CLINICAL ARTICLE

Re-alignment-procedures for Skeletal Dysplasia in Three Patients with Genetically Diverse Syndromes

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Objective: Disruption to endochondral ossification leads to delayed and irregular bone formation and can result in a heterogeneous group of genetic disorders known as osteochondrodysplasias. These genetic disorders arise through disturbances in the complex processes of skeletal growth causing development of unsightly skeletal deformities.

Methods: Each syndrome was diagnosed on the basis of detailed clinical and radiographic assessment. Lower limb deformities were the prime presenting feature.

Results: Here are presented three patients with diverse genetic syndromes, namely Wolcott–Rallison syndrome (WRS), Kniest dysplasia (KD) and Desbuquois dysplasia (DS). Genetic testing was performed in the patients with WRS and DS. The diagnosis of KD was made purely on a clinical and radiographic basis. Variable orthopaedic interventions to realign these patients' lower limbs were implemented with the aim of improving their balance and gait.

Conclusions: The aim of this paper is twofold. The first part is to outline the importance of diagnosing the causes of various skeletal abnormalities in patients with osteochondrodysplasias by phenotypic and genotypic characterization. The second part is to demonstrate our techniques for surgical corrections in patients with joint laxity and malalignment and show how far techniques for growth modulation, re-alignment and ligament reconstruction have advanced.

Key words: Phenotypic/genotypic correlation; Re-alignment procedures; Skeletal dysplasia

Introduction

Wolcott–Rallison syndrome (WRS) is a rare autosomal recessive disorder characterized by the association of permanent neonatal or early-infancy insulin-dependent diabetes, multiple epiphyseal dysplasias and growth retardation, and other variable multi-systemic clinical manifestations. The main features are multiple epiphyseal and spondyloepiphyseal dysplasia associated with diabetes mellitus. Onset is in early infancy; the diabetes may precede the bone dysplasia. WRS is characterized by insulin-requiring diabetes that generally appears during the neonatal period or within the first six-

months of life; the disease onset is frequently acute, presenting typically as severe diabetic ketoacidosis^{1–3}.

Desbuquois syndrome (DS) is reminiscent of Larsen syndrome in that there is joint laxity with multiple dislocations. The eyes are prominent, the nasal bridge tends to be flat, and there can be marked micrognathia. Radiological changes are distinctive. Clinical features include supernumerary phalanges, characteristically situated between the metacarpal and proximal phalanx of the index finger, osteoporosis, a short narrow thorax, metaphyseal enlargement and platyspondyly. DS is a rare autosomal recessive chondrodysplasia syndrome,

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characterized clinically by pre and postnatal growth deficiency, craniofacial dysmorphism, and marked ligamentous hyperlaxity^{4, 5}. Because of our patient's severe knee instability, surgery in the form of McIntosh extra-articular anterior and posterior cruciate ligaments (ACL and PCL) reconstruction was indicated.

Kniest dysplasia (KD) is a type II collagenopathy characterized by delay in ossification of the proximal epiphyses and platyspondyly. When ossification occurs, the epiphyses are large, resulting in dumbbell-shaped long bones. Severe short stature is present from birth and the face is usually flat with the head disproportionately large. The eyes may be prominent and there is often a cleft palate. Many infants have respiratory problems in the neonatal period^{6,7}. The types of KD include the lethal forms of achondrogenesis, spondyloepiphyseal dysplasia congenita and spondylometaphyseal dysplasia, the moderate form of Stickler syndrome and the mild form of late onset spondyloepiphyseal dysplasia with premature osteoarthritis⁸. Persistent genu valgum in our patient was corrected gradually by means of a circular external fixator (Taylor Spatial Frame [TSF], Smith & Nephew, Memphis, TN, USA) with knee inclusion.

Clinical Data

The study protocol was approved by the Medical University of Vienna (Ethics Committee, EK Nr. 921/2009), and informed consent was obtained from the patient's guardians. All our patients were of Austrian origin.

Our patients' records were reviewed in the Osteogenetic Department of the Orthopaedic Hospital of Speising, Vienna. Detailed phenotypic and genotypic characterization was performed in the patients with WRS and DS. The diagnosis of KD was based on detailed clinical and radiographic assessment. In addition, extensive chart and imaging reviews were performed on these three patients because they are illustrative of the broad spectrum of skeletal abnormalities in patients with skeletal dysplasias. Genu valgum was encountered in the patients with WRS and KD, whereas, bilateral knee joint instability was the major orthopaedic abnormality in our patient with DS.

Patient I

Wolcott–Rallison Syndrome

A 5-year-old boy who had presented with generalized defects of spondyloepiphyseal dysplasia associated with early infancy insulin-dependent diabetes was referred to the orthopaedic department because of progressive genu valgum (Fig. 1).

His gestation period had been uneventful. The father was 169 cm tall and the mother 155 cm tall. Review of three generations of family members revealed a cousin and uncle with short stature and early infantile insulin dependent diabetes mellitus.

The baby had developed diabetes at six weeks of age. However, he had no history of diabetic ketoacidosis or recurrent bouts of hypoglycemia suggestive of hepatic impairment, and renal failure or both. In addition, he had no history of

Fig. 1 Standing photograph of Case 1 showing genu valgum (knock knees) as the most prominent orthopaedic abnormality.

increased hepatic enzyme concentrations or hepatomegaly. His spleen was normal, as was Doppler ultrasound examination of the kidneys and the glomerular filtration rate and serum creatinine concentration. His joints were stiff and he had mild thoracic kyphosis and stiffness with associated loss of physiological lumbar lordosis. Radiographic documentation at the age of four years had shown dysmorphic bones in the hands and wrists.

The patient's parents were concerned about their child's gait (knees rubbing together), his frequent complaints of pain in the thigh and calf and frequent falls. On examination, significant malalignment and an increased Q angle of the quadriceps extensor mechanism were noted. The patellofemoral joints were unstable and there was a propensity toward patellar subluxation. It was considered possible that he would develop degenerative arthritis of the knees.

Genetic Testing

Genomic DNA was extracted from the peripheral blood cells of the patient and both parents by standard methods. Subsequently, the patient's entire GDF6 coding regions were amplified by PCR (primers and PCR conditions are available on request). Fragments were verified on a 1% agarose gel and sequencing in both forward and reverse directions was performed by cycle sequencing using an ABI BigDye Terminator Cycle Sequencing Kit according to the supplier's protocol and

was analyzed on an ABI3100 genetic analyzer (both ABI, Foster City, CA, USA). The results were aligned and compared with the GDF6 reference sequence NM_001001557.2. Sequence analysis revealed a homozygous nonsense mutation resulting in a premature stop codon (c.2707C>T, p.R903X). Both parents were identified as heterozygous carriers of this mutation. This mutation had previously been reported by Rubio-Cabezas *et al.* in a German patient³. Because of the different reference sequence for the mutation in this publication (AF110146.1), which contained a dbSNP deletion of three base pairs, the nomenclature differs by one amino acid (c.2704C>T, p.R902X).

Treatment

Precise schedules for the required surgery and follow-up times were organized.

Anteroposterior (AP) lower limbs radiograph showed small ossific nuclei in the proximal femoral epiphyses that were slightly flattened with an irregular outline and punctate appearance. The metaphyses were enlarged and sclerosed. Knee and ankle epiphyseal nuclei were also flattened and wide in the transverse plane, with irregular perimeters and stippling extending into the cartilage of the epiphyses. The growth plates looked as if they would soon fuse. Knock knees were noted (before treatment). The schedule for surgery was bilateral eight plates for the distal medial femora and proximal medial tibias to correct valgus deformity of both knees on 4 September 2009. The eight plates were removed on 27 October 2010. The last follow-up was planned for 15 February 2012, at which time the patient had physiological valgus positions of both lower extremities, mechanical axis 5 mm lateral on both sides, and free range of motion of both knees (Fig. 2).

This technique was chosen as an alternative to acute correction to avoid shortening of the bones by closing-wedge osteotomy.

Patient II

Kniest Dysplasia Syndrome

A 9-year-old boy was referred to our department for clinical assessment and diagnosis. He had been born by vaginal delivery at term. His birth weight was 3200 g, length 46 cm (10th percentile) and head circumference 36 cm. Clinical examination showed a combination of facial dysmorphic features including depressed nasal bridge, large nose, long philtrum, full cheeks and a large mandible. Large ears and a short neck that sat directly on the trunk were evident. His height was below the third percentile and his cranium large (75th percentile). He had a short trunk with mild thoracic kyphosis, and lumbar lordosis characteristic of short-limbed dwarfism. All his peripheral joints had progressively enlarged causing development of progressive genu valgum. He had the painful joints with associated tenderness. His development has been remarkably retarded because of limited joint mobility. At the age of six years, he had a severe limp and distinct limitations in joint mobility.

Fig. 2 Postoperative standing photo of Case 1 showing physiological valgus position of both lower limbs.

The severity of this child's genu valgum was assessed by clinical and radiographic measurements of the weight-bearing tibiofemoral angles and clinical measurements of the intermalleolar distance (Fig. 3). An AP radiograph of the lower limbs showed shortness and dumbbell appearance of the long bones caused by splaying of the metaphyses associated with significant retardation of epiphyseal ossification, irregular punctate epiphyses, irregularity of growth plates, cloud effect, flattened acetabula and loss of the normal trabecular pattern. Similarly, the knees showed severe genu valgum. Scattered confluent areas of high density randomly distributed in the non-properly ossified epiphyses were noted (cloud effect, Fig. 4). Genu valgum of less than 20° or an intermalleolar distance of less than 15° are considered moderate. Our patient manifested greater deformities and was classified as having severe genu valgum.

His skin was neither hyperextensible nor bruised easily, and he had no signs of dystrophic scarring. Examination showed normal prepubertal genitalia. His hearing and intelligence were normal. Echo-cardio-Doppler and abdominal ultrasound were normal. The following biochemical variables were within the normal range: serum and urinary oligosaccharides,

Fig. 3 Standing photograph of Case 2 showing severe genu valgum.

mucopolysaccharides, serum lactate, pyruvate, creatine phosphokinase, alkaline phosphatase, calcium, phosphorus, and vitamin D metabolism. Chromosomal studies were normal. Hormonal investigations including thyroid hormones; adrenocorticotrophic hormone and growth hormone were also normal. Logistic reasons prevented genetic testing of this child.

Treatment

This child's severe genu valgum was corrected gradually by means of a circular external fixator (TSF, Smith & Nephew) with knee inclusion, which was fitted on 28 October 2003. On 18 May 2004, after removal of the TSF (Smith & Nephew) from the right femur, intramedullary rodding was inserted and a TSF simultaneously fitted to the left femur to lessen the serious effects of progressive and recurrent genu valgum. On 18 February 2009, a TSF was again fitted to the right femur, an osteotomy performed distally to correct against valgus deformity and the right knee bridged with an Ilizarov system (Smith & Nephew). On 14 December 2009 the TSF was removed and re-osteotomy performed, after which a rush pin was inserted into the right femur to realign it. On 16 June 2010 recurrent valgus deformity of the left femur was addressed by fitting a TSF and performing a distal femoral osteotomy correction against valgus deformity and bridging of the left knee. On 24 January 2011, the left TSF was removed and the left leg fixed with a spica cast for 6 weeks. Later, on 26 April 2011, a supracondylar fracture of left femur occurred; this was managed by applying fixation with k-wires, and fitting a hip spica on the left. On 06 June 2011, the cast and the k-wires were removed.

At follow-up on 07 June 2011 after removal of the cast, the patient's lower extremities were both in good alignment and mobilization for short distances was commenced.

A recent standing photo shows satisfactory re-alignment of the right lower limb though, as expected because of the severity of the pre-existing anatomical abnormalities, there is a persistent slight valgus deformity on the left side (Fig. 5).

Patient III

Desbuquois Dysplasia Syndrome

On clinical examination this patient had retarded growth associated with dysmorphic facial features which included an unusual round facies, deep-seated eyes, synophrys, curly eyelashes, flat nasal bridge, small nose, and relative prognathism. Hand radiographs at the age of 3 years showed multiple carpal ossification equivalent to a bone age of 7 years and 4 months. Radiograph of the pelvis showed horizontal acetabula, coxa vara, and short femoral necks with prominence of the lesser trochanters producing a "monkey wrench" appearance in the

Fig. 4 Anteroposterior radiograph of the lower limbs of Case 2 showing shortness and dumbbell appearance of long bones due to splaying of metaphyses associated with significant retardation of epiphyseal ossification, irregular punctate epiphyses, irregularity of growth plate, cloud effect, flattened acetabula and loss of normal trabecular pattern. Similarly, the knees show severe genu valgus.

Fig. 5 Postoperative standing photograph of Case 2 showing successful re-alignment of the right lower limb with persistence of slight valgus deformity on the left.

proximal femora. Remarkably prominent lesser trochanters were noted (Fig. 6). An AP knee radiograph showed hyperextension of 20° on both sides with bilateral anterior dislocation of the tibias (Fig. 7).

Genetic Testing

Analysis of CANT1 showed a mutation in the patient, who was homozygous for this gene, C.898C>T located in exon 4 (p.R300H). The child's parents were both heterozygous for this mutation (findings courtesy of Dr. C. Huber and Dr. V. Cormaire-Daire, Necker Hospital, Hospital for Sick Children, Paris, France).

Treatment

On 2 November 2009, at the age of 7 years, surgical correction by McIntosh reconstruction of the right extra-articular ACL and PCL was performed. After the extra-articular PCL recon-

Fig. 6 Radiograph of the pelvis of Case 3 showing horizontal acetabula, coxa vara, and short femoral necks with prominence of the lesser trochanters producing a "monkey wrench" appearance of the proximal femora. Note the remarkable prominence of the lesser trochanters.

struction had been done, the anterior limb of the fascia lata was passed under the patellar ligament to the medial side and then through a window in the medial joint capsule. It was then passed through a tunnel under the adductor magnus tendon and the knee flexed, after which the graft was sutured back onto itself under tension. An above-knee cast was fitted for 6 weeks, after which another brace with a flexible knee joint was prescribed.

Fig. 7 Anteroposterior radiograph of the knees of Case 3 showing bilateral hyperextension of 20° with bilateral anterior dislocation of the tibias.

Because the above described procedure produced good results, three months later, on 22 February 2010, a similar procedure was performed on the left knee. An extra-articular ACL reconstruction was performed on the left knee using a graft of the iliotibial tract. This involved reconstruction of the medial collateral ligament using the tendon of the gracilis muscle, reconstruction of the lateral collateral ligament using a part of the iliotibial tract and fixation of the collateral ligaments with the help of resorbable screws at the femoral condyles. Similarly, another above-knee cast was used for 6 weeks, after which an above-knee-brace for the left lower leg was prescribed.

The patient is now able to walk very well with both braces, which are strictly recommended at this stage to prevent the severe laxity of both knee joints from having any adverse effects. The re-alignment procedures produced positive results (Fig. 8). At follow-up on 24 April 2012, the patient was walking very well using the two above-described knee splints with mobile knee joints. The range of motion on both sides was full extension, normal position in full flexion, and 160° flexion in the sagittal plane and there was persistent instability of the collateral ligaments on both sides (the left more than the right). A recent postoperative standing photo shows that

Fig. 8 Anteroposterior radiograph of the knees of Case 3 showing positive results of the re-alignment procedures.

Fig. 9 (a) Postoperative photograph of Case 3 showing that normal alignment has been achieved. (b) Above-knee-splints were recommended because of severe collateral ligament laxity.

normal alignment has been achieved. Nevertheless, continuing use of the above-knee splints is recommended because of severe collateral ligament laxity (Fig. 9a, b).

Discussion

The lower femoral epiphysis undergoes considerable changes in shape during normal development. At birth it is almost round, at 1 year egg-shaped and by 2 years it develops the shape of a Dutch clog shoe. At this stage the lateral condylar part of the bony epiphysis appears larger than the medial and there is disseminated calcification streaming from its medial side. The medial condyle enlarges to become equal in size to the lateral by the age of 3 years but does not enlarge to become larger than the lateral condyle until the age of 6 years. These changes, which are the same in children with or without significant genu valgum, do not reflect the changes in the shape of the condyles⁹⁻¹¹.

Valgus alignment of the lower limbs is normal in children between 2 and 8 years old. The maximum amount of physiologic valgus occurs between 2–4 years, after which the alignment of the lower limbs assumes a mild valgus femoral-tibial angle, the normal alignment in an adult. Therefore, by 8 years of age there should be little or no further change in alignment of the lower limbs. Thus, preparation for treatment of what is deemed excessive physiologic valgus may be made at this age. In younger children passing through the physiologic valgus phase, radiographs are not indicated unless there are unusual phenotypic features compatible with a skeletal dys-

plastic disorder. After 8 years of age, correction of excessive idiopathic genu valgum may be indicated when there is gait disturbance, difficulty in running, knee discomfort, patellar malalignment, evidence of ligamentous instability, or excessive cosmetic concern^{10,12}.

In our patient with WRS, some form of hemiepiphysiodesis was planned^{13,14}. Hemi-epiphysiodesis procedures have the advantage of producing unilateral physeal inhibition, thus achieving correction gradually and close to the joint, where correction of the deformity will be most effective. Hemi-epiphysiodesis 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. Nevertheless, such patients have osteoporotic bones and staple extrusion is possible, therefore, strict follow-up is mandatory.

In our patient with KD, persistent and progressive genu valgum warranted gradual treatment to alleviate symptoms and prevent progression^{9,10,15}. On the basis of our findings in this patient and our previous experience with patients with skeletal dysplasias (particularly patients with type II collagenopathies), we postulate that the development of progressive/persistent genu valgum in this child was a sequela of a poor anatomical configuration at the metaphyseal junction. The diminished mineral deposition may be attributable to a fundamental defect in bone development and mineralization that is related to the connective tissue disorder and is a direct consequence of the presumed genetic mutation in COL2A1^{16,17}.

Congenital hyperextension deformities of the knee can be classified as congenital hyperextension, subluxation or dislocation of the knee on the basis of physical examination and radiographic assessment¹⁸. The degree of passive flexion of the knee also helps determine prognosis and treatment. If the knee will flex and reduce with gentle stretching of the quadriceps, the deformity is classified as grade 1, or congenital hyperextension of the knee. In grade 2, or congenital subluxation of the

knee, the knee will not flex beyond neutral, but the femoral and tibial epiphyses are in contact and do not subluxate when flexion is attempted. If knee flexion is not possible and the tibia, which is anteriorly translated in the resting position, displaces laterally on the femur when more vigorous flexion is attempted, the deformity is classified as grade 3, or true irreducible congenital dislocation of the knee. True congenital knee dysplasia is always associated with significant quadriceps fibrosis and shortening. Some consider this the main cause of the deformity¹⁹. The differential diagnosis of DS is with multiple joint dislocation syndromes (especially Larsen, the Reunion Island variant of Larsen syndrome and diastrophic dysplasia), and Catel–Manzke syndrome, in which there are similar hand abnormalities²⁰.

Phenotypic/genotypic characterization is the baseline from which to approach a diagnosis in children with skeletal dysplasia. However, no genotype–phenotype correlations have been identified for many skeletal dysplasias. Because some dysplasias place patients at increased risk of future medical problems, it is important to remember that making a diagnosis has major prognostic and pathogenetic implications.

In most case, skeletal abnormalities such as progressive genu valgum, particularly when associated with a dysplastic bone abnormality or traumatic lesion, need operative correction. Surgical intervention is sometimes the only means of correcting the deformities of patients with skeletal dysplasia. When providing surgical treatment for skeletal dysplasias, because the epiphyses are narrow and dysplastic, additional care is required to avoid penetration of the joint or physis (the margins of the physes are typically indistinct) especially when inserting staples or 8-plates.

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