Title
Severe Hypertension – An Infantile Feature of Jansen Metaphyseal Chondrodysplasia?

Running Title
Hypertension in Jansen Metaphyseal Chondrodysplasia

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Abstract

Jansen metaphyseal chondrodysplasia (JMC) is a rare autosomal dominant skeletal dysplasia caused by gain-of-function mutations in the parathyroid hormone receptor 1 gene, PTH1R. We report on a patient presenting in the neonatal period with clinical signs of JMC in addition to severe hypertension. A pathogenic mutation in PTH1R was demonstrated, but investigations for hypertension yielded normal results. Hypertension has not been previously associated with JMC. Given aberration of the parathyroid hormone (PTH)/parathyroid-related protein (PTHrP) pathway is the underlying pathogenic mechanism attributed to JMC, and also given evidence that hyperparathyroidism plays an important role in blood pressure homeostasis, we propose that hypertension is a hitherto unrecognized feature of JMC.

Introduction

Jansen metaphyseal chondrodysplasia (JMC) is a rare skeletal dysplasia with fewer than 25 cases reported in the medical literature to date. While described patients predominantly initially present in late infancy or early childhood, neonatal presentation has been reported on at least six occasions (Charrow & Poznanski, 1984; Saito et al., 2018; Savoldi et al., 2013; Schipani et al., 1999), none of which have had hypertension reported.

The characteristic clinical features of JMC include short-limbed short stature; leg bowing; waddling gait; contracture deformities of the joints; short hands with clubbed fingers; and prominent upper face with small mandible. Neonatal findings can include
choanal atresia; micrognathia; proptosis with hypertelorism; dolichocephaly; prominent cheeks; wide cranial sutures; and a high-arched palate (Silve & Juppner, 2005). Radiological findings vary with age, but cardinal characteristics include generalized osteopenia and osseous cortical thinning; disorganized irregular metaphyses; large epiphyses; a widened epi-metaphyseal distance in the long bones; and a sclerotic skull base (Kozlowski, Campbell, Azouz, & Sprague, 1999; Nazara et al., 1981). Biochemically, hypercalcemia and hypercalciuria with relative hypophosphatemia are observed. Despite the radiological and biochemical features being consistent with hyperparathyroidism, parathyroid hormone (PTH) levels are depressed (Kruse & Schutz, 1993). To date, hypertension has not been a reported feature of JMC.

JMC is an autosomal dominant condition whose biochemical features are accounted for by heterozygous gain-of-function mutations in the parathyroid hormone receptor 1 gene PTH1R (Schipani, Kruse, & Juppner, 1995), explaining why the biochemical profile mimics that of hyperparathyroidism. The PTH1R protein is a G-protein-coupled receptor. Normally, the binding to one its ligands, PTH or PTH-related protein (PTHrP), activates the cAMP signalling pathway (Juppner et al., 1991). In JMC, the receptor is constitutively activated.

Hyperparathyroidism is a known independent risk factor for hypertension (Jorde, 2006; Jorde, Sundsfjord, Haug, & Bonaa, 2000). Here, we present a patient diagnosed with JMC in the neonatal period who concurrently had severe hypertension. Given that the molecular pathogenesis of JMC mimics that of hyperparathyroidism, we propose that hypertension is a feature of JMC which has not been previously recognized.
Case

Informed consent was formally obtained from the patient’s mother and legal guardian to report on this case. The patient was a male neonate, first born to a white Australian mother and Afghani father (non-consanguineous). Both parents were of normal stature and neither had any family history of note. The prenatal period was unremarkable; the mother had a normal second trimester morphology scan. Induction of labor occurred at term for prolonged rupture of membranes. The birth weight was 4080g, length 52cm, and head circumference 36.5cm (all parameters between 90th and 99th percentiles). Respiratory distress was noted and subsequently right choanal stenosis was diagnosed. A nasopharyngeal tube was inserted and continuous positive airway pressure instituted with good effect. Routine observations noted persistent hypertension, with systolic blood pressure frequently above 100mmHg (reference range [RR] 50-70mmHg). Captopril 0.1mg/kg q8h was commenced and titrated up to 0.2mg/kg q8h, at which point normotension was achieved. Occasional episodes of systolic blood pressure of 75mmHg persisted.

On examination, a number of dysmorphic features were noted including a large anterior fontanelle; brachycephaly; hypertelorism; proptosis; downsllanting palpebral fissures; low set ears with slightly dysplastic pinnae; micrognathia; and a tented palate (figure 1). The thorax was hypoplastic and the peripheries were normal.

A skeletal survey demonstrated diffuse abnormalities and generalized hypomineralization. In the spine, there was thoracic platyspondyly and ovoid lumbar vertebral bodies. The ribs were slender and the iliac wings were small. All long bones were under mineralized, undetubulated, mildly bowed, and subperiosteal
resorption was evident. There was generalized metaphyseal cupping and splaying (figure 2). A clinical diagnosis of JMC was made. Genetic sequencing was organized (Genetaq Laboratories, Malaga, Spain) and a PTH1R: c.668A>G (p.His223Arg) mutation was identified in the heterozygous state, confirming the diagnosis of JMC (Schipani et al., 1995).

Biochemical results at week one of life included: serum Ca\(^{2+}\) 2.54mmol/L (RR 2.05-2.90), PO\(_4^-\) 1.56mmol/L (RR 1.8-3.0), alkaline phosphatase 153mmol/L (150-300) and PTH 1.2pmol/L (RR 2.0-9.5). At two weeks of age, aldosterone was 1700pmol/L (RR 50-5800) and the aldosterone to renin ratio was 7 (RR<70). By 10 weeks of age, serum Ca\(^{2+}\) had increased to 3.06mmol/L, PO\(_4^-\) was 1.47mmol/L, and PTH <1.2pmol/L. Alkaline phosphatase was elevated at 614U/L (RR 70-250). Normal biochemistry included thyroid function tests, lysosomal enzymes, carbohydrate deficient transferrins, and serum vitamin D.

Further investigations included normal serial renal ultrasounds and renal artery Doppler; echocardiography; plasma catecholamines; serum adrenocorticotropic hormone; and serum cortisol. The proband was discharged from hospital on oral captopril, which was weaned over the first twelve months of life, by which time the patient was normotensive.

Discussion

With fewer than 25 cases reported in the medical literature since the original case report by (Jansen, 1934) it is evident that the incidence of JMC is very rare and the phenotype is likely yet to be fully elucidated. The majority of patients with this short-
limbed skeletal dysplasia present after infancy, suggesting clinical signs of the bony dysplasia are frequently not evident until after independent weight bearing and ambulation are established. That said, antenatal and neonatal presentations have been described (Charrow & Poznanski, 1984; Gordon et al., 1976; Savoldi et al., 2013; Schipani et al., 1999).

Despite the preferred term “metaphyseal chondrodysplasia”, JMC initially presents as a generalized skeletal dysplasia. Wide-spread skeletal hypomineralization and ragged metaphyseal irregularities are suggestive of rickets or hypophosphatasia (Charrow & Poznanski, 1984), but the biochemical findings are inconsistent with either of these differential diagnoses. Calcium is elevated in blood and urine, while phosphate is depressed. Serum PTH is either normal or slightly depressed. Alkaline phosphatase is mildly elevated (Kruse & Schutz, 1993). In early childhood, the skeleton appears increasingly ossified, but bowing of the long bones becomes more pronounced, particularly in the lower limbs. The metaphyses progressively become expanded and irregularly ossified. By adulthood, fully ossified and widened metaphyses give the long bones a club-like appearance (Charrow & Poznanski, 1984; Silve & Juppner, 2005). Although biochemical parameters trend towards normality with age, the pattern of elevated calcium, low phosphate and low-normal PTH remain (Onuchic, Ferraz-de-Souza, Mendonca, Correa, & Martin, 2012).

JMC is caused by heterozygous gain-of-function mutations in PTH1R, rendering the translated G-protein coupled receptor protein (parathyroid hormone 1 receptor, or PTH1R) constitutively active. To date, five pathogenic mutations have been described: c.668A>G(p.His223Arg), c.1228A>C(p.Thr410Pro), c.1373T>G(p.Ile458Arg), c.1373T>G (p.Ile458Lys), all resulting in the classical phenotype, while c.1229C>G (p.Thr410Arg) has been observed in one kindred with
attenuated disease (Saito et al., 2018).

Although predominantly expressed in kidneys, bone and cartilage, PTH1R is expressed in a myriad of other fetal and adult tissues including cardiac, placental, breast, pulmonary, and many epithelial derivatives. This suggests its role goes beyond that of simple calcium homeostasis (Schipani & Provot, 2003). While JMC initially appears as a generalized disorder of skeletal ossification, with increasing age it becomes clear that clinically the metaphyses are preferentially affected by the pathophysiology. This observation is explained by the very high expression of PTH1R in perichondrial cells and the proliferating chondrocytes in the growth plates, as demonstrated in murine expression studies (Lanske et al., 1996; Vortkamp et al., 1996).

To date, hypertension has not been documented in the medical literature in any patients with JMC. In our patient, hypertension was noted in the first days of life and persisted throughout infancy. Given the lack of an alternate organic cause, we hypothesize that the elevated blood pressure observed was a result of the constitutive activation of PTH1R. Epidemiological studies have demonstrated that high circulating PTH levels are an independent risk factor for elevated blood pressure (Chan et al., 2012; Jorde, 2006). A biological mechanism for this association has not been definitively demonstrated to date. In vitro, both cardiac and renal tissues increase norepinephrine release when the PTH1R receptor is activated, suggesting a possible sympathomimetic mechanism (Potthoff et al., 2011), although our patient had no clinical or biochemical indicators of a generalized increase in sympathomimetic activity.
Alternate hypotheses exist as to how constitutive activation of PTH1R in JMC may cause hypertension. Both (Luigi et al., 2012) and (Broulik et al., 2011) described a high prevalence of hypertension in individuals with primary hyperparathyroidism (PHPT). Each group documented resolution of elevation of both systolic and diastolic pressures post parathyroidectomy. However, their cohorts did have a number of other cardiovascular risk factors (features of the metabolic syndrome) and so such cofounders do not allow us to definitively attribute the normalization of blood pressure directly to the normalization of PTH levels. Even if such a direct link was proven, the findings cannot explain the spontaneous resolution of hypertension in our patient where PTH1R remains constitutively active.

The acute and short-term activation of PTH1R, when bound to one of its ligands (PTH or PTHrP), acts as a potent vasodilator through increasing endothelial intracellular calcium, mediated via the cAMP signalling system (Nickols, Metz, & Cline, 1986). Prolonged exposure of the PTH1R receptor to a ligand, as occurs in PHPT, results in a paradoxical effect - vasoconstriction. Murine modelling strongly indicates this occurs because prolonged exposure of PTH1R to PTH results in biochemical decoupling of cAMP from PTH1R (Hanson & Linas, 1994). This would potentially explain why the hypertension in our patient commenced in the neonatal period as the receptor was acting autonomously through the gain of function mutation, in effect already being ‘decoupled’ from cAMP. The resolution of the hypertension over the course of infancy, however, is less easy to explain. One would assume the constitutively active endothelial receptor would exert its effects throughout life. That said, temporal expression studies of the PTH1R gene throughout the lifecycle of the vasculature, including in the heart and kidneys, appears to be lacking. It may be possible that PTH1R expression in these tissues decreases throughout the first year of
life, offering an explanation for the apparent spontaneous resolution. This would also explain why hypertension has not been documented in other patients with JMC, most of whom were diagnosed after 12 months of age. Such PTH1R temporal expression studies of the vasculature are warranted to further explore this hypothesis.

Conclusion
We report a patient with JMC with severe idiopathic hypertension, the latter of which resolved over the first 12 months of life. Given rarity of JMC, and the fact most reported cases thus far were not diagnosed until after the age independent ambulation, we propose that hypertension is a cardinal feature of JMC, at least in the infantile period. We provide a hypothesise as to why hypertension resolves in JMC over the course of infancy, explaining why this association has not been previously reported. We recommend vigilant monitoring of blood pressure in all individuals diagnosed with JMC, especially during the neonatal and infantile periods.

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Figure 1. The patient at six weeks of age demonstrating a wide forehead indicative of a large anterior fontanelle; hypertelorism; proptosis; downslanting palpebral fissures; and micrognathia.

Figure 2. Skeletal survey of the patient taken during the neonatal period. (A) Hypomineralized calvarium with sclerotic base of skull. (B) Under mineralized, undertubulated, and mildly bowed ling bones with generalized metaphyseal irregularities and cupping. (C) Ovoid lumbar vertebral bodies. (D) Slender ribs and thoracic platyspondyly. (E) Hypoplastic iliac wings with further examples of undermineralized bowed long bones and diffuse metaphyseal irregularities.