Section: Medicine

Case Report

POLYGLANDULAR SYNDROME TYPE 1 COMPLICATED WITH DILATED CARDIOMYOPATHY: A CASE REPORT

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Abstract

The autoimmune polyglandular syndrome (APS) is a rare recessive inherited syndrome that presents a discrete pattern of endocrine abnormalities. There are 3 types of APS: type 1, type 2, and type 3. The rarest type is type 1 acute polyglandular syndrome. Type 1 polyglandular syndrome targets endocrine and nonendocrine tissues in an autoimmune-destructive process. Our case report is about a 27-year-old male who came with complaints of fever, dysarthria, and dysphagia and presented with oral candidiasis and nail dystrophy, along with complaints of alopecia since he was 7 years old, progressively worsening with time. In the following year, he was diagnosed with hypoparathyroidism and dilated cardiomyopathy. Laboratory results display hypocalcemia, hyperphosphatemia, low Parathyroid hormone (PTH) levels suggestive of hypoparathyroidism, and serum morning cortisol levels in the normal range- these features of mucocutaneous candidiasis and hypoparathyroidism contribute to the diagnosis of APS-1. The non-contrast Computed tomography (CT) scan of the brain revealed a unique finding: bilateral symmetrical calcifications, including subcortical white matter in the frontal, parietal, temporal lobes, and basal ganglia. He was treated with oral calcium, an antifungal oral suspension, and managed conservatively for dilated cardiomyopathy with beta-blockers, angiotensin receptor/neprilysin inhibitor (ARNi), and diuretics. At the same time, dysphagia and dysarthria settled after the resolution of candidiasis. This case of a rare disease brings knowledge about the discrete manifestations of APS type 1. **Learning points:** APS-1 in patients present with diverse symptoms, especially those involving endocrine, autoimmune, and cardiac manifestations. A collaborative healthcare approach, involving specialists in endocrinology, cardiology, and other relevant fields is significant to address the diverse manifestations of APS-1 and tailor an effective management plan. Diagnostic utility of imaging, such as brain CT scans, in identifying symmetrical calcifications in the basal ganglia, provide crucial insights into the underlying metabolic disease process.

INTRODUCTION

APS type 1 is a rare autoimmune condition that affects multiple endocrine and nonendocrine organs and is also known by multiple names. It is also referred to as Online Mendelian Inheritance in Man (OMIM) 240300, Autoimmune Polyendocrinopathy-Candidiasis-ectodermal Dystrophy (APECED), or APS-1.[1]

Autosomal recessive inheritance pattern is responsible for the inheritance of APS-1. Unlike its type 2 counterpart, APS-1 typically affects only one generation. Multiple siblings tend to present with at least one of the components of the classical triad. The mutation responsible for the disease is found to be seen at a high frequency among some ethnic groups, including Iranian Jews (1:9000), Sardinians (1:14000), and Finns (1:25000), who also happen to be historically isolated groups susceptible to high

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rates of consanguineous marriages. The principal etiology behind the disease is a mutation of the autoimmune regulator (AIRE) gene on chromosome 21. The AIRE gene is 13 kb long and has 14 exons. The most common mutations associated are a nonsense mutation in exon 6 (a Finnish major mutation) and a 13-base-pair deletion in exon.[1]

APS-1 is the only known monogenetic autoimmune disease with full gene penetration. It also has no Human leukocyte antigen (HLA) association with the population, unlike APS-2. The AIRE gene codes for the AIRE protein, which acts like a transcription activator that promotes the expression of tissue-restricted antigen on the surface of medullary epithelial cells of the thymus. The mutation leads to the absence of this protein, which causes autoreactive cells to avoid central deletion and leads to autoimmunity in multiple endocrine and nonendocrine organs. The affected organs produce proteins that trigger the production of autoantibodies, leading to autoimmunity. Autoantibodies generated in response to IL-17 and IL-22, for instance, contribute to heightened vulnerability to candidiasis. Thorne and Hendley recognized the first association between mucocutaneous candidiasis and glandular fever in 1929.[2]

APS-1 presents with the classical symptoms as early as infancy. The earliest manifestation is mucocutaneous candidiasis of the mouth and nails, more commonly followed by the skin and esophagus. This is followed by the development of hypoparathyroidism and adrenal insufficiency, or Addison's disease. The interval between the diagnosis of one component and the onset of symptoms of the next can span decades. Other elements that patients may present with include gonadal failure, hypoplasia of dental enamel, and, less frequently, type 1 diabetes mellitus and autoimmune thyroid disease. The nonendocrine manifestations include pernicious anemia, alopecia, vitiligo, intestinal malabsorption, chronic active hepatitis, and nail dystrophy.[3]

Diagnosis of the condition is made when a person presents with two or three of the main three components, including mucocutaneous candidiasis, hypoparathyroidism, or adrenal insufficiency. Siblings of the affected are said to have the disease, even if one of the components is present. Other causes should be analyzed for each of the clinical presentations. Detecting autoantibodies is very helpful in diagnosing almost all cases of APS-1. Identifying an AIRE gene mutation would provide an absolute diagnosis, but it is not usually available routinely.[3]

We present a case of a 27-year-old male who was diagnosed with hypoparathyroidism and alopecia at 7 years old and was recently diagnosed with oral candidiasis and nail dystrophy. In addition, dilated cardiomyopathy further complicates this case. He was being managed conservatively on the basis of hypoparathyroidism and dilated cardiomyopathy.

Case Presentation

A 27-year-old male with consanguineous parents presented with aphasia, dysphagia, fever, and decreased mobility. His medical history included recurrent seizures since age 7, leading to a diagnosis of hypoparathyroidism and dilated cardiomyopathy [Figure 1].

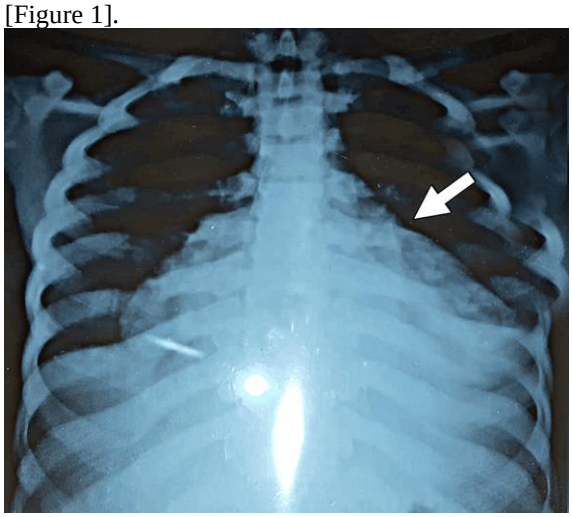

Figure 1: Chest X-ray Posteroanterior View.

Legend: Dilated Cardiomegaly visible

The patient experienced compromised cognitive function. On general examination, we found oral candidiasis [Figure 2], a yellow lesion as shown, suggestive of nail dystrophy of both upper and lower limbs, and alopecia [Figure 3-5].

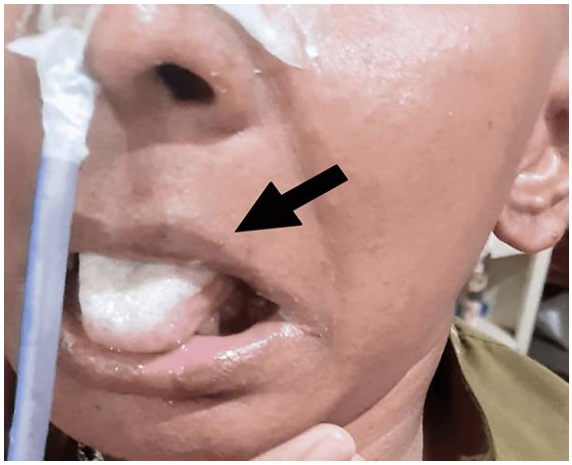

Figure 2: Oral Candidiasis.

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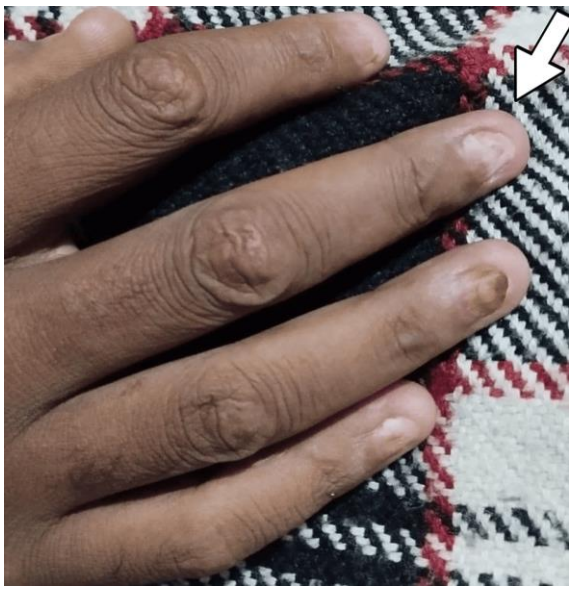

Figure 3: Nail dystrophy (Upper limbs)

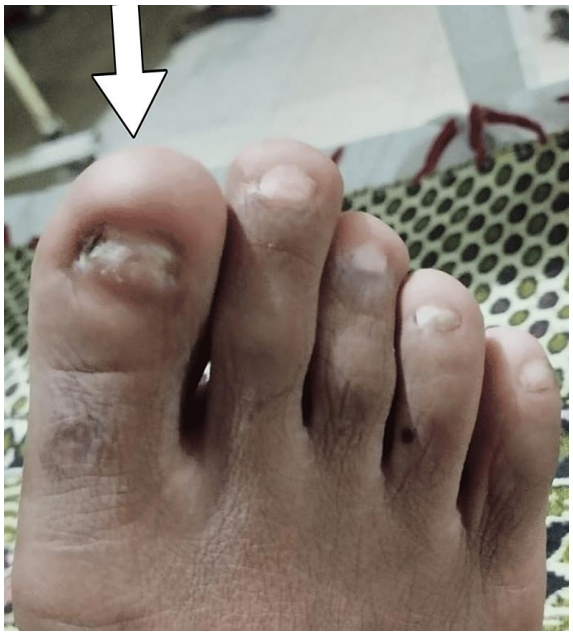

Figure 4: Nail dystrophy (Lower limbs)

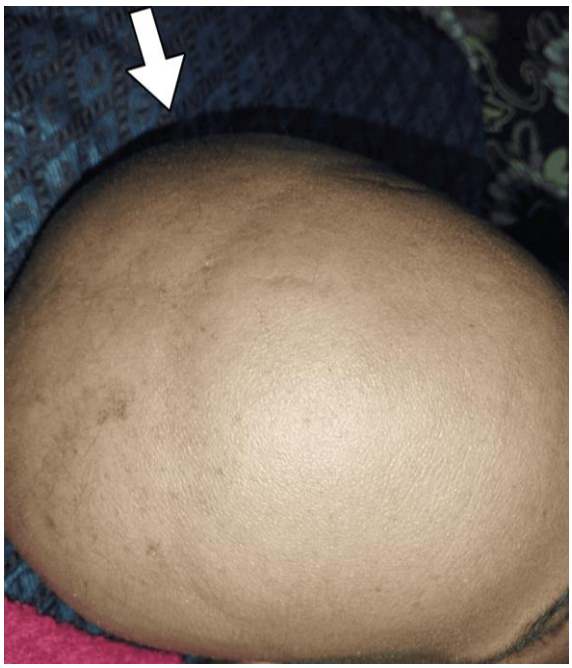

Figure 5: Alopecia

Investigation

Brain MRI indicated basal ganglia calcifications, supporting a metabolic disease process. The autoimmune profile, including ANA, was negative. Abdominal ultrasound revealed mild to moderate ascites. Liver function tests showed elevated SGPT (Serum glutamic pyruvic transaminase (ALT), SGOT (Serum glutamic-oxaloacetic transaminase), and alkaline phosphatase, consistent with cholecystitis [Table 1].

Table 1: Liver Function Test Results.

Liver function tests			
Test Description	Result	Unit	Normal Range
TOTAL BILIRUBIN	0.8	mg/dl	0.02-1.01
SGPT (ALT)	107	u/l	5-42
SGOT (AST)	69	u/l	5-45
ALKALINE PHOSPHATE	235	u/l	80-306

Legend: SGPT: Serum glutamic pyruvic transaminase (ALT), SGOT: Serum glutamic-oxaloacetic transaminase (AST).

A brain Computed Tomography scan without contrast revealed symmetrical calcifications on both sides, involving subcortical white matter in the frontal, parietal, temporal, and basal ganglia areas [Figure 6]. This suggests that the calcifications are widespread.

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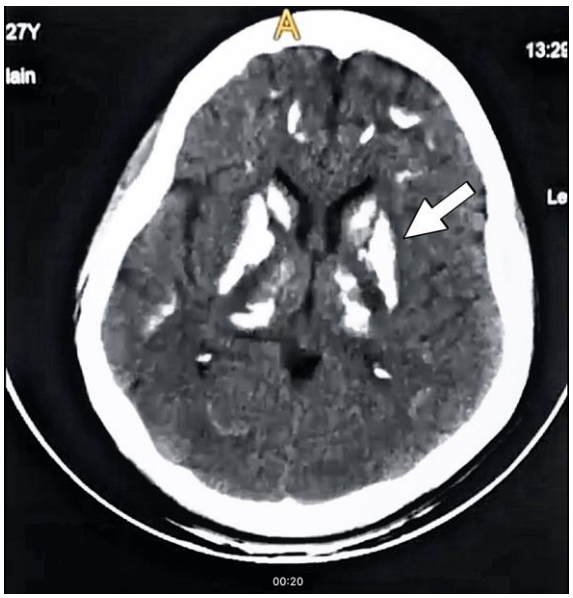

Figure 6: CT scan basal ganglia calcification

Physical examination demonstrated oral candidiasis, nail dystrophy, and alopecia. Abdominal examination revealed hepatic tenderness, while pelvic examination indicated right-sided hydrocele and left-sided varicocele. Laboratory results showed hypocalcemia, hyperphosphatemia, and anemia. The hematological lab findings were as follows, as shown in [Table 2].

Table 2: Results of complete blood count.

Parameter	Result	Reference values
CBC		
1) Hemoglobin	2.7 g/dl	13-18 g/dl
2) RBC count	0.7 million/cumm	4.5-6.5 million/cumm
3) Total count	14,300 cells/cumm	4000-11,000 cells/cumm
Differential leukocyte count		
1) Neutrophils	75%	40-75%
2) Lymphocytes	20%	20-45%
3) Eosinophils	2%	1-6%
4) Monocytes	3%	2-10%
Packed Cell Volume (hematocrit)	63.2%	47-77%
MCV	102 fl	76-96 fl
MCH	37 pg	27-32 pg
MCHC	36 %	30-35%
Platelet count	5.15 lakhs/cumm	1.5-4.5 lakhs/cumm

Legend: MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration

The echocardiogram results indicated normal measurements for the Aortic Root (29 mm), Left Atrium (57*60 mm), Left Ventricular (LV) End Diastole (61 mm), LV End Systole (51 mm), Interventricular Septum (IVS) Thickness (10 mm), and Left Ventricular Posterior Wall (LWPW) Thickness (10 mm). The Left Ventricular Ejection Fraction (LVEF) was within the normal range (>55%). Doppler findings included E/A ratios and various peak and mean gradients for different valves. Color Flow Imaging showed mild Mitral Regurgitation (MR), Aortic Regurgitation (AR), Tricuspid Regurgitation (TR), and Pulmonary Regurgitation (PR). Overall, the echocardiogram revealed normal cardiac dimensions and function with minor regurgitation noted in certain valves [Table 3].

Table 3: Echo Results.

Reference	Range	Mm	Lv function			Doppler	Color flow imaging	
			ref	Range				
Aortic Root	20-37	29	LVEF	>55%	30%	E/A	MR	+++
Left Atrium	20-39	57*60	FS	30-45	35%	MV Gradient Peak= Mean=	AR	
LV End Diastole	Female=39-53 Male=4256	61	Ref	Range		AV Gradient Peak= Mean=	TR	+
LV End Systole	Female=27-38 Male=3040	51	MAPSE			PV Gradient Peak= Mean=	PR	
IVS Thickness	Female=6-9 Male=6-10	10	EPSS		20	TV Gradient Peak= Mean=	PASP	50mmHg
LWPW Thickness	Female=6-9 Male=6-10	10	E/e Septal TDI <10 N>15			DP/DT	TVPG	

Legend: LVEF: Left ventricular ejection fraction, FS: Fractional shortening, MAPSE: Mitral annular plane systolic excursion, EPSS: E point-septal separation, IVS: Interventricular septum, LWPW: left ventricular posterior wall, TVPG: The transvalvular pressure gradient, PASP: Pulmonary arterial systolic pressure

Treatment

The patient's management plan involved a comprehensive approach to address the diverse manifestations of Autoimmune Polyglandular Syndrome Type 1 (APS-1). The therapeutic regimen

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aimed to alleviate specific symptoms and manage the underlying endocrine and cardiac abnormalities. The physician prescribed the following medications:

The healthcare provider administered Nilstat Suspension (600,000 units four times a day) to combat oral candidiasis, targeting the localized infection and promoting the resolution of symptoms. Calcium Carbonate (1250 mg, 4 tabs daily): Calcium supplementation was crucial for managing hypocalcemia associated with hypoparathyroidism, providing essential support to normalize calcium levels. Alfa Calcidol tablets (0.5 mg, 2 tablets daily) enhance calcium absorption, aid in managing hypoparathyroidism, and support bone health. Tab Metoprolol (25 mg, half per oral, twice a day): The regimen included Metoprolol, a beta-blocker, to manage dilated cardiomyopathy by reducing the workload on the heart and improving its efficiency.

Tab Savesta (Sacubitril + Valsartan) 50mg per oral twice a day: Savesta, a combination of Sacubitril and Valsartan, played a crucial role in addressing cardiomyopathy, offering neurohormonal modulation and improving heart function. Tab Levitracaetum (500 mg per oral twice a day): The healthcare provider likely included Levitracaetum, an antiepileptic medication, to manage the patient's history of recurrent seizures since the age of 7. Tab Moduretic (Amlodipine + Hydrochlorothiazide) 5/50 per oral once a day: The doctor prescribed Moduretic, a combination of amlodipine and hydrochlorothiazide, to manage blood pressure and potentially address fluid retention associated with heart failure.

Outcome and follow-up

The patient, meeting the diagnostic criteria for APS-1 based on the presence of two of the three major criteria (hypoparathyroidism and chronic mucocutaneous candidiasis), showed significant improvement in symptoms. After successfully managing the patient, we discharged them with a maintenance therapy plan to ensure ongoing stability and symptom control. The plan includes calcium and vitamin D supplements, Tab Savesta, Tab Metoprolol, and Tab Levitracaetum. This approach aims to provide long-term care and enhance the patient's quality of life.

DISCUSSION

Generally, the first signs of APS-1 appear in childhood, with the complete development of the three main diseases occurring within the first two decades of life. However, additional associated conditions can emerge up until the fifth decade. Candidiasis is often the first symptom, usually appearing before the age of 5, followed by hypoparathyroidism before age 10, and Addison's disease typically before the age of 15. While these three main components of APS-1 tend to occur in a specific chronological order, they are only present in about one-third to one-half of the cases. The case in discussion is unique as it highlights the presence of endocrine abnormalities from the age of 7. However, the patient did not develop mucocutaneous candidiasis until their third decade. This deviates from the more common chronological pattern of APS-1 symptoms.[3]

Ectodermal dystrophy is a group of problems related to Autoimmune Polyendocrine Syndrome Type 1 (APS-1). These problems include changes in the nails, underdeveloped dental enamel (mostly in permanent teeth), hair loss, keratopathy, and vitiligo. These manifestations do not necessarily occur in all APS-1 patients. Autoimmune reactions specifically attribute alopecia and vitiligo, while chronic candidiasis often causes nail deformities. The exact cause of dental enamel hypoplasia in APS-1 remains unclear. In the discussed case report, the patient exhibited alopecia and nail dystrophy, affecting both feet and hands. Treatment for the nail dystrophy involved terbinafine lotion.[4] An autosomal recessive pattern of inheritance is observed in APS-1. Over 60 identified mutations in the AIRE gene contribute to the disease's presentation and progression variability. Notably, more than 95% of APS-1 patients have one of two common mutations: an arginine substitution at position 257 or a 13-base pair deletion in exon 8. Specific mutations in the AIRE gene have been observed in certain populations, including the R257X mutation in Finnish patients, the 1094-1106del13 deletion in British, Irish, Norwegian, and North American patients, and the Y85C missense mutation in Iranian Jewish patients. However, clear correlations between specific AIRE mutations and patient clinical outcomes remain unclear.[5,6]

Chronic Mucocutaneous Candidiasis (CMC) usually manifests early in life, typically between 3 and 5, and is the most common of the three main diseases associated with APS-1. It affects the nails, skin, and mucous membranes of the oral cavity, vagina, and esophagus. In some instances, CMC can lead to severe complications like esophagitis, oesophagal stricture, retrosternal pain, and dysphagia. In this particular case, the patient presented with symptoms of oral mucocutaneous candidiasis, dysphagia, and dysarthria. Initiating nystatin treatment significantly improved the symptoms, underscoring the efficacy of antifungal therapy in treating oral manifestations of APS-1. Patients with APECED face a heightened risk of developing oral cancer at a younger age, even without traditional risk factors. A Finnish study found a significant incidence of squamous cell carcinoma in these patients.[3,7] Additionally, enamel defects, such as grooves or pits, primarily in permanent teeth, are a significant oral manifestation of APECED. Patients with APS-1 often suffer from poor oral health, including increased dental caries, enamel erosion, and periodontal disease. Medication side effects and difficulties in maintaining oral hygiene due to enamel defects and persistent oral candidiasis can worsen these issues.[7]

Autoimmune polyendocrine syndrome type 1 (APS-1), also known as APECED (Autoimmune

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polyendocrinopathy-candidiasis-ectodermal dystrophy), MEDAC (multiple endocrine deficiency autoimmune candidiasis syndrome), juvenile autoimmune polyendocrinopathy, or Whitaker syndrome, is a very rare autosomal recessive genetic condition that causes multiple organs to become autoimmunized. It is usually found in early childhood. In clinical terms, APS-1 is when at least two of the classic triad conditions are present at the same time. These are hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis. Additionally, it may encompass immunological disorders unrelated to the endocrine system.[8]

Mutations in the autoimmune regulator (AIRE) gene on the short arm of chromosome 21 cause Autoimmune Polyglandular Syndrome Type 1 (APS-1). This gene is crucial for producing the 'autoimmune regulator' protein, predominantly expressed in the thymus gland, which plays a vital role in developing thymus-derived T lymphocytes. T-cells can interact with self-antigens and escape into circulation instead of being destroyed in the thymus due to a deficiency in this protein. This escape can lead to autoimmunities, often affecting the endocrine glands. Researchers have acknowledged four core classifications of APS, with each category exhibiting a unique set of autoimmune endocrine abnormalities. APS-1 is characterized by chronic mucocutaneous candidiasis, primary hypoparathyroidism, and autoimmune adrenal insufficiency. Relatives of a patient can establish the diagnosis of APS-1 in the presence of any of these diseases. In type 2 autoimmune polyendocrine syndrome (APS), autoimmune adrenal insufficiency is present along with concurrent autoimmune thyroid illness and/or type 1 diabetes mellitus. The coexistence of autoimmune thyroid disease and other autoimmune disorders characterizes type 3 autoimmune polyglandular syndrome (APS). However, it is important to note that this classification specifically excludes chronic candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency. Type 4 (APS) refers to instances where individuals present with two or more autoimmune disorders specific to certain organs but do not satisfy the requirements for Types 1, 2, or 3 APS.[8]

This case report details a 27-year-old man born from a consanguineous marriage with a medical history including alopecia, intellectual disability, epilepsy, hypothyroidism, type 1 diabetes, and dilated cardiomyopathy, starting at age 7. His chief complaints upon presentation were dysarthria, dysphagia, and lethargy. A general examination revealed oral candidiasis, nail dystrophy in both upper and lower limbs, and alopecia. The tests showed that the person had anemia (hemoglobin 2.7 g/dl), low calcium levels (5.3 mg/dl), low parathyroid levels (PTH 3.0 pg/ml), and calcifications on both sides of the white matter in the frontal, parietal, temporal, and basal ganglia. Together with the mucocutaneous candidiasis and hypoparathyroidism found, these results led to the diagnosis of Autoimmune Polyendocrine Syndrome Type 1 (APS-1). This case is unique in its combination of multiple autoimmune and endocrine issues. Despite his conditions, the patient wasn't severely ill until the development of dysarthria and dysphagia, which prompted a visit to a local physician and subsequent referral to the reporting institute.

In our case, the patient has presented with seizures since age 7, and the most notable finding was an MRI showing the presence of bilateral basal ganglia/thalamic calcification. Fahr syndrome is a rare neurological disorder characterized by the deposition of calcium compounds in the basal ganglia, thalamus, dentate nucleus, hippocampus, cerebral cortex, and cerebellar subcortical white matter. The calcium deposits are usually calcium carbonate and calcium phosphate. The exact etiology of the disease is not known but is usually associated with endocrine-affecting calcium homeostasis, mitochondrial myopathies, dermatological abnormalities, and infectious diseases. A prevalent clinical presentation of Fahr syndrome is seizures. Patients also present with other neurological symptoms of the extrapyramidal system, neuropsychiatric abnormalities, and movement disorders like Parkinsonism, tremors, and chorea.

CONCLUSION

In conclusion, this case highlights the intricate interplay between autoimmune disorders and their potential cardiac complications. Polyglandular Syndrome Type 1, in conjunction with dilated cardiomyopathy, poses a complex medical challenge. The comprehensive management of such cases necessitates a multidisciplinary approach, integrating endocrinological and cardiological expertise. Ongoing research and clinical insights will be pivotal in refining therapeutic strategies and enhancing the overall prognosis for individuals with this rare and intricate syndrome

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