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Case Report Hybrid Open Access

Highly Elevated Tyrosine Phosphatase Antibodies in a Type 1 Diabetic Patient with Advanced Diabetic Complications and Exocrine Pancreatic Dysfunction

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Abstract

Objective and importance: Pancreatic exocrine insufficiency (PEI) is a phenomenon observed in type 1 diabetic mellitus (T1DM) patients interpreted as a disease complication and explained by several hypothesis: Impairment of enteropancreatic reflex and changes in gastrointestinal peptides due to diabetic autonomic neuropathy (DAN) is one of them. Autoimmune damage is speculated as one of the underlying cause in the DAN pathogenesis. Recent studies report that high levels of tyrosine phosphatase antibodies (IA-2Abs) may predict rapid pancreatic β cell failure and could be indicative for more aggressive autoimmunity.

Case presentation: A 55-year old T1DM male patient with 13 years diabetes duration presented with the symptoms of tingling and spasms in the hands and legs and every day diarrhea followed by meals. Several times he has been hospitalized at the Department of Gastroenterology due to diarrhea. No bacteriological or viral causes were found.

Intervention: Neurological examination has showed severe case of DAN. Fecal fat tests as well as muscle fiber presence in stool were positive. Immunology tests for T1DM specific antibodies revealed highly positive IA-2Ab (2128.0 IU/mL), low glutamic acid antibody titre (12,9 IU/mL) and negative islet cell antibody titre (<5 JDF U). Following the metoclopramide three times 10 mg per os and pancreatin three times 400 mg per os daily, the patient started to recover and was subsequently discharged.

Conclusion: We consider high IA-2Ab levels are involved in the pancreatic and autonomic nerve tissue damage either simultaneously or predominantly on one of them which consequently lead to the development of the another.

Keywords: Type 1 diabetes mellitus; Autoantibodies; Pancreatic exocrine insufficiency; Diabetic polyneuropathy

Abbreviations:

PEI: Pancreatic exocrine insufficiency; T1DM: Type 1 diabetic mellitus; DAN: Diabetic autonomic neuropathy; DPN: Diabetic polyneuropathy; ICA: Islet cell antibodies; GAD: Glutamic acid antibodies; IA-2A: Tyrosine phosphatase antibodies; IAA: Insulin antibodies; HbA1c glycated hemoglobin; eGFR: Estimated glomerular filtration rate.

Background

Pancreatic exocrine insufficiency (PEI) is a phenomenon observed in 26-76 % type 1 diabetic mellitus (T1DM) patients [1]. It is mostly interpreted as a disease complication and explained by several hypothesis: lack of insulin as a trophic factor for exocrine tissue, elevated levels of somatostatine, autoimmunity and impairment of enteropancreatic reflex or changes in gastrointestinal peptides due to diabetic autonomic neuropathy (DAN). Although there are very few studies focused on direct correlations between DAN and PEI, the correlation between decreasing C-peptide levels and PEI as well as DAN has been reported by a consistent body of literature, which interprets PEI as a complication of diabetes mellitus caused by autonomic neuropathy [1-3]. DAN is often coupled with symmetric peripheral mostly sensory nerve dysfunction and referred as diabetic polyneuropathy (DPN) [4]. Several different factors have been implicated as underlying cause in the pathogenesis process including: metabolic insult to nerve fibers, neurovascular insufficiency, neurohumoral growth deficiency and autoimmune damage [4]. T1DM is an autoimmune disease characterized by presence of islet cell antibodies (ICAs), glutamic acid antibodies (GADs), tyrosine phosphatase antibodies (IA-2s) or insulin antibodies (IAAs) [5]. The association between those autoantibodies and DPN pathogenesis has not yet been exactly defined but autoimmune mechanisms are definitely implicated in the pathophysiology of DPN [4,5]. Additionally, recent studies report that high levels of IA-2Abs may predict rapid pancreatic β cell failure and could be indicative for more aggressive autoimmunity [3]. Consistent with this, DPN development could be mediated by high levels of IA-2Ab.

Case presentation

A 55-year old T1DM male patient with 13 years diabetes duration presented with poorly controlled glycemia (glycosilated hemoglobin (HbA1c) 11,1%), with the symptoms of tingling and spasms in the hands and legs and every day diarrhea followed by meals. He had

known DPN and cervicobrachial and lumbosacral syndrome. Several times he has been hospitalized at the Department of Gastroenterology due to diarrhea. No bacteriological or viral causes were found. He was taking insulin aspart three times a day (6+8+8 i.u.) and insulin detemir twice daily (18+18 i.u.), carbamazepin 200 mg per os daily, fludrocortisone 0,1 mg per os daily and pancreatin 150 mg per os three times a day.

Physical examination revealed malnourished afebrile man with body weight 56 kg, height 182 cm, body mass index 17 kg/m2, waist/hip circumference 76/89 (0,854) cm, blood pressure level 80/40 mmHg and pulse rate 100 beats per minute.

Laboratory findings revealed low red cell blood count level (3,07x1012/L), hemoglobin (95g/L), hematocrit (0,286) and serum iron level (6 umol/L). Immunology tests for T1DM specific antibodies have shown highly positive IA-2Ab (2128.0 IU/mL), low GADAb (12,9 IU/mL) and negative ICAAb (<5 JDF U). Stool test for Salmonella spp., Shigella spp., Campylobacter spp., Yersinia enterocolitica and presence of worm larvae or eggs were negative. Fecal fat tests as well as muscle fiber presence in stool were positive. The rest of the laboratory findings are given in Table 1. Neurological examination has showed severe case of DPN with chronic peripheral sensomotory neuropathy determined with electroneuromyography testing but predominantly autonomic neuropathy with severe damage of parasympatic and sympatic autonomic nervous system. Oftalmological examination has showed proliferative/laser treated retinopathy and, and doppler examination bilateral carotid atherosclerosis.

Leukocytes (x109/L)	8.7
Thrombocytes (x109/L)	231
HbA1c (%)	11.1
Total cholesterol (mmol/L)	7.78
LDL cholesterol (mmol/L)	4.11
HDL cholesterol (mmol/L)	1.19
Tryglicerides (mmol/L)	6.86
Creatinine (umol/L)	116
eGFR (mL/min)	61
Urin albumin secretion (mg/dU)*	16.82
TSH (mU/L)	0.64
fT3 (mU/L)	3.7
fT4 (mU/L)	15.9
HbA1c: glycated hemoglobin, eGFR: Estimated glomerulal filtration rate, *two day awerage	

Table 1: Patients laboratory findings not presented in the text.

Diagnosis of PEI and DAN were established and the metoclopramide three times 10 mg per os a day was started as well as pancreatin in higher dose, three times 400 mg per os a day. The patient started to recover and was subsequently discharged.

Conclusions

Gastrointestinal symptoms like diarrhea or fecal incontinenece in diabetes have been described in detail. They might arise from DAN but also from PEI which is probably even more common concidering the prevalence of about 50% for PEI and 30% for DAN in T1DM1. DAN as an underlying cause in PEI pathogenesis has been taken into concideration in several studies emphasising impairment of enteropancreatic reflex which mediates about 50% of exocrine pancreatic response to a meal as linking mechanism [1,2]. The correlation between diabetes duration and remaining C-peptide leves and PEI was also established [1,3]. Given the thought that DAN incidene increases with disease duration, it might indeed induce pancreatic exocrine dysfunction [5]. Concurrent T1DM, EPI and DAN may be due to simultaneous damage of the endocrine and exocrine pancreatic tissue, as well as autonomic nervous tissue which could be caused by T1DM specific antibodies. It was recently suggested that the presence of high levels of IA-2 to be associated with rapid disese progression and predictors for oncoming decrease of C-peptide levels, thus complete β cell faliure, and higher insulin requierments while predominantly positive GADAb were associated with slow disease progression [4,5]. Additionally, they suggest IA-2Ab to be an indicative marker of severe humoral autoimmunity. Given the thought that the incidence of DAN inversely correlates with C-peptide levels and that IA-2Ab was also found in T1DM patients with concomitant neurological autoimmune disorders, there is a possibility that they might play an important role in DAN pathogenesis as well [4].

We reported a case of a T1DM patient with relatively short disease duration with extremely high IA-2Ab levels but low GADAb and negative ICA who already developed DPN with predominant autonomic nerve dysfunction and PEI. We concider high IA-2Ab levels are involved in the pancreatic and autonomic nerve tissue either simultaneously or predominantly on one of them which concequently lead to the development of the another. However, the role of IA-2Ab in the pathogenesis in diabetic complication development needs further study evaluation and must be strongly encouradged.

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