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Leri-Weill dyschondrosteosis; a rare type of mesomelic short stature in a Sri Lankan family

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Introduction

Short stature is a common medical problem in paediatric practice. Among the aetiologies, endocrinopathies, nutritional deficiencies, chronic disorders, genetic syndromes and skeletal dysplasias predominate. Disproportionate dwarfism is strongly linked to skeletal dysplasia (1, 2).

Leri-Weill dyschondrosteosis (LWD) is a rare genetic disorder causing skeletal dysplasia and the exact prevalence is unknown (1, 20). It was first described by Leri and Weill in 1929 (3). Disproportionate short stature due to short lower segment, mesomelic limb abnormality and Made lung deformity (abnormal misalignment of the wrist) are characteristic clinical and radiological features (2, 4).

Heterozygous mutations in the short stature homeobox-containing (SHOX) gene or its enhancers located on the pseudo-autosomal region 1 (PAR1) of the X or Y chromosomes are known to be linked to the disease expression (2, 5). A pseudo-autosomal dominant inheritance pattern is described as the cases have been reported in consecutive generations involving both sexes though the gene is located in sex chromosomes (6, 7). However, not all patients with LWD exhibit SHOX alterations where the mutations were reported only in 67% in certain published literature (5). In contrast, SHOX mutations are associated with other types of short stature such as Turner syndrome, idiopathic short stature and langer mesomelic dysplasia (LMD) in addition to LWD (1).

Though the reported literature describes widely on SHOX gene abnormalities, cases of LWD are sparse (8). There are no reported cases from Sri Lanka to the best of our knowledge. Furthermore, the index case is usually a female as the more severe phenotype is classically observed in females and it is often an adult (6-8). We report a Sri Lankan family with Leri-Weill dyschondrosteosis involving three consecutive generations highlighting the key features. The index case was a 10-year-old boy along with his mother and grandmother who were diagnosed subsequently.

Case presentation

A 10-year-old boy (patient 1) presented to Colombo North Teaching Hospital, Sri Lanka for evaluation of short stature as he was the shortest student in the class. He was born to non- consanguineous parents and had an uneventful perinatal period. There were no chronic medical illnesses reported and intellect was age appropriate. His height on examination was 116.9 cm which was far below the 3rd percentile for his age. Upper segment to lower segment ratio (US/LS) was 1.1 and mesomelia was noted in all four limbs. There were no facial dysmorphic features, spinal deformities, muscular hypertrophy or high arched palate. He did not experience pain or restriction of movements of the wrist joints. Basic haematological and biochemical investigations were normal.

The family members were explored given the clinical picture was suggestive of a skeletal dysplasia. Examination of his mother (patient 2) revealed short stature and mesomelia of all four limbs with muscular hypertrophy (Figure 1). In addition, she had bilateral Madelung deformity with painful restricted movements at wrist joints (Figure 2). Similar phenotype was observed in maternal grandmother (patient 3) though the pain and restriction of wrist movements were milder. Child's father did not have short stature and was phenotypically normal.

Figure 1: Phenotypic appearances of patient 1, 2 & 3 (from right to left)

With familial mesomelic short stature and bilateral wrist abnormality in both adults a clinical diagnosis of Leri-Weill dyschondrosteosis was made which was well supported by radiological features. Radiographs of the mother revealed bilateral prominent Madelung deformity, shortening and bowing of the radii and the triangulation of distal radial epiphysis causing an ulnar slant to the articular surface (Figure 3). Though child's radiograph did not show fully evolved Madelung deformity his limbs were abnormal in configuration and lower segment was short in keeping with the diagnosis. SHOX gene evaluation was not performed due to financial constraints. Family was counselled and symptomatic and supportive management were initiated with analgesia and physiotherapy.

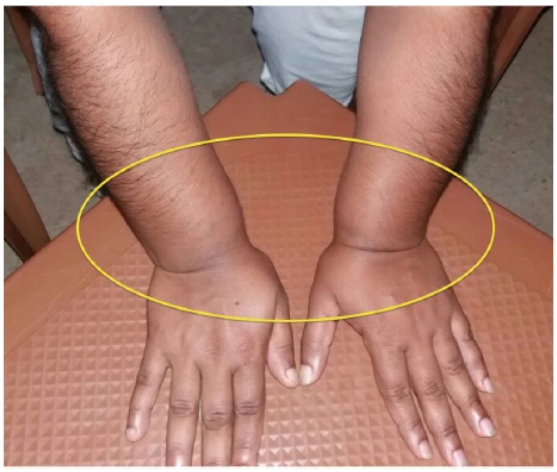

Figure 2: The hands of patient 2 shows bilateral Madelung deformity

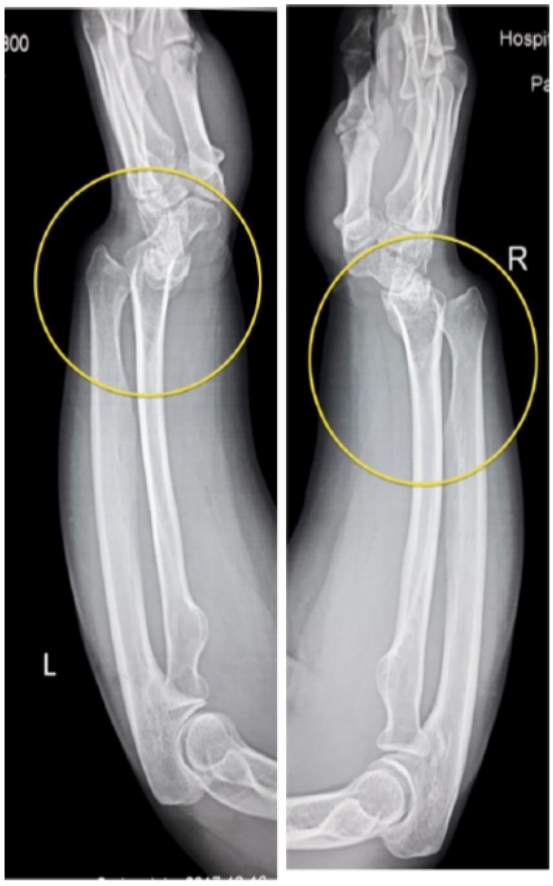

Figure 3: Radiographs of hands showing Madelung deformity in patient 2

Discussion

LWD is a rare type of skeletal dysplasia and this case highlights the clinical phenotype and its extension across three generations within a Sri Lankan family. Disproportionate short stature, mesomelia and Madelung deformity were striking features. In keeping with the pseudo-dominant inheritance, three consecutive generations and both males and females were affected in this case whilst the parents of the index case (patient 1) were non-consanguinous.

Females are known to have the severe phenotype due to hormonal effects as oestrogen promotes earlier fusion of the growth plate (3, 5, 8). In this case, index case was a male child who presented at 10 years of age and the two adults in the family were diagnosed subsequently. As Madelung deformity is known to be fully apparent in adult age and known to progress after puberty, it was less evolved in patient 1, however was classically present in patient 2 and 3 (9, 10). In many cases short stature had been the sole clinical feature at diagnosis (5). Limited cases have been reported in children as the manifestations are subtle in early ages and inter as well intra-familial phenotypic differences have been reported (11). In this case full phenotype was not apparent in patient 1 whilst patient 2 seems to have more pronounced phenotype demonstrating classic mesomelia, muscular hypertrophy and restriction of wrist movements with Madelung deformity on radiographs. In patient 1, more discrepancy between upper and lower segment is anticipated with further growth towards adolescence as growth of the legs will be less compared to upper limbs in LWD (2, 6). This raises the importance of investigating the family as full phenotype may not be apparent in childhood other than the short stature.

Importantly, patient 2 and 3 were able to function normally in day today life and were intellectually normal. Though, they appreciated mild pain in the wrist joints and some restriction of wrist movements on direct enquiry, they had not sought medical attention for themselves at any point prior to this encounter.

Among the other differential diagnoses; Turner syndrome is unlikely as patient 1 being a male and patient 2 and 3 had good fertility. Langer mesomelic dysplasia (LMD) is another diagnostic mimic, however there are key features which would differentiate it from LWD (11). LMD is described as a more severe version of LWD in certain literature and is characterised by severely short limbs with both mesomelia and rhizomelia in contrast to absence of rhizomelia and less severe mesomelia in LWD. Apart from that LMD is known to exhibit pseudo-autosomal recessive inheritance, hence prevalent in consanguineous families and would not affect consecutive generations (1, 11). Normal intellect is reported in both LMD and LWD hence is not a feature in differentiation (6, 11). All three subjects in this family were of normal intelligence.

Though genetic mutations involving SHOX gene are known to associate with LWD, it is not a constant finding in all reported cases where mutations were not detected despite of screening (1, 5). Gatta *et al.,* reported that only 67% of patients with LWD have demonstrated SHOX abnormalities and there are cases reported with classic clinical phenotype supported by unique radiological features (5, 11). In this case genetics were not carried out due to lack of availability locally and financial constraints which prevented us from sending samples to another laboratory overseas. Involvement of the family across three consecutive generations would support an underlying genetic abnormality in this case in contrast to a s sporadic occurrence.

This case reports Leri-Weill dyschondrosteosis, a rare type of skeletal dysplasia in a Sri Lankan family with classic clinical and radiological features. LWD should be considered as a differential diagnosis in familial mesomelic short stature with Madelung deformity. Full clinical and radiological features may not be apparent in young childhood warranting screening the family to aid the diagnosis.

Though the severe phenotype commonly is reported in females and in adulthood, in this case, the index case was a male who was in his childhood. This case highlights the importance of considering LWD as a differential diagnosis in childhood short stature and screening of the family members could provide important clues to the diagnosis.

Informed written consent was obtained from the guardian to publish this case report with photographs.

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