Downbeat nystagmus, ataxia and spastic tetraparesis due to coeliac disease

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Source / Izvornik: **Neurological Sciences, 2011, 32, 911 - 914**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1007/s10072-011-0506-7

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:464371

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Abstract

A 25-year-old female presented to a university neurology clinic with a one-month history of progressive ataxia, downbeat nystagmus and spastic tetraparesis. Personal history revealed polyarthralgias and weight loss. Family history was negative. After thorough history, laboratory, neurophysiological and MRI investigations, a diagnosis of cerebellar ataxia due to coeliac disease was made. The patient was treated with strict gluten-free diet and intravenous immunoglobulins. Although there are many controversies about neurological manifestations of coeliac disease, this case pointed to strong association between these two disorders. The findings of elevated protein content in the cerebrospinal fluid with positive oligoclonal bands suggested an immune-mediated process, further supported by positive anti-endomysium antibodies and anti-transglutaminase antibodies in the cerebrospinal fluid.

Key words: ataxia, coeliac disease, immunoglobulin A anti-endomysium antibodies, immunoglobulin A anti-transglutaminase antibodies, cerebrospinal fluid

We describe a case of ataxia, spastic tetraparesis and cognitive decline due to coeliac disease.

Case Report

A 25-year-old woman was referred to our department because of ataxia. Her personal history revealed polyarthralgia three years before because of which she was evaluated at internal medicine department; immunological tests were negative and she was diagnosed with reactive arthritis. Therapy with low dose corticosteroids resulted in complete recovery. After that, she developed postural tremor in her upper extremities, was examined by local neurologist and prescribed propranolol for presumed essential tremor. Two years later, she was hospitalized at Department of Internal Medicine for recurrent polyarthralgia. *Ureaplasma urealyticum* was isolated from cervical smear; therapy with doxycycline led to full recovery.

One month before admission to our department, she was hospitalized again at local Department of Internal Medicine for 15 kg weight loss and polyarthralgia especially affecting her hands. At the same time, she started developing walking difficulties, oscillopsia and occasional diplopia. Her complaints were initially thought to be consequential to depression; therefore, she was transferred to Department of Psychiatry, where therapy with sertraline and sulpiride was initiated. As she did not recover, a neurologist was consulted and the patient was transferred to our department.

On admission, neurological examination revealed fully alert patient, her speech showed scanning dysarthria. She had downbeat nystagmus in all directions of gaze, more pronounced in full lateral gaze (Video 1), spastic tetraparesis, muscle strength was 3/5 on the right hand, 4/5 on the right hand, 2/5 on the right leg and 3/5 on the left leg, decreased reflexes (1+) and positive Babinski bilaterally. She had severe dysmetria and intentional tremor on all four extremities, and she could neither walk nor sit on her own. Cognitive examination showed Minimental state examination 29/30, ACE-R 94/100, mainly due to the visuospatial

component of the test, which could be explained by motor and coordination problems. Family history for ataxia was negative.

Laboratory results showed elevated erythrocyte sedimentation rate (40 mm/h), and normal complete blood count, electrolytes, liver and kidney function tests, and C-reactive protein. She had normal T3, T4 and TSH levels, but elevated anti-TPO antibodies (>2000 IU/mL). She also had normal values of Fe, UIBC, TIBC, serum protein electrophoresis, IgA, IgG and IgM, ACE, coagulation tests, vitamin B12, folic acid, antiganglioside antibodies, tumour markers, anti-Hu, -Yo and -Ri antibodies, hepatitis B, C, HIV, VDRL, TPHA, and *Borrelia burgdorferi* serology. Genetic tests for SCA 1,2,3,6 and Friedrich ataxia were negative. Immunologic tests (ANA; dsDNA, ENA, anticardiolipin antibodies, ANCA, C3, C4, CH50) were negative. Brain MRI showed normal results. Cerebrospinal fluid (CSF) analysis revealed 2 small lymphocytes/mm^3, elevated proteins 0.93 g/L (n.v. <0.37 g/L), and positive oligoclonal bands. Electroneurography showed signs of mild sensory polyneuropathy. Because of weight loss and polyarthralgias, we performed upper endoscopy with distal duodenal biopsy. Histopathology showed villous atrophy, crypt hyperplasia, increased mononuclear infiltration of the lamina propria and an increased number of intraepithelial lymphocytes (25 *per* 100 epithelial cells). PAS staining was negative. We then performed serum IgA anti-endomysium antibodies (EMA), which were negative, and serum IgA anti-transglutaminase antibodies (tTG), which were positive (68 RU/mL), with normal levels of serum IgA. We also performed additional CSF analysis for these antibodies and both were positive (EMA positive titre and tTG 84 RU/mL). HLA genotyping revealed the HLA DQ 2 allele.

The diagnosis of cerebellar ataxia due to coeliac disease (CD) was made. The patient was treated with 50 g of intravenous immunoglobulins with modest recovery and she was transferred to stationary rehabilitation on strict gluten free diet. On follow-up at 3 and 6

months, she was stable, with modest improvement of motor strength but persistent ataxia. Repeat EMA and tTG antibodies were negative, and gastrodudenoscopy was normal, confirming the patient was adherent to the diet.

Discussion

In this case, the patient presented with severe cerebellar syndrome. The most prominent neurological feature was downbeat nystagmus (DBN) (Video 1). DBN is often the result of a bilateral lesion of the flocculus or paraflocculus, or is caused by a lesion at the bottom of the 4th ventricle[1,2]. It is estimated that DBN is either a drug-induced dysfunction or is associated with structural lesion (25% of cases with craniocervical junction anomalies, e.g., Chiari malformation and 20% with cerebellar degeneration); however, the etiology remains unknown in about 50% of cases[2]. Our patient also had signs of pyramidal tract involvement and brain MRI was completely normal indicating a more diffuse pathological process. Another important fact was the history of polyarthralgia and weight loss, which indicated systemic illness. That is why upper endoscopy with distal duodenal biopsy was performed to yield histopathologic findings consistent with CD. These findings were confirmed by positive serum IgA tTG. The final diagnosis was based on positive EMA and tTG in the CSF. Coeliac diseases is a chronic immune mediated disorder that primarily affects the gastrointestinal tract. Many patients, especially adults, may be asymptomatic or have only extraintestinal symptoms at the onset, without any of the classical coeliac symptoms[3]. The best described neurological complications of CD are ataxia, peripheral neuropathy and epilepsy, and more controversial ones include myopathy, autonomic neuropathy, white matter lesions, headache, cognitive impairment, multiple system atrophy, dystonia and childhood stroke[4]. There is strongest evidence for the association of ataxia and CD. The only pathological studies performed in patients with CD and ataxia showed that there was

lymphocytic infiltration of the cerebellum, damage to the posterior columns of the spinal cord, and sparse infiltration of the peripheral nerves[5]. These findings support the hypothesis that neurological manifestations of CD are immune mediated. Evidence suggests that there might be antibody cross-reactivity between antigenic epitopes on Purkinje cells and gluten proteins. Serum from patients with gluten ataxia and from patients with CD without neurological symptoms showed cross-reactivity with epitopes on Purkinje cells of both human and rat cerebellum[6]. Other studies have shown no association between CD and ataxia[7]. However, CD was found in 36% of patients with idiopathic cerebellar ataxia with extracerebellar presentation (autonomic instability, parkinsonism, or pyramidal dysfunction in varying combinations)[8]. Similarly, our patient had cerebellar symptomatology with pyramidal tract involvement. All of these studies had many limitations[4], and although there are no prospective studies, evidence weighs in support of causal relationship between ataxia and CD. However, one prospective study indicated that neuropathy, usually subclinical, may accompany CD and antibody titres did not seem to correlate with neurological symptoms and/or signs or diet[9]. It is also worthy mentioning that subclinical neurological abnormalities associated with CD are found in 11% of children with CD, meaning that these patients should be carefully monitored for neurologial compliacations[10]. Some patients with ataxia who have normal duodenal biopsy and positive antigliadin antibodies may also have HLA haplotypes that are associated with CD[11], indicating a wide spectrum of clinical manifestations of gluten sensitivity and suggesting the possibility that such patients might develop CD at some time point[12].

Only few studies investigated the role of antigliadin, tTg and EMA in the CSF. In one study, the authors analyzed the presence of IgA and IgG tTG in 129 samples and found positive titres in 27 and 63 CSF samples, respectively. Unfortunately, there are no clinical data on the patients and on the possible presence of CD in these patients[13]. Another study showed

negative CSF antigliadin antibodies and EMA in all study patients with ataxia and CD[11]. The role of tTG and EMA CSF antibodies remains to be elucidated.

Differential diagnosis of sporadic, adult onset ataxias is broad, especially if neurological findings such as pyramidal or sensory tract involvement are present. Autosomal dominant spinocerebellar ataxias may have diverse associated neurological features including retinopathy, optic atrophy, extrapyramidal or pyramidal signs, peripheral neuropathy, cognitive impairment, or epilepsy, but in most instances family history is positive, although it may not be clearly visible[14]. Autosomal recessive ataxias are generally associated with peripheral sensorimotor neuropathy, most notably with loss of proprioception and vibration sense, and tend to have involvement outside the nervous system[15]. Although most of recessive ataxias have their onset in childhood, late-onset Freidreich ataxia (FA) (>25 years of age) can present with gait and limb ataxia, dysarthria, loss of vibration sense, abnormal eye movements, limb spasticity and retained reflexes[16]. The patient presented had all these features, but genetic tests for FA and for most frequent dominant ataxias were negative.

When the symptoms are not restricted to the central nervous system, systemic diseases should be considered. In this case study, associated polyarthralgia and weight loss suggested neuro-Whipple's disease. Neuro-Whipple's disease can present with gastrointestinal or rheumatologic features, or as a primary central nervous system infection, but neurological manifestations do not distinguish primary from secondary form of the disease, emphasizing that brain MRI can be normal and any abnormalities are non-specific[17]. The diagnosis is made by duodenal, lymph node or brain biopsy, polymerase chain reaction (PCR) analysis and CSF analysis; MRI is crucial during follow-up, and treatment consists of prolonged antibiotic therapy with drugs able to cross the blood-brain barrier[18]. In our patient, Whipple's disease was excluded by negative duodenal biopsy.

Ataxia associated with CD can have almost identical presentation as neuro-Whipple's disease, as discussed in more detail in previous chapter. Hypothyroidism can also present with ataxia, however, these patients usually do not have weight loss. Patients with neurological manifestations and positive anti-TPO antibodies are often diagnosed with Hashimoto encephalopathy, but this disease almost never presents with ataxia[19]. On the other hand, patients with CD often have associated autoimmune disorders, the pathogenesis of which is not known, but these conditions share similar HLA haplotypes, so screening of high risk patients for CD, such as those with autoimmune diseases, is a reasonable strategy given the increased prevalence[20].

Currently, the only treatment for CD is adherence to strict gluten-free diet[21]. However, neurological manifestations, especially neuropathy and ataxia, seem to be resistant to strict gluten-free diet[11]. Recently, there is evidence for the effect of intravenous immunoglobulins in ataxia and peripheral neuropathy associated with CD[22,23]. Maintenance IVIG treatment may be needed for long-term management of these disorders[22,23]. The fact that neurological symptoms improve or are even reversible in response to IVIG suggests an immune-mediated process that may be occurring independently of gluten exposure[23]. The effect of IVIG treatment in our patient was modest; there was significant improvement of nystagmus and muscle strength, but only modest in ataxia. Although we are in need of prospective randomized trials in the management of neurological complications of CD, it seems reasonable to put these patients on strict gluten-free diet and treat them with either corticosteroids or IVIG until clinical improvement.

Conclusion

The patient discussed in this case study presented with cerebellar syndrome and pyramidal tract involvement. The differential diagnosis of adult-onset cerebellar ataxia with normal

brain MRI findings is very wide and includes genetic, inflammatory, endocrinological, paraneoplastic and systemic illnesses. After thorough investigation, the diagnosis of ataxia due to CD was made based on duodenal biopsy and positive antibodies in both serum and CSF. Other causes were excluded by appropriate tests.

Although there are many controversies about neurological manifestations of CD, this case demonstrated strong association between these two disorders. The findings of elevated protein content in the CSF with positive oligoclonal bands suggested an immune-mediated process, further supported by positive tTG and EMA in the CSF.

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Video1. Down-beat nystagmus in all directions of gaze; more pronounced in full lateral gaze.