

CASE REPORT

Novel presentation of autoimmune polyglandular syndrome II in a child with simultaneous Addison's disease, type 1 diabetes, and Hashimoto's thyroiditis: A case report

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Abstract

Providers should remain vigilant of autoimmune polyglandular syndrome type II in the context of persistent low blood sugar in type I diabetes. Correction of adrenal insufficiency is key for regulation of blood sugar and thyroid function.

KEY WORDS

Addison's, autoimmune, diabetes type 1, Hashimoto's, polyglandular

1 | INTRODUCTION

We present an 11-year-old girl diagnosed with autoimmune polyglandular syndrome type II. This case is notable for atypical age of onset and simultaneous manifestation of three endocrinopathies: Hashimoto's thyroiditis, type I diabetes, and Addison's disease which has not been described in literature in a child.

Autoimmune polyglandular syndrome (APS) type II is an exceptionally rare disorder that requires a high degree of clinical suspicion for recognition and diagnosis. The autoimmune polyglandular syndromes as a class are a constellation of multiglandular, autoimmune-driven endocrinopathies with each subtype necessarily including one particular gland in order to diagnose. APS type II requires a diagnosis of Addison's disease, and includes either autoimmune thyroid disease (69%–82% of cases) or type I diabetes mellitus (30%–52% of cases).¹ The triad of Addison's, autoimmune thyroid disease, and type 1 diabetes (T1DM) occur concomitantly in approximately 11.6% of APS type II cases.² Other associated

endocrinopathies are occasionally present as well, including celiac disease, vitiligo, hypergonadotropic hypogonadism, autoimmune hepatitis, pernicious anemia, and autoimmune hypophysitis.^{2–9} The incidence for APS type II is approximately 4–5 cases per 100,000 individuals.¹⁰ It has a peak incidence in the third and fourth decade of life and is more prevalent in females 3:1. APS II is autosomal dominant, linked with the HLA-DR3 and HLA-DR4 haplotypes with variable expressivity.¹¹

Autoimmune polyglandular syndrome type II, already rare, is even more so in the pediatric population. Between 1970 and 2004, Betterle et al² noted 13 pediatric cases of APS type II out of their total 146-case cohort. Documented APS type II incidence in children is limited to sparse case reports, and, in our review of the literature, six case reports were documented, with their demographic information presented in Table 1.^{4–9} Although rare, it is critical to note that, with the increased likelihood of another autoimmune disorders after the first is diagnosed, keeping a high level of clinical suspicion is key with T1DM which is most

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TABLE 1 Cases of APS type II reported in pediatric population as of September 2020

	P1 (4)	P2 (5)	P3 (6)
Sex	Female	Male	Male
Origin	Bangladesh	Iran	Greece
Age of diagnosis	14 years—Addison's disease, Hashimoto's thyroiditis	7 years—Addison's disease 11 years—autoimmune thyroiditis + T1DM	12.5 years—Addison's disease, Hashimoto's thyroiditis
Additional autoimmune conditions	Hypogonadism	Macrocytic anemia, keratitis	Autoimmune hypophysitis at 14 years with only GH deficiency
Family history of autoimmunity	Not described	Not described	Maternal grandmother—rheumatoid arthritis (diagnosed age 25)

	Reference range	February 2014	May 2014
HbA1c (%)	<6	>12.0	6.7
Anti-glutamic acid decarboxylase (GAD) Ab (IU/ml)	0–5	0.0	69.3
Thyroid stimulating hormone (TSH; μ IU/ml)	0.35–4.0	7.12	8.06
Anti-thyroid peroxidase (TPO) Ab (IU/ml)	<35	>1000	
ACTH (pg/ml)	6–55		1753
Morning cortisol (μ g/dl)	3.1–22.4		1.3
Aldosterone (ng/dl)	4–31		<1.6
Anti-adrenal Ab (μ /ml)	<1		3946
Celiac panel			Unremarkable

TABLE 2 Diagnostic lab values

prevalent in the pediatric population. Although T1DM is most associated with autoimmune thyroid conditions, its relationship with Addison's disease is also well understood in the literature.³ Additionally, an autosomal dominant disorder found in a child is either inherited from a parent or, oftentimes, a new fresh (de novo) mutation in the child. It is rare to find an autosomal dominant genetic condition in which the child's diagnosis precedes that of the parent. We describe a case of APS type II in an 11-year-old girl with newly diagnosed T1DM and persistent hypoglycemia after stopping insulin.

2 | CASE DESCRIPTION

An 11-6/12 year old Tanner stage II female presented in February 2014 with polyuria, polydipsia, and a 10-pound weight loss. She had no family history of endocrinopathy on either side of her family. Laboratory studies at this time (see Table 2) revealed new-onset type I diabetes mellitus. She was started on insulin at this time. She began to develop significant hypoglycemia on insulin and was taken off entirely in March 2014.

In May 2014, she was persistently losing weight despite good oral intake and experiencing a decline in her academic performance. During this time, blood sugars tested at home were found to be normal. Physical examination at this time revealed mild thyromegaly and flattening of growth curves. Repeat laboratory studies are demonstrated in Table 2. A diagnosis of autoimmune polyglandular syndrome type II was made at this time with the full triad of Addison's disease, Hashimoto's thyroiditis, and type 1 diabetes mellitus. Treatment was initiated with fludrocortisone 0.05 mg daily and hydrocortisone 9.4 mg/m²/day. Once control of Addison's was achieved, levothyroxine was started. Following treatment with fludrocortisone, hydrocortisone, and levothyroxine, she returned to her baseline academic performance as an A-student. She is currently well controlled as of January 2021 on her regimen of hydrocortisone 9.2 mg/m²/day, fludrocortisone 0.05 mg daily, levothyroxine 44 mcg daily, basal-bolus insulin therapy delivered by insulin pump, and continuous glucose monitoring. She has additionally been screened for additional autoimmune conditions, including pernicious anemia, celiac disease, and myasthenia gravis, none of which are positive as of January 2021. She has not required any immune-regulatory therapy to this point.

P4 (7)	P5 (8)	P6 (9)	P7
Male	Male	Male	Female
Michigan, USA	Italy	Turkey	Pennsylvania, USA
15 years–Addison's disease, Hashimoto's thyroiditis	16 months–T1DM 4 years–Hashimoto's thyroiditis 16 years–Addison's disease	11 years–Hashimoto's thyroiditis 11.5 years–Addison's disease	11.5 years–Addison's disease, T1DM, Hashimoto's thyroiditis
Celiac	None	Normal glucose, positive T1DM antibodies; celiac disease	None
Not described	Not described	Not described	Mother–Addison's age 42, after diagnosis of daughter

In 2017, the patient's biological mother presented at age 42 with new onset fatigue, positional lightheadedness, weight loss, nausea, abdominal pain, and skin hyperpigmentation. She was found to have thyroid nodules at that time. Laboratory results in May 2017 revealed ACTH of 1127 pg/ml (reference range 6–76 pg/ml), Cortisol 9.2 µg/dl, Aldosterone <3 ng/dl, and Adrenal antibodies 110.5 µ/ml. She has since been diagnosed by her endocrinologist with adrenal insufficiency in the setting of potential APS type II and treated accordingly. As of April 2021, thyroid function tests have been within normal limits and she has not developed diabetes mellitus, nor has she required any immune-regulatory therapy.

3 | DISCUSSION

To our knowledge, we present the first known case where complete APS type II was diagnosed in a child with each endocrinopathy in the same time frame. APS type II is rare in the pediatric demographic with few cases noted in the literature. As evidenced in Table 1 above, incomplete APS type II is most common in pediatric patients with only Addison's and Hashimoto's. Our patient is the only child to have complete APS type II manifest concomitantly without multiple years between diagnoses.

Gaining control of adrenal insufficiency is paramount in order to achieve stable control of other endocrinopathies in APS type II. As highlighted in each case report, gaining control of the adrenal insufficiency often places thyroid and glucose measurements out of controlled range,^{4–9} thus placing added emphasis on diagnosing the Addison's promptly to enhance the control of the other endocrinopathies. This case presents an excellent example in which stabilization of adrenal insufficiency unmasked the true extent of her other endocrinopathies.

In APS types II–IV, T1DM is often the first clinical manifestation of the disease.³ Clinical suspicion for adrenal insufficiency should be heightened in the setting of T1DM and persistent hypoglycemia, insulin sensitivity is

increased and counter-regulation is disrupted in the setting of extremely low cortisol levels. Diagnosis in this case is complicated by insulin regimens, as the most common reason for hypoglycemia in a newly diagnosed type I diabetic is overdose of insulin, especially during the honeymoon period. Our patient experienced persistent hypoglycemia even after the cessation of insulin, thus prompting the work up for Addison's disease. Another pediatric case⁹ describes a similar phenomenon, but with a 16-year time lapse between diagnosis of T1DM and Addison's disease. This instance may have provided a higher clinical suspicion as the honeymoon period had long passed, although surreptitious insulin use cannot be excluded in the differential for hypoglycemia in the setting of T1DM.

Furthermore, APS type II is associated with autosomal dominant pattern of disease. Our patient had no known family history at diagnosis, but her mother was diagnosed 3 years later with Addison's disease. Although it is unclear at this time whether the patient's mother will progress to complete APS type II, this highlights the importance of a high degree of clinical suspicion in first degree family members of those presenting with APS type II.

Autoimmune polyglandular syndrome (APS) type II is a complex diagnosis requiring a high degree of clinical suspicion. Autoimmune polyglandular syndrome type II is extremely rare in the pediatric population, presenting with Addison's disease and Hashimoto's thyroiditis and/or type 1 diabetes. In the setting of persistent hypoglycemia after halting insulin, it is imperative to check for adrenal insufficiency as a possible cause of persistent lows. We also demonstrate an example of a pediatric case of APS type II preceding diagnosis of a parent with Addison's disease. As APS type II is an autosomal dominant disease, this prompts a potential avenue for screening parents following the diagnosis of pediatric APSII cases in a retrograde manner.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

PA: clinically diagnosed and treated the patient, conceived of the report, and reviewed and approved the final version for publication. KS: conception of the work, drafting the article, and discussion.

ETHICAL APPROVAL

The author subscribes the 1964 Declaration of Helsinki for Medical research involving human subjects. The study of this patient was preceded by informed consent from the patient's family. The patient and her family's identity are protected. Case reports are exempt from our Institutional Review Board approval on account of the study design.

PATIENT CONSENT

The patient and her family consent to publication of this case report. We grant permission to reproduce material from other sources.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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