Late-onset autoimmune polyendocrine syndrome type 1: a case report and literature review

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Received: 14 November 2020 / Accepted: 7 February 2021 / Published online: 18 February 2021
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Abstract
Autoimmune polyendocrine syndrome type 1 (APS-1), also referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), a rare monogenic disorder, is classically characterized by a triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency. The identified causative gene is autoimmune regulator (AIRE), which encodes a critical transcription factor and is essential for self-tolerance. Here, we describe a late-onset Chinese case who presented with symptoms of persistent tetany due to hypocalcemia. Extensive clinical evaluations revealed that the patient manifested beyond the classic triad of the disease, and next-generation sequencing identified a known homozygous AIRE mutation (p.R139X). APS-1 is a rare inherited immunodeficiency disease with high clinical and genetic heterogeneity. By retrospectively analyzing the disease, we comprehensively reviewed the phenotypic features, summarized the genotype spectrum, and discussed the possible immunological mechanisms of the disease to enhance earlier recognition and implement targeted preventive and therapeutic strategies.

Keywords Autoimmune polyendocrine syndrome type 1 · APECED · Autoantibodies · AIRE · Mutation

Introduction
Autoimmune polyendocrine syndrome type 1 (APS-1), or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare and complex primary immunodeficiency disease [1, 2]. In 1929 Thorpe and Handley firstly described the association between hypoparathyroidism and chronic candidiasis [3]. In 1946 a classic triad of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and adrenal insufficiency was recognized [4]. According to different combinations of endocrinopathies and other non-endocrinial manifestations, Neufeld classified three types of APS in 1980 [5]. In 1994, a genetic link between APS-1 and genes located in 21q22.3 was identified, and subsequently the autoimmune regulator (AIRE) was confirmed as the causative gene [6, 7]. The overall prevalence of the disease is lower than 10/million population but a higher prevalence in historically isolated populations such as Iranian Jews (1/9,000), Sardinians (1/14,000), and Finns (1/25,000) and lower in Norwegians (1/80,000) and Poland (1/129,000), while scarce in East Asians [8–10]. Clinically, it is a highly variable disease manifested with autoimmunity primarily involved in endocrine organs (parathyroid, adrenals, thyroid, gonads, pituitary) and non-endocrine organs (skin, liver, kidney, lung, eye, intestine) [8, 11]. Genetically, APS-1 is a monogenic inherited disorder, which is typically autosomal recessive, while heterozygous dominant-negative variants have also been reported [12–14]. For a long time, clinical diagnosis has relied on the development of any two of the classic triad components or only one component if a sibling has already been diagnosed. In addition, a diversity of autoantibodies is also highly suggestive of APS-1 [15, 16]. Based on the spectrum of phenotypes related to AIRE mutations, APS-1 tend to exhibit either “classical” or “non-classical” type. Classical APS-1 is characterized by recessive inheritance and have at least two of the three main symptoms in childhood-onset and with high titer interferon (IFN) antibodies, while non-classical shows a dominant heterozygous mutation with a moderate, less penetrant
phenotype with relatively late-onset ag, and less IFN antibod-
ies [17]. However, with such a rarity and high variability, the
disease can be easily misdiagnosed or delayed. Herein, a late-
onset Chinese patient with a documented homozygous AIRE
mutation was described, and a detailed literature review of
APS-1 was made to summarize the clinical manifestations,
genetic spectrum, and the possible immunological pathogen-
esis to enhance the early recognition, shed light on the patho-
genic study, and improve the systematic prevention and ther-
apy for this disorder.

Materials and methods

Patient, exome sequencing, and data analysis

With written informed consent from the guardians, extensive-
ly clinical evaluation including laboratory test and brain im-
ageing were performed in a 42-year-old Chinese patient.
Genomic DNA was extracted from peripheral blood using
the standardized phenol/chloroform extraction protocol.
Exome sequencing was performed using Agilent SureSelect
v6 reagents for capturing exons and Illumina HiSeq X Ten
platform for sequencing. The variant was analyzed by the
following bioinformatics strategies: firstly, the synonymous
and intronic variants (splice sites not included) were excluded;
then, the variants were searched in the reference database:
1000 Genomes Project (http://www.internationalgenome.
org), dbSNP database (http://www.ncbi.nlm.nih.gov/
projects/SNP), the Exome Aggregation Consortium (http://
exac.broadinstitute.org/), and HGMD (http://www.hgmd.cf.
ac.uk/ac/index.php); and finally, Mutationtaster [http://www.
mutationtaster.org], PolyPhen-2 [http://genetics.bwh.harvard.
edu/pph2], and SIFT [http://sift.jcvi.org] were used to pre-
dict the pathogenicity of the nucleotide and amino acid
conservation. The pathogenic of the variant was interpreted
and classified following the American College of Medical
Genetics and Genomics (ACMG) Standards and Guidelines
[18]. Sanger sequence and segregation analysis were further
applied to confirm the genetic findings.

Results

Clinical data

A 42-year-old Chinese man from a nonconsanguineous family
(Fig. 1a) referred to our Neurology Intensive Care Unit with a
40-day history of repetitively intermittent tetany due to hypo-
calcemia. The symptom was relieved with antiepileptic and
calcium supplement. About 2 weeks prior to admission, the
patient progressed to durative epileptic seizures and developed
into a coma with unstable vital signs, and then tracheal
intubation and ventilator-assisted ventilation were operated.
Through detailed medical history tracking, the patient had an
ambiguous history of chronic oral mycosis without taking it
seriously. At age 37, he had severely decreased vision caused
by keratitis, and then he performed a bilateral corneal surgery.
His wife reflected that he had decreased sexual function in the
recent few years. Physical examination revealed that the ema-
ciated patient was unconscious with scattered skin vitiligo,
pigmentation, alopecia, and dystrophic nails. The muscle ten-
sion was highly increased with hyporeflexia. Bilateral Babinski signs were not elicited, and meningeal irritation
was negative.

Accessory examinations

The abnormal laboratory data were summarized in Table 1.
Other serum hormones, triiodothyronine, free triiodothyro-
ine, thyroid-stimulating hormone, calcitonin, growth hor-
mone, luteinizing hormone, follicle-stimulating hormone,
and estradiol, were normal. Brain computed tomography
showed multiple intracranial calcifications (Fig. 1c).

Treatment

The patient started with the replacement therapy of glucocor-
ticoid, calcium, and calcitriol supplementation, as well as anti-
infection and other symptomatic and supportive treatment.
Vital signs were basically stable, the seizures were significant-
antly reduced, while he was still in a comatose state, and died of
severe infection (Acinetobacter baumannii) and respiratory
failure 2 weeks later.

Genetic findings

Exome sequencing revealed a documented homozygous AIRE
mutation c.415C>T(p.R139X), which is the Sardinian foun-
der mutation and predicted to confer mRNA instability via
nonsense-mediated decay and resulted in a prematurely trun-
cated protein [19]. Further Sanger sequencing showed that the
asymptomatic parents, little brother, and children of the pa-
tient were heterozygous carriers (Fig. 1b), which coincide
with the autosomal recessive pattern. Pathogenicity assess-
ment according to the ACMG revealed that the mutation is
pathogenic.

Discussion

In the present study, combining with the clinical and genetic
data, we diagnosed a Chinese APS-1 case. Through medical
history review, the course of the disease is roughly as follows:
the patient usually had a poor constitution, and easy to feel
fatigued in early time, which is considered as part of the
nonspecific manifestations of early stage of adrenal insufficiency. As the disease progressed, the patient gradually developed mucocutaneous candidiasis and ectodermal manifestations and recently then sought medical advice for recurrent tetany due to hypoparathyroidism. The combined symptoms may include autoimmune keratitis and hypogonadism. Unlike the Sardinians or Italians, these presented with an earlier onset age (the average age is 4–6), and almost 95% of patients’ initial symptom is CMC or ectodermal features [19, 20]. Our patient started with a late and insidious onset, and no obvious manifestations of polyglandular insufficiency after birth, childhood, or adolescence, or due to lacking the early attention, which made the early diagnosis much more difficult.

APS-1 usually begins during childhood or adolescence with additional manifestations emerging later in life. It is reported that CMC is usually occurring before age 5, mostly affecting the oral mucous membranes, nails, and esophagus, presenting as white or gray plaques and hyperkeratosis. Hypoparathyroidism appears in the age 5–15, while the symptoms are nonspecific, such as paresthesias, dry hair, rough skin, muscle cramps, and tetany, seizures may occur in more severe cases [2]. While adrenal insufficiency is during the second decade of life. Fatigue, dizziness, abdominal pain, weight loss, diarrhea, and hyperpigmentation are common, while in severe cases, adrenal crisis may occur [17, 21]. Other endocrinopathies includes hypergonadotrophic hypogonadism, type 1 diabetes mellitus, autoimmune thyroid diseases, and pituitary failure. The more complicated nonendocrine features include ectodermal dystrophy (alopecia, vitiligo, nail dystrophy, dental enamel dysplasia, and keratopathy), immuno-mediated gastrointestinal diseases (malabsorption, diarrhea, autoimmune gastritis, and pernicious anemia), autoimmune hepatitis, asplenia, hemolytic anemia, bronchiolitis, tubulointerstitial nephritis, and cutaneous vasculitis [11, 22]. Immunologically, high titer autoantibodies against a great variety of tissue-specific antigens and cytokines are a hallmark of APS-1 [15], especially the neutralizing autoantibodies against IFN have been suggested as a sensitive and specific diagnostic tool due to the early emergence and high specificity [22, 23]. Up to now, only about 20 Chinese APS-1 patients

Table 1 The abnormal data of laboratory test

| Test items                       | Results                                                                 |
|----------------------------------|------------------------------------------------------------------------|
| Biochemical function             | Blood glucose 2.47mmol/l (reference 3.9–6.1), albumin 24g/l (40–55), alanine aminotransferase145.9U/l (13–69), aspartate aminotransferase 299.3U/l (8–45), urinary free cortisol: super linear (21–111μg /24h urine) |
| Serum electrolytes               | Calcium 1.41mmol/l (2.0–2.75), phosphate 2.49mmol/l (1.1–1.3), sodium 133mmol/l (135–155), chlorine 94mmol/l (96–108) |
| Thyroid and parathyroid function | Thyroxine 42.13nmol/l (62.67–150.84), free thyroxine 8.34pmol/l (9.01–19.04), thyroglobulin antibody 13.92IU/ml (<4.11), thyroid peroxidase antibody 63.06IU/ml (<5.61), parathyroid hormone 0.1pg/ml (15.0–68.3) |
| Adrenal function                 | Adrenocorticotropic hormone (08:00) 904.01pg/ml (7.0–65.0), cortisol 1.91μg/dl (6.7–22.6) |
| Gonadal function                 | Testosterone 0.39ng/ml (1.75–7.8), prolactin 1.87ng/ml (2.64–13.14), progesterone <0.1ng/ml (0.1–0.84) |
| Sputum culture                   | Acinetobacter baumannii(+)                                             |
have been reported, the female/male ratio was 1.2, and the median age at diagnosis was 12.6 years (range 0.25–57 years). Autoimmune thyroiditis, type 1 diabetes mellitus, and hepatitis were more frequent minor components with onset age in the late teens [10, 24].

The responsible gene AIRE encodes a 545-amino acids transcription regulator, which is mainly expressed in medullary thymic epithelial cells [25]. AIRE can facilitate the negative selection of T cells in the thymus, build the thymic microarchitecture, and induce regulatory T cell production; thus, it plays a significant role in the development and maintenance of immune tolerance, which crucially depends on its proper nuclear localization and the intermolecular interactions with transcriptionally active or chromatin-associated proteins [24, 26, 27]. In line with its effect in transcription, AIRE contains a combination of functional domains (Fig. 2) [28]. So far, more than 140 AIRE mutations have been identified (http://www.hgmd.cf.ac.uk/ac/index.php?gene=AIRE) [13, 28]. The dominant negative mutations are mainly clustered in PHD1 domains (Fig. 2). Some short mutations correspond to isolated populations, suggesting a potential founder effect, such as Finns (p.R257X), Sardinians (p.R139X), and Iranian Jews (p.Y85C) [19], while 1094-1106del13 is enriched among North American, Norwegian, British, and Irish APS-1 patients [11, 22]. Despite considerable variations in APS-1 phenotype, correlations with respective genotypes are far from definite. To date, several cellular functional assays showed that mutations in SAND and PHD zinc finger domains resulted in the abnormal polypeptide aggregation in the cytoplasm and decreased transcriptional capacity [24, 29, 30]. Additionally, acting as a highly collaborative protein, AIRE is associated with a broad set of partners to initiate the transcription process, as well as regulate the AIRE itself [26]. It has been reported that one of the coactivators CREB-binding protein can interact with and acetylate AIRE and enhance the expression of AIRE-regulated genes, while mutant AIRE that mimicked acetylated site had impaired transactivation activity [31, 32]. Furthermore, the experiments in transgenic mouse models found that there were naive self-reactive T cells, neutralizing autoantibodies in the periphery, which may result from the aberrant thymic microenvironment affected by the AIRE deficiency [8, 33, 34]. Moreover, the activation process of the naive self-reactive T cells relay on multiple predisposing and triggering factors, which is consistent with the varied APS-1 clinical spectrum between individuals [35]. All in all, the dysfunction of AIRE activity causes

**Fig. 2** The protein functional domains and diagram of AIRE mutations (NM_000383). Mutations in black, homozygous or compound heterozygous; mutations in red, dominant heterozygous. Gross deletions and gross insertions are not included in the figure. Homogeneously staining region (HSR) responsible for homo- and multimerization; nuclear localization signal (NLS) implicated in nuclear transport; Sp100, AIRE, NucP41/75 region, and deformed epidermal autoregulatory factor 1 (SAND) domain likely to involve in protein-protein interaction and DNA binding; two plant homeodomain (PHD) zinc fingers separated by a proline-rich region (PRR) participated in chromatin-mediated transcription regulation; four leucine zipper (LXXLL) motifs engaged in promoting gene transcription

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disturbances in immunological homeostasis and tolerance, which underline the significant role of autoimmunity in the pathogenesis of APS-1 [36–39]. Nevertheless, the highly phenotypic heterogeneity, organ specificity, and the molecular genetic mechanism of the disease are still beyond fully understood.

The significant clinical variability even among siblings with identical AIRE genotype points to the possibility of interaction among genetic, epigenetic, and environmental factors. Therefore, the diagnosis mainly based on the traditional “tried” certainly will be missed or delayed. Recently, the clinical data from American ASP-1 cohort showed that some non-endocrine presentations were particularly prominent in the early stage of the disease [22]. Thus, it is proposed to expand the diagnostic criteria by incorporation of the non-endocrine manifestations into the classic triad criteria, which was confirmed to foster a much earlier diagnosis in European APS-1 cohorts [40]. It is appropriate to perform the molecular genetic analysis to differentiate APS-1 from APS-1-like conditions. In addition, it is indispensable to test for IFN antibodies in suspected cases where mutual analysis is restricted or complicated [28]. It may take more than 5–10 years or even longer to progress from one endocrinopathy to APS-1; once the patient is suspected or diagnosed, lifelong management and structured follow-up through a multidisciplinary team are required. The current overall management is symptomatic and supportive treatment, while personalized therapeutic strategy is advocated [2, 17]. Close monitoring of mineralocorticoid or glucocorticoid supplementation in adrenal insufficiency is paramount to avoid the electrolyte disturbance or adrenal crisis. For hypoparathyroidism, oral calcium and vitamin D supplements with monitoring of calcium in serum and urine are recommended to avert the formation of iatrogenic kidney stones. Immunosuppressive treatment is critical for the control of autoimmunity in multiple organs with a goal to prevent irreversible end-organ damage, while a comprehensive assessment of the initiation, benefits, and risks of preventive immunomodulation is urgently required [41, 42]. Since the rapidly progressive course and high mortality of the disease, earlier recognition and diagnosis is much more crucial to provide timely intervention, accurate genetic counseling, and avert the emergence of severe, irreversible autoimmune complications.

Conclusions

APS-1 is a complex syndrome involved in multiple-organ damage. By describing a genetically confirmed late-onset Chinese ASP-1 patient, we further summarized the clinical, genetic, and immunological mechanisms to enhance learning and awareness raising of the disease. Early recognition is helpful for prompt appropriate treatment, to avoid the serious adverse events and improve the quality of life. Although the past two decades have significantly expanded our understanding of the disease in every aspect, numerous unresolved issues related to the specific diagnosis, therapeutic strategies, and pathogenic mechanism still remain to be explored. More research in the future is required to gain deeper insight into the organ-specific damage in AIRE-dependent immune tolerance, to develop novel screening, diagnostic and prognostic tools, as well as the targeted interventions.

Acknowledgements

We would like to thank the guardians of the patient for the cooperation.

Author contribution

Feixia Zhan contributed to investigations, data analyses, and drafting of the manuscript.

Li Cao contributed to conceptualization and design.

All authors approved the final version of the manuscript.

Funding

This work was supported by the grants from the National Natural Science Foundation of China (Nos. 81870889 and 82071258).

Data availability

The datasets are available from the corresponding author on reasonable request.

Compliance with ethical standards

This protocol was approved by the local ethics committee. Written informed consent was obtained for participant.

Conflict of interest

The authors declare that they have no conflict of interest.

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