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CASE REPORT

Autoimmune polyglandular syndrome type 2 in an 15-year-old boy

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ABSTRACT

Autoimmune polyendocrine syndromes (APS) include a diverse group of clinical conditions, characterized by functional impairment of many endocrine glands. Type 2 APS is characterized by the mandatory presence of Addison's disease, which may be associated with either autoimmune thyroid diseases as a Schmidt's syndrome or type 1 diabetes mellitus as a Carpenter syndrome.

The described patient with well-controlled diabetes mellitus type 1, presented with sudden, frequent episodes of hypoglycemia, daytime somnolence and weariness, as well as remarkable hyperpigmentation of the skin. Laboratory tests revealed adrenal insufficiency with a positive titer of anti-adrenal antibodies, which led to APS-2 diagnosis in the presented case.

As the clinical outcome at the early onset of the APS-2 is not distinctive, the authors would like to emphasize the significance of screening methods, especially in patients with other hormone abnormalities, to protect them from the consequences of life-threatening disturbances.

KEY WORDS:

Addison's disease, diabetes mellitus type 1, autoimmune polyglandular syndrome, rare diseases, carpenter syndrome.

INTRODUCTION

Autoimmune polyendocrine syndromes (APS) include a diverse group of clinical conditions, characterized by functional impairment of many endocrine glands due to a destructive impact of specific autoantibodies. The failure of many glands in a single patient was first described by Schmidt. In 1926, he reported a combination of hypothyroidism and adrenal insufficiency with lymphocyte infiltration of both thyroid and adrenal glands [1]. There are four types of APS (APS-1, APS-2, APS-3 and APS-4), which are based on the combination of organs affected. Addison's disease (AD) is a prominent component of APS-1 and APS-2. APS-1 occurs mainly at the early age and most frequently reported symptoms include: mucocutaneous candidiasis, hypoparathyroidism and AD, commonly accompanied by different autoimmune disorders. APS-2, on the other hand, mainly occurs in middle-aged women and a specific sequence of symptoms has not been described [2].

APS-2, according to the original classification of Neufeld and Blizzard, is characterized by the mandatory

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FIGURE 1. Our patient – hyperpigmentation of the skin

FIGURE 2. Our patient – hyperpigmentation of the skin

presence of AD, which may be associated with either autoimmune thyroid diseases (AITDs) as a Schmidt's syndrome or type 1 diabetes mellitus (T1DM) as a Carpenter syndrome. The association with AITDs (69–82% of cases) is more frequent than that with T1DM (30–52% of cases) [3]. The classical triad of AD, AITDs and T1DM appears only for approximately 10–20% of cases [4]. Other diseases less commonly associated with APS-2 include: celiac disease, vitiligo, pernicious anemia, myasthenia gravis, stiff man syndrome, alopecia, hypergonadotropic hypogonadism and hypophysitis [5–8]. These clinical features, occurring at a greater frequency among these patients, are not included in the diagnostic criteria.

This manuscript presents a case of APS-2, its symptoms, course and clinical outcome. It aims to draw one's attention the rare occurrence of specific combinations of endocrine pathologies and difficulties in a proper treatment initiation.

CASE REPORT

The patient was born at 41st weeks of gestation following an uneventful pregnancy. The postnatal period and infancy progressed correctly – the boy's development remained within the normal range. Family history does not provide any relevant data. At the age of 8, the boy was diagnosed with T1DM. In the following year insulin pump therapy was administered.

For the next five years the patient remained in good condition with well-controlled diabetes – the mean HbA_{1c} level remained within 6–6.5%. However, after he turned 14, many episodes of hypoglycemia unexpectedly occurred and at that time the level of HbA1c dropped to 6–6.7%. Eventually, the boy was admitted to a hospital with severe hypoglycemia, loss of consciousness and seizures as the level of his blood glucose dropped to 50 mg/dl. Despite the 50% reduction of basal insulin dose (to the level of 32 units/day), the episodes of hypoglycemia reoccurred, leading to another hospitalization three months later. In the following months, the patient presented daytime somnolence and weariness. Therefore, he was admitted to a hospital due to suspected adrenal insufficiency.

On admission, the patient remained in a good condition. He presented with remarkable hyperpigmentation of the skin, mainly in the lumbar area, the buttocks and the elbows and on the chest (Figures 1, 2). Many pigmented nevi were also visible. The boy was mediocrely nourished – his body mass index (BMI) was at the 3rd percentile line, he weighed 48.2 kg, while his height was 177.2 cm. The development of the secondary sexual characteristics was undisturbed – the boy was assessed according to the Tanner scale as G5 P5. Blood pressure was also measured, and the results were within the normal range.

Laboratory tests revealed serum potassium within normal range and serum sodium at the lower limit. Moreover, prominent hypocortisolemia occurred, while the levels of adrenocorticotropic hormone (ACTH) were increased. 21-hydroxylase autoantibodies, directed at the adrenal cortex, were detected (Table 1).

The level of thyroid-stimulating hormone (TSH) was also elevated with low levels of free thyroxine at the same time, whereas anti-thyroid peroxidase (anti-TPO) antibodies were not present. Levels of luteinizing hormone (LH) and folliculotropic hormone (FSH), as well as testosterone, were within the normal range. Moreover, mild anemia (Hb 11,6, N: 12.5–16.1) and vitamin D deficiency occurred during the hospitalization (Table 1).

The patient underwent abdominal and thyroid gland ultrasound – no vital abnormalities were found.

The hormone levels abnormalities strongly corresponded to the features of primary adrenal insufficiency. Adrenal insufficiency with a positive titer of anti-adrenal antibodies in a boy with type 1 diabetes allows the diagnosis of APS-2 syndrome, which is unusual for a boy of this age. The boy has begun a suitable treatment with

hydrocortisone. Owing to the patient's good overall condition, along with blood pressure within the normal range, and no signs of dehydration, vomiting or abdominal pain, it was decided to administer hydrocortisone orally. Initial daily dosage was 20 mg/m^2 in three administrations: 15 mg in the morning, 10 mg in the afternoon and 5 mg at 6 p.m. Mineralocorticoids substitution was considered unsuitable in this case, given normal levels of serum electrolytes and adequate blood pressure values, as well as expected hydrocortisone activity. Among other recommendations, vitamin D supplementation was prescribed in a daily dose of 2000 IU and the patient was advised to monitor his blood pressure and heart rate.

The treatment of diabetes in the initial period of hydrocortisone replacement therapy was a demanding process. The boy required frequent insulin dose adjustments due to insulin resistance, occurring mainly in the morning (the highest dose of hydrocortisone). The metabolic control of diabetes deteriorated (HbA_{1c} 7.7%). The total daily dose of insulin increased 32–45 units/day (nearly 1 unit/kg body weight). Fortunately, after a few months of strict diet and stabilization of hydrocortisone dosage, glycemic control improved and the HbA_{1c} level decreased to 6.6%.

Despite the fact that the level of TSH was elevated, thyroxine supplementation was not recommended. The increased level of TSH, even reaching as high as 10 μIU/ml, might be a manifestation of adrenal insufficiency; therefore thyroxine supplementation that time might have resulted in significant deterioration of the patient health deterioration. Since the anti-TPO level and thyroid ultrasound remained normal, it was decided not to evaluate the level of antithyroglobulin antibodies (ATG). Decreased levels of free thyroxine with TSH at the upper limit suggested hypothyroidism; therefore the anti-TSH receptor antibody (TSHrAb) level was not determined.

Hydrocortisone dosage was adjusted at discharge, 10 mg in the morning, 7.5 mg at 3 p.m. and depending on the boy's evening activity, 2.5 mg at 6 p.m. Currently the patient remains under regular multispecialty care. The dose of hydrocortisone has been maintained and the laboratory tests are within the normal range. Adrenocorticotropic hormone levels have decreased significantly 1670–200 pg/ml, after two months of therapy. Nevertheless, obtaining normal levels of ACTH requires at least 3–6 months of treatment. Moreover, the thyroid gland functioning gradually returned to normal (Table 2).

TABLE 1. Laboratory test results during hospitalization

Laboratory tests	Results	Reference ranges
Serum potassium [mmol/l]	4.56	3.50–5.00
Serum sodium [mmol/l]	135	135–148
Serum total calcium [mmol/l]	2.4	2.10–2.55
Serum ionized calcium [mmol/l]	1.08	1.13–1.32
Serum phosphate [mmol/l]	1.44	0.81–1.45
Total vitamin D [ng/ml]	17.41	30–80
Plasma corticotropin (ACTH) [pg/ml] (at 8 a.m.)	1670	7.2–63.3
Serum cortisol [μg/dl] (at 8 a.m.)	0.614	5–25
Serum parathyroid hormone [pg/ml]	24.08	15–65
Serum thyroid-stimulating hormone [μIU/ml]	5.427	0.27–4.2
Serum free thyroxine [ng/dl]	0.79	0.93–1.7
21-hydroxylase antibodies	Present (+)	RU/ml

ACTH – adrenocorticotropic hormone

DISCUSSION

The prevalence of autoimmune disorders among individuals suffering from a single autoimmune disease is 30–50 times higher than in the general population. Moreover, the possibility of familial aggregation in APS-2 makes it necessary to consider the presence of endocrine disorders among first-degree relatives of children suffering from this disease [3].

More recently some authors have suggested that APS-2, APS-3 and APS-4 should not be considered as separate entities, but could be included in the context of a single syndrome, which has been named as APS-2. It is said to be the most frequent polyglandular syndrome (incidence 1–2 : 10000/year), which occurs more often in females (ratio 3 : 1) and presents no specification in terms of age profile [3], but mostly occurs during the third and fourth decades. The prevalence rate of APS-2 for children is rather low. To date, only several cases have been described, with the presence of different endocrine disorders, such as T1DM [9], Graves' disease [10], Hashimoto disease [11–13] or T1DM coexisting with autoimmune thyroiditis [14].

TABLE 2. Laboratory test results at 1 and 2 months

	Laboratory tests results (reference ranges in brackets)			
Therapy duration	Serum cortisol concentration [μg/dl] (morning, 1 hour after hydrocortisone supplementation)	Plasma corticotropin (ACTH) concentrations [pg/ml] (morning)	Serum thyroid-stimulating hormone concentration [μIU/ml]	Serum free thyroxine concentration [ng/dl]
1 month	21.45 (6.7–22.6)	–	3.31 (0.68–3.35)	0.88 (0.65–1.48)
2 months	21.25 (6.2–19.2)	200.9 (7.2–63.3)	2.65 (0.27–4.2)	1.63 (0.93–1.7)

ACTH – adrenocorticotropic hormone

APS-2 is determined by polygenes and an association with specific human leukocyte antigen DR3 and DR4 (HLADR3 and HLADR4) haplotypes has been described [15]. Within some families, autoimmune endocrine disease susceptibility appears to be an autosomal dominant trait associated with a specific HLA haplotype. Pathogenesis is based on genetic endowments, epigenetic external factors, such as viral or bacterial infections, and psychosocial factors that might induce an autoimmune cascade [16]. Our patient presented a surprisingly early onset of the illness, but no predisposing factors were confirmed during the diagnostic process.

Clinical symptoms of adrenal insufficiency include fatigue, weakness, nausea, vomiting, abdominal pain, anorexia, myalgias, hyperpigmentation of the skin and salt craving. Moreover, the laboratory outcome often reveals hypoglycemia, hyponatremia, hyperkalemia, and hypotension [17]. The clinical data about our patient, collected throughout the diagnostic process, were not indicative enough to establish the diagnosis at first. No electrolyte imbalance or hypotension was detected. Hypoglycemia was the only symptom typical of Addison's disease, but was not initially considered as such, due to coexisting diabetes in the present case. Furthermore, the described exhaustion was suspected to be an effect of blood glucose variability.

Hypoglycemia itself is not a common feature of AD, but it has been associated with both primary and secondary glucocorticoid deficiency. Treatment of T1DM and AD at the same time might be challenging, as the medicines that are mainly used – insulin and glucocorticoids – have an opposite impact on glucose homeostasis. Glucocorticoids induce insulin resistance and glucose intolerance, and cause diabetes in susceptible individuals. Conversely, the circulating glucocorticoids level decrease leads to an insulin sensitivity increase. Hence, patients with T1DM may present a reduced insulin requirement at AD development [18]. Therefore, particularly in patients presenting abrupt reduction of insulin requirements and good compliance for dietetic and therapeutic regimens, the diagnosis of AD should be considered after excluding other potential causes of hypoglycemia, such as intestinal malabsorption (mainly celiac disease), excessive physical activity, significant reduction of carbohydrate intake, alcohol abuse, chronic kidney disease, and liver disease [14]. In addition, recent studies have proved that once-daily administration of dual-release oral hydrocortisone may be a suitable therapy for such this group of patients, rather than conventional immediate-release oral hydrocortisone [18].

Crucial aspect regarding APS are early diagnosis and proper treatment implementation, in order to prevent life-threatening abnormalities, including adrenal crisis.

According to presented data, proper steroid supplementation is sufficient for normalization of thyroid functioning, whereas cortisol level influences the thyroid axis at the level of pituitary and hypothalamus. Glucocorticoid administration results in serum TSH suppression by acting on the pituitary gland, not affecting serum thyroxine level directly at the same time [19]. In addition to replacement therapy, regular check-ups are required among patients with APS-2 [15].

Recently, it was decided to use morning serum cortisol and ACTH in screening for AD among patients with T1DM with recurrent hypoglycemia [18]. However, routine screening among children with T1DM is not popular in practice, unless a strong clinical suspicion or family history of AD is present [20]. However, there is a 100-fold increase in the risk of developing AD as part of the autoimmune polyglandular syndromes (APS-1 and APS-2) in patients with type 1 diabetes and the presence of the DRB1*0404 allele or expression of anti-21-hydroxylase antibodies [8, 21].

CONCLUSIONS

As the clinical outcome at the early onset of APS-2 is not distinctive, it is important to be vigilant for minor abnormalities among examined individuals at risk of autoimmune disorders. The authors would like to emphasize the significance of screening methods for APS-2, especially in patients with a relevant family history of hormone abnormalities or suffering from endocrine disorder. Early diagnosis and proper treatment can prevent the consequences of life-threatening disturbances. The diagnosis of Addison's disease in a child with diabetes is very uncommon, usually unexpected and associated with great difficulties, but delaying this process can be particularly dangerous.

DISCLOSURE

The authors declare no conflict of interest.

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