Scientific Research Publishing

Case Reports in Clinical Medicine, 2020, 9, 208-216
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Unusual Presentation of Precocious Puberty and Alopecia Universalis in Saudi Patients with Autoimmune Polyglandular Syndrome Type 1 (APS1) without Any Other Manifestation of the Disease: Case Report and a Brief Review of the Literature

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How to cite this paper: Al Jabri, A., Al Essa, A. and Al Shaib, S. (2020) Unusual Presentation of Precocious Puberty and Alopecia Universalis in Saudi Patients with Autoimmune Polyglandular Syndrome Type 1 (APS1) without Any Other Manifestation of the Disease: Case Report and a Brief Review of the Literature. *Case Reports in Clinical Medicine*, **9**, 208-216.
https://doi.org/10.4236/crcm.2020.97029

Received: June 22, 2020
Accepted: July 14, 2020
Published: July 17, 2020

Abstract

Autoimmune polyglandular syndrome type 1 (APS-1) is one of the rare inherited disorder that affects both sexes alike. Although in specific autoimmune dysfunction associated with this syndrome found to be more common in females than males. It has specific criteria usually presented at a specific age. The object of this clinical case report is to highlight this unusual presentation of such condition which is the presence of APS-1 with precocious puberty and alopecia Universalis without any associated symptoms of APS-1 and the gene variations that never had been found before. And up to our knowledge, this is the 1st case in our population and worldwide that has such combination and this is unusual clinical presentation.

Keywords

APS-1, Alopecia Universalis, Precocious Puberty

1. Introduction

Autoimmune polyglandular syndrome type 1 (APS-1), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy/dysplasia (APECED), is a

rare autosomal recessive syndrome affecting 1 in every 2 to 3 million newborns, and usually presents in childhood with equal sex distribution [1] [2].

This disorder results from defects in the autoimmune regulator (AIRE) gene. This gene located on chromosome 21q22.3, is approximately 13 kb in length and is composed of 14 exons, and it has a role in induction of T-cell tolerance. To date, more than 70 different mutations of the AIRE gene have been identified, but the most common mutations have been found to be the nonsense mutation R257X, the Y85C missense mutation, the nonsense mutation R139X, and the deletion 967-979del13. Notably, different mutations have not been correlated with specific phenotypes. Individuals with the same mutations present with different clinical manifestations and variations of the disease course. Therefore, other modifying factors may be involved, such as environmental factors [3] which lead to immune destruction of multiple endocrine and non-endocrine organs [1].

Autoimmune polyglandular syndrome type 1 has three major clinical tried which are chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and autoimmune adrenal insufficiency, and the patient must have at least two of clinical tried to confirm the diagnosis [4]. Besides, patients can have other autoimmune disorders, such as alopecia, keratitis, gastritis, pernicious anemia, type 1 diabetes mellitus, autoimmune hypothyroidism, primary hypogonadism [1] [4], and autoimmune premature ovarian failure in the female which affects their fertility [2].

So, management of this disorder needs collaboration among different specialties [1]. In this paper, we report a 9-year-old girl who presented with universal alopecia and precocious puberty and on further evaluation was found to have APS type 1.

2. Case Report

An 11-year-old Saudi girl is from Alahsa and originally from North of Saudi Arabia. She was born at term at a local hospital without any complication. She is the youngest child in her family and her parents are first cousins. In November 2012 and at the age of 4 years and 7 months, she started to have Bilateral enlarge of her breast with Tanner stage II and scanty pubic hair. Investigations for precocious puberty were done, her bone age was equal to 8 years and 10 months according to Greulich and Pyle and Girdany and Golden methods. Pituitary fossa MRI was normal. The hormonal assessment was high (LH was 1.7 IU/L and FSH was 4.4 IU/L), then repeated after that by 2 months and it was increased with LH was 31.39 IU/L and FSH was 12.8 IU/L.

Diagnosis of Central Precocious Puberty (CPP) was made and since then she is on GnRH analogue intramuscular every 4 weeks with normal follow up labs and bone age.

In April 2014 and at the age of 6 years, she becomes alopecic, started as alopecia areata then progress to become alopecia Universalis on December 2014. Seen by a dermatologist and treated with steroids without any improvement.

In December 2018 started to have bone pain with low Vitamin D and slightly high PTH, cholecalciferol treatment was initiated.

Other investigations include ACTH, cortisol, electrolyte, and thyroid function tests were within normal limit. Pancreatic and adrenal antibodies also were negative.

Family history was positive for pernicious anemia in her mother and her sister has Systemic Lupus Erythematosus (SLE).

With the collection of these symptoms, we suspected the presence of autoimmune disease, so the AIRE gene sent and found to be positive for missense variant c.44G > A p. (Arg15His) (chr21:45705933; hg19) in exon 1 of the AIRE gene. To the best of our knowledge, this variant has not been described in the literature so far. Allele frequencies in the general population have been documented as 0.00077%.

3. Discussion

Autoimmune polyglandular syndrome type 1 is a rare disorder affected mainly by certain populations due to consanguineous marriages like special groups of Finns, Sardinians, and Iranian Jews. There is no published data about the prevalence of APS-1 in KSA although there is a study conducted in King Faisal Specialist Hospital reviewed the patient's files from 2000-2009 and found that Autoimmune polyglandular syndrome type 1 an uncommon disorder in Saudi [5].

In another center, Al Ali and colleague conduct a retrospective, hospital-based study (at King Khalid University Hospital, Riyadh, Saudi Arabia in the period January 1995 and December 2014), they found that Autoimmune polyendocrine syndrome (APS-1) is not uncommon in Saudi children [6].

Both studies didn't determine the prevalence of the disease in KSA.

In most cases, APS-1 appears in children aged 3 - 5 years, with female to male ratio range between 0.8:1 and 2.4:1 indicate that is predominant among females [3]. In this case, our patient started to develop the first clinical manifestation at the age of 6 years.

In a study by Betterle *et al.* of 41 patients with APS-1, they found the first manifestation was observed in 37 patients (90%) in childhood and 4 (10%) in adulthood at a mean age of 7.4 yr (range, 1 - 37 yr). The female/male ratio was 2.4/1 [7].

Guo and colleague mention in their study that the median age of early disease onset was 3.5 years (range, 0.2 - 14 years), and there is a tendency towards female preponderance (female: male = 2.4:1), especially for some of the APS-1 manifestations such as autoimmune hepatitis, with a female to male ratio of 5:1 and hypergonadotropic hypogonadism of 7:1 [8].

Furthermore, the onset of the first manifestation of this disease can occur from the age of a few months until adulthood [9].

In APS-1, There are three major clinical manifestations develop in chronological order: candidiasis, followed by hypoparathyroidism, and finally, adrenal in-

sufficiency [1].

Chronic mucocutaneous candidiasis is the first manifestation that usually occurs before the age of 5 years.

Most of the lesion affected skin, nails, oral and anal mucosa but no more than 5% of the skin surface. It has a prevalence of 100% in Finnish APECED patients, while in Iranian Jews it is rarely reported [9].

Esophageal involvement may complicate stenosis and stricture which can cause substernal pain and dysphagia. In Female patients, there is increasing the risk of vulvovaginitis [1] [3].

Hypoparathyroidism is the second manifestation that usually occurs before the age of 10 years. It has been reported in 70% - 93% of the cases with APS-1, and it is more common in females, affecting 98% of female patients, but only 71% of male patients [1] [3] and its conceder as commonest presenting endocrine disease among APS-1 patients was hypoparathyroidism [5].

Primary adrenal insufficiency or Addison's disease is the third manifestation, usually occur before the age of 12 years. It is a life-threatening condition that should be diagnosed before it becomes symptomatic and early treated [1] [3].

This manifestation is not a must to present in consecutive order or specific age. There was a poster display by Wonil Tae and college, when they present a 73-year-old male known to have Addison's disease diagnosed at age of 15 years, hypoparathyroidism when the patient was in his late 50's, and onychomycosis in the 60's [10].

There is another clinical manifestation of APS-1 but it is less common such as hypergonadotropic hypogonadism or primary hypogonadism, it appears in 12% - 60% of the APS-1 patients. Most of the affected female patients develop primary, and others may develop premature ovarian failure [1] [3].

Alopecia can appear at any age, but there are increasing prevalence to 40% by middle age [1] [4]. And alopecia universal is one of the common findings [5]. It involves the scalp, eyelashes, eyebrows, axilla, pubis, and could be progressive to universal alopecia.

Other clinical manifestations such as Autoimmune thyroid diseases, Chronic atrophic gastritis, pernicious anemia, Ectodermal dystrophy, Spleen aplasia or hypoplasia, vasculitis, Pulmonary disease, Autoimmune hepatitis, Intestinal dysfunction and malabsorption, Vitiligo, and Keratoconjunctivitis [1] [3]

Another severe phenotype showed in Sardinian APECED patients with autoimmune hepatitis occurred in 27% of cases with a higher incidence in females (5:1) [9].

Type 1 diabetes is uncommon in APS-1 rather than APS-2, Babiker *et al.* published an article about Screening for autoimmune diseases in type 1 diabetes, it was a retrospective study of 308 children who diagnosed with type 1 diabetes, only one of them presented with other manifestations of APS-1, hypoparathyroidism and chronic candidiasis, with a positive AIRE gene mutation [11]. While in the same center another study was conducted, they study the patient with APS-1 and they found that type 1 diabetes mellitus has been described in 40%,

which indicates that type 1 diabetes is common compared to other reports [6].

Fierabracci A. comment in his article about the Type 1 DM incidence, which varies from 1% - 18% of cases in different series of APECED patients and deferent counties and ethnic groups [9]. Although it's mentioned in Another study that it is five times more common in these patients than the general population [12].

There are several cases were report for patients who had signs that not consistent with the usual presentation of APS-1. In 2014 Improda and colleague report a 7-month-old female who presented with a skin rash (purple plaques with irregular and erythematous margins), which were mainly found in her trunk and limbs, mild splenomegaly and joint pain with fever. Vasculitis was confirmed by skin biopsy. At the age of 5 years, she had recurrent oral candidiasis, alopecia, autoimmune thyroiditis, abdominal pain, and diarrhea.

Based on the persistence of candidiasis, cutaneous manifestations, and autoimmune thyroiditis, the AIRE gene was performed and it became positive.

At the age of 9 years, she was noted to have areas of vitiligo and Hypoparathyroidism. Addison's disease was diagnosed at the age of 11 years. The patient's pubertal development was normal and at age of 10 years she experienced menarche. However, at the age of 12 she had secondary amenorrhea and after investigations diagnosed as a premature ovarian failure due to autoimmune oophoritis [13].

The other case was an 8 years old Pakistani girl presented initially with twisting movement in her face secondary to hypocalcemia followed by a generalized seizure. She had dystrophic nails and vitiligo patches over her trunk and face as well as increased pigmentation, particularly of oral mucosa and palmer creases.

Based on clinical findings and investigations, she was diagnosed with a case of polyglandular autoimmune syndrome type I. She was started on intravenous calcium gluconate, alfacalcidol. Twitching improved but despite that, she still has multiple episodes of generalized tonic-clonic seizure then becomes status epilepticus (normal ionized calcium levels at that time).

Her CSF examination and brain image were normal. EEG showed multifocal and generalized epileptiform activity. Seizures being unresponsive to calcium, anti-convulsants were considered [12].

Guttmann *et al.* publish a unique case of APS 1 for a 6 years old girl presented with immunoglobulin deficiency, mucocutaneous candidiasis, and hypothyroidism. Although this patient does not meet the exact clinical diagnostic criteria of APS1, genetic testing was done and a definitive diagnosis of APS1 (homozygous mutation of AIRE gene) was made [14].

A cross-sectional study done in a single center in India showed 3 out of 37 (Eight percentage of patients) with isolated hypoparathyroidism had elevated IFN-α antibody levels and AIRE mutation-positive APS 1 [15].

Another case of a 13-year-old male with a history of chronic diarrhea at age of 9 years, severe short stature, followed by arthritis at age of 10 years, his weight

was 17.7 kg (−7.66 SDS), and height was 117.6 cm (−5.22 SDS) has immature facial features, high pitched voice, dry skin, and hyperpigmentation. Primary adrenal insufficiency was suspected and the ACTH test confirms the diagnosis. Also, to reach the cause of chronic diarrhea with persistent acidosis colonoscopy done and the biopsy revealed eosinophilic ileitis.

They thought about IPEX syndrome but FOXP3 gene mutation was not detected. The sweat test was negative as well.

Next-generation sequencing (NGS) done and revealed a mutation in the *AIRE* (autoimmune regulator) gene [16].

In 2019 Chinello *et al.* published 2 Ukrainian female sisters, the 1st one had the typical manifestation of APS-1, while the 2nd one had an unusual presentation of APS 1, she is a 6 years old girl, at age of 3 years presented with paleness and an isolated normochromic normocytic anemia was detected. Further investigations were done include bone marrow cytogenetics (fluorescent *in situ* hybridization) and it was negative for ant trisomy or deletion also no disorder of the sex chromosomes was identified. Genetic mutations for Fanconi anemia and Diamond-Blackfan anemia resulted in negative. The serological test did not reveal any evidence of virus infection. The patient was treated with red blood cells (RBC) transfusion every 7 - 10 days and a plan for BM transplantation was made. During pre-transplant work-up the brain MRI showed mild cerebellar hypoplasia and as a part of the routine blood, exams showed severe hyponatremia (sodium 122 mmol/L). The presence of hyponatremia and the recent diagnosis of APS-1 in her sister led to suspect the same diagnosis in this patient, so, AIRE gene study done and become positive for the homozygous mutation [17].

Another unusual presentation of APS 1 was published by Pun *et al.*, for an infant at age of 3 months diagnosed as a case of moderate- to- severe Tetralogy of Fallot, then at 3 years of age, she was diagnosed with juvenile rheumatoid arthritis. Also, she suffered from dental caries conductive hearing loss, requiring the use of hearing aids. At five years of age, she presented with seizures, which were initially attributed to hypocalcemia due to hypoparathyroidism. She was started on vitamin D replacement with calcitriol. Further investigations included an EEG which demonstrated diffuse encephalopathy the patient was diagnosed with a seizure disorder and started on Phenobarbital.

At eleven years of age, she was diagnosed with DM 1. Three years later, diagnosed with Addison disease. The patient had recurrent episodes of chronic mucocutaneous candidiasis and angular stomatitis. At the age of fourteen years, diagnosed with growth hormone deficiency when growth hormone replacement started. The patient suffered from primary amenorrhea with labs and signs consistent with primary ovarian failure. At the age of nineteen years, the patient was diagnosed with bilateral cataracts.

At the age of twenty-six years, she presented with alopecia totals. She also presented with dysphagia and diagnosed with esophageal webs. Also, she was diagnosed with pernicious anemia and started on vitamin B12 supplementation [18].

Moreover, 3 siblings known as cases of Isolated Hypoparathyroidism diagnosed by Exome Sequencing as a case of APS-1 when gene study reveals Mutations in the AIRE gene. To date, the two brothers have had no clinical or biochemical features of additional endocrine, autoimmune, or developmental disorders, and all are in good health. The sister developed premature ovarian failure at age 33 years [19].

Wani *et al.* report a case of a young girl who presented with classic features of APS1 and reversible dilated cardiomyopathy [20].

Another case describes a preschool-age girl who presented with hypoparathyroidism, hepatitis, interstitial pneumonitis, and chronic polyarthritis at 4 years of age and was found to have compound heterozygous disease-associated mutations in the AIRE gene [21].

Interestingly, our patient doesn't develop any of three major components, although she has universal alopecia and recurrent asthma attack. In addition, she has central precious puberty instead of gonadal failure although we have to follow this patient in long term and assess her ovarian function.

Our patient has been finding to have AIRE gene mutation, heterozygous missense variant c.44G > A p. (ARG 15 His) (Chr 21:45705933; hg 19), which consider the first case has been reported with this mutation.

The treatment of APS-1 depends on which organ has been affected. For the most part, Replacement therapy and education of the patient about chronic conditions are a major part of treatment success [3].

As adrenal insufficiency is a life-threatening condition, Glucocorticoid replacement must be initiated immediately and doses should be adjusted according to a patient condition like in periods of acute stress infections and surgery, the doses should be increased [1] [3].

Also, vitamin and mineral replacement should be given whenever necessary [3].

4. Conclusion

To the best of our knowledge, this is the first report of a Saudi APS-1 patient with a combination of these variations. In addition, the patients who carry this missense variant c.44G > A p. (Arg15His) (chr21:45705933; hg19) in exon 1 of the AIRE gene can present with uncommon APS-1 features. This study expands the diversity of variants that could cause APS-1.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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