CASE REPORT

Pycnodysostosis with novel gene mutation and severe obstructive sleep apnoea: management of a complex case

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SUMMARY

Pycnodysostosis is a rare genetic disease. Impaired osteoclastic function is the basis for typical phenotypic features and bone fragility. The main differential diagnosis is osteopetrosis, also associated with altered bone remodelling, but with a more severe prognosis. We describe the case of an 8-year-old boy who presented life-threatening obstructive sleep apnoea successfully managed with non-invasive ventilation. Haematological overlap phenotype included anaemia and altered bone marrow, more common in osteopetrosis. Molecular analysis of the CTSK gene revealed a mutation not previously described in the literature.

BACKGROUND

Pycnodysostosis is a rare form of skeletal dysplasia, first described by Lamy and Maroteaux¹ in 1962. This autosomal recessive disease, results from an inborn error of bone matrix degradation, in which osteoclastic function is impaired due to mutations in the cathepsin gene, localised to the chromosomal region 1q21. Clinical manifestations are closely related to the resulting defective bone growth and remodelling, including short stature, typical dysmorphic appearance with particular cranial conformation, general osteosclerosis and hypoplasia of several bones, as well dental abnormalities. Pycnodysostosis with visceral manifestations and anaemia have been rarely described.²⁻³ Moreover this case presents a phenotypical overlap with osteopetrosis, another genetic condition with osteoclast failure, so that a common genetic link may be reasoned.⁴

Complications include sleep disordered breathing, ranging from snoring to severe obstructive sleep apnoea (OSA) and increased susceptibility to bone fractures.

Our aim was to describe a rather complex case of pycnodysostosis in a child with respiratory and visceral complications, and the contribution of the multidisciplinary approach to the outcome.

CASE PRESENTATION

A 11-month-old male child, native from São Tomé transferred to Portugal to investigate craniofacial and hand dysmorphism, short stature and recurrent respiratory infections.

The patient is the third child of non-consanguineous, apparently healthy parents. He has a 5-year-old sister with similar phenotype and a sister who died at the age of 4, of unknown causes.

His perinatal history was uneventful, with a normal birth weight and length. He had experienced multiple hospital admissions for respiratory infections and he had remarkable failure to thrive, with weight and height below the third centile.

He was admitted at 15 months of age to the paediatric intensive care unit for pneumonia and acute respiratory failure and needed endotracheal mechanical ventilation for 6 days, and was transferred to a paediatric specialised respiratory care unit for further treatment and investigation.

He presented with short stature, craniofacial dysmorphism with a large head, frontal and bilateral parietal bossing, wide anterior and posterior fontanelles, and a separated sagittal suture, marked mid-face hypoplasia, a flat nasal bridge, exophthalmos with blue sclera, micrognathia and a high narrow palate (figure 1). The limbs were shortened, mainly proximally, and he had short digits, with wide extremities and dystrophic nails (figure 2). At this point he also presented with increased respiratory rate with chest retractions, chronic cough, inspiratory stridor, hypoxaemia and CO₂ retention. Owing to severe airway obstruction, he had sleep fragmentation and clinically significant respiratory distress during sleep.

There were no known previous fractures.

Figure 1 Phenotypic features in pycnodysostosis.

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Figure 2 Hand features in pycnodysostosis.

INVESTIGATIONS

Long bone X-rays showed a diffuse increase in bone density, compatible with osteosclerosis, with obliteration of medullary space (figure 3). He had hypoplastic maxilla and mandible, with an obtuse mandibular angle, as well as a dense skull base (figure 4). The digits showed hypoplastic distal phalanges.

Polysomnography revealed severe OSA and hypoxaemia. Initial broncofibroscopy had findings compatible with laryngomalacia and pulsatile extrinsic compression of lower trachea and main bronchi, but these were not confirmed in a subsequent investigation.

Cardiac evaluation revealed pulmonary hypertension, secondary to chronic hypoxaemia.

Haematological findings included haemoglobin 8.1 g/dL, low platelet count (91 000/mL), no leukocytosis or leucopenia and normal leucocyte differential count. The peripheral smear showed normocytic and normochromic red blood cells and a few target cells. There were no abnormal cells or parasites seen. Sickling test, haemoglobin electrophoresis, iron levels, folate, cobalamin and Coombs tests all showed normal results.

Further investigation showed glucose-6-phosphate dehydrogenase deficiency. Owing to worsening haemoglobin level (lowest 6.5 g/dL), he underwent bone marrow biopsy; which showed hypercellularity with parameters compatible with dysmyelopoiesis, increased reticulin, but no fibrosis. Blood transfusions were required on two occasions, and the haemoglobin stabilised around 9 g/dL.

Figure 3 Radiograph of superior limb.

Molecular analyses of the CTSK gene located in chromosome 1 identified substitution c.953G>A homozygosity in the eight exon of this gene.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis is osteopetrosis, also associated with altered bone remodelling, but with a more severe prognosis.

TREATMENT

The patient started on bilevel nasal mask non-invasive ventilation (NIV) (IPAP 15, EPAP 6 cm H₂O) during sleep time, with progressively increased tolerance. The surgical approach was considered and discussed with maxillofacial surgery team, but the decision was not to proceed due to the life-threatening risk of surgery, and proven efficacy of NIV, which already induced regression of pulmonary hypertension. At age 3 he was presented to adenotonsillectomy with further symptomatic improvement of his OSA.

OUTCOME AND FOLLOW-UP

It was only 9 months after he was first admitted to hospital that discharge was made possible. The patient was then well adapted to NIV, had stable haemoglobin values, and better weight gain, approaching the 5th-centile. He was stable enough to return to his original country and pursue further follow-up in a regular basis, both in Portugal and in São Tomé.

From the respiratory point of view, he maintained NIV during night sleep which he was well adapted to and compliant with. No side effects were seen. Currently, he has no stridor at rest, and blood gases are normal. He had progressively fewer hospital admissions because of respiratory problems. At the age of 8, he underwent polysomnography for adjustment of ventilator settings (IPAP 13 mm Hg, EPAP 4 mm Hg and respiratory rate of 14 breaths/min).

Haematologically at age 3, a small degree of hepatosplenomegaly was noted. At the age of 4, he underwent bone marrow biopsy, showing few haematopoietic cells and empty medullar spaces, but this was difficult to interpret because of the small sample. At the age of 5, he repeated these investigations again, showing normocellular bone marrow, with normal granulocytic/erythroblastic ratio, considered a normal examination. He has currently stable haemoglobin, around 10 g/dL, and normal platelet levels. He maintains regular haemoglobin and peripheral smear evaluations in São Tomé.

Figure 4 Radiograph of skull.

He is currently 9 years old and has been evaluated on a regular basis biannually in the hospital. His cognitive development is normal. He continued to gain weight regularly, currently in the fifth centile, but his height is still under the third centile.

DISCUSSION

Pycnodysostosis is a very rare genetic disease. The incidence has been estimated in 1–1.7/1 000 000 persons, with less than 200 cases reported until 2009.^{4 5} The most common feature of pycnodysostosis is short stature, that can be related to short long bones.⁵

The main features of this disease include large head with frontal and parietal bossing, open fontanelles, separated sutures, limited development of facial bones with an obtuse mandibular angle. Oral abnormalities include dental abnormalities with mal-positioned teeth, prone to dental caries, high arched bone palate and a long soft palate with long uvula. Deciduous teeth may persist into adulthood, with dental crowding. Patients may present with proptosis and blue sclera. The limbs are short, with short, broad hands and feet, and dystrophic nails. Asymmetric osteolysis of the distal phalanges may give an aspect of uneven digits. There can be trunk deformities, namely kyphosis, lordosis or narrow chest.^{6–8} Radiological abnormalities include general increased bone density, with decreased medullar space. There can be non-pneumatized frontal sinuses and a sclerotic skull base, as well as thick, dense ribs.^{6–8} Also, dysplasia of the acromial ends of clavicles is a distinctive feature.^{6–8} In most cases, cognitive development is normal,^{6–8} as well as life span. The diagnosis of pycnodysostosis is mainly clinical, based on phenotypic features and radiological findings.^{7 8} The disease is in itself non-progressive, but complications such as increased bone fragility with fractures and increased susceptibility to osteomyelitis may contribute to prognosis.

This is an autosomal recessive disease, and is due to the mutations in the gene encoding for the cathepsin K protein. This is a lysosomal enzyme, highly expressed in osteoclasts, and with critical importance in bone degradation and remodelling,⁶ particularly in impairing the osteoclastic degradation of type 1 collagen⁶ which represents 95% of the organic bone matrix. The gene is localised to the chromosomal region 1q21, multiple different mutations identified.⁶

The case presented has a long-term follow-up from clinical diagnosis of pycnodysostosis at 15 months of age to his growing 9 years of age. To our knowledge, less than 10 cases have been described in Portugal⁶ and this is the first case originally from São Tomé.

The most remarkable feature in this patient was respiratory distress, with severe OSA, severe nocturnal hypoxaemia and signs of pulmonary hypertension. OSA is a recognised complication from pycnodysostosis,^{4 9} and its approach can present a number of challenges, occasionally needing aggressive treatment, including orthognathic surgery or tracheostomy.^{9 10} In spite of initial suspicion of malacia as a contributing factor in our patient, this was not confirmed in posterior investigation, possibly due to a more stable clinical state. Therefore, the authors believe that OSA was solely caused by marked facial dysmorphism. In this case, a multidisciplinary approach with initiation of NIV proved to be a valuable choice.

Even though its use in infants has not been approved by the Food and Drug Administration, NIV has been recommended as an option in childhood severe sleep apnoea^{11 12} with good results including in young children.¹³ After started on NIV, the patient underwent adenoidectomy, with further clinical improvement. Recently, Della Marca *et al*¹⁴ described a case of

a 5-year-old patient with pycnodysostosis and severe sleep apnoea that was successfully treated with a combination of upper airway surgery and NIV. Also this case illustrates NIV as an alternative treatment to maxillofacial surgery, avoiding the associated risks including for life. Nevertheless, this conservative approach was not easy to implement, mainly because of difficulties in parametre and nasal mask adjustments. However, at last good compliance was achieved, with no side effects, resulting in resolution of symptoms and pulmonary hypertension and reduced number of hospital admissions.

The patient also presented with anaemia and thrombocytopenia. Further investigation showed glucose-6-phosphate dehydrogenase deficiency, but also decreased marrow cells in marrow biopsy, and at 3 years of age, minor hepatomegaly and splenomegaly was noted. Anaemia and extramedullary erythropoiesis are commonly seen in a closely related disease, osteopetrosis, in which osteoclast reabsorption of bone matrix is impaired. This results in obliteration of marrow spaces leading to medullary insufficiency. Short stature, open fontanelles or dysplastic clavicles are not present, and help to make the differential diagnosis. Even though anaemia is typical of osteopetrosis, a few cases of pycnodysostosis with haematological abnormalities have been described.^{2 3 7 9} These manifestations may represent a common link between these diseases, and a study on the genetic regulation of cathepsin K expression, linking osteopetrosis and pycnodysostosis has been published.¹⁵ Nevertheless, none of these studies provided long-term follow-up on haematological function. Our patient is now 9 years old, with a diagnosis of dysmyelopoietic anaemia at 2 year old. For 7 years of follow-up, there has been no apparent progression of his haematological condition, which we believe constitutes valuable information about a rare manifestation of a rare disorder. The unknown future of this particular manifestation warrants close follow-up for the possibility of bone marrow failure.

To our knowledge, the mutation c.953G>A (p.Cys318Tyr) has not been previously described in the literature. The analysis of this alteration in the programmes PolyPhen and SIFT indicates that it is most probably pathogenic and it will be the cause of the disease in our patient. This new variant of the cathepsin gene has never been described before; hence the follow-up of this child may provide important new information on the gene's function and the pathogenesis of pycnodysostosis.

Learning points

- ▶ Pycnodysostosis is a rare disease, characterised by osteosclerotic changes leading to a particular phenotype, namely short stature and open fontanelles.
- ▶ Associated obstructive sleep apnoea (OSA) can be approached conservatively with non-invasive ventilation, enabling reversal of OSA and pulmonary vascular hypertension secondary to chronic hypoxia, and in this particular child allowed return to his original country.
- ▶ Rare complications such as anaemia and bone marrow failure have to be closely monitored, due to its unknown evolution, and further studies in this area are necessary.
- ▶ Haematological complications are overlapping characteristics with osteopetrosis. This may suggest a common genetic link, but the mechanism is still unknown.
- ▶ The responsible gene is the CTSK located in the chromosomal region 1q21, and this unique case provides a novel mutation.

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Contributors IG researched, reviewed the available material concerning the patient and wrote the case. TN and AM provided guidance and direction regarding the selection of material and the writing for the case. TB provided expert commentary and reviewed the case.

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