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CASE REPORT

Autoimmune polyglandular syndrome type 2 in the form of Carpenter syndrome in a 16.5-year-old girl

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ABSTRACT

Autoimmune polyglandular syndrome type 2 (APS-2) is the coexistence of Addison disease and at least one of the disorders like autoimmune thyroid diseases and/or type 1 diabetes mellitus. We discuss the case of 16.5-year-old girl who had been diagnosed with APS-2 at the early age of 13.5 years. The girl presented recurrent abdominal pain and emesis for about 3 years, occurring about every 6 months. Moreover, in physical examination, characteristic skin hyperpigmentation furrows in the hands, nipples, and mucosa in the oral cavity were noticed. Due to the clinical picture and laboratory data, autoimmune thyroiditis and primary adrenal insufficiency were diagnosed. After initiating substitution treatment, the girl developed full-blown diabetes mellitus, probably masked earlier after primary adrenal insufficiency. It should be kept in mind that during the diagnosis of autoimmune disease, other autoimmune disorders may coexist; thus, such patients should be under specialists' close supervision.

KEY WORDS:

Carpenter syndrome, autoimmune polyglandular syndrome, girl.

INTRODUCTION

Autoimmune polyglandular syndrome type 2 (APS-2) is a complex condition in which different autoimmune disorders can coexist [1]. Autoimmune polyglandular syndrome type 2 is recognised when Addison disease (AD) is present and at least one other disorder, such as autoimmune thyroid diseases (AITDs) and/or type 1 diabetes mellitus (T1DM) [1]. According to Bapat *et al.*, 100% of patients with APS-2 have AD, whereas AITD occurs with a frequency of 69–82%, and T1DM in 30–52%. Non-endocrine disturbances like celiac disease, alopecia, pernicious anaemia, vitiligo, and myasthenia gravis may coexist [2].

Several APSs are distinguished based on clinical manifestation and affected organs: APS type 1, type 2, type 3, and type 4 [1, 3].

Autoimmune polyglandular syndrome type 2 is associated with lymphocyte infiltration, leading to organ-specific failure [4]. The inheritance is polygenic [4]. *HLA-DR3* and *HLA-DR4* haplotypes and the class 2 *HLA* alleles *DQ8* and *DQ2* are probably associated with a rise in predisposition to APS-2 [4]. However, non-HLA genes such as *CD25-interleukin-2 receptor*, *CTLA-4 (cytotoxic T-lymphocyte protein 4)*, and *PTPN-22 (protein tyrosine-protein phosphatase, non-receptor type 22)* may also be related to this syndrome [1, 4]

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Autoimmune polyglandular syndrome type 2 is a rare condition. Bapat *et al*. stated that the frequency of APS-2 is about 1.4–4.5 cases *per* 100,000 persons [2]. It is a significant difference between men and women, who are 3 times more often affected than men [2]. Usually, the age of onset is in the range of 20–40 years [4].

It is worth pointing out that the names Carpenter and Schmidt syndrome are used for specific types of APS-2 [4]. Carpenter syndrome is a triad of AD, AITD, and T1DM [4]. The coexistence of AD and chronic lymphocytic thyroiditis is called Schmidt syndrome [4].

The main diagnostic difficulty is that clinical manifestation can differ in patients [1]. Moreover, autoimmune diseases have become increasingly common, but they are usually diagnosed as single and isolated [1]. Additionally, the second autoimmune disorder may have a late manifestation (even decades may pass after the initial diagnosis); thus, the diagnostic process can be significantly delayed [1]. Hence surveillance should be carried out over a lifetime because of the possible development of other autoimmune diseases [5]. There is also a need to value specific autoantibodies because they are often present during the long latency period [3].

We discuss an APS-2 case of a girl diagnosed at the early age of 13.5 years with adrenal insufficiency, autoimmune thyroiditis, and type 1 diabetes.

Presenting this case, we would like to underline the importance of the wide range of diagnostics towards autoimmune diseases in paediatric patients who have already been diagnosed with an autoimmune disorder and have a positive family history of autoimmunity.

CASE REPORT

The 13.5-year-old girl was admitted to the Department of Paediatric Endocrinology and Rheumatology, Institute of Paediatrics, Poznań University of Medical Sciences, because of suspected adrenal insufficiency and hypothyroidism. The girl had had recurrent abdominal pain and emesis for about 3 years, occurring about every 6 months. For this reason, the patient needed hospitalisation, and she felt better after giving the drips. She also noticed that her infections lasted long, and she had recently felt general malaise. Outpatient thyroid stimulating hormone (TSH) test showed a slightly increased result (6.5 uIU/ml).

The girl was born during the second pregnancy, the second delivery. Her birth weight was 3750 g. She was assessed 10 points on the Apgar scale and underwent the preventive vaccination program with no adverse events following immunisation. During pregnancy, a urinary tract infection in the mother, treated with antibiotic, was diagnosed. There had been autoimmune diseases in the girl's family: her mother suffered from autoimmune thyroiditis (diagnosed after pregnancy with the presented patient), her father had vitiligo, and her older brother had T1DM and celiac disease (Figure 1).

After admission, in the physical examination, it was observed that the girl was very thin. Her height was 164.5 cm (50–75 pc), and she weighed 38 kg (3–10 pc). Her body mass index (BMI) was 14 kg/m^2 (< 3 pc). Also, hyperpigmentation of her skin, nipples, furrows in the hands, and mucosa in the oral cavity was noticed (Figure 2A, B). The patient had a goitre at grade 1. On the Tanner scale, she was rated as thelarche 3, axillarche 3, and pubarche 3. At that time, the girl was not menstruating.

The girl underwent several laboratory tests in the hospital (Tables 1, 2). Due to low cortisol concentrations after adrenocorticotropic hormone (ACTH) stimulation (250 μg), markedly elevated ACTH, hyponatraemia, and hyperkalaemia, primary adrenal insufficiency was diagnosed. Moreover, significantly high anti-thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb), together with subclinical hypothyroidism (elevated TSH concentration and normal free tetraiodothyronine concentration) and typical ultrasound picture

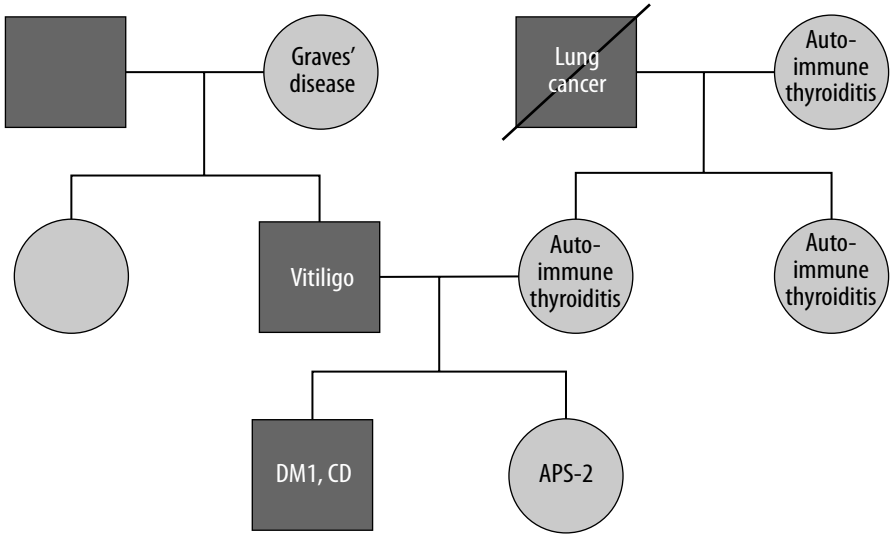

FIGURE 1. The patient's family medical history

APS-2 – autoimmune polyglandular syndrome type 2, CD – celiac disease, APS-2 – autoimmune polyglandular syndrome type 2, TDM1- diabetes mellitus type 1

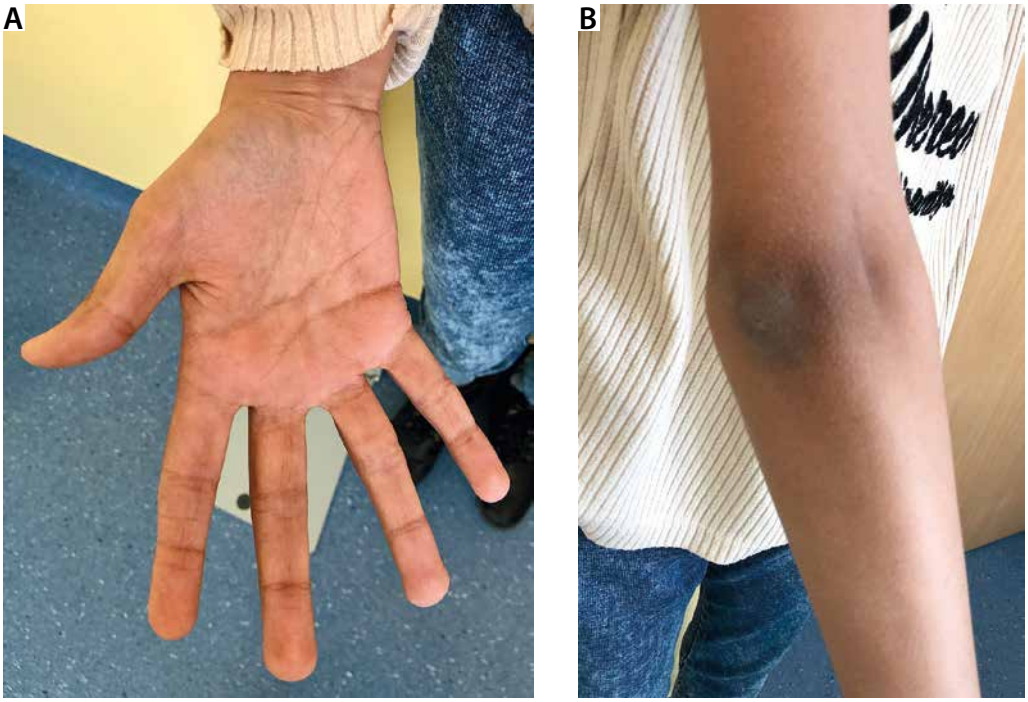

FIGURE 2. Hyperpigmentation of the furrows in the hands (**A**) and the skin on the elbow (**B**) of the patient

indicated autoimmune thyroiditis were found. Figure 3 shows the ultrasound picture of the thyroid gland.

The positive antibodies against the adrenal cortex confirmed the autoimmune aetiology of adrenal cortex insufficiency. Despite cortisol deficiency, the fasting glucose concentration was 101 mg/dl, and the glycated haemoglobin (HbA_{1c}) was 5.7%. Anti-glutamic acid decarboxylase antibodies (GADAb) were positive, indicating an autoimmune process, and the observation of diabetes mellitus was recommended.

The girl was ordered to take hydrocortisone (20 mg daily), fludrocortisone acetate (0.075 mg daily), and levothyroxine sodium (37.5 mg/dl). In the following month, after the initiation of treatment, the girl had her menarche.

About a month later, the girl was admitted in an emergency to the Department of Paediatric Diabetes, Clinical Auxology and Obesity, Institute of Paediatrics, Poznań University of Medical Sciences, because she had presented polydipsia and polyuria for about 3 weeks. Before this admission, the glucose level was 600 mg/dl. The marked level of HbA_{1C} was 7.1%. The test found glucosuria and a lack of ketone bodies in the urine. The girl was diagnosed with T1DM. The patient was ordered insulin therapy and was discharged home in good general condition.

At the same time, the diagnosis of APS-2, which consisted of primary adrenal insufficiency, autoimmune thyroiditis, and T1DM, was confirmed.

The girl remains under the control supervision of the endocrinology and diabetology outpatient clinic. The regression of hyperpigmentation was observed. From the diagnosis time, in just over a year, the patient has gained weight, so her BMI increased to 18.20 kg/m^2.

Table 1 presents selected laboratory results in the year of diagnosis and in the 3rd year of treatment.

DISCUSSION

Autoimmune polyglandular syndrome type 2 is a rare condition [6]. Moreover, only in about 10–20% of APS-2 Addison disease, T1DM, and AITD occur together in one patient [1]. Our patient presented this rare combination of conditions.

Adrenal insufficiency symptoms include emesis, fatigue, hyperpigmentation, and abdominal pain. Also, hyponatremia and hyperkalaemia are characteristic of this condition [5]. The described girl presents all these listed clinical and laboratory signs. The typical signs of hypothyroidism, like weakness and fatigue, overlapped with the symptoms of AD [7]. After initiating adrenocortical and thyroid hormone replacement, our patient showed typical symptoms of diabetes mellitus as polydipsia and polyuria, very quickly [7].

There is another possible manifestation of APS-2 that may not directly point to this syndrome, like subacute combined spinal cord degeneration. Still, our patient showed more classic symptoms [2].

According to Pham-Dobor *et al.*, APS-2 is revealed especially in young adulthood [1]. Our patient was before the completion of 14 years of age when the APS-2 appeared; thus, our case shows that even in a younger generation, this disorder may be revealed, so while diagnosing a paediatric patient, this syndrome should be remembered. Additionally, the literature shows that APS-2 is about 3 times more common in women, and our patient was a young girl at the time of diagnosis [4].

TABLE 1. Results of the selected laboratory parameters of the patient in the year of diagnosis and in the third year of therapy

Parameter	Results in the year of diagnosis	Reference value	Results in the third year of treatment	Reference value
FT3 [pg/ml]	**4.76**	2.5–3.95	3.27	2.31–3.71
FT4 [ng/dl]	0.94	0.86–1.37	1.09	0.7–1.37
TSH [uIU/ml]	**8.138**	0.470–3.410	2.077	0.470–3.410
Fasting serum glucose [mg/dl]	101	60–101	**106**	60–101
K [mmol/l]	**6.60**	3.1–5.1	4.17	3.1–5.1
Na [mmol/l]	**130**	132–145	139	132–145
25-OH-D [ng/ml]	**10.4**	30.0–50.0	36.3	30.0–50.0
ALT [IU/l]	19	< 23	12	< 23
AST [IU/l]	**31**	< 25	17	< 25
Ca [mmol/l]	2.52	2.2–2.65	2.34	2.2–2.65
PTH [pg/ml]	**71.0**	15.0–68.3	67.0	15.0–68.3
HbA_{1c} (%)	**5.7**	< 5.7	**6.2**	< 5.7
ACTH [pg/ml]	**> 2100**	10.0–60.0	26.8	10.0–60.0
PRA [ng/ml/h]	**Lying position: 10.88 Standing position: 20.37**	Lying position: 0.3–1.9 Standing position: 0.48–4.88	–	–
Aldosterone [pg/ml]	**Lying position: 50.8 After verticalisation: 52.8**	Lying position: 80–203 After verticalisation: 85–469	–	–
PRL [ng/ml]	8.82	5.18–26.53	–	–
FSH [mIU/ml]	2.9	Depending on the age and phase of the cycle	–	–
LH [mIU/ml]	2.29	Depending on the age and phase of the cycle	–	–
DHEA-S [µmol/l]	**0.63**	1.02–7.16	–	–
TPOAb [IU/ml]	**359**	Negative < 5.61	–	–
TgAb [IU/ml]	**> 1000.00**	Negative < 4.11	–	–
GADAb [U/ml]	**45.3**	Negative < 1	–	–
IAA (%)	5.1	Negative < 5.5	–	–
IA-2Ab [U/ml]	0.8	Negative < 1.0	–	–
Antibodies against the adrenal cortex	**Positive**	Titre < 1 : 5 – negative	–	–
tTG/IgA [RU/ml]	Negative	Negative < 20	Negative	Negative < 20

25-OH-D – 25-hydroxy vitamin D, ALT – alanine aminotransferase, AST – aspartate aminotransferase, DHEA-S – dehydroepiandrosterone sulphate, FSH – follicle-stimulating hormone, FT3– free triiodothyronine, IAA – insulin autoantibodies, IA-2Ab – tyrosine phosphatase antibody, LH – luteinising hormone, PRA – plasma renin activity, PRL –prolactin, PTH – parathyroid hormone, tTG/IgA – tissue transglutaminase antibodies in the IgA class
The results outside the normal range are presented in bold.

TABLE 2. Results of the adrenocorticotropic hormone (250 µg) stimulation test

The cortisol concentration [ng/ml]	Time after administration ACTH [min]
37	0
39	30
37	60
36	90
35	120

Pham-Dobor *et al.* also pointed out that the diagnostic process may be delayed and even decades can pass until another syndrome component appears [1]. The first symptoms in our patient, like vomiting and stomach pain, were reported for about 3 years before the AD and AITD were confirmed. Moreover, in our case, the third component of APS-2 in the form of T1DM appeared less than a month after initiating the treatment of primary adrenal insufficiency and hypothyroidism.

One of the laboratory signs of primary adrenal insufficiency is hypoglycaemia; conversely, the main manifes-

tation of diabetes mellitus is hyperglycaemia [7]. The girl had a 101 mg/dl glycaemia level while hospitalised at the Department of Paediatric Endocrinology and Rheumatology. We think that, already at that time, diabetes was probably the reason for such a concentration of glucose in the blood. Still, this disease could have been hidden after primary adrenal insufficiency. Cortisol stimulates gluconeogenesis, so the introduction of the supplementation of glucocorticosteroids in the form of hydrocortisone in the described girl, because it probably overlapped with already smouldering diabetes, could lead to the symptoms of this hidden diabetes in the form of polyuria and polydipsia, and the laboratory signs like hyperglycaemia revealed what probably happened to this patient [6, 7]. Aijaz *et al.* described a similar situation [6]. Other authors presented a case of a 15-year-old boy with well-controlled T1DM, who had sudden, frequent episodes of hypoglycaemia, and finally was diagnosed with AD, which led to APS-2 diagnosis [8].

Singh and Jialal reported that patients with AD on the grounds of autoimmune polyendocrine syndrome have a 2.5-fold higher risk of adrenal crisis [4]. Our patient experienced a few episodes of stomach pain and vomiting, which may manifest as a deficiency of adrenal cortex hormone, even suggesting an adrenal crisis.

Fernández Miró o *et al*. pointed out that non-endocrine diseases may often accompany the APS-2 [9]. The literature shows that there may be such disorders as pernicious anaemia, vitiligo, celiac disease, and alopecia [1, 2, 4, 9]. However, luckily they have not manifested in our patient yet. Interestingly, some of them were revealed in her closest family. Her father has vitiligo, and her older brother suffers from celiac disease. Thus, we must keep our patient under the control of other conditions.

Moreover, her brother also has T1DM, and our patient's mother has autoimmune thyroiditis. The risk of autoimmune diseases is higher in the first-degree relatives of the patient who suffers from APS-2 [2]. It seems to be confirmed in the case of our patient.

The described patient started menstruating shortly after the introduction of the supplementation of thyroid and adrenal cortex hormones. It is hard to state unequivocally its extent when the girl would generally start menstruating, when her organism was just ready for it, and how much the patient's hormone treatment was affected. It is also worth noting that in our patient, after a little over a year after her diagnosis, her BMI was significantly higher compared to her hospitalisation at the Department of Paediatric Endocrinology and Rheumatology.

There are autoantibodies like, for example, TPOAb for AITD, an anti-21-hydroxylase antibodies for AD, and GADAb for T1DM, that may be detected before the manifestation of APS-2 [4, 9]. However, it should be remembered that the presence of such autoantibodies is not equivalent to glandular failure [4]. In our patient, GADAb was detected before full-blown DM1 developed.

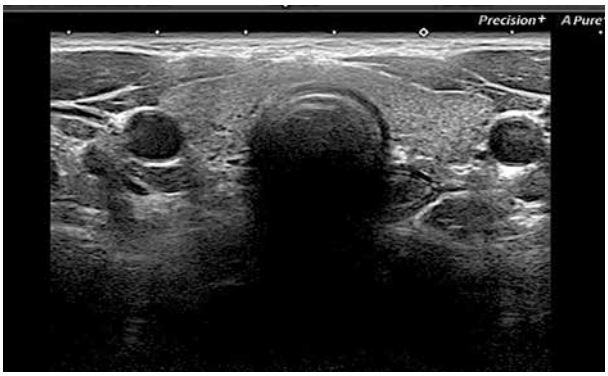

FIGURE 3. The actual ultrasound picture of the thyroid gland in the patient. The thyroid gland is not enlarged, but it is hypoechogenic
Thyroid ultrasound was performed with a Toshiba Premium Aplio 400.

CONCLUSIONS

We present the case of an early manifestation of APS-2 with a diagnosis of 3 autoimmune diseases at almost the same time. Undoubtedly, it should make us wonder if all laboratory signs are explained clearly by the diagnosis made so far because another disease may coexist. Patients with APS-2 should be under long-term observation because, as the case of our patient confirms, it is possible to develop clinical symptoms of another autoimmune disease after the initial diagnosis and introduction of adequate primary treatment.

The patient and her parents agreed to the publication of the case and photographs.

DISCLOSURE

The authors declare no conflict of interest.

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