Case Report

Progressive Deformity of the Lower Limbs in a Patient with KID (Keratitis-Ichthyosis-Deafness) Syndrome

Oleg Kozhevnikov,1 Svetlana Kralina,1 Yulia Yurasova,1,2 Vladimir Kenis,3 Susanne Gerit Kircher,4 and Ali Al Kaissi5,6

1Orthopedic Children’s Department, Central Research Institute of Traumatology and Orthopedics n.a. N.N.Priorov, Moscow, Russia
2Department of Hospital Pediatrics No. Two of Russian National Research Medical University, Moscow, Russia
3Department of Foot and Ankle Surgery, Neuroorthopaedics and Systemic Disorders, Pediatric Orthopedic Institute n.a. H.Turner, Saint Petersburg, Russia
4Department of Medical Chemistry, Medical University of Vienna, Vienna 1090, Austria
5Ludwig Boltzmann Institute of Osteology at Hanusch Hospital of OEGK and AUVA Trauma Centre Meidling, 1st Med. Dept. Hanusch Hospital, Vienna, Austria
6Paediatric Department, Orthopaedic Hospital of Speising, Vienna, Austria

Correspondence should be addressed to Ali Al Kaissi; ali.alkaissi@oss.at

Received 5 March 2020; Revised 23 June 2020; Accepted 29 June 2020; Published 11 July 2020

Academic Editor: Paul E. Di Cesare

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Purpose. Progressive deformity of the lower limbs can be encountered in a long list of syndromic associations. The baseline tool in the management of such disorders is to approach to a definite diagnosis. Methods. We describe a 4-year-old girl who presented with the clinical phenotype and genotype of congenital erythrokeratoderma, keratosis, and sensorineural hearing loss (keratitis-ichthyosis-deafness syndrome) (KID syndrome). She manifested progressive contractures of the knees associated with talipes equinovarus of the feet. The latter deformities were the main reasons behind her severe retardation in acquiring the normal locomotor functions. Results. The analysis revealed mutations in intron 1 of the GJB2 gene of C.32G>A (p.Gly11Glu) and c.35delG in the compound heterozygous state. The presence in the genotype of the “dominant” mutation c.32G>A (p.Glu11Glu) was compatible with the clinical phenotype of KID syndrome. Conclusion. Surgical interventions through the extension of the hamstring tendons have been performed successfully via the application of an external distraction apparatus, namely, Volkov-Oganesyan. The latter procedures resulted in total release of her awkward knee contractures. Eventually, the child was able to regain the physiological alignment of her lower limbs and resume walking. To the best of our knowledge, the overall management of this child could be the first in the literature.

1. Introduction

Keratitis-ichthyosis-deafness (KID) syndrome is a rare form of ectodermal dysplasia caused by certain mutations in the GJB2 gene (connexin 26 gene) with characteristic lesions of the skin, hair, and hearing. For the first time, generalized congenital erythrokeratoderma was described by Burns in 1915 [1]. Skinner et al. in 1981 gave the name of the syndrome—keratitis-ichthyosis-deafness (KID) syndrome [2]. Congenital erythrokeratoderma, keratosis, and sensorineural hearing loss are the essence of the diagnosis. The skin is characterized by congenital erythrokeratoderma, which involves the cheeks; nose; chin; ears; limbs, especially the extensor and flexor surfaces of the elbows and joint areas of the knees, hands, and feet; and the buttocks. In some cases, scalp involvement results in partial or complete alopecia. The nails are frequently thickened and dystrophic. The palmar and plantar areas usually show hyperkeratosis characterized by a stippled or dotted pattern [3–5]. The nails are variably affected, and the hair is scanty and brittle. Hair histology might resemble that seen in trichothiodystrophy with bright and dark bands. Sweating is usually decreased.
The deafness is congenital and of a sensorineural type, and a vascularized keratitis develops which is always preceded by photophobia. Many patients have a troublesome tendency to develop candida infections, supposedly because of an immune deficiency [6].

Mutations in the gene GJB6 (Cx30) also implicated in the Clouston syndrome have been found in KID with congenital atrichia [7], though Clouston syndrome is composed of a different clinical phenotype (of a hidrotic ectodermal dysplasia) characterized by fine, depigmented hair which is sparse on the head, eyebrows, and body. In addition, the nails are dystrophic, and there is often dyskeratotic skin on the palms and soles, which cracks easily and is rough to the touch. The skin over the knuckles, elbows, knees, axillae, and pubic areas shows hyperpigmentation and looks clinically like acanthosis nigricans. An X-ray of the skull might show thickening of the whole body, alopecia totalis, and no eyebrows and eyelashes. Extensive palmoplantar hyperkeratosis and hypoplastic nails are additional prominent features.

Distraction test via her mother’s voice was positive. Musculoskeletal examination showed fixed flexion contracture of the knees. At this stage, the child was unable to extend the knees and she could only crawl (Figures 1(a) and 1(b)). We assessed the flexion deformity of the knees through studying the active and passive range of the hip, knee, ankle, and foot, in order to determine at which point the spastic muscles grab. The patient had a difficulty sitting on the floor with the knees in extension. She has to flex her knees to diminish the pull of the hamstrings on the ischium and pelvis. In patients with moderate hamstring contracture, when they sit, their lumbar spines assume a kyphotic posture. Our current patient manifested severe contracture of the hamstring; she tends to slide down the chair and has to be strapped down with the knees in flexion.

On the bases of skeletal survey, AP pelvis radiograph showed coxa valga associated with defective ossification of os pubis. Lateral knee radiograph showed fixed flexion deformity of the knee associated with small patella, and the foot showed equinus deformity.

2.1. Molecular Genetics. DNA was studied to search for mutations in the gene GJB2 encoding the protein connexin 26. The whole coding region of the GJB2 gene (exon 2) was sequenced by PDRF analysis of splicing site mutation c.-23+1G>A (IVS1+1G>A) in intron 1 of the GJB2 gene. The analysis revealed mutations of c.32G>A (p.Gly11Glu) and c.35delG in the compound heterozygous state.

In this study, we identified GJB2-associated hearing loss with palmoplantar keratoderma caused by compound heterozygous autosomal dominant c.32G>A (p.G11E) and autosomal recessive GJB2 gene c.35delG (p.Gly12Valfs*2) mutations. The combination of autosomal dominant syndromic hearing loss GJB2 mutation with an autosomal recessive nonsyndromic hearing loss GJB2 mutation is quite rare and limited in number of reports to date.

The c.35delG is the most frequently recessively inherited mutation reported in nonsyndromic hearing loss, which is predicted to result in loss of functional Cx26 due to frameshift and premature termination codon at the early part of the protein. The development of the epidermis is not affected in the case of homozygous c.35delG patients.

The autosomal dominant inherited from GJB2 mutations associated with hearing loss has been reported in both nonsyndromic and syndromic hearing loss patients.

The heterozygous c.32G>A mutation has been reported before in a Caucasian patient with KID syndrome (DOI: 10.1016/j.jbrc.2010.03.098).

There is no family history of hearing loss, suggesting either the low penetrance of this mutation or it being a de novo mutation only present in the affected child. Therefore, the combination of the 2 identified mutations leads to a
severe phenotype when they are found in affected individuals as seen in our patient.

The constellation of the clinical features in our patient and the presence in the genotype of the “dominant” mutation c.32G>A (p.Gly11Glu) which leads to KID syndrome are totally compatible with the clinical phenotype of “keratitis-hearing loss-ichthyosis syndrome.”

3. Treatment

Conservative measures to treat the knee contractures were the first applied, which consisted of prone posturing with the hips and knees in extension and gentle passive manual elongation of the hamstrings to prevent permanent shortening. Active exercises to increase the motor strength of the quadriceps and the use of a night cast that holds the knee in extension and the ankle at neutral position have been tried. Crawling was not allowed, and other modalities of locomotion were offered.

Knee extension was assessed with the foot dorsiflexed and plantar flexed to estimate the contribution made by the gastrocnemius and with the hip abducted and adducted to assess the part being played by the gracilis. Most common muscles that are likely to be tight are the semitendinosus, gracilis, and biceps. When the quadriceps is strong, and flexion deformity is not greater than 40°, hamstring release is usually sufficient to provide correction and to restore muscle balance.

Unfortunately, the response to the aforementioned procedures was not convincing enough to rely on. Therefore, we referred to a Volkov-Oganesyan apparatus, as it is specially organized for the correction of knee contractures (Figure 2). In the apparatus, there is a special ellipsoid hinge, which, simultaneously with the extension of the tibia, slightly shifts the anterior articular surface of the tibia, thereby preventing the formation of a posterior subluxation. When using the device, it was important to align the knee joints with the center of rotation of the knee. On the 5th day after the operation, gradual correction of contracture began, 5-8° degrees per day has been achieved. The full extension of the knee was satisfactory after 14 days (Figures 3(a) and 3(b)). Afterwards, a stabilization period was carried out in the apparatus. The second stage of surgical treatment was the removal of the frame from the lower limb and subcutaneous extension of the Achilles, with correction of foot deformation. Fixation in a cast lasted for 2 months, followed by the application of the knee-ankle-foot orthoses. After 6 months, a similar intervention was carried out on the opposite lower limb by the same applied methodology.

Orthopedic procedures were complicated because of secondary infections associated with skin problems due to the pathological nature of the skin in KID syndrome patients. The result of treatment, after 1 year from the beginning, showed dramatic improvement and total control over infections. The child regained her locomotor capability through standing and walking. She started to walk with the support of the hand with the fixation of the lower extremities in the knee-ankle-foot orthoses. The mobility of the knee joints approached to somehow convincing results. Full extension, feet in the middle position, and with support of the entire plantar surface of the feet have been approached successfully (Figure 4). Currently, rehabilitation to enhance movements along the knees and ankle joints has been carried out. We recommended avoidance of increasing the flexion of the knee joint more than 90° and to continue the constant long-term wearing of orthoses to ensure the prevention of possible recurrence of contractures during the growth of the child.

4. Discussion

Keratitis-ichthyosis-deafness (KID) syndrome is characterized by congenital ichthyosis, but nevertheless, during the first weeks of life, there might be widespread erythroderma with desquamation. This is followed by the development of hyperkeratotic plaques, often localized on the face and limbs. Plantar and palmar hyperkeratosis is almost invariable, and it has a stippled and dotted pattern. The nails are variably
affected and the hair is scanty and brittle. Hair histology might resemble that seen in trichothiodystrophy with bright and dark bands [1, 2, 6].

Previous studies described a broad spectrum of associated anomalies/deformities in patients with KID syndrome. Senter et al. [12] described a 13-year-old boy with atypical ichthyosiform erythroderma associated with congenital sensory-neural deafness. The parents were first cousins. There were no corneal abnormalities. Clouston [8] demonstrated mutations in the connexin 26 (GJB2) gene. Van Geel et al. [17] described another syndrome, called hystrix-like ichthyosis-deafness (HID) syndrome through specific missense mutation in connexin 26 (GJB2), which strongly resembles the KID syndrome. They assumed that HID and KID disorders are distinguished mainly on the basis of electron microscopic findings and hypothesized that KID and HID syndromes may be genetically related.

Montgomery et al. [18] described a congenitally deaf white male with mild palmoplantar keratoderma, ichthyosiform scaling, follicular hyperkeratosis, and mild keratitis, features consistent with keratitis-ichthyosis-deafness syndrome. But the patient’s major problem was severe, disfiguring, inflammatory dissecting folliculitis of the scalp, hidradenitis suppurativa, and cystic acne, features comprising the follicular occlusion triad. This unusual phenotype is associated with a novel heterozygous point mutation (C119T) in the gap junction beta2 gene that substitutes a valine for alanine at codon 40 (A40V) in the connexin 26 protein. The phenotype and the natural history of the disease plus the genotype of our current patient are different.

5. In Summary

We presented a girl with phenotypic/genotypic characterization consistent with the diagnosis of KID syndrome. Fixed flexion deformity of the knees was a major malformation which hindered dramatically the locomotor system. Flexion deformity of the knees is not a common deformity encountered in children with KID syndrome. It was imperative to determine the primary site of the flexion deformity. Surgical procedures about the knees were performed with great caution.

In most cases with fixed flexion deformity of the knees, we usually start with correction of the flexion deformity of the hip. In cases with no hip deformity, or it has been corrected, it may still be profitable to correct deformities via preliminary passive stretching or serial plaster casts.

An Volkov- Oganesyan external hinged distraction device was applied through using transosseous pins and adjustable attachments. The overall success rate in our
current patient was assessed via walking capacity, range of motion (ROM), and joint space width (JSW). The outcome of the application of external hinged distraction revealed that our results showed remarkable clinical improvement with regard to resuming standing and walking capabilities, with respect to knee motion, JSW, and tibiofemoral angle. As a result of treatment, we managed to eliminate contractures and restore the axis of the lower limbs, and the child began to walk.

Consent

Written informed consent allowing publication of this case has been obtained from the patient’s father.

Conflicts of Interest

Authors declare no conflict of interest.

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