A case study of siblings with Autoimmune Polyendocrinopathy Syndrome Type 1

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Case Background

This male patient presented at 7 years of age, initially to primary care with loose stools. He was otherwise well. Two months later he was referred to secondary care due to ongoing loose stools and concerns over weight loss. On clinical review, he was well grown with a height on 25th centile and weight on 50th centile for age. He had a history of episodes of oral thrush until the age of 18 months.

Laboratory findings and clinical course

Initial Review in secondary care

- Faecal calprotectin: Normal
- Faecal elastase: Normal

Further review (4 months later)

- Adjusted Calcium : 1.34 mmol/L (lowest 1.29 mmol/L)
- PTH: 0.7 pmol/L
- Consistent with hypoparathyroidism
- Referral to Paediatric Endocrinology
- Enterocyte, goblet cell, parathyroid and adrenal antibodies: All negative
- Gastrointestinal symptoms resolved on correction of the hypocalcaemia
- Genetics: Compound heterozygous for pathogenic *AIRE* gene variants

AIRE gene variants

The *AIRE* gene encodes an autoimmune regulator protein involved in immunological tolerance.

The AIRE protein is expressed in stromal cells of primary and secondary lymphoid tissues, including thymic medullary epithelial cells. It regulates the expression of tissue-specific antigens which play a critical role in the elimination of self-reactive T-cells and the induction of a specific subset of regulatory T-cells in the thymus.

Recent studies suggest that certain mutations in *AIRE* may also contribute in milder, more common forms of organ specific autoimmune disorders, including pernicious anaemia and autoimmune thyroid disease.

Figure 1: Structure of the AIRE protein encoded by the *AIRE* gene.
Image Source: Chan, A & Anderson, M. (2015) Central tolerance to self revealed by the autoimmune regulator. Ann N Y Acad Sci. 1356(1): 80-9. Accessed: https://pubmed.ncbi.nlm.nih.gov/26579596/

Sibling testing

The patient had one older sister, aged 12. She was found to have enamel hypoplasia and dystrophic toe nail.

- Adjusted Calcium : 1.39 mmol/L
- PTH: <0.2 pmol/L
- Consistent with hypoparathyroidism
- Referral to Paediatric Endocrinology

Autoimmune Polyendocrinopathy Syndrome Type 1

Autoimmune polyendocrinopathy syndrome Type 1 (APS1) is characterised by multiorgan autoimmunity leading to endocrine hypofunction of various glands. Endocrine organs such as the adrenal cortex, ovaries and parathyroid glands are typically affected resulting in clinical presentation with adrenal insufficiency, hypoaldosteronism, delayed puberty, premature ovarian failure and hypoparathyroidism. Patients often have marked life threatening hypocalcaemia requiring urgent action, as in this case.

APS-1 is clinically defined as the presence of at least two components of a classic triad.

Classic triad in APS1:

- Chronic mucocutaneous candidiasis
- Hypoparathyroidism (present in >80% of APS1 patients)
- Adrenal insufficiency

In those patients with adrenal insufficiency, autoantibodies are reactive to the 21-hydroxylase enzyme essential to glucocorticoid synthesis.

The parathyroid specific antigen in APS1 has not been defined however, Alimohammadi et al (2008) proposed NALP5 expressed in the cytoplasm of chief cells in the parathyroid glands as a possible autoantigen.

Family follow up

On further investigation under the Paediatric Endocrinology team, both siblings were found to have an adequate cortisol response to Synacthen which excludes adrenal involvement at this stage. As APS1 is a progressive condition, they will both undergo regular biochemical and clinical monitoring to assess for any further disease progression.

Summary

A rare cause of hypoparathyroidism presenting in children is APS1 as a result of *AIRE* gene variants. This case study of siblings presenting with APS1 with marked hypocalcaemia highlights the need for awareness of investigation into the underlying cause of autoimmune disorders in children and the need for family screening.

Additional cases of APS1 may be reported in future due to the increasing use of genetic panel tests. This may result in detection of patients with an earlier, milder stage of disease but also the potential for detection of cases with a milder clinical phenotype without further progression who may otherwise not have been identified.

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