Case Report

Hypoadrenalism as the Single Presentation of Autoimmune Polyglandular Syndrome Type 1

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Abstract

Type 1 autoimmune polyglandular syndrome (APS1) is a rare hereditary disease affecting nearly 600 patients worldwide. The first of its cardinal manifestations, chronic mucocutaneous candidiasis, hypoparathyroidism, or Addison’s disease, presents in childhood. Additional nonclassical landmarks of APS1 continue to develop as late as the fifth decade of life. Two thirds of patients develop the full triad before 25 years of age. Only 20% of patients develop the entire triad simultaneously. Addison’s disease is rarely reported as the first manifestation. According to APS1 classifications, restricted criteria for a single cardinal component, although elements of suspicion are not sufficient to diagnose APS1. This case report is peculiar as hypoadrenalism was the first and only manifestation of APS1 for nearly 3 decades since its diagnosis. Theoretically, exceptions from the protocol of APS1 diagnostic criteria would be recognized as acceptable for diagnosis in the future, when similar case reports of only 1 component of APS1 appear.

Key Words: Addison’s disease, AIRE1 gene, APS1, autoimmune polyendocrinopathy, hypoparathyroidism

Schmidt described chronic mucocutaneous candidiasis (CMC) associated with hypoparathyroidism (HPT) in 1926 [1]. Thereafter, in 1946, a triad composed of these 2 conditions together with autoimmune adrenal insufficiency, namely Addison’s disease (AD), was termed autoimmune polyglandular syndrome (APS) [2].

In 1981, Neufeld proposed the classification of APS into 3 types, namely, APS1, APS2, and APS3, where APS1 is characterized by at least 2 components of the triad HPT, CMC, and AD [3]. It is also called autoimmune polyendocrinopathy candidiasis ectodermal dystrophy [4,5].

APS2 is common beyond childhood and is characterized by CMC and AD, together with minor components, such as autoimmune thyroiditis and/or insulin-dependent diabetes mellitus, but without HPT [6]. APS3 is compliant with APS2; however, CMC is the sole major manifestation, combined with minor features.

Husebye broadly categorized APS1 as a rare mononucleotide monogenic mutation, compared with the more common APS2, which is polygenic and characterized by severe morbidity [7].

The most frequent first component of APS1 to manifest is CMC, which presents in early childhood. HPT is the first
endocrine manifestation of APS1 [8], and to the best of our knowledge, AD has not been the first component to manifest among cardinal and minor landmarks of APS1.

While only 20% of APS1 patients manifest with all 3 components of the triad simultaneously, nearly 70% of patients develop the complete triad before 25 years of age [9]. Other components of APS1 continue to develop as late as the fifth decade of life.

Long intervals between cardinal components and late presentations of atypical features of APS1 may contribute to delayed diagnosis [9,10]. Unexplained deaths in siblings of patients with APS1 are possibly due to overdue diagnosis and indicate the need to closely monitor APS1 patients and their siblings.

The rarity of APS1, variable spectrum of the clinical and laboratory findings, and manifestation of minor features, such as acute autoimmune hepatic failure, alopecia, nephritis, and thyroiditis [6], emphasizes the central role of practitioners, including dermatologists, gastroenterologists, endocrinologists, and gynecologists, in catching these cases and requires the clinician to mindfully ponder the scattered cases and obtain the family genetic background.

Herein, we report a patient with primary AD, as a single and unique classical feature for more than 27 years since the diagnosis. It is one of the first case reports of an APS1 patient with only 1 classical feature, which is a phenotype of a single-nucleotide missense mutation in the \(AIRE1\) gene.

**Case Presentation**

A 12-year-old male, who had a normal birth and early development, was admitted to the emergency department of a regional hospital because of diarrhea, vomiting, weakness, and nausea, while conscious. Ten days of constant headache with abdominal pain preceded 5 days of diarrhea and vomiting until referral to the hospital. This was the first bout of these complaints.

**Investigation**

Upon admission, the patient was pale and had no dyspnea. The teeth and nails were normally developed. The mucosa and palm streaks were free of hyperpigmentation. The skin turgor was poor with no neck stiffness. The abdomen, heart, lungs, and tendon reflexes were normal. Vital signs and laboratory findings are shown in Tables 1 and 2, respectively. Within hours, the patient gradually dropped into a coma and transitioned to the pediatric intensive care unit. Twenty minutes later, the metabolic laboratory panel revealed that the serum sodium level decreased from 132 to 117 mEq/L.

**Table 1.** Vital signs and routine laboratory findings, preadmission, during hospitalization, and postadmission

| Laboratory and clinical findings (normal range) | Preadmission | Admission | Deterioration | Treatment | Discharge |
|-----------------------------------------------|--------------|-----------|--------------|-----------|-----------|
| Vital signs                                   |              |           |              |           |           |
| Systolic BP, mmHg                             | 110          | 80        | 68           | 108       | 111       |
| Diastolic BP, mmHg                            | 72           | 50        | 53           | 67        | 65        |
| Heart rate, beats/min                         | 88           | 98        | 132          | 100       |           |
| Respiratory rate/min                          | ND           | 16        | 23           | 22        |           |
| Height, cm                                    |              |           |              | 183       | 75.5      |
| Weight, kg                                    |              |           |              |           |           |
| Laboratory                                    |              |           |              |           |           |
| Sodium, mEq/L (135-145)                       | ND           | 132       | 117          | 137       | 137       |
| Potassium, mEq/L (3.5-5.)                     | 4.6          | 5         | 4.4          | 4.6       | 4.6       |
| Chloride, mEq/L (96-106)                      | ND           | 99        | 99           | 101       |           |
| HCO\(_3\), mEq/L (22.1-28.3)                  | ND           | 21        | 21           |           |           |
| Calcium, mEq/L (8.6-11)                       | 4.8          | 4.3       | 4.6          | 4.3       |           |
| Phosphorus, mEq/L (2.5-5)                     | 11           | ND        |              |           |           |
| WBC, K/microL (4.5-11)                        |              |           |              | 8.4       |           |
| Hemoglobin, g/dL (13-17)                      |              |           |              | 15        |           |
| Platelets, K/microL (150-450)                 |              |           |              | 247       |           |
| Glucose, mg/dL (65-99)                        |              |           |              | 65        | 67        |
| Blood urea, mg/dL (7-20)                      |              |           |              | 24        |           |
| Creatinine, mg/dL (0.5-1.2)                   |              |           |              | 1.6       | 0.8       |
| Magnesium, mg/dL (1.7-2.2)                    |              |           |              | 1.9       |           |
| EKG                                           |              |           |              | Normal    |           |

Data show the increase in serum potassium concentration, although slight; the evident decrease of serum sodium and blood pressure; and the increase in heart rate during the clinical deterioration period.

Abbreviations: BP, blood pressure; EKG, electrocardiogram; ND, not detected; WBC, white blood cells.
Table 2. Laboratory tests and clinical investigation findings for the various type 1 autoimmune polyglandular syndrome components

| APS1 component/related organ function (reference range) | Examination results at specific ages, years |
|--------------------------------------------------------|---------------------------------------------|
|                                                       | 9  | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 38 |
| Chronic mucocutaneous candidiasis and teeth            |    |    |    |    |    |    |    |    |    |
| Keratitis/cataracta                                    |    |    |    |    |    |    |    |    |    |
| Enamel hypoplasia                                      |    |    |    |    |    |    |    |    |    |
| Alopecia                                               |    |    |    |    |    |    |    |    |    |
| Nail candidiasis                                       |    |    |    |    |    |    |    |    |    |
| Anti-interferon antibodies testa                       |    |    |    |    |    |    |    |    |    |
| Hypoparathyroidism                                     |    |    |    |    |    |    |    |    |    |
| PTH, pg/mL (10-60)                                     |    |    |    | 89 |    |    |    |    | 37.7 |
| Vitamin D (25-OH) nmol/L (75-125)                      |    |    | 132 |    |    |    |    |    | 50.5 |
| Calcium serum pg/mL (8.6-10.8)                         | 9.4 | 9.4 | 9.8 | 9.7 | 9 | 8.7 | 9 | 7.9 | 9.1 |
| Calcium ionized pg/mL (4.4-5.2)                        |    |    | 4.8 |    |    |    |    |    | 5 |
| Phosphorus pg/mL (3.4-4.5)                             | 4.9 | 5.4 | 6 | 4.9 | 5 | 5 | 4 | 5 | 4.3 |
| 24-h (normal-diet) urine calcium mg/day (100-300)       | 182 |    |    |    |    |    |    |    | 220 |
| Anti-interferon antibodies testa                        |    |    |    |    |    |    |    |    | Unavailable |
| Carpal/pedal tetany ± tingling extremities             |    |    |    |    |    |    |    |    | None |
| Autoimmune adrenalitis (Addison's disease)             |    |    |    |    |    |    |    |    |    |
| Antiadrenal-cortex autoantibodies b                    |    |    |    |    |    |    |    |    | Highly positive |
| Cortisol, nmol/L (138-635)                             | 163 |    | 401 | 725 | 72 | 486 | 28 | 111 | 27.6 |
| Sodium, mEq/L (135–145)                                | 136 | 135 | 128 |    |    |    |    |    | 135 |
| Potassium mEq/L (3.5-5.5)                              |    |    |    |    |    |    |    |    | 4.6 |
| ACTH stimulation test and renin activity d             |    |    |    |    |    |    |    |    | Not performed |
| EKG                                                    |    |    |    |    |    |    |    |    | Normal |
| Diabetes mellitus                                      |    |    |    |    |    |    |    |    |    |
| Glucose, mg/dL (60-100)                                | 77  | 81  | 73  | 81  | 89 | 69 | 77 | 90 | 80 |
| HgA1c% (5.7-6.5)                                       |    |    |    |    |    |    | 5.7 |    | 5.5 |
| Autoimmune liver disease                              |    |    |    |    |    |    |    |    |    |
| Direct bilirubin, mg/dL (0.1-0.3)                       | 0.17 |    | 0.2 | 0.2 | 0.1 | 0.1 | 0.2 | 0.2 | 0.2 |
| GPT, U/L (7-35)                                        | 16  | 18  | 26  | 39 | 26 | 16 | 27 | 22 | 22 |
| GOT, U/L (5-40)                                       | 19  | 17  | 16  | 32 | 23 | 16 | 35 | 16 |    |
| Alkaline phosphatase, IU/L (40-147)                    | 66  | 80  | 77 |    |    |    |    |    | 73 |
| GGTT, U/L (9-48)                                      | 16  | 19  | 40 |    |    | 27 | 23 | 22 |    |
| CPK U/L (26-308)                                      | 71  | 52  | 70 | 388 | 99 | 118 | 131 |    |    |
| INR, (<1.1)                                           | 1.1 | 1.1 | 1.0 | 1.1 | 1.0 | 1.0 | 1.1 |    |    |
| Thyroiditis                                            |    |    |    |    |    |    |    |    |    |
| TSH, mU/L (0.5-5.8)                                    | 2.3 | 0.9 | 1.6 | 2.1 | 1 | 1.1 | 1.6 |    |    |
| FT4, mcg/dL (5-12)                                     | 17  | 15.8 | 16 | 23 | 16 | 18 | 15 |    |    |
| FT3 mcg/dL (5-12)                                     | 3.2 | 5.6 | 7.1 | 5.6 | 4 |    | 2.2 |    |    |
| Antithyroid-peroxidase, KIU/L (28-59.9)                 | 31  |    |    |    |    |    |    |    | 60 |
| Thyroglobulin antibodies, IU/mL (<20)                  |    |    |    |    |    |    |    |    | <20 |
| Iodine in urine, mcg/L (100-200)                       |    |    |    |    |    |    |    |    | 172 |
| US thyroid gland                                       |    |    |    |    |    |    |    |    | Normal |
| Anti-interferon antibodies testa                       |    |    |    |    |    |    |    |    | Test unavailable |
| Nephritis                                              |    |    |    |    |    |    |    |    |    |
| cGFR, mL/min/1.73 m² (90-130)                           | 0.83 |    | 0.8 | 0.8 |    |    |    | 118 | 112 |
| Cr, mg/dL (0.5-1.2)                                    |    |    |    |    |    |    |    | 0.9 |    |
| Microalbumin/Cr, mg/dL (<30)                           |    |    |    |    |    |    |    | 0.9 |    |

Note: All data are presented as mean values unless specified otherwise.
Intravenous glucose and sodium failed to restore consciousness. In the late evening, the patient’s parents informed his primary care physician, who urgently called the head of the children’s department to inform that there were other relatives of the patient who suffered from APS1, featured by Addison’s crisis as a component of their APS1. Consequently, intravenous injection of 100 mg hydrocortisone was initiated. A profound and rapid clinical improvement was observed. His serum sodium level rose to normal levels (144 mEq/L) after sunrise.

After recovery from coma, blood pressure measurements were below the median for age (systolic 96-110 mmHg, diastolic 60-71 mmHg), despite continued high sodium intake during the hospital stay. After recovery from coma, blood pressure measurements were below the median for age (systolic 96-110 mmHg, diastolic 60-71 mmHg), despite continued high sodium intake during the hospital stay.

Oral hydrocortisone was then initiated at 10 mg every 6 h, and the dose was gradually decreased to 10 mg once daily, with dose adjustment according to concurrent illnesses and stresses. Oral fludrocortisone acetate was initiated according to the serum sodium and potassium levels.

Outcome and Follow-up

After discharge from the hospital, the diagnosis of primary autoimmune adrenalitis was confirmed twice using enzyme-linked immunosorbent assay. The test’s positive control number was C017N/C017N-0.5, the negative universal control number was C000N/CO00N-0.5, the buffer pack number was RO02, and the mounting medium number was RO05. The results showed highly positive (4+) fluorescence of the antiadrenal autoantibodies.

In 2017, the Sanger sequencing method for DNA analysis of APS1-suspected candidates was approved for use by the Israeli Ministry of Health. At the age of 37 years, the patient was the first of his extended family group of patients who underwent Sanger sequencing and was homozygous for the mutation c.47C > T (p.Thr16Met) in exon 1 of the AIRE1 gene (ABI 3500 Genetic Analyzer, Applied Biosystems, Warrington, UK; deposited as c.47C > T p.Thr16Met AIRE gene position: NM 000383.3. Genome Browser assembly ID: hg38; http://genome.ucsc.edu).

At the time of this report, the patient was 39 years old; however, HPT has not been reported to date. Serum calcium and 24-h urinary calcium levels remained within normal ranges. The latest 25-OH vitamin D low levels could be attributed to the recent COVID-19 and to the delta variant epidemics, which resulted in less sun exposure. There were no episodes of carpal tetany or arrhythmia. The patient’s corneas were intact, vision was normal, and the nails were smooth, with no clubbing or infection by Candida, thus ruling out mucocutaneous disease as a major manifestation. Nonstimulated cortisol plasma levels were below the lower limit in most of the results during hydrocortisone treatment (Tables 1 and 2). Anti-interferon antibody measurement, although important for revealing other components of APS1 [11], is not available in Israel.
The remaining signs and symptoms of APS1 were ruled out one by one using various laboratory tests. The patient was fertile and reproduced; his physical development was satisfactory and, as mentioned, was under treatment with cortisol.

As shown in Table 2, renin activity and adrenocorticotropicin level were not measured during the adrenal crisis, although tests are important for diagnosing primary adrenal insufficiency, especially when both elevated serum renin levels and low aldosterone levels, concomitant with increased adrenocorticotropicin and decreased cortisol [12].

Although adrenal mineralocorticoid failure stimulates the renin release, appropriate mineralocorticoid production remains crucial in preventing electrolyte depletion. So, in severe adrenal failure (ie, in Addison’s crisis), the homeostatic role of renin-angiotensin system may be impaired, even when an appropriate renin response to aldosterone deficiency occurs [12]. As a result, a decreased secretion of potassium in urine causes a life-threatening hyperkalemia. The urinary sodium wasting is a variable feature of the mineralocorticoid failure [12]; hence, the absolute indication for treatment with fludrocortisone is hyperkalemia, not hypernatremia, although severe hyponatremia, in itself, is an important signal for the diagnosis of AD, as in this case.

Fludrocortisone treatment was started 3 days after the adrenal crisis, with serum potassium level rising to 5.0 mEq/L, and hyponatremia of 133 mEq/L, and it was discontinued after 2 years because of stabilized serum electrolytes. (Table 2). Fludrocortisone treatment was started again on 2 more occasions, when asymptomatic hyperkalemia accompanied with slight hyponatremia had appeared. Treatment was stopped after 2 months, when equilibrium has been retained.

Subsequently, the same mutation was detected in 2 other members of the extended family, a 21-year-old and 53-year-old, both manifesting with CMC, HPT, AD, chronic keratitis, and total alopecia. Severe autoimmune hepatic failure was reported in 1 patient, a member of the same family, who suffered from CMC, HPT, and AD. Eight sisters and 4 brothers of the 3 homozygous patients were found to be heterozygous; the remaining extended family members were mutation-free. Six affected patients from the same family rejected an offer to get tested for mutations.

Currently, AD is the only component of APS1 that the patient presents.

**Discussion**

The course of the patient’s acute illness, increment in blood pressure readings despite high sodium intake during the hospital stay, and rapid recovery after administering hydrocortisone suggested acute primary adrenal insufficiency. The anamnesis of a familial medical history of APS1, in parallel, has further suggested APS1 as the current clinical diagnosis.

Even though the sequence of appearance of the classic features of APS1 is important in the clinical diagnosis of the syndrome, the appearance of AD as the first manifestation in our case was unexpectedly different from the conventional. This fact strengthens the idea that diagnosis of APS1 should be considered in all patients who present with 1 of the classic clinical manifestations [13].

The absence of additional disease features to reach a full triad before 25 years of age [9] makes this case report a rare presentation of APS1. Indeed, laboratory tests performed through the patient’s lifespan do not support the presence of additional, undetected major or minor features of APS1 [6,14,15]. Early diagnosis of APS1, despite relying on only a major component of the triad, may allow a close monitoring of the patient and prevent further complications of the syndrome such as adrenal crisis or acute hypocalcemia (Table 2). This case report highlights the following points: (1) hypoadrenalism has been the first and unique manifestation for about 3 decades; (2) the diagnosis was inferred in exceptional circumstances: a simple episode of gastroenteritis had deteriorated to a dangerous hyponatremia, which culminated in a deep coma; (3) availability of data pertaining to other APS1 cases in the family’s pedigree and, thereafter, beneficial glucocorticoid institution was lifesaving; (4) the genetic study, performed later at 37 years of age, confirmed it as a real monogenic APS1; and (5) the presence of AD has been proven using extensive periodical workup, which led us to unequivocally rule out other asymptomatic signs of the syndrome.

**Conclusion**

Although the sequence of appearance of the classic features of APS1 is important in the clinical diagnosis of the syndrome, the appearance of AD as the first manifestation in our case was unexpectedly different from the conventional. This fact strengthens the idea that diagnosis of APS1 should be considered in all patients who present with one of the classic clinical manifestations.

The absence of additional disease features to reach a full triad before 25 years of age makes this case report a rare presentation of APS1, imposing a special clinical challenge.

**Learning Points**

- Our case, in which Addison’s disease was the first manifestation to appear, suggests that the sequence of appearance of major manifestations may be widely heterogeneous and sometimes unusual.
- Diagnosis of type 1 autoimmune polyglandular syndrome (APS1) should be considered in every patient presenting with 1 of the classic clinical manifestations.
• In a patient who suffers from APS1, the presence of a single major component calls for a lifespan workup to identify other landmarks of the syndrome.
• Cooperation among community clinicians and in-hospital practice is important for exchanging key data in unusual clinical situations.
• In an unresponsive onset of a metabolic presentation, seeking family history is advised.

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Author Contributions
N.H.N, the named physician of the patient who drafted this article, critically revised it after the reviewers’ comments, wrote the rebuttal to the reviewers, and provided final approval for the publication of this version. N.G.S. performed the genetic study of the case, reviewed the manuscript, and made essential amendments. D.D.N. actively revisited this article, critically reviewing its composition and referencing.

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Patient Consent
Written informed consent was obtained from the patient for publication of the submitted article and the accompanying images.

Patient’s Perspective
Genetic testing has become a part of my family’s lives. Identifying the genetic basis of my disease has enabled my family members to undergo mutation carrier testing as a preventive measure.

Additional Information
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