

A rare case of Addison's disease, hepatitis, thyreoiditis, positive IgG anti-tissue transglutaminase antibodies and partial IgA deficiency

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Abstract

Introduction: Selective IgA deficiency (IgAD) is the most prevalent type of primary immune deficiencies, but partial IgA deficiency is even more common. Addison's disease is a rare condition associated with primary adrenal insufficiency due to infection or autoimmune destruction of the adrenals. The association between IgA deficiency and Addison's disease is very rare.

Case and laboratory data: We observed a 22-year-old male patient with marked darkening of the skin, especially on the palms and areolae, jaundice on the skin and sclera, astheno-adyndamia, hypotension (80/50 mm Hg), and pain in the right hypochondrium. The laboratory investigations revealed increased serum levels of total and indirect bilirubin, AST, ALT, GGT and LDH, negative HBsAg, anti-HBc IgM, anti-HCV and anti-HAV IgM, very low serum IgA levels (0.16 g/l) with normal IgG and IgM, negative ANA, ANCA, AMA, LKM-1, anti-GAD-60, anti-IA-2, anti-thyroglobulin antibodies, a mild increase in anti-TPO antibodies titer, a marked increase in IgG anti-tissue transglutaminase antibodies, with no typical changes in cellular immunity, negative T-SPOT-TB test, HLA – A*01; B*08; DRB1*03; DQB1*02, karyotype – 46, XY.

Conclusions: We present a rare case of partial IgA deficiency with Addison's disease, hepatitis, thyroiditis and positive anti-tissue transglutaminase antibodies. IgAD and some autoimmune disorders share several predisposing HLA genes, thus explaining the increased prevalence of IgAD in certain patient groups.

Key words: Addison's disease, partial IgA deficiency, thyreoiditis, tissue transglutaminase antibodies.

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Introduction

Selective IgA deficiency (IgAD) is the most prevalent type of primary immune deficiencies. Serum IgA level of less than 0.07 g/l with normal values of IgG and IgM is considered as selective IgA deficiency in patients older than 4 years. If the serum IgA level is higher than this value but two standard deviations below the normal for age, the condition is described as partial IgA deficiency [1]. Selective IgA deficiency has variable prevalence in different ethnic groups. The lowest prevalence is reported among Japanese blood donors – from 1 : 14 840 to 1 : 18 500 [2]. In Caucasian blood donors it varies from 1 : 300 to 1 : 1 200 [3]. Partial IgA deficiency is even more common [1].

Most persons with IgAD are asymptomatic [1]. Serum IgAD is usually associated with recurrent respiratory tract infections (in approximately half of the affected), autoimmune diseases (in 28%), asthma and allergic diseases and conditions (in 13%) [4]. There are a few publications on the association between serum IgAD and Addison's disease (AD).

Case report

We observed a 22-year-old male patient with marked darkening of the skin, especially on the palms and areolae, jaundice on the skin and sclera, astheno-adyndamia, hypotension (80/50 mm Hg), pain in the right hypochondrium.

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The physical examination revealed asthenic constitution, height 180 cm, body weight 55 kg, reduced facial and body hairs, reduced subcutaneous fat tissue, jaundice on the skin and visible linings, heart rate 105 bpm, enlarged liver, brownish spots on the gums and on the hands. The patient reported that several years ago he was treated with local antimycotic agents for alopecia areata and subsequently received local antimycotics for perioral rash and oral lesions.

The clinical-laboratory investigations revealed increased serum levels of total and indirect bilirubin, AST, ALT, GGT and LDH, low serum sodium and chlorides, but normal potassium, a mild increase in FT4 with increased TSH, very high morning ACTH levels with serum morning cortisol below the normal ranges, and normal testosterone. Whole blood count, biochemical studies, coagulation, glucose, iron, copper, iron-binding capacity, urine sediment, were normal at baseline and during the follow-up. The patient was HBsAg, anti-HBc IgM, anti-HCV and anti-HAV IgM negative.

The immunological investigations showed very low serum IgA levels (0.16 g/l) with normal IgG and IgM, negative ANA, ANCA, AMA, LKM-1 antibodies, anti-GAD-60, anti-IA-2, anti-thyroglobulin antibodies, a mild increase in anti-TPO antibodies titer, a marked increase in IgG anti-tissue transglutaminase antibodies – 200 U/ml

(Table 1), with no changes in cellular immunity (Th, Ts, B and NK cells with normal CD4/CD8 ratio), negative T-SPOT-TB test; HLA type – A*01; B*08; DRB1*03; DQB1*02; karyotype – 46, XY.

The thyroid ultrasound examination revealed normal homogenic glandular parenchyma, thyroid volume 7.8 ml. The abdominal ultrasound failed to visualize the adrenal glands. The liver biopsy showed no inflammation, no fibrosis.

The computed tomography (CT) of the brain revealed normal position and symmetrical narrowing of the ventricular system, narrowing of the subarachnoid spaces, normal hypothalamus and pituitary gland.

The patient was diagnosed with partial serum IgA deficiency together with primary hypocorticism (Addison's disease) based on typical skin darkening, astheno-adenia, hypotension, very high ACTH levels with low morning serum cortisol, no CT changes in the hypothalamus and pituitary gland. He was treated with saline and glucose infusions, Mannitol, Famotidine, intravenous glucocorticosteroids (methylprednisolone 60-80 mg per day), Fludrocortisone 0.1 mg. The patient was discharged with improvement and remained on the following treatment: Dehydrocortisone 5 mg 1 + 1/4 tablet, Fludrocortisone 0.1 mg 1/2 tablet every morning (1/4 tablet in winter months).

Table 1. Biochemical results and immunological investigations of the patient

Parameter	Patient's value	Normal values
Total serum bilirubin	43	3.4-21 µmol/l
Direct serum bilirubin	8.6	0.8-8.5 µmol/l
Serum AST	49	5-40 U/l
Serum ALT	152	5-40 U/l
Serum GGT	623	< 50 U/l
Thyroid stimulating hormone	8.6	0.35-5.5 mIU/l
Serum FT4	21.37	9-20 pmol/l
Plasma morning ACTH	1880	8-66 pg/ml
Serum morning cortisol	62.9	124-662 nmol/l
Serum sodium	100	136-151 mmol/l
Serum chlorides	66	96-110 mmol/l
Serum potassium	4.2	3.5-5.6 mmol/l
IgG	13.35	5.4-16.1 g/l
IgM	0.85	0.5-2 g/l
IgA	0.16	0.8-2.8 g/l
Anti-thyroid peroxidase antibodies	42	0-34 mU/l
IgG anti-tissue transglutaminase	200	< 15 U/ml

Discussion

In 1855, Thomas Addison described an unknown condition with "anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and peculiar change of color of the skin, occurring in connection with a diseased condition of the suprarenal capsules" [5]. In 1856, A. Trousseau called the adrenocortical insufficiency "Addison's disease" [6]. The symptom complex described by T. Addison is thought to be the first case of autoimmune adrenalitis as a separate disease entity. Adrenocortical insufficiency could be primary (due to destruction of the adrenal glands) or secondary (due to pituitary and/or hypothalamic disease). In the past, the major cause of the disease was tuberculosis, and in the past 40-50 years the main pathogenetic mechanism is autoimmune adrenalitis. Addison's disease could be a separate disease entity or a part of autoimmune polyglandular syndromes (APS) type I, II or IV: type I (AD, chronic candidiasis, chronic hypoparathyroidism – at least 2/3); type II (AD, autoimmune thyroid diseases, type I diabetes mellitus); type IV (two or more organ specific autoimmune diseases, which do not fall into previous types) [7, 8]. Type III APS does not include AD [7].

Betterle *et al.* [5] described the most frequent organ-specific autoimmune diseases and conditions that accompany AD in 1240 European patients. According to their data, chronic hepatitis is found in 1.6-3% of AD patients. In APS I the prevalence of chronic active hepati-

tis is 5-31% [6]. In these patients, a transitory increase in serum aminotransferase levels is found and some of the affected have positive LKM-1 antibodies [7]. In APS type II chronic hepatitis is found in a lower percentage of the patients – 4 %, there are no data concerning the prevalence of chronic hepatitis in APS type IV [6]. In our patient, the disease onset was 1-2 years before the appearance of the classical AD symptoms, with alopecia areata, perioral rash and changes in oral lining treated successfully with antimycotics. Later the patient was admitted for Addison crisis. He had increased aminotransferase total and indirect bilirubin levels but ANA, antimitochondrial, LKM-1 antibodies were negative, as were the serological markers for hepatitis A, B and C. Abdominal ultrasound and liver biopsy showed no pathological findings.

Addison's disease is frequently associated with autoimmune thyroid diseases – Hashimoto's thyroiditis (3.7-32%) and Graves' disease (2-22.7%), and 1.2-8% of patients have celiac disease [6]. Our patient had laboratory data for autoimmune thyroid disease with mild changes in FT4, TSH and anti-TPO antibodies, but without ultrasound changes in the thyroid gland. The patient reported no gastro-intestinal symptoms but IgG anti-tissue transglutaminase antibodies were positive (Table 1). In the available medical literature we found two reports of the association of AD with celiac disease and IgAD. In 1997, Heneghan *et al.* [9] found 2 cases of AD and selective IgA deficiency among 700 patients with biopsy-proven celiac disease. In 2006, Betterle *et al.* [10] found clinical, silent or latent forms of celiac disease in 6/109 (5.4%) of the investigated AD patients (1 – with APS type I, 4 – with APS type II, 1 – with AD). Two of these patients had serum IgAD and all had normal anti-gliadin antibody levels. In patients with negative IgA anti-tissue transglutaminase antibody levels and suspected celiac disease serum IgA levels should be investigated and if the total IgA is low, IgG anti-tissue transglutaminase should be evaluated [11]. Our patient was recommended dietary changes with exclusion of gluten because of the risk of future development of malabsorption associated with AD and celiac disease. Like O'Leary *et al.* [12], we share the opinion that the detrimental effect of substitution treatment for AD on the patient's gastro-intestinal tract should not be underestimated because this could lead to further worsening of the patient's condition.

No changes in immunophenotyping of blood lymphocytes were found. T-SPOT-TB was negative and this practically excludes the tuberculosis as a cause of AD.

The low IgA serum levels (0.16 g/l, normal range 0.8-2.8 g/l) classify our patient as having partial IgAD [1]. The selective IgAD is underestimated due to the cut-off value of 0.07 g/l that distinguishes partial from selective IgAD. It remains disputable whether the patients with partial IgAD are more prone to infections and autoimmune diseases. Shakkottai *et al.* [13] describe spondyloarthropathy, Sjögren's syndrome, Raynaud's syndrome, joint pain

and edema, morning stiffness, frequent infections, allergies and eczema in children with partial IgAD, and in some of them – positive ANA (1 : 80 to 1 : 320) can be detected.

IgA deficiency is characterized by a defect of terminal lymphocyte differentiation, leading to lack of IgA in serum and mucosal secretions. A strong association between IgAD and autoimmune diseases has been widely described. Both major histocompatibility complex (MHC) and non-MHC genes contribute to susceptibility to the disease. Interestingly, the ancestral 8.1. haplotype is also reported to be associated with Grave's disease, systemic lupus erythematosus, type I diabetes and celiac disease [14, 15]. It is therefore possible that IgAD and some autoimmune disorders share some of the predisposing genes, thus explaining the increased prevalence of IgAD in certain patient groups. On the other hand, the common HLA genotype in autoimmune conditions and in IgAD poses a question whether IgAD itself is an autoimmune disease. The HLA type of our patient was: A*01; B*08; DRB1*03; DQB1*02. The most frequent haplotype in patients with IgAD is haplotype 8.1. (HLA – A1; B8; DR3; DQ2) that is detected in 45% of the cases compared with 16% of the general population [3]. A high prevalence of HLA-DR3 is found in isolated AD as well [5]. HLA-DRB1*0301, DQA1*0501 DQB1*0201 have been described in APS II [5].

On the other hand, the possibility of coexistence of IgAD and autoimmune polyglandular syndrome (APS) type II should not be excluded in this patient. APS type II is a relatively common autoimmune disease, affecting approximately 1-2 patients/10 000 a year with a female : male ratio of 3 : 1 [5, 8, 10, 16]. APS type II manifests from childhood to early adulthood with autoimmune thyroid disease, type I diabetes, Addison's disease, hypoparathyroidism, hypopituitarism, typically without chronic candida infections [16]. Cases of autoimmune endocrinopathies and selective IgAD have been described [10, 17]. Of particular importance in our patient is the possibility for development of autoimmune diabetes (type 1 diabetes mellitus) and, therefore, dynamic follow-up of glucose metabolism is needed.

The association of IgAD and Addison's disease is rare. In the described patient these two conditions are associated with several autoimmune diseases – hepatitis, thyroiditis and celiac disease. The hepatitis was presumed autoimmune as no causative viral, metabolic or toxic agent was found, despite the negative anti-liver antibodies. The thyroiditis was considered of anti-TPO type (Hashimoto thyroiditis). Moreover, the patient had serological data for celiac disease – positive IgG anti-tissue transglutaminase levels. We support the thesis of A. Shakkottai *et al.* [13] that in patients with celiac disease with normal IgA anti-tissue transglutaminase levels, the IgG subtype of these auto-antibodies should be investigated and selective or partial IgAD should be sought.

The authors declare no conflict of interest.

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