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RESEARCH ARTICLE

Aetiological Diagnosis of children with False Diagnosis of Arthrogryposis Multiplex Congenita

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ABSTRACT

Background: Arthrogryposis multiplex congenita is the usual misdiagnosis given for children born with multiple joint dislocation syndromes. The purpose of the study was to refute the term arthrogryposis multiplex congenita as well as contractures and replace them with a precise diagnostic entity.

Methods: Eight unrelated children referred to our orthopaedic departments with the presumptive misdiagnosis of arthrogryposis multiplex because of multiple joint contractures. Five boys and three girls (aged 1 month-5 year) and one adult-15-year-old-boy have been included. We performed extensive clinical and radiographic phenotypic characterization of every single patient associated with confirmatory genotype.

Results: We accomplished the diagnoses in all these children. Three diagnostic entities emerged. Larsen syndrome, diastrophic dysplasia and Escobar syndrome. The genotype has been performed accordingly.

Conclusion: The reason for presenting this study is threefold; Firstly, to illustrate the necessity of the etiological diagnosis in children with the misdiagnosis of arthrogryposis multiplex congenita in connection with the presumptive misdiagnosis of fetal akinesia, Pena-Shokeir syndrome or congenital myopathy. Secondly, full consideration of the phenotypic characterization and the additional pathological features allowed us to achieve proper management. Thirdly, is to clarify that excessive vigorous attempts to correct the dislocations in children with skeletal dysplasia were felt to not be recommended because of the risk of damaging the dysplastic epiphyses.

Keywords: Congenital multiple contractures; Arthrogryposis Multiplex congenita; Clinical phenotype; Radiological phenotype; Genotype

1. Introduction

Children born with multiple joint contractures are almost always given the diagnosis of arthrogryposis multiplex congenita. Multiple joint contractures is a heterogeneous group of disorders. The etiology of multiple congenital contractures stems from diverse etiological backgrounds, such as osteogenic (skeletal dysplasia, heritable forms of connective tissue disorders and syndromic associations), neurogenic/myogenic as in lesions of the central nervous system and with myogenic metabolic disorders, and so forth [1,2]

Fetal akinesia (OMIM 208150) was the most common syndromic misdiagnosis given to our group of children, since the vast majority of babies born with multiple joint contractures, which are routinely explained on bases connected to decreased fetal movement during intrauterine life. These reasons encompassed prenatal pathologies adversely correlated to one of the following; cerebral, spinal cord and or peripheral neuromuscular [3]. Pena-Shokeir syndrome (OMIM 20815) was another misdiagnosis given to two children with multiple congenital joint contractures [4].

Congenital myopathy (multicore disease) (OMIM 255320) has been wrongly considered in one enfant because of multiple contractures and severe muscle wasting [5]. Comprehensive clinical and radiological phenotypic characterization is the only methodology to confirm or rule out the above-mentioned misdiagnoses. We were able to refute the aforementioned misdiagnoses and three diagnostic entities of Larsen syndrome, diastrophic dysplasia and Escobar syndrome have been respectively diagnosed in our group of children.

Larsen syndrome (OMIM 150250) autosomal dominant type characterized by distinguished facial dysmorphic features of prominent forehead, flat face with mid-face hypoplasia, widely spaced eyes and a depressed nasal bridge. In some children cleft palate and or cleft uvula can be present. Congenital multiple joint dislocations, particularly of the hips, elbows and the knees (give the phenotype of genu recurvatum). Scoliosis, cervical spine malformation, mostly hypoplasia of the mid cervical vertebral bodies causing unpleasant cervical kyphosis. The hands are with cylindrical fingers associated with relatively short metacarpals with notable supernumerary carpal bones associated with broad and irregular metacarpal bones. There is lack of distal tapering of proximal and middle phalanges and premature fusion of epiphyses and shaft of the first distal phalanx. Club foot, mostly pes equinovarus with forefoot torsion are frequent. Extra calcaneal ossification center appearing in late infancy or later which eventually fusing with the main ossification center mostly on the age of 8-year of age [6-9]. Children with autosomal dominant type of Larsen syndrome showed heterozygous mutation in *FLNB* mapped on *3p14.3* encoding an actin-binding protein, filament B [10].

Diastrophic Dysplasia is a severe short limb dysplasia (OMIM 222600), is characterized at birth by multiple joint contractures, mostly the shoulders, elbows, interphalangeal joints and hips. Notable abnormalities are short limbs, especially rhizomelic shortening, severe talipes, hitch-hiker thumbs, a cleft palate in many, a characteristic swelling of the pinnae, which assumes the character of a cauliflower ear (usually appearing between the first day and the 12th week of life). Cleft palate is seen in 50 % of babies with diastrophic dysplasia. Progressive kyphosis of the cervical spine and progressive thoraco-lumbar kyphosis in correlation with irregular deformities of the vertebral bodies associated with narrowing of the interpedicular distances mainly over the lower spine segments are frequent findings. Respiratory problems, due to a narrow chest and micrognathia, can be a cause of early mortality. Radiologically there is shortening of the first metacarpal, irregular lengths of the metacarpals, and bizarre ossification of the hand bones. Distinctive flattening of the epiphyses with marked retardation of the capital femoral epiphyses because of under ossification [11-13]. Hastbacka et al., isolated the gene by positional cloning (a novel sulphate transporter gene *DTDST*). Hastbacka et al., reported the Finnish founder mutation (*GT->GC transition* (c.*-26+2T*>C)) in the splice donor site of a previously undescribed *5'*-untranslated exon of the *DTDST gene* [14-16].

Infants born with the non-lethal Escobar syndrome variant (OMIM 26500) are manifesting distinguished facial dysmorphic features associated with multiple joint contractures, giving the wrong clinical phenotype of arthrogryposis multiplex congenita. Additional overlooked deformities of camptodactyly and club foot are usually passed unnoticed by the clinicians and mostly considered as part of the presumptive diagnosis of arthrogryposis multiplex. Escobar variant, is predominantly caused by homozygous or compound heterozygous mutation in the *CHRNG* gene [16-18].

The current study points up the impact of the immediate clinical and radiological phenotypic characterizations as a paramount necessity through

the delineating the etiological diagnosis in babies with congenital multiple joint contractures/arthrogryposis multiplex congenita.
A detailed clinical assessment for the parents, siblings and relatives is empirical and can immensely assist with precious data to establish the diagnostic process.

2. Material and Methods

The study protocol was approved by the Ethics Committee of the (Ilizarov Scientific Research Institute, No.4 (50)/13.12.2016, Kurgan, Russia). Informed consents were obtained from the patient's Guardians. We fully documented children through detailed clinical and radiological phenotypic characterizations at the osteogenetische ambulanz in orthopaedic Hospital of Speising (Paediatric department), Vienna and through the scientific collaboration of the first author with Ilizarov Center, Kurgan, Russia and with the department of Foot and Ankle Surgery, Neuroorthopaedics and Systemic Disorders, Paediatric Orthopaedic Institute n.a. H. Turner, Saint Petersburg, Russia. Eight unrelated children referred to our orthopaedic departments with the presumptive misdiagnosis of arthrogryposis multiplex because of multiple joint contractures. Five boys and three girls (aged 1 month-5 year) and one adult-15-year-old-boy have been included.

Clinical and radiological phenotypic characterizations are the first and the foremost tools of investigation applied to babies/children with congenital malformation complex.

The first task in clinical examination for babies with congenital multiple contractures is to search for growth abnormalities, dysmorphic craniofacial features which includes, macrocephaly/ microcephaly, the size of the anterior fontanelle, frontal bossing, facial asymmetry, hyper/ hypotelorism, nasal bridge, macro/microstomia, length of the philtrum, cleft lip/palate, the size and position of the ears, pterygium colli, abnormal skin stigmata (cafe-au lait spots, hemangioma, hypo/ hyperpigmentations), congenital cardiothoracic defects, rhizomelia. The spine for congenital scoliosis or any abnormal skin dimples or hair tuft. Morphology of the hands and feet, as well as the phenotype of the external genitalia. Musculo-skeletal examination to confirm or rule out hypotonia/severe ligamentous hyperlaxity and or stiff joints. Furthermore, excessive care has been given to investigate the gestational history of every child, through studying the antenatal, prenatal and postnatal associated with precise assessment of every unusual maternal event. Remarkable number of mothers who gave birth to children with syndromic associations had had a history of multiple spontaneous miscarriages particularly in the first trimester, stillbirth and perinatal mortalities. Maternal history of feeble fetal uterine movements played a confusing factor in including infants among the phenotypes of arthrogryposis with subsequent misdiagnosis of fetal akinesia/Pena-Shokier syndrome. All these markers are of utmost importance in monitoring the foetal intrauterine growth and development. We proceed with traditional laboratory investigations encompassing, full blood tests, hormonal, screening for mucopolysaccharidoses (MPSs) and so forth. In two families, we excluded structural chromosomal aberrations via 20 CAG-banded mitoses. There were no microdeletions or microduplication after performing Array-CGH-analysis. One of the infants with Escobar syndrome has been misdiagnosed with congenital myopathy (multicore disease), because of evident multiple contractures associated with severe muscle wasting and multiple contractures. In this child webbing was not evident at birth. Multiple pterygium were evident late in his first year of life. Parents were first related cousins raising the possibility of an autosomal recessive pattern of inheritance. Vigorous investigation included muscle biopsy and molecular genetic studies for *RYR1* mutations showed negative results.

We subdivided our patients in accordance with the definite diagnosis. Three diagnostic entities arise, Larsen syndrome, diastrophic dysplasia and Escobar syndrome.

3. Results

I. LARSEN SYNDROME

Three unrelated children from different backgrounds aged (1 month-2 year). At birth all showed the typical misleading musculoskeletal history of hypotonia. Severe ligamentous hyperlaxity associated with hypermobility of joints associated with multiple joint contractures were misleading signs for the paediatricians. Therefore, different misdiagnoses emerged, ranging from Pina Shokier syndrome to congenital myopathy (multicore disease). All these children underwent a series of sophisticated and highly costly investigations, which all turned negative. Multiple congenital joint dislocations associated with severe ligamentous hyperlaxity were the major clinical presentations. Spine malformations yielded variable spine mal-alignment. Ranging between the life-threatening cervical spine kyphosis to the more common thoraco-lumbar scoliosis. Entire skeleton radiograph of a-one- month-old-girl with Larsen syndrome showed the misleading

phenotype of arthrogryposis multiplex congenita (figure 1).

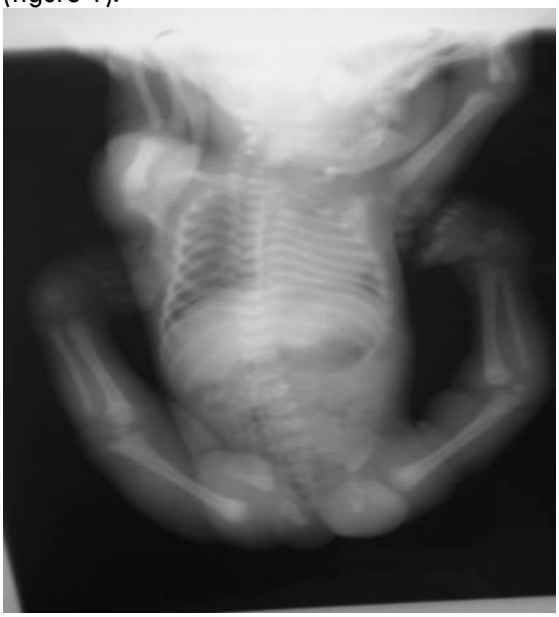

Figure 1. Entire skeleton radiograph of a-one- month-old-girl with Larsen syndrome showed the misleading phenotype of arthrogryposis multiplex congenita

Clinical phenotype of a –two-year-old –boy with Larsen syndrome showed the full-blown picture of typical craniofacial dysmorphic features of bossing of the forehead, depressed nasal bridge, hypertelorism, and dish-like face. Congenital multiple joint dislocations, mostly involved the hips, knees (genu recurvatum), and elbows. In addition he manifested thoraco-lumbar scoliosis in connection with hemivertebrae and bilateral talipes equinovarus (figure 2,a). AP standing pelvis-lower radiograph of a-2-year –old-boy showed bilateral dislocated hips and medially subluxed knees. Apparent epiphyseal maldevelopment. Note bilateral talipes equinovarus (figure 2,b). Lateral foot radiograph of an 18-months.old-girl with Larsen syndrome showed two ossification centres of the calcaneus associated metatarsophalangeal subluxations (figure 3 a,b.). Two children manifested heterozygous mutation in FLNB mapped on 3p14.3, encoding an actin-binding protein, filamin B. The third child underwent sequencing to localize the mutation hot spots of the *FLNB-gene. Exons 2-4* and *Exons 25 to 33*. There were no mutations in these exons, but gross deletions or insertions are not covered with this analysis.

Clinical phenotype of a –two-year-old –boy with Larsen syndrome showed the full blown picture of typical craniofacial dysmorphic features of bossing of the forehead, depressed nasal bridge, hypertelorism, dish-like face. Congenital multiple joint dislocations, mostly involved the hips, knees (genu recurvatum), and elbows. In addition he manifested thoraco-lumbar scoliosis in connection with hemivertebrae and bilateral talipes equinovarus (figure 2,a). AP standing pelvis-lower radiograph of a-2-year –old-boy showed bilateral dislocated hips and medially subluxated knees. Apparent epiphyseal maldevelopment. Note bilateral talipes equinovarus (figure 2,b).

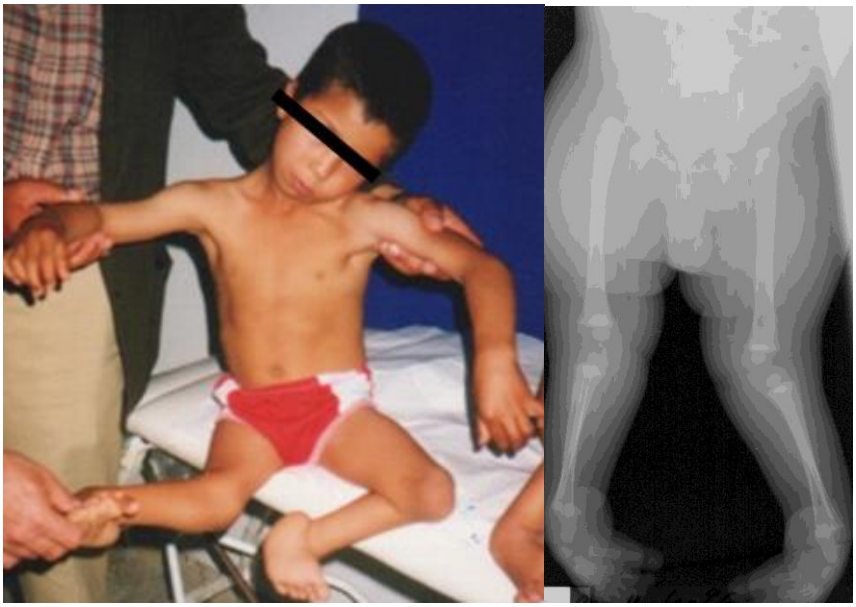

Figure 2 (a,b) : Clinical phenotype of a –two-year-old –boy with Larsen syndrome showed the full blown picture of typical craniofacial dysmorphic features of bossing of the forehead, depressed nasal bridge, hypertelorism, dish-like face. Congenital multiple joint dislocations, mostly involved the hips, knees (genu recurvatum), and elbows. In addition he manifested thoraco-lumbar scoliosis in connection with hemivertebrae and bilateral talipes equinovarus (figure 2,a). AP standing pelvis-lower radiograph of a-2-year –old-boy showed bilateral dislocated hips and medially subluxated knees. Apparent epiphyseal maldevelopment. Note bilateral talipes equinovarus (figure 2,b).

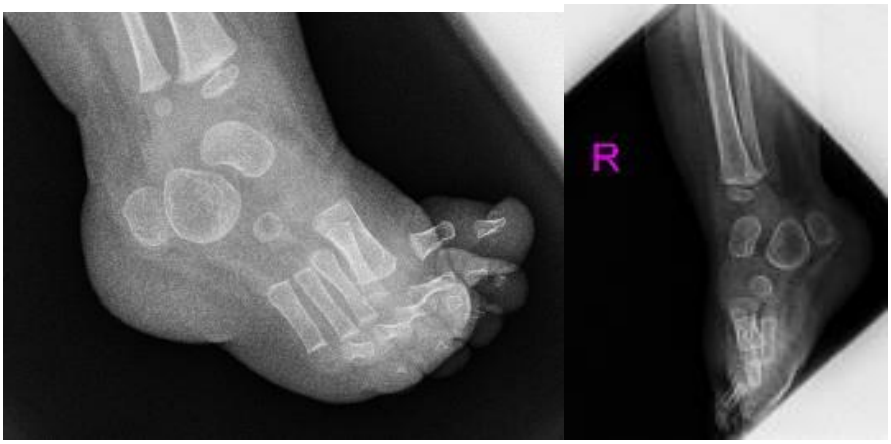

Figure 3 (a,b): Lateral foot radiograph of an 18-months.old-girl with Larsen syndrome showed two ossification centres of the calcaneus associated metatarsophalangeal subluxations.

II. DIASTROPHIC DYSPLASIA

Two infants showing micromelic dwarfism associated with flexion contractures of the peripheral joints have been given the presumptive diagnosis of arthrogryposis multiplex congenita and the suggested misdiagnosis was Pina-Shokier syndrome.

On the basis of comprehensive clinical and radiological phenotypic characterizations, we were able to establish a definite diagnosis of diastrophic dysplasia. Cervical spine kyphosis was present at birth, progression is expected and can lead to hazardous medullary compression with serious neurological deficits, which might end up in quadriplegia and possibly death.

Six weeks old-boy was referred with the misdiagnosis of Pina-Shokier syndrome. Clinical examination showed pre and postnatal growth retardation associated with rhizomelic shortening of the limbs and micromelia associated with overwhelming multiple joint contractures and apparent thoracic kyphosis. Craniofacial dysmorphic features of frontal bossing with narrow nasal root and broad mid-nose, cauliflower deformity of the pinnae, microstomia, cleft palate and micrognathia, lateral projection of thumbs (a). 3D reformatted CT scan of a -3- months –old boy –with diastrophic dysplasia showed life-threatening cervical spine kyphosis in connection with mal-segmentation of 3-5 cervical spine segments associated with atlanto-axial instability (figure 4, a). 3D reformatted CT scan of a -3-month –old boy –with diastrophic dysplasia showed life-threatening cervical spine kyphosis in connection with severe congenital hypoplasia of C1-5 spine segments associated with atlanto-axial instability (b). Mutations of the diastrophic dysplasia sulfate trasporter *(DTDST)*gene have been confirmed in one child. And for logistical reasons, genetic study was to a certain extent difficult to be done.

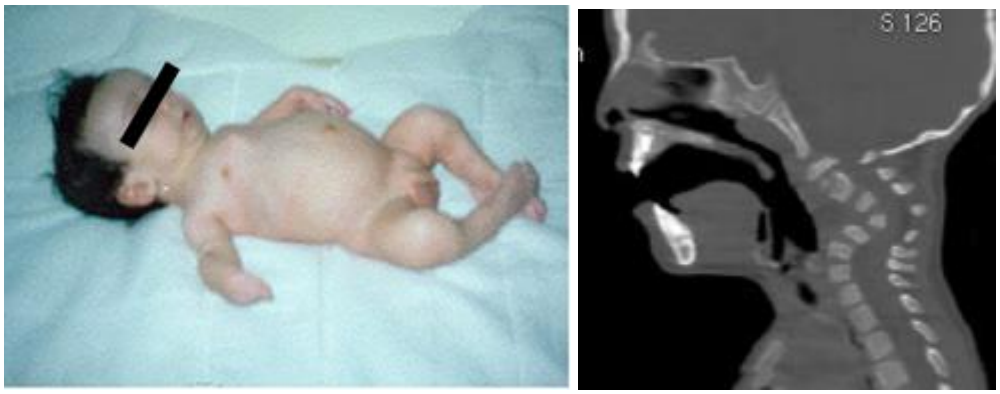

Figure 4 (a,b) Six weeks old-boy was referred with the misdiagnosis of Pina-Shokier syndrome. Clinical examination showed Pre and postnatal growth retardation associated with rhizomelic shortening of the limbs and micromelia associated with overwhelming multiple joint contractures and apparent thoracic kyphosis. Craniofacial dysmorphic features of frontal bossing with narrow nasal root and broad mid-nose, cauliflower deformity of the pinnae, microstomia, cleft palate and micrognathia, lateral projection of thumbs (a). 3D reformatted CT scan of a -3- months –old boy –with diastrophic dysplasia showed life-threatening cervical spine kyphosis in connection with severe congenital hypoplasia of C1-5 spine segments associated with atlanto-axial instability (b)

III. ESCOBAR SYNDROME (MULTIPLE PTERYGIUM SYNDROME)

Two unrelated children from different backgrounds (one girl and one boy, aged 2-4 year) and a -15-year-old boy were referred to our departments with diagnosis of arthrogryposis multiplex congenita. Clinical examination showed distinctive facial features of a relatively mask-immobile face with downturned corners to the mouth, epicanthic folds and ptosis. Webs seen clearly at the neck, axillae, antecubital, groin, popliteal region and in between the camptodactyly fingers. The phenotype of a -15-year-old-boy-showed the apparent webbing of the axilla, pectus excavatum, camptodactyly and the multiple inter-digital –webbing (Figure 5). Lateral spine radiograph in a-4-year-old-boy with Escobar syndrome showed progressive thoraco-lumbar kyphoscoliosis (figure 6,a). 3D Reconstruction Spine CT scan of a-4-year-old-boy with Escobar syndrome showed severe congenital scoliosis due to non-segmented bar Th11-L5 on the left side (figure 6,b).

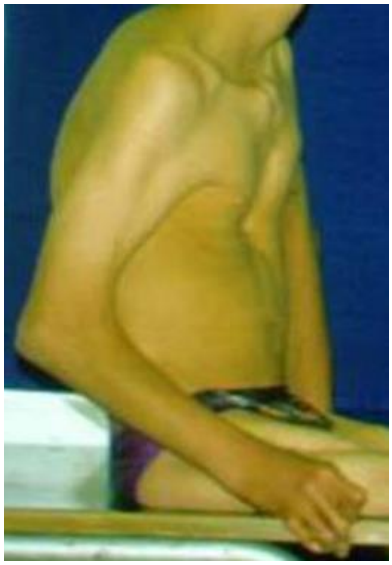

Figure 5. The clinical phenotype of a -15-year-old-boy-showed the apparent webbing of the axilla, pectus excavatum, camptodactyly and the multiple inter-digital –webbing

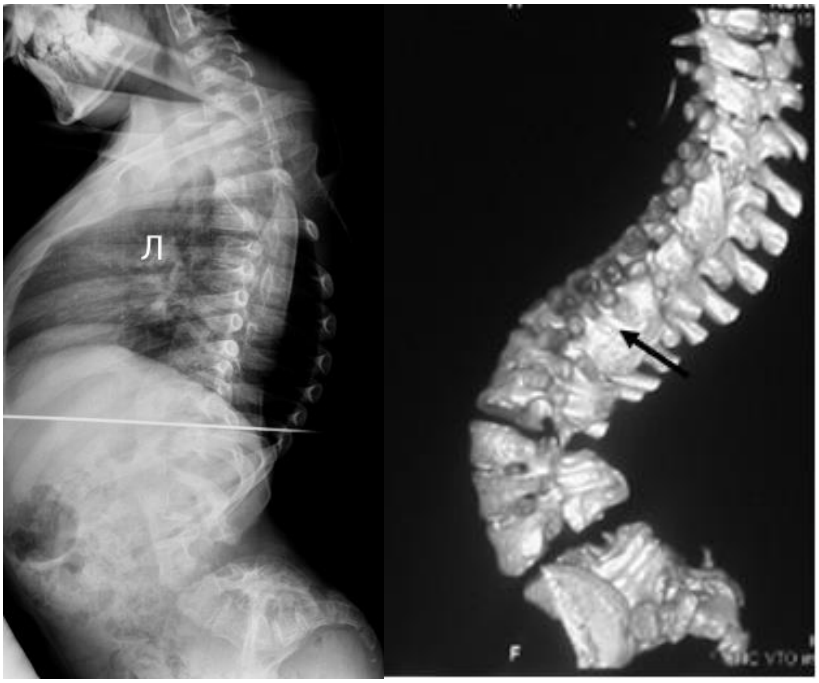

Figure 6 (a,b) Lateral spine radiograph in a-4-year-old-boy with Escobar syndrome showed progressive thoraco-lumbar kyphoscoliosis (figure 6,a). 3D Reconstruction Spine CT scan of a-5-year-old-boy with Escobar syndrome showed severe congenital scoliosis due to non-segmented bar Th11-L5 on the left side (figure 6,b) (arrow).

4. Discussion

Infants born with abnormal joint contractions often manifest a constellation of characteristic clinical and radiological phenotypes that should reflect their pathophysiology as well as the disrupted anatomy and eventually in well trained physicians can lead to definite diagnosis. Unfortunately, the precise etiology behind the term arthrogryposis as the causation of chronic locomotor disabilities in children has been underestimated. Surprisingly, the existence of minor or major craniofacial dysmorphic features and variable minor malformations in most of the clinical sessions are missed/overlooked by the vast majority of pediatricians/physicians and drastically considered as of no immediate priority as given to sophisticated laboratory investigations which are

supposedly the last in the list in the diagnostic process.

Several congenital disabilities are still attributed to be idiopathic. Genetic disorders in the fetus can be understood as aberrations of the sequence of normal growth and developmental processes and are encompassed within a specific genetic program and diverse forms of disorders. We presented this group of children with complex clinical presentations. Although the unusual and the clear-cut clinical phenotype of these children were evident at birth as well as the very suggestive maternal and family histories. Sadly speaking, all these markers have been largely neglected by the pediatricians and neurologists. Unfortunately, despite the tremendous published studies pointing out the etiology of arthrogryposis, still a large number of article correlated the reason of arthrogryposis as is caused by lack of movement in utero [19]. In practice, lack of movement in utero is a relative causation and its occurrence might be either in connection with syndromic hypotonia, or hypertonia. For instance, fetuses with cerebral palsy have been described by mothers as being moving all the time (in fact it is a sliding fetal movement but not a normal physiological activity). In the literature amyoplasia or "classic arthrogryposis' 'have been misclassified with a misconception of being syndromes in children with camptodactyly, distal arthrogryposis, several symphalangism and popliteal syndromes [20].

Beals [21] described distal arthrogryposis type I as the most common type characterized by clenched hands with overlapping fingers, ulnar deviation, and club feet and the hips are affected. Obviously, he missed a sum of clinical signs of great clinical importance, which were supposed to be connected to build up either a recognizable or a novel type of syndromic association. Other previous studies stressed that distal arthrogryposis is a separate diagnostic entity and molecular genetics have been established accordingly [22, 23, 24]. Unfortunately, it speaks that not only distal arthrogryposis has been considered as a separate clinical diagnostic entity. Others took a similar approach, for instance Miller et al [26] discussed the genetic analysis of structural elastic fiber and collagen genes in familial adolescent idiopathic scoliosis [25]. Likewise, Bianco et al described what they called the exact contribution of PITX1 and TBX4 Genes in Clubfoot Development. The aforementioned studies are not the adequate to reach for the etiological understanding. Evidently, it is all aligned with segmental medicine (isolated deformities) and not with the fact that the human body is a composite of multisystem which are anatomically and physiologically interrelated-interconnected and can never be partitioned.

Toydemir et al [27], described Freeman-Sheldon syndrome and Sheldon-Hall syndrome as the first disorders in connection with distal arthrogryposis type II. Al Kaissi et al, [28] described, severe skew foot deformity associated with metatarsus adductus in a child with Freeman-Sheldon syndrome as an additional skeletal malformation stem from a constellation of malformation complex. and not as an isolated type II distal arthrogryposis Freeman-Sheldon [29] is a constellation of clinical and radiological phenotypic criteria and can never be restricted on segmental false basis in what's called distal arthrogryposis. Others, like Moore and Weaver [30] described five individuals from a multi-generational family study and described type I distal arthrogryposis and facial abnormalities in addition to a combination of craniofacial abnormalities. This misconception is of common practice. It reflects failure to categorize the disrupted anatomy of the foot malformation complex in connection with other minor or major clinical and radiological abnormal features in the same patient, which is immensely problematic. In other words, lack of knowledge in interpreting the detailed clinical and the anatomical malformations via radiographs of the foot made distal arthrogryposis as the easiest terminology chosen by the vast majority of clinicians.

5. Conclusion

We considered that arthrogryposis multiplex congenita is a symptom complex rather than a distinctive diagnostic entity until proven otherwise. Comprehensive clinical phenotypic and radiological characterization are the base line tools to initiate the diagnostic process in every single child with multiple malformations/deformities. The key factor for any form of presumed syndrome can only be considered when a detailed skeletal survey is planned. Skeletal survey should include, lateral skull radiograph, lateral and dynamic cervical spine to assess C1/2, AP spine and lateral lumbar radiographs. Therefore, the necessity for comprehensive clinical/radiological interpretations of minor or major malformations is the cornerstone in any successful clinical practice. My colleagues and I, our main objectivity was and still is the searching for aetiology understanding. We stress that the genotype can rarely explain the extent of skeletal malformation complex and or the natural history of the disease. Revising the PubMed, textbooks of congenital malformations, birth defects, skeletal dysplasia, heritable connective tissue disorders and so forth, clinicians can find

more than 311 syndromic entities in which arthrogryposis multiplex congenita is a symptom complex rather than a separate diagnostic entity.

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