Juvenile Paget's disease

Juvenile Paget's disease (JPD), an ultra-rare, debilitating bone disease due to loss of functional osteoprotegerin (OPG), is caused by recessive mutations in TNFRFSF11B. A genotype-phenotype correlation spanning from mild to very severe forms is described.

A study aimed to describe the complexity of the human phenotype of OPG deficiency in more detail and to investigate heterozygous mutation carriers for clinical signs of JPD.

Grasemann et al., investigated 3 children with JPD from families of Turkish, German, and Pakistani descent and 19 family members (14 heterozygous).

A new disease-causing 4 bp-duplication in exon 1 was detected in the German patient, and a microdeletion including TNFRFSF11B in the Pakistani patient. Skeletal abnormalities in all affected children included bowing deformities and fractures, contractures, short stature and skull involvement. Complex malformation of the inner ear and vestibular structures (2 patients) resulted in early deafness. Patients were found to be growth hormone deficient (2), displayed nephrocalcinosis (1), and gross motor (3) and mental (1) retardation. Heterozygous family members displayed low OPG levels (12), elevated bone turnover markers (7), and osteopenia (6). Short stature (1), visual impairment (2), and hearing impairment (1) were also present.

Diminished OPG levels cause complex changes affecting multiple organ systems, including pituitary function, in children with JPD and may cause osteopenia in heterozygous family members. Diagnostic and therapeutic measures should aim to address the complex phenotype [1].

1)
Grasemann C, Unger N, Hövel M, Arweiler-Harbeck D, Herrmann R, Schündeln MM, Müller O, Schweiger B, Lausch E, Meissner T, Kiewert C, Hauffa BP, Shaw NJ. Loss of Functional Osteoprotegerin: More Than a Skeletal Problem. J Clin Endocrinol Metab. 2017 Jan 1;102(1):210-219. doi: 10.1210/jc.2016-2905. PubMed PMID: 27809640.