Osteopetrosis: classification, pathomorphology, genetic disorders, clinical manifestations (literature review and clinical case report)


Abstract. Osteopetrosis is a hereditary disease with an autosomal recessive or autosomal dominant type of inheritance, caused by a disruption in the functional activity of osteoclasts due to gene mutation. The article systematizes data on etiology, classification, pathomorphology, gene disorders based on the analysis of 38 sources of literature, and deals with the modern approaches to the treatment of osteopetrosis. Three types of osteopetrosis with different severity degrees of skeletal disorders and pathological severity are described. The main pathomorphological changes in the structural organization of bone tissue are presented and features of the state of osteoclasts are shown depending on the mutation of genes controlling their functional activity. There are no protocols for the treatment of this pathology, but treatment methods based on the use of hematopoietic stem cells are under development. The paper presents with clinical case report of a patient with marble bone disease.

Keywords: osteopetrosis; classification; pathomorphology; osteoclasts; gene disorders; diagnosis; treatment

Introduction

Osteopetrosis was first described by Albers-Schönberg in 1904 [1]. Osteopetrosis (congenital family osteosclerosis, marble bone disease, Albers-Schönberg disease) is an umbrella term for a range of rare isolated inherited disorders characterized by skeletal sclerosis [2, 3, 4, 5, 6, 7]. At this moment, there are at least 11 forms known for their different inheritance and severity types. Autosomal-recessive osteopetrosis afflicts 1 in 250 thousand newborns, while autosomal-dominant one – 1 in 20 thousand newborns [6].

Review’s purpose is to systematize data on osteopetrosis’ etiology, classification, pathomorphology of genetic disorder, treatment methods and to present our own clinical observation study.

Information search has been made in Google, Google Scolar, AcademicResoucesIndex, PubMed, РІНЦ (Russian Science Citation Index) for the following keywords: osteopetrosis, osteoclasts, etiology, classification, genetic disorders, treatment.

Osteopetrosis’ etiology

Osteopetrosis’ etiology and pathogenesis require a further study. One of the principal pathogenetic mechanisms involved in this disorder is osteoclasts’ developmental and functional breakdowns.

Osteoclasts are highly-specialized cells in charge of bone mineral and organic matrix resorption. This process is pivotal for the bone reconstruction, its biochemical strength and mineral homeostasis. Adult skeleton is completely renewed every 10 years [8].

Osteoclasts are derived from the mononuclear precursor cells of hematopoietic myeloid line, also giving rise to macrophages and monocytes. Having united, the precursor cells form osteoclasts with up to 20 nuclei. Their life cycle takes only up to 14 days.

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For osteoclasts to get differentiated, both receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) are required. For this purpose, they are produced by osteoblastic cellular differon. Precursor cell and osteoclast activation is initiated by RANKL’s interaction with osteoblastic RANK receptors. Osteoprotegerin, a protein synthesized by osteoblastic line cells, is a soluble RANKL-binding receptor which prevents its interaction with osteoblastic RANK receptors, along with osteoclastic activation and bone resorption.

Osteoclast is a polar cell sticking to the bone tissue by a β3 integrin-produced corrugated fringe. Resorptive lacunae occur due to enzymes destroying organic and mineral matrix (Fig. 1). Osteoclastic intracellular pH is maintained by carbonic anhydrase and electric-neutral HCO₃⁻ / Cl⁻ ion exchange.

Mineral matrix destruction is mediated by hydrochloric acid produced in the resorptive lacunae by chlorine ions penetrating them through the protein-made chlorine-specific ion channel (CLCN7) on the osteoclastic membrane and osteoclast-specific ATP driven proton pump [9]. Organic matrix is destroyed by Cathepsin K. Once genes in charge of osteoclastic differentiation and their functional activity become mutated, osteopetrosis occurs.

This disorder develops with reducing or partial/complete loss of osteoclastic function, which leads to bone resorption disorders. In two thirds of patients osteoclasts are being formed; however, they are incapable of a successful bone resorption. Osteoclastic functional disorder is caused by at least 10 genetic mutations; these are considered osteopetrosis-provoking and are revealed in 70% of osteopetrosis patients [11]. Osteoclastic formation may also be deranged due to precursor cells’ inability to differentiate.

Among the best researched mutations there are those occurring in CLCN7, CAІІ (carbonic anhydrase ІІ) and TCIRG1 (V-ATPase pump) and OSTM1 (trans-membrane protein-associated osteopetrosis). Mutations disrupt pH organelle regulation and cellular secretion, affecting osteoclastic bone resorption [6].

Fig. 2 represents a complex regulation of osteoclastic differentiation and functional activity by means of intracellular signal molecules, RANKL–RANK receptors, cytokines, enzymes. Mutations of genes in charge of this cell’s functioning lead to osteopetrosis.

Disorder is inherited by different pathways: autosomal-recessive and autosomal-dominant.

**Bone pathomorphology**

While studying bones of osteopetrosis patients, researchers find significant bone formation sites on the surface, in the medullary canal and inter-trabecular spaces of trabecular bone. Structural organization of the newly formed bone tissue is irregular, mosaic, characterized by the pronounced pathological modifications. Lamellar bone tissue with irregular cementation lines is interspersed with coarse-fibered bone tissue. Within the medulla, there are bone and cartilage islets, osteoid accumulations [3]. Bone trabeculae seem thickened, their inter-trabecular spaces narrowed [12]. Osteoclastic density may vary under different osteopetrosis types ranging from low to normal; however, bone resorption sites are isolated, reflecting osteoclastic resorptive disorders.

Based on bone biopsy and genetic analysis of osteopetrosis patients, it was found that a significant number of osteoclasts (normal or even elevated rate) in the medulla might signify their disrupted functions, namely due to TCIRG1, CLCN7, SNX10 and OSTM1 gene mutations while presence of isolated osteoclasts or even their absence are connected to a rare osteopetrosis type, caused by RANK and RANKL gene disorders [3].

**Osteopetrosis classification**

For practical considerations, various osteopetrosis forms might be classified in terms of their clinical characteristics, severity of clinical manifestations, medullar histology and genetic basis [3, 13].

The most severe one is autosomal-recessive heredity pathway as it might be associated with α-subunit of ATPase gene defects, namely TCIRG1 (classical type), osteopetrosis-associated protein gene, i.e. OSTM1 (neuropathic type), and carbonic anhydrase Type II, i.e. CA-II (associated with renal tubular acidosis) [3]. Autosomal-recessive osteopetrosis is also provoked by CLCN7 mutations, more rarely by SNX10, RANK and RANKL mutations. It was revealed that RANK-RANKL-OPG signal pathway disorders result in autosomal-recessive osteopetrosis due to the osteoclasts’ reduced number and functional capacities, as this pathway regulates differentiation and activation of osteoclasts [14]. Medullar biopsy reveals cellular shrinking signifying a hemopoietic reduction.
Autosomal-recessive osteopetrosis may manifest itself at the fetal stage, while the neonates and infants are afflicted with progressive anemia, hepatosplenomegaly, macrocephalia or hydrocephalia, as well as nerve restraint resulting in blindness or deafness. This form is qualified as ‘malignant’ osteopetrosis. With neonatal osteopetrosis form, survival rate is low, while the life span is no more than 2-10 years. Disorder is characterized by multiple fracture osteosclerosis, may result in osteomyelitis, vision loss and hemopoietic disorders. Among its typical features, there are broadened facial skull, nasal and lateral anatomic disorders. Mental retardation and progressive neural degeneration may be caused by CLCN7 and OSTM1 gene mutations [9, 15]. CLCN7 gene has 20 mutations. This osteopetrosis type is characterized by bone dysplasias.

Intermediary osteopetrosis is clinically and genetically irregular; its course being less pronounced but also severe. Its hereditary pathways could be both dominant and recessive. Protein-encoding gene (CLCN7) becomes less active, while its mutation leads to several forms of recessive osteopetrosis and autosomal-dominant osteopetrosis Type II [16, 17]. CLCN7 gene defects also provoke intermediate osteopetrosis; CLCN7 being protein domain gene, the same as Pleckstrin homology domain-containing gene also known as PLEKHM1 [6]. Intermediary recessive form is characterized by medullar calcification, renal tubular acidosis caused by carbonic anhydrase Type II gene (CA-II). These patients often have mental disorders [18].

Osteopetrosis might also be induced by RANK, SNX10 and TCIRG1 gene mutations [6, 9, 19, 20, 21]. Other intermediary forms are characterized by a moderate osteosclerosis, low height and fragility fractures.

Moderate autosomal-dominant osteopetrosis is characterized by the irregular and late manifestations referred to as a ‘benign’ adult form. Light osteopetrosis may be asymptomatic in half the cases [13], while in others are associated with pathological fractures under minimal trauma; and that is very often the only sign of disorder afflicting adults. Fractures’ union is delayed. Disorder is associated with aching bones, osteomyelitis complications and cerebral nerve affliction [2, 22]. Bone fragility is aggravated by architectonic disorders and atypical bone formation. The most wide-spread complication is optic nerve atrophy due to the bone tissue accretion in cavities and canals, leading to blindness. Autosomal-dominant osteopetrosis is more frequent among the older children and adults; its main manifestation being pathological fractures. With late osteopetrosis, bone lesions become rarer as usual [23]. Early mortality is infrequent, life span is similar to the statistically relevant; however, the quality of life is compromised [10].

There are two types of adult osteopetrosis. In case of autosomal-dominant osteopetrosis Type I, phenotypic pathological manifestations are caused by missence mutation (point mutation leading to a modified codon starting to encode another aminoacid) in LRP5 [24, 25, 26]. In case of autosomal-dominant osteopetrosis Type II, missence mutation might affect CLCN7 [27].

Osteopetroses types are genetically determined and may be referred to as osteoclast-autonomous osteopetrosis and osteoclast-nonautonomous osteopetrosis [28, 29]. With nonautonomous osteopetrosis, genetic effect may be associated with cells affecting osteoclast precursors differentiation or mature cell functions. With osteoclast-autonomous osteopetrosis, genetic defect may be present either in osteoclasts themselves or in their precursors.

Although all osteopetrosis forms are genetically determined, this disorder may be induced in children by the bisphosphonates, as the latter favor osteoclast apoptosis [30, 31]. In this case, bone dysplasias are formed.

![Fig 2. Causes of differentiation and osteoclastic activation disorders](adapted from 6, 9, 10, 11 with additions)
Diagnostics

Osteopetrosis diagnostics involves clinical and X-ray evaluation by means of bone densitometry. To confirm the diagnosis, it is important to rely on genetic studies as well.

Diagnosis is based on the following X-ray characteristics described by Stark Z. and Savarirayan R. [6]:
- presence of diffuse osteosclerosis in the skull, spine, pelvis and limb bones;
- long cortical metaphysis is widened (Erlenmeyer flask), dense and has linear defects;
- ‘bone-in-bone’ phenomenon ‒ dual bone contour, especially for vertebrae and finger phalanges;
- focal osteoporosis of skull vault, pelvis and vertebral endplates, i.e. ‘vertebral sandwich’, ‘striped spine’;

Based on X-ray data, there are two types of autosomal-dominant osteopetrosis singled out [2]. Type I is characterized by skull vault thickening, while Type II is primarily known for ‘striped spine’ and fan-like stripes in the iliac bone wings, as well as for cortical densification. In both types, medullary cavities are narrowed. The disorder affects all skeletal bones; however, most prominent lesions occur in long, skull, spinal, rib and pelvic bones. DEXA reveals BMD values 2-4 times and over as normal.

Hematological study presupposes blood count, namely reticulocyte count in blood sample, and lactic dehydrogenase in blood serum; both are necessary for evaluating the hematological disorder severity. Reduced hemoglobin, reticulocyte and platelet count are associated with medullar disorders.

By contrast, increased white blood cell count, along with immature granulocytes and increased lactic dehydrogenase usually reveals an extra-medullar hematopoiesis.

Laboratory tests of adult patients show Calcium (general and ionized), Phosphorus and acid phosphatase levels in blood plasma to be within normal bounds. However, these parameters may also reveal hypercalcemia. Children are more often afflicted by hypophosphatemia and moderate hypocalcemia. Acid phosphatase levels are usually increased in blood plasma.

Treatment

There are no protocols of osteopetrosis treatment. It is symptomatic, assisted by a maintenance therapy. Frequent fractures and secondary complications, namely a delayed fragment consolidation or fracture disunion, require orthopedic observation and a special surgical approach [5, 32].

In the recent years, hemopoietic stem cell transplantation enabled achievement of a 5-year survival rate in 73 % of autosomal-recessive cases [23]. This therapy is used, taking into consideration the hematological osteoclast origin. Mostly positive (> 50 %) results were received for autosomal-recessive osteopetrosis treatment; however, certain undesired complications were observed, namely vision impairment right after the transplantation [8, 12, 33]. Similar positive results were received while treating patients with carbonic anhydrase mutations Type II [10]. Nevertheless, in case of RANK and RANKL receptor gene mutations this method is ineffective.

There is little clinical evidence that high calcitriol doses may reduce osteopetrosis symptoms [23], while recombinant parathyroid hormone is effective in case of fractures [34, 35]; however, no evidence base exists for these drugs. There are recent pre-clinical trials of new therapies going on: namely, RANKL and denosumab replacement therapy for osteopetrosis with RANK mutation [6, 7, 36].

Success of the drug development is no doubt restricted by absence of animal models which would replicate human disease course. In was in 2017 only that autosomal-dominant osteopetrosis Type II model was developed and tested on mice. Its advantage lies in the fact that phenotype severity degree was changed; now it resembles a broad phenotype range typical of human patients [37]. Authors suggest that this model will help to identify mutant genes or factors affecting severity and penetrability of this osteopetrosis type, favoring innovative treatment methods being tried out.

Clinical case


Antecedent anamnesis

Dates the onset since 1972, when while undergoing fluorography, was diagnosed with marble bone disease due to a significant densification of bone tissue. At the diagnosis, the patient had no complaints. First ones (lumbar pain and headaches) started in 1979 (at the age of 27) after the second labor. Patient was monitored at the SI “Institute of orthopedics and traumatology”, regularly treated for symptomatic signs. In 2016-2017, pain syndrome’s intensity grew, affecting lumbar spine and lower limbs.

Anamnesis vitae

Female patient, 65 y.o., no history of smoking, no alcohol use. Denies any professional harm. Allergic anamnesis is not aggravated. Age of menarche ‒ 14 y.o., age of menopause ‒ 49 y.o., no replacement therapy undertaken. Denies any other co-morbidities or medications.

Objective status

Hypersthenic, 164 cm tall, 96 kg, BMI – 35.7 kg/m². Skin and visible mucous membranes of normal color.
Peripheral lymphatic nodes are not swollen. Pulse rate – 68 strokes/min, AP – 130/80 mm of mercury column, breathing rate – 14 per min. Heart tones are rhythmic, attenuated, accent of II tone on the aorta. Vesicular lung breathing, no rales. Stomach is soft under palpation, no pain. Lower liver edge next to the end of rib curve. Spleen is not palpable. No peripheral swelling. Diuresis is normal, stool normal as well.

Walking is slowed down; however, with no support. Stature is normal, physiological spine curves are extenuated. Cervical and lumbar movement is greatly reduced, moderately painful; while moving, cracking occurs. Paravertebral muscles are hypertonic, paravertebral pain sites at C₄-S₁. Upper limb joint mobility is completely preserved, but painful. Knee joints are swollen, no inflammation signs. Knee joint mobility is associated with pain, completely preserved, and followed by cracking. At palpation: projection of knee articular cavity is painful. Hand joints are moderately swollen, painful at movement. Strength and muscular tonus of limbs preserved.

**Laboratory results.** General clinical examination revealed no clinically significant deviation. Complete blood count (10.07.2017) results: erythrocytes – 4.76 (normal: 3.8-5.8*10¹²/l), hemoglobin – 140 (120-140 g/l), leukocytes – 5.4 (4-10*10⁹/l), lymphocytes – 37.9 (17.0-48.0%), monocytes – 5.2 (4.0-10.0%), granulocytes – 56.9 (43.0-76.0%), platelets – 272 (150-400*10⁹), ESR – 28 (2-18 mm/hour). Blood chemistry: albumin – 40.6 (32.0-52.0 g/l), alanine aminotransferase – 27 (up to 41 mmol/l), aspartate aminotransferase – 24 (up to 40 mmol/l), blood glucose – 5.9 (3.8-6.1 mmol/l), uric acid – 5.0 (2.5-8.3 mmol/l), creatinine – 70.4 (53.0-97.0 mcmol/l). Bone metabolism parameters are normal: total Ca – 2.36 (2.15-2.58 mmol/l), total Vitamin D (25(OH)D) – 34.41 (optimum level – 30.0-50.0 ng/ml). Bone remodeling marker rates are elevated: pro-

![Fig. 3. Lumbar spine (A), proximal hip (B), total body (C) BMD values](image-url)
peptides of Type I Procollagen (P1NP) – 157,4 (16,3-73,9 ng/ml), β-terminal telepeptides of Type I Collagen (β-CTX) – 1,13 (<1,008 ng/ml).

**Instrumental test results:**


Ultrasoundsonography of abdominal cavity (18.07.2017) – cysts in hepatic lobes, hepatic lipid dystrophy, chronic cholecystitis signs, diffuse pancreatic alterations.


**Dual-energy X-ray absorptiometry (DXA, 13.07.2017)** revealed a significant increase of BMD at all the examined sites: lumbar BMD – T = 11,0, femoral neck – right T = 8,4, left T= 8,4, total body – T = 13,8, forearm – T = 5,9 (Fig. 1). Normal T values are within the range of –1 to +1. Trabecular bone quality index (TBS) – 1,630.

Diagnosis: Osteopetrosis (marble bone disease) with static-dynamic disorders and pronounced irritative-pain syndrome was made according to clinical and X-ray findings rather than genetic testing.

Thus, osteopetrosis is a hereditary disease grounded in osteosclerosis. Pathology is attributed to disordered osteoclast differentiation and activity, reveals itself in structural bone changes, compactization and increased fragility, increased fracture risk. Osteopetrosis is a genetically-bound disorder with autosomal-recessive and autosomal-dominant heredity types, greater severity being associated with autosomal-recessive type.

**Conflicts of interests.** Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

**References**


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Остеопетроз: класифікація, патоморфологія, генетичні порушення, клінічні прояви (огляд літератури та власне клінічне спостереження)

Резюме. Остеопетроз — спадкове захворювання з автосомно-рецесивним чи автосомно-домінантним типом успадкування, спричинене порушенням функціональної активності остеокластів внаслідок мутації генів. У статті на основі аналізу літературних джерел систематизовані дані про етіологію, класифікацію, патоморфологію, генні порушення і висвітлені сучасні підходи до лікування остеопетрозу. Описано три типи остеопетрозу з різним ступенем вираженості порушення у скелеті та тяжкості патології. Подані основні патоморфологічні зміни у структурній організації кісткової тканини, відзначені особливості стану остеокластів залежно від мутації генів, які контролюють їх функціональну активність. Протоколів лікування цієї патології немає, але проводиться розробка методів лікування на основі використання гемопоетичних стовбурових клітин. Наведено клінічний приклад пацієнтки з остеопетрозом.

Ключові слова: остеопетроз; класифікація; патоморфологія; остеокласты; генні порушення; діагностика; лікування