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Dyggve-Melchior-Clausen Syndrome with Peripheral Pancytopenia: New Observation: Case Report

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Abstract **Case Report**

Dyggve Melchior Clausen syndrome is an autosomal recessive osteochondrodysplasia characterized by the association of staturo-ponderal retardation, spondylometaphyseal dysplasia and mental retardation. The aim of the study is to describe clinical, radiological and biochemical findings. Our patient is a 10 years old boy, thirth child of consanguineous parents presented with failure to thrive and mental retardation. He had short trunk, protruding sternum. Radiographs show generalized platyspondyly, double vertebral humps and «beardlike» or «lacelike» iliac crests. Dyggve Melchior Clausen syndrome is a rare skeletal dysplasia. The diagnosis is made by radiology that shows characteristic signs. Prognosis is dominated by mental retardation and motor disability. The treatment is symptomatic hence the value of genetic counselling.

Keywords: Dyggve-Melchior-Clausen syndrome–osteochondrodysplasia–failure to thrive – mental retardation–pancytopenia.

INTRODUCTION

Dyggve-Melchior-Clausen (DMC) syndrome is a rare constitutional bone disease with autosomal recessive inheritance. It is classified as an osteochondrodysplasia according to the 1977 Paris nomenclature of the European Society of Pediatric Radiology. Clinically, DMC is characterized by progressive spondyloepimetaphyseal dysplasia associated with intellectual impairment, and radiologically by specific features that are sufficient to make a positive diagnosis, namely generalized platyspondyly with deformity of the iliac crests. The gene responsible for this syndrome is located on chromosome 18q21.1. In this context, we report a case of DMC syndrome diagnosed in our department on the basis of clinical and radiological data. This patient also presented with an associated pancytopenia which, to our knowledge, has never been described in the literature.

PATIENT AND OBSERVATION

S., aged 10 years, was admitted to our department for the management of staturo-ponderal retardation associated with an anemic syndrome. He is the 3rd of 5 healthy siblings, not attending school and living in Tangier. His parents are 1st degree consanguines. There is no short stature in the family. S. was born at term by vaginal delivery. He was breastfed for 2 months, then fed artificial milk. Dietary diversification began at 6 months of age. Symptoms began at the age of 8 months, with delayed weight-bearing, worsening with age, delayed walking, which was acquired at the age of 3, delayed language, with first words at the age of 5, and learning and memory disorders. In addition, the mother reported physical asthenia with pale skin for several weeks. Clinical examination on admission revealed a child in fairly good general condition, apyretic, with slightly discolored conjunctivae, a peculiar facies, delayed staturo-ponderal development with a weight of 13kg (-3DS), a height of 98cm (-3DS) and severe microcrania with a head circumference of 45cm (-4DS). The neck and trunk were short. Bone age was 10 years according to the Atlas of Greulich and Pyle. The abdomen was distended, without hepatomegaly or splenomegaly and without umbilical hernia. The hands were large with short, pudgy fingers and the lower limbs were in moderate bilateral genu-valgum. Thorax examination revealed sternal protrusion with thoracic and rib deformity. Lung, cardiovascular and external genitalia examinations revealed no abnormalities. Neurological examination revealed a waddling gait, with no sensory or motor deficits. The child psychiatric approach revealed a significant psychomotor deficit. Ophthalmological examination was

normal. Biologically, the blood count showed pancytopenia with WBC at 4290 E/mm3 and neutropenia at 1050 E/mm3, hemoglobin at 8.3 g/dl with reticulocytosis at 101,000 E/mm3 and platelets at 23,000 E/mm3. A urine mucopolysaccharide test was negative. The cytological appearance of the bone marrow was suggestive of a reaction marrow associated with peripheral pancytopenia. Direct coombs test was positive. Standard radiographs of the spine from the front and side showed generalized platyspondyly with a "double hump" appearance of the vertebral bodies [fig.1]. X-rays of the pelvis revealed a scalloped areolar appearance of the otherwise small "bearded-looking" iliac crests, a coxa-valga, an enlarged pubic symphysis and wide, irregular sacroiliac joints. Femoral necks were short, acetabular cups hypoplastic and femoral heads irregular, hypoplastic with diffuse demineralization [fig.2]. The sella turcica radiograph was normal, as was the abdominal ultrasound. The diagnosis of Dyggve-Melchior-Clausen syndrome was made in view of the association of mental retardation, a dysmorphic syndrome and, above all, the specific radiological aspects of this disease. This patient also presented with peripheral pancytopenia, reversible after 1 month of corticosteroid therapy. A genetic study is in progress.

FIGURES

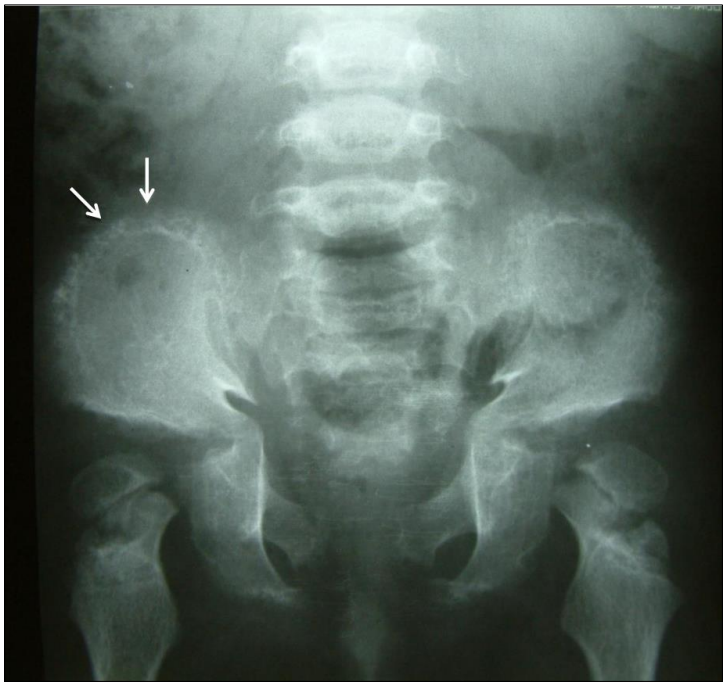

Fig. 1: Front pelvis X-ray: scalloped "bearded" appearance of the otherwise small iliac crests (white arrows), wide sacroiliac joints and symphysis pubis, coxa-valga. Femoral necks short, irregular femoral heads hypoplastic and demineralized, acetabular cups hypoplastic.

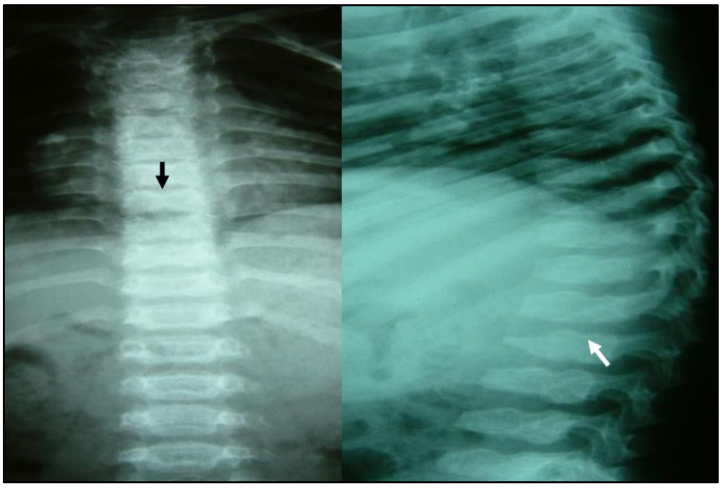

Fig. 2: Spine X-ray (front and side): generalized platyspondyly with double hump (white arrow) and central notch (black arrow) of vertebral bodies.

DISCUSSION

DMC dysplasia is rare. It was first described in 1962 by Dyggve and al. and then in 1975 by Spranger and al. who completed the description of its clinical and radiological features [11, 12]. More than sixty cases have been described in the literature to date. From an etiopathogenic point of view, a metabolic disorder secondary to a genetic anomaly has been evoked in DMC syndrome. The incriminating gene is thought to be located on chromosome 18q.21.1. In one study, the authors described 7 deletion-type mutations in this gene in the 10 families studied with the disease [5]. This gene encodes a protein called (Dyggve-Melchior-Clausen syndrome protein) or DYMECLIN, which is thought to play a role in the intracellular process of protein digestion [7, 8]. In addition to that, studies have found a novel homozygous frameshift variant [c.1670delT, p.(Leu557Argfs*20)] in exon 15 of the *DYM* gene that leads to a premature stop codon, which causes deleterious truncation of dymeclin [20]. The sanger sequencing of the coding exons and exon intron borders of the DYM gene in a study that has been done in Pakistan revealed a novel homozygous nonsense variant [DYM (NM_017653.6):c.1205T>A, p.(Leu402Ter)] in affected individuals [21]. Importantly, the transcribed product of this gene is abundant in chondrocytes, osteoblasts and nerve cells. In addition, biochemical analyses of cartilage fibers in carriers of the syndrome have shown elevated levels of keratan sulfate, and the presence of numerous vacuoles and cytoplasmic inclusions in chondrocytes [13]. Electron microscopy reveals large rough endoplasmic reticulum (RER) cisternae [9]. Finally, clinical data and progressive evolution suggest that Dyggve-Melchior-Clausen syndrome is the result of the accumulation of an unidentified abnormal component [8- 10]. Taken together, these findings suggest that Dyggve-Melchior-Clausen syndrome is due to the loss of function of a protein (DYMECLIN) involved in the intracellular digestion process and necessary for normal skeletal development and brain function. Clinical signs are evident before the age of 18 months, and include staturo-ponderal retardation, poly-malformative syndrome and mental retardation. The absence of corneal opacity is strongly suggestive of this dysplasia [2]. Staturo-ponderal retardation is present in all patients described in the literature and varies between -3 and -4 DS. The polymalformative syndrome may involve the skull, spine, thorax and limbs. Cranial microcephaly is frequently described by authors [3]. Facial features are coarse, with prognathism. Protrusion of the tongue and protrusion of the superciliary arches can be observed. In the spine, there is generalized plathyspondyly with double hump vertebral bodies including central constriction, posterior protrusion of the intervertebral disc in the lumbar spine and widening of the posterior common vertebral ligament [14]. All curvature anomalies can be found and even associated with each other in the same patient. Dorsal kyphosis is the most frequently described deformity in the literature, followed by dorsal scoliosis and hyperlordosis. Odotoid hypoplasia confers instability on the atlantoaxial joint, which can lead to spinal cord compression, a preventable complication of the disease [15]. In the thorax, the most common feature is sternal protrusion, which may be moderate or very pronounced. As regards the limbs, a waddling, shuffling gait is noted by many authors. Other anomalies most frequently described in the literature include shortening of the proximal segments of the upper and lower limbs [1- 3]. Hands and feet are wide, with short fingers and toes, particularly the thumb [4]. In the knees, a more or less severe genu-varum or valgum may be present. Limitation of joint mobility can affect both large and small joints, leading to more or less severe disability. Abdominal hepatomegaly may be observed, but remains rare [2- 4]. Umbilical hernia has also been described in this syndrome [3]. Mental retardation varies from moderate to severe and worsens with age [14]. It distinguishes CMD from another similar dysplasia, isolated by Spranger *et al*., in 1976, and referred to as Smith McCort syndrome (CMD syndrome without mental retardation or microcephaly) [1]. In fact, both diseases are allelic expressions of the same mutated gene [16]. In most people with CMD, MRI scans of the brain have been normal [14]. However, one observation of cortical atrophy has been reported, and another of corpus callosum [14- 17]. Morquio disease, often confused with CMD, is distinguished by the presence of mucopolysaccharides in the urine, the presence of corneal opacity and distinct radiological signs. These radiological signs vary with age, but the most typical abnormalities appear between the ages of 8 and 12 [4, 5]. Other extremely rare manifestations, represented by 1 case of mania and 1 case of schizophrenia described in 2 separate observations [18, 19]. But no case of CMD associated with peripheral pancytopenia has yet been described in the literature. From an evolutionary point of view, survival appears to be better than in mucopolysaccharidosis, but limb deformities increase with age, leading to motor disability, while mental retardation remains highly disabling and a source of great socioeconomic dependence. Treatment is essentially symptomatic, aimed at correcting skeletal deformities through orthopedic measures, and must also include psychomotor rehabilitation. When there is hypoplasia of the odontoid process with partial dislocation of the cervical vertebrae, stabilization by spinal fusion is recommended to prevent spinal cord-related paralysis. Surgery is also indicated to correct other skeletal anomalies, such as subluxation or dislocation of the shoulder and hip joints, or to perform a hip prosthesis.

CONCLUSION

DMC is a rare osteochondroplasia. Diagnosis is based on clinical and, above all, radiological signs specific to this disease. We have attempted, through this new case diagnosed in our department, to bring together all the data specific to this disease. This newly diagnosed case presents a particular biological feature, the presence of associated pancytopenia. Advances in recent years

have made it possible to identify the gene and coded protein involved in the genesis of this disease. This opens up new possibilities for optimizing prenatal diagnosis, and for the search for a treatment for this pathology, which remains essentially symptomatic and adjuvant.

Conflicts of Interest: The authors declare no conflicts of interest.

Authors' Contributions: All authors have read and approved the final version of the manuscript.

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