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CASE REPORT

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Bone dysplasia with optic atrophy, vascular malformation and seizures in a 14-year-old girl – a case report

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Summary

Background: The heritable skeletal dysplasias or osteochondrodysplasias are a large heterogeneous group of disorders associated with abnormal shape, growth, or integrity of bones. Osteopetrosis is a collective term for a range of sclerosing bone diseases with various degree of defective remodeling.

Increased bone density is the predominant radiologic feature. The skull is often involved with basal sclerosis and the sinuses are obliterated. The most serious consequences of the osteopetroses are seen in the nervous system. Because of perturbed remodeling of the skull bones, many aspects of the brain and cranial nerve function are endangered. Cranial nerves, blood vessels and the spinal cord may be compressed by progressive occlusion of cranial foramina.

Carious, misplaced teeth, dysplastic fingernails, tendency to pathologic fractures are the other clinical manifestations.

Case report: The authors present a 14-year-old girl with dysmorphic features, optic atrophy, CNS vessel malformation, pathologic fractures and seizures. The girl had a wide range of clinical and radiographic symptoms of bone dysplasias together with a giant left internal carotid artery aneurysm and epilepsy.

Conclusions: On the basis of clinical and radiological features, a disease belonging to the group of skeletal dysplasias was recognized in our patient. The configuration of the presented symptoms does not allow at the moment strict classification to hitherto determined forms of dysplasia. This leads to the necessity of extending diagnostics, especially by molecular tests, and further long-lasting observations, which perhaps would allow classification of the presented syndrome to one of the known groups, or determination of a new clinical entity.

Key words: bone dysplasia • vascular malformation • osteopetrosis • optic atrophy

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Background

Bone dysplasias, or osteochondrodysplasias, constitute a large group of hereditary anomalies. They are characterized by abnormalities in the development of bones and cartilages, which leads to disturbances in growth, modeling and mineralization of bone tissue. The recent advances in both molecular and biochemical diagnostics has allowed to determine the pathogenetic background of many entities, as well as identification of new ones [1]. International Nosology and Classification of Constitutional Disorders of Bone of 2001 lists ca. 300 entities divided into 33 groups. The classification was based, where possible, on biochemical deficits associated with mutations of particular genes according to the data presented in OMIM. In the remaining cases, the classification was based on clinical and radiological assessment [2].

Because of their character and potential complications, dysplasias involving increased bone density and modeling

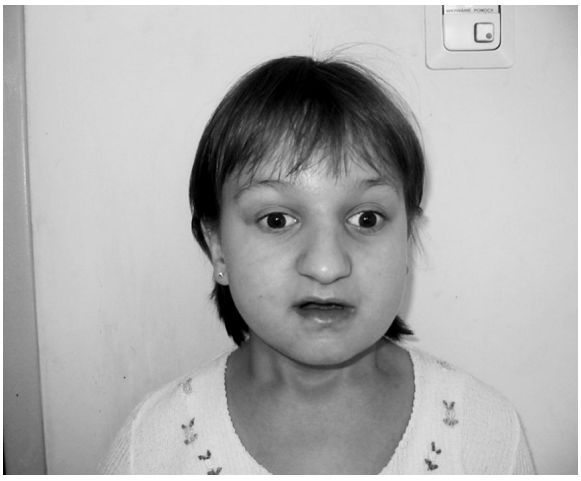

Figure 1. Patient K.A. – a 14-year-old girl.

abnormalities, collectively referred to as osteopetroses, constitute a clinically important group [3]. Depending on proportions between ossification and modeling abnormalities, they are divided into osteoscleroses (group 26) craniodiaphyseal dysplasias (group 28 according to the International Classification) [2]. The symptomatology of these diseases includes also several abnormalities of other systems and organs, and the nervous system in particular. Excessive ossification of the skull bones results in exposure of the cranial nerves, blood vessels and spinal cord to compression due to occlusion or growth abnormalities of the cranial foramina. Progressive atrophy of the optic nerves often leads to blindness. The patient may also develop deafness, trigeminal and facial nerve paralysis, increased intracranial pressure syndrome. Strokes, epileptic seizures and sudden deaths due to wedging of the cerebellar tonsils into the foramen magnum have been described. Some patients present with mental retardation. Ectodermal changes, such as dentogenesis disturbances and abnormal nail growth are frequently observed. Narrowing of the nasal meatuses and paranasal sinuses favors the development of inflammatory conditions. Formation of bones with abnormal, hyperdense structure is a cause of recurrent pathologic fractures. Imaging techniques play a crucial role in preliminary diagnostics.

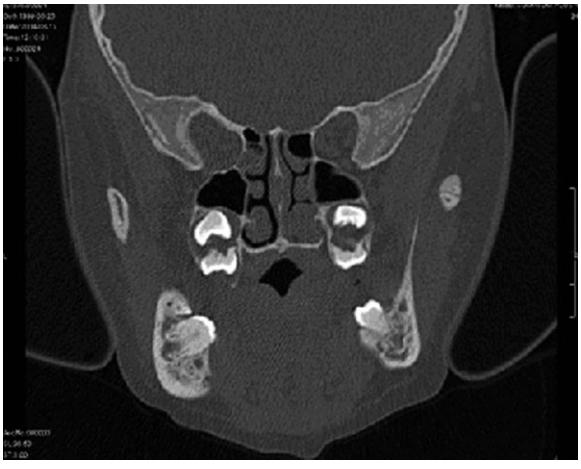

Figure 3a. CT examination – unerupted misplaced teeth in the maxillary sinuses.

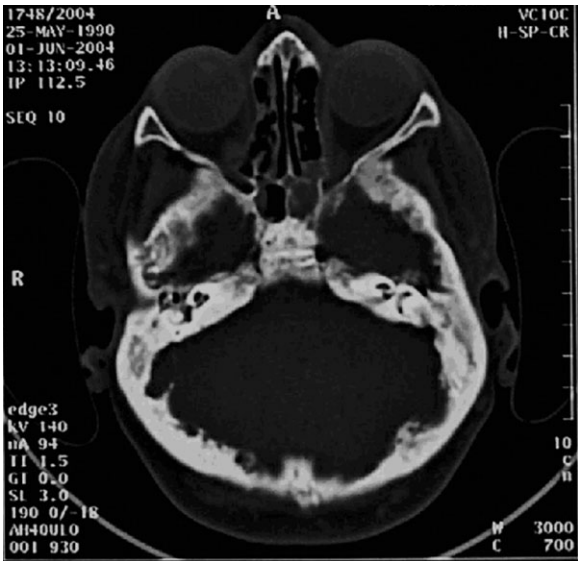

Figure 2. CT examination – the skull base and petrosal sclerosis.

Case report

K.A., a 14-year-old girl (fig. 1), with family history noncontributory, born from normal course first pregnancy by Cesarean section with 4600g body weight, in good clinical condition (Apgar score 10). Nystagmus and no reaction to visual stimuli were observed from the moment of birth. At the age of 5 months, bilateral atrophy of the optic nerves was diagnosed. She reached the milestones of psychomotor development at normal times.

Anamnesis revealed: frequent infections of paranasal sinuses. Starting from 7 years of age, frequent pathologic fractures: of the femoral neck and diaphysis, left crural bones, right clavicle, ribs. During hospitalization associated with treatment of these fractures in the Department of Pediatric Surgery, Collegium Medicum, Jagiellonian University in Cracow in 1998, a suspicion of Pyle syndrome was raised, on subsequent hospitalizations a provisional diagnosis of osteopetrosis was established. There are no data concerning any extended diagnostics in that center.

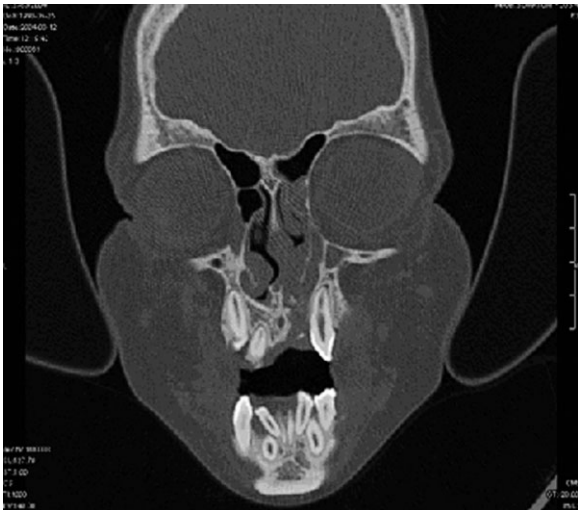

Figure 3b. CT examination – fistulization of the hard palate.

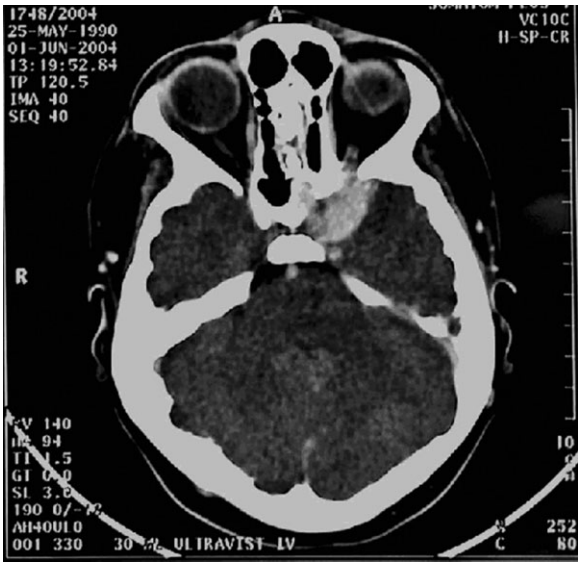

Figure 4. CT examination as above post contrast medium.

Starting from 13 years of age, the girl had three generalized epileptic seizures – in November 2003, March 2004 and September 2004. For that reason, she was admitted to the Department of Pediatrics and Developmental Age Neurology for diagnostics in October 2004. EEG revealed generalized paroxysmal discharges in the left cerebral hemisphere, and treatment with Lamitrin was instituted. No seizures were observed during hospitalization.

Physical examination revealed: low body height (146 cm < 3 pc.), signs of facial dysmorphia: asymmetrical mandible

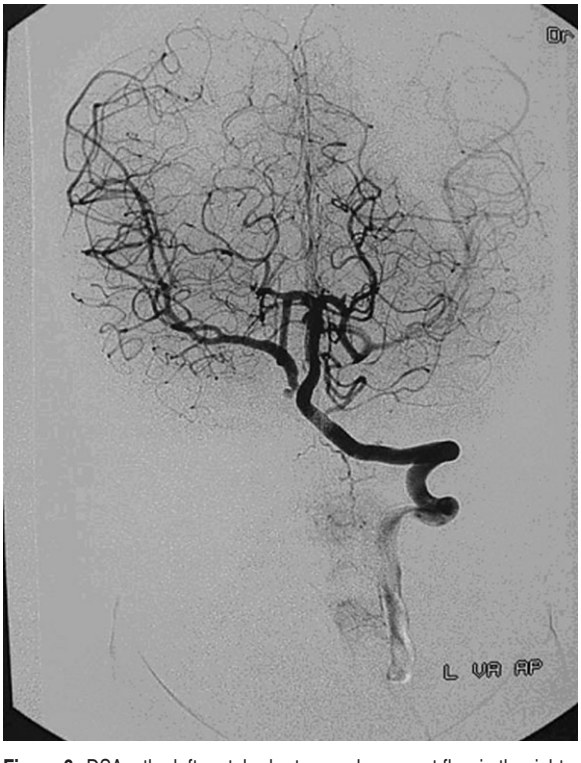

Figure 6. DSA – the left vertebral artery and recurrent flow in the right internal carotid artery.

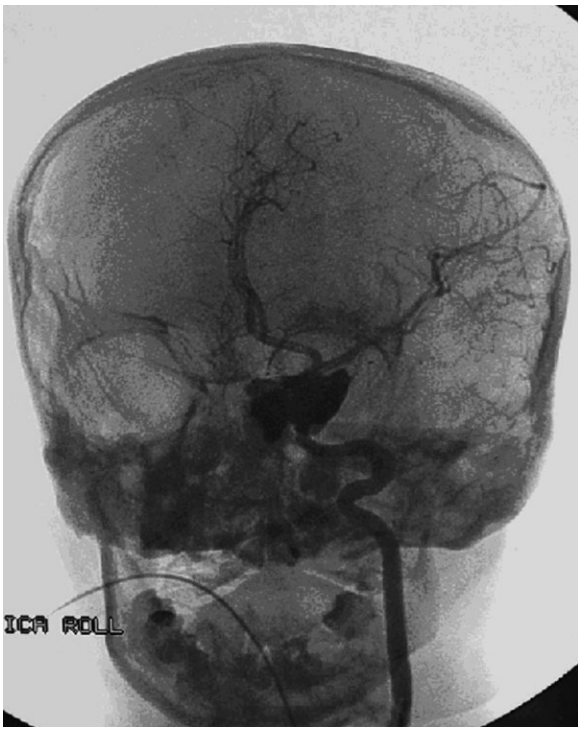

Figure 5. Digital subtraction angiography (DSA) – oblique view – a large aneurysm of the left internal carotid artery.

and forehead, and prominent nose, asymmetric hard palate with right-sided bulging, dysplastic incomplete dentition, deformity of the knee joints, bent lower legs, hypoplastic nails, shortened left lower extremity with compensative scoliosis (condition after surgical treatment of the left hip joint after femoral neck fracture).

Neurological examination: „swimming" eyeballs with periodic nystagmus, slightly decreased muscle tone and strength in the extremities with retained tendoperiosteal reflexes, gait with tendency to talipes varus. Blood cell count values, basic biochemical indexes, calcium and phosphate levels were normal. Mental development, assessed by means of WISC-R verbal scale test, was within normal limits (IS= 106).

Cranial (fig. 2) and craniofacial CT (fig. 3 a, b), apart from normal brain structures revealed thickening and osteosclerotic remodeling of skull base bones, apneumatic mastoid processes, destruction of the body and wings of the sphenoid bone and the the ethmoid bone, the presence of ectopic teeth in the maxillary sinuses and hard palate fistulization. The cross-section of the left cavernous sinus revealed an increased density area (fig. 4). The picture required differentiation between an aneurysm and a meningioma. MRI and angio-MR of the head visualized a vascular anomaly: an aneurysm of the left internal carotid artery and absence of the right internal carotid artery. By courtesy of Asst. Prof. Joanna Gibińska from the Department of Radiology at the Central Clinical Hospital of the Silesian Medical University, classic panangiography was performed, which allowed to confirm the presence of a giant aneurysm of the left internal carotid artery (fig. 5), invaginating into the sella turcica and the left side of the sphenoid sinus, causing

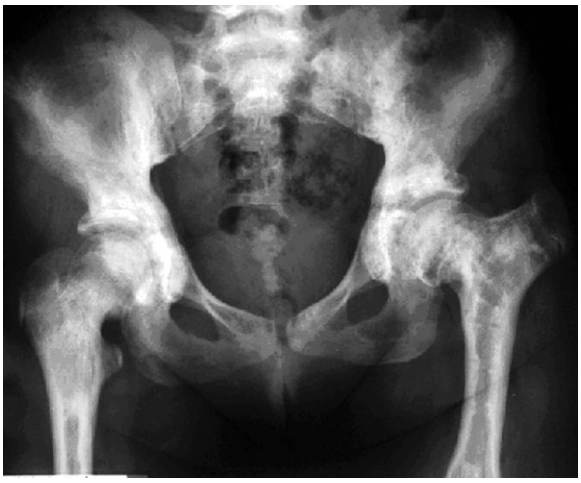

Figure 7. Radiography of the pelvis – sclerosing of the ischio-pubic rami, pubic bones hyperostosis. Left-sided coxa vara deformity.

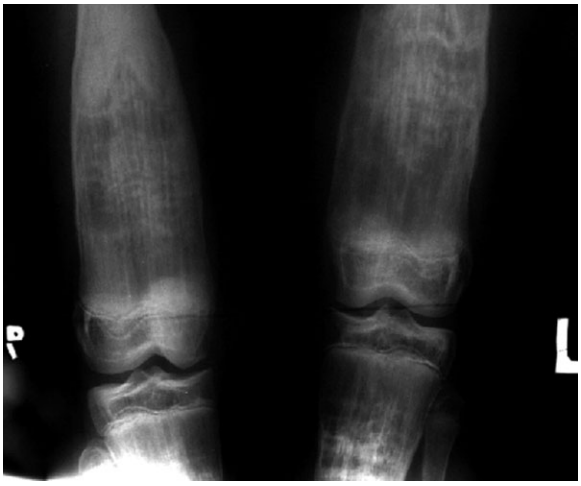

Figure 9. Radiography of the knee level – distal ends of the femora and proximal ends of the tibiae have widened metaphyses with undertubulation.

the bone destructions seen on CT. The absence of the right internal carotid artery in the whole intracranial segment was visualized, with retrograde flow through the intracranial segment of the right internal carotid artery from the posterior communicating artery on angiography of the left vertebral artery (fig. 6).

Because of the observed abnormalities, plain radiography of the skeleton was performed, which revealed sclerotization of the pelvic bones, proximal diaphyses of the femoral bones and distal lumbar vertebrae, hyperostosis of the pubic bones (fig. 7), as well as changes in shape and structure of long bones: oar-like metaphyseal widening of the distal femoral bones and proximal tibial bones (fig. 8, 9), S-shaped bowing of bones of the lower legs (fig. 10).

The syndrome presented by the girl allows to suppose that the symptoms are due to a genetically determined form of dysplasia with abnormal bone structure and metaphyseal modeling disturbances. The complete clinical picture includes: blindness since the moment of birth, facial

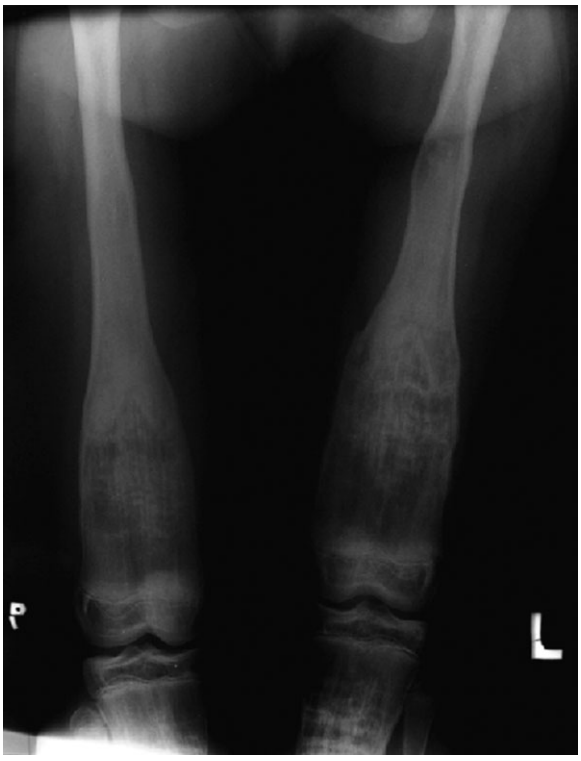

Figure 8. Radiography of the femora – widening of the metaphyses and undertubulation of he lower end of both femora. An old healed fracture of the left femur.

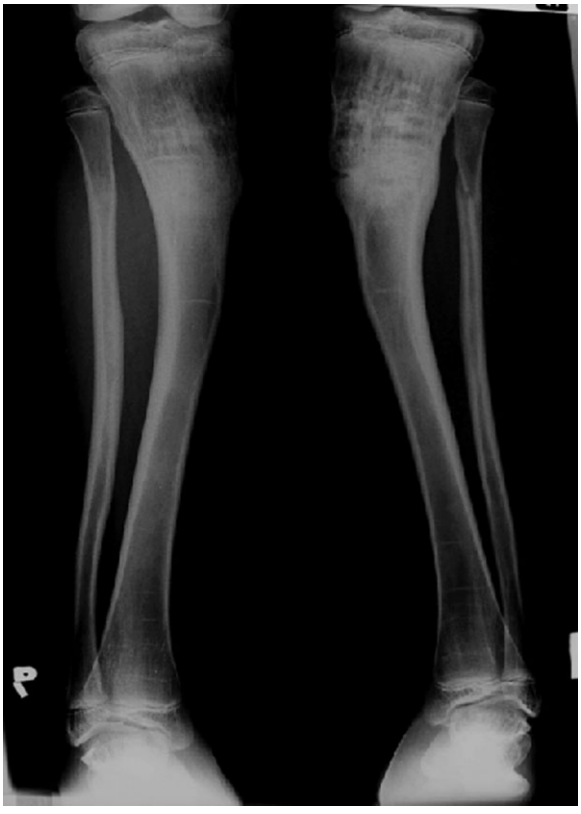

Figure 10. Radiography of the lower legs – the tibiae show lateral S-shaped bowing and proximal flaring. An old healed spiral fracture of the fibula.

dysmorphia with asymmetry and prominent nose, deficient body height, dysplastic teeth and nails S-shaped bowing of the lower legs, pathological fractures, vascular malformations and epileptic seizures. Radiological examinations revealed abnormalities of bone structure – sclerotization, especially of the skull base, mandible, pelvic bones, vertebral bodies and femoral bones, oar-like widening of the distal femoral and proximal tibial metaphyses with marked decrease in bone density.

Discussion

The clinical picture presented above justifies taking into consideration in differential diagnostics both osteoscleroses (Albers-Schonberg disease, dysosteosclerosis, pycnodysostosis) and craniodiaphyseal dysplasias (Pyle type metaphyseal dysplasia, craniometaphyseal dysplasia).

In both variants of Albers-Schonberg disease (autosomal dominant: OPTA2, called also Osteosclerosis Fragilis Generalisata, MIM 166600 and autosomal recessive: OPTB1 – Autosomal Recessive Osteopetrosis, MIM 259700) [4], besides increased to various extent skeletal and cranial bone density, progressing with age, tendency to pathologic fractures, damage of cranial nerves, bone marrow dysfunction due to progressive obliteration of marrow cavities is typical. Depending on the severity of the syndrome, a wide range of hematological abnormalities is possible: from mild anemia to severe anemia with thrombocytopenia, extramedullary hematopoiesis and hepatosplenomegaly – no changes of this type were observed in our patient. As the disease progresses, the distal metaphyseal long bone portions assume a flask-like shape, often with bright areas in the submetaphyseal regions. Heterogeneous vertebral sclerotization results in radiological picture of striated ,,rugger jersey", and periosteal ossification a "bone inside a bone" pattern. Progressive loss of vision is in most cases associated with compression of the optic nerves, but also primary retinal atrophy has been described [3, 4].

In both entities described above, the underlying abnormality is impaired function of ostaoclasts, which are unable to balance osteoblastic bone formation, which consequently leads to structural abnormalities with hyperostosis. The autosomal dominant form is associated with mutations of the CLCN7 gene on chromosome 16p13,3, encoding the CLC-7 subunit of the osteoclastic chloride channel. The autosomal recessive form shows heterogeneity, it has been demonstrated to be associated with mutations within the following genes: TCIRG1 (T-cell immune regulator 1) on chromosome 11q13,4-13,5, OSTM1 (osteopetrosis-associated transmembrane protein 1), CLCN7. The product of the TCIRG1 gene is the osteoclast-specific proton pump subunit: H(+)-ATPase, supporting osteoclastic ostaolysis by acidification of extracellular resorption areas [2, 3, 4].

Dysosteosclerosis, regarded as a variant of osteopetrosis (inherited predominantly as an autosomal recessive trait, MIM 224300) also presents several clinical and radiological characteristics similar to those observed in the reported case: low body height, nystagmus manifested from the time of birth with optic nerve atrophy, abnormalities of dentogenesis, hypoplasia of the nails, pathologic fractures. Radiological investigations reveal progressive metaphyseal hyperplasia and sclerotization of long and skull base bones. According to the literature data, in late childhood the presentation of dysosteosclerosis differentiates into two variants, one with osteopenia and reduced cortical layer thickness in the widened metaphyses, and the other with bone sclerotization and bending. Epileptic seizures or stroke episodes have been described. Additional abnormalities typical of this syndrome, not observed in our patient, include mental retardation, particularly with respect to speech development, and in radiological picture platyspondylia with band-like areas of hyperostosis and wide intervertebral spaces, as well as characteristic shape of the ribs, thickened in the peripheral portions. The genetic background of dysosteosclerosis has not been determined to date [2, 4, 5].

We can see many characteristics common with the observed syndrome in pycnodysostosis (a disease inherited as an autosomal recessive trait, MIM 265800): low body height, facial dysmorphia with a prominent nose, brittleness and deformity of the nails, dental abnormalities with anodontia and delayed eruption of teeth, hypoplastic sinuses, generalized hyperplasia of bone tissue and bone fragility. The symptomatology of this syndrome includes also delayed ossification of cranial sutures, frequent acroosteolysis of distal phalanges – no changes of this type were observed in our patient. Generally no cranial nerve damage and metaphyseal dysplasia are observed in this syndrome [4].

Pathogenesis of the disease involves the deficiency of cathepsin K, the main cysteine protease, a lysosomal enzyme with high, tissue-specific expression in the osteoclasts. This leads to disturbances in proteolytic degradation of organic bone matrix, predominantly type I collagen, resulting in sclerotization of particular skeletal elements.

The gene locus has been mapped on chromosome 1q21 [2, 4, 6].

Pyle type metaphyseal dysplasia (inherited as an autosomal recessive trait, MIM 265900) is characterized primarily with metaphyseal modeling abnormalities with their widening in oar-like manner (so that they resemble an Erlenmeyer flask in shape) in the distal part of the femur and hyperostosis of the proximal part of the tibia, pubic bone, mandible and clavicles, as well as progressive sclerotization of the bones of the skull base with age. The clinical presentation includes frequently also genu valgum, brittleness of bones, muscular weakness and misplaced teeth. The mental development is normal. There are no data concerning damage of the cranial nerves, epileptic seizures and vascular anomalies, but considerable body height of the patients is described. The genetic background of the abnormality has not been determined so far [2, 4, 7, 8, 9].

A presentation of the metaphyses similar to Pyle syndrome is observed in caraniometaphyseal dysplasia (inherited both as autosomal dominant trait, MIM 123000, and a recessive one, MIM 218400), however, the coincidence

of osteosclerotic changes within the long bones and the cranial bones, affecting both the skull base and cranial vault bones is more visible in the latter disease. The bone anomalies result in damage to the cranial nerves, with potential atrophy of the optic nerves, deafness, facial nerve paralysis, occlusion of the sinuses with recurrent infections. Abnormalities in the development of teeth are also observed. The mental development of the patient is usually normal. There are no reports concerning pathologic fractures, which occurred several times in our patient. The radiological abnormalities progress with age, headaches, intracranial hypertension, hydrocephalus due to venous congestion may develop. According to the literature data, the pathogenesis of the disease involves impaired bone reabsorption due to dysfunction of osteoclasts. The genes responsible ofor the recesive and dominant forms of the disease have been localized on the chomosomes 6q21-22 and 5p15,2-p14,1, respectively [2, 4, 10, 11, 12, 13].

Conclusions

Considering the clinical and radiological symptoms presented by our patient and the fact of their occurrence in the described nosologic entities, the classification of the reported case as representative of the group of bone dysplasias seems to be undoubted. The presence of an aneurysm could not be associated with any of the aforementioned syndromes – which, in our opinion, enriches the characteristics of this group of diseases.

Currently, the configuration of the presented symptoms does not allow to classify the case into any of the groups of dysplasias distinguished so far. This makes it necessary to extend the diagnostics, especially by molecular investigations, and to conduct further, long-term observation, which may allow to assign the presented case to one of the known groups, or to identify a new clinical entity.

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