Genetic Causes of Rickets: Clinical Manifestations, Debut and Orthopaedic Treatment

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Abstract

The pathology of phosphocalcic metabolism has piqued the interest of physicians since ancient times due to its side effects which have aroused curiosity in the social environment. Many skeletons from that time have been preserved, and today they represent the prototype of the spontaneous evolution of the disease in the absence of treatment.

The physiological and pathophysiological studies of phosphocalcic metabolism have contributed to improvements in the treatment of rickets, especially in rickets due to deficiency. Exposure to the sun has led to a reduction in the cases of osteomalacia. Over the past few years, cases of vitamin D-resistant rickets have been selected, and, recently, genetic studies have shown that these forms are the expression of genetic mutations. Thus, molecular diagnostic methods have been perfected, which will allow future treatment with genetic implants. Genetic studies allow the selection of cases of genetic rickets, and the diagnosis of severe and lethal forms.

Perinatal hypophosphatemic rickets is the form with the highest mortality. In the foetal period and at birth, the limbs are shorter and deformed, the ribs are deformed and distorted, and the skull is intensely demineralised.

Dwarfism occurs in 40% of patients with genetic rickets.

Keywords: Hypophosphatemic Rickets; X-Linked Rickets; Rickets with Hypercalciuria; Hypophosphatemic Rickets; Surgical Treatment

Introduction

Genetic rickets is a disease studied not only by geneticists and obstetrician-gynaecologists, but also by physicians specialising in pediatrics, paediatric orthopaedics, orthopaedics and traumatology, internal medicine, radiology and imaging, etc [1].

Rickets are diseases caused by phosphocalcic metabolism disorders. The concentration of phosphocalcic salts is influenced by several factors that depend on the endocrine glands, digestive tract, liver and kidneys. Their pathophysiology can generate functional disorders as a result of some genetic diseases that target these systems and organs. Genetic rickets are forms of rickets resistant to vitamin D treatment, which is why they are also called vitamin D-resistant rickets [2]. Genetic studies have allowed the individualisation of several forms of rickets, some of them overlapping with types of rickets previously described eponymically or idiopathically [3].

Genetic studies allow the selection of cases of genetic rickets, and the diagnosis of severe and lethal forms [4].

**X-linked rickets**

Genetic X-linked rickets are caused by the inactivation of the PHEX gene in chromosome X. This mutation causes imbalance in the phosphocalcic metabolism by the loss of phosphates through urine, which is associated with hypophosphatemia, a characteristic sign of this type of rickets. Three genetic mutations responsible for X-linked hypophosphatemic rickets were detected: C59S, Q394X and W602. The molecular examination can reveal the deletion of the long arms of the chromosome, and the loss of exons that can give various types of rickets with polymorphic manifestations [5].

**Hypophosphatemic rickets**

X-linked hypophosphatemic rickets is caused by mutations in the PHEX gene and inactivity of the membrane-bound endopeptidase, resulting in impairment of both Na-dependent P-cotransporter and vitamin D metabolism [6]. It is a dominant form of X-linked rickets different from other forms by its resistance to vitamin D treatment even at high or excessive doses. The low phosphate level occurs due to the loss of phosphorus in urine, which causes disturbances in phosphocalcic metabolism followed by decreased bone resistance and the appearance of axial deviations of the limbs [7].

Hypophosphatemic rickets can be associated with idiopathic hypercalciuria. Subjects with hypercalciuria and patients with HHRH report a leakage of hereditary renal phosphate leading to hypophosphataemia, increased serum concentrations of 1,25-(OH)2D, increased absorption of intestinal calcium and hypercalciuria. The size of hypophosphatemia, which regulates levels of 1,25-(OH)2D, seems to determine which subjects will have hypercalciuria alone and who will also have bone disease [8].

This condition is caused by the mutation of the PHEX gene with Xp22.2-p22.1 localisation in chromosome X. It has an autosomal dominant transmission, differentiated according to the affected parent [9]. The genetic causes of HR can be divided into two groups: FGF23-dependent and FGF23-independent groups. The most common genetic cause of HR is XLDHR resulting from PHEX mutations [10].

The symptoms are varied; there are mild forms in which only hypophosphatemia is present, moderate forms with added bone changes (Figure 1) and severe forms in which important changes of bone structure, long bone configuration and axial deviations that exceed 30 degrees occur. The first signs and symptoms appear after the child starts to walk, when the bones of the limbs are subjected to body weight during orthostatism and walking [11]. Thus, coxa vara occurs in conjunction with curved femurs and tibiae, genu varum or genu valgum, or weight-for-height deficit as a predictive sign of dwarfism (Figure 2). Other symptoms that may occur in the evolution of the disease include: bone pain as a result of skeletal microfractures (Figure 3), hypotonia and muscle pain, joint pain caused by heterotopic ossification, tendons and ligaments, waddling, unsynchronised walking, and abnormal development of the teeth. In adults, joint pain, dental abscesses, partial calcifications of the tendons, ligaments and capsule may occur. These partial calcifications give frequent enthesitis that impair walking [12].

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Figure 1: Moderate form of hypophosphatemic rickets with genu valgum straight 30 degrees genu left valgum 15 degrees and left tibia curved.

Figure 2: Female patient aged 7 with a weight-for-height deficit; her weight and height are that of a 4-year old.

The most common symptoms present in 80-99% of cases are: abnormal tooth enamel, abnormal metaphyses, genu varum, hypophosphatemia, joint dislocations, osteomalacia, rachitic rosary and dental abscesses [5].

Some symptoms are found in smaller proportions in 30 - 79% of cases: craniosynostosis, enthesitis, osteoarthritis and dwarfism. Recurrent fractures and hearing impairment occur in 5 - 29% of cases.

Laboratory tests show low phosphatemia, normal or low serum calcium levels, and slightly or moderately low urinary calcium levels. Alkaline phosphatase is high.

The gait is limped and disharmonic with obvious lack of synchronisation between pelvic and thoracic limbs. Patients with an accentuated genu valgum tend to tire quickly and often avoid walking long distances. When the axial deviations exceed 30 degrees, the gait becomes ungainly. When the deviation in the valgum is greater than 50 degrees, walking is no longer possible. Severe varum or valgum modifications make walking uncomfortable for children, and sometimes spontaneous fractures can occur.

Growth is slowed, and its cessation occurs earlier, which is why dwarfism occurs in about 40% of patients. These patients do not exceed a height of 140 cm. The evolution of the disease stops with the cessation of growth but can reappear after a pregnancy or after the age of 40 - 50.

The radiological exploration reveals aspects similar to those of rickets due to deficiency. In addition to long bone curvatures and axial deviations of the pelvic limbs, a bony structure with larger areoles and thickened bone framework are noted. Bone nuclei have an irregu-
lar structure, are smaller with respect to age, and the metaphyses are enlarged and sometimes irregular. As a result of the evolution of the disease in the immediate vicinity of the growth cartilage, metaphyseal transverse ossification bands appear.

Exostoses may occur on the contour of the cortex. In some patients, cystic images or signs of fractures are present. In the spine, vertebral bodies have a blurred structure especially in the lumbar segment, become rectangular, and have slightly hollowed out plateaus. The radiograph of the skull shows scaphocephaly and the early closure of sutures.

**Rickets due to pseudo-deficiency**

Rickets due to pseudo-deficiency is the most common form of genetic rickets and exhibits skeletal lesions similar to those seen in rickets due to deficiency. These lesions are differentiated according to the severity of the disease and may start early or late. It is a vitamin-resistant rickets, with a homeostatic phosphate imbalance similar to the one in hypophosphatemic rickets, caused by the loss of phosphate through urine, and is characterised by hypophosphatemia and normal or low 1,25-dihydroxycolecalciferol levels [5].

Prader rickets - with an early onset - is a form of rickets due to pseudo-deficiency that starts in the first year of life and has a serious evolution. Clinically severe deformities of the limbs, chest and spine occur. The frequency of spontaneous fractures depends on the curvature of the bones and the severity of the disease.

Laboratory tests show hypocalcaemia and phosphatemia at the lower limit of normal values. Sometimes aminoaciduria may also be present.

The osteoarticular manifestations are similar to those found in rickets due to deficiency. Clinically, curved limb segments, especially in the thigh and leg, and axial deviations are present.

Radiologically, the skeleton is blurred, the cortices are thin, the metaphyses enlarged, the growth cartilages higher and imprecisely delimited to the diaphysis. Consolidated fracture lines can be seen in the correct position or are malunited, especially in the curved bones, where the curvature has the maximum amplitude. The epiphyseal nuclei appear late, the length of the long bones is smaller, and the height of a large number of children with this condition does not exceed 140 cm. Dwarfism due to rickets can be surgically corrected. Treatment with high doses of vitamin D, 6 - 8 grams per day, in some cases, results in normal or quasi-normal growth.

McCance rickets - with a late onset. Manifestations of the disease occur in adolescence or adulthood. The disease starts in the spine (Figure 4) and limbs [13]. Spinal deformities in the form of kyphosis or kyphoscoliosis occur often and axial deviations occur later, especially in the limbs and as genu varum or tibia vara (Figure 5).

![Figure 4: McCance Rickets: Discrete lumbar scoliotic deviation accompanied by pain and followed shortly by genu varum.](image-url)
The radiological examination shows a bone structure with thick and rare bone framework so that the alveoli become very evident. In severe forms, the metaphyseal segments have a transparency similar to soft parts, and the cortices are much thinner or are missing. Spontaneous fractures can occur, both metaphyseal and diaphyseal, which have the character of the fractures found in the Milkman-Looser syndrome.

The biochemical examination shows very low phosphatemia, normal serum calcium levels, and sometimes high alkaline phosphatases levels. Pseudo-deficiency vitamin D resistant rickets has a belated onset within children and can be linked to a phosphate reabsorption anomaly [14].

Treatment with high doses of vitamin D3 in combination with calcium and phosphorus may lead to healing. This treatment has no effect on the axial deviations and curvatures. These are treated surgically by hemiepiphysiodesis, if the deviations occur in the early adolescence, or by osteotomies. When inequalities of limbs less than 4 - 5 cm appear, epiphysiodesis is performed, and elongations of limbs are performed in the case of dwarfism [15].

**Hereditary rickets with hypercalciuria - Royer rickets**

Royer rickets has a hereditary character highlighted by many authors. Data show that the disease is genetically certain. Royer described this condition as idiopathic hypercalciuria. It shows rickets-type manifestations when accompanied by hypocalcaemia [4].

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Excessive calcium excretion has a number of consequences, the most common being renal lithiasis. A diagnosis is given based on clinical data, laboratory investigations and radiological images. Molecular studies will specify the location of the gene responsible for this type of rickets.

Secondary hypercalciuria is not included in this form of rickets. This hypercalciuria occurs when excess urinary calcium appears after a known pathological process.

It starts in the first 3 years of life, showing tetany attacks as a result of the hypocalcaemia. Excessive loss of calcium causes growth disorders. Dwarfism due to hereditary hypercalciuria is accompanied by osteoporosis and genu varum or valgum.

Radiologically, the skeleton has long bones with a thinned cortex. The epiphyseal nuclei appear later, and have a volume consistent with dwarfism.

The orthopaedic treatment is concerned with axial changes and the correction of the changes in the varum or valgum of the hips, knees and ankles.

**Hypophosphatemic rickets**

This is a rare form of rickets. The incidence is 1:100,000 live neonates. The phosphocalcic metabolism disorder is characterised clinically by a defect of bone mineralised, and biochemically by the deficient activity of alkaline phosphatase.

Most of the alkaline phosphatase is produced in the liver and bones, and in smaller quantities in the intestines, kidney and placenta.

Described for the first time by Rathbun in 1948 for a 9-week old infant, hypophosphatasia was later studied by several authors who made important contributions especially in the genetic field. In 1957, Fraser classified the hypophosphatemic rickets, in relation to the age of onset, as: perinatal, infant or neonatal, childhood and adult.

**Biology**

Non-specific alkaline phosphatase, TNSALP (tissue non-specific alkaline phosphatase) deficient in osteoblasts and chondrocytes disrupts bone mineralisation inducing rickets and osteomalacia [16]. TNSALP with low values is a pathognomonic sign and is determined by one of the 200 genetic mutations that may occur in the ALPL gene that encodes TNSALP. Genetic transmission is autosomal recessive for perinatal and infant or neonatal forms, and for the other forms it is either autosomal recessive or autosomal dominant [7].

Pathophysiologically, TNSALP produces the hydrolysis of several substances including inorganic pyrophosphate and pyridoxal 5-phosphate, an important form of vitamin B6. Inorganic pyrophosphate accumulates outside the cell when TNSALP has low values, and inhibits the formation of hydroxyapatite, one of the main bone components causing rickets in infants and children and osteomalacia in adults. Pyridoxal 5-phosphate is the main form of vitamin B6 and must be dephosphorylated by TNSALP in order to cross the cell membrane. Vitamin B6 deficiency in the brain causes seizures.

Perinatal hypophosphatemic rickets is the form with the highest mortality. In the foetal period and at birth, the limbs are shorter and deformed, the ribs are deformed and distorted, and the skull is intensely demineralised [12]. This form quickly causes death through respiratory disorders. The number of dead neonates is unknown, and long-term survival is rare. Infants who survive have respiratory disorders, osteomalacia and underdeveloped, hypoplastic lungs. Respiratory failure may be the cause of late death. Epilepsy can occur and is often lethal. Extended bone non-mineralisation causes myelodysplastic anaemia. The characteristic signs, symptoms and complication
of perinatal hypophosphatasia can be grouped into skeletal manifestations (thoracic deformities, curvatures, craniosenosis), vitamin B avidity, and respiratory disorders.

The unavailability of the deficient enzyme implantation therapy leads to a mortality rate in these patients of between 58% and 100%. In the less aggressive forms, only the long bone curvature and the Bowdler spur appear. There are some authors who argue that the mortality rate is 100%.

The incidence in Canada for the 1957 birth rate was 1 in 100,000 live neonates. As a rare disease, its true incidence is unknown. According to an estimate from 2000 - 2009 based on molecular diagnostics, the incidence of this disease in Europe is 1:538,000. An increased incidence was encountered in the Mennonite communities in Canada and in villages with endogamous marriages in Hungary.

The forms that start during childhood, usually after the age of 6 months, are forms of moderate severity and show weight-for-height hypotrophy, deformations of the limbs secondary to bone mineralisation deficiency, and sometimes by the deficient consolidation of fractures. A clinical examination reveals epiphyseal rings, rachitic rosary or the premature fall of the teeth. The anterior fontanelle may remain open for a longer period.

The adult form, also called odontophosphatasia, manifests only by the early fall of the teeth. In some cases, dwarfism or short height, bone fragility or axial deviation of the limbs are also associated.

Laboratory tests show consistently low alkaline phosphatase, with serum calcium and phosphatemia within normal limits or increased. An increased amount of phosphoethanolamine is present in urine.

The ultrasound examination of the foetus shows signs of bone spurs, a pathognomonic sign for hypophosphatemic rickets [17]. The evaluation of ossification in foetuses is done by ultrasound. The data obtained by the radiological examination of some abortions show differentiation of the ossification according to age. At 11 weeks, there is no ossification of the cranial cap, cervical vertebral bodies, thoracic bodies, sacrum, ischium and pubis. At 14 weeks, the ossification of all vertebral bodies occurs, but the ossification of the skull cap, base of the skull, ischium, and pubis remains absent. At 15 weeks, the ossification of the ischium and pubis finally occurs.

The radiological examination, in infant or neonatal form, shows segments of limb where the skeleton is partially visible. The metaphyses are broad and concave. The diaphyses are also distorted with cystic resorption areas at the level of the metaphyses. The ribs are deformed and very thin. In children over 6 months, the metaphyses are large and hollow, and areas of osteolysis occur suprametaphysally which lead to a confusion with an osteomyelitic process, but there is no periosteal reaction. The ossification nuclei appear late and are hypomineralised and smaller. Metaphysical disorders have varying degrees of amplitude.

The histological structure is atypical, bone tissue is poorly represented, and areas of osteoid and cartilaginous tissue appear. Growth cartilages have a deficient structure in which calcium salts and columns of seriated cartilage are missing.

**Treatment**

Medical treatment with vitamin D3 and calcium is ineffective in genetic rickets, which is why this type of rickets is also called vitamin D-resistant rickets. Improvements obtained in some types and cases occur as a result of the genetic types of rickets and as the skeleton matures [15]. Vitamin D deficiency rickets associated with cutabate manifestations such as ichthyosis have disorders in vitamin D metabolism. Some of these forms of rickets behave similarly to genetic rickets [18]. Treating the underlying ichthyotic condition is important as it may probably contribute in restoring back the normal vitamin D metabolism [19].

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Orthopaedic treatment applies when these children have fractures, and especially in neonates and young children. The common orthopaedic deformities associated with the various long-standing types of rickets include genu varum, genu valgum, femoral torsion, anterior angulation of the femora, coxa varus, intrapelvic protrusion of the acetabulum, kyphosis and scoliosis [20].

Surgical treatment is currently essential and aims to treat the evolutionary complications that occur in genetic rickets: axial deviations, dwarfism, spontaneous fractures, etc.

Axial deviations are evaluated periodically by studying the pelvis and pelvic limbs topogram. Axial deviations are not always visible in orthostatism and gait. There are situations in which the limbs appear normal, but, in reality, there is a varum or valgum which can have consequences later [21]. In children, these deformities are treated by hemiepiphysiodesis with eight plates or a trans-hemiepiphysial screw. In adolescents, femur subtrochanteric, supracondylar or tibia proximal osteotomies are performed.

Diaphyseal curvatures are factors that favour recurrent fractures. The place of the maximum amplitude of the curvatures is determined by the study of the anatomical axes. Large amplitude curvatures sometimes require a double osteotomy to be corrected. When the curvatures are accompanied by osteoporosis, complementary osteosynthesis methods, reconstruction plates or periprosthetic synthesis plates are used.

Dwarfism occurs in 40% of patients with genetic rickets. Elongations in rachitic dwarfs are made according to the classical principles of elongating long bones by \( \frac{1}{3} \) of their length, and correcting associated lesions, or according to modern principles: elongation in double focal point on a splint formed by TEN rods, oblique osteotomies, and the concomitant correction of deformities in the valgum, varum or curvatures with the protection of the joints. Taylor-type fasteners (Figure 6) are more useful when bone resistance decreases, being safer and more efficient.

![Figure 6: Taylor fastener applied on a 7-year old with dwarfism due to rickets and curved tibia.](image)

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Spontaneous fractures can be treated with rods, ordinary plates, NBC plates, screws or pins. The efficiency of the screws is complementary and is difficult to understand by beginners or those who do not know the osteosynthesis technique or practice paediatric orthopaedics theoretically.

Arthroses sometimes occurs early due to the strain of incongruous joints as a result of axial deviations. Hip and knee prostheses require knowledge and experience tailored to each case.

Annotations and observations

The study presents only the genetic rickets that have in the foreground, as manifestations clinical, skeletal lesions of the rickets type.

There are also genetic rickets in which rickets appear in the background and we find them in primitive complex tubular insufficiency from Toni-Debre-Fanconi syndrome, Lowe or in pseudo-deficiency rickets from primitive distal tubular acidosis, pseudohyperparathyroidism and hypo-hyperparathyroidism.

To our knowledge, a series of doctors and researchers have contributed to the development of the presented data: Ratbun, Marotoux, Acar, Mumm, Glanc, Shi, Rumack, Unger, Demir, Suciu and Cernea. In the field of pediatric orthopedics in Romania P Moroz and Al. Pesamosca has made a remarkable contribution in the treatment of children with skeletal manifestations. They had the highest number of cases of children with genetic rickets. They preferred toothed ostotomies that allowed them to be corrected without using osteosynthetic materials.

They instituted surgical treatment as an indication only after the age of 7 years. No one was allowed to operate until this age. Thus, it was possible to select vitamin-D-resistant cases, which at that time were not known to be genetic, and the number of surgeries for this disease was significantly reduced.

This indication was taken over by the other clinics in the country and it is still preserved today. Along with him, other renowned professors and doctors with a vast experience in the field brought their contribution: M. Socolescu, A. Varna, R. Mironescu, Z. Moldovan, D. Tica, D. Gotia, G. Aprod, P. Tepeneu, I. Ionescu and others.

Conclusion

All forms of vitamin-D-resistant rickets are genetic rickets. Genetic studies allow the selection of cases of genetic rickets from other forms of rickets and allow the diagnosis of severe and lethal forms.

The most common clinical manifestations are axial deviations of the limbs, spontaneous fractures and dwarfism present in 40% of patients with rickets. The first harbinger of dwarfism is weight loss. Hypophosphatemic rickets in moderate and severe form begins around the age of 1 year when the child begins to walk.

Pseudocarential rickets is the most common form of genetic rickets. Prader-type rickets begins in the first year of life and has a serious evolution. The Mc Cance type begins in adolescence or adulthood and has manifestations in the spine and limbs.

Royer-type rickets in familial hypercalciuria begin in the first 3 years of life through tetanus attacks.

Hypophosphatasia rickets is the most serious form of rickets and has a mortality rate between 58 and 100%. It can start intrauterine, during childhood after 6 months or in adulthood. Availability of TNSALP implantation will decrease or eliminate the number of deaths.

Orthopaedic treatment is currently basic and targets axial deviations, spontaneous fractures and dwarfism.

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