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Research Article

Chronic Knee Pain is the Paramount Presentation in Patients with Nail-Patella Syndrome

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Abstract

Background: Arthralgia in connection with patellar instability have been studied thoroughly in a number of pediatric and adult patients. Small and dysplastic patellae accompanied by hypoplasia of the lateral femoral condyle may results in recurrent subluxation or dislocation of the patellae, knee discomfort and pain. We aimed to detect the underlying etiology of every single patient.

Patients and Methods: A total of seven children presented with long term painful knee joints have been refered from the departments of rheumatology. We added adult female patient of a-35-years-old. She was a chronic client of rheumatology clinics since her postadulthood. In addition to her early life knee pain. Recently she experienced additional chronic pain of the groin (located at the posterior buttocks). All our patients showed episodes of knee pain with variable intensity as a constant complaint and all received antirheumatic treatments for years despite the negative results of the implemented tests. In order to commence the diagnostic process, clinical and radiological phenotypic characterization were the main core of our stratregy followed by molecular genetic confirmation.

Results: Seven unrelated children (aged from 8-17 years old) were consistent with the diagnosis of Nail- Patella syndrome. The adult female patient of a-35-years-old- manifested patellar instability since her early childhood. Her clinical phenotype was totally compatible with the diagnosis of Nail-Patella syndrome. Surprisingly, the clinical examination of the female patient and the standing AP pelvis radiograph revealed massive encroachment of the medial aspect of the femoral neck and the lesser trochanters onto the ischium. The latter resulted in the diagnosis of Ischiofemoral Impingement (IFI) syndrome. Her genetic tests showed heterozygous mutation in the LIM-homeodomain protein LMX1B on chromosome 9q33.

Conclusion: Arthralgia associated with abnormal gait (mostly antalgic gait and waddling gait) was the paramount clinical presentation in all our patients. Dysplasia of the nails and patellar instability were the characteristic clinical findings in our patients with the definite diagnosis of osteo-onychodysplasia syndrome. We approached to the diagnosis from the first session of clinical examination. Interestingly, the constant groin pain in the adult female patient which has been totally overlooked by other instutions, were in favor of the diagnosis of Ischiofemoral Impingement (IFI) syndrome. As well as the existing abnormality of the elbows associated with defective pronation and supination as due to impingement of the olecranon. The task of establishing the diagnostic process in complex clinical conditions is the most challenging. Sadly speaking, none of the aforemnetioned dignostic criteria attracted the attention of dozens of clinicians. Admistering medications to overcome knee pain through dozens of useless laboratory tests were the main false issue. Clinicians who are actively involved in clinical diagnosis with minimal dependency on laboratory aid are generally at the forefront of their medical fields.

Keywords: Arthralgia, Patellar instability, Impingements Syndromes, Nail-Patella syndrome, Radiology

Introduction

Repetitive patellar instability is the outcome of either secondary to osteogenic abnormalities, such as patella alta, dysplastic patella and trochlear dysplasia, or it can result from soft tissue abnormalities such as a traumatic medial patellofemoral ligament or myogenic as weakened vastus medialis obliquus or neurogenic as in cerebral palsy. Knee pain is one of the most common presentations in orthopedics. There is a long list of possible differential diagnoses, including femoral trochlear dysplasia (in which the disruptive anatomical geometry of the shape and depth of the trochlear groove mainly in connection with absent or dysplastic patella). This may lead to patellar instability, which in turn results in intractable knee pain [1-3]. Patients with symptomatic patellar instability will have either objective patellar instability (true atraumatic dislocation with an anatomical abnormality) or in connection with genetics, presented as potential patellar instability (pain, catching or locking of the patellofemoral joint and inability to rehabilitate quadriceps with an anatomical abnormality) [4].

Nail-Patella syndrome /osteo-onychodysplasia syndrome is a condition characterized by dysplasia affects the nails, the skeleton and nephropathy. Turner noted that in addition to a triad of congenital anomalies of the finger nails, elbows and knees, some subjects showed flaring of the iliac crests [5]. Thompson, et al., described the radiographic phenotype accompanied with other abnormalities of the nails, knees and elbows [6]. The nails are abnormal from birth and are either absent or small and longitudinally ridged. Nails on the radial side of the hand are proved to be more severely affected, so that the 4th and 5th finger nails may be relatively normal. Triangular lunules at the base of the nails are shown to be particularly characteristic. Absent distal finger creases are also frequent. Skeletal abnormalities include talipes equinovarus and other joint contractures, posterior iliac horns, a malformed capitellum of the radius, Madelung deformity and absent or hypoplastic patellae are associated deformities. Nail-Patella Syndrome (NPS) is caused by heterozygous mutation in the LIM-homeodomain protein LMX1B on chromosome 9q33. Dreyer, et al., demonstrated mutations in the LMX1B gene. Molecular studies of LMX1B , in connection with genetic and immunohistochemical investigation of different alpha chains of type IV collagen in the LMX1B null mice kidney, a mouse model for NPS, confirmed the correlation of LMX1B mutation in the pathogenesis of Nail-Patella syndrome glomerulopathy [7-10]. Nephropathy with proteinuria as a known hazardous complication in patients with Nail-patella syndrome has been described in about 10 percent of patients [11-13].

Previous studies described Ischiofemoral Impingement (IFI) as a distinctive syndromic entity correlated to impingement of the ischium and femur. Trauma or previous hip surgeries have been blamed as the etiological background [14]. In our current study, the clinical history of groin pain in a female adult patient with Nail-Patella syndrome as well as the clinical examination and the standing AP pelvis radiograph were in favor of the highly likely diagnosis of Ischiofemoral Impingement (IFI). The encroachment of the medial aspect of the femoral neck and the lesser trochnaters onto the ischium was a notable diagnostic criteria. It speaks that the pre-existing abnormality of pronation and supination in this patient which is connected to impingement of the olecranon and it could be related to the pathological mechanism and the etiology understanding of (IFI).

Materials 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. Seven patients (five children and two adults) have been enrolled in this study. We fully documented these children through detailed clinical and radiological phenotypic characterizations at the clinics of spinal pathology and rare diseases in orthopaedic Hospital of Speising (Pediatric department) and through the scientific collaboration of the first author with Ilizarov Center, Kurgan, Russia.

At the rheumatology clinics, all patients were primarily treated as patients due to rheumatologic background. All underwent several useless, sophisticated and expensive investigations. Three children received the wrong diagnosis of Juvenile Rheumatoid Arthritis (JRA). Exhaustive and coastly investigations have been carried out to confirm the diagnosis of (JRA), at the end of the day all rheumatic investigations were negative and the antirheumatic treatments were of no effect. These patients (children and adults) were referred to our departments because of progressive orthopaedic problems such as difficult pronation and supination, scoliosis and abnormal gait. Interestingly, none of the patients showed any trace of abnormal inflammatory markers. Clinically, they did not manifest any sort of skin stigmata, lymphadenopathy and or sacro-iliitis. A series of long lists of laboratory investigations were undertaken in other institutes and have been repeated several times and included ESR, CRP, RF,

ANA and HLA-B27, finally all were within the normal limits.

The differential diagnosis of arthralgia encompassed a long list of osteogenic, myogenic, neurogenic and a miscellaneous of abnormalities. We clinically documented our patients in accordance with our strategy of clinical and radiological phenotypic characterizations. All our patients underwent ophthalmological and neurological examinations to check any associated visual pathology and or neurological deficits.

The clinical presentations of Nail-Patella syndrome and the accompanied arthralgia in our group of patients were variable in intensity and depends heavily on the severity of the syndrome. The symptoms which have been encountered in these patients were diverse. In this study we focused on the skeletal manifestations as analyzed via conventional and tomographic studies. The patellar instability in our patients were mainly correlated to different grades ranging between absent patellae to patellar dysplasia.

Results

All our patients underwent ophthalmological and neurological examinations to check any associated visual pathology or neurological deficits. We fully documented these children through detailed clinical and radiological phenotypic characterizations at the clinics of spinal pathology and the Osteogenetische Ambulanz in Orthopaedic Hospital of Speising (Pediatric department) and through the scientific collaboration of the first author with Ilizarov Center, Kurgan, Russia.

The clinical presentations of Nail-Patella syndrome in our group of patients were variable and depends heavily on the severity of the syndrome. The symptoms which have been encountered in these patients were diverse. In this study we focused on the skeletal manifestations as analyzed via conventional and tomographic studies. The patellar instability in our patients were mainly correlated to different grades ranging between absent patellae to dysplasia.

All patients manifested short stature (-2 SD to -3 SD), craniofacial dysmorphic features (widow´s peak, high frontal hairline, frontal bossing, ptosis of the eyelids and high vault palatine were characteristic features with variable gait abnormalities and all showed difficulties in pronation and supination. The nails as described by the parents of being abnormal since birth. We noticed that nails on the radial side of the hand are severely dysplastic. But nevertheless, the nails of the fourth and fifth digits showed less marked abnormality (near normal). All patients showed hypotonic quadriceps and dysplastic tendons of the rectus femoris muscles associated with patellar instability. 3D sagittal CT scan of the knee of a-17-years-old-boy presented with antalgic gait. Nail-Patella syndrome in this patient showed a noticeable painful flexion deformity of the knee associated with hypoplastic/fragmented and a dislocated patella on top of long term knee deformity and osteoporosis (Fig. 1). The skyline view-follow up of the same patient at the age of 22 years showed progressive severe dysplasia and subluxation of the patellae associated with aplasia of the trochlear groove (Fig. 1). Another patient of a -14-years -old-boy presented with waddling and painful gait. Apparent patellar instability associated with painful flexion deformity of the knees were evident. Painful bouts of patellae instability was the prevailing long term symptomatology. Clinical examination showed short stature, mild dysmorphic facial features. He manifested the pathological features of nail hypoplasia, roughening and spooning, these features were most apparent on the radial side. Lateral knee radiograph at the age of a 14-years-old boy showed small and dysplastic rounded patella (Fig. 2). Another child of a-10-years-old- presented with antalgic gait and fulfilled the full blown picture of NPS. 3D axial CT scan of a-10-years-old-boy showed a fragmented and irregular trochlear dysplasia (Fig. 2). An 8-years-old-boy presented with waddling gait associated with flexion deformity of the knees. Lateral knees radiograph in this 8-years-old boy showed biateral and symmetrical absent patellae (Fig. 3). A follow-up via 3D axial CT scan of another patient with Nail-Patella syndrome of a 13-years-old-boy showed a rudimentary dysplastic patella but almost a rounded dysplastic type and irregular and dysplastic trochlea, note the maltracking and the notable instablilty of the dysplastic patella (Fig. 3).

A-35-years-old female patient was a chronic client at the rheumatology clinics since her post-adulthood period. She appeared in our department because of severe groin pain more marked with walking in addition to difficulties in pronation and supination. The diagnosis of Nail-patella syndrome was fulfilled. She presented with short stature -2SD and manifested less pronounced facial features of NPS. She underwent ophthalmologic examination, to rule out any associated vision pathology such as glaucoma. Investigations for proteinuria revealed mild proteinuria via a 24-hour urine collection, slightly more than 150

milligrams per day, though the patient is asymptomatic (other blood biochemistry parameters such as uric acid, urea and creatinine were within normal limits). Strikingly Hypoplasia of the patellae and apparent iliac horns (bilateral flaring of the iliac wings) were apperant. Bilateral inability to extend the elbows and difficulties in pronation and supination (impingement of the olecranon). Because of groin pain, we performed impingement test, which showed pain especially amid adduction in extension and no pain when extension with abduction was implemented. Her genetic tests were consistent with heterozygous mutation in the LIM-homeodomain protein LMX1B on chromosome 9q33. Radiographic examination was organized for this lady. AP standing pelvis radiograph showed coxa valga, apparent iliac horns (bilateral flaring of the iliac wings-arrows). The Neck-Shaft Angle (NSA) in this patient appears beyond 134.4°. A-35-years-old female patient with a history of arthralgia (knee and groin pain) since postadulthood. AP standing pelvis radiograph showed coxa valga, apparent iliac horns (bilateral flaring of the iliac wings-arrows). Apparent massive encroachment of the medial aspect of the neck femur and the lesser trochanters onto the ischium leads to narrowing of the ischiofemoral and quadratus femoris space with a clinical and radiological diagnosis of ischio-femoral impingement syndrome. Note the zero distance between the ischium and the lesser trochanter causing massive and evident impingement, in addition there was a notable hypertrophy of the lesser trochanters (arrow heads). Lateral knee radiograph showed dysplastic and a dislocated patella. AP radiograph of the elbow showed impingement of the olecranon with subsequent development of difficulties in pronation and supination (Fig. 4).

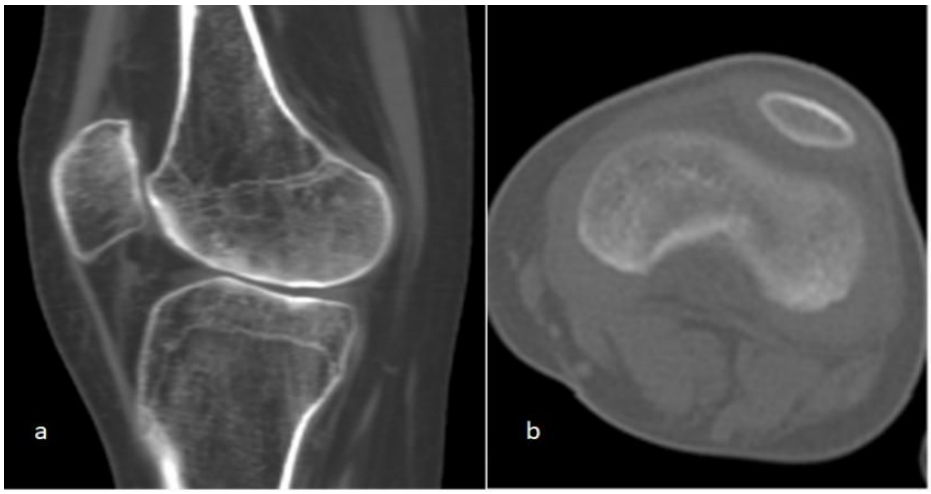

Figure 1: 3D sagittal CT scan of the knee of a-17-years-old-boy with nail patella syndrome showed mild and painful flexion deformity of the knee associated with hypoplastic/fragmented and a dislocated patella on top of long term knee deformity and osteoporosis (a). The skyline view of the same patient at the age of 22 years showed progressive severe dysplasia and subluxation of the patellae associated with aplasia of the trochlear groove (b).

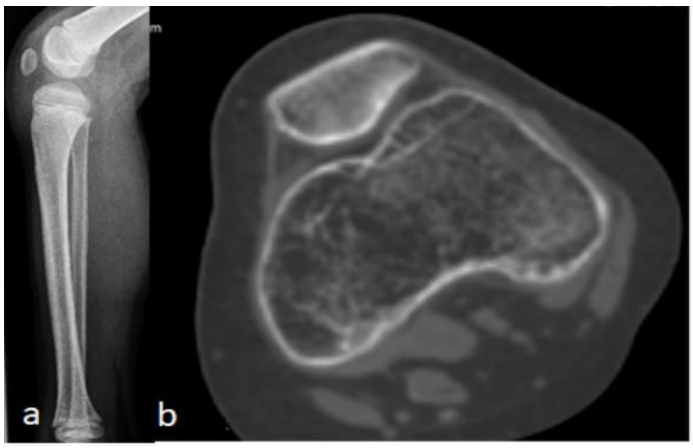

Figure 2: Lateral knee radiograph in a 14-years-old boy showed small and dysplastic rounded patella (a). 3D axial CT scan of a-10-years-old-boy (different patient) showed a fragmented and irregular trochlear dysplasia (b).

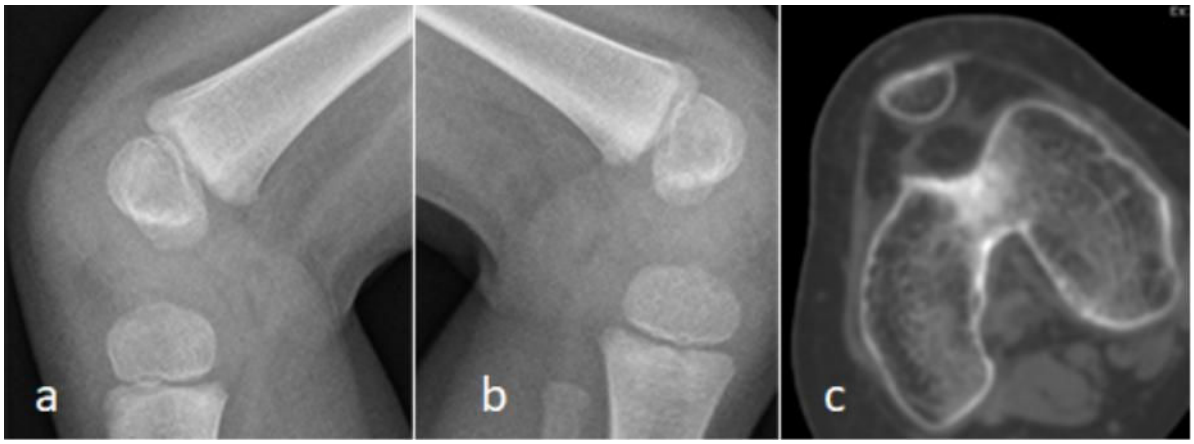

Figure 3: Lateral knees radiograph in an 8-years-old boy showed biateral and symmetrical absent patellae (a,b). 3D axial CT scan of another patient with Nail-Patella syndrome of a-13-years-old-boy showed a rudimentary dysplastic patella but almost a rounded dysplastic type and irregular and dysplastic trochlea, note the maltracking of the instable and dysplastic patella (c).

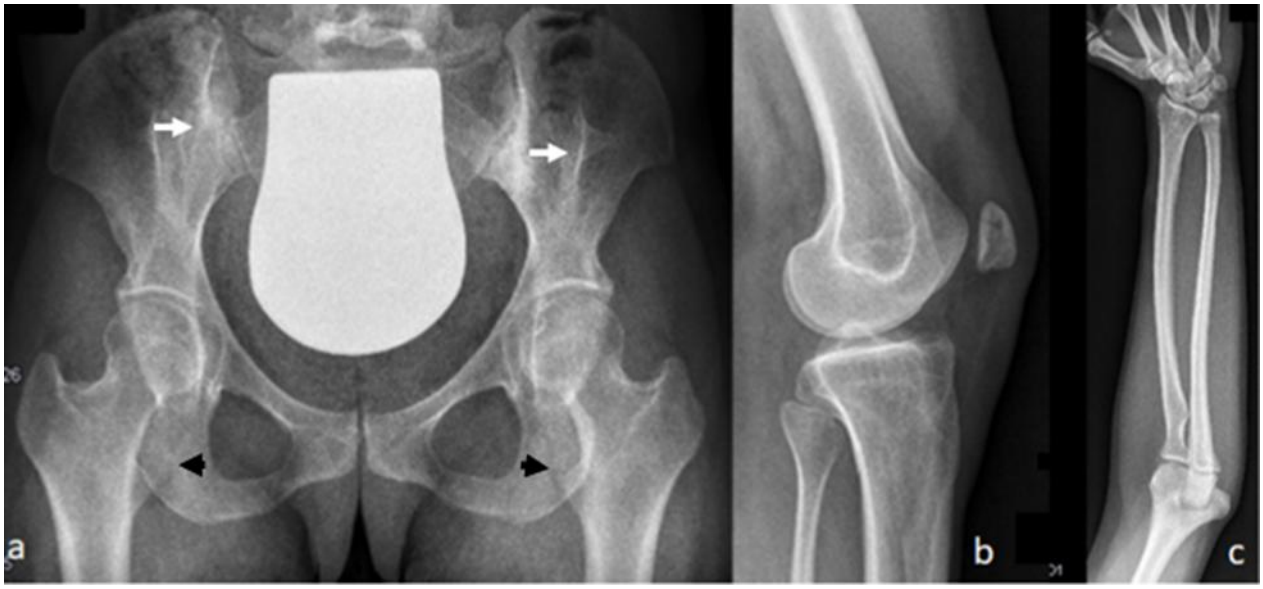

Figure 4: A-35-years-old female patient with a history of arthralgia (knee and groin pain) since post adulthood. AP standing pelvis radiograph showed coxa valga, apparent iliac horns (bilateral flaring of the iliac wings-arrows). The Neck-Shaft Angle (NSA) in this patient appears beyond 134.4°. Apparent massive encrouchment of the medial aspect of the neck femur and the lesser trochanters onto the ischium (black arrow heads) leads to narrowing of the ischiofemoral and quadratus femoris space with a clinical and radiological diagnosis of ischio-femoral impingement syndrome (a). Note the zero distance between the ischium and the lesser trochanters causing massive and evident impingement, in addition there was a notable hypertrophy of the lesser trochanters (arrow heads). Lateral knee radiograph showed dysplastic and a dislocated patella (b). AP radiograph of the elbow showed impingement of the olecranon with subsequent development of difficulties in pronation and supination (c).

Discussion

Trochlear dysplasia is an abnormality of the shape and depth of the trochlear groove mainly in its proximal extent. This was defined radiologically by Dejour, et al., on the basis of the crossing sign (croisement) [2]. If the line of the trochlear floor crosses the anterior border of one or both condyles, the trochlea is said to be flat at that level. Trochlear dysplasia was further classified by Dejour and Locatelli and Tavernier and Dejour [3,5].

Nail Patella Syndrome (NPS) is a unique syndromic entity characterized by abnormal nails from birth and are either absent or small and longitudinally ridged. Skeletal abnormalities include talipes equinovarus and other joint contractures, posterior iliac

horns, a malformed capitellum of the radius, Madelung's deformity and absent or hypoplastic patellae [6-9].

The differential diagnosis of patellar dysplasia encompassed a long list of osteogenic, myogenic, neurogenic and a miscellaneous of abnormalities. We subdivided our patients in accordance with the finalization of the diagnostic process.

We totally excluded other patients with different syndromes in which absent nail or nail dyplasia is a major feature. Patients with anonychia congenita, hypohidrotic ectodermal dysplasia syndrome of alopecia, onychodysplasia, hypohidrosis, hyperkeratosis, deafness and other abnormalities as well as children with Brachymorphism-onychodysplasia-dysphalangism syndrome [15,16]. Similarly we excluded all patients who presented with patellar instability/dysplastic patellae as a symptom complex in connection with other syndromic entities with flexion deformities of the knees and are within the false diagnosis of arthrogryposis multiplex (in which children manifest a constellation of skeletal abnormalities (a combination of skeletal abnormalities are evident such as dislocated hips and contractures involving the knees, elbows and shoulder joints) [17]. Children with Stickler syndrome type I, who are presented with ligamentous hyperlaxity and patellar instability as one of the main features. Children with this group of syndromic entity have been totally excluded [18]. Other forms of malformative syndromes like Coffin-Siris syndrome, Brachymorphism-onychodysplasia-dysphalangism and Rubinstein-Taybi syndrome) have been excluded as well.

Ischiofemoral Impingement Syndrome (IFI) is one of the etiologies in patients with groin pain. The main issue in IFI is the anatomical configuration and structure of the proximal femur and the pelvis. Several anatomical factors are involved such as, the femoral neck-shaft angle, the lesser trochanters the ischium angle and spacing. In addition the other myogenic indices which are directly related to the bone pathology is the quadratus femoris muscle and the hamstring tendons [19-21].

The first study of IFI was published by Johnson as he described the dramatic relieve of groin pain in his patients after the resection of the lesser trochanters. The latter was followed by several studies defining the pelvis phenotype in association of a painful disorder of the hip in connection with ischium tuberosity and the narrowing space of the femoral lesser trochanters, which leads to impingement of the quadratus femoris muscle [22].

Conclusion

The overall clinical and radiological phenotypic characteristics in our group of patients with nail patella syndrome have been thoroughly studied via clinical phenotype and radiographic and 3 DCT scan. Not only for the purpose of diagnosis but for follow ups. The tomographic follow ups aimed to assess the prognostication and the fate of the patellae. I have been very cautious in my clinical work when it comes to calling a disease rare or orphan disease. As in practice this denomination, can only denote severe and immediately recognizable syndromes (which are in fact rare), but the mild and moderate types are much more frequent and the latter and the former must not be confused. Rare disease manifests mostly soon after birth. Whereas the mild and moderate forms manifest later in life. Physicians frequently fall into the pitfall of using the term 'rare' or idiopathic with little acknowledgement to the more frequent moderate types. In fact, the mild and the moderate types of genetic disorders pose the realest threat in orthopaedic practices and in other medical disciplines, as the gene hides itself for a decade or more only to trigger health problems that manifest later in life. As such, the pathologic clinical picture will remain partial and the diagnosis and management will naturally be flawed. The major part of our work as a team is focused around one basic rule that every skeletal deformity /abnormality must have an underlying etiology that needs to be thoroughly studied and explored. This comes from the conviction that the vast majority of patients with skeletal deformities - if not all- do not occur randomly.

Conflict of Interest

The authors have no conflict of interest to declare.

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