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# Brachymelic Dwarfism, Intellectual Disability and Pug Like Nose Are the Paramount Phenotype in Children with Acrodysostosis Syndrome

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## ABSTRACT

**Background:** Children born with pre and postnatal growth deficiency associated with mild/moderate dysmorphic facial features with evident shortening in the upper limbs require prompt clinical awareness.

**Material and Methods:** Three girls (1, 5 and 11 years old) were brought to our department because of pre and post-natal growth retardation associated with dysmorphic facial features and shortening of the digits of the hands and feet. Global developmental retardation associated with intellectual disability with attention deficit disorders (ADHD) were the most evident manifestations. Clinical and radiographic phenotypic characterizations are the first and the foremost baseline tools that were immediately applied in our clinics. Congenital heart defects have been diagnosed at birth in two girls. Radiographic documentation showed a severe form of cone-shaped phalanges of the hands and feet bilaterally. Other features of first ray hyperplasia of the foot and advanced skeletal maturation, mental retardation and coarse hair were present. Family history revealed mothers and other siblings are partially affected.

**Results:** Clinically all children manifested brachymelic dwarfism. Radiographic phenotypic characterization showed a severe form of cone-shaped phalanges of the hands and feet bilaterally. Other features of first ray hyperplasia of the foot and advanced skeletal maturation, intellectual disability and coarse hair were present. Family history revealed mothers and other siblings are partially affected. Our patients presented with the severe type of peripheral dysostosis. Three children showed the manifestations of hormone resistance, with elevated levels of Parathyroid Hormone (PTH) and Thyroid-Stimulating Hormone (TSH) associated with apparent features of clinical hypothyroidism. One child underwent genetic testing and she showed heterozygous mutation in the PRKAR1A gene.

**Conclusion:** Clinical awareness is essential for paediatricians to identify affected children as early as possible, as delayed or missed diagnosis can lead to a constellation of neurological, skeletal and visceral complications. Early and accurate diagnosis may also help clarify why other family members exhibited intellectual disability, spinal stenosis and ADHD. The clinical phenotype of children with acrodysostosis is distinctive. In our clinical practice, the triad of brachymelic dwarfism, intellectual disability and a pug-like nose represent the most apparent and consistent features. The differential diagnosis includes Pseudohypoparathyroidism

(PH) and Pseudo-Pseudohypoparathyroidism (PPH). In Albright hereditary osteodystrophy and normocalcemic PPH, the degree of peripheral dysostosis is typically less pronounced than in our patients.

**Keywords:** Brachymelic dwarfism, Acrodysostosis Syndrome, Dysplasia, Hypertelorism

**Abbreviations:** PHP: Albright's Hereditary Osteodystrophy; PPHP: Pseudo-Pseudohypoparathyroidism

## 1. Introduction

Children with acrodysostosis presented with brachymelic dwarfism, pug nose and intellectual disability (OMIM 101800), is a rare skeletal dysplasia, first described by Maroteaux and Malamut. The disorder is characterised by growth failure, short stature, brachymelic dwarfism with shortening more marked in upper limbs and enlarged great toe associated with specific craniofacial dysmorphic features. Peripheral dysostosis (gross shortening of the hands and feet), intellectual disability, short and saddle nose (pug nose) and maxillary hypoplasia. The facial appearance is characteristic in that the nose is hypoplastic. Hypertelorism and epicanthal folds occur frequently. Pre and postnatal growth retardation with birth weight and length below the third percentile[1-6].

Molecular pathology in patients with acrodysostosis is characterized by heterozygous mutations in PRKAR1A (OMIM 188830), which encodes the cyclic AMP (cAMP)-dependent regulatory subunit of protein kinase A (PKA), were found in a subset of acrodysostosis cases resistant to multiple hormones. In acrodysostosis, which is characterized by intellectual disability, skeletal and neurological abnormalities, five different point mutations within the PDE4D gene have been identified as the genetic cause[7-9].

Albright's hereditary osteodystrophy and Pseudo-Pseudohypoparathyroidism (PPHP) are variants of the same condition and both can mimic the phenotype of acrodysostosis.

Though the original descriptions of PHP referred to patients with hypocalcaemia, hyperphosphatemia, obesity, a short stocky build, a round face, short bones in the fingers, especially the 4$^{th}$ and 5$^{th}$ metacarpals and subcutaneous calcification. Other skeletal abnormalities which can be encountered in patients with PPHP are Osteoporosis, osteomalacia, small epiphyses, acetabular dysplasia, exostoses and an advanced bone age are common manifestations and less well known is the frequent shortening of the distal phalanx of the thumb. Mental retardation occurs in about 70% of hypercalcaemic and 30% of normocalcaemic cases Patients with PPHP do not have demonstrable abnormalities of calcium metabolism, however precise clinical diagnosis is difficult because periods of normo-calcaemia can occur in patients with PHP. In patients with Albright's hereditary osteodystrophy and pseudo-pseudohypoparathyroidism weight and height can be normal. Cataracts can occur in the hypercalcaemic form of the condition. Osteoporosis, osteomalacia, small epiphyses, acetabular dysplasia, exostoses and an advanced bone age are common manifestations and less well known is the frequent shortening of the distal phalanx of the thumb. Intellectual disability occurs in about 70% of hypo-calcaemic and 30% of normocalcaemic cases. Ectopic calcification frequently occurs in the kidneys, brain (basal ganglia) and other tissues[10-18].

## 2. Material and Methods

Three girls' studies protocol was approved by the Ethics Committee of the (Ilizarov Scientific Research Institute, No.3(35)/09.12.2013, No.4(50)/13.12.2016, Kurgan, Russia). Informed consents were obtained from the patient's Guardians to publish. Three girls aged 1, 5 and 11 years old have been included. We fully documented these children through detailed clinical and radiological phenotypic characterizations at the osteo genetische ambulanz (orthopaedic Hospital of Speising, Vienna, Austria and at the National Medical Research Center for Traumatology and Orthopedics n.a. G.A. Ilizarov, Kurgan, Russia Ilizarov Center, Russia.

The principal rules applied in our departments are primarily based on, detailed clinical and radiographic phenotypic characterizations of every patient. Family history is the corner stone to understand the pathological mechanism and the inheritance pattern. We studied every family in connection with unusual pathological events regarding gestational histories of multiple miscarriages, bleeding, stillbirths, premature labour and evidence of intrauterine growth retardation, followed by details of the labour and any evidence of foetal distress during delivery. Baby´s basic measurements at birth, weight, length and OFC. History of neonatal illnesses; respiratory distress, jaundice, neonatal convulsions and failure to thrive. Retrospective developmental milestones were essential tools for the evaluation. Family study included the health status of other family subjects, both physical and mental, as this helps to correlate the current child disorder with relevant features in one of the parents, siblings and relatives. Other aspects of child health, of growth deficiency, obesity, abnormal clinical phenotype which is often seen in children with various forms of heritable disorders. Neurological examination revealed weak deep tendon reflexes. Attention deficit disorder (ADHD) has been encountered in three girls associated with speech and language retardation resulting in poor schooling achievement. Examination of the genitalia showed hypoplasia of the minor labia in all girls. Ophthalmologic examination showed hypermetropia with relative amblyopia of the right eye in two girls. Cardiac ultrasonography found aortic stenosis with left ventricular hypertrophy in one girl with conserved systolic function associated with minimal tricuspid insufficiency with no impact on the right cavities. Abdominal ultrasound showed a rudimentary uterus and hypoplastic vagina in two girls. Three children showed the manifestations of hormone resistance, with elevated levels of Parathyroid Hormone (PTH) and Thyroid-Stimulating Hormone (TSH) associated with apparent features of clinical hypothyroidism. One child underwent genetic testing and she showed heterozygous mutation in the PRKAR1A gene.

## 3. Results

In our group of patients, we encountered growth failure (all children were -3SD), apparent brachymelic dwarfism with shortening more marked in the upper limbs, enlarged great toe. Craniofacial dysmorphic features of round face with scalp showed thick hair with tough texture, wide frontal area, faint eyebrows, depressed nasal bridge (pug nose), short philtrum, high palate, an inversion of the dental articulate, delayed teeth eruption (oligodontia) and prognathism. Clinical phenotypic features of three unrelated girls aged (1, 5 and 11 years old). All showed similar facial abnormal features of round face, thick hair with tough texture, wide frontal area/bossing, faint eyebrows, depressed nasal bridge (pug nose), short philtrum, high palate, an inversion of the dental articulate, delayed teeth eruption (oligodontia). Short neck with excessive wrinkling of the skin of the chin (Figure 1a-1d). Hypogonadism, evident psychomotor retardation and seizures have been recorded in two girls. The hands are characteristic in that they are short and broad, with relatively a trident configuration (Figure 2a and 2b). AP hands radiograph showed large carpal bones, accelerated bone age associated with cone shaped epiphyseal dysplasia of all the carpo-metacarpo-phalangeal, which appeared as broad and short. The anteroposterior foot radiograph showed short and broad tarsal and metatarsal phalangeal joints with cone shaped distal phalanges and significant hyperplasia of the first ray of the foot peripheral dysostosis. Generally speaking, the hands and foot phenotype showed short metacarpals and metatarsals, short phalanges, cone-shaped epiphyses seen mostly in the hands and feet give the phenotype of metacarpophalangeal pattern profile (Figure 3a and 3b). AP spine radiograph of an 11-years-old-girl showed dysplastic pedicles along the thoraco-lumbar spine associated with narrow interpediculate distance with the propensity to develop spine stenosis. Lateral spine radiograph of the same child showed posterior end plate scalloping of the L4-5 (Figure 4).

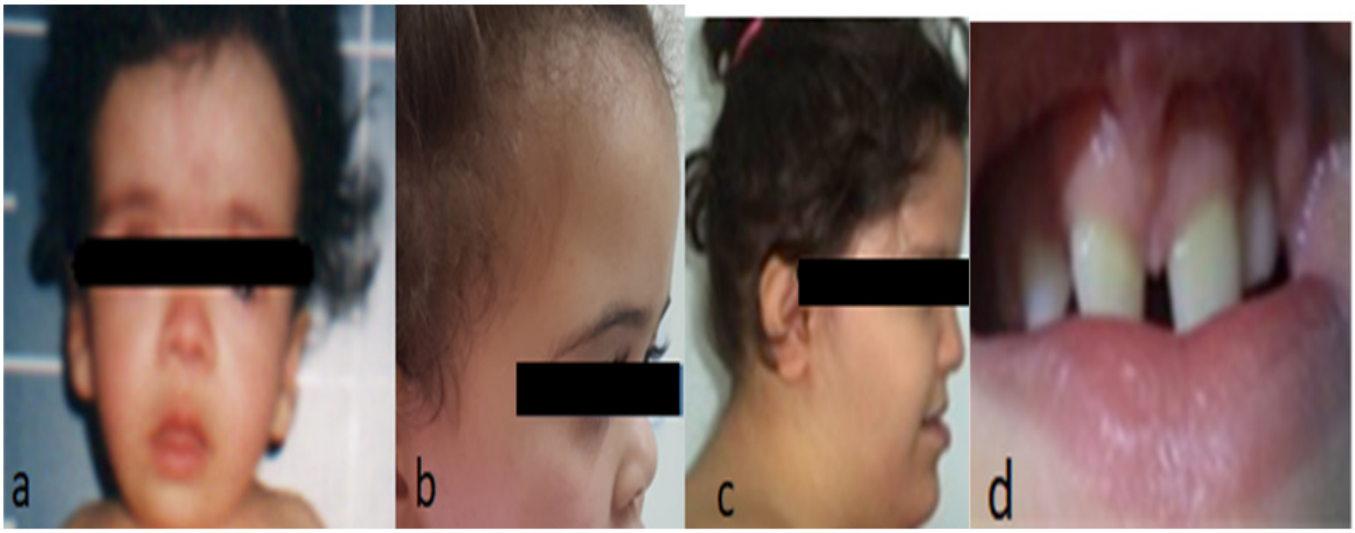


**Figure 1a-1d:** Craniofacial dysmorphic features of three unrelated girls aged (1, 5 and 11 years old). All showed similar facial abnormal features of round face, thick hair with tough texture, wide frontal area/bossing, faint eyebrows, depressed nasal bridge (pug-like nose), short philtrum, high palate, an inversion of the dental articulate, delayed teeth eruption and oligodontia in an 11-years-old-girl.

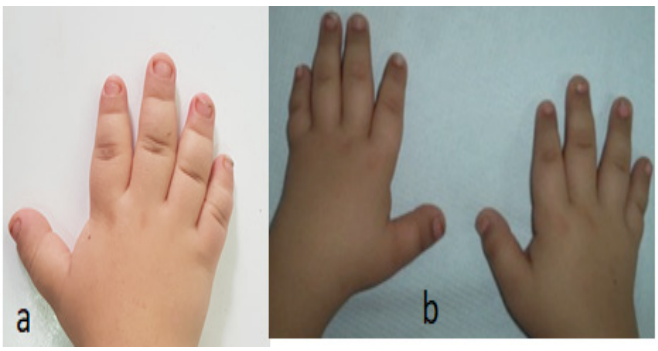


**Figure 2a and 2b:** The hands of two unrelated girls of 5 and 11 years old showed characteristic in short and broad, with relatively a trident configuration.

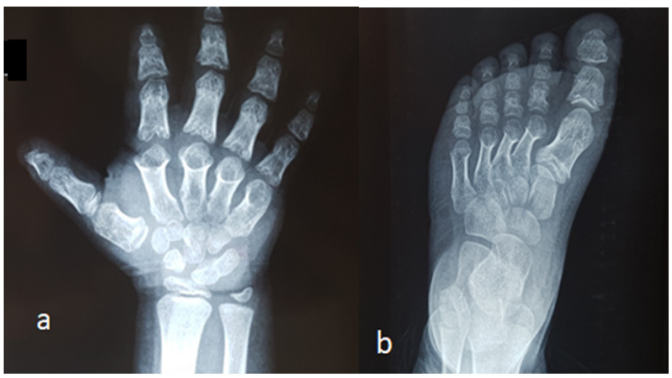


**Figure 3a and 3b:** AP hands radiograph showed large carpal bones, accelerated bone age associated with cone shaped epiphyseal dysplasia of all the carpo-metacarpo-phalangeal, which appeared as broad and short (3a). The anteroposterior foot radiograph showed short and broad tarsal and metatarsal phalangeal joints with cone shaped distal phalanges and significant hyperplasia of the first ray of the foot peripheral dysostosis. Generally speaking, the hands and foot phenotype showed short metacarpals and metatarsals, short phalanges, cone-shaped epiphyses seen mostly in the hands and feet give the phenotype of metacarpophalangeal pattern profile (3b).

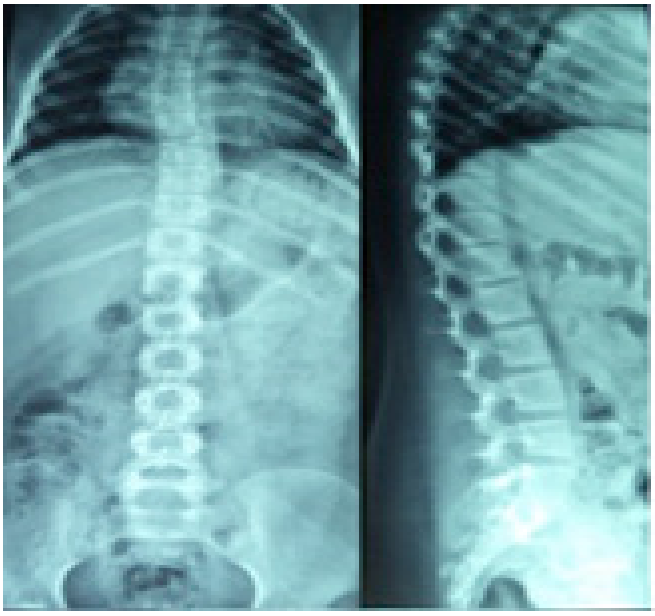

**Figure 4:** AP spine radiograph of an 11-years-old-girl showed dysplastic pedicles along the thoraco-lumbar spine associated with narrow interpediculate distance with the propensity to develop spine stenosis. Lateral spine radiograph of the same child showed posterior end plate scalloping of the L4-5.

## 4. Discussion

The clinical phenotype of children with acrodysostosis is characterized by growth failure, peculiar face, short hands, pug-nose and brachymelic dwarfism. Intellectual disabilities are first noted in early childhood. Neurological signs of spinal claudication may develop which leads to profound muscular weakness, hyperreflexia and asymmetric deep tendon reflexes. Variable degrees of lumbar spine stenosis occur in up to 75 percent of patients. Cervical spine stenosis and narrow occipital foramen can occur though with rarity[1-6].

Growth deficiency, cone shaped epiphyses might be a feature encountered in pseudohypoparathyroidism (Albright's hereditary osteodystrophy) and pseudo-pseudohypoparathyroidism which are differentiated by the different skeletal abnormalities, laboratory results and less common intellectual disability. Other disorders that can mimic acrodysostosis is PTHLH-related brachydactyly E syndrome is a genetic disorder caused by mutations in the *PTHLH* gene leads to short stature, mental deficiency and very short metacarpals and metatarsals. molecular analysis confirms the diagnosis[16-19]. Brachydactyly-mental retardation syndrome (OMIM 600300) is another clinical entity which resembles acrodysostosis. It is caused by deletions or mutation of HDAC4, located on chromosome 2q37.3. Also known as Albright hereditary osteodystrophy -like syndrome shares multiple features with acrodysostosis and must be excluded via molecular analysis[20]. Acromesomelic dysplasia differs by the platyspondyly and more severe shortness of the of the forearms and the shanks[21]. Most authors now accept that Albright's Hereditary Osteodystrophy (PHP) and Pseudo-Pseudohypoparathyroidism (PPHP) are variants of the same condition. The original descriptions of PHP referred to patients with hypocalcemia, hyperphosphatemia, obesity, a short stocky build, a round face, short bones in the fingers, especially the 4$^{th}$ and 5$^{th}$ metacarpals and subcutaneous calcification. Patients with PPHP do not have demonstrable abnormalities of calcium metabolism; however precise clinical diagnosis is difficult because periods of normo-calcaemia can occur in patients with PHP.

## 5. Conclusion

Differentiation between acrodysostosis and related skeletal dysplasias can be challenging, particularly in early childhood. Several disorders, including Albright's hereditary osteodystrophy, pseudohypoparathyroidism due to Gs-protein abnormalities, pseudopseudohypoparathyroidism, brachydactyly type E and acromesomelic dysplasia, share overlapping phenotypic features. However, unlike acrodysostosis, these conditions typically do not present with a pug-nose appearance, intellectual disability or the distinctive constellation of genetic traits associated with acrodysostosis. The diagnosis of acrodysostosis is commonly established between three and four years of age, when characteristic skeletal changes become more apparent. In our patients, however, the diagnosis was made as early as one year of age, facilitated by the presence of a recognizable clinical phenotype and a positive family history. The latter included short stature, intellectual disability and, in one affected mother, a history of lumbar spinal stenosis requiring laminectomy at 28 years of age. It is well recognized that children with acrodysostosis exhibit a slowly progressive clinical course throughout the growth period. Because of the impaired epiphyseal development subsequently leads to progressive growth restriction and disproportionate short stature. Because the epiphyses are primarily involved, growth compromise is a hallmark of the disorder. It is also possible that some cases historically labeled as acrodysostosis actually represent normocalcemic pseudohypoparathyroidism or AHO, given the phenotypic overlap. Nevertheless, in our cohort, the severity of peripheral dysostosis exceeded that usually observed in AHO, supporting the diagnosis of true acrodysostosis.

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