LADA TYPE DIABETES, CELIAC DIASEASE, CEREBELLAR ATAXIA AND STIFF PERSON SYNDROME. A RARE ASSOCIATION OF AUTOIMMUNE DISORDERS

Zsuzsanna SOÓS[1], Mónika SALAMON[1], Katalin ERDEI[2], Nóra KASZÁS[2], András FOLYOVICH[2], Anna SZÜCS[3], Gábor BARCS [3], Zsuzsanna ARÁNYI[4], József SKALICZKI[5], Károly VADASDI [2], Gábor WINKLER[1, 6]

[1]Semmelweis University, 2nd Department for Internal Medicine, Diabetology, Budapest
[2]St. John's Hospital, Department of Neurology, Stroke Center, Budapest
[3]National Institute of Neuroscience, Budapest
[4]Semmelweis University, Department of Neurology, Budapest
[5]Péterfy Sándor Hospital, Department of Pathology, Budapest
[6]University of Miskolc, Faculty of Health Care, Institute for Theoretical Health Sciences, Miskolc

Celiac disease – in its typical form – is a chronic immune-mediated enteropathy with typical clinical symptoms that develops against gliadin content of cereal grains, and is often associated with other autoimmune diseases. In cases of atypical manifestation classic symptoms may be absent or mild, and extra-intestinal symptoms or associated syndromes dominate clinical picture. The authors present a longitudinal follow-up of such a case. A 63-years old woman was diagnosed with epilepsy at the age of 19, and with progressive limb ataxia at the age of 36, which was initially thought to be caused by cerebellar atrophy, later probably by stiff person syndrome. At the age 59, her diabetes mellitus manifested with type 2 diabetic phenotype, but based on GAD positivity later was reclassified as type 1 diabetes. Only the last check-up discovered the celiac disease, retrospectively explaining the entire disease course and neurological symptoms. By presenting this case, the authors would like to draw attention to the fact that one should think of the possibility of celiac disease when cerebellar ataxia, progressive neurological symptoms and diabetes are present at the same time. An early diagnosis may help to delay the progression of disease and help better treatment.

Keywords: *type 1 diabetes, celiac disease, stiff man/person syndrome, epilepsy, cerebellar ataxia, differential diagnosis*

LADA-TÍPUSÚ DIABETES, COELIAKIA, CEREBELLARIS ATAXIA ÉS STIFF-PERSON-SZINDRÓMA. AUTOIMMUN HÁTTERŰ BETEGSÉGCSOPORT RITKA TÁRSULÁSA

Soós Zs, MD; Salamon M, MD; Erdei K, MD, Kaszás N, MD; Folyovich A, MD; Szücs A, MD; Barcs G, MD; Arányi Zs, MD; Skaliczki J, MD; Vadasdi K, MD; Winkler G, MD

Ideggyogy Sz 2014;67(5–6):205–209.

Kapcsolódó cikk online

A coeliakia típusos formájában jellegzetes klinikai tünetekkel járó, a gabonafélék gliadintartalmával szemben kialakuló krónikus immun enteropathia, amely gyakran társul más autoimmun mechanizmusú kórképekkel. Atípusos megjelenése esetén klasszikus tünetei hiányozhatnak vagy enyhék, és az extraintestinalis tünetek vagy a társult szindrómák állnak a klinikai kép előterében. A szerzők ilyen eset hosszmetszeti követését mutatják be. A most 63 éves nőbetegnek 19 éves korában kórismézték epilepsziáját, 36 éves korában előbb cerebellaris atrophiára, majd stiff-person-szindrómára visszavezetett, progrediáló végtagataxiáját. Ötvenkilenc éves korában, 2-es típusú diabetes fenotípusával manifesztálódott, GAD-pozitivitás alapján utóbb 1-es típusúként reklasszifikált cukorbetegsége. Csak a legutóbbi kivizsgálás derített fényt a coeliakiára, amivel retrospektíve a teljes kórlefolyás, neurológiai tünetei is magyarázhatóvá váltak. Az eset bemutatásával a szerzők arra hívják fel a figyelmet, hogy cerebellaris ataxia, progrediáló neurológiai tünetek és diabetes társulása esetén érdemes gondolni coeliakia lehetőségére. Az időben történő kórismézés ugyanis segíthet a folyamat lassításában, eredményesebb kezelésében.

Kulcsszavak: *1-es típusú diabetes, coeliakia, stiff man/person szindróma, epilepsia, cerebellaris ataxia, differenciáldiagnosztika*

Correspondent (levelező szerző): András FOLYOVICH MD, Szent János Hospital, Department of Neurology, Stroke Center; 1125 Budapest, Diós árok 1–3. E-mail: andras.folyovich@janoskorhaz.hu

Érkezett: 2013. március 1. Elfogadva: 2013. május 30.

www.elitmed.hu

Type 1 diabetes mellitus (T1DM) is often associated with other autoimmune conditions including celiac disease (CD), also called gluten-sensitive enteropathy. Celiac disease has a prevalence of 0.97–16.4% in children[1, 2], and 2–5% in adults with T1DM, depending on the method of detection used[3]. Based on epidemiologic observations, its prevalence has been increasing[4]. It is easily diagnosed when the classic signs of celiac disease postprandial diarrhoea, flatulence and weight loss are present, however, these symptoms are often absent in adults, and extra-intestinal, mainly neurological symptoms, anaemia, infertility, osteopenia and disturbance of carbohydrate metabolism dominate the clinical picture[3, 4]. Gluten sensitivity (GS), not damaging the intestinal villi is not identical with the above mentioned entity, abdominal signs and symptoms are also absent, *only extra-intestinal symptoms draw attention of the clinician*. In rare cases, both conditions may be associated with neurological signs, sometimes even dominating the clinical presentation[5].

A case history of a female patients is presented to demonstrate: the combination of different neurologic conditions lasting several decades associated later with latent autoimmune type diabetes (LADA) could be consistent with CD, recognised unfortunately with an important delay.

ABBREVIATIONS

AGA: antigliadin antibody
anti-tTG: anti-tissue transglutaminase antibody
BMI: body mass index
CD: coeliac disease
EMA: endomysium antibody
GAD: glutaminic acid decarboxylase
GM: grand mal
GS: gluten sensitivity
Ig: immunglobulin
LADA: latent autoimmune type diabetes of adults
SPS: stiff person syndrome
T1-, T2DM: type 1 and type 2 diabetes mellitus
tTG: tissue transglutaminase

Case report

The 69 years old female was transferred to our department because of elevated blood sugar. She was diagnosed with epilepsy with typical grand mal (GM) seizures and temporal spikes on her EEG at age 19: she was treated by phenytoin for years. She was 36 when she first noticed a clumsiness of her left leg. Neurological investigations suggested cerebellar atrophy due to phenytoin toxicity as a possible cause of the progressive limb ataxia. The drug was withdrawn, and replaced by carbamazepine to treat the recurrent seizures.

Shortly thereafter a periodic painful stiffness manifested in the left leg, then the trunk muscles, and her speech became scanning. Stiff person's syndrome was hypothetized based on severe muscle spasticity and exertional tachycardia. This assumption was supported by the EMG finding and serum glutaminic acid decarboxylase (GAD) antibodies. Since the age of 53 she has been unable to walk and she had to use wheelchair. Since the menopause – appearing at age 54 – she had not seizures any more, even without any antiepileptic medication.

The patient's diabetes was revealed at age 59 in an other institute. Because the GAD antibody result was unknown there, type 2 diabetes was assumed and treated with diet and combined oral antidiabetic therapy, buformin and gliclazide. The patient was seen in our department 4 years later, at the age 63, and because of bad glycaemic control she was switched to insulin. Based on the relatively rapidly developing secondary sulfanylurea resistance, the nutritional status (BMI: 17.8 kg/m^2) and the now presented GAD antibody finding (163 IU/ml, ELISA kit, Euroimmun AG), the type of diabetes was reclassified and LADA was diagnosed. Awkwardness of her both legs and truncal ataxia were already present wih scanning speech and spastic paraparesis. Abdominal complaints (diarrhoea, flatulence, distension) were negligible so in the past as in the present. The emaciation and the evaluation of the case history raised the possibility of CD. The assumption was confirmed by a positive endomysium antibody (EMA) finding (EMA IgG>1:64, selective IgA deficiency). Subsequent duodenoscopy and biopsy also justified the diagnosis: mild-moderate villous atrophy could be detected **(Figure 1.)**. The cranial CT showed frontal and cerebellar atrophy. The confirmation of CD and LADA raised the possibility that the uncommon sequence of her neurological deficits might also be associated with gluten sensitivity. A gluten-free diet was introduced and an outpatient follow up of the patient was decided. Although she seemed to be cooperative at the beginning, in fact she was lost for several years.

She was admitted to our department at the age 69 again, because her elevated blood sugar levels could not be satisfactorily managed at home. The HbA_{1c} value was 9.9%, therefore the insulin dose was modified. Laboratory tests showed serum C-

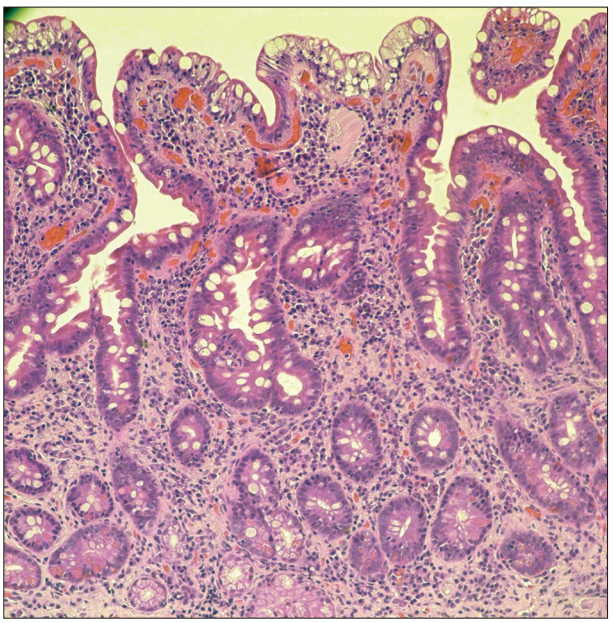

Figure 1. *Duodenal mucosa, partial villous atrophy, PBA II (HE, 600×). The ration of villi/crypts 1/1, the villi are shortened, widened, the number of the intraepithelial lymphocytes reaches >50. Mild chronic inflammatory cell infiltration in tunica propria of mucosa is seen, with widened capillaries*

peptide levels below the normal (>0.1 ng/mL), folic acid (18.3 nmol/L) and B12 (332 pmol/L) levels were within normal range. In addition to selective IgA deficiency, IgG type anti-transglutaminase levels of >400 mikromol/ml were detected indicating that the patient has not kept a strict gluten-free diet, possibly explaining her progressive neurological symptoms.

A neurological assessment was performed again showing dysarthria, scanning speech, severe spastic paraparesis. Not only truncal and limb ataxia were present but the clumsiness of her arms, too. The EEG detected moderate, diffuse cortical dysfunction without epileptiform signs. Investigations for peripheral sensory neuropathy revealed a mild small fiber damage. HLA determination was performed, the presence of DQ2.2 allel was found by the patient (DQA1*02:01, DQB1*0202), which in not typical in CD. The presence of one allel of the DQ2 heterodimer (DQ2.x) is seen very rarely[6], but not unknown. Nevertheless she was carrying HLAB1*07, too, which also corralates to CD.

With the modified insulin treatment, keeping a strict gluten-free diet the patient became free from complaints. At outpatient control one month later her medical check-up showed stable state corresponding the underlying disease.

Discussion

CD is a chronic, immune-mediated, inflammatory disease in patients with genetic predisposition. It is based on a T-cell mediated immune response against gliadin proteins of cereal grains, such as wheat, barley, rye, and oats. If the disease – in its typical form – arises with malabsorption, inflammation is seen at the proximal part of the small intestine with destruction of the brush border and the intestinal villi. However, classic symptoms – diarrhoea, weight loss – may be absent. Atypical manifestations are often seen in adult-onset cases[7], where intestinal symptoms are mild or absent and extra-intestinal symptoms (anaemia, osteoporosis, growth retardation, infertility, hepatopathia) dominate. Some diseases frequently associate with CD, e.g. enteropathy assocated T-cell lymphoma, type 1 diabetes mellitus, autoimmun thyreoiditis, dermatitis herpetiformis During, some neurological diseases: epilepsy, cerebellar ataxia, neuropathy.

The diagnosis of CD is primarily based on serological investigations: elevated anti-tTG and EMA levels are typical, both, their sensitivity and specificity are over 90%. In doubtful cases, biopsy of the small intestine can confirm the diagnosis. The measurement of anti-gliadin antibodies (AGA) performed routinely earlier, has recently lost its significance because of low sensitivity and specificity (75 vs. 80%). In the latent form of the disease serological findings – anti-tTG, EMA – are positive, however, biopsy of small intestine shows only minimal changes. Patients with this form of the disease should also be considered to have celiac disease, and usual dietary restrictions should be introduced because exacerbations may occur at any time.

Gluten sensitivity[7, 8] (GS) is considered to be a different entity from CD. These patients have sensitivity to gliadin (mainly to wheat gluten). After ingestion of food containing gliadin abdominal discomfort and flatulence may occur, but without true enteropathy and damage to the brush border and intestinal villi. It is much more common than CD, affecting 6-10% of the population. It is more difficult to diagnose, because anti-tTG and EMA levels are normal, only IgA or IgG type AGA titres are elevated. The latter finding is often misleading, as AGA can be elevated in 10–20% of the population, even without GS. This condition can only be firmly diagnosed during follow-up, based on AGA positivity and elimination of complaints by a gluten-free diet.

In 6–10% of patients with celiac disease neurological symptoms emerge, most often cerebellar ataxia, polyneuropathy, epilepsy and later demen-

tia[7–10]. Only 1/3 of those with neurological symptoms have a diagnosis of CD, most of them have only GS without enteropathy[5].

The exact mechanism of the development of neurological symptoms is still unclear. In the past, vitamin-B1, -B12 and -E deficiency was proposed based on malabsorption[10], but other investigations did not confirm low serum vitamin levels, and the above neurological symptoms were also observed in patients without biopsy-proven villous atrophy[5, 11]. In post mortem examinations perivascular inflammation could be observed in the central nervous sytem and peripheral nerves[12], while other observations found the loss of cerebellar Purkinje-cells[13]. It has been suggested that anti-gliadin antibodies are neurotoxic, initiating an autoimmune inflammatory process in the nervous tissue[14]. Gluten ataxia may improve with introduction of gluten-free diet, but clinical response depends on the duration of ataxia[15], and is inversely related to the extent of irreversible loss of cerebellar Purkinje-cells.

One of the most reputed experts of gluten ataxia, *Hadjivassiliou* also described that mainly anti-TG2 levels increase when gastrointestinal symptoms are present, and anti-TG6[15] levels are higher when neurological symptoms are present. The latter can be observed in GS, e.g. without villous atrophy, too. These tests are not yet available in Hungary. While in CD, HLADQ2 and/or DQ8 are carried in almost 100% of patients[6], it was observed only in 80% of cases with GS, and HLA-DQ1 carriage in the remaining 20%[5].

For the sake of completeness, it is worth mentioning that although serological findings normalize a few months after introducing gluten-free diet, it may happen in about 1% of cases[16] that CD does not improve. (The monitoring of anti-tTG and EMA levels is also an efficient method to control diet and patient compliance. Lack of or insufficient decrease of levels may indicate dietary inaccuracies.)

The neurological symptoms of our patient had begun before diagnosis of CD. Her cerebellar ataxia was initially ascribed to the adverse effect of phenytoin, however, her gait instability did not improve, even progressed after long-term withdrawal of the drug. The main features of the subsequently proposed stiff person syndrome (SPS) are rigidity and spasticity, affecting mainly the trunk and the left leg muscles. The present of the anti-GAD antibody could refer to SPS, epilepsy or cerebellar ataxia on the basis of literature[17, 18]. SPS is often associated with T1DM, and anti-GAD antibodies are often detected in both conditions[19]. According to the literature avaible[20] ataxia may be associated to SPS in some cases. Moreover Hadjivassiliou states that anti-GAD positive SPS and gluten sensitivity are overlapping entities[21]. Absence of the degenerative cerebellar disease in her family history is inconsistent with the diagnosis of spinocerebellar ataxia; the early onset of her neurological symptoms, the absent of autonomic dysfunction and parkinsonism reduce the probability of multiple system atrophy (cerebellar subtype).

Based on the entire history we can state that the probability of the gluten ataxia and associated SPS is fairly high in the background of her neurological symptoms, even the epilepsy in her young ages could be the first sign of CD in retrospective. She had atypical CD, therefore, unfortunately, serological examinations of diagnostic value were initially not performed. Interestingly, her anti-GAD antibody positivity was forgotten during treatments, explaining the fact that her diabetes was diagnosed as T2DM, and treated with oral antidiabetics. The compliance of our patient as she has also admitted – was initially inappropriate: she kept only loosely to the recommended gluten-free diet, which also explains the temporary worsening of the neurological symptoms. Gluten-free diet can improve her neurological symptoms in the future and so could give an ultimate proof of gluten ataxia, too.

With the presented case history we wanted to draw attention to a possible, but often overlooked comorbidity of T1DM, the development of CD and GS. In case of cerebellar ataxia and progressive neurological symptoms, one should think of a causal relationship of abnormal findings, and perform comprehensive investigations to confirm or rule out their association.

ACKNOWLEDGEMENTS

We are thankful to Gábor Gonda MD, consultant pathologist (Péterfy Sándor Hospital, Department of Pathology) for handing over the histological picture and finding.

REFERENCES

1. *Holmes GKT*. Screening for coeliac disease in type 1 diabetes. Arch Dis Child 2002;87:495-8.
2. *Freemark M, Levitsky LL*. Screening for coeliac disease in children with type 1 diabetes. Two views of the controversy. Diabetes Care 2003;26:1932-9.
3. *Bouguerrá R, Ben Salem L, Chaâbouni H, Laadhar L, Essais O, Zitouni M, et al*. Celiac disease in adult patients with type 1 diabetes mellitus in Tunisia. Diabetes Metab 2005;31:83-6.
4. *Greco L, Timpone L, Abkari A, Abu-Zekry M, Attard T, Bougerrá F, et al*. Burden of coeliac disease in the Mediterranean area. World J Gastroenterol 2011;17(45): 4971-8.
5. *Hadjivassiliou M, Grünewald RA, Davies-Jones GAB*. Gluten sensitivity as a neurological illness. J Neurol Neurosurg Psychiatry 2002;72:560-3.
6. *Megiorni F, Pizzuti A*. HLA-DQA1 and HLA-DQB1 in celiac disease predisposition: practical implication of the HLA molecular typing. J Biochem Sci 2012;19:88. doi: 10.1186/1423-0127-19-88.
7. *Grossman G*. Neurological complications of celiac disease: what is the evidence? Pract Neurol 2008;8:77-89.
8. *Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PHR, Hadjivassiliou M, et al.* Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Medicine 2012;10:13. doi:10.1186/1741-7015-10-13.
9. *Cooke WT, Thomas-Smith W*. Neurological disorders associated with adult coeliac disease. Brain 1966;89:683-722.
10. *Freeman HJ*. Neurological disorders in adult celiac disease. Can J Gastroenterol 2008;22:909-11.
11. *Bürk K, Bösch S, Müller CA, Melms A, Zühlke C, Stern M, et al*. Sporadic cerebellar ataxia associated with gluten sensitivity. Brain 2001;124:1013-9.
12. *Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, Jarratt JA, et al*. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet 1998;352:1582-5.
13. *Bhatia KP, Brown P, Gregory R, Lennox GG, Manji H, Thompson PD*. Progressive myoclonic ataxia associated with coeliac disease. The myoclonus is of cortical origin, but the pathology is in the cerebellum. Brain 1995;118: 1087-93.
14. *Hadjivassiliou M, Boscolo S, Davies-Jones AB, Grünewald RA, Phil D, Not T, et al*. The humoral response in the pathogenesis of gluten ataxia. Neurology 2002;58:1221-6.
15. *Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DSS, Woodroofe N, Aeschlimann D*. Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase. Ann Neurol 2008;64:332-43.
16. *Ryan MB, Kelleher D*. Refractory celiac disease. Gastroenterol 2003;119:243-51.
17. *Manto MU, Laute MA, Aguera M, Rogemond V, Pandolfo M, Honnorat J*. Effects of anti-glutamic acid decarboxylase antibodies associated with neurological diseases. Annals of Neurology 2007;61(6):544-51.
18. *Vianello M, Bisson G, Maschio M, Vassanelli S, Girardi S, Mucignat C, et al*. Increased spontaneous activity of a network of hippocampal neurons in culture caused by suppression of inhibitory potentials mediated by anti-GAD antibodies. Autoimmunity 2008;41(1):66-73.
19. *Baekkeskov S, Aanstoot HJ, Christgau S*. Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Nature 1991;347:151-6.
20. *Honnorat J, Saiz A, Giometto B, Vincent A, Brieva L, de Andres, C, et al*. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. Arch Neurol 2001;58:225-30.
21. *Hadjivassiliou M, Aeschlimann D, Grünewald RA, Sanders DS, Sharrack B, Woodroofe N*. GAD antibody associated neurological illness and its relationship to gluten sensitivity. Acta Neurol Scand 2011;123:175-80.