CLINICAL ARTICLE

Corrections of Lower Limb Deformities in Patients with Diastrophic Dysplasia

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Objective: Accurate understanding of the cause of the underlying pathology in children with diastrophic dysplasia would help in designing targeted management of their locomotion.

Methods: Diastrophic dysplasia was diagnosed in twelve patients (nine girls and three boys; age range 1–14 years), all of whom presented with small stature and apparent short extremities. Club foot (mostly talipes equinovarus) was the most frequent and consistent abnormality. Concomitant abnormalities such as hip flexion contracture, flexion contractures of the knees with excessive valgus deformity and lateral patellar subluxation, were also encountered. Muscle ultrasound and muscle magnetic resonance imaging showed no myopathic changes and muscle biopsies and the respiratory chain were normal. Serum choline kinase and plasma lactate concentrations were normal.

Results: Surgical correction of the foot and ankle in patients with diastrophic dysplasia is extremely difficult because of the markedly distorted anatomy. In all of these children, plantigrade foot was achieved along with the improved function of the locomotor system. Mutations of the diastrophic dysplasia sulfate transporter (also known as solute carrier family 26 member 2) were encountered.

Conclusion: Arthrogryposis multiplex is the usual terminology used to describe the abnormality in infants with multiple contractures. Diligent orthopaedic care should be provided based on an accurate understanding of the associated syndromes in such children.

Key words: Complex orthopaedic deformities; Diastrophic dysplasia; Plantigrade foot

Introduction

Diastrophic dwarfism, an autosomal recessive disorder, was first described by Lamy and Maroteaux¹. This disorder can be recognized at birth by the characteristic abducted, hypermobile, proximally placed thumb (hitchhiker's thumb). Other deformities include short broad hands with ankylosis of the proximal interphalangeal joints, clinodactyly of the little finger, absence of flexion creases, shortness of stature with micromelia (proximal segments affected most) and severe

bilateral clubfoot deformities. Radiologically there is marked shortening of the first metacarpal, the metacarpals are of irregular length and there is bizarre ossification of the hand bones². The epiphyses and metaphyses are irregular and there are V-shaped or chevron deformities at the distal ends of the femora and tibiae. The vertebral bodies are irregular.

During the neonatal period, these patients have acute swelling in the pinnae of the ear which eventually progress to calcification or ossification³. They usually develop multiple

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Fig. 1 The clinical appearances of children with diastrophic dysplasia showing the characteristic craniofacial features (A–C).

complex problems with joint contractures, subluxation and dislocations, degenerative joint disease and spinal deformity⁴. The club foot deformity is difficult to treat. Serial casting should begin soon after birth. Once the maximum benefits of casting have been achieved, any residual deformity should be corrected by soft tissue surgery and prolonged casting. The equinus component is difficult to correct and maintain, particularly in patients with hip and knee contractures; correction is unlikely to succeed unless the hip and knee problems have been corrected. If the deformity recurs, or if the patient is first seen in the toddler years, the best form of management is simple observation and accommodation of the deformities in appropriate shoes⁵ because some patients may function adequately despite incomplete correction^{5,6}. Mutations of the diastrophic dysplasia sulfate transporter (DTDST) gene impede cellular incorporation of sulfate and result in production of undersulfated cartilage proteoglycans, disrupting the assembly of cartilage matrix^{7,8}.

Materials and Methods

This is a study of 12 patients (nine girls and three boys; age range 0–14 years). The study was approved by the Medical University of Vienna (Ethics Committee, EK Nr.921/2009) and signed informed consents were obtained from their guardians. The children had various ethnic origins. The distinctive deformed appearance of the limbs and joints (particularly the short limbs with contractures of the joints and the bilateral talipes equinovarus) had misguided some referring physicians to diagnose some of these patients as having “arthrogryposis multiplex”. Myopathy was the suggested primary underlying pathology in a remarkable number of these children. Several causes for these children’s syndromes had been proposed by their referring physicians, including progressive muscle weakness and metabolic disorders of glycogenoses, lipidoses and mitochondrial defects. Nevertheless, muscle ultrasound and

muscle magnetic resonance imaging (MRI) had shown no myopathic changes and muscle biopsies and the respiratory chain were normal. Serum choline kinase and plasma lactate concentrations were normal. However, the misdiagnosis of “arthrogryposis” had persisted.

Clinical examination and phenotypic characterization were carried out in our department and showed that micromelic dwarfism was responsible for the small stature (four standard deviations below the mean height for age and sex) and short limbs and the associated constellation of various abnormal craniofacial contours: large head, square face and or full face with broad forehead, upturned nostrils, macrostomia with the lower lip thicker than the upper lip, narrow root and broad mid-nose, square jaw and or micrognathia, long and full face with broad forehead were present to varying degrees. Some stage of cystic swelling of the external ears, subsequent calcification resulting in twisted and deformed ears, or later thickened and furrowed lobes associated with narrowed external auditory canals and a cauliflower-like shape was invariably present. The extreme small stature and short extremities were associated with deformed great toes, the hands were short and broad, and the thumb deformity was the distinctive feature known as “hitchhiker’s thumb”. Ulnar deviation of the hands, fingers of irregular length, abduction of hypermobile and proximally inserted thumbs, flexion contracture, limitation of motion of peripheral joints, progressive postnatal dorsal lordosis and scoliosis were present. All patients manifested congenital contractures of the elbows, wrists, hips and knees associated with severe foot deformities (bilateral talipes equinovarus). Children with diastrophic dysplasia have characteristic craniofacial features (Fig. 1). Figure 1A shows a 10-year-old boy with severe short stature, thickened ear lobes and multiple contractures (elbows, pelvis, and knees). Figure 1B shows a 2-year-old girl with severe short stature, thickened ear lobes and swellings of the pinnae associated with

Fig. 2 Anteroposterior radiographs of the hands of three children (A–C) showed irregular length and form of metacarpals and phalanges associated with short, often ovoid, first metacarpals, proximally located thumbs.

narrow external auditory canals. Figure 1C shows a 6-month-old boy with micromelic dwarfism, a characteristic craniofacial contour and contractures of the elbows and knees. Figure 1D shows a 12-year-old girl whose knees had been operated on to relieve the contractures; however, the contractures had recurred.

Physical examination showed a reduced range of movement in the spine in all patients. Two of the children presented with thoracolumbar scoliosis, neither of them appeared to have vertebral malformation complex. Though a cuneiform appearance and platyspondyly were observed in one patient, the degree of scoliosis was measured on plain radiographs using Cobb's method. MRI imaging was performed to assess the relationship between the vertebral column and spinal cord. Two of 12 had cervical kyphosis. All patients had stiff joints. In two girls, dislocation had been detected immediately after birth by ultrasound. Three children (one boy and two girls) had developed dislocation of the hips and knees when they attempted to walk.

Examination of the knees showed severe morphological and structural changes with 90° fixed flexion contractures associated with marked shortening, progressive valgus deformity and lateral positioning of the patellae. There were additional ossification centers in the medial condyles, which were associated with delayed ossification of the hypoplastic patellae. The development and position of the patellae may determine whether contraction of the quadriceps muscle results in exten-

sion of the knees. In three boys, paradoxical flexion of the knees occurred, causing severe difficulty with walking.

Radiographic Features

In three children, anteroposterior radiographs of the hands (Fig. 2A–C) showed irregular length and form of metacarpals and phalanges associated with short, often ovoid, first metacarpals, proximally located thumbs, (Fig. 2B,C) radial subluxation of the metacarpophalangeal joints of the thumbs and epiphyses that appeared to be bracketed. Their wrists showed delta wrist deformities associated with radial head dislocation. Characteristic features included unusually shaped and accessory carpal bones with under-modeled metacarpals, epiphyseal irregularity and hypoplastic, almost ovoid, first metacarpals (hitchhiker thumb) with epiphyseal irregularity.

In three children, anteroposterior pelvic radiographs (Fig. 3A–C) showed uniform hip deformities with broad trochanteric regions. Anatomical distortion of the capital femoral epiphyses had resulted in development of neck-shaft angles of >130° (coxa valga). The metaphyses were broad and flared and associated with proximal displacement of the femoral heads.

Anteroposterior and lateral radiographs of the knees (Fig. 4A–C) in patients of various ages with diastrophic dysplasia showed severe flexion deformities associated with delayed and irregular ossification of the distal femoral epiphyses, flaring of the metaphyses and hypoplastic patellae.

Fig. 3 Anteroposterior pelvic radiographs in three children with diastrophic dysplasia showed uniform hip deformities with broad trochanteric regions (A–C).

Fig. 4 Anteroposterior and lateral radiographs of the knees in three patients of various ages with diastrophic dysplasia (A–C) showed severe flexion deformities associated with delayed and irregular ossification of the distal femoral epiphyses and flaring of the metaphyses and hypoplastic patellae.

In three children, radiographs of the feet (Fig. 5) showed mixed and variable degrees of foot deformities including talipes equinovarus club foot (Fig. 5A), adductus varus (Fig. 5B) and a severe form of talipes equinovarus (Fig. 5C). The first metatarsals were short and triangular in shape (Fig. 5A,C), and the whole of the forefeet were medially deviated with the hallux in greater varus angulation than the lesser toes. The hindfeet and ankles were in extreme equinus posture (Fig. 5A,C) whereas the hind foot deformities were mild (Fig. 5B).

Surgical Procedures

Surgical correction of the foot and ankle in patients with diastrophic dysplasia is extremely difficult because of the markedly distorted anatomy. Typically, the hindfoot is in severe equinus with the subtalar joint deformed into valgus and moving more posteriorly. In contrast to idiopathic clubfeet, the navicular is markedly angulated laterally on the talus. The medial cuneiform is deviated medially on the navicular articulation. The forefoot is foreshortened and in marked varus positioning with varus of all of the metatarsals. The second to fifth metatarsals bend and curve near their bases as they tilt toward the first metatarsal.

The Ponseti method of clubfoot treatment⁹ was used in the five children who had presented at the age of 1–3 months;

plantigrade foot was achieved primarily in all of them. Bracing in a standard abduction brace was poorly accepted by children and families, both because of the rigid residual deformity (limited abduction and dorsiflexion) and because of the shape of the foot (shortening, wide forefoot and slim calcaneal part). Early relapse (within 6–12 months) occurred in all cases, in two of which repeated casting with re-tenotomy of the Achilles tendon achieved sufficient correction (follow-up not more than 1 year after second stage of Ponseti management). In two cases, posteromedial release was performed after 1 year of age because of the severity and rigidity of the deformity.

In the remaining cases, equinovarus of the foot was corrected by soft tissue release when the child was about to learn to walk (slightly older than 1 year of age). In some children, the deformity was very resistant, even to aggressive release. Post-operative bracing with ankle-foot orthoses was applied in an attempt to delay recurrence. However, recurrent deformity required repeated surgery: in some children a plantigrade foot was achieved and maintained. Talectomy and talar decancellation were also performed. The hip dislocations were very rigid, behaving like teratologic hip dislocations. Open reduction and femoral shortening required femoral osteotomy.

Supracondylar extension osteotomy (fixation with K-wires) was performed in 3-year-old boy who presented with

Fig. 5 Radiographs of the feet in three children with diastrophic dysplasia showed mixed and variable degrees of foot deformities; talipes equinovarus club foot (A) adductus varus (B) and severe form of talipes equinovarus (C). The first metatarsals are short and triangular in shape (A,C), and the whole in forefoot is medially deviated with the hallux in greater varus angulation than the lesser toes. The hindfoot and the ankles were in extreme equinus posture (A,C). Whereas the hind foot deformity is mild (B).

Fig. 6 Radiographs of the feet (A) 1 month after correction of foot deformities by the Ponseti method in a 3-year-old child showing plantigrade feet with an acceptable ability to wear shoes. (B) Another child 18 months after correction of foot deformities by the Ponseti method showing partial relapse. (C) A 6-year-old girl who had severe equinovarus deformity and underwent treatment by the Ponseti method followed by 10 sessions of casting and Achilles tenotomy showing plantigrade feet with an acceptable ability to wear shoes.

bilateral knee flexion deformities. His foot deformities were dealt with by casting and implementing the Ponseti method.

Results

One month after correction of foot deformities by the Ponseti method, a 3-year-old child had plantigrade feet with acceptable ability to wear shoes (Fig. 6A). Another child had partial relapse 18 months after correction of foot deformities in accordance with the Ponseti method (Fig. 6B). A 6-year-old girl with severe equino-varus deformity was treated by the Ponseti method followed by 10 sessions of casting and Achilles tenotomy; she achieved plantigrade feet with acceptable ability to wear shoes (Fig. 6C).

Mutations of the *DTDST* (also known as solute carrier family 26 member 2 [*SLC26A2*]) gene were found in four patients (this gene impedes the cellular incorporation of sulfate, resulting in production of under-sulfated cartilage proteoglycans, thereby disrupting assembly of the cartilage matrix).

Discussion

The *DTDST* (also known as *SLC26A2*) gene is responsible for sulfate/chloride antiporter, which is widely expressed on the plasma membrane of many cell types, including fibroblasts, chondrocytes and osteoblasts¹⁰. *SLC26A2* is the only gene mutations of which are known to cause diastrophic dysplasia. The following three other phenotypes, all of which have an autosomal recessive mode of inheritance, are associated with mutations in *SLC26A2*. Achondrogenesis type 1B, one of the most severe skeletal disorders in humans, is characterized by severe hypodysplasia of the spine, rib cage, and extremities, with a relatively preserved cranium. Achondrogenesis 1B is invariably lethal in the perinatal period. Atelosteogenesis type 2 is a neonatally lethal chondrodysplasia with clinical and histologic characteristics that resemble those of diastrophic dysplasia but are more pronounced. Recessive multiple epiphyseal dysplasia (also known as epiphyseal dysplasia, multiple, 4) is characterized by joint pain (usually in the hips and knees), deformities of the hands, feet and knees, and scoliosis. About 50% of these individuals have abnormal findings at birth (club foot, cleft palate or cystic ear swelling). The median height in

adulthood is at the tenth centile. The different clinical phenotypes are related to the residual activity of the sulfate transporter and thus to the resulting degree of proteoglycan under-sulfation. Functional defects of *SLC26A2* can cause a reduction in the intracellular sulfate pool, leading to synthesis and secretion of under-sulfated proteoglycans. Proteoglycan under-sulfation can result in altered architecture and mechanical properties of the extracellular matrix. The consequences of these alterations are most evident at the cartilage level, because cartilage is very rich in proteoglycans that, under normal conditions, are massively sulfated. Thus, defects in the *SLC26A2* can cause a chondrodysplastic phenotype. This hypothesis is based on the correlation between certain mutations in the *DTDST* gene and clinical phenotypes^{11,12}.

In diastrophic dysplasia, the hips are generally normal at birth, but may progressively subluxate and even dislocate. The acetabular roof is slanted laterally. Symptoms of degenerative joint disease may develop prior to full ossification of the femoral head. Valgus intertrochanteric osteotomies alone or in combination with an acetabuloplasty may prevent or delay degenerative joint disease. Once these joints have developed degenerative changes, total hip replacement is the only option. In these patients, total hip replacement may require the use of specially designed femoral components as well as acetabular augmentation procedures similar to those used in joint replacements for congenital hip dysplasia. Hip, knee and elbow flexion contractures may be severe: they are caused by a combination of cartilaginous joint deformity and soft tissue contracture. Femoral and/or rotational pelvic osteotomy to keep the femoral head contained within the acetabulum is the most commonly recommended surgical procedure for hip contracture⁴.

Progressive hip dysplasia occurs in 80% of patients with diastrophic dysplasia. Joint contractures in the lower limbs are among the most common orthopaedic complications in these patients. Vaara *et al.* described 50 patients with diastrophic dysplasia: 93% had hip flexion contractures, the mean contracture being 23°, and all contractures progressed with patient growth¹³. Helenius *et al.* reported that the contractures are caused by a combination of the abnormal femoral head shape (flattened with a double-hump deformity) and contractures of flexors and periarticular soft tissues¹⁴.

The knee joints are severely affected, generally with flexion contractures, excessive valgus deformity and lateral patellar subluxation. Soft-tissue release at the knee should be combined with correction of flexion contracture of the hips. It is not uncommon for flexion deformity of the knee to recur, which makes extension close-up wedge osteotomy of the distal femur mandatory. Dislocated patellae should be reduced early in life by release of the contracted iliotibial band and realignment of the quadriceps mechanism. Failure to achieve early correction results in these dislocations becoming irreducible. Peltonen *et al.* studied 46 patients and found anteroposterior tibiofemoral instability in 85% of their knees, 28 (60%) of the patients having spontaneous subluxation¹⁵.

With resurgence in the use of the Ponseti method, extensive surgical procedures to correct foot deformities are less frequently performed^{9,16}. The most effective and commonly used treatment for club foot is the Ponseti method, in which the deformities are gradually and simultaneously corrected by manipulation and serial long leg casting of the foot. Patients who have undergone extensive soft-tissue releases reportedly have poor long-term outcomes on measures of foot function and quality of life¹⁷. Ippolito *et al.* compared the results in patients treated with the Ponseti method versus manipulation followed by posteromedial surgical release of the club foot. Follow-up studies at a mean age of 25 years for those treated with the Ponseti method and 19 years for those treated with surgery found that a good or excellent result was achieved in 78% of those treated with the Ponseti method and 43% of those treated with surgery¹⁸. Zwick *et al.* compared the short-term outcomes (range of motion and functional rating system)

of the Ponseti method versus posteromedial release in patients with idiopathic club foot and also found that the Ponseti method achieved superior results¹⁹. Richards *et al.* compared the Ponseti method with the French functional physical therapy method and found that the two are equally effective²⁰.

Infants who present with multiple contractures are usually given the label of “arthrogryposis multiplex”. The resultant ambiguity and misconception ultimately leaves parents with vague and muddled expectations and makes it immensely difficult for orthopaedic surgeons to plan fruitful management. Muscle ultrasound and muscle MRI imaging can contribute positively to identifying patients with myopathy; however, without accurate interpretation of clinical signs/features, the entire process becomes time consuming and has adverse outcomes. The corner stone in the management of children with complex orthopaedic abnormalities is the definition and evaluation of the patient’s clinical status. Although sulfate transport activity plays a major role in determining the phenotype in diastrophic dysplasia, comprehensive phenotypic characterization is more important in guiding physicians/orthopaedic surgeons to formulate an initial differential diagnosis and eventually the correct definitive diagnosis.

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