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CONSIDERATIONS ABOUT RICKETS AND ASSOCIATED TOOTH PATHOLOGY

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Rickets is a disorder characterized by defective chondrocyte differentiation and the growth plate and defective osteoid mineralization. The condition recognizes several etiopathic forms, respectively: nutritional rickets, genetic causes, various medical conditions: chronic renal failure, medications, malignancy. Teeth are mineralized organ, composed of enamel, pulp-dentin and cementum and supported by surrounding alveolar bone. Odontogenesis differs from osteogenesis but tooth mineralization occurs parallel processes as skeletal mineralization and is susceptible of disturbances of mineral metabolism. Dental pathology have been described in patients with nutritional rickets (delayed tooth eruption-no incisors by 10 months of age, no molars by 18 months of age) but especially in genetic causes of rickets (enamel defects, dentin mineralization defects, thin dentin, enlarged pulp chambers, short roots, dental abscesses and bacterial infiltration, periodontal disease, malocclusion). Conventional treatment of rickets does not ensure in many situations the improvement of dental pathology. Curative treatment of rachitic tooth should be individualized. Development of new therapeutic classes which improve skeletal mineralization and dental defects would be the optimal solution in this condition.

Keywords: rickets, dental pathology, therapy.

INTRODUCTION

Severe vitamin D deficiency generates in children the condition called rickets and in adult osteomalacia. Vitamin D (the most active form of the hormone is 1, 25-dihydroxyvitamin D) is a important regulators of calcium and phosphorus homeostasis and skeletal metabolism. Vitamin D increases intestinal calcium absorption and in an adequate vitamin D state approximately 30% of dietary calcium is absorbed and only 10 to 15% in a vitamin D deficient state. Vitamin D increases the dietary phosphorus absorption by 15–20%. The effects of vitamin D on bone includes the promotion of the mineralization of osteoid and regulates the expression of several bone proteins (it promotes the transcription of osteocalcin and has effects on type I collagen and alkaline phosphatase gene transcription)[1]. Other regulators of the calcium and phosphorus homeostasis are parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). Increased PTH secretion as a consequence of hypocalcemia generates increased 1, 25-dihydroxyvitamin D, renal reabsorption of calcium, bone turnover to release calcium and reducing serum phosphorus by effect on kidneys. FGF23 decrease serum phosphorus by reducing cotransporters in the renal proximal tubule, antagonizes vitamin D metabolism by decreasing renal expression of 25-hydroxyvitamin D 1 alpha hydroxylase[2, 3]. Rickets is a disorder characterized by defective chondrocyte differentiation and the growth plate and defective osteoid mineralization[4].

THE ETIOLOGY OF RICKETS

The condition recognizes several etiological forms, respectively:

1. Nutritional rickets generated by vitamin D deficiency, calcium and phosphorus deficiency, inadequate sunlight exposure or secondary to malabsorption syndromes.

2. Vitamin D dependent rickets (VDDR) which includes: type I or pseudo vitamin D deficiency rickets generated by abnormalities in the gene coding for 25-hydroxyvitamin D 1 alpha hydroxylase and type II generated by defective vitamin D receptors. Are described two variants of type I VDDR respectively IA and IB. Type IA is generated by of mutation in the cytochrome P450, family 27, subfamily B, polypeptide 1 (CYP27B1) that encode the 25-hydroxyvitamin D 1 alpha hydroxylase. Type IB is a rare autosomal recessive affection generate by mutation in the gene cytochrome P450, family 2, subfamily, member 1 (CYP2R1). Type II VDDR comprises 2 subtypes: IIA as a result of the mutation in the vitamin D receptor gene and IIB generate by abnormal expression of a hormone response element-binding protein that interferes with normal function of receptor vitamin D.
3. Vitamin D-resistant rickets or hypophosphatemic rickets. The classification for hypophosphatemic rickets include causes with increase plasma FGF23 or with normal or decreased plasma FGF23. FGF23 related rickets include: X-linked dominant hypophosphatemic rickets generated by mutation of phosphate regulating gene with homologies to endopeptidases on the X-chromosome (PHEX), autosomal dominant hypophosphatemic rickets (ADHR) generated by mutations in the proteolytic cleavage domain of FGF23, autosomal recessive hypophosphatemic rickets (ARHR) due to inactivating mutation of dentin matrix acid phosphoprotein 1 gene (DMP1)-type 1 or inactivating mutation in ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)-type 2, hypophosphatemic rickets with hyperparathyroidism, other genetic causes (osteoglophonic dysplasia, McCune-Albright and Raine syndrome, opsismodyslasia). FGF23 independent rickets recognises the following causes: hereditary hypophosphatemic rickets with hypercalciuria due to inactivating in the solute carrier family 34, member 3 (SLC34A3), hypophosphatemic rickets with nephrolithiasis and osteoporosis secondary mutations in SLC34A3-type 1 or solute carrier family 9, member 1, regulator 1 (SLC9A3R1)-type 2, dent disease.
4. Other causes: chronic renal failure, medications (antacids, anticonvulsants, corticosteroids, loop diuretics) tumour induced inhibition of renal 25-hydroxyvitamin D 1 alpha hydroxylase[5, 6].

THE CLINICAL PRESENTATION IN RICKETS

Clinical and radiographic features associated with nutritional rickets are represented by:

1. Skeletal signs and symptoms: swelling wrists and ankles, delayed fontanelle closure, leg deformity, costochondral beading (rachitic rosary), frontal bossing, craniotabes, bone pain;
2. Radiographic features: splaying, fraying, cupping and coarse trabecular pattern of metaphyses, widening of the growth plate, pelvic deformities;
3. Extraskeletal hard tissues: hypocalcemic seizure and tetany, hypocalcemic dilated cardiomyopathy, delayed gross motor development with muscle weakness, serious dental complications[5, 7].

DENTAL PATHOLOGY IN RICKETS

Teeth are composed of enamel, pulp-dentin and cementum and supported by surrounding alveolar bone. Odontogenesis differs from osteogenesis but tooth mineralization occurs parallel processes as skeletal mineralization and is susceptible of disturbances of mineral metabolism[8].

Dental pathology have been described in patients with nutritional rickets (delayed tooth eruption-no incisors by 10 months of age, no molars by 18 months of age) but especially in genetic causes of rickets[4, 8, 9, 10, 11].

In 2014, Foster BL and co-workers published in *Endocrine Reviews* a report on the dental defects of the rachitic disorders. The authors specify that the three structures of teeth show mineralization defects under rachitic condition. Enamel defects is commonly present in VDDR I and II and ARHR and inconsistently for X-linked hypophosphatemia; to mention that the mechanism for the observed effects of rickets on enamel is poorly understood. Dentin defects are remarkably present under the same three conditions outlined above. In the inhibition of dentin mineralization are involved hypocalcemia, hypophosphatemia, low level of 1, 25-dihydroxyvitamin D, hyperparathyroidism, local changes such reduced function of PHEX and DMP1 and increases in mineral-inhibiting peptides. Alteration of cementum has been reported in ARHR and X-linked hypophosphatemia. Bone mineralization is compromised as a result of rickets and alveolar bone is rapidly remodelling[8]. The most common reported dental defects in rickets are presented in Table 1.

Table 1

Dental defects in rickets

Rachitic disease	Dental Pathology
VDDR type I and II	Hypoplastic enamel, dentin mineralization defects, thin dentin, enlarged pulp chambers, short roots, periodontal disease, malocclusion
FGF23 dependent rickets: 1. PHEX	Enamel defects and fractures, thin dentin with mineralization defects, enlarged pulp chambers, roots dysplasia, dental abscesses and bacterial infiltration, periodontal disease, malocclusion
2. ADHR	Dental abscesses
3. ARHR	Rapid attrition of enamel, thin dentin, enlarged pulp chambers, traumatic tooth loss, hypoplastic teeth and caries
4. Raine syndrome	Enamel hypoplasa

THE DIAGNOSIS OF RICKETS

According to Global Consensus Recommendations on Prevention and Management of Nutritional Rickets published in the year 2016 "*The diagnosis of nutritional rickets is made on the basis of history, physical examination, and biochemical testing, and is confirmed by radiographs"*[4]. Medical history includes: the infant's gestational age, diet (vitamin D and calcium intake) and degree of sunlight exposure. A family history of short stature, orthopedic abnormalities, poor dentition may signify genetic causes of rickets. Complete physical and dental examination should be performed in children with rickets. Biochemical testing include determination of 25-hydroxyvitamin D, serum phosphorus, calcium, PTH, alkaline phosphatase, urinary phosphorus and calcium. The most helpful in diagnostic of rickets are anteroposterior radiograph of growing areas such as the knee or wrist. The skeletal abnormalities in this affection are most pronounced at the knees, wrist and anterior rib ends, the classic findings including: widening of the distal physis, fraying and widening of the metaphysic as well as angular deformities of the arm and leg[5].

TREATMENTS OF RICKETS ACCORDING TO ETIOLOGICAL FORM

*Treatment of nutritional rickets***.** Treatment of nutritional rickets includes preventive and curative therapy.

Prevention of nutritional rickets is achieved by:

– vitamin D supplement of 400 IU/day for all infants from birth to 12 months of age and beyond 12 months of age, all children need to meet their nutritional requirement for vitamin D through diet and/or supplementation, which is at least 600 IU/day.
– adequate dietary calcium intake: for babies from 0–6 months of age: 200 mg/day, for babies from 6–12 months of age: 260 mg/day and for children over 12 months of age daily calcium requirement: 700–1300 mg depending on age.
– association of sunlight exposure. Solar radiation stimulates synthesis of previtamin D which isomerizes to cholecalciferol and is subsequently metabolized to 25-hydroxyvitamin D precursor of the active form of vitamin D[4, 12].

The Global Consensus Recommendations on Prevention and Management of Nutritional Rickets also mentions the need of implementation of international food fortification to ensure nutritional sufficiency of vitamin D and calcium for the whole population[4].

Treatment of nutritional rickets is achieved by:

– administration of vitamin D-the minimal recommended dose is 2000IU/day for a minimum 3 months. Oral treatment with ergocalciferol (D2, preparations use in children with rickets: calciferol, drisdol) or colecalciferol (D3: calcitriol, alfacacidol) is recommended.
– simultaneous administration of calcium (500 mg/day) with vitamin D[4, 5].

TREATMENT AND MANAGEMENT OF CONGENITAL RICKETS

Vitamin D dependent rickets

VDDR type I. Treatment of type IA includes administration of calcitriol or alfacacidol in doses 10–20 ng/kg/day in association with 50–75 ng/kg/day of elemental calcium at the beginning of treatment. Effectiveness of treatment should determine low-normal serum levels of calcium (high-normal levels of serum calcium generated hypercalciuria and subsequent development of

nephrocalcinosis), normal phosphate levels and high-normal PTH values[6, 13, 14]. Calcitriol in doses 10–20 ng/kg/day is the only choice of treatment for type IB[6].

VDDR type II. In both subtypes A and B it is recommended high doses of oral calcitriol (1–6 μg/kg/day) and calcium (1–3 g/day elementary calcium)[6, 15]. Monitoring of treatment requires the determination of serum levels of calcium, phosphate, PTH, alkaline phosphatase, urine calcium excretion; it is recommended to perform renal ultrasound because of the risk of nephrocalcinosis. Other therapeutic options are: long-term parenteral high-dose calcium therapy[16].

Vitamin D-resistant rickets

FGF23 dependent rickets. Conventional treatment consists in phosphate (30–70 mg/kg/day elemental phosphate) and calcitriol (20–70 ng/kg/day) replacement and the main of treatment is to achieve low-normal serum phosphate and high-normal alkaline phosphatase levels. Patients should be monitored at tree month interval. A clinical, anthropometric, biochemical and hormonal evaluation will be carried out. Laboratory assessments include serum levels of calcium, phosphate, PTH, alkaline phosphatase, urinary calcium and creatinine. Renal ultrasonography (for monitoring the development of nephrocalcinosis) and skeletal X-ray (for monitoring of the development of skeletal findings) is recommended to be performed annually before treatment and during treatment[6,17,18]. Conventional treatment improves biochemical and skeletal abnormalities in some cases but in some patients mild of moderate deformities may persist. For these patients devices or surgical procedures can be considered[6, 19]. Some patients not achieve the desired height velocity related to delayed therapy or deficit in growth hormone (GH)[20,21]. In these patients, the administration of recombinant human GH treatment in the pre-pubertal has been demonstrate to improve height velocity and positively contributes to final height[22–24]. Recent concerns about the treatment of this form of rickets have been focused in the development of inhibitors of FGF receptor signalling[6].

FGF23 independent rickets. In the most forms of FGF23 independent rickets oral phosphate alone is sufficient; phosphate therapy decrease serum levels of calcitriol and consequently urinary calcium excretion returns to normal[14].

TREATMENT OF THE RACHITIC TOOTH

Conventional treatment of rickets does not ensure in many situations the improvement of dental pathology. Prevention of rachitic tooth include: good oral hygiene, periodical and detailed examination by pediatric dentists, prudent use of sealants and fluoride to help prevent and stop caries progression, procedures to protect against progression of infections of the dentoalveolar complex[25]. Foster BL and co-workers in a previously mentioned report it states that „*early diagnosis and preventative dental treatment in these circumstances will minimize major dental pathologies requiring more extensive interventions. Periodontic and orthodontic treatment can improve outcome in terms of tooth retention and function and also may significantly add to dental aesthetics and quality of life for patients"*[8]. Curative treatment of rachitic tooth should be individualized. Development of new therapeutic classes which improve skeletal mineralization and dental defects would be the optimal solution in this condition.

CONCLUSION

Teeth are mineralized organ that is susceptible to similar failures as bone under rickets condition. Conventional treatment of rickets does not ensure in many situations the improvement of dental pathology. Curative treatment of rachitic tooth should be individualized. Development of new therapeutic classes which improve skeletal mineralization and dental defects would be the optimal solution in this condition.

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