

Jansen's metaphyseal chondrodysplasia

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Abstract

Jansen's metaphyseal chondrodysplasia (JMC) (OMIM 156400) is a rare autosomal dominant disorder characterized by short-limbed dwarfism and severe, agonist-independent hypercalcemia. Four different mutations in the gene encoding the PTH/PTHrP receptor (PTHR1) were identified in several unrelated JMC patients. When expressed in vitro, these mutant PTHR1s cause agonist-independent cAMP accumulation. The PTHR1, a member of a distinct family of G protein-coupled receptors, is abundantly expressed in kidney and bone, where it mediates the PTH-dependent regulation of calcium and phosphorus, and in the growth plate, where it mediates the PTHrP-dependent regulation chondrocyte growth and differentiation. The presence of PTHR1 mutations that induce constitutive activity thus provides a plausible explanation for the abnormal regulation of mineral ion homeostasis and growth plate development in JMC.

Keywords

chondrodysplasia, delayed endochondral bone maturation, autosomal dominant, *PTHR1* gene

Disease name

Jansen's metaphyseal chondrodysplasia (JMC)

Definition

Jansen's metaphyseal chondrodysplasia (JMC) (OMIM 156400) is a rare autosomal dominant human disorder characterized short-limbed dwarfism due to delayed chondrocyte differentiation and an associated, usually severe hypercalcemia and hypophosphatemia, despite normal or undetectable serum levels of PTH or

PTHrP (1). These abnormalities are caused by mutations in the *PTHR1* that lead to constitutive, PTH- and PTHrP-independent receptor activation (2-4). Since the PTHR1 is most abundantly expressed in kidney and bone, and in the metaphyseal growth plate, these findings provide a likely explanation for the abnormalities observed in mineral homeostasis and growth plate development associated with this disorder.

Clinical features

The first patient was described by Murk Jansen (5), and follow-up was reported by De Haas *et al.* (6); descriptions of several other patients with the severe form of the disease followed (7, 8, 9, 10, 11, 12, 13). At birth, some JMC patients appear to be healthy (7, 11), while others show dysmorphic features which can include micrognathia, prominent eyes, high skull vault, hypertelorism, prominent cheeks, wide cranial sutures, and a high-arched palate (6, 10, 12-14). Due to choanal atresia and/or rib fractures, patients often develop post-partum respiratory distress and require intubation. During the first years of life, patients typically decline progressively from their normal growth curves, may have feeding difficulties, recurrent episodes of vomiting and dehydration, and present with short stature and with other findings which may include waddling gait, enlarged joints, prominent supraorbital ridges, frontonasal hyperplasia, and a "bell-shaped" thorax with widened costochondral junctions. The legs, in particular the tibiae, are typically bowed, and are short in comparison to the relatively long arms. Tooth development and enamel formation appear to be normal. Recently, a less severe form of JMC has been described (15). Longitudinal growth was closer to normal in the three affected members of this small kindred, and their laboratory and radiological findings were less prominent. Intelligence is within normal limits in all reported cases of JMC (6, 9-14, 16).

Laboratory findings

In the newborn period, blood calcium and phosphorus concentrations are typically in the upper normal range, while alkaline phosphatase activity, a marker of osteoblast activity, can already be elevated (9-14). Severe but asymptomatic hypercalcemia, usually develops during the first months after birth (especially if vitamin D treatment is initiated for suspected rickets), and is most pronounced during infancy and childhood when serum calcium can reach 20 mg/dl. Hypercalcemia is caused through at least two mechanisms: increased tubular reabsorption of calcium in the kidney (17) and markedly increased bone resorption as reflected by increased excretion of urinary hydroxyproline and hydroxypyridinoline, markers of osteoclastic activity. As a result of increased osteoblastic activity, serum alkaline phosphatase activity and osteocalcin concentrations are elevated. After puberty, and coinciding with the radiological improvement of the growth plate abnormalities and with an improvement in tubular calcium reabsorption, blood calcium levels improve, but remain elevated throughout life (9, 17, 18, 19).

Nephrogenous cAMP excretion is elevated or in the upper normal range, and urinary phosphate excretion is markedly increased. Similar to the bone histological findings, these laboratory abnormalities in Jansen's disease are, despite normal or undetectable concentrations of PTH, reminiscent of those observed in patients with mild primary hyperparathyroidism (6, 9-11, 13, 14, 17).

Radiologic and histologic analysis of the skeleton

Radiological studies in patients affected by the severe form of JMC usually show marked rachitiform metaphyseal changes of the long bones, i.e. widening, fraying, and cupping, which are best seen in the knee joints, and pathological fractures. However, distinct from the findings in rickets, metacarpals and metatarsals are also involved, and the base of the skull and the calvaria are sclerotic. Loss of the normal cortical outline, subperiosteal bone resorption, and generalized osteopenia are reminiscent of the changes seen in hyperparathyroidism. During childhood almost all tubular bones show irregular patches of partially calcified cartilage that protrude into the diaphyses. The metaphyseal regions are enlarged and expanded, resulting in the club-like appearance of the ends of the shafts. The changes at this stage of development are no longer reminiscent of rickets, and persist until the onset of puberty. The spine and the vertebral bodies show only mild or no obvious abnormalities (6, 9-14, 16). After adolescence, the irregular masses of cartilaginous tissue in the metaphyses gradually disappear. However, the ends of most tubular bones remain expanded, deformed, and radiolucent, but a more normal trabecular pattern gradually emerges. The large calcified masses in the metaphyses turn into bone, and result in the bulbous deformities. The base of the skull remains hyperostotic and a partial hearing loss, noted in the follow-up report of Jansen's original patient, was thought to be secondary to narrow internal auditory meati.

Only few histological descriptions of the growth plate abnormalities in JMC patients are currently available; these show wide, irregular masses of abnormal, protruding cartilage, a lack of the regular columnar arrangement of the maturing cartilage cells, and a severe delay in endochondral ossification of the metaphyses. There is no excess osteoid, usually indicative of active rickets or osteomalacia, and little or no evidence for osteitis fibrosa (7, 10, 16, 20). In contrast, bone specimens of adult JMC patients show significant fibrosis, beside extensive osteoblastic and osteoclastic activity. In one

patient an iliac crest biopsy after double tetracycline labeling showed cortical, but not cancellous, osteopenia, increased osteoclast surfaces, high normal apposition rates, and increased formation rates; these findings are similar to those observed in patients with mild, non-progressive hyperparathyroidism (17).

Pathogenesis

Studies in transgenic mice demonstrated that the PTHrP/PTHr1 signaling pathway is an essential regulator of endochondral bone development (21) and epithelial-mesenchymal interactions during the formation of the mammary glands and teeth (22). The findings in patients with JMC are the mirror image of those observed in Blomstrand's lethal chondrodysplasia (OMIM 215045) (1) and in mice homozygous for the ablation of *PTHrP* or the *PTHr1* (23, 24).

Molecular genetics

Four different mutation in the *PTHr1* gene were described in genomic DNA from patients affected by JMC. Three different, heterozygous mutations of the *PTHr1* were identified in the severe form of Jansen's disease; these involve codon 223 (His→Arg; H223R), codon 410 (Thr→Pro; T410P), and codon 458 (Ile→Arg; I458R) (2-4, 25). Expression of the PTHr1s carrying these mutations in COS-7 cells resulted in constitutive, ligand independent accumulation of cAMP, while the basal accumulation of inositol phosphates was not measurably increased (2-4). Furthermore, when the human PTHr1 with the His223Arg mutation was transgenically expressed in mice under the control of the rat α_1 (II) promoter (26), which targets expression to the layer of proliferative chondrocytes, there was a prominent delay in differentiation into hypertrophic cells. Furthermore a mild impairment in growth of long bones was observed, at least in animals with multiple copies of the transgene. These observations are consistent with the conclusion that expression of a constitutively active human PTHr1 in growth plate chondrocytes causes the characteristic metaphyseal changes in patients with JMC.

Recently, a novel heterozygous *PTHr1* mutation, codon 410 (Thr→Arg; T410R), was identified in several members of a small kindred with an apparently mild form of JMC (15). Affected individuals had, compared to patients with the previously identified activating *PTHr1* mutations (2-4), less severe growth plate abnormalities, relatively normal stature, normal plasma calcium concentration, yet significant hypercalciuria and normal or suppressed plasma PTH levels. When tested *in vitro*, the PTHr1 with the T410R mutation showed less

constitutive activity than that observed with the previously described T410P mutant (3, 27). This less pronounced agonist-independent cAMP accumulation induced by the T410R mutation is consistent with the less severe skeletal and laboratory abnormalities observed in this milder form of JMC.

Of note, mutations in the *PTHr1* gene have been associated to three diseases in addition to JMC, [Blomstrand's lethal chondrodysplasia](#) (OMIM 215045) (1), Eiken familial skeletal dysplasia (28), and [enchondromatosis \(Ollier's disease\)](#) (OMIM 16600) (29).

Genetics/Prevalence

JMC occurs in families of different ethnic backgrounds and appears to affect males and females equally. The mode of inheritance is autosomal dominant.

Genetic counseling

It is the genetic counseling of a rare autosomal disorder.

Antenatal diagnosis

In families with individuals known to be affected by JMC, diagnosis should be attempted through amniocentesis and appropriate molecular testing.

Treatment

There is no treatment.

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