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Research Article

Distinctive Skeletal Phenotype in Patients with Kniest Dysplasia

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Abstract

Background: A group of children presented with diverse forms of spine and joint pathologies in correlation with heritable bone disorders.

Patients and Methods: Five children aged from 9 -13 years, presented with a constellation of growth retardation, craniofacial dysmorphic features, axial (scoliotic short and barrel chested with marked diminution of spine biomechanics) and painful enlarged joints and sometimes with the propensity to develop mal-alignment (knock knees). We included a 38-years-old-lady, a mother of an affected boy because of her long term history of joint pain and intractable tinnitus. Clinical and radiographic phenotypic characterizations were the first line tools applied.

Results: The clinical and radiographic phenotypes of all five children were consistent with the diagnosis of Kniest dysplasia. Strikingly, the reason behind the tinnitus in the short statured 38-years-old- lady was due to congenital hypoplasia of the posterior arch of the atlas (the hypoplastic posterior arch of the atlas was in connection with the developmental failure of chondrogenesis). Two children underwent the genetic testing and showed a genetic defect of encoding type II collagen (*COL2A1*).

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Conclusion: Sadly speaking, soon after birth the vast majority of children born with skeletal dysplasia received the misdiagnosis of achondroplasia by their pediatricians and geneticists. In practice, a misdiagnosis can lead to hazardous repercussions for the affected children and their families. Correctly interpreting the clinical and the radiological phenotypes and relating them to etiologies is an essential basis for the proper management. In the field of hereditary bone disorders, the existence of mild and moderate forms of the same disease within other family subjects is a well-known fact (as seen in a 38-years-old- short statured- lady, a mother of an affected boy with Kniest dysplasia). To counter the overlooked maldevelopment of the atlanto-axial effectively, we need to delineate the disrupted anatomical structures of the craniocervical junction as early as possible. It is important to understand that many of these diseases are so mysterious and daunting that they frighten even some practitioners. Therefore, educating physicians is a priority.

Keywords

Kniest Dysplasia; Cervical Spine Abnormality; Lower Limbs Mal-Alignment, Radiology

Introduction

Kniest dysplasia is a type II collagenopathy characterized by delay in ossification of the proximal epiphyses and platyspondyly. When ossification takes place, the epiphyses are enlarged 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 might be prominent and there is often a cleft palate. Many infants will have respiratory problems in the neonatal period [1,2]. Mutation of this gene produces a heterogeneous family of type II collagenopathies. They include the lethal forms of achondrogenesis type of Kniest dysplasia, spondyloepiphyseal dysplasia congenita and spondylometaphyseal dysplasia, the moderate forms of Stickler syndrome and the mild form of late onset spondyloepiphyseal dysplasia with premature osteoarthritis [3-5]. There is certainly a lethal neonatal form that may represent the severe end of the clinical spectrum [3]. Other problems include myopia, which might lead to a detached retina, and sensorineural deafness. Diagnosis must be confirmed via clinical and radiological phenotypic characterizations. Radiographs show the characteristic picture of epiphyseal irregularities associated with broad metaphases. There is platyspondyly of the vertebrae and there is an additional ossification center at the distal end of the middle phalanx. Histologically there is a characteristic 'Swiss-cheese' appearance of the cartilage. Kyphoscoliosis develops in infancy and is resistant to treatment because of dysplastic backbones which resists attempts for interventions and surgical fusion. Angular deformities of the lower extremities are best treated by osteotomy in the ambulatory patient. Although

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recurrence of deformity is common in patients with skeletal dysplasias. Degradation of articular cartilage leads to severe arthritis in adolescence, with few patients able to walk. Type II collagen is the major fibrillar collagen of the hyaline cartilages, fibrocartilages, intervertebral discs, vitreous humor and inner ear [5,6]. Genu valgum (knock knees) is an inward slant of the thigh in which the knees are close together and the ankles are far apart. It can develop in connection with other forms of metabolic skeletal dysplasia such as Morquio's Syndrome (MPS type IV), multiple epiphyseal dysplasia, and hypophosphataemia. In these children not only the mechanics of gait are compromised but also, with significant angular deformity, associated with anterior and medial knee pain (these symptoms reflect the pathologic strain on the knee and its patello-femoral extensor mechanism). In general, knock knees is associated with more patello-femoral complications and its management is problematic for the orthopaedic surgeons than bowlegs.

Material and Methods

The study protocol was approved by 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. This study was conducted by the first author through his work at Orthopedic Hospital of Speising and his research partnership as a visiting Prof. to Ilizarov Scientific Research Institute (Kurgan) and Turner Institute (Saint Petersburg), Russia and department of pediatric orthopedics, children Hospital, Tunis. Five children (three boys and two girls) were referred to our department for clinical assessment and diagnosis. Our diagnostic process includes other family subject who manifested skeletal or extra-skeletal abnormalities. In this study, we included a short statured 38-years-old-lady, a mother of a boy with Kniest dysplasia because of her long history of tinnitus and joint pain. Two children were born via vaginal delivery at term and CS was applied for the rest of the deliveries. Their birth weight was ranging between 2600-3.200 g, length 44-46 cm (10th percentile), and head circumference 35-36 cm.

Results

Clinical phenotype was characteristic, all manifested a combination of facial dysmorphic features such as depressed nasal bridge, large nose, long philtrum, full cheeks, and a large mandible. Large ears and short neck sit directly on the trunk were evident. Their heights were below the third percentile, the cranium was large in comparison to their heights (70- 75th percentile). Short necks and trunks, thoracic kyphosis, lumbar lordosis associated with short-limbed dwarfism were uniform criteria. Their peripheral joints were progressively enlarged with subsequent development of progressive lower limbs mal-alignment. Painful joints

associated with tenderness was a characteristic feature in all patients. Their subsequent course of development has been of remarkable retardation because of limited joint mobility. At the age of four to six-years, all patients showed severe limping and limitations of joint mobility. The severity of mal-alignment in two children were assessed from the clinical and the radiographic measurements of the weight-bearing tibiofemoral angles, and from clinical measurements of the intermalleolar distance. Their skeletal age was determined using atlas of Greulich and Pyle (1959). Two children with genu valgum manifested less than 20° or an intermalleolar distance of less than 15° as moderate. Other clinical examinations showed, skin was neither hyperextensible nor bruised easily, signs of dystrophic scarring were not evident. Hearing and intelligence were normal. Echo-cardio Doppler was normal. All other investigations including thyroid, and parathyroid hormones were normal. Abdominal ultrasound, karyotyping and metabolic tests, which aimed to test calcium, phosphorus and vitamin D metabolism were normal.

Axial and appendicular skeletal examination showed greater restrictions in backbone movements with severe painful diminution of the spine biomechanics. In addition, mobility of both hips were severely restricted with prominent pain. All patients showed positive FABER Test which is a passive screening test for musculoskeletal pathologies of the lumbar, hip, S1 joint dysfunction and to identify iliopsoas spasm. FABER test stands for the assessment of Flexion, Abduction and External Rotation. The value of these three motions is to localize a clinical pain provocation test and to find pathologies at the hip, lumbar and sacroiliac region. Anterior and posterior impingement tests were positive and ROM (range of motion); right 75 degrees/left 105 degrees, extension right 15 degrees/left 20 degrees were elicited. In General, the radiographic phenotype is the clear cut to finalize the diagnostic process. In general, there is irregular epiphyses associated with broad dysplastic metaphyses especially around the knees. There is platyspondyly and coronal clefts of the vertebrae. Additional ossification center at the distal end of the middle phalanx. Histologically there is a characteristic 'Swiss-cheese' appearance of the cartilage. Open mouth radiograph of a 10-years-old boy showed hypoplasia of the odontoid process, spina bifida occulta of the upper cervical vertebrae and osteoporosis (Fig. 1). Lateral cervical spine of a 9-years-old girl with Kniest dysplasia showed exaggerated cervical lordosis, platyspondyly, and osteoporosis (Fig. 1). Axial CT scan of a 38-years-old lady showed aplasia of the posterior arch of the atlas in a mother of a 10-years-old- boy with Kniest dysplasia). She complained of tinnitus since her post-adulthood (Fig. 1). AP pelvis radiograph showed of a 9-years-old girl showed bilateral hip dislocation, significant epiphyseal dysplasia, and broad metaphyses (Fig. 2). AP pelvis radiograph of a 10-years-old-boy showed epi-metaphyseal dysplasia, shortness and dumbbell appearance of long bones due to splaying of metaphyses (Fig. 2). Coronal pelvis CT scan of a 9-years-old child with Kniest dysplasia showed significant retardation of epiphyseal ossification (Fig. 2). Lateral whole body radiograph of a 12-years-old-child with Kniest dysplasia showed massive lumbar lordosis associated with scoliotic short/compressed back bone and barrel chested phenotype (Fig. 3).

AP knee radiograph of a -12-year's old boy showed enlarged joints and severe genu valgum (knock knees). Note the scattered confluent areas of high density randomly distributed in the non-properly ossified epiphyses (cloud effect) (Fig. 3). Axial CT of the pelvis in a 13-years-old-girl showed irregular punctuate epiphyses of the acetabulo-femoral, note the irregularity of growth plate, cloud effect, flattened acetabulae and loss of normal trabecular pattern (Fig. 3). AP radiograph of a-10-years-old-child showed the massively compressed 5th lumbar vertebra (Fig. 4). Note the defects of the pars is evident, and the irregular margin of the 5th lumbar vertebra causing spondylolisthesis (Fig. 4). Lateral upper lumbar radiograph of a -9-years-old-boy with Kniest dysplasia showed platyspondyly and coronal clefts of the vertebrae (Fig. 4). The cytogenetic analysis of 23 Giemsa-stained metaphases as well as the investigation of 22 metaphases by FISH showed negative results. Kniest Dysplasia is a severe form of type 2 collagenopathies, it is an autosomal dominant disease caused by mutations in the collagen type II alpha-1 gene (*COL2A1*, OMIM 108300). *COL2A1* gene is mapped to chromosome 12q13.1-q13.2, comprises of 54 exons, and encodes a 1487-amino acid, a type II procollagen alpha-1 chain protein, the predominant protein in chondrocytes which is essential for functional collagen.

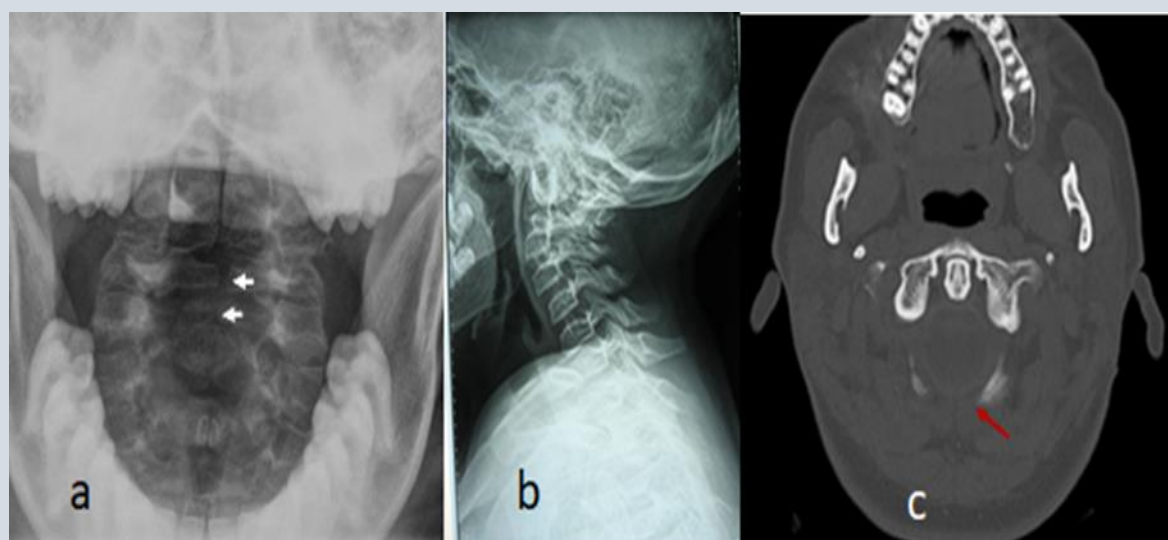


Figure 1: Open mouth radiograph of a 10-years-old boy showed hypoplasia of the odontoid process, spina bifida occulta of the upper cervical vertebrae and osteoporosis (arrows) (a). Lateral cervical spine of a 9-years-old girl with Kniest dysplasia showed exaggerated cervical lordosis, platyspondyly, and osteoporosis (b). Axial CT scan of a 38-years-old short-statured lady showed aplasia of the posterior arch of the atlas (red-arrow) in a mother of a 10-years-old- boy with Kniest dysplasia). She presented with short stature and a history of long term joint pain and intractable tinnitus since her post-adulthood (c).



Figure 2: AP pelvis radiograph showed of a 9-years-old girl showed bilateral hip dislocation, significant epiphyseal dysplasia, and broad metaphyses (a). AP pelvis radiograph of a 10-years-old-boy showed epi-metaphyseal dysplasia, shortness and dumbbell appearance of long bones due to splaying of metaphyses (b). Coronal pelvis CT scan of a 9-years-old child with Kniest dysplasia showed significant retardation of epiphyseal ossification (c).

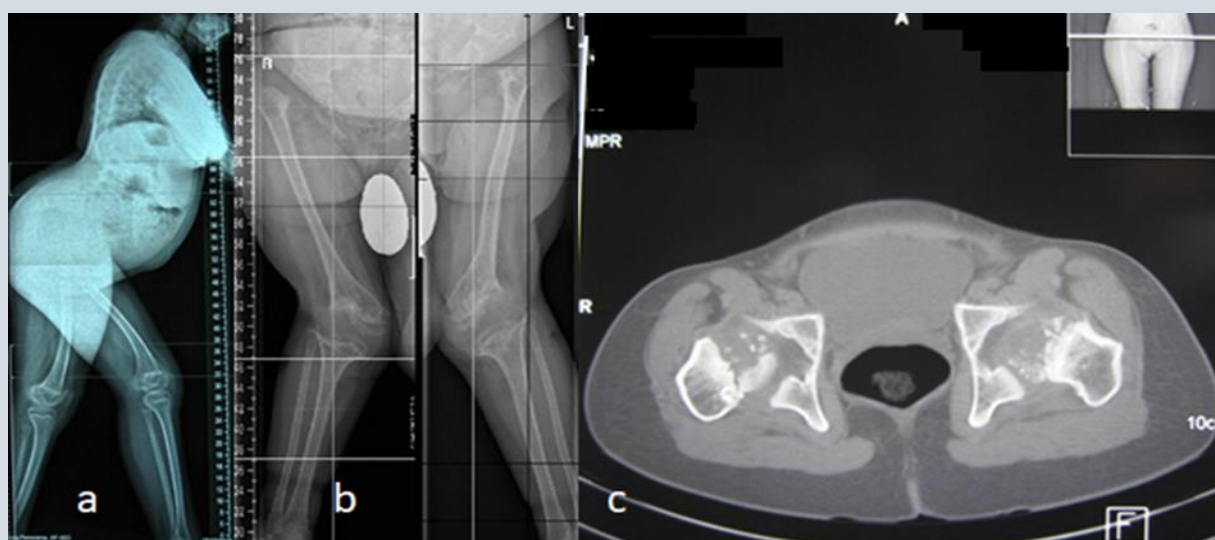


Figure 3: Lateral whole body radiograph of a-12-years-old-child with Kniest dysplasia showed massive lumbar lordosis associated with scoliotic short/compressed back bone and barrel chested phenotype (a).

AP knee radiograph showed of a 12-years old boy showed enlarged joints and severe genu valgum (knock knees). Note the scattered confluent areas of high density randomly distributed in the non-properly ossified epiphyses (cloud effect) (b). Axial CT of the pelvis in a 13-years-old girl showed irregular punctuate epiphyses of the acetabulo-femoral joint, note the

irregularity of growth plate, cloud effect, flattened acetabulae and loss of normal trabecular pattern.

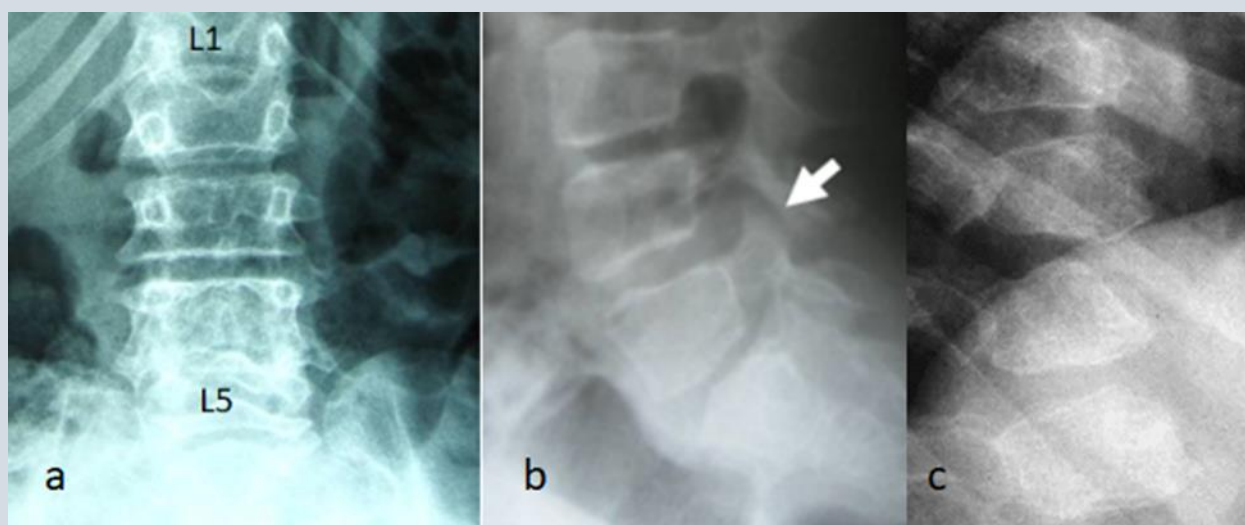


Figure 4: AP radiograph of a 13-years-old girl with Kniest dysplasia showed the massively compressed 5th lumbar vertebra (a). Note the defects of the pars inter-articularis is evident, and the irregular margin of the 5th lumbar vertebra causing spondylolisthesis (b). Lateral upper lumbar radiograph of a 9-years-old boy with Kniest dysplasia showed platyspondyly and coronal clefts of the vertebral bodies (c).

Discussion

Kniest dysplasia is a severe form of spondyloepiphyseal dysplasia with short trunk dwarfism, kyphoscoliosis, enlarged joints, midface hypoplasia, cleft palate, myopia, and deafness. Heterozygous mutations of *COL2A1* in Kniest dysplasia include a deletion of exon 12; partial skipping of exon 12; a point mutation in exon 12 resulting in the substitution of glycine 103 by aspartate, partial skipping of exons 21 and 49 and skipping of exon 24.

The partial or complete skipping of exons resulted from point mutations that altered the processing of the ribonucleic acid transcripts from the *COL2A1* gene [1-5]. Mutations in *COL2A1* gene are responsible for a spectrum of autosomal dominant skeletal dysplasias with variable phenotypic severity [9-11]. So far more than 500 mutations have been reported in public databases and literature (253 pathogenic variants, 160 likely pathogenic variants, 292 variants of uncertain significance and 75 conflicting interpretations).

In the literature, several missense changes have been reported (c.905C>T, p.Ala302Val; c.908G>A, p.Gly303Asp; c.980G>A, p.Gly327Asp; c.1366G>C, p.Gly456Arg; c.1375G>C,

p.Gly459Arg; c.3383G>T, p.Gly1128Val). The c.905C>T, p.Ala302Val change, which appears to be the commonest cause of Kniest dysplasia [12,13].

Winterpacht, et al., reported a further case of Kniest syndrome with a *COL2A1* mutation affecting a splice site in intron 20 [14]. The father had a mild form of spondyloepiphyseal dysplasia congenita with premature osteoarthritis and evidence was provided that he was a mosaic for the mutation. Wilkin, et al., emphasized that the most common mutation is an in-frame deletion in the *COL2A1* gene usually located between exons 12 and 24 [15]. Splice donor sites mutations usually results in exon skipping. The authors concluded that Kniest dysplasia results from a shorter type II collagen protein. Genu valgum is characterized by the typical pattern of circumduction, requiring that the individual swing each leg outward while walking in order to take up steps without striking the planted limb with the moving limb.

In children younger than 6 years, physiologic genu valgum is common but self-limiting and innocuous. In children with pathologic genu valgum, when the axis deviates into or beyond the lateral compartment of the knee, regardless of the etiology, a remarkable number of problems may ensue. Pathologic genu valgum warrants aggressive treatment to alleviate symptoms and prevent progression. Surgical intervention is the only successful intervention for correcting the deformity, this include osteotomy and hemiepiphysiodesis (growth manipulation) [16]. Hemiepiphysiodesis can be accomplished using the classic Phemister bone block technique, the percutaneous method, hemiphyseal stapling or the application of a single 2-hole plate and screws around the physis. Hemiepiphysiodesis may be planned either temporarily with staples/transphyseal screws or permanently via timed hemiepiphysiodesis. In skeletal dysplasias, the epiphyses are narrow and dysplastic, thereby, additional care is required to avoid penetration of the joint or the physis (in most the margins of the physes are indistinct). In addition, such patients are manifesting osteoporotic bones and staple extrusion is possible. The Taylor Spatial Frame (TSF) is a known tool for external ring fixation system developed for correction of axial, sagittal, planar and rotational deformities of the extremities. A specialized feature of the TSF is its virtual hinge, which allows for the simultaneous gradual correction of multiplanar deformities and limb lengthening through one osteotomy site. The power of the spatial frame lies in its precise control over the final limb length and alignment and its ability to correct a residual deformity. The stability of this multiplanar circular fixator permits early weight-bearing and provides an ideal environment for both new-bone formation and soft tissue healing [17].

Conclusion

We described a combination of skeletal abnormalities in children with Kniest dysplasia. All presented with the full phenotypic features of Kniest dysplasia. Dysmorphic facial features associated with axial and appendicular abnormalities have been elicited. The axial skeleton

showed generalized platyspondyly. Interestingly, all patients showed atlanto-axial instability, hypoplastic vertebral bodies associated with dysplastic pedicles. Noteworthy axial abnormalities in our current patients such as spina bifida occulta of the cervical spine, cervical spine hypoplasia (axial abnormalities and loss of the spine biomechanics causing exaggerated lumbar lordosis) associated with severe appendicular abnormalities of stiff ligaments and progressive lower limbs mal-alignment, were overwhelmed by limited joint mobility, large and painful joints. Nevertheless, and on the basis of our current findings in these patients and with our previous experiences in patients with skeletal dysplasia, we might postulate that the development of progressive/persistent genu valgum in this child was sequelae of poor anatomical arrangements at the metaphyseal junction.

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We wish to thank the collaboration of the families and the guardians of the patients.

Informed Consent Statement

A signed consent form was obtained from the patient's Guardians.

Authors' Contributions

AAK conceptualization and methodology; software, VK and SB; validation, AAK, VK and SR; formal analysis, AKK, SR, FG, SB; investigation, MS, SGK; data curation, AKK, VK, FG; writing original draft preparation, AKK; writing review and editing FG; visualization, AKK; supervision AKK.

Conflict of Interest

All the authors declare no conflict of interest regarding any aspect of the manuscript.

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