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Introduction: Familial hypoparathyroidism is a rare cause of hypocalcaemia. We report a case of long-standing hypocalcaemia secondary to hypoparathyroidism caused by a novel *GATA3* variant resulting in multiple organ involvement. **Case**: A 20 year old girl was referred to our bone metabolic clinic for hypocalcaemia. Her past medical history included Bechet's disease, epilepsy and depression. She had bilateral sensorineural hearing loss and encephalitis as a child. She underwent right nephrectomy for an atrophic non-functioning kidney at the age of 16. Current medication included hydroxychloroquine, diazepam, oral calcium and cholecalciferol. It was noted that the hypocalcaemia dated back to 8 years, she denied any typical symptoms of hypocalcaemia but she did report visual and auditory hallucinations, fatigue and had low seizure threshold. She sustained recurrent fractures of her arm, elbow and wrist. **Initial investigations**: Corrected calcium 1.88 (2.20-2.60mmol/L), Phosphate 1.54 (0.80–1.50mmol/L), PTH 1.2 (1.6–6.9pmol/), 25-OH vitamin D 37 (50-120nmol/L). Myeloma screen, thyroid, renal and liver functions were all within the normal reference range. **Other bone markers**: Serum Procollagen Type 1 Amino Terminal Peptide was mildly raised at 82 (19-69ug/L), CTX 0.42 (0.1-0.5ug/L), 1,25 OH Vitamin D 29 (55-139pmol/L), 24,25-dihydroxyvitamin D was normal with normal 25:24,25 Dihyroxyvitamin D ratio at 18 normal. Bone density was in the normal range for her age. MRI of the brain was normal with no evidence of calcification. There was a family history of hypocalcemia in her estranged father. Subsequent genetic analysis showed a novel likely pathogenic *GATA3* missense variant (c.961T>C p.(Cys321Arg). She was started on alfacalcidol and achieved near normocalcemia with adjusted calcium levels of 2.18nmol/L. **Conclusion:** Pathogenic variants in the *GATA3* gene are responsible for *Hypoparathyroidism*-deafness-renal dysplasia (HDR) syndrome. In our patient, a novel missense variant in *GATA3*, p.(Cys321Arg), has been detected. This variant disrupts one of four conserved cysteine residues within a zinc-finger domain, which is involved in DNA binding and is presumed to have a deleterious effect on protein function. Patients may have longstanding asymptomatic hypocalcaemia with atypical features hence genetic testing is recommended in patient with multi-organ involvement. Alfacalcidol successfully restored calcium homeostasis in this case.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORT

A Novel Mutation in SOST Gene Causes Sclerosteosis

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Background: Sclerostin is a *SOST* gene product that inhibits osteoblasts activity and prevents excessive bone formation by antagonizing Wnt signaling pathway. Sclerosteosis has been linked to the loss of function mutation in *SOST* gene. It is a rare autosomal recessive disorder characterized by craniotubular hyperostosis leading to gigantism, cranial nerves entrapment, and fatal cerebellar herniation.
Objectives To report a novel mutation of *SOST* gene in a patient with sclerosteosis.
Clinical Case: A 25-year-old female was referred to the endocrine clinic for suspected GH excess. The patient noted the onset of headache, progressive bilateral blurred vision and hearing disturbance, irregular menses, and generalized arthralgia; at the age of 23 years. Subsequently, she observed a progressive increase in the size of shoes and hands, proptosis, and protrusion of the chin. She was the second of seven siblings from non-consanguineous parents with normal antenatal and neonatal history except for syndactyly. All family members were phenotypically normal except for a sister with similar physical appearance who had cranial decompression 20 years back. MRI pituitary was done initially due the suspicion of pituitary adenoma and it revealed an enlarged sella turcica with normal pituitary gland. Surprisingly, the MRI showed diffuse osseous thickening with narrowing of skull base foramina, narrowing of optic and internal auditory canals, secondary compression of cerebral parenchyma and bilateral cerebellar tonsillar herniation. Further image revealed extremely increased bone mass density with Z-score values of +12, generalized increase cortical thickness, vertebral end plates sclerosis, and deformed left index finger. Biochemical and endocrine tests revealed normal GH, IGF -1, TSH, prolactin, short Synacthen test, FSH, LH, estradiol, calcium, phosphorus, PTH and alkaline phosphatase. Due to progressive worsening of vision with compressive optic neuropathy, optic nerve fenestration with decompression hemicraniotomy was performed. Sclerosteosis was suspected due to the predominant craniotubular hyperostosis with syndactyly. There was no definite therapy. Management aimed at relieving symptoms and preventing complications, so she was commenced on calcitriol and prednisolone to suppress the osteoclasts. Genomic sequencing of the *SOST* was performed. We identified a novel deletion mutation in *SOST* gene (c.387delG, p.D131fs*) which disrupts the sclerostin function causing sclerosteosis in this patient.
Conclusion: We describe a novel mutation in the *SOST* gene in a patient with sclerosteosis in Saudi Arabia, that has not been previously described. Closing the gap between the genomic knowledge and clinical applications will add the benefit of success in development of targeted therapies in such a fatal disease.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORT

A Rare Case of Perinatal Hypophosphatasia Treated With Asfotase Alfa

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