



Arthrogryptic Syndrome is the Usual Misnomer in Children with Du Pan Syndrome

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Abstract

Objective: The term arthrogryptic syndrome is of common usage by different medical disciplines. The hallmarks of acromesomelic dysplasia Du Pan Syndrome are characteristic facial features, severe growth deficiency and multiple contractures.

Material and Methods: Seven children (four females and three males) age range of (1-10 years) were sought in our departments from the period of 1994-2018. All patients were given the diagnosis of arthrogryposis in other institutions. Though, all demonstrated the classical features of abnormalities which are consistent with the diagnosis of Du Pan syndrome.

Results: The distinctive clinical and radiological phenotype was consistent with Du Pan syndrome. Strikingly, multiple dislocations along the hips and knees, elbows and ankle joints were detected which gives the false impression of arthrogryptic syndrome.

Conclusion: Unfortunately, on the one hand, the terms arthrogryptic and or amyoplasia syndrome still prevails in many medical disciplines. The clinical phenotype is the corner stone in establishing diagnoses in the vast majority of children who are born with multiple contractures. On the other hand, it is mandatory to search for extra-skeletal malformations in patients with Du Pan syndrome.

1. Introduction

Children born with multiple contractures are usually given the term of arthrogyposis by overlooking the associated clinical features. The term arthrogyposis does not represent a specific diagnosis, in most cases arthrogyposis is a symptom complex. There is some confusion in the terminology of Du Pan Syndrome (MIM 228900), as it has been reported more than once under different titles. In addition it was reported by Grebe et al in 1955 as Grebe's 'other' syndrome (Grebe-Quelce-Selgado syndrome; MIM 200700).¹ The hallmarks of the condition are fibular aplasia, a complex form of brachydactyly and very hypoplastic ('ball-like') toes. The length of individual fingers can be very variable.^[1,2]

In the initial report by Martin Du Pan et al the cardinal features were brachydactyly and bilateral absence of the fibulae.^[3] In the hands, the thumbs were radially deviated and the index finger was abnormal, due to an absent proximal phalanx. The middle and ring fingers were deviated in an ulnar direction and the middle phalanges of the index, middle and little fingers were short. The carpal bones were hypoplastic. The feet were in an equinovalgus position and the phalanges of all the toes were hypoplastic or absent.

Grebe et al reported two sibs who were the offspring of first cousin parents.^[1] The sibs had short metacarpals, small carpals, a trapezoid configuration to the middle phalanx of the index finger, and radial deviation of that finger. The fibulae were bilaterally almost absent, with tibio-tarsal dislocation, and the toes were short and deviated laterally.

Mutations in the cartilage-derived morphogenetic protein-1 (CDMP1) also known as growth and differentiation factor 5 (GDF5) gene account for several related types of skeletal dysplasia, a rare subgroup of osteochondrodysplasias. The phenotype of these skeletal malformations ranging from prenatally lethal to very mild chondrodysplasias. Dominant mutations in GDF5 were previously reported in angel-shaped phalango-epiphyseal dysplasia (ASPED; MIM 105835),^[4,5] brachydactyly type A2

(BDA2, MIM 112600),^[6-8] proximal symphalangism 1B (SYM1B, MIM 615298) [7,9], multiple synostoses syndrome type 2 (SYNS2, MIM 610017)^[10,11] brachydactyly C (BDC; MIM 113100),^[4,12] whereas severe entities of grebe-type chondrodysplasia (GTC, MIM 200700),^[13-16] Hunter-Thompson (AMDH, MIM 201250),^[9,17] Brachydactyly, type A1, C (BDA1C, MIM 615072)^[18] and fibular hypoplasia and complex brachydactyly (Du Pan syndrome)^[19,20] were caused by homozygous loss-of-function mutations. A dominant transmission was also reported Du Pan syndrome and BDA1C.^[18,21] Moreover, a single nucleotide polymorphism (SNP) in the 5'UTR of GDF5 gene was reported to cause osteoarthritis (OS5, MIM 612400) in Asian populations.^[22]

The GDF5 gene is localized on chromosome 20q^[11,22] and comprises only two coding exons. GDF5 (also known as bone morphogenetic proteins 14 (BMP14)) belongs to a transforming growth factor beta (TGF- β) superfamily was found to be expressed in cartilaginous tissues of the long bones during embryonic development and binds with BMP receptors BMPR1A and BMPR1B, with high affinity to BMPR1B during development.^[23-26] GDFs like other BMPs have a crucial role in cartilage formation and chondrocyte differentiation.^[24,25,27-30] Du Pan syndrome. is very rare autosomal recessive condition caused by homozygous or compound heterozygous mutations in the GDF5 gene, usually disrupt GDF-5 receptor binding and/or activity,¹⁹ More than 40 mutations in GDF5 gene have been reported so far, with only 3 mutations have been found to associated with Du Pan syndrome.^[19,20,31] Stange et al Has identified a homozygous hypomorphic mutation in BMPR1B that cause Du Pan acromesomelic dysplasia in Moroccan family.^[32]

2. Material and Patients

The study protocol was approved by the Ethics Committee of the Turner Scientific Research Institute, No.3/2016, Saint-Petersburg, Russia. A signed consent form was obtained from the patient's Guardians. This study was conducted based on clinical and radiographic evaluation of a group of

children and their parents/grandparents and relatives and was carried out between first of January 1994 to March 2018. All patients showed the classical clinical phenotype of Du Pan syndrome showed severe short stature (ranging between -3/-4 SD), short limbs and acromelia of the upper limbs. The clinical phenotype of all children showed frontal bossing, rounded facies, mid-facial hypoplasia, up slanting palpebral fissure, short philtrum, low set ears (but not markedly malformed) and micrognathia. Musculo-skeletal examination, all children manifested stiff/rigid joints. Intelligence, communicative skills, hearing, vision and neurological examination were normal.

All children manifested the complex type of brachydactyly (button-like and radially deviated thumbs, short metacarpals, short phalanges and hypoplasia of the carpal bones. Equinovarus deformity of the feet, ball like hypoplastic toes and hypoplastic nails. At birth all these children have been given the diagnosis of arthrogryposis multiplex.

Hip contractures in conjunction with bilateral hip dislocation (manifested by flexion, abduction, and external rotation). Knee deformities were another prominent feature in all patients. Fixed flexion deformity of the knees (it was the most disabling deformity affecting the locomotor system). The foot and ankle deformities showed tibio-tarsal dislocation, and the toes were short and deviated laterally. Developmental skills were severely disturbed, particularly of gross motor development, which was markedly retarded because of multiple dislocations and congenital fixed flexion deformity of the knees and gross developmental retardation of the fine motor because of the button like fingers. The latter is a distinctive abnormality in children with Du Pan syndrome.

The hallmarks of Du pan syndrome are severe short stature (-4SD), acromelia of the upper and lower limbs, fibular aplasia, a complex form of brachydactyly and very hypoplastic ('ball-like') toes and club foot (fig 1a-d).



Figure 1 (a,b,c,d): The clinical phenotype in children with Du Pan syndrome (age from 18 months-7 years). The hallmarks of Du pan syndrome are severe short stature (-4SD), acromelia of the upper and lower limbs, fibular aplasia, a complex form of brachydactyly and very hypoplastic ('ball-like') toes and club foot

3. Results

All children manifested limb shortening which became progressively more severe distally. Dysplastic dislocated hips, short tibiae, fibulae replaced by distal triangular remnants and single phalanges in the toes (Bilateral and symmetrical dysplasia of the capital femoral epiphyses with subsequent development of bilateral hip dislocation

in 9 out of ten patients). Upper limbs, all manifested dislocated hypoplastic radial head & ulna, with severe bone retardation, and massive aplasia of the metacarpal-phalangeal, and only a small trace of bone in the fingers left.

AP hand radiograph in a one-year-old boy showed ulnar deviation of the hand, short phalanges, short hypoplastic metacarpals, hypoplastic thumbs, radially deviated thumbs and the index finger plus

abnormalities of the index fingers. The middle and ring fingers are deviated in an ulnar direction and the middle phalanges of the index, middle and little fingers were short. The carpal bones are hypoplastic, note the button like digits (fig 2a). AP elbow radiograph showed radio-ulnar dislocation in a 3 year-old-girl because radial head dysplasia (2b). AP standing radiograph in a 7-year-old-girl showed coxa valga, defective ossification of os pubis, mid-diaphyseal dysplasia, bilateral aplastic fibulae (fig 2c). 3D reconstruction CT scan of the foot of an 8-year-old boy with Du Pan syndrome showed hypoplastic metatarsals associated with severe hypoplasia of the toes including phalanges and very hypoplastic ('ball-like') toes (2d). AP standing radiograph of a 4-year-old girl showed bilateral hip dislocation (severe dysplasia of; acetabulae, capital femoral epiphyses, and defective ossification of os

pubis), bilateral knee dislocation associated with absent patellae (fig 2e). AP standing radiograph of the legs in a 10-year-old-boy showed bilateral aplastic fibulae and bilateral tibio-tarsal dislocation (fig 2f).

Laboratory investigations included karyotype blood electrolytes, liver functions, kidney functions, showed normal results. All showed normal calcium and normal phosphate levels normal, ranging between (0.83-1.48 mmol/l). Serum 25-hydroxy vitamin D was evaluated by radioimmunoassay and was found at the level average of about (39-42 nanograms per milliliter). MPS (mucopolysaccharidosis) urine screening and plasma chromatographic examinations yielded normal results. Ultrasound (abdominal and pelvic) examination revealed nothing of significance. Echocardiography: normal.



Figure 2 (a-f): AP hand radiograph in a one-year-old boy showed ulnar deviation of the hand, short phalanges, short hypoplastic metacarpals, hypoplastic thumbs, radially deviated thumbs and the index finger plus abnormalities of the index fingers. The middle and ring fingers are deviated in an ulnar direction and the middle phalanges of the index, middle and little fingers were short. The carpal bones are hypoplastic, note the button like digits (fig 2a). AP elbow radiograph showed radio-ulnar dislocation in a 3 year-old-girl because radial head dysplasia (2b). AP standing radiograph in a 7-year-old-girl showed coxa valga, defective ossification of os pubis, mid-diaphyseal dysplasia, bilateral aplastic fibulae (fig 2c). 3D reconstruction CT scan of the foot of an 8-year-old boy with Du Pan syndrome showed hypoplastic metatarsals associated with severe hypoplasia of the toes including phalanges and very hypoplastic ('ball-like') toes (2d). AP standing radiograph of a 4-year-old girl showed bilateral hip dislocation (severe dysplasia of; acetabulae, capital femoral epiphyses, and defective ossification of os pubis), bilateral knee dislocation associated with absent patellae (fig 2e). AP standing radiograph of the legs in a 10-year-old-boy showed bilateral aplastic fibulae and bilateral tibio-tarsal dislocation (fig 2f).

4. Discussion

An arthrogryptic condition is generally classified by group.^[33,34] Group I describe children born with involvement of the limbs only (distal arthrogryposis such as Freeman-Sheldon syndrome)

and Beals syndrome. Group II describes children born with involvement of the limbs and other body areas (abnormal craniofacial contour, spine, and or additional congenital anomalies e.g cardiac/ and or genito-urinary defects). Escobar syndrome and Larsen syndrome have been wrongly included in this group.

Group III describes children born with involvement of the limbs and the central nervous system as, seen in children with sacral agenesis.

Al Kaissi et al described two different families, in which both manifested the associations between maternal hyperthermia in connection with hypohidrotic ectodermal dysplasia and the birth of children with EEC syndrome and or phacomelia.^[35]

Du Pan syndrome is characterized by severe hypoplastic/dysplastic short tubular and round, hand and feet bones, absent or rudimentary fibulae, hypoplastic distal ulnae, grossly normal humeri, femora and tibiae, and valgus deformity of the feet. Carpal/tarsal fusions are distinctive features.^{1,3}

The similar Hunter. Thompson syndrome shows more severe joint abnormalities (dislocated hips, knees, radial heads and hypoplastic femoral condyles and short forearm and leg bones. There are slightly different radiological aspects of the hands and feet. However radial head and knee dislocations occur in Du Pan syndrome and minor round bone fusions were observed in Hunter-Thompson syndrome.^[21,36]

Multiple Joint dislocation is a common clinical phenotype usually seen in children with Larsen syndrome,^[37] Desbuquois syndrome,^[38] multiple joint dislocation with joint laxity (Beighton type),^[39] and otopalatodigital syndrome.^[40]

Reduction of dislocated syndromic hips has led to high rates of recurrent dislocation, stiffness, osteonecrosis, and persistent deformity. A long-term follow-up study found that dislocated arthrogryptic hips were generally painless and stable after open reduction with any necessary pelvic or femoral osteotomies.^[41]

Congenital hyperextension deformities of the knee comprise a spectrum of lesions, including simple hyperextension, subluxation, and complete dislocation. At least half of the babies presenting with these deformities will have some passive flexion at birth that can be managed with casting and/or a Pavlik harness to maintain knee flexion for a few weeks. Fixed subluxation/dislocation is more difficult to treat and often accompanies the fixed dislocation of the hips in the neonate.^[42-44]

Traditional treatment for congenital knee dislocation involves the extensive lengthening of the quadriceps mechanism to achieve flexion and an anterior arthrotomy to release the intra- and extra-

articular adhesions that prevent congruous knee flexion and to mobilize the patellofemoral joint.^[45]

The literature suggests that patients with non-syndromic knee dislocations respond well to conservative management of these dislocations with serial casting and or traction and may have a better prognosis than patients with syndromic multiple dislocations. Flexion contractures of the knees may be the most disabling deformity, because the quadriceps extensor mechanism often is poorly defined or absent in a patient with a knee contracture. These contractures are difficult to treat, and multiple surgical techniques have been proposed. Recurrence is common regardless the technique.^[46] Stretching casts may be beneficial for a neonate, although care must be taken to avoid posterior dislocation.^[47]

5. In Summary

Du Pan syndrome is a syndrome of malformation complex caused by dominant or recessive mutations in GDF5 or BMPRI1B genes. Less than 30 cases have been described in the literature so far. This syndrome is allelic to other skeletal malformations with overlapping clinical presentations causing a diagnostic challenge, particularly with arthrogryposis multiplex congenita and or amyoplasia. The misdiagnosis of syndromic entities by the vast majority of pediatricians, physicians and orthopedic surgeons, particularly when dealing with disorders presented with multiple contractures is apparent. Multiple contractures are classified within the diagnosis of arthrogryposis multiplex. The latter is categorized within congenital myopathy. Congenital myopathy often entails a long and strenuous journey of unnecessary investigations. The distinctive clinical and radiological phenotypic characterizations are fundamental tools to specify and successfully categorize cases of multiple contractures into their respective diagnosis.

The initial clinical assessment of any child with multiple contractures should be based on family history and the clinical phenotypic characterization. Careful clinical examination of the craniofacial contour, musculoskeletal system, searching and exploring for minor and major malformations and so forth are mandatory

parameters. Otherwise, the journey of such families within different medical departments would be more or less futile. The clinical sign is not a sign if a physician cannot read it and similarly if a radiological feature is missing, abnormalities are difficult to recognize. Alleviating pain and discomfort for families with children suffering from severe locomotor disability is the main objective for any medical discipline. To mitigate the patients' and their families' suffering, diagnosis with the utmost precision should be given.

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