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Polyglandular autoimmune syndrome type I – a novel AIRE mutation in a North American patient

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Abstract

Autoimmune polyglandular syndrome type 1 (APS-1), also referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare autoimmune disease that results from autosomal recessive mutations of the human autoimmune regulatory (AIRE) gene. We present the case of a 17-year-old North American girl of primarily Norwegian descent with a novel AIRE gene mutation causing APS-1. In addition to the classic triad of chronic candidiasis, hypoparathyoidism and autoimmune adrenocortical insufficiency, she also has vitiligo, intestinal malabsorption, autoimmune hepatitis, autoimmune hypothyroidism, myositis, myalgias, chronic fatigue, and failure to thrive. Genetic testing revealed heterozygosity for c. 20_115de196 and c.967_979del13 mutations in the AIRE gene. The AIRE gene c.20_115de196 mutation has not been previously reported.

Keywords

AIRE gene; autoimmune polyglandular syndrome; mucocutaneous candidiasis

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Introduction

Autoimmune polyglandular syndrome type 1 (APS-1), also referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare autoimmune disease that results from autosomal recessive mutations of the human autoimmune regulatory (AIRE) gene. The syndrome is characterized by at least two of the following major criteria: chronic mucocutaneous candidiasis, autoimmune adrenocortical insufficiency (Addison's disease), and hypoparathyroidism (1). Other APS-1 autoimmune diseases include gonadal failure, type 1A diabetes mellitus, hypothyroidism, alopecia, vitiligo, pernicious anemia, chronic diarrhea, autoimmune hepatitis, and keratoconjunctivitis (2). We present the case of a 17-year-old North American girl of primarily Norwegian and German descent with a novel AIRE gene mutation causing APS-1.

Case

A child born to nonconsanguineous parents of primarily Norwegian and German heritage (Table 1) presented at age 3½ years with hypocalcemic seizures secondary to hypoparathyroidism. She had a history of chronic recurrent oral candidiasis and a family history significant for rheumatoid arthritis, hypothyroidism, and acromegaly (Table 2). Her hypoparathyroidism was initially well controlled by calcium, 1,25-dihydroxyvitamin D (calcitriol) supplementation and a strict low phosphorous diet. Initial cellular immune system workup showed normal T-cell proliferation studies. One year later, an adrenal antibody panel was positive, but adrenocorticotropic (ACTH) and cortisol levels in response to provocative low dose ACTH testing were normal. Antithyroid (antithyroid peroxidase and antithyroglobulin), antiparietal, cell, antimitochondrial, and anti-islet cell antibodies were all negative. At age 7 years, she developed extensive vitiligo and intestinal malabsorption with daily foul-smelling diarrhea. The malabsorption was initially attributed to exocrine pancreatic insufficiency and was treated with pancreatic enzyme replacement. A few months later, she was hospitalized for abdominal pain, lethargy, anal spasms, hypocalcemia and hyperphosphatemia. At that time, she had a normal ultrasound of the kidneys and bladder with no renal calculi identified. Her liver enzymes were elevated, but she did not have chronic active hepatitis. Because malabsorption prevented absorption of calcitriol and calcium supplementation, she was enrolled in a National Institutes of Health (NIH) study at age 7 to receive synthetic human parathyroid hormone 1–34 (PTH) replacement therapy.

At age 10 years, she had elevated hepatic enzymes, and a liver biopsy was consistent with mild autoimmune hepatitis. Concurrently, her malabsorption had worsened, and she had failure to thrive with a weight at approximately the 3rd percentile. At age 11, she was diagnosed with adrenal insufficiency, which was treated with daily replacement of glucocorticoids and mineralocorticoids. At age 15, she developed a bilateral fine action tremor, muscle weakness, myalgias, and fatigue.

Repeat liver biopsy at age 16, revealed prominent plasma cells and interface hepatitis consistent with autoimmune hepatitis, which had worsened from previous biopsy. She also had positive antinuclear antibody (ANA) titers at this time. Azathioprine therapy was begun to prevent disease progression. Hashimoto thyroiditis was diagnosed and treated with daily

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levothyroxine. A 6-kg weight loss occurred following a 1-month history of severe diarrhea and intestinal malabsorption. The gastrointestinal workup was unremarkable with negative upper endoscopy and colonoscopy, and negative esophageal, gastric, duodenal, colon and rectal biopsies. She was negative for bacterial overgrowth and immunoglobulin A deficiency, as well as antibodies for celiac disease (tissue transglutaminase) and irritable bowel disease (antineutrophilic cytoplasmic antibody screen and anti-Saccharomyces cerevisiae antibodies). A percutaneous endoscopic gastrostomy tube was inserted to treat the persistently inadequate oral intake and ongoing weight loss.

AIRE gene testing revealed heterozygosity for two AIRE mutations, one common and one previously undescribed. The mutations were denoted c.967_979del13 and c.20_115de196 at the cDNA level of the AIRE gene. The first mutation is a common mutation that has previously been reported in association with APS-1 (3). The second mutation is a novel mutation that is a large deletion of 96 nucleotides in exon 1. The normal sequence with the bases that are deleted in brackets is: GGCGC{de196}CCGAG. At the protein level, this mutation is denoted p.Leu7_Val38del.

Discussion

Autoimmune polyglandular syndrome type 1

APS-1 is characterized by at least two of the following major criteria: chronic mucocutaneous candidiasis, autoimmune adrenocortical insufficiency (Addison's disease), and hypoparathyroidism (1). In addition to the three major criteria, our patient also has vitiligo, intestinal malabsorption, autoimmune hepatitis, autoimmune hypothyroidism, myositis, myalgias, chronic fatigue, and failure to thrive. As in our patient, the most common initial manifestation is typically chronic mucocutaneous candidiasis – a recurring fungal infection of the mucosal surfaces, skin and nails – that generally presents in infancy. This is typically followed by hypoparathyroidism, often in the early childhood years, and/or Addison's disease, predominately in teens or young adults (4, 5). The syndrome is most prevalent in Finnish, Italian, Sardinian, and Iranian Jewish populations (6–8).

The AIRE gene

The AIRE gene is located on chromosome 21q22.3, is primarily expressed in thymic medullary epithelial cells, with lesser amounts in lymph nodes and tonsils, and controls induction and maintenance of immune tolerance to self-antigens (9, 10). T-cells originate in the bone marrow and migrate to the thymus to develop and mature (11). Random somatic gene rearrangement generates T-cells with receptors that recognize a range of antigens. In the thymus cortex, only T-cell receptors that have sufficient affinity for major histocompatibility (MHC)-restricted self-antigens are activated and survive to pass to the thymic medulla. In the medulla, T-cell receptors encounter MHC-restricted self-antigens, and T-cells with excess affinity for self-antigens are deleted by negative selection. The process of positive selection followed by negative selection produces circulating T-cells able to appropriately distinguish between self and nonself antigens. The AIRE gene prevents autoimmunity by regulating this negative selection of autoreactive T-cells (12). AIRE gene mutations can also promote anti-interferon-ω and -α antibodies, detection of which can aid

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in the diagnosis of APS-1 (5). The functionality of these antibodies is unclear, however, as patients with APS-1 do not have increased susceptibility to viral infections as would be expected with interference of interferon activity.

The wild-type AIRE gene consists of 14 exons and encodes a transcription regulator of 545 amino acids with a molecular weight of approximately 58 kDa (13). Over 60 mutations in the AIRE gene have been reported (9). AIRE gene mutations are almost exclusively autosomal recessive, although an autosomal dominant mutation has been reported in animal models (10). Most mutations of the AIRE gene that have been associated with APS-1 are located in exons 6, 8, and 10, and cause transcription of a truncated protein (14). The two most common mutations are a nonsense mutation in exon 6 (R257X, “Finnish major mutation”) and a 13 base-pair deletion (967-979del13bp) in exon 8. Our patient, of predominately Norwegian ancestry, was found to be heterozygous for both a known c. 967_979del13 mutation (15) and a c.20_115de196 mutation in the AIRE gene. To our knowledge, c.20_115de196 is a novel mutation that has not been reported as a disease-causing mutation or as a benign polymorphism. This large deletion causes 32 normal amino acids to be removed from the protein and is predicted to cause loss of normal protein function through protein truncation. The normal sequence with the bases that are deleted in brackets is GGCGC{de196}CCGAG. At the protein level, this mutation is denoted p.Leu7_Val38del. In this patient, the presence of an *AIRE* gene mutation on each allele is consistent with the diagnosis of APS-1. The large size of her novel mutation may correlate with the severity and extent of her disease, when compared to patients homozygous for the 967-979del13bp mutation (16).

Correlation between genotype and phenotype

APS-1 is typically an autosomal recessive disease. Individuals can be homozygous for an identical mutation of each AIRE allele, or as is the case in our patient, possess different AIRE allele mutations leading to compound heterozygosity and decreased AIRE protein activity. Previous reports have demonstrated associations between genotypic mutations and resultant phenotypes. For example, due to different AIRE gene mutations, candidiasis is prevalent in Finnish patients with APS-1 but rare in Iranian Jews with APS-1 (6). In the case of this patient, it is expected that her constellation of diseases is related to her particular genotype, and her novel c.20_115de196 mutation is of interest as we clarify patterns of expected phenotypic expression in individuals of given genotypes.

Care of patients and families with APS-1

Unfortunately, there is a paucity of evidence-based clinical recommendations for treatment of APS-1. The majority of treatment guidelines available in the literature are based on personal experience. In our experience, pediatric patients with APS-1 should be followed closely by a specialist in pediatric endocrinology and seen frequently with laboratory reassessment to evaluate dosing of hormone replacement and evaluate for development of additional autoimmune conditions. The inclusion of regular screening for autoantibodies can help identify higher risk for development of additional autoimmune diseases (1). Between visits, monitoring of serum calcium levels should be done at least monthly if significant malabsorption is present or if the patient is receiving injectable PTH. Patients and their

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families should be educated regarding symptoms and sick day management of adrenal insufficiency and hypoparathyroidism.

Although immune therapies, such as vaccines, are being studied for autoimmune endocrine disease, hormone replacement and symptom management are currently the only therapeutic options in treatment of endocrine disease (17, 18). Mucocutaneous candidiasis has been associated with esophageal strictures or squamous cell carcinoma of the oral mucosa in patients with APS-1, and should be treated aggressively.

Isolated case reports have described the use of immunosuppressive agents to treat autoimmune manifestations of APS-1. Treatment with cyclosporine has resulted in symptomatic improvement of keratoconjunctivitis, intestinal malabsorption, and alopecia in one adolescent patient (19). Malabsorption has also been successfully treated with methylprednisolone and methotrexate (20). Standard therapy for autoimmune hepatitis is a combination of corticosteroids and azathioprine (21). This case highlights the need for further studies of the role of immunosuppressive agents in treatment of APS-1, as our patient's symptoms persisted despite the use of azathioprine.

When a diagnosis of APS-1 is made, first-degree relatives should be offered screening for APS-1 by genotyping or anti-interferon-ω antibodies. Interestingly, one study indicated up to half of heterozygous family members displayed autoimmune disorders, such as hypothyroidism, vasculitis, polycythemia vera, and rheumatoid arthritis (7).

Conclusion

APS-1 is characterized by chronic mucocandidiasis, hypoparathyroidism, adrenal insufficiency and severe chronic malabsorption due to mutations of the AIRE gene. We describe a 17-year-old patient with manifestations of APS-1 and a previously unreported c. 20_115de196 disease-causing AIRE gene mutation that includes a large deletion in the AIRE gene. Description of this novel genotypic variant adds to the body of knowledge regarding this rare disease and provides insight into the phenotypic profile that may result in other patients.

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References

1. Perheentupa J. APS-I/APECED: the clinical disease and therapy. Endocrinol Metab Clin N Am. 2002; 31:295–320. vi.
2. Meloni A, Willcox N, Meager A, Atzeni M, Wolff AS, et al. Autoimmune polyendocrine syndrome type 1: an extensive longitudinal study in Sardinian patients. J Clin Endocrinol Metab. 2012; 97:1114–1124. [PubMed: 22344197]
3. Scott HS, Heino M, Peterson P, Mittaz L, Lalioti MD, et al. Common mutations in autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy patients of different origins. Mol Endocrinol. 1998; 12:112–119.

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4. Ahonen P, Myllärniemi S. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med. 1990; 322:1829–1836. [PubMed: 2348835]
5. Rosatelli MC, Meloni A, Meloni A, Devoto M, Cao A, et al. A common mutation in Sardinian autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients. Hum Genet. 1998; 103:428–434. [PubMed: 9856486]
6. Zlotogora J, Shapiro MS. 1992 Polyglandular autoimmune syndrome type I among Iranian Jews. J Med Genet. 1992; 29:824–826. [PubMed: 1453436]
7. Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. Nat Rev Endocrinol. 2010; 6:270–277. [PubMed: 20309000]
8. Eldershaw SA, Sansom DM, Narendran P. Expression and function of the autoimmune regulator (Aire) gene in non-thymic tissue. Clin Exp Immunol. 2011; 163:296–308. [PubMed: 21303359]
9. Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet. 1997; 17:399–403. [PubMed: 9398840]
10. Cihakova D, Trebusak K, Heino M, Fadeyev V, Tiulpakov A, et al. Novel AIRE mutations and P450 cytochrome autoantibodies in Central and Eastern European patients with APECED. Hum Mutat. 2001; 18:225–232. [PubMed: 11524733]
11. Akirav EM, Ruddle NH, Herold KC. The role of AIRE in human autoimmune disease. Nat Rev Endocrinol. 2011; 7:25–33. [PubMed: 21102544]
12. Anderson MS, Venazi ES, Chen Z, Berzins SP, Benoist C, et al. The cellular mechanism of Aire control of T cell tolerance. Immunity. 2005; 23:227–239. [PubMed: 16111640]
13. Vogel A, Strassburg CP, Obermayer-Straub P, Brabant G, Manns MP. The genetic background of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and its autoimmune disease components. J Mol Med (Berl). 2002; 80:201–211. [PubMed: 11976729]
14. Scott HS, Heino M, Lalioti MD, Betterle C, Cohen A, et al. Common mutations in autoimmune ectodermal dystrophy patients of different origins. Mol Endocrinol. 1998; 12:1112–1119. [PubMed: 9717837]
15. Ward L, Paquette J, Seidman E, Huot C, Alvarez F, et al. Severe autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy in an adolescent girl with a novel AIRE mutation: response to immunosuppressive therapy. J Clin Endocrinol Metab. 1999; 84:844–852. [PubMed: 10084559]
16. Pearce SH, Cheetham T, Imrie H, Vaidya B, Barnes ND, et al. A common and recurrent 13-bp deletion in the autoimmune regulator gene in British kindreds with autoimmune polyendocrinpathy type 1. Am J Hum Genet. 1998; 65:1675–1684. [PubMed: 9837820]
17. Padeh S, Theodor R, Jonas A, Passwell JH. Severe malabsorption in autoimmune dystrophy syndrome successfully treated with immunosuppression. Arch Dis Child. 1997:532–534. [PubMed: 9245854]
18. Vergani DM. Pharmacological management of autoimmune hepatitis. Expert opinion on pharmacotherapy. Arch Dis Child. 2011; 12:607–613.
19. Cervato S, Mariniello B, Lazzarotto F, Morlin L, Zanchetta R, et al. Evaluation of the autoimmune regulator (AIRE) gene mutations in a cohort of Italian patients with autoimmune-polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED) and in their relatives. Clin Endocrinol. 2009; 70:421–428.
20. Gentile NM, Murray JA, Pardi DS. Autoimmune enteropathy: a review and update of clinical management. Curr Gastroenterol Rep. 2012; 14:380–385. [PubMed: 22810979]
21. Padeh S, Theodor R, Jonas A, Passwell JH. Severe malabsorption in autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy syndrome successfully treated with immunosuppression. Arch Dis Child. 1997; 76:532–534. [PubMed: 9245854]

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Table 1

Patient ancestry.

Maternal grandfather	100% Norwegian
Maternal grandmother	50% German and 50% French
Paternal grandfather	100% Irish
Paternal grandmother	100% German

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Table 2

Family autoimmune medical history.

Rheumatoid arthritis	Mother, paternal grandmother, paternal aunt, maternal uncle, maternal great grandfather
Hypothyroidism	Mother
Acromegaly (from prolactinoma)	Maternal uncle