

A Constellation of Orthopaedic Deformities in Connection with Cartilage Oligomeric Matrix Protein Mutation

Ali Al Kaissi^{1,2}, Maher Ben Ghachem³, Vladimir Kenis⁴, Eugene Melchenko⁴, Franz Grill², Rudolf Ganger², Susanne Gerit Kircher⁵

¹Ludwig Boltzmann Institute of Osteology, at the Hanusch Hospital of WGKK and, AUVA Trauma Centre Meidling, First Medical Department, Hanusch Hospital, Vienna, ²Orthopaedic Hospital of Speising, Paediatric Department, Vienna, Austria, ³Paediatric Orthopaedic Surgery, Children Hospital, Tunis, ⁴Pediatric Orthopedic Institute N.A.H. Turner, Department of Foot and Ankle Surgery, Neuroorthopaedics and Systemic Disorders, Parkovaya Str., Pushkin, Saint-Petersburg, Russia, ⁵Institute of Medical Chemistry, Medical University of Vienna, Austria

Abstract

Background: Trendelenburg's gait can be observed in Legg-Calvé-Perthes disease, antalgic gait observed in osteoarthropathy and waddling gait is usually seen in genu varum and circumduction gait in patients with genu valgum. Disabling pain was a prime manifestation in slipped capital femoral epiphysis (SCFE). Limited joint range of motion with an inability to bear full weight on an affected extremity with swaying and wide-based gait is seen in patients with malalignment of the lower limbs. All the above-mentioned deformities have been labelled as idiopathic. The main objective of this article is to approach to the aetiology understanding. **Patients and Methods:** Ten children (3 girls and 7 boys with age average of 9 years) presented with variable deformities; Perthes-like deformity, genu varum/valgum and osteoarthropathy and one patient with SCFE. Clinical and radiological phenotypes were the baseline tool of diagnosis. Genotypic characterisations were performed. **Results:** Diverse clinical presentations of Perthes-like disease, osteoarthropathy, genu varum/valgum and SCFE were the most prominent skeletal abnormalities in patients manifested cartilage oligomeric matrix protein (COMP) gene mutation. **Conclusion:** The value of presenting this article is fourfold; first to signify that mutation study was essential for the increment of knowledge related to the genotype-phenotype relationships. Second, to indicate that professional awareness is needed to differentiate between the hidden pathologies in patients with Perthes-like deformity, genu varum, genu valgum and early osteoarthritis in correlation with COMP gene mutation. Third, it is mandatory to question the validity of the term idiopathic. Fourth, this article is an attempt to sensitise orthopaedic physicians and surgeons that deformities might be stemmed from diverse forms of intrinsic bone disorders.

Keywords: Cartilage oligomeric matrix protein mutation, orthopaedic deformities, surgery

INTRODUCTION

Disturbances of skeletal growth presenting at birth or developing in childhood produce a bewildering array of clinical, radiological and pathological syndromes. The cartilaginous dysplasias are those that are thought to arise from abnormal chondrocyte differentiation and metabolism growth.^[1] Pseudoachondroplasia is characterised by short-limbed dwarfism in which both the epiphyses and metaphyses are involved. Affected individuals have significantly short stature, loose ligaments and a predisposition to premature osteoarthritis (OA). Pseudoachondroplasia is usually transmitted as an autosomal dominant trait.^[2,3]

Development appears normal during the first 2 years of life, but walking may be delayed, followed by waddling gait

and growth retardation. Genu valgum/varum or windswept deformities of the legs occur commonly. Scoliosis and/or kyphoscoliosis develops in >50% of the patients. Premature degenerative OA and cervical instability with subsequent development of neurological deficits have been reported in a remarkable number of patients with pseudoachondroplasia. Premature degenerative OA often begins in early life along the weight-bearing joints (hip and knee joints), respectively. Later

Address for correspondence: Dr. Ali Al Kaissi, Ludwig Boltzmann Institute of Osteology at the Hanusch Hospital of WGKK and AUVA, Hanusch Hospital and Orthopedic Hospital of Speising-Pediatric Department Vienna, Austria. E-mail: ali.alkaissi@oss.at

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in life, degenerative OA progresses to involve the shoulders, elbows, ankles and feet.^[1,3,4]

Multiple epiphyseal dysplasia (MED) is an osteochondrodysplasia characterised clinically by mild short stature and early-onset degenerative joint disease. Typically, on radiological examination, the contour of the epiphyses is irregular and fragmented with a non-uniform osseous structure. The ossification centres appear at different times, which gives the impression of stippled epiphyses, which is due to the multiple calcifications in or near the epiphyses.^[5-7]

Abnormalities in the ossification centres, together with evidence of fragmentation of the epiphyseal growth plate and metaphyseal expansion are thought to be the pathogenetic causation in the development of hip pain in children with skeletal dysplasias.^[1,3,4,7-12]

Clear differentiation and distinction are mandatory in documenting patients with skeletal dysplasias and its variants. Awareness is needed before label a deformity as idiopathic.

PATIENTS AND METHODS

The study protocol was approved by the Ethics Committee of the Turner Scientific Research Institute (No. 3/2016, Saint-Petersburg, Russia). Informed consents were obtained from the patient's guardians to publish. Ten children (3 girls and 7 boys with age average of 9 years). We analysed these patients through the clinical and radiographic phenotypic characterisation at the Osteogenetic Department of the Orthopaedic Hospital of Speising, Vienna, Austria, and at the Department of Foot and Ankle Surgery, Neuroorthopaedics and Systemic Disorders, Parkovaya str., 64–68, Pushkin, Saint-Petersburg, Russia. We subdivided our group of patients in accordance with the clinical presentations.

Evaluation of the hips should be performed by an anteroposterior (AP) view of the pelvis in the upright position. Hip dysplasia is measured using the acetabular index in all children with open triradiate cartilages. For children with closed triradiate cartilages, sharp's acetabular angle has to be applied. The centre edge angle of Wiberg is generally applied for patients older than 5 years of age (in conjunction with either the AI or Sharp's angle), or when there is an appropriate amount of proximal femoral epiphyseal ossification to allow determination of the true centre of the femoral head. Sharp's acetabular angle is considered normal if $<39^\circ$. The acetabulum index is considered normal if $<20^\circ$ and the centre-edge angle is usually considered normal if $>20^\circ$. Sharp's angle, measured between 39° and 42° , is in the upper limit of normality and values $>42^\circ$ represent acetabular dysplasia. Lower extremity alignment is best evaluated with a single AP view.

Group I: Patients with Legg–Calvé–Perthes' disease

One girl and two boys, their records were analysed and all received the preliminary diagnosis of Legg–Calvé–Perthes (LCP) disease. Two patients manifested short stature associated with distinctive and diverse bone changes along

the craniocervical, acetabulofemoral, metacarpal and the metaphysis of the weight-bearing joints. At the craniocervical junction, dolichodontoid was associated with the persistence of axial synchondrosis and was diagnosed in two patients (magnetic resonance imaging has illustrated the remnant of the dentocentral synchondrosis and dolichodontoid). One boy manifested normal height. The appearance of fragmented ossific nuclei of the femoral heads may resemble what is seen in LCPs disease [Figure 1a and b]. Stature was ranging between 140 cm and 160 cm, ligamentous hyperlaxity was a variable abnormality in its severity, though hypermobility of the knee joints with genu recurvatum and ankle instability with severe flexible pes planovalgus were encountered in two patients.

Group II: Patients with osteoarthropathy

Degenerative OA of the weight-bearing joints was the reason behind disability in three patients who manifested antalgic gait in connection with premature degenerative OA associated with incongruity of the femoral head with the acetabulum [Figure 2a and b]. The limbs were rhizomelic and the hands were small and stunted. There was exaggerated lumbar lordosis and associated with discrete scoliosis. One girl showed significant metaphyseal striations around the knees associated with severe premature OA [Figure 3]. One patient presented with OA because of slipped capital femoral epiphysis (SCFE).

Group III: Patients with genu varum/valgum

In four patients, genu varum was the presenting deformity and the bony deformity was evident in both the proximal tibia and distal femur (genu varum and varus ankle are common with irregularity of the epiphyses and eventual OA) [Figure 3a and b]. Natural history is one of the inexorable progressions in children with genu varum. Moreover, two children with genu valgum have been documented. Genu varum if not treated may result in a number of skeletal problems, namely, premature closure of upper medial tibial physis, tibiofemoral subluxation and degeneration which might end up in arthrosis of the medial

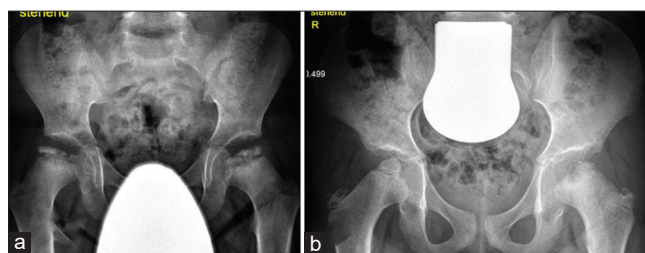


Figure 1: AP radiograph of the pelvis in three different patients, (a) AP radiograph in 8-year-old boy who was diagnosed with Legg–Calvé–Perthes' disease. He presented with hip pain with restricted movements, radiograph showed bilateral and symmetrical fragmentation and flattening of the capital femoral epiphyses, his phenotype/genotype correlation was compatible with multiple epiphyseal dysplasia (AD). (b) AP radiograph of a 10-year-old girl presented with antalgic gait, showed irregular, but asymmetrical dysplasia of the capital femoral epiphyses, her phenotype/genotype correlation was compatible with pseudoachondroplasia. AP: Anteroposterior, AD: Acetabular dysplasia

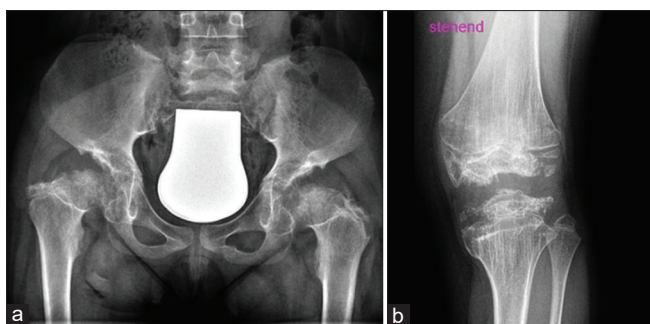


Figure 2: (a) AP pelvis radiograph of a 9-year-old girl presented with severe antalgic gait showed severe bilateral and symmetrical epiphyseal fragmentation of the capital femoral epiphyses (non-spherical) associated with a shallow and irregularly ossified acetabular roof causing effectively the development of bilateral coxa vara. Her phenotype/genotype was consistent with the diagnosis of pseudoachondroplasia. (b) AP knee radiograph showed severe dysplastic irregularities and fragmentations/stippling of the inferior femoral and the superior tibial epiphyses associated with extensive metaphyseal striations around the knee. AP: Anteroposterior

compartment of the knees. Therefore, surgical correction of significant and symptomatic malalignment is warranted.

SURGICAL INTERVENTIONS AND RESULTS

Careful preoperative planning with weight-bearing radiographs of the entire lower extremity was necessary to correct the malalignment. As the epiphysis in patients with pseudoachondroplasia is pathological and less resistant against loading stress and any malalignment, deformity of the lower limbs bears a high risk of deterioration and premature degenerative joint disease and therefore has to be corrected at an early stage to prevent early OA and to allow the patients to perform daily life activities as long as possible.

Surgical planning for any type of guided growth procedure to correct skeletal deformity must simultaneously address the post-operative asymmetric growth and the amount of growth remaining. If the surgery is performed too early with respect to remaining growth, an overcorrection may develop. This can be rectified by removing the implant if the hemiepiphysiodesis or guided growth procedure is reversible. If the surgery is performed too late, an undercorrection or failure may develop (this cannot easily be reversed).

Guided growth – temporary hemiepiphysiodeses – using eight plates is a minimally invasive procedure to correct genu valgum or varum. Guided growth holds promise for complete correction of the deformity and may reduce or eliminate the need for more invasive osteotomies.

Coxa vara has to be corrected by proximal femoral valgus osteotomy and acetabular dysplasia, respectively, misfit of a coxa magna with a decreased acetabular femoral head coverage by pelvic osteotomy or shelf procedure. Proximal femoral osteotomy (PFO) has been performed to restore normal anatomy and optimal joint congruency to prevent medium and long-term degenerative deterioration of the hip [Figure 4a-c].

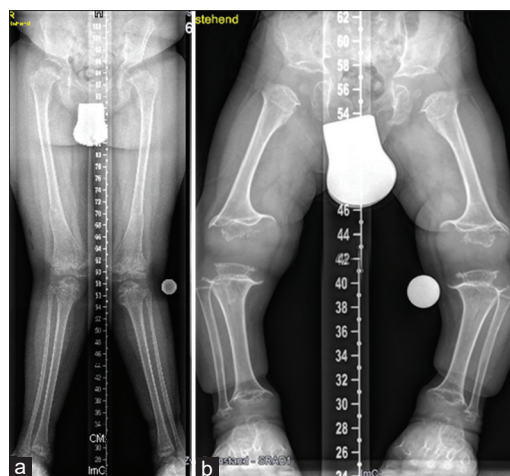


Figure 3: (a) AP standing lower limbs radiograph in a 10-year-old boy showed bilateral Legg–Calvé–Perthes-like disease associated with genu valgum with marked epiphyseal involvement (capital femoral epiphyses, inferior femoral epiphyses and superior tibial epiphyses) his phenotype/genotype was consistent with pseudoachondroplasia, (b) AP standing radiograph of the lower limbs showed bilateral genu varum in a 12-year-old boy, his phenotype and genotype were confirmed for pseudoachondroplasia. AP: Anteroposterior

The surgical technique used depends on age and specific hip pathomorphology. In case of painful OA, joint replacement has been indicated. One patient who presented with SCFE has been diagnosed with MED in conjunction with cartilage oligomeric matrix protein (COMP) mutation. In a 9-year-old boy, a proximal varus osteotomy on the proximal left femur with LCP plate was performed. The surgery was followed by pelvis-leg plaster and he showed no post-operative complications. He manifested the phenotype/genotype of MED (COMP gene mutation) [Figure 5].

Molecular analysis

In some patients, DNA was processed for mutation analysis of COMP. Pseudoachondroplasia patients showed heterozygous mutations in the COMP gene on chromosome 19p13.11, encoding for cartilage oligomeric matrix protein. Also children with COMP-related MED (autosomal dominant) showed heterozygous mutations in COMP gene (EDM1).

DISCUSSION

Pseudoachondroplasia is usually transmitted as an autosomal dominant trait. Wynne-Davies *et al.* proposed that four forms exist: autosomal dominant severe, autosomal dominant mild, autosomal recessive severe and autosomal recessive mild.^[13]

It represents the second most common type of short-limbed dwarfism after achondroplasia. The disorder is not detectable at birth, the rhizomelic shortening becoming evident at 1–3 years of life. Patients usually develop a waddling gait and excessive lumbar lordosis. There is generalised involvement of the epiphyses and metaphyses of the tubular bones. The epiphyses are delayed in their appearance and are small and fragmented when they appear. The central portions appear normal, but the periphery is markedly deformed, especially at the sites of

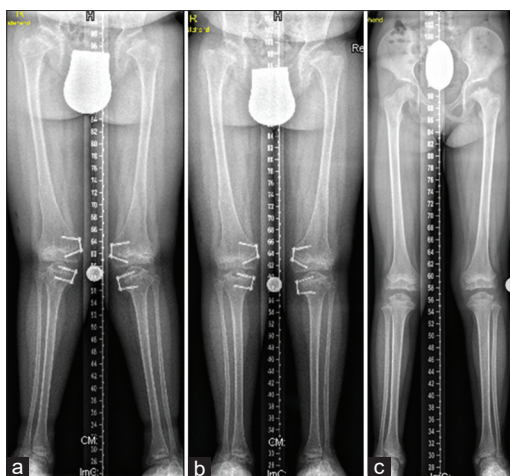


Figure 4: (a-c) AP standing radiographs showed the stages of correction of genu valgum in a 10-year-old boy through the usage of 8-plate. AP: Anteroposterior

ligament insertions. The metaphyses are splayed and frayed. Adult height ranges from 106 to 130 cm. Genu valgum or varum may occur. The appearance of fragmented ossific nuclei of the femoral heads may resemble what is seen in spondyloepiphyseal dysplasia and even bilateral LCPs disease.^[1,3,5,13]

In classical MED, the primary defect is delayed and abnormal ossification since the anlagen of the epiphyseal centres appear to be normal; an observation recently confirmed in transgenic mouse models of PSACH-MED.^[15,13,14] MED was formerly divided into two broad groups; Fairbank type (severe) and Ribbing type (mild), but it is now clear that MED represents a continuous spectrum of severity.^[2,5] There have been numerous reports demonstrating that autosomal dominant cases of MED can result from mutations in at least five different genes; those encoding COMP (COMP: EDM1), type IX collagen (COL9A1, COL9A2 and COL9A3; EDM6, EDM2 and EDM3, respectively) and matrilin-3 (MATN3: EDM5).^[15] Unger *et al.* reviewed the radiographic phenotypes of MED patients with either type IX collagen or COMP gene mutations. They postulated that patients with type IX collagen defects had more severe joint involvement at the knees and relative hip sparing, while the patients with COMP mutations had significant involvement at the capital femoral epiphyses and irregular acetabuli.^[16]

Kawaji *et al.* described the pathologic correlation of precocious osteoarthropathy due to a mutation of the COMP gene in patients with autosomal dominant type of MED.^[17]

Mechanical loading of the osteonecrotic femoral head undergoing repair is thought play a significant role in the development of the femoral head deformity. LCP disease (LCPD) remains indefinite from an aetiologic point of view and unforeseeable in its evolution. Children younger than 4 years of age suffering from LCPD do not necessarily have a good prognosis.^[18-21]

Clinical examination is not contributory to specific diagnosis or prognosis. The symptoms may be intermittent at first and

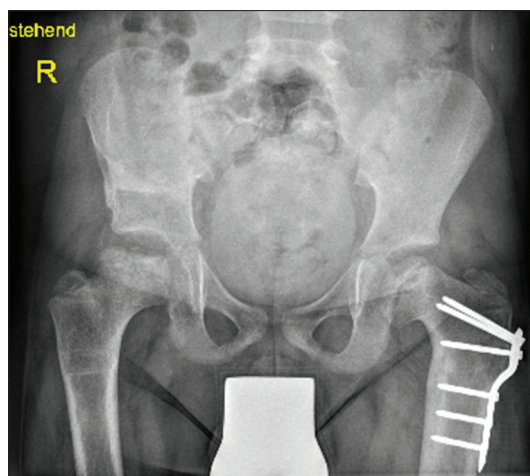


Figure 5: AP radiograph, hip surgery of proximal varus osteotomy on the left proximal femur with Legg–Calvé–Perthes plate in a 9-year-old boy. The surgery was followed by pelvis-leg plaster and he showed no post-operative complications. He manifested the phenotype/genotype of multiple epiphyseal dysplasia (cartilage oligomeric matrix protein gene mutation). AP: Anteroposterior

are aggravated by activity and relieved by rest. In a typical case, there are some limitations of all movements of the hip but particularly of abduction, medial rotation, flexion and extension. Certain clinical ‘at risk’ signs may suggest the development of severe disease, whatever the age of the child is. These are: rapid and progressive limitation of movement, the presence of fixed adduction or flexion and adduction deformity, or a child who is overweight relative to his age. Abnormalities in the secondary ossification centres, together with evidence of fracture, fragility, friability and fragmentation of the epiphyseal growth plates, have been encountered in children with different forms of skeletal dysplasias in connection with the early/late development of LCPD. Several papers focus on these issues in an effort to provide further knowledge regarding the aetiological understanding and in the clinical care of Perthes’ disease. Other reports entailed the familial occurrences of LCPD and few reports gave the correlation of LCPD with syndromic complex association.^[18,19]

O’Sullivan *et al.*^[20] described four cases in one family, but Wynne-Davies and Gormley^[21] found no obvious pattern of genetic inheritance. Additional reports by Stulberg *et al.*^[22] studied the development of OA in correlation to the hip at maturity congruity. They concluded that if there was a non-spherical or flat femoral head with a similarly shaped acetabulum, mild-to-moderate OA developed in late adult life. However, nevertheless, none of these reports signified the coexistence of a syndromic complex association.

Wiberg^[23] described acetabular dysplasia as the main causation of OA by mechanically overloading the primary weight-bearing portions of the acetabular articular cartilage. He postulated that when the hips are with a centre-edge angle of less than 20° are definitely pathologic and can lead to OA.^[23]

From within our experience, the time of onset of OA and the grade of its severity which causes activity-related groin

pain and abductor fatigue are in strong correlation and more frequently seen in patients with hip flexion and internal rotation in relation with severe types of skeletal dysplasia.

Hemiepiphysiodesis is a lesser surgical procedure than osteotomy and avoids the possible neurovascular complications of the latter, as well as the complications attendant on delayed union or malunion and surgical infection. The 8-plate (8-Plate; Orthofix, McKinney, TX, USA) can be used to create guided growth.^[24] This implant is similar to a staple except that the screw toggles in the holes in the plate, using a tension band concept to move the fulcrum of asymptomatic growth to the bone surface. The technique slows growth on one side of the bone while allowing normal growth on the opposite side to correct a deformity such as genu varum. A slight overcorrection is recommended because some rebound growth stimulation has been reported after the removal of a guided-growth implant. The 8-plate is a tension band construct designed to allow guided growth in deformity correction. The 8-plate is positioned on the cortex of the bone, moving the fulcrum of correction to the side of the bone, to allow more rapid correction of angular deformities. The toggling of the screws allows most of the growth plate to grow normally while preventing growth directly under the 8-plate.^[23] Wiemann *et al.* compared 39 limbs treated with staple hemiepiphysiodesis and 24 limbs treated with an 8-plate. There was no difference between the two groups in the rate of correction or the frequency of complications. The rate of complications was greater in patients with pathologic physes.^[25]

One patient presented with SCFE has been diagnosed with MED in conjunction with COMP mutation. He manifested proximal femoral deformity associated with limitations in range of motion. He was treated by PFO. In addition, PFO plays an important role in the treatment of numerous hip disorders in children.^[26] The indications are not limited to dislocations or subluxations in children with neurological hip diseases. Modern imaging has confirmed the arthrogenic role of morphological femoral head or head/neck disturbances such as LCPD, SCFE, development dysplasia of the hip, OA of the hip and congenital or acquired coxa vara. Varus osteotomy has an important role in treating patients with severe LCP, particularly in the presence of fragmentation or for early reconstruction, and in patients with malalignment but without hinge abduction (this is based on the principle of femoroacetabular containment).^[27]

CONCLUSION

Skeletal dysplasias are a heterogeneous group of genetic intrinsic bone disorders. The role of the orthopaedic surgeon is fundamental in determining whether if the deformity is idiopathic or it's strongly correlated to a syndromic entity. Comprehensive documentation is the key figure towards proper clinical and radiological phenotypic characterisations. The above-mentioned strategy is a basic tenet of the medical profession. Major advances in molecular genetics and exome

sequencing are evident now a day. However, nevertheless, such advances are in mass need for more profound understanding regarding the optimal clinical and radiological interpretations. Gaps in current understanding of these two essential baseline tools have become apparent. On the one hand, genetic analysis done without proper understanding of the clinical phenotype can partly explain the genetic contribution to diverse forms of deformities. Moreover, on the other hand, the genotype is not a precise index to understand the natural history and the complexity of malformations in syndromic entities.

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Conflicts of interest

There are no conflicts of interest.

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