

## Hypocalcemia, Prolonged QT Interval and Massive Brain Calcifications in an Iranian Jewish Woman with APECED

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Brain calcifications are not rare in hypoparathyroidism or pseudohypoparathyroidism. Massive brain calcifications were found in brain computed tomography scans performed after an episode of pre-syncope in an Iranian Jewish woman known to have hypoparathyroidism and hypothyroidism. We present the case and briefly discuss recent progress in the understanding of the molecular basis of the inherited disorder APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), also termed autoimmune polyglandular syndrome type 1 (APS-1). Since Iranian Jews have a higher incidence of APECED, in Israel the ancestry of patients presenting with hypocalcemia should be investigated.

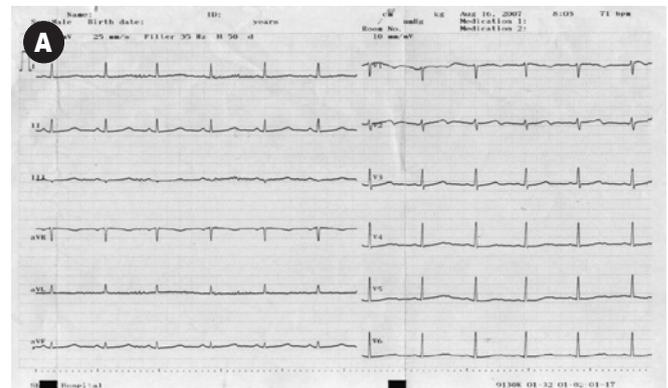
### Patient Description

A 55 year old woman was hospitalized in our ward after being accidentally electrified by an unprotected electrical wire in her home. She then experienced an episode of pre-syncope followed by a prolonged period of palpitations accompanied by mild chest discomfort and elevated blood pressure values varying between 150/90 and 180/100 during the first 2 hours after the event. On admission, her blood pressure was 110/70, pulse 70, saturation 97% and temperature 36.6°C. The abnormal physical examination findings were ptosis of the left eyelid, vertical diplopia upon gazing upward, very mild ataxia and a slightly positive Romberg test. The laboratory examinations revealed calcium level of 6.8 mg/dl, phosphorus 6.1 mg/dl and parathyroid hormone < 3.0 pg/ml (normal 16–87 pg/ml). Albumin, cortisol and thyroid-stimulating hormone levels were normal. An electrocardiogram demon-

strated a markedly prolonged corrected QT interval of 510 msec [Figure A]. Brain CT followed by magnetic resonance imaging showed massive brain calcifications [Figures B and C].

The patient was of Iranian ancestry from the city of Isfahan and her parents were first-degree cousins. She was known to have hypocalcemia due to hypoparathyroidism and hypothyroidism since she was 13 and was regularly treated with vitamin alpha D3, calcium and thyroxin. She admitted to not adhering strictly to the therapy and that she had been hospitalized once due to symptomatic hypocalcemia. Her father had

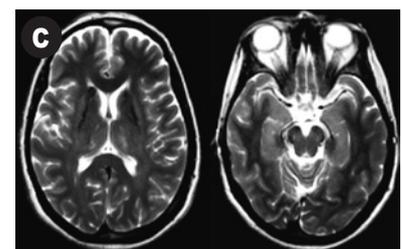
had Dubin-Johnson syndrome and died of alcoholic cirrhosis. One of her cousins had hypocalcemia and recurrent episodes of oral mucocandidiasis that started at the age of 9 years. The patient's only complaint was of recent loss of short-term memory. Calcium levels rose quickly with adequate oral supplementation and the



**[A]** Electrocardiogram at the time of admission showing prolonged QTc interval of approximately 510 msec.



**[B]** Non-enhanced CT brain images show heavy calcification in the cerebellum, bilateral white matter, basal ganglia and thalami.



**[C]** MRI T2 weighted images show, in addition, bilateral basal ganglia atrophy and symmetrical abnormal signal in thalami and midbrain.

QTc on her ECG normalized during the hospitalization. A neurology consultant raised the possibility that her neurological complaints were related to her massive brain calcifications.

### Comment

Based on the patient's laboratory results, ancestry and family history, we reached the diagnosis of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, also termed autoimmune polyglandular syndrome type 1. This is an autosomal recessive disorder that is diagnosed based on the presence of two of its three most common clinical manifestations – namely, hypoparathyroidism, primary adrenocortical insufficiency and chronic mucocutaneous candidiasis [1]. The disease usually presents in childhood and adolescence [1]. Other autoimmune manifestations may include autoimmune hepatitis, intestinal malabsorption including pernicious anemia, diabetes mellitus, primary hypothyroidism, alopecia and vitiligo. APECED is a rare disorder, yet it has a higher frequency in certain populations such as Finns, Sardinians and, probably most commonly, Iranian Jews – with a prevalence of about 1:9000. Zlotogora and Shapiro [2] described a cluster of Israeli patients of Iranian ancestry (all from the cities of Tehran, Isfahan or Yasd) with APECED. Of the 23 patients (from 19 families), in 10 the only manifestation of the disease was hypoparathyroidism,

and the authors suggested that all Jewish patients of Iranian ancestry with hypoparathyroidism have APECED.

Prolongation of the QTc interval on ECG was previously described in two Turkish patients with APECED [3]. Hypocalcaemia prolongs phase 2 of the action potential. This is accompanied by prolonged QT interval.

Another interesting finding was the massive brain calcifications on CT and MRI. Hypoparathyroidism and pseudohypoparathyroidism are well-recognized causes of extensive cerebral calcifications. These may occur diffusely or at specific areas such as the basal ganglia, and cause various clinical manifestations such as choreoathetosis. Other causes for brain calcifications include idiopathic calcifications, familial calcifications and Fahr's syndrome (idiopathic familial cerebrovascular ferrocaldinosis) [4].

A major breakthrough in the understanding of APECED and autoimmunity in general was the identification of the defective gene by positional cloning in 1997 [5]. Over 60 mutations were thus far described [1]. The gene is located on chromosome 21 (21q22.3) and encodes a protein of 545 amino acids termed autoimmune regulator. AIRE, which has features of a transcription factor, is expressed in lymphoid organs, especially in the thymus medullary epithelial cells. AIRE knockout mice have a human disease-like phenotype [1]. Comparison of gene expression of thymic medullary epithelial cells from wild-type and

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AIRE = autoimmune regulator

AIRE knockout mice showed that AIRE promotes the transcription of a large number of peripheral tissue antigens, thereby enabling induction of central (thymic) tolerance towards these antigens and preventing autoimmunity [1]. An important question regarding AIRE is whether its understanding will lead to improved treatment of autoimmune diseases. To conclude, in Israel, the ancestry of patients presenting with hypocalcemia should be investigated. APECED should be suspected in appropriate cases.

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### References

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QTc = corrected QT

APECED = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy