Case Report

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Intracranial Calcifications in Autoimmune Polyendocrine Ectodermal Dystrophy Syndrome (APECED): About A Case Report

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ABSTRACT

Autoimmune polyendocrinopathy ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type I (APS I), is an uncommon, but debilitating autosomal recessive disease caused by mutations in the autoimmune regulator (AIRE). It is characterized by a broad and diverse clinical spectrum which can lead to severe metabolic alterations and eventually life-threatening events. Hypoparathyroidism is one of the major criteria for clinical diagnosis, in addition to chronic mucocutaneous candidiasis and autoimmune adrenal insufficiency. This component is responsible for the forming of brain calcifications which tend to have a characteristic predilection for the basal ganglia. In this article, we report an additional case to the literature and provide a literature review of the expanding radiological spectrum of this syndrome.

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Introduction

Autoimmune polyendocrinopathy ectodermal dystrophy (APECED), also referred to as autoimmune polyglandular syndrome type I (APS I), is a very rare and devastating autosomal recessive disorder, accounting for about 400 cases reported worldwide and that is caused by loss-of-function mutations in the autoimmune regulator (AIRE) gene located in chromosome 21 region p 22.3, the clinical features vary broadly and involves various endocrine and non-endocrine autoimmune manifestations. APECED usually begins during early childhood and the clinical diagnosis implies the existence of two of the three main criteria (Whitaker's triad): chronic mucocutaneous candidiasis (CMC), autoimmune hypoparathyroidism (HP), and Addison's disease (AD). However multiple other diseases, mostly autoimmune, may arise in patients [1-5]. Figure 1.

Figure 1: Clinical Features in APECED Syndrome

Cerebral calcifications subsequent to hypoparathyroidism have been documented in many patients with APECED [6]. The aim of this work is to report the case of APECED syndrome with intra cranial calcifications of the basal ganglia, and to outline the imaging findings attributed to this component of the syndrome.

Case Report

We report the case of a nine-year-old girl, who is the eldest of two siblings from a 1st degree consanguineous marriage; her past medical history was marked by: oral Chronic candidiasis since the age of 4. She had, since 2018, a frequent apyretic partial right-sided hemi convulsive seizures, each episode lasted for few minutes and spontaneously resolved with no postictal behaviors and symptoms such as the loss of consciousness or enuresis. The evolution of the symptoms was highlighted by the occurrence of spontaneous clonus of the ankle, associated with numbness and tingling in the hands and feet, and asthenia. Accordingly, the patient was kept on sodium valproate combined with carbamazepine but with no significant improvement.

On physical examination, there were extensive bilateral nail dystrophic changes (onychomycosis, weak and brittle nails), oral mucocutaneous candidiasis, dry skin and bilateral ptosis. The thyroid was not palpable and there were no skeletal abnormalities or neurological deficits.

Laboratory investigations revealed hypocalcemia, hyperphosphatemia and low parathyroid hormone levels, the rest of the laboratory profile was found to be normal. A renal ultrasonography demonstrated the presence of calcifications identified within the renal parenchyma, outside the collecting

system referring to a grade 1 nephrocalcinosis. An unenhanced cerebral CT scan was performed (Figure 2) and showed dense bilateral symmetrical calcifications of the basal ganglia (lenticular nucleus).

Figure 2: Unenhanced CT Scans Showing Dense Bilateral Symmetrical Calcifications of the Basal Ganglia (lenticular nucleus).

On the basis of the constellation of findings described above, the diagnosis of autoimmune ectodermal polyendocrinopathy candidiasis syndrome (APECED) was established. The patient received a symptomatic treatment based on oral administration of Calcium and Vit D in addition to a fungal treatment. All symptoms improved.

Discussion

APECED syndrome is a rare autoimmune disorder featuring multiple endocrine system failure and cutaneous manifestations, it tends to affect some ethnically isolated populations, namely; Iranian Jews (1:9,000), Sardinians (1:14,000) and Finns (1:25,000) [4-10].

The range of possible disease components includes about 30 disorders. The initial manifestation may not include any of the known three typical components; chronic mucocutaneous candidiasis, hypoparathyroidism or Addison's disease, the diagnostic strategy should be based on knowledge of the clinical findings, taking into account the characteristics of the ectodermal dystrophy [11].

The imaging findings of APECED syndrome are commonly associated with the hypoparathyroidism component of the syndrome. These calcifications tend to be extensive, bilateral, and symmetrical with a typical predilection for the basal ganglia. Calcification may rarely extend intracranially beyond the basal ganglia, reaching the cerebellum and frontal lobes of the cortex, involvement of the brain stem was reported by Alkaphoury et al in a case report published in 2015 which adds to the diversity of this rare syndrome.

The mechanism of intracranial calcifications in hypoparathyroidism is not yet completely understood, it originates from a degenerative vascular process in the extra-pyramidal system, possibly initiated by the deposition of calcium crystals; decreased levels of serum parathyroid hormone and calcium in addition to hyperphosphatemia increases the calcium-phosphorus product, overcoming its solubility in serum and leading to deposition of calcium and phosphorus in the blood vessels [12-17].

Computed tomography is the most sensitive way to identify brain calcifications, intracranial calcification can be physiological or pathological, physiological brain calcification is found in men and women of all ages and ethnic backgrounds ; they are commonly single or multiple asymmetrical and has a predilection for specific anatomical locations such as the pineal gland, the habenular commissure, the glomus of the choroid plexus, the basal ganglia, the dentate nucleus, the falx, the tentorium, the petroclinoid and interclinoid ligaments, and the arachnoid granulations.

On the opposite, pathological calcification of the brain has been reported as a possible and extremely rare manifestation in patients with infectious diseases such as congenital fetal infections (TORCH diseases), tuberculosis, neurocysticercosis and chronic viral encephalitis. Primary brain tumors or metastatic lesions, namely, Calcifying metastases, craniopharyngioma, chordoma, neurocytoma, ependymoma, meningioma, choroid plexus papilloma, medulloblastoma, germ cell tumors, primitive neuroectodermal tumor, ganglioglioma, astrocytoma, pinealoma/pineal blastoma and schwannoma. In some developmental disorders such as Gorlin syndrome, Sturge-Weber syndrome, hemangioma or arteriovenous malformations, Cockayne syndrome, neurofibromatosis, tuberous sclerosis. Regarding Congenital syndromes and certain metabolic disorders, they are more likely to cause multifocal symmetrical intracranial calcifications and include respectively hypoparathyroidism, pseudohypoparathyroidism, hyperparathyroidism and Fahr syndrome, Goutières Aicardi syndrome, COL4A1 mutation-related disease, cerebral microangiopathy with calcifications and cysts, infantile Krabbe disease, juvenile Alexander disease, APECED syndrome and more [13, 18, 19].

Conclusion

APECED is a rare autosomal recessive disease that involves mutations in the autoimmune regulator (AIRE) gene, a number of criteria are required for the clinical diagnosis of such rare disease, early diagnosis is vital to avoid serious consequences by reaching noble organs such as the heart, the liver or the brain.

Cerebral calcifications secondary to hypoparathyroidism have been previously documented in many patients with APECED. In this article, we described intracranial calcifications in a case of APECED and pointed out other feature expanding the phenotype of this condition; we further reviewed the literature and shed light on the different clinical manifestations of this rare disease in affected patients.

Radiologists must be cautious about this diagnosis and consider it in their list of differential diagnoses for bilateral symmetrical brain calcifications.

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