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Juvenile Paget disease

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ABSTRACT

Juvenile Paget disease (JPD) is a rare disorder, mainly caused by mutations in the gene *TNFRSF11B* that encodes osteoprotegerin (OPG). Loss of OPG action causes generalized, extremely rapid bone turnover. The clinical manifestations are both skeletal - progressive skeletal deformity that develops in childhood - and extra-skeletal, including hearing loss, retinopathy, vascular calcification and internal carotid artery aneurysm formation. The severity of the phenotype seems to be related to the severity of *TNFRSF11B* gene deactivation. JPD is characterized biochemically by very high alkaline phosphatase activity, as well as other bone turnover markers. Bisphosphonates are commonly used to reduce the greatly accelerated bone turnover and can ameliorate the skeletal phenotype, if started early enough in childhood and continued at least until growth is complete. Limited evidence from patients treated with recombinant OPG or denosumab also provided favorable results. Recombinant OPG would represent a replacement treatment, but it is unavailable for clinical use. It seems that life-long treatment with anti-resorptives is required, since the disease is reactivated after treatment discontinuation. An international collaborating network for the continuous registration and follow-up of JPD patients could be helpful in the future.

1. Introduction

Juvenile Paget disease (JPD; MIM #239000) is a rare disorder that was first described by Bakwin and Eiger in 1956 [1]. In 1958, Swoboda described it as a separate entity combining characteristics of congenital hyperphosphatasia and Paget's disease of bone, without being identical with either [2]. In 1958, Choremis et al. also described a milder case of the disease [3]. The same disease has been also termed: hyperostosis corticalis deformans juvenilis, familial idiopathic hyperphosphatasia, chronic congenital idiopathic hyperphosphatasemia and familial osteoectasia. JPD results from mutations in the *TNFRSF11B* gene encoding osteoprotegerin (OPG) that result in loss of OPG activity [4,5]. Due to the close relationship between the deactivation of the *TNFRSF11B* gene and JPD, it has been proposed that JPD might be better termed "OPG deficiency" [6].

JPD is classified as a craniotubular dysostosis with hyperphosphatasia [5]. It is characterized by generalized, extremely rapid bone turnover. Bone turnover markers are all very high. As with other high turnover diseases, the

Abbreviations: ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase; BMD, bone mineral density; BP, bisphosphonate; CTX, C-terminal telopeptide of type I collagen; ELISA, enzyme-linked immunosorbent assay; JPD, juvenile Paget disease; MIM, Mendelian inheritance in man; PINP, total procollagen type I N-terminal peptides; OPG, osteoprotegerin; PPi, inorganic pyrophosphate; PTH, parathyroid hormone; RANK, receptor activator of nuclear factor-κB; RANKL, RANK ligand; TALP, total alkaline phosphatase; TNFR, tumor necrosis factor receptor; TRAP, tartrate-resistant acid phosphatase.

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growing skeleton is particularly vulnerable, and in JPD progressive skeletal deformity develops in childhood and worsens in adolescence. There are also extra-skeletal manifestations [5,7].

The aim of this review is to update the pathogenesis, clinical presentation and diagnosis of JPD, as well as available treatment options.

2. Literature Search

We performed a computerized literature search in the PubMed electronic database, not limited by publication time or language. We used the query: "(Juvenile Paget disease) OR (Juvenile Paget's disease) OR (hyperostosis corticalis deformans juvenilis) OR (familial idiopathic hyperphosphatasia) OR (chronic congenital idiopathic hyperphosphatasemia) OR (familial osteoectasia)", which provided 72 articles (last update August 23, 2017). The literature search was extended to the reference list of each selected article. Finally, automatic alerts (up to the submission of the review) were activated in PubMed ("My NCBI") to add relevant articles published after the initial search.

3. Prevalence

The exact prevalence of JPD remains largely unknown. Based on the above-mentioned search, approximately 80 cases of JPD have been reported in the literature to date. Making the assumption that one fourth of the patients may have been reported, the prevalence of JPD may be estimated to be <1 in 10 million. Being a recessively-inherited disease, it is more prevalent in cultures where marriage with close family members is practised. The Navajo people of the south-western USA do not practise kinship marriage, but it is estimated that 1 in 100 may be a heterozygous carrier [8]. The Navajo suffered a devastating loss of population in the 1860s through forced expulsion from their ancestral lands, and the current population has grown from a very small survivor group, permitting recessively-inherited disorders to become more prevalent [7,9].

4. Pathogenesis

4.1. *Osteoprotegerin Structure*

OPG is synthesized by preosteoblasts and osteoblasts [10] as an ~55 kDa monomer and then dimerized within the cell to an approximately 110 kDa molecule with disulfide links. It is secreted into the marrow space, largely in a dimeric form [11]. Its N-terminal harbors four cysteine-rich tumor necrosis factor receptor (TNFR) domains (designated I-IV); its C-terminal portion is unrelated to any known protein sequence [9,12]. The presence of two to six cysteine-rich motifs in the extracellular ligand-binding region is the classical signature of the TNFR family, to which OPG belongs. Domains I, III and IV each have four cysteines that form two disulfide bridges per domain; (SS1 and SS3); domain II has six cysteines that form three disulfide bridges (SS1, SS2 and SS3) [13]. *TNFRSF11B* gene has five exons. All of cysteine-rich domains I and II and a large proportion of III are encoded by the exon 2; exon 3 encodes the remainder of domain III and all of domain IV [13]. The function of the C-terminal domain remains largely unknown, but it has been early associated with the homodimerization OPG, heparin-binding and apoptosis [14].

4.2. *Early Experimental Studies in Osteoprotegerin Knock-out Mice*

OPG knock-out mice develop severe, early-onset, high turnover osteoporosis [15,16]. Although the bones appear normal at birth, bone loss starts at the first and fourth week of age in trabecular and cortical regions, respectively. Older mice develop long bone and vertebral fractures and severe deformity [15,16]. Bone loss, resulting from accelerated bone turnover, is accompanied by destruction of growth plate and a decrease in bone strength [16]. OPG knock-out mice also exhibit vascular calcification [15,16], a finding also encountered in some JPD patients.

4.3. *Genetics in JPD*

Most patients with JPD have homozygous mutations in the *TNFRSF11B* gene on chromosome 8q24, that either delete or cause loss-of-function resulting in OPG deficiency [5]. To our knowledge, only one patient with compound heterozygous mutations has been described [17]. OPG is a decoy receptor for the receptor activator of nuclear factor-κB (RANK) ligand (RANKL), and the mutations impair the ability of OPG to inhibit RANKL-induced bone resorption [18]. The mutant OPG produced by the affected gene fails to block the interaction between RANKL and RANK. In consequence there is continuous rapid bone resorption and formation, which impair growth, bone modeling and remodeling throughout the entire skeleton.

OPG can be shortened to amino acid 186 (close to the end of exon 3) and still maintain in vitro activity against osteoclastogenesis [14]. The degree of OPG disruption largely determines the phenotype and the disease severity. Mutations that result in severe OPG deficiency include those that cause major deletions [13], affect the start codon [19], cause failure of splicing of exons 3 and 4, or disrupt the SS1 or SS3 disulfide bonds. In the case of the deletion of the whole gene, there is complete OPG deficiency [4]. Mutations resulting in major deletions result in small OPG molecules (e.g., with 10 aminoacids [13]) and similarly severe OPG deficiency. The failure of splicing exon 3 to 4 possibly leads to an hypomorph, i.e., severe OPG deficiency. The disruption of SS1 and SS3 disulfide bonds possibly leads to the loss of tertiary structure of the ligand-binding domain of OPG, therefore impairing RANKL binding [9]. Mutations affecting the final cysteine residue preceding the SS3 disulfide bond [5] or the cysteine residue adjacent to SS1 bond possibly result in reduced affinity for RANKL binding due to unstable loop function and are considered as intermediate [9]. Finally, missense mutations affecting the C-terminal domain, thus not affecting the ligand-binding domain, result in mild forms of JPD. These

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