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Chronic Congenital Hyperphosphatasia (Juvenile Paget's Disease) - A Review

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ABSTRACT

Chronic Congenital Hyperphosphatasia (or «Juvenile Paget's Disease") is an exceptionally rare bone disease, which registers currently just over fifty cases in worldwide literature. It is an inherited skeletal disorder, with very early onset, extremely high bone turnover and bone mineralization disorders that affects the whole skeleton. This review examines the published case reports to date and focuses on the pathogenesis, clinical features, epidemiology, diagnosis and therapeutic approaches of the disease.

KEY WORDS: Hyperphosphatasia, Juvenile, Paget, Pathogenesis, Treatment

1. Introduction

The term «hyperphosphatasia» or «hyperphosphatemia» describes the elevation in both alkaline phosphatase (ALP) serum levels and enzyme activity beyond normal levels. Hyperphosphatasia applies to many normal and pathological conditions such as skeletal growth, pregnancy, liver and bile duct diseases, endocrine diseases like acromegaly and hyperparathyroism, bone fractures and metabolic bone diseases such as Paget disease, osteomalacia, bone tumors, osteogenesis imperfecta, fibrous dysplasia and, of course, chronic congenital hyperphosphatasia (CCH). [1,2] Obviously, CCH receives its name from the above-mentioned laboratory finding that is due to the extremely high rate of bone turnover affecting both bone formation and resorption. Bakwin and Eiger first presented the disease as a separate clinical entity in 1956. Since then CCH has been described with numerous names like "juvenile Paget's disease", "chronic (or congenital, or familial) idiopathic hyperphosphatasia", "familial osteoectasia with macrocephaly", "inherited hyperphosphatasia" and "skeletal dysplasia with hyperphosphatemia." [3-5]. Clinically, it concerns a generalized skeletal disorder that appears in the first two years of life and leads to the disruption of normal bone growth and maturation, with consequently severe and time-developing bone deformities, increased vertebral and long bones

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fracture liability, as well as the onset of related complications from other systems.

2. Methods

In order to carry out this research, we reviewed the international literature from 1956 to 2019 via the PubMed database. As keywords, we used the terms: Hyperphosphatasia AND Juvenile Paget AND Chronic Hyperphosphatasia AND Idiopathic Hyperphosphatasia AND Clinical features, Epidemiology, Etiology, Pathogenesis, Diagnosis, Management, Treatment, Bisphosphonates, Denosumab, Prognosis. We focused on eighteen case report articles, twenty interventional trials and thirteen older reviews pertaining to the clinical features, epidemiology, pathogenesis, diagnosis and treatment of CCH.

3. Epidemiology

CCH can be classified as an exceptionally rare metabolic bone disease of childhood that currently registers only 56 cases worldwide. The first clinical manifestations occur a few months after birth. The disease itself seems to have no preference for gender or race/ethnicity. Moreover, despite the lack of an established geographical distribution, a significant number of patients have been reported in Puerto Rico child population as well as the Balkan, including Greece. Even more, the disease shows an increased frequency in societies where marriage between close relatives is widespread. [6,7]

4. Pathophysiology

4.1. The role of Osteoprotegerin:

The inherited deficiency of osteoprotegerin activity is essentially the basis of CCH pathophysiology. Osteoprotegerin (OPG) represents a soluble glycoprotein that belongs to the Tumor Necrosis Factor (TNF) Receptor superfamily and is secreted by osteoblasts and osteogenic stromal cells. It carries out its action by forming homodimeric complexes, which act as deactivating receptors of Receptor Activator of Nuclear factor kappa-B Ligand (RANKL), an action that has regulatory effect in bone remodeling, thus protecting bones from excess bone resorption. Another significant and parallel action of OPG is the vascular protection against intense calcification. [1,2,4,8-10] The human gene that encodes OPG is known as TNFRSF11B, it is located on the long arm of chromosome 8 at position 8q24a and consists of five exons and four introns. Numerous cytokines and hormonal factors regulate the gene expression in osteoblastic line cells, either enhancing (interleukin-1β, TNFα, vitamin-D) or inhibiting (glucocorticoids, prostaglandin-E2) protein secretion. [11] There is experimental and clinical proof that the reduced or absent activity of OPG is responsible for the development of high-turnover osteoporosis, as well as of calcifications of the tunica media of large elastic arteries. [10]

In CCH, due to the reduced - or absent - OPG action, high concentrations of active RANKL remain in circulation and bone tissue, resulting in an uninterrupted RANKL-RANK interaction. This phenomenon accelerates immensely bone resorption, which leads to a secondary increase of bone formation. Because of the high rate of bone turnover the membranous bone formation becomes impaired and the bone matrix fails to develop in normal hard and compact haversian bone, producing a generalized skeletal disorder. [4,6,12,13] The result is the excessive production of immature cortical and cancellous bone, which is responsible for bone thickening in the skull and other parts of the skeleton. [6,12] Moreover, bone resorption is relatively higher than formation, which leads in failure of complete osteolytic lesions recovery, resulting in gradual thinning of the bone trabeculae and cancellous bone weakening. The intertrabecular space also enlarges over time and gets filled with loose connective tissue and adipocytes. Although the mineralization rate of the osteoid remains normal, excessive production of newly formed bone results in the development of multiple under-mineralized bone areas. [6,13,14] The abnormal bone resulting from these procedures is called "woven-bone", is characterized by significantly lower quality and strength than healthy bone and resembles to affected bone lesion in Paget's disease. [6,7,12,14]

4.2. Heredity

CCH is the first hereditary human disease described

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as a result of OPG gene mutations and appears to be transmitted mostly with the autosomal recessive inheritance pattern. However, models of autosomal dominant heredity have also been proposed from time to time, and any correlation with sex-related heredity has been excluded. [6,15] Genetically speaking, the responsible impaired gene is TNFRSF11B and approximately 60% of CCH phenotype positive cases are patients with homozygous inactivating gene mutations. The mutations affect the four cysteine-rich extracellular domains (I-IV) of OPG molecule, which are encoded by exons 2 and 3 and represent critical areas for ligand binding and consequently, protein activity. [4,7,16-18] The mutations detected so far in the genome of CCH patients show variety such as missense mutations, frameshift mutation, base insertion and deletion, or even entire TNFRSF11B gene deletion. [4,7,17] The clinical manifestations and phenotype is relevant to the type of mutation. Thus, in cases of a simple addition or deletion of a few bases, the serum levels of OPG remain practically normal, once the production of the mutated protein is normal but the protein has reduced binding activity. The mutations generating amino-acid addition or deletion at the carboxyl-terminal end of the molecule are correlated with the mildest phenotypes of the disease. Missense mutations that do not affect cysteine sequences related to ligand-binding areas of OPG demonstrate medium severity phenotypes. Finally, total gene TNFRSF11B deletion - a state at which OPG levels are undetectable and protein activity absent - corresponds to the most severe phenotype of the disease. [4,5,7,16,18-20]

All the above information explains adequately the clinical manifestations of CCH in most cases. However, there is a small but significant percentage of the patients - less than 40% with milder clinical image - in which no mutation nor TNFRSF11B gene deletion can be detected and the underlining cause remains undefined. [4,7,17] The existence of those CCH case reports suggests that the etiopathogenesis of CCH is more complicated and has not yet been fully elucidated. Nonetheless, some authors support the possibility of misclassification due to clinical similarities with other conditions such as polyostotic fibrous dysplasia or familial expansile osteolysis. [7,16,19]

5. Clinical Image

5.1. Clinical manifestations:

CCH is a serious clinical entity that affects the entire skeleton. The severe bone lesions are time-aggravating and occur mostly during skeletal growth and until skeletal maturation. The impaired bone quality affects negatively the human functionality and therefore the quality of life of the patients.

5.1.1. Skeletal deformities:

The dominant clinical manifestations of CCH are bone anomalies and deformities. They are bilateral, symmetrical and progressive and always present throughout the skeleton. All the long bones, including the finger and toe phalanges, develop cortical thickening with the diaphysis being the most affected area of the bone. The consequence is intense diaphyseal deformities that lead to shorter than normal bone length. The reduced bone strength in addition to the insufficient mineralization produce the characteristic diaphyseal anterolateral bowing. Coxa vara and acetabular protrusion are two other frequent complications of CCH. [6,21] The skull is another bone complex that develops overgrowing lesions, specifically the diploe which appears sclerotic and enlarged. The development of macrocephaly with hypertelorism although disease characteristic is not always present and usually is observed in children of older age. Very rarely coexists aplasia or dysplasia of the paranasal cavities, mostly the maxillary, the frontal and the sphenoid sinuses. [6,20] As far as the dentition is concerned, adult teeth appear normal, however they delay significantly to erupt. Regarding the primary dentition, there is frequent premature loss of deciduous teeth. [12,22,23] Spinal deformities contribute often and severely to the clinical picture, through the development of osteopenia or osteoporosis, vertebral subsidence, or even kyphosis and/or scoliosis. The chest wall and the pelvis also demonstrate dysplastic lesions deformities, with major representative the pectus carinatum. [24,25]

Due to the presence of severe bone deformities, the patient's growth rate gets impaired resulting in low stature below the 3rd percentile position on the corresponding growth charts to gender and height. Bone pain, headache and increased spontaneous fracture

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risk represent concomitant manifestations and complication of CCH. Fractures are usually multiple and most often complicate children with less severe phenotypes. This incident can be explained by those patients ability to be more active and have better mobility and therefore to have increased likelihood to suffer falls and injuries. [7,15] As far as walking ability, the impairment of the gait shows variety being relevant to the severity of the disease. The children usually delay to conquer walking and they have an ungainly gait. Sometimes walking is not obtained at all or obtained over a short period of time and then lost. In other, milder, cases the ability to walk may remain intact. [23-25]

5.1.2. Neurological and sensory complications:

On the ground of CCH, nerve foraminal stenoses with consequential neurological and sensory disorders are a common occurrence deteriorating with aging. The stenoses develop as a result of the overproduction of the pathological bone near the cranial foramina, gradually filling the foraminal space entrapping the passing nerves and causing from nerve compression up to nerve paralysis. All the cranial nerves may be affected through the same mechanism, but the cochlear and optical are predominately the nerves that are implicated. [21] Thus, the patients often exhibit bilateral hearing loss, typically established before puberty, which is due to cochlear nerve impairment. Especially for hearing loss, other causes apart from inner ear bone stenosis have been mentioned occasionally, such us the congenital auditorial ossicle absence, eardrum thickening and extra bone masses in the middle ear derived from bone overgrowth. [20-22,26]

Severe visual disorders also start to appear around the end of puberty and have already been described in twelve of the fifty-six patients that have been reported worldwide with CCH. The most harmful condition is the progressive blindness due to optical nerve atrophy. Clinical findings from the eyes that occur with increased incidence in CCH include the gradually progressive retinitis pigmentosa, visual field restriction, central vision black spots, choroidal neovascularization, macular degeneration and angioid streaks. The last ones are recognized as ruptures of a thickened and calcified Bruch's membrane and represent the most common pathological finding from the eye in patients. [6,21,23,27] The exact formation pathway is yet to be determined. However, it is speculated that in the absence of normal OPG activity there is a predisposition for calcification of the elastin-rich elastic layer of the Bruch's membrane. [27]

5.1.3. Vascular complications:

One of the most compounding factors concerning the prognosis of patients with CCH is the increased incidence of concomitant vascular disorders, the most common of which are arterial hypertension and elastic pseudoxanthoma. Worth mentioning is a CCH case of an 18year old teenager with concomitant severe angiopathy that passed away succumbing to an extensive stroke. [6] Arterial hypertension has been reported in a relatively large number of patients. Elastic pseudoxanthoma, on the other hand, is one of the less frequent complications of the disease and is rather observed in older patients. It regards progressive, aggravating calcification of tissues rich in elastin, such as the middle and inner layer of elastic blood vessels. Coronary heart disease and renal artery occlusion are two of the primary consequences resulting from this specific pathological process. [23] Considering the mechanism, it is mentioned that the smooth muscle fibers and the endothelial cells of the arteries secrete RANKL in both the atherosclerotic plaque and blood circulation. Therefore, it is most likely that due to the inadequate action of OPG in CCH, the negative effects of RANKL on the blood vessels can not be sufficiently controlled. [28,29]

5.1.4. Other complications:

Beyond the above mentioned major clinical manifestations, the patients with CCH often experience low-threshold fatigue and progressively worsening muscle weakness, accompanied by muscle limb atrophy, sometimes to such an extent that the affected persons can not even sit down. Atrophy and painful swelling of periostotic soft tissues generally coexist. Additionally, the disease has also been linked to a relatively high incidence of nephrolithiasis. [12,21,24] Finally, the majority of the authors support the state-

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ment that the age of puberty's onset and mental status remain in normal range. Only exception to the last is the reduced learning capacity that the patients with neurosensory loss of hearing demonstrate, a condition though that falls in to frame of hearing disability and impaired aural comprehension. [6,7,14,23]

5.2. Time of clinical onset of CCH:

Generally, the onset of the disease and the time of diagnosis shift to earlier age as more severe becomes the mutation of OPG gene. The patients appear healthy at birth, but further on, they gradually develop the skeletal deformities mentioned above. At first, they always develop the long bone lesions as the primary disease manifestation and later on the concomitant disorders that regard child development and growth. Most commonly, the disease appears between 3 and 18 months of age but the diagnosis is put around toddlerhood until early preschool age, a time when the signs and symptoms have become clearly obvious. Rarely, in the mildest cases, the disease can be diagnosed in late childhood. [7,12]

5.3. Severity of the disease:

The severity of clinical manifestations of CCH vary significantly from patient to patient and is relevant to the degree that the genetic lesion affects the activity of OPG. In most cases the clinical image is severe, leading to serious bone lesions and complications. In general, the clinical phenotypes of the patients can be grossly classified as follows: [7,30]

- **Severe:** The bone deformities begin to be recognized during the first 18 months of life, while the child fails to conquer walking ability. Even if the patient manages sometime to walk, this happens markedly late and eventually gets lost during the early childhood.
- **Moderate:** Skeletal deformities occur later, approximately two years after birth, and the child begins walking at normal age. However, bone lesions are progressively aggravated, causing a steadily lower stature below the 3rd percentile position on growth charts according to gender and age.
- **Mild:** The bone lesions begin after the second year of life. Patients pertain a satisfying mobility, while their stature remains within normal limits.

The severity of clinical manifestations is further influenced by two separate parameters, regardless of phenotype: The first is the age, as bone deformities develop gradually and affect mostly patients in puberty and adolescence or older ages. The second factor is the anti-osteoclastic therapy administered to CCH individuals, as the successful application of treatment can greatly influence the progression of CCH and its final clinical image. [7]

6. Imaging assessment

The usually severe clinical presentation of CCH, with the extended skull, body and limb deformities, predicts the findings from the imaging assessment of the patients. It is essential to make the remark that the radiological image of the patients with mild or moderate phenotypes of CCH is in basically better that those with severe disease forms. Only exception to that are the pathological fractures that occur most frequently to more ambulatory patients. [6,7,31]

(a) Simple X-rays. In the severe cases of the disease - especially when macrocephaly is present - the bones of the skull appear thickened and enlarged. The diploic space is distended and the mastoid processes loose their natural pneumatic appearance. These lesions develop symmetrically and progress over time. [12] The paranasal sinuses are often hypoplastic (or rarely aplastic), while the "cotton wool" appearance of the skull - representing multiple localized spots due to the coexistence of osteopyknotic and osteolytic lesions - is very common. [6,24] The rest of the bones show predominately osteopenia combined with osteosclerotic areas. Trabecular bone has a rough and irregular appearance, while cortical bone is quite thick, although there are areas extremely thin like "paper". The spine usually consists of biconvex vertebrae with reduced height. The intervertebral spaces are increased and the whole backbone receives deformities like scoliosis, kyphosis and lordosis. [32,33] The long bone lesions regard mainly the excessive diaphyseal widening in comparison to the normal appearing epiphyses, the development of bowing, the marked cortical thickening of the femur-medial cortex and the occurrence of multiple fractures. Transverse lines through the area

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of the diaphysis are quite often and represent locations of vascular micro-infarctions. Acetabular protrusion and coxa vara are two more common radiological findings. [7,12,23,25,31,33] The ribs, the scapula and clavicle share similar deformities, having enlarged dimensions with the presence of areas of increased and decreased bone density. [6,12,25,31]

(b) Cross-sectional imaging assessment. Evaluation via computed tomography (CT) or magnetic resonance imaging (MRI) is more adequate to diagnose lesions that cause nerve compression or other complications due to the overwhelming bone growth. Typical example is the cranial or spinal foraminal narrowing, causing nerve entrapment and the consequent sensory and neural deficits. [21]

(c) Bone Scintigraphy. In CCH patients bone scan is not considered to be an essential examination to perform. Only two cases in the past were submitted to bone scan, which produced diffused and increased uptake of the radioactive agent throughout the entire skeleton. [21]

7. Laboratory findings

Beyond the clinical and imaging particularities of CCH, an important and critical role in diagnosing the disease has the laboratory evaluation, which reflects the markedly increased bone turnover of the patients. Thus, the serum levels of ALP (total and bone fraction), measure five to ten time above the upper limits of normal ranges, a finding that is caused by the increased osteoblastic activity. That extend of ALP elevation is a main element and rule in the disease. [21,24,25] However, scarcely though, in sporadic CCH cases with mild phenotype, ALP levels have been observed to be just above the higher limits or within the normal ranges of the enzyme. Nonetheless, a correlation between the severity of the clinical phenotype and the degree of elevation of serum ALP has not been established. [6,7] Apart from ALP, other enzymes are also traced in pathologically elevated concentrations in serum (such as acid phosphatase and leukine aminopeptidase) [21,22,34] as well as type-I collagen degradation products that are determined in urine [such as amino-terminal collagen crosslinks (NTX), carboxyl-terminal collagen crosslinks (CTX) and proline], due to the overactivity of the osteoclasts. [13,24] Regarding the blood concentrations of calcium, phosphorus and magnesium, they remain always within normal range of values. Serum levels of uric acid can be within normal values, or slightly elevated probably due to the cellular overactivity. Finally, hypercalciuria or/and hyperuricosuria are mentioned relatively frequently, although there were some cases with 24hour urinary calcium concentrations below normal. [7,24,34]

8. Anatomical pathology data

The histological findings reflect the disturbed bone turnover that characterizes the disease. Typically, there is marked increase in the number and size of the osteoclasts as well as the osteoblasts, but in a lesser degree. Even though the activated osteoclasts enlarge they never reach the typical form of the gigantic multinuclear cells that are met in Paget's disease in adults. [6,7,14,32] Finally, both cortical and cancellous bone are gradually transformed into a matrix of rough, thickened, immature and weak bone (woven bone), the main characteristics of which are the thin trabeculae, the presence of soft connective tissue and adipocytes filling the distended intertrabecular space and the impaired mineralization of osteoid. As a result, the normal haversian systems disappear, fibrosis develops and in the end the affected osseous tissue receives a completely unruly and chaotic structure. [6,13,22,24,35] Thus, the cement lines of the cortical bone are distinct and irregularly distributed, the architecture of the thin trabeculae of the cancellous bone is completely disorganized and surrounded by thick bands of osteoid, while the periosteum shows focal thickening and increase count in cells. [7,13,32]

9. Differential Diagnosis

9.1. Adult Paget's Disease of Bone (PDB)

CCH as a disease bears significant resemblance to PBD, hence the term "juvenile Paget's disease" that had been predominately used in world literature. Nowadays, it has been established that the two diseases are two separate, individual clinical entities. [8] The similarities between them regard mainly to the increased rate of bone turnover, the increased bone fra-

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gility and bowing of long bones of limbs, the intense bone pain, the significant elevation in bone fraction of serum ALP and, mostly, the positive response of both diseases to antiosteoclastic treatment. [7,18,22] Nevertheless, the existing differences are greater and rather more than the similarities. Thus, CCH is diagnosed in infants, toddlers and children while PDB in individuals older than 25 years. Moreover, the bone lesions in the first are generalized and symmetrical, in contradiction with PDB that are more localized and lack symmetry. Macrocephaly, short stature, sensory and vascular disorders as well as dental deficits do not develop in PDB. Finally, the osteosarcoma development has never been reported in CCH, in opposition to PDB. [7,8,12] Histologically, the trabecular bone volume appears diminished in CCH and increased in PDB, while the characteristic gigantic multinuclear osteoclasts are present exclusively in PDB. [8,35,36] Lastly, down to the level of pathogenesis, in PDB there are genetic factors which involve mutations that affect proteins RANK and p62, in addition to environmental influence such as viral infections. On the other hand, CCH is related to an inheritable lack or insufficient action of the OPG protein due to gene TNFRSF11B malfunction. [7,8,18]

9.2. Diseases that are caused by mutations in the TNFRSF11A gene.

The TNFRSF11A gene is located at chromosomal position 18q22.1 and is responsible for the encoding of factor RANK. The diseases that are caused by activating mutations of that particular gene are quite rare, transmitted on to next generations by autosomal dominant inheritance and resemble significantly with the clinical image of CCH, since they also involve the biological pathway of OPG/RANK/RANK, leading in a similar manner to over-activation of osteoclasts. Familial expansile osteolysis, Early-onset Paget's disease and Expansile skeletal hyperphosphatasia are the three known to date genetic disorders that form the specific group of diseases. [8,19,29,37,38]

9.3. Other relevant pathological conditions

There are some pathological conditions of the skeleton that are very alike CCH and have to be included in the differential diagnosis process. These are Rickets, IBMPFD (Inclusion-Body Myopathy, PDB, Frontotemporal Dementia) syndrome, Engelmann's disease, Polyostotic fibrous dysplasia within the McCune-Albright syndrome, type-I Osteogenesis imperfecta, Van Buchem disease, Sclerosteosis, Hyperphosphatasia with mental retardation syndrome, Marbry syndrome, Pyle's disease, Pseudorheumatoied and Spondyloepiphysial dysplasia, Kashin-Beck disease and Transient benign Hyperphosphatasemia. [6,33,34,36-41]

10. Therapeutic Approach

The rare nature of CCH has been an obstacle in acquiring randomized controlled studies, even nowadays, investigating the therapeutic approach of the patients. The first patients in the 1960's received as treatment sodium fluoride, a medication that, although reduced significantly serum ALP values, did not practically improve the clinical image nor did reduce fracture incidence. [32,42] During the following decades, successful treatments were proven to be calcitonin and mainly bisphosphonate agents, which directly act on osteoclasts reducing their excessive activity. As a result, administration of these medications improved laboratory findings and imaging and ameliorate overall the clinical condition of the patients. [7,17,30,43]

Calcitonin treatment was used up until late 1990's in longtime intramuscular, subcutaneous or intranasal administration protocols. At the daily dose of 100 IU calcitonin achieved a 50% reduction of serum ALP levels and a significant pain-relieving effect. It also decelerated disease progression, reduced the number of fractures and improved the quality of patients' life. It's mechanism of action led to a reduction in bone resorption in favor of normal bone formation and to better mineralization, quality and density of bones. [13,14,22,24,42]

Bisphosphonates (BPNs) were firstly introduced in CCH treatment in 1992 by Spindler et al. [44] and continue to be until today the current choice of treatment, since they have proven to be more effective than calcitonin, are generally well tolerated and have a satisfactory safety level even during longtime treatment periods. The prompt administration of in-

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tensified treatment regimens with intravenously (IV) administered bisphosphonates appears to produce the most impressive results, strongly suppressing the rate of bone turnover and therefore preventing the occurrence of bone deformities as much as neurological and sensory complications. [7,17,43] Of all the previously tested protocols, cyclic IV administration of pamidronate appears to be superior. There is evidence supporting its ability to reduce up to 90% serum ALP, restore to normal values the biochemical bone turnover markers, significantly increase bone density, therefore improving in whole the skeleton and eventually promoting child growth. [7,17,43] Adequately good outcome had IV ibandronate in high doses. [30] Zolendronic acid administration has been tried in very few CCH patients but didn't yield good enough results. Elaborating, even though the patients demonstrated significant clinical improvement, serum ALP levels had a lesser reduction in comparison to other IV bisphosphonates. Moreover, the possibility of serious hypocalcaemia after administration was much greater. [43] Regarding the oral administration of BPNs, it is mainly reserved for older children due to better compliance. Etidronate and alendronate have been used in CCH and have yielded positive results regarding clinical condition, histological image and laboratory profile, with a significant drop in serum ALP and urinary hydroxyproline levels. [21,24,36] As a general observation, in CCH no BPN restores the rate of bone remodeling to normal when administered in conventional dosage and this goal can be obtained in most cases only through higher doses. However, due to the lack of relevant studies, specific therapeutic regimens have not yet been defined. [30]

Another promising therapeutic approach is the administration of Denosumab, a monoclonal antibody targeting the RANKL ligand and inhibiting its binding to receptor RANK. To date only three CCH patients have received Denosumab treatment in various schemes, with very good response to bone pain control and bone metabolism markers improvement. [45-47] One of the side effects that must be taken into consideration is the risk of post administration hypocalcaemia in the context of hungry-bone syndrome. Furthermore, the drug influence on CCH complications and the safety profile during long time administration are yet to be identified. In any case, it is also noteworthy that bone resorption inhibitors must be a treatment for life in CCH patients, as any drug discontinuation is always followed by significant reactivation of the disease. [47]

The administration of recombinant OPG could potentially be a satisfactory "replacement treatment" in CCH, however it is not yet used in clinical practice. Experimental administration of the drug, firstly in OPG knock-out mice and secondly in two patients with CCH, resulted in complete suppression of high bone resorption rate, milder reduction of bone formation, increase in cortical bone mass, improvement of radiological imaging and reversal of a large part of the bone pathology of the disease. [17,48] Mild transient symptoms of hypocalcaemia in combination with secondary hyperparathyroidism were also in this case the most important adverse effects. [17,48] It is important to note that due to the mutational nature of the disease, with concomitant OPG gene defect or even absence, it is theoretically possible for patients to develop antibodies against recombinant OPG and then neutralize it. [4,17]

11. Natural History and Prognosis

The high rate of bone remodeling that characterizes CCH continues to fluctuate at abnormal levels for many years after birth, leading to constantly progressive and deteriorating lesions. Therefore, if the disease is not treated timely and adequately, it has a rapid progress in time, with the development of marked bone lesions and complications. The whole progression of CCH often leads to severe disability and shortening of life expectancy to such an extent that the disease can become fatal in the young adult life or even childhood. [7,12,20,36] The leading causes of death in CCH are the severe constrictive lung disease and the accompanying infections of the respiratory system. [27] Other causes of premature death include vascular incidents in older ages and visual disorders, due to which the possibility of serious injuries and fractures increases significantly. [4,7,14] In general, the clinical course and, therefore, the prognosis of CCH depend completely on the severity of each phenotype, the age

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of disease onset and the type of treatment intervention to be followed in each patient. [24]

12. Conclusions

CCH is an exceptionally rare inherited clinical entity that deranges bone metabolism and becomes apparent in infancy and early childhood. The disease presents with variable phenotypes of different severity and demonstrates an excessively high rate of bone turnover throughout the skeleton, resulting in the replacement of normal osseous tissue by pathological, insufficiently mineralized and reduced strength bone. That functional and histological upheaval is the reason for the serious, generalized and progressive bone deformities, the excessive increase in fracture frequency and the development of severe physical and neurological disabilities that influence in a variant negative manner life quality and expectancy of CCH patients. In the majority of cases, inactivating mutations of the TNFRSF11B gene - responsible for OPG encoding - are etiologically implicated. The diagnostic process is based on careful evaluation of clinical, laboratory and imaging data, as the combination of the various particular elements of the disease is not found in other pathological conditions. Therapeutically, current data has established BPNs as a treatment of choice, especially when administered in higher than conventional doses. However, new and more targeted treatments, such as denosumab, may further improve the clinical image and prevent the progression of the disease.

Conflict of interest:

The authors declared no conflicts of interest.

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