

Case Report

## A Case Report of Pycnodysostosis Associated with Multiple Pituitary Hormone Deficiencies and Response to Treatment

### Multiple Pituitary Hormone Deficiency in Pycnodystosis

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#### What is already known on this topic?

Pycnodysostosis is a rare autosomal recessive osteosclerotic bone disorder caused by a mutation in the cathepsin-k gene. Growth hormone (GH) deficiency is associated with nearly half of the patients suffering from Pycnodysostosis. The treatment is mainly conservative and supportive. Recombinant human growth hormone (rhGH) may be tried in a selected group of patients.

#### What does this study add?

We report a female with Pycnodysostosis with associated with GH deficiency who was managed with rhGH. She had a favourable response with improvement in height SDS of 1 over 18 months of treatment. rhGH can unmask central hypothyroidism requiring l-thyroxine replacement. A patient of pycnodysostosis requires monitoring for central hypothyroidism and other pituitary hormone deficiencies, especially if rhGH treatment is being offered.

#### Abstract

Pycnodysostosis is a rare autosomal recessive osteosclerotic bone disorder associated with short stature and multiple bony abnormalities. Growth hormone (GH) deficiency may contribute to short stature in about 50 % of patients. Available literature has rarely reported other pituitary hormone deficiencies in pycnodysostosis. Though the management remains conservative, recombinant human growth hormone (rhGH) is tried in selected patients. Here we present a case of pycnodysostosis which was evaluated for associated co-morbidities and found to have multiple pituitary hormone deficiencies. A 7-year-old girl was referred to our centre for evaluation of short stature. On examination, she had frontal and occipital bossing, limited mouth opening, hyperdontia with multiple carries, short and stubby digits and short stature. Investigation revealed dense sclerotic bones with frontal and occipital bossing, non-fusion of sutures with obtuse mandibular angle, non-pneumatized sinuses, small 'J' shaped sella turcica, acro-osteolysis of digits and absent medullary cavities. Cathepsin K gene mutation analysis confirmed the diagnosis of pycnodysostosis. She was screened for associated co-morbidities and was detected to have concomitant GH deficiency. Treatment with rhGH brought about an increase of 1 SDS in height over 2 years. rhGH treatment unmasked central hypothyroidism at three months necessitating l-Thyroxine replacement.

**Keywords:** Pycnodysostosis, Short stature, Multiple pituitary hormone deficiencies

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#### Introduction

Pycnodysostosis is a rare autosomal recessive osteosclerotic bone disorder.<sup>1</sup> It is caused by homozygous or compound heterozygous mutation in the Cathepsin-K (CTSK) gene, which maps chromosome 1q21.<sup>2-4</sup> The disease is characterised by specific bony abnormalities, facial features and short stature.<sup>5,6</sup> Growth hormone (GH) deficiency is associated in about half the patients of Pycnodysostosis.<sup>5</sup> However, other pituitary hormone deficiencies have not been reported in the available literature.

Presently, there is no established therapy for pycnodysostosis.<sup>7,8</sup> The management is primarily symptomatic and preventive.<sup>9</sup> In a case series of 8 patients of pycnodysostosis four patients had associated GH deficiency and they responded well to GH treatment with normalisation of Insulin-like growth factor – 1 (IGF-1) and acceleration in growth velocity.<sup>5</sup> Karamizadeh et al., in a cohort of 8 patients with pycnodysostosis, have reported a positive impact on linear growth on GH treatment.<sup>10</sup> GH treatment based on IGF-1 based dosing regimen when offered to 3 children with pycnodysostosis and 16 children of idiopathic short stature, resulted in near-normal stature and body proportion.<sup>11</sup> Genetic testing and counselling is often a neglected aspect in pycnodysostosis and should be offered to all patients and relatives.

Here we present a case of pycnodysostosis associated with GH deficiency. The patient responded favourably to recombinant human growth hormone (rhGH) treatment. However, rhGH treatment unmasked central hypothyroidism, necessitating l-thyroxine replacement.

#### Case report

A 7-year-old girl was referred to our centre for evaluation of short stature. She was the product of a second-degree consanguineous marriage. She had two elder sisters aged 16 and 18 years who had similar morphological features and a

brother aged 14 who was healthy. (Figure 1) The sisters had attained menarche at 14 years of age. Anti-natal and peri-natal periods were uneventful. Her birth weight was 2.1 Kg. The parents reported a poor gain in height since birth. She had a history of two fractures on trivial trauma one involving right tibia and one involving left radius at 4 and 5 ½ years of age respectively. The fractures took a long time to heal. Height and weight were plotted on the Indian association of paediatrics (IAP) growth chart for Indian girl aged 5-18 years.<sup>12</sup> On physical examination, her height was 84 cm (-5.6 SDS), and the head circumference was 68.5 cm. (Figure 2) The mother's height was 158 cm, and the father's height was 172 cm, and her target height was 158.5 cm. The affected sisters aged 16 and 18 were 110.5 and 114 cm, respectively. (Both below 5<sup>th</sup> centile). The height of unaffected elder brother was 158 cm (Appx 50<sup>th</sup> centile). The brother had not reached a final height. The sibling sisters have attained a final height as the epiphyses have fused. The height of the sibling sisters was less even when compared to patients of Pycnodystosis. On examining the historical records, it was observed that her height velocity had been 1.2 cm/year for the last two years. Her sexual maturity rating was pre-pubertal. She had facial dysmorphism with frontal, occipital bossing and limited mouth opening. (Figure 3) She had short hands with short and stubby fingers with dystrophic nails. (Figure 4) Anterior fontanelle had not closed and measured 1.8 cm. The fontanelles of the affected sisters had closed. Examination of the oral cavity revealed hyperdontia, multiple caries and a grooved palate. Hepatosplenomegaly was present.

Laboratory examination revealed normal haematological parameters. The serum calcium, urea, creatinine, phosphorus, alkaline phosphatase, intact parathyroid hormone and 25 (OH) Vit D levels were normal. Her Insulin-like growth factor-1 (IGF-1) level was 56 ug/l (Normal range 58-367 ug/l for a seven-year-old girl). A growth hormone (GH) stimulation test was carried out with clonidine and revealed a peak value of 1.1 ng/ml, indicating GH deficiency. Her basal and ACTH stimulated cortisol levels were within normal limits. T4 was 6.5 ug/dl (Normal value 4.6-12 ug/dl), and TSH was 3.2 mIU/ml. The IGF-1 for the affected sister aged 16 years was 182.6 ug/l (Normal range 127-541 ug/l) and of the sister aged 18 years was 201.2 ug/l (Normal range 121-486 ug/l) with a normal thyroid profile. Radiographic examination revealed generalised osteosclerosis. The medullary cavities were absent in the long bones. Skull radiography revealed frontal and occipital bossing, non-fusion of sutures with obtuse mandibular angle, absence of mastoid air cells and small 'J' shaped sella turcica. (Figure 5) Terminal phalanges of hands showed acro-osteolysis. (Figure 4) MRI Sella revealed a hypoplastic anterior pituitary with a volume of 121 mm<sup>3</sup> (< 5<sup>th</sup> centile for age)<sup>13</sup> and a typical posterior pituitary bright spot. Thyroid function test and both basal and stimulated cortisol were normal. Arterial blood gas analysis did not reveal any hypoxia.

Polysomnography did not show any evidence of obstructive sleep apnoea. Audiometry and ophthalmic examination were normal.

Molecular testing of Cathepsin-K (CTSK) gene showed a homozygous missense variant CTSK:C.890G>C. The parents were found to be carriers of the same variant. Consent could not be obtained from the affected sisters and the unaffected brother for genetic testing due to the financial constraints of the family. The parents were counselled regarding their carrier status, and the siblings advised regarding the benefits of genetic testing.

She was offered conservative and symptomatic management. Orthodontic and Endodontic treatment was provided for caries and malposition of teeth. Counselling regarding oral hygiene, fracture prevention and other psychiatric aspects of the disease were undertaken.

Because of the GH deficiency, recombinant human Growth hormone was administered at 0.16 mg/kg/week. An IGF-1 level was repeated after four weeks which was still low. On the IGF-1 response, the dose was gradually increased to 0.48 mg/kg/week. An incremental IGF-1 response and increase in height velocity ruled out GH resistance. The compliance to treatment was proper on regular monitoring. On follow-up, a repeat evaluation of her thyroid axis at three months of treatment revealed a T4 of 3.1 ug/dl and TSH of 9.2 mIU/ml. She was started on l-thyroxine replacement of 50 ug/day after which the T4 normalised to 10.4 ug/dl at the end of 2 months of treatment. At the end of 18 months of treatment, her height was 97 cms. She had exhibited a 9 cm increase in stature over the first year of treatment and four cms over the next six months. Her height velocity was 8.7 cm/year over 18 months, and there was a gain of 1 SDS in height over this treatment period. There was no adverse effect on GH treatment.

### Discussion

Pycnodysostosis remains a rare cause of short stature. However, in patients suffering from the disease, short stature is a constant feature afflicting 90.32 % of cases ranging from -1.5 to -6 SDS as in our case.<sup>13</sup> The short height is primarily due to impaired bone remodelling and subsequent sclerosis of the bones. Other contributors of short stature in pycnodysostosis are malnutrition, chronic airway obstruction and hypoxemia.<sup>5</sup> Our patient had a healthy BMI, and arterial blood gas analysis and these abnormalities were ruled out in our patient. Pycnodysostosis may be associated with hypopituitarism.<sup>4</sup> In our patient, the Pituitary-adrenal was intact. However, she had a low IGF-1. As alteration in the GH-IGF-1 axis has not been studied in Pycnodysostosis, we decided to confirm GH secretory defect with a GH stimulation test with an inadequate secretory response indicating GH deficiency. GH deficiency has been demonstrated in 50 % of the patients of pycnodysostosis. The deficiency may be due to pituitary hypoplasia caused by an increased bone volume of the sella and increased intrasellar pressure.<sup>5</sup> Bone age cannot be commented on as disease-specific nomograms are not available. Bone age determination is difficult to assess in these patients.

The diagnosis is based on relevant history, clinical features and radiological examination as was in this case. If available, a genetic analysis should be carried out. We could demonstrate a CTSK gene homozygous missense variant CTSK:C.890G>C on molecular genetic testing. The mutation is known in humans (HGMD CS072172). The mutation results in change in protein structure Serine to Threonine at position 297 of the cathepsin-K protein (S297T).<sup>14</sup> Polyphen-2 predicts the mutation to be "Possibly damaging" and the Mutationtaster predicts the mutation to be "Damaging".<sup>15,16</sup> Genetic analysis may reveal novel CTSK gene mutation in a homologous or a compound heterozygous pattern.<sup>2</sup> Genetic testing, and counselling is often a neglected aspect of the disease. Genetic testing was offered to the index patient and the parents, however, due to financial constraints, could not be extended to the siblings.

The treatment remains conservative and primarily targets preventive counselling. The patients can live a near-normal lifestyle. Growth hormone (GH) and IGF-1 have an anabolic role in bone metabolism.<sup>17</sup> Only a few studies have

demonstrated the efficacy of recombinant human growth hormone (rhGH) treatment for pycnodysostosis. Rothenbühler et al. initiated GH treatment in 3 children with Pycnodysostosis in a dose of 29 ug/kg/day, 67 ug/kg/day & 120 ug/kg/day and observed near-normal adult stature and normalisation of the skeletal proportions.<sup>11</sup> GH treatment, in a dose of 18 U/m<sup>2</sup>/week, significantly improved growth velocity from 3.3 ± 0.8 cm/year to 9.4 ± 2.1 cm/year during the first year and 7.5 ± 1 cm/year in the second year.<sup>5</sup> Height SDS and growth velocity increases on rhGH treatment, in a dose of 50 ug/kg/day, when compared to pre-treatment level and after stopping the GH therapy in patients manifesting with GH deficiency in pycnodysostosis.<sup>10</sup> The dose used by us was initially 23 ug/kg/week, which was gradually increased to 68 ug/kg/week based on IGF-1 levels. The doses of rhGH required for pycnodysostosis are higher as compared to those used in Idiopathic short stature and Growth hormone deficiency<sup>18</sup>, and the same was also demonstrated in our patient.<sup>5,11,10</sup> Our patient had an increase in growth velocity to 8.7 cm/year. The SDS also improved from -5.6 to -4.59, a gain of 1 SDS. rhGH treatment may unmask central hypothyroidism in 36-47 % of patients who appear euthyroid before initiation of rhGH treatment.<sup>19</sup> Central hypothyroidism though rarely reported in pycnodysostosis was exposed by rhGH therapy in our patient requiring l-thyroxine replacement.

### Conclusion

Pycnodysostosis remains a rare cause of short stature and is associated with various skeletal and dental abnormalities. GH deficiency may be present in nearly half of these patients. Other contributors to short height like malnutrition, chronic hypoxemia, hypopituitarism and intrinsic short stature should be evaluated in all patients. Though the primary management remains conservative GH treatment is effective in selected patients. Other pituitary hormone deficiencies may be associated with pycnodysostosis, and rhGH treatment may unmask underlying central hypothyroidism in this group of patients. Genetic counselling should be offered to all patients and their family.

### Key learning points

- Correctable contributors to short stature in Pycnodysostosis are chronic hypoxia, under-nutrition, intrinsic short stature and hypopituitarism.
- The proband and the family members should have CTSK gene mutation analysis and genetic counselling.
- Pycnodysostosis with GH deficiency shows good response to rhGH treatment.
- Evaluation of other pituitary hormone deficiency needs to be carried out in all patients of Pycnodysostosis.
- rhGH treatment may unmask underlying central hypothyroidism and require l-thyroxine replacement.

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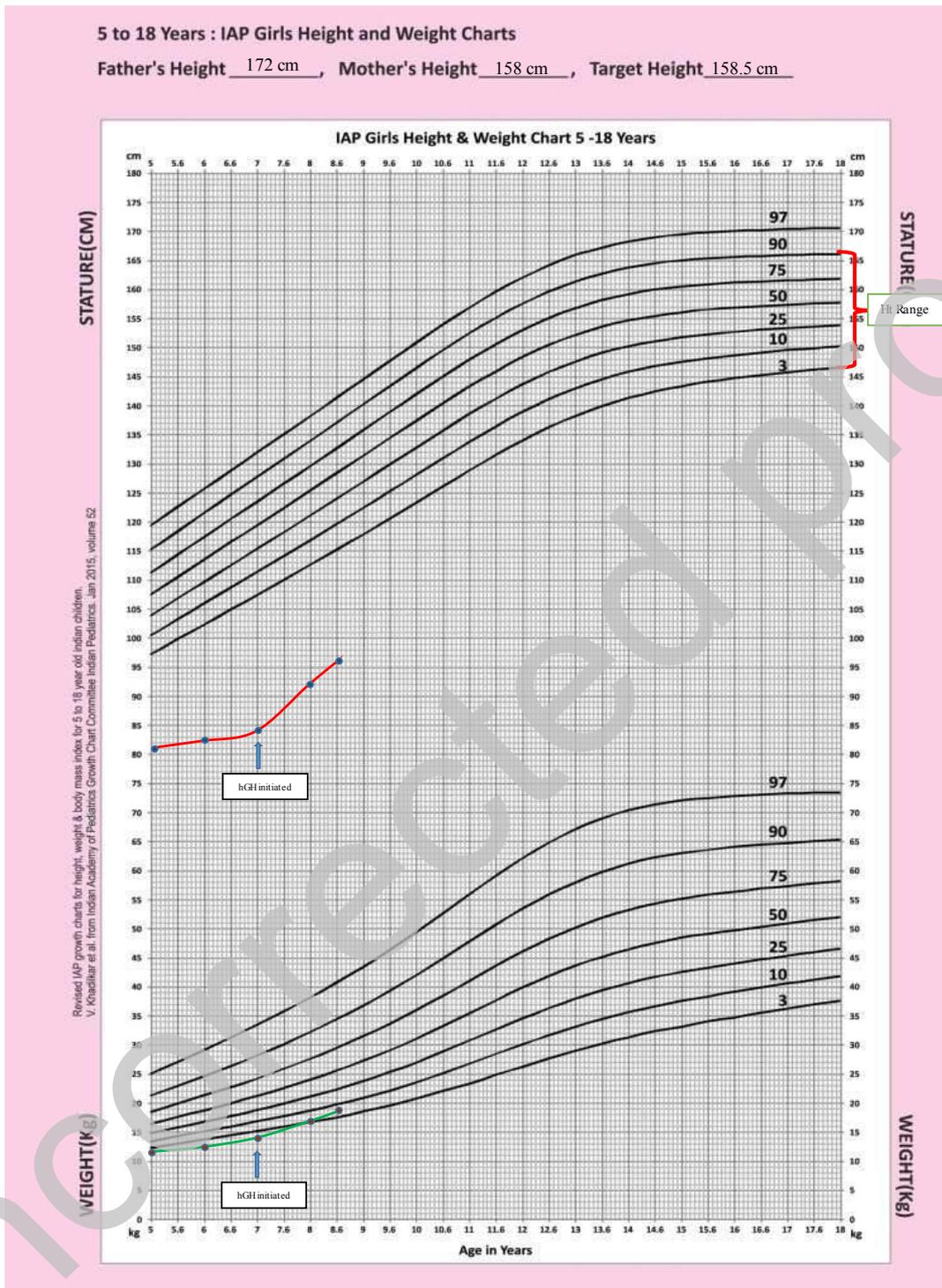
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Figure 1. The Index case (Extreme right) and the sibling sister aged 16 years (Centre ) and 18 years (Extreme left) share the same phenotypic features.

Uncorrected proof

Figure 2. Growth Chart





**Figure 3.** Clinical image of the index patient. Frontal bossing and typical facies are present. The carrying angle is wide



Figure 4. The image shows short and stubby digits. X-Ray reveals acro-osteolysis of the terminal phalanges. The medullary cavity is absent in the long bones of the hand



Figure 5. X-Ray skull lateral view showing open fontanelles, Obtuse mandibular angle and non-pneumatized sinuses. Also noted is acro-osteolysis of the clavicle.