

# Genetically proven APS type 1 in two siblings

D. Yordanova, E. Stefanova, K. Kazakova, Z. Todorova, M. Dimitrova  
University Children's Hospital, Sofia, Department of Endocrinology

**Background:** APS type 1 also known as Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) is characterized by an autosomal recessive inheritance. The clinical diagnosis is based on the presence of at least two of the three following diagnostic criteria: chronic mucocutaneous candidiasis, chronic hypoparathyroidism and autoimmune adrenal insufficiency. Patients often develop other diseases as well such as: hypogonadism, alopecia, chronic hepatitis, chronic atrophic gastritis, pernicious anemia, vitiligo, malabsorption, hypothyroidism, keratoconjunctivitis, hypophysitis and IDDM. The presence of a single disease criterion is sufficient to suspect APS-1 and to indicate genetic study. APS type 1 is caused by mutations in the AIRE (autoimmune regulator) gene found on chromosome 21 (21q22.3) which encodes the AIRE protein. More than 60 mutations in the AIRE gene have been identified. Some of these genetic changes lead to the production of an abnormally short, nonfunctional version of the autoimmune regulator protein. Other mutations change single protein building blocks (amino acids) in critical regions of the protein. AIRE mutations reduce or eliminate the function of the autoimmune regulator protein. Without enough of this protein the immune system can malfunction resulting in autoimmunity. This abnormal reaction leads to inflammation and can damage otherwise healthy cells and tissues. For reasons that are unclear defects in the autoimmune regulator protein primarily affect hormone-producing (endocrine) glands. The clinical utility of genetic analysis of AIRE gene include: confirmation of a clinical diagnosis, selection of appropriate treatment, identification of at-risk family members, prenatal diagnosis and carrier testing in siblings or other relatives.

**Clinical case:** 10 year old girl, from a second normal pregnancy, first delivery, born 20 days before term with a birth weight of 2700 g and length of 51 cm. The disease started from the age of 3 years with hypoparathyroidism. One year later she developed dystrophic nail changes, mucocutaneous candidiasis and alopecia areata. The girl presented to us with adrenal insufficiency when she was 4 years and 9 months old. From the age of 5 years she was also found to have autoimmune thyroiditis with normal thyroid function. From the age of 8 years the ultrasound of the kidneys showed increased parenchymal echogenicity. Her treatment includes Dihydroxycholesterol, Magnesium, Hydrocortisone and Fludrocortisone.

We also evaluated her 6 year old brother, born from a normal pregnancy, birth weight 3350 g and length of 54 cm. He developed hypoparathyroidism since he was 3 years old. From the age of 4 years the boy also had dystrophic nail changes, mucocutaneous candidiasis and alopecia areata. His therapy is with Dihydroxycholesterol and Magnesium.

Both children have normal physical growth and neurological development. Family history of a grandfather with diabetes mellitus.

In January 2014 molecular genetic analysis of the AIRE gene was performed in the two siblings and it indicated the presence of a homozygous mutation in exon 6 of the AIRE gene. The results confirm the clinical diagnosis of APS type 1. Their parents are heterozygous carriers of the same mutation.



**Conclusion:** APS-1 presents as an extremely variable combination of autoimmune endocrine and non-endocrine disorders. The endocrine failures are managed by conventional hormonal replacement which may be complex when a patient has several endocrine deficiencies. The prognosis is variable depending on how organs are affected and the severity of the disease. AIRE gene mutation analyses proved useful in establishing the diagnosis in the patient with incomplete or unusual clinical presentation. Mutation analysis of the AIRE gene will help in early diagnosis of the disease and prevention of serious and fatal complications. In our case the disease has an early onset and rapid manifestation of the autoimmune diseases.