Familial Pseudo hypoparathyroidism associating autoimmune polyendocrinopathy: Description of two cases and identification of a new GNAS variant

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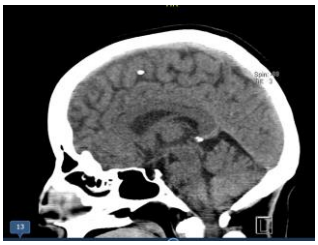
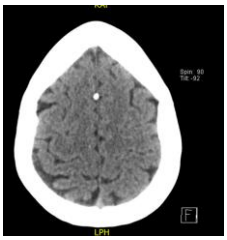
Introduction: The term pseudohypoparathyroidism was introduced in 1942 by Albright et al. to describe several patients presenting hypocalcemia and hyperphosphatemia in association with short stature, short metacarpals and metatarsals, obesity as well as neurocognitive impairment (1). These findings are now referred as Albright's hereditary osteodystrophy (AHO). Autoimmune polyendocrinopathy is characterized by autoimmune activity against more than one endocrine organ. We herein present a family (the mother and the daughter) affected with AHO and autoimmune polyendocrinopathy features. We show some preliminary genetic studies.

Case reports: The index case is a 69 years old woman (patient A) , measuring 1m 47 and weighting 58 kg. She was diagnosed with Hashimoto Thyroiditis in 1982 and Biermer disease in 1982 (autoimmune polyendocrinopathy type 3, *see table 1*). Because of muscle cramps, biological investigation revealed in 2010: serum calcium: 2.10 mmol/L (2.15-2.6), phosphates: 1.08 mmol/L (0.74-1.51), PTH: 187 pg/ml, 25 vitD: 35 ng/ml (>20), IGF1: 114 ng/ml (32-226), GH: 0.7 ng/ml. In 2018, AHO was suspected on the basis of hypocalcemia, short stature and bilateral short 4th and 5th metacarpals and phalanges. Osteodensitometry was normal. GNAS gene sequencing identified a novel heterozygous **variant c.970 56GT>T** (class III). *In silico* analysis predict splicing defects.

Her daughter (Patient B) is 47 years old, measures 1m45 and weights 41 kg. She was diagnosed with Hashimoto Thyroiditis in 1989. Biological investigations revealed: serum calcium: 2.10 mmol/L (2.15-2.6), phosphates: 1.2 mmol/L (0.74-1.51), PTH: 131 pg/ml, 25 vitD: 24 ng/ml (>20). She presented Raynaud's phenomenon and cryoglobulinemia in 2022. Because of short stature, brain calcifications, and bilateral short 4th and 5th metacarpals, autosomal dominant AHO is also suspected. Genetic analysis is ongoing

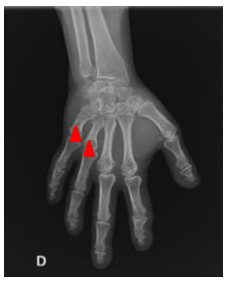




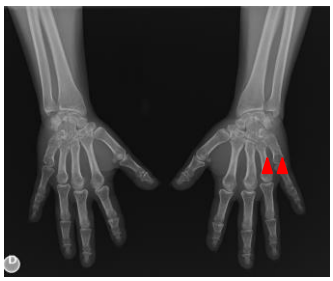
PATIENT B (daughter): Brain calcifications

Autoimmune syndromes (APS)	APS type 1	APS type 2	APS type 3
Major components	Chronic candidiasis Hypoparathyroidism Adrenalitis	Auto-immune Thyroiditis Adrenalitis	Auto-immune Thyroiditis, Biermer, DBT 1,etc
Familial History	25%	frequent	frequent
Genetic	AIRE gene	HLA DR3 Polygenic ?	HLA DR3 Polygenic ?

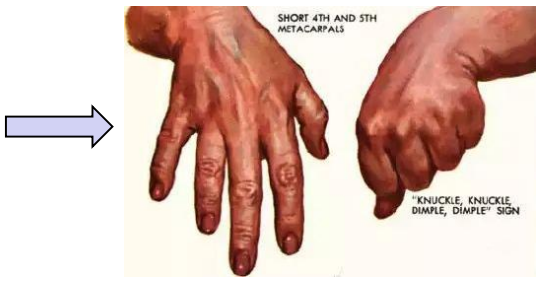
Table 1: Polyendocrine auto-immune syndromes, adapted from **(2)**



PATIENT A (mother): short 4th and 5th metacarpals (arrows)



PATIENT B (daughter): short 4th and 5 th metacarpals (arrows)



Credits: Pseudohypoparathyroidism. Basic Science

Conclusion: AHO is caused by mutations and/or epigenetic changes at the complex of GNAS locus on chromosome 20q13.3. It is an underdiagnosed cause of paresthesias and Fahr's disease. Heterozygous maternal GNAS mutations cause variable degrees of PTH resistant hypocalcemia. Reduced Gsa activity may result in loss of endocrine function, and can develop resistance to other hormones including TSH, GH, gonadotropins, and calcitonin. The combination of AHO and autoimmune polyendocrinopathies is very rare

References

(1) Valdes-Socin H, Betea D. Fuller Albright (1900-1969): The Researcher and the Patient Behind the Syndrome. VCP 2021

(2) Calvete, Reyes, Valdes-Socin et al. Alterations in SLC4A2, SLC26A7 and SLC26A9 Drive Acid-Base Imbalance in Gastric Neuroendocrine Tumors and Uncover a Novel Mechanism for a Co-Occurring Polyautoimmune Scenario. Cells 2021