front al areas with occasional runs of irregular to semirhythmic slowing, mostly from independent temporal regions bilaterally but also from the fronto-central areas. There were no periodic sharp waves. Brain MRI performed 2 months after onset was normal; the cerebellum was not atrophic and there were no FLAIR or DWI hyperintensities in the cortex or the basal ganglia. Chest, abdomen and pelvis CT scan with and without oral and IV contrast were normal and showed no evidence of malignancy.

Screening of CSF and serum (J. Dalmau, University of Pennsylvania) revealed elevated anti-GAD antibodies in the serum and CSF (serum: 1:12,800; CSF: 1:100). Fig. 1 shows binding of patients CSF to GAD positive cells in rat cerebellum. Additional testing at another laboratory for anti-GAD65 antibody revealed highly elevated levels in serum (1752 nmol/l (normal <0.02)) and CSF (1.46 nmol/l (normal <0.02)) (V. Lennon, Mayo Clinic). Repeat CSF analysis (Mayo Medical Laboratories) 1 month after the initial positive 14-3-3, found normal levels of 14-3-3 (<2.0 ng/ml) and neuron specific enolase (16.2 ng/ml; <20 normal).

Two and half months after onset, the patient began a 5 day course of intravenous methylprednisolone (1000 mg/day), followed by oral prednisolone 80 mg/day for 1 month with a taper over the next month. Three weeks after starting steroids, she had three plasma exchanges every other day, followed by every 2 week exchange. Plasmapheresis was not tolerated and was stopped. Three months after starting steroids there was noticeable improvement in her dysarthria, gait ataxia and right leg dysmetria, but the right arm was still dysmetric. Serum GAD65 levels had decreased significantly (110 nmol/l), but still remained above normal (<0.02 nmol/l). Five months after initial steroid treatment mycophenolate mofetil (CellCept®) at 1 g bid was started and IV methylprednisolone was restarted in monthly 1 g boluses. About 1 year after initiating steroid treatment mycophenolate mofetil was temporarily increased (1.5 g bid) and methylprednisolone was reduced from 1000 to 500 mg monthly pulses due to side-effects. Soon after, mycophenolate mofetil was decreased back to 1 g bid. At last follow-up, about 15 months after starting treatment, her gait ataxia continued to improve although her serum GAD65 levels were still elevated (101 nmol/l). Although improved from her clinical nadir, she still has dysarthria, limb dysmetria and gait ataxia. She walks independently at home, but requires a walker or scooter outside. She felt that her memory has improved. Additional treatments under consideration were use of intravenous gamma globulin (IVIG) and substituting cyclophosphamide for mycophenolate mofetil.
3. Discussion

Glutamic acid decarboxylase converts glutamic acid to GABA. The presence of GAD-Ab has been reported with stiff person syndrome [13], cerebellar ataxia [14], epilepsy and palatal myoclonus [15], mouth floor tremor [16] and a variety of autoimmune diseases [17] such as insulin dependent diabetes mellitus and thyroiditis. The 14-3-3 protein, a sensitive marker for acute or subacute neuronal damage, is sometimes elevated in CJD, as well as many other neurological conditions, including stroke, multiple sclerosis, paraneoplastic limbic encephalitis, vasculitis and even neurodegenerative diseases such as Alzheimer’s and Lewy Body Disease [5,18].

Here we describe a patient with rapid progressive ataxia, visual complaints, mild extrapyramidal symptoms and cognitive complaints. She had three of the four symptoms required for WHO diagnosis of CJD, but she did not have dementia at the time of evaluation; her presentation was therefore consistent with early CJD [19]. The relative sparing of cognition compared to the severity of the cerebellar ataxia would be unusual in CJD, particularly later in the course. The lack of supportive findings on the EEG and particularly on FLAIR and DWI MRI also suggested against the diagnosis of sporadic CJD [20,21].

Anti-GAD cerebellar ataxia had been reported to be associated with autoimmune diseases including insulin dependent diabetes mellitus (IDDM), thyroiditis, celiac disease, pernicious anemia, myasthenia gravis and psoriasis. In one report on 14 patients, 10 had late onset IDDM and 7 had IDDM that antedated the cerebellar syndrome with a time range of 2–12 years. Most of these patients also had elevated anti-parietal cell, anti-thyroxine antibody and anti-nuclear antibodies [14]; our patient had collagenous colitis, which is often associated with other autoimmune diseases, 10 years prior to the onset of ataxia and these autoantibodies were negative. We found no relationship reported in the literature between collagenous colitis and elevated anti-GAD65 antibody levels. Recent reports suggest that the high titer of anti-GAD65 antibodies in the serum do not necessarily predict the presence of a neurological disorder, but rather it may be the presence of intra-thecal anti-GAD that is pathogenic for the cerebellar ataxia [14,22] and stiff-person syndrome [23,24]. The elevated CSF anti-GAD antibody level in our patient provides supportive evidence for this.

This is the first reported case of an elevated 14-3-3 protein associated with GAD65-Ab cerebellar ataxia. In the mouse model, 14-3-3 proteins help phosphorylate protein kinase A and with long term potentiation of granule-purkinje cells [25]. We speculate that damage to the cerebellum caused the high 14-3-3 level in our patient. The normalization of the 14-3-3 test at follow-up in our patient may have been due to a decrease in cell injury or death. It has been suggested that the diagnostic specificity of 14-3-3 protein in CJD is improved if the threshold is set greater than 8 ng/ml, instead of 4 ng/ml [26]; this, may have been helpful in this case. In any case, the use of the 14-3-3 test as a diagnostic marker for CJD is fraught with false-positives, including cases that may clinically mimic CJD [5]. Although our patient did not have a paraneoplastic condition, subacute ataxia with anti-GAD antibodies may be associated with cancer (S. Eggers, unpublished results) and therefore one should always screen for cancer causing a paraneoplastic condition in such cases. A European working group has recently stated that the 14-3-3 protein should not be used as a screening test for CJD but only used as a confirmation test if all other diagnostic screens are
negative and all alternative diagnoses ruled out. We advise interpreting the 14-3-3 result with caution [5,6,11].

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References