CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Prenatal Presentation and Postnatal Evolution of a Patient With Jansen Metaphyseal Dysplasia With a Novel Missense Mutation in PTH1R

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Manuscript Received: 11 March 2013; Manuscript Accepted: 30 May 2013

Wave-shaped ribs were detected at prenatal ultrasound in a 20^{+1} week female fetus. At birth, skeletal radiographs showed marked hypomineralization and suggested hypophosphatasia. However, elevated blood calcium and alkaline phosphatase excluded hypophosphatasia and raised the possibility of Jansen metaphyseal dysplasia. Molecular analysis of the PTH/PTHrP receptor gene (*PTH1R*) showed heterozygosity for a previously undescribed transversion variant (c.1373T>A), which predicts p.Ile458Lys. In vitro evaluation of wild type and mutant PTH/PTHrP receptors supported the pathogenic role of the p.Ile458Lys substitution, and confirmed the diagnosis of Jansen metaphyseal dysplasia. This disorder may present prenatally with wavy ribs and in the newborn with hypomineralization, and may therefore be confused with hypophosphatasia. The mottled metaphyseal lesions typically associated with this disease appear only in childhood.

Key words: Jansen metaphyseal dysplasia; PTH/PTHrP receptor; PTH1R

How to Cite this Article:
Savoldi G, Izzi C, Signorelli M, Bondioni MP, Romani C, Lanzi G, Moratto D, Verdoni L, Pinotti M, Prefumo F, Superti-Furga A, Pilotta A. 2013. Prenatal presentation and postnatal evolution of a patient with Jansen metaphyseal dysplasia with a novel missense mutation in PTH1R. Am J Med Genet Part A 161A:2614–2619.

INTRODUCTION

Jansen metaphyseal dysplasia (JMD) is a rare autosomal-dominant skeletal disorder caused by mutations in the PTH/PTHrP receptor gene (*PTH1R*), leading to constitutive activation of the receptor independent of PTH or PTHrP [Schipani et al., 1995, 1996]. This disorder is characterized by short stature, bowed legs, waddling gait, contracture deformities of the joints, and short hands with clubbed fingers. The radiographic hallmarks of JMD are the severe metaphyseal changes, best identified in childhood, which lead to short-limbed short stature. The associated diagnostic laboratory findings are hypercalcemia, hypercalciuria, and mild hypophosphatemia, with normal or low levels of PTH or PTHrP in plasma [Jansen, 1934; Gram et al., 1959; Silverthorn et al., 1987; Kruse and Schtz, 1993].

Four distinct mutations in *PTH1R* have so far been described in patients with JMD: three of them were identified in the classic form of the disease (p.His223Arg, p.Thr410Pro, p.Ile458Arg) [Schipani et al., 1995, 1996, 1999] while the fourth one (p.Thr410Arg) appears to be associated with less pronounced skeletal and laboratory abnormalities [Bastepe et al., 2004].

Most reported patients have apparently de novo mutations [Schipani et al., 1995, 1996, 1999], while familial cases are very

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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 15 August 2013
DOI 10.1002/ajmg.a.36115

rare with only three reported to date [Charrow and Poznanski, 1984; Bastepe et al., 2004].

The diagnosis of JMD is difficult because of the rarity of this condition: most patients have been diagnosed in childhood or adulthood. Prenatal ultrasound signs have never been described. An earlier diagnosis is often driven by presence of complications in the neonatal period, such as respiratory distress or difficulty in feeding [Gordon et al., 1976; Schipani et al., 1999].

Here, we present a child with skeletal anomalies observed in the prenatal period. Only the clinical and laboratory findings at birth suggested the diagnosis of JMD.

CLINICAL REPORT

Prenatal Data

A 32-year-old woman (gravida 3, para 1), with unremarkable family and personal history, was referred to our prenatal diagnosis unit after a routine fetal anomaly scan at 20^{+1} weeks showed abnormal ribs. A repeat scan at 20^{+5} confirmed that the ribs had a wave-shaped deformity with an external concavity in the midst of their length (Fig. 1A). This resulted in a bell-shaped thorax (Fig. 1B) and small chest circumference. The facial profile showed micrognathia and retrognathia (Fig. 1C). The long bones of lower and upper limbs measured near the 50th centile (femur 31 mm, humerus 31 mm) [Romero et al., 1987], with normal shape and echodensity. Mineralization and shape of the cranium and vertebral bodies were also normal, as well as joints and movements. Overall fetal size (biparietal diameter 44 mm, head circumference 170 mm, abdominal circumference 153 mm) was also normal [Nicolini et al., 1986], with a normal amount of amniotic fluid. No other visceral abnormalities were found.

Multiple fractures were suspected to cause the abnormal rib shapes and parents were informed that osteogenesis imperfecta (OI) was a possible diagnosis. However, no other signs suggestive of OI were found. An amniocentesis karyotype was 46,XX; paternal uniparental disomy for chromosome 14, reported as a possibly associated with abnormal rib shape, was ruled out [Offiah et al., 2003]. No other genetic test was performed during pregnancy.

Monthly ultrasound examinations showed an unchanged shape of the thorax, with a mild degree of thoracic hypoplasia. The fetal growth was regular until birth, with the exception of femur and humeral length (60 and 51 mm, respectively), which slowed down from 32 weeks, and by 36^{+2} weeks were in the low normal range, but still above the 10th centile. The shape and echodensity of the long bones remained sonographically normal.

Postnatal Data

The baby was born at 37^{+6} weeks by cesarean. The birth weight was 3,190 g (63rd centile), length 49 cm (56th centile) and head circumference 34 cm (62nd centile) according to [Bertino et al., 2010]. The Apgar was 9 at both 1 and 5 min. Soon after birth, respiratory distress was noted and the baby was transferred to the Neonatal Care Unit, for oxygen-therapy. The first clinical examination showed, in addition to the facial dysmorphic features described prenatally, a bulbous nose, short philtrum, and low set ears. No craniotabes was apparent, the anterior fontanel was 4 cm $\times$ 4 cm and posterior fontanel was present. No other skeletal anomalies were noted on clinical evaluation, except for a bell-shaped thorax and long fingers. Examination of the heart and abdomen were normal. Axial muscular tone was decreased, with normal segmental tone, strength and deep tendon reflexes.

Radiological Data

At the age of one day, radiographic studies showed diffuse abnormalities of the bones, characterized by patchy ossification, metaphyseal irregularity, and periostal thickening. A fragmented appearance and slight widening of the pelvis, lower and upper limbs, including metacarpals and phalanges, was observed (Fig. 2A). Similarly to what observed on prenatal ultrasound, the

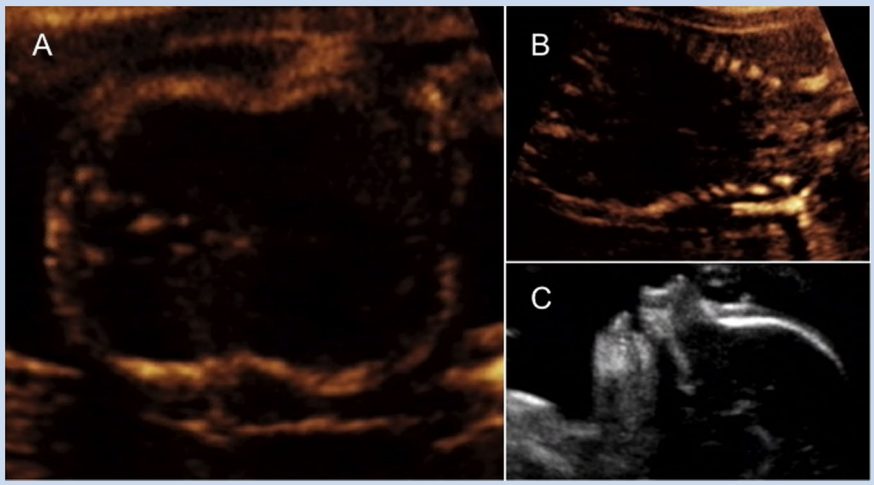

FIG. 1. Prenatal ultrasound appearance at 20 weeks. A: Transverse section of the thorax, B: Surface view of the ribs. The abnormal wave-shape of the ribs with the concavity in the central portion and the related mild lung hypoplasia were the main prenatal features C: Facial profile showing micrognathia and retrognathia.

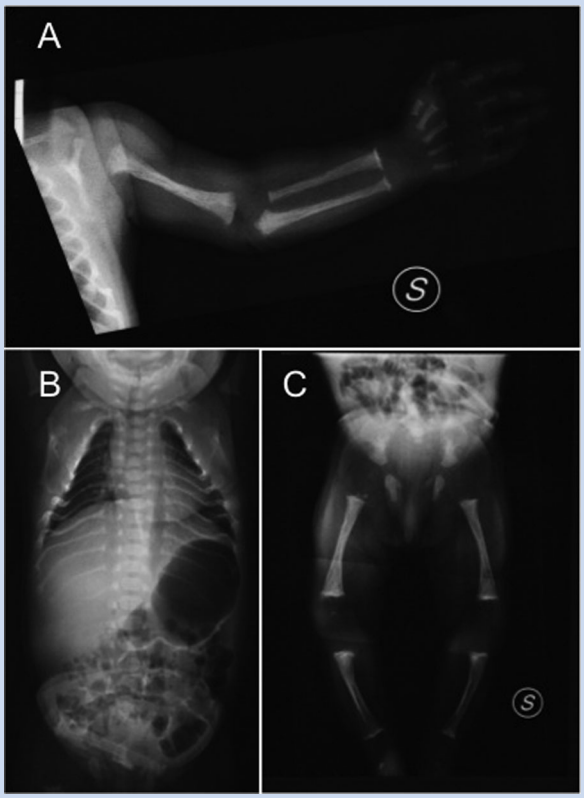

FIG. 2. One-day old girl. Panoramic radiograph of the left superior limb shows irregular metaphyses of the radio and ulna, and periosteal thickening of both bones. Metacarpals and phalanges demonstrate a slight widening (A). Radiograph shows abnormal ribs that appear spindly with irregular mineralization. No morphological changes in the spine can be observed (B). Radiograph showing bilateral erosion of the pelvis (C).

ribs showed irregular mineralization, and appeared short and spindly (Fig. 2B). A bilateral erosion of the pelvis was also present (Fig. 2C). The spine appeared normal. This radiological picture was strongly suggestive of hypophosphatasia.

Laboratory Data

At birth, hematologic measurements, serum electrolytes, hepatic and renal function were normal, as well as calcium and phosphorus (respectively 8.7 mg/dl—laboratory normal range 8.6–10.6 mg/dl; 6.7 mg/dl—laboratory normal range 5.0–8.5 mg/dl). Subsequently, calcium concentrations increased, reaching a peak (11.7 mg/dl) at 5 months of age, while phosphorus remained in the lower normal range. Alkaline phosphatase showed the same upward trend as calcium: constantly elevated concentrations were found since the second month of age (724 U/L, at 3 months of age—normal <462 U/L). Normal or undetectable concentrations of intact PTH were identified during the follow-up; after 8 days of vitamin D supplementation, the plasma concentration of 1-25-dihydroxyvitamin D was high (159 pmol/L—normal 48–110 pmol/L). After vitamin D suspension calcium concentration decreased, remaining in the upper normal range; at 3 months of age the calciuria/creatininuria ratio was 0.7 (normal for age < 0.4), without other urinary abnormalities and with normal renal function.

Clinical Course

After the age of 6 months, the growth rate decreased for both length and weight. At 2 years, weight was 9,700 g (3rd–10th centile), length 74.5 cm (<3rd) and head circumference 48 cm (25–50th centile). Serum calcium and phosphorus were respectively 10.3 mg/dl (normal 8.6–10.6 mg/dl) and 4.5 mg/dl (normal 5.0–8.5 mg/dl). The baby presented small stature, waddling gait and enlarged joints. The neurological examination showed apparently normal psychomotor development, but formal neurocognitive testing has not been performed.

The only notable finding was a reduction in dietary intake of calcium from the 17th month of age. At 2 years of age, repeated radiographs showed the characteristic signs of JMD. Particularly, in the pelvis, progression of metaphyseal involvement characterized by irregular and fragmented ossification, large epiphyses, wide distance between epiphyses, and metaphyses with irregular acetabula were observed (Fig. 3A). Conversely, the spine was overall normal, and the ribs showed improved ossification (Fig. 3B).

METHODS AND RESULTS

Biochemical Studies

Serum calcium, phosphorus, and alkaline phosphatase were measured by standard technique with an automated analyzer. Serum intact PTH was measured by a chemiluminescent automated system. Plasma 1-25-dihydroxyvitamin D was assayed by high performance liquid chromatography (HPLC).

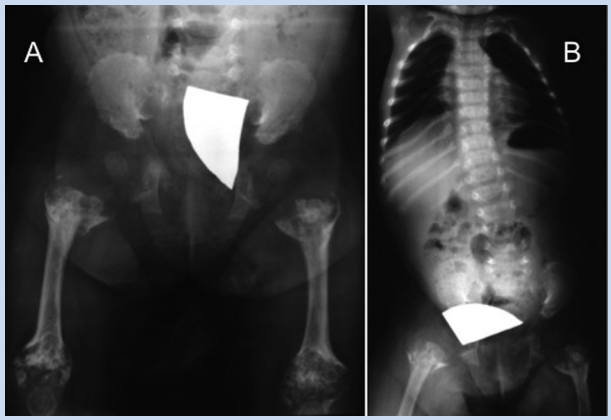

FIG. 3. Radiographic examination of the pelvis at 2 years shows progress of metaphyseal involvement with irregular ossification and wide distance between epiphyses and metaphyses (A). The vertebral bodies were normal in size and well ossified, as well as the ribs (B).

Mutation Screening and In Vitro Evaluation of Wild Type and Mutant PTH/PTHrP Receptors

Genomic DNA was extracted from peripheral whole blood with an automated nucleic acid extraction system (Maxwell® 16 System, Promega Corporation, Madison, WI), according to the manufacturer's recommendations, after informed consent was obtained from the patient's parents. The coding region of *PTH1R* (exons 1–14) was amplified by PCR using specific forward and reverse primers (details available on request), PCR products were analyzed by electrophoresis on 2% agarose gels and sequenced using the BigDye Terminator Cycle sequencing kit V 3.1 (Applied Biosystems, Foster City, CA) with an ABI PRISM 3130 Genetic Analyzer (Applied Biosystems), according to the manufacturer's recommendations. A heterozygous c.1373T>A variant was identified, which predicts p.Ile458Lys. This predicted amino acid change is localized in the seventh transmembrane domain of the receptor.

The PCR products corresponding to exon 13 of *PTH1R* from the affected patient, asymptomatic parents, and 150 control subjects were screened by DHPLC (Denaturing High-Performance Liquid Chromatography, Transgenomic, Omaha, NE). The mutation identified in the patient and corresponding to an abnormal DHPLC elution pattern was not identified in the healthy parents or in the normal controls. Review of the available databases showed that this mutation has not been reported, but a different amino acid substitution in the same codon has been reported in a patient with JMD [Kruse and Schtz, 1993; Schipani et al., 1999].

To evaluate the in vitro activity of the mutant receptor, the c.1373T>A mutation was introduced by site-directed mutagenesis (QuikChange® II Site-Directed Mutagenesis Kit, Stratagene, La Jolla, CA) in a plasmid DNA encoding the human PTH/PTHrP receptor cDNA containing the previously described p.Ile458Arg mutation (kindly provided by Prof. E. Schipani) [Schipani et al., 1999]. The same plasmid was used to obtain the wild type receptor and all introduced mutations were verified by sequencing analysis.

In order to compare the activity of wild type and mutant receptors, Chinese Hamster Ovary (CHO-S) cells were transiently transfected with varying amounts of the plasmids encoding the mutant or the wild type receptors. Briefly, cells were cultured in CHO Medium supplemented with 8 mM L-Glutamine and 10 mM HT Supplement in a 37°C/5% CO_2 incubator, plated (100.000 cells/well) in 24 well plates until 80% confluence and then transfected by Lipofectamine (Lipofectamine 2000™, Invitrogen Co, Carlsbad, CA), with increasing concentration (0.5, 1.0, or 1.5 μg/well) of plasmid DNA encoding p.Ile458Arg, p.Ile458Lys mutants or wild type receptors. Transfection efficiency was verified by co-transfection with one microgram of pmax-GFP vector encoding green fluorescent protein (GFP). After continuing culture for 24 hr, cells were lysed and cAMP measurements were obtained using a cAMP ELISA assay (Parameter™ Cyclic AMP kit Assay, R&D System, Minneapolis, MN).

Depending on the dose of plasmid DNA used for transfection, the basal cAMP levels in cells transiently expressing p.Ile458Arg and p.Ile458Lys mutants were four- to fivefold higher than the level in the cells expressing the wild type receptor (mean ± SE, 19.7 ± 1.4, and 20.1 ± 1.6 vs. 4.3 ± 0.4 pmol/ml in 100.000 cells transfected with 1.5 μg/ml plasmid DNA), consistent with the hypothesis that the mutant receptor has ligand independent constitutive activity (Fig. 4).

In order to test the expression ability of the mutated forms of PTH/PTHrP receptor, we transfected 100,000 CHO-S cells with 1.5 μg of the wild type and each of the mutated vectors. We then measured cell surface density of transfected cells with a three-step flow cytometric assay using a PTH/PTHrP receptor mouse anti-human monoclonal antibody (PTH/PTHrP-R (3D1.1)), Santa Cruz Biotechnology, Santa Cruz, CA) followed by staining with biotinylated goat anti-mouse IgG1 monoclonal antibody (Santa Cruz Biotechnology) and R-Phycoerythrin-conjugated Streptavidin (BD Pharmingen, San Diego, CA). Comparison of cell surface expression profile and mean fluorescence intensity between cells transfected with the wild type and the mutated form of the receptors did not show significant differences in triplicate experiments (data not shown), suggesting that expression of the mutant receptor was similar to that of the wild type receptor.

DISCUSSION

The prenatal detection of apparently isolated wave-shaped ribs in this patient, a rare and an unusual sonographic finding, had first suggested a differential diagnosis of OI and uniparental disomy for chromosome 14, both of which were excluded. The subsequent diagnosis of JMD identifies this disorder as yet another cause for this sonographic sign. The radiographic appearance at birth was considered suggestive of hypophosphatasia, because of defective bone mineralization, bilateral pelvic ossification defects and periostal thickening. However, the laboratory findings (hypercalcemia, increased serum alkaline phosphatase and normal or undetectable PTH) in association with low phosphoethanolamine in the urine were not compatible with hypophosphatasia and led instead to the suspicion of JMD.

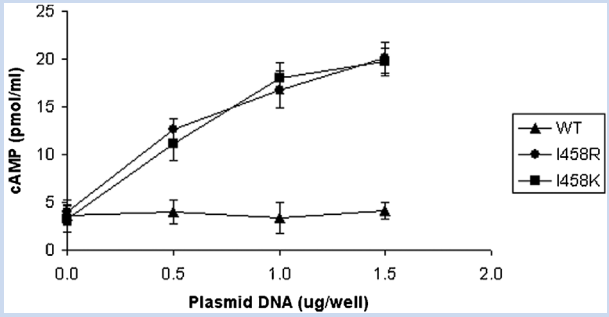

FIG. 4. Basal cAMP level in CHO-S cells transiently transfected with plasmid encoding the wild type receptor (▲), the p. Ile458Lys mutant (■) and the p.Ile458Arg mutant (●). Cells were transfected with different amounts of wild type and mutant plasmid and analyzes for cAMP concentration after 24 hr transfection, as described in Results and Methods Section. The data are given in picomoles/mL and represent the mean of three independent experiments.

The diagnosis of JMD is usually suggested by clinical and radiographic findings at birth such as enlarged joints and typical metaphyseal changes, but these were absent in the patient reported here. Moreover, the baby was of normal length and body proportions in contrast with the reported patients with JMD that are typically short and disproportionate. The diagnosis of JMD was first suspected after observation of elevated calcium and ALP in plasma. Molecular analysis of the *PTH1R* gene confirmed the hypothesis of JMD.

Mutation analysis showed a single nucleotide variation of *PTH1R* gene that predicts p.Ile458Lys. This sequence variation was not observed in the clinically unaffected parents, which suggests that this mutation is de novo.

Up to date only four different mutations in the *PTH1R* gene have been described: p.His223Arg, p.Thr410Pro, p.Ile458Arg, p. Thr410Arg. In distinctron from the other three mutations, p. His223Arg has been identified in several patients [Schipani et al., 1995, 1996, 1999; Bastepe et al., 2004]. The mutation described here (p.Ile458Lys) lies in the same codon as the previously reported p.Ile458Arg mutation. In vitro functional studies demonstrated that, in the absence of agonist, cells expressing the receptor with the activating p.Ile458Arg mutation accumulate two- to eight-fold more cAMP than cells expressing the wild-type receptor [Schipani et al., 1999]. Given the similar chemical nature of the two substituting amino acids, lysine and arginine (both being cationic), we hypothesized that the p.Ile458Lys mutation could have similar effects as the previously reported p.Ile458Arg substitution and was pathogenic. Our functional study data obtained in CHO-S cells, transiently transfected with plasmids encoding either the wild type or the mutant p.Ile458Lys receptor, showed that the basal cAMP levels increased approximately fourfold in the presence of the mutant receptor, supporting our hypothesis that this variant is pathogenic.

A genotype–phenotype correlation it is not yet possible in JMD because of the great variability in the clinical and radiological features and because of the lack of molecular characterization in the few reported cases.

The patient described with the p.Ile458Arg mutation in the same codon as the present patient (p.Ile458Lys) was complicated by polyhydramnios during pregnancy. Weight at birth was 3.4 kg, but no relevant clinical data were reported for the first 2 years. At the age of 2 years, skeletal radiographs showed findings typical of JMD, and height was significantly below the third percentile [Schipani et al., 1999]. In the patient reported here, fetal ultrasound at 20 weeks of gestation showed abnormally shaped ribs, bell-shaped thorax, small chest circumference, micrognathia, and retrognathia. The long bones of lower and upper limbs were of normal length, shape and echodensity, and only showed a reduction in growth rate towards the end of the pregnancy, with no other associated findings and normal amount of amniotic fluid.

Reported patients with p.His223Arg, p.Thr410Pro, or p. Ile458Arg mutations were characterized by early onset of the typical clinical and laboratory anomalies and by a worsening trend. In contrast to these, the p.Thr410Arg mutation was found in two affected sons and in their father and was characterized by less pronounced agonist-independent cAMP accumulation in vitro and by a milder clinical phenotype. In this family the milder phenotype delayed the diagnosis: the two brothers were referred for evaluation of bone dysplasia associated with kidney stones; the father was considerably taller than all other previously reported patients; all three showed normal serum calcium and phosphate concentration, but elevated urinary calcium excretion and elevated serum 1,25 dihydroxy vitamin D3 [Bastepe et al., 2004].

Considering the unreported prenatal onset of the disease and the absence of typical radiographic findings at birth, we conclude that the present patient enlarges the spectrum of clinical manifestation of JMD. The features at birth led us to hypothesize an atypical form of the disease, while the clinical and biochemical features at 2 years of age have unexpectedly showed the classic radiological findings of the disease.

The detection of rib anomalies in the prenatal period is probably related to an atypical presentation of the dysplasia in the present case; only long-term clinical observation will allow us to better define the clinical course and picture of the disease in this patient. Also, it is possible that the detection of prenatal anomalies may be explained by the improvement in prenatal sonography. The only prenatal anomaly reported in JMD patients so far is polyhydramnios [Gordon et al., 1976; Schipani et al., 1999], which was however absent in the present patient. It is noteworthy that even the most recent comprehensive atlas of fetal sonography in skeletal dysplasias does not contain an image of JMD [Hall et al., 2012]. The observation of prenatal sonographic findings and the illustration of the skeletal dysplasia in the newborn period in the present patient may be useful for the early diagnosis of JMD.

ACKNOWLEDGMENTS

The authors thank the patient and her family for participating in the study. A special thanks to Prof. E. Schipani who kindly provided the plasmid encoding the human PTH/PTHrP receptor cDNA containing the p.Ile458Arg mutation and for her valuable comments and suggestions.

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