Title: "Novel presentation of Autoimmune Polyglandular Syndrome II in a child, with simultaneous Addison's disease, type 1 diabetes, and Hashimoto's: a case report"

Short title: APS type II in a child: Case report

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Ethics approval statement: 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. Her and her family's identity are protected. Case reports are exempt from our Institutional Review Board approval on account of the study design.

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Abstract

We present an 11-year-old female with persistent hypoglycemia in the setting of new-onset type I diabetes mellitus, with further diagnosis of both Hashimoto's thyroiditis and Addison's disease for a diagnosis of autoimmune polyglandular syndrome type II, an autosomal dominant syndrome. Three years later, the child's mother was subsequently diagnosed.

Key Clinical Message

We present an 11-year-old female with persistent hypoglycemia in the setting of new-onset type I diabetes mellitus, with further diagnosis of both Hashimoto's thyroiditis and Addison's disease for a diagnosis of autoimmune polyglandular syndrome type II, an autosomal dominant syndrome. Three years later, the child's mother was subsequently diagnosed.

1 Introduction

Autoimmune polyglandular syndrome (APS) type II is an exceptionally rare disorder that requires a high degree of clinical suspicion for recognition and diagnosis. APS type II is comprised of Addison's disease in 100% of cases, and either autoimmune thyroid disease in 69-82% of cases or type I diabetes mellitus in 30-52% of cases[1]. When Addison's, autoimmune thyroid disease, and type 1 diabetes (T1DM) occur concomitantly, APS type II is also referred to as Carpenter's syndrome, occurring in approximately 11.6% of APS type II cases[2]. Other associated endocrinopathies are occasionally present as well, including celiac disease, vitiligo, hypergonadotrophic 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].

APS II, already rare, is even more so in the pediatric population. Between 1970 and 2004, Betterle et al noted 13 cases of pediatric APS type II out of their 146-case cohort[2]. 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 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 child is either inherited from a parent or, oftentimes, a 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 girl presented to our care in May following diagnosis of T1DM at another local endocrine clinic. In February, she was noted to have polyuria, polydipsia, and a 10-pound weight loss.

She had no family history of endocrinopathy on either side of her family tree. Lab studies at this time are available in Table 2, revealing new-onset type I diabetes mellitus without positive antibodies. She was started on insulin at this time. She began to develop significant hypoglycemia on insulin and was taken off entirely in March of that year.

In May, she was persistently losing weight despite good oral intake and experiencing a remarkable decline in her academic performance. During this time blood sugars tested at home were found to be normal. Physical exam at this time revealed mild thyromegaly as well as flattening of growth curves. Repeat lab studies are demonstrated in Table 2. A diagnosis of autoimmune polyglandular syndrome type II was made at this time with the full triad of Carpenter's syndrome consisting of Addison's disease, Hashimoto's thyroiditis, and type 1 diabetes mellitus. Treatment was initiated with fludrocortisone 0.05 mg daily and hydrocortisone 9.4mg/m^2/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 on her regimen of hydrocortisone 9.2mg/m^2/day, fludrocortisone 0.05mg 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 at the time of this writing.

Three years later, 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, Cortisol 9.2 ug/dL, Aldosterone <3 ng/dL, and Adrenal antibodies 110.5 u/mL. She has since been diagnosed by her adult endocrinologist with adrenal insufficiency in the setting of likely APS type II and treated accordingly.

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. 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 Carpenter's syndrome manifest concomitantly without multiple years between diagnoses. 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.

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, as insulin sensitivity is increased in the setting of extremely low cortisol levels. Diagnosis in this case is complicated by insulin regiments, 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 case[9] 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 was long worn off, 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 Addison's disease in the

setting of likely APS type II. This is the first documented case of a child with APS preceding the diagnosis of a parent with APS. With a known autosomal dominant inheritance pattern, this suggests a possible avenue to screen parents of pediatric patients affected by APS type II, as subclinical or not yet manifest disease may be present in one of the child's parents, who notably may have entered their third or fourth decade of life, APS type II's peak incidence.

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. 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.

4 Ethics Statement

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. His and his family identity are protected. Case reports are exempt from our Institutional Review Board approval on account of the study design.

5 Conflict of Interest

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7 Abbreviations

APS- autoimmune polyglandular syndrome; T1DM- type 1 diabetes mellitus

8 TABLES

Table 1- Cases of APS type II reported in Pediatric Population as of September 2020

	P1 (4)	P2 (5)	P3 (6)	P4 (7)	P5 (8)	P6 (9)
Sex	Female	Male	Male	Male	Male	Male
Origin	Bangladesh	Iran	Greece	Michigan, USA	Italy	Turkey
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	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
Additional Endocrinopathies	Hypogonadism	Macrocytic anemia, keratitis	Autoimmune hypophysitis at 14 years with only GH deficiency	Celiac	none	Normal glucose, positive T1DM antibodies; celiac disease
Family History of autoimmunity	Not described	Not described	Maternal grandmother- rheumatoid arthritis	Not described	Not described	Not described

			(diagnosed age 25)			

Table 2- Diagnostic lab values

	Reference Range	February	May
HbA1c (%,)		>12.0	6.7
Anti-GAD Ab (IU/mL)	0-5	0.0	69.3
TSH (uIU/mL)	0.35-4.0	7.12	8.06
Anti-TPO Ab (IU/mL)	<35	>1000	
ACTH (pg/mL)	6-55		1753
AM Cortisol (ug/dL)	3.1-22.4		1.3
Aldosterone (ng/dL)	4-31		<1.6
Anti-Adrenal Ab (u/mL)	<1		3946
Celiac Panel			Unremarkable