Early genetic diagnosis and orthopedic care improves the outcome of diastrophic dysplasia.

Learning Point of the Article:
Early genetic diagnosis and orthopedic care improves the outcome of diastrophic dysplasia.

Introduction:
Diastrophic dysplasia (DTD) results from SCN26A2 gene mutation, with autosomal recessive inheritance and widely variable phenotype. The gene has been mapped to chromosome 5q32-q33.1.

Case Report:
We present a case of a 4-year-old female with short stature, bilateral feet and knee deformity, and dysplastic facies. SCN26A2 mutations were seen in patient as well as parents. She underwent multiple orthopedic procedures involving metatarsals, gastrosoleus, and distal femur. Based on typical clinical features, DTD was suspected. Genetic studies of patient and parents provided the exact diagnosis in this case.

Conclusion:
Genetic diagnosis and family counseling are important caveat of management. Key features like ear abnormalities help to suspect diagnosis which requires a high index of suspicion. Associated bony and soft-tissue abnormalities of lower limb may require surgical intervention for improvement of gait, functions, and cosmesis.

Keywords: Diastrophic dysplasia, Skeletal dysplasia, Ear abnormalities, SCN26A2, Osteotomy.

Case Report
A 4-year-old female presented to genetic OPD for evaluation of short stature. Her weight = 16.2 Kg (median to −2 standard deviation [SD]), height = 92 cm (< −3SD). On examination, the patient had thickened auricular cartilage (Fig. 1) with preauricular pits, blue sclerae, dental caries with enamel dysplasia (Fig. 2), syndactyly, brachydactyly, and joint laxity. The patient had unassisted bipedal gait with bilateral intoeing and equinus at the right ankle. There was bilateral genu valgum deformity with patellar subluxation. The clinical tibiofemoral angle was 13° on the right side and 15° on the left side. The Apprehension test for a patellar subluxation was negative. There was an extension lag of 10° on both knees and equinus deformity of 20° at the right ankle. Bilateral metatarsus adductus was present. Radiographs of the pelvis with both hips revealed bilateral...
Serial casts for foot deformity were applied but there was no improvement. Metatarsus adductus on each side was corrected by multiple dome osteotomies of metatarsals (Figs. 4a and b). Surgical correction of bilateral genu valgum by medial distal femoral hemiepiphysiodesis was done (Figs. 5a and b). The right side equinus deformity was treated by the Vulpius V-Y plasty of gastrosoleus aponeurosis. On the latest follow-up at 1 ½ years post-surgery, residual genu valgum deformity was noted on the left side and so osteotomy at appropriate age was planned. Clinical correction of metatarsus adductus was achieved with a plantigrade foot (Fig. 6).

Clinical features of this case bilateral symmetrical cystic ear swelling (hypertrophic ear cartilage), equinus deformity in feet, brachydactyly with ulnar deviation, and short stature are consistent with DTD (due to SLC26A2 mutation) [3]. Persistence of ear abnormalities is seen only in this form of SLC26A2-related disorders (Table 1). The DTDST protein has a complex structure with 12 membrane-spanning domains. Multiple mutations have been noted which result in a myriad combination of clinical features, either through protein truncation or through the reduction in mRNA levels [4]. Mutations leading to amino acid substitutions in the transmembrane portion of protein have severe phenotypical expression than substitutions involving extracellular or cytoplasmic part (N-terminal and C-terminal). It is postulated that there is a leftover activity associated with some mutations and the degree of this leftover activity determines the clinical phenotype [4]. Both skeletal dysplasia and achondroplasia have similar features but morbidity is significantly higher with DTD.

Based on these features, the diagnosis of skeletal dysplasia was suspected, and genotyping was offered to the family after counseling.

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**Molecular data**

Getting the preliminary data and report by NGS, Exon 3 of the SLC26A2 gene was PCR amplified and the product was sequenced using Sanger sequencing. In case of mosaicism in leukocytes, the detection limits of Sanger sequencing for the presence of variation are ~12%. The sequence was aligned to available reference sequence ENST00000286298 to detect variation using variant analysis software programs. Figs 7, 8, and 9 show variation in the SLC26A2 gene in patient, her father, and mother, respectively.

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Yilmaz et al. in their study consisting of 29 patients of skeletal dysplasia with genu valgum deformity in 38 legs showed hemiepiphysiodesis to be effective in the treatment of genu valgum deformity in skeletally immature patients [5].

Cavovarus deformity which is often present is treated with the Ponseti method of casting in patients in the age group <6 months. There is a need for soft-tissue release in patients with after the walking age and in resistant cases, it may need aggressive release [6]. Metatarsus adductus deformity if...
Skeletal dysplasias are heterogeneous disorders with widely varying clinical presentations – from mildly symptomatic to overtly fatal. Diagnosis of such cases is tricky in our setup due to lack of investigative set up as well as high costs. However, efforts into a search for diagnosis and dedicated management by a team of skilled clinicians have potential to improve quality of life for patients afflicted by such disorders.

A multidisciplinary approach is indicated with the treating team comprising a pediatrician, orthopedic surgeon, audiologist, orthodontists, and physical therapists. Genetic studies have a crucial role in diagnosis, but importance of clinical suspicion (based on certain characteristic deformities) cannot be emphasized more.

**Clinical Message**

A multidisciplinary approach is warranted for providing best possible management to such patients. Selected certain anomalies serve as a key feature to identify a disorder (ear abnormalities in this case) and clinicians should be mindful of these. Family counseling regarding prognosis and genetic implication forms the crux of care and helps in improving outcomes, long-term care, and further family planning.
Table 1: Clinical features

| Achondrogenesis, type IB; ACG1B (OMIM NO. 600972) | Atelosteogenesis, type II; AO2 (OMIM NO. 256050) | Diastrophic dysplasia; DTD (OMIM NO. 222600) | Epiphyseal dysplasia, multiple, 4; EDM4 (OMIM NO. 226900) |
|--------------------------------------------------|-------------------------------------------------|---------------------------------|---------------------------------------------------|
| **Growth** | **Head, face, and neck** | **Respiratory insufficiency** | **Lungs** |
| Height – Short-limbed dwarfism identifiable at birth | Head – Flat face | Respiratory insufficiency, pulmonary hypoplasia | Respiratory insufficiency |
| Height – Short-limbed dwarfism identifiable at birth | Face – Midface hypoplasia, micrognathia, flattened nasal bridge, cleft palate | Neck – Short neck | Respiratory insufficiency, pulmonary hypoplasia |
| Height – Mean birth length 42 cm, specific growth curve available – Adult height 100–140 cm, short-limb dwarfism | Head – Normocephaly | Ears – Neonatal cystic lesions of the pinnae, hypertrophic auricular cartilage, ossified pinnae, hearing loss | Cystic lesions of the pinnae at birth usually disappear with age |
| Height – Short stature (3rd–90th centile) | **Height** | **Laryngotracheal stenosis** | **Chest** |
| **Head, face, and neck** | **Neck** | **Respiratory insufficiency** | **Chest** |
| Head – Flat face | Short neck | Respiratory insufficiency, pulmonary hypoplasia | Narrow chest |
| Face – Midface hypoplasia, micrognathia, flattened nasal bridge, cleft palate | Ears – Neonatal cystic lesions of the pinnae, hypertrophic auricular cartilage, ossified pinnae, hearing loss | - Small thorax | - Small thorax |
| Head – Normocephaly | **Mouth** | **Spine** | **Skull & spine** |
| Neck – Short neck | - Cleft palate | - Kyphoscoliosis | Skull |
| Ears – Neonatal cystic lesions of the pinnae, hypertrophic auricular cartilage, ossified pinnae, hearing loss | Pelvis – Hip dysplasia, small femoral heads | Pelvis – Hypoplastic cervical vertebrae | Spine |
| **Chest** | **Skull** | **Spine** | **Skull & spine** |
| - Narrow chest | Spine | Spine – Scoliosis | Skull – Kyphoscoliosis |
| - Small thorax | Spine | Pelvis – Hip dysplasia, small femoral heads | Pelvis – Hypoplastic cervical vertebrae |
| - Thins short ribs | - Kyphosis | - Flattened proximal femoral epiphyses | - Hypoplastic cervical vertebrae |
| - Occasional rib fractures | - Limited elbow flexion, double-layered patella, arthrogryposis, small humeral, distal radii, and ulna epiphyses, mildly shortened ulna, flat proximal femoral epiphyses | - Flat acetabulae | - Hypoplastic cervical vertebrae |
| - Umbilical and inguinal hernias | Pelvis – Hip contractures | - Hypoplastic, rounded middle phalanges | - Pelvis |
| - Distended abdomen | Pelvis | - Subluxed patella | - Unossified ischium and pubis |
| - Unossified ischium and pubis | - Shortened sacroiliac notches | - Mild shortened metacarpals | - Absent or minimally ossified vertebral bodies |
| - Shortened sacroiliac notches | Limbs | - Clubfoot | - Small iliac bones |
| Limbs | - Short, thick tubular bone, with broad metaphyses and flattened, irregular epiphyses | - Brachydactyly | - Flat acetabulae |
| - Severe micromelia | - Severe micromelia | - Bifid distal humerus | - Small iliac bones |
| - Marked shortness, broad tubular bone | - Subluxed patella | - Metaphyseal spurring | - Short, dumbbell femur |
| - Metaphyseal spurring | - Mild shortening metacarpals | - Short finger with ulnar deviation | - Short finger with ulnar deviation |
| - Abducted thumbs and great toes | - Clubfoot | - Gap between first and second toe | - Clubfoot |
| - Gap between first and second toe | - Hitchhiker thumb | - Hypoplastic, rounded middle phalanges | - Talipes equinovarus |
| - Talipes equinovarus | - Flat proximal femoral epiphyses | - Talipes equinovarus | - Talipes equinovarus |
| Skin | - Glabellar hemangioma | - Normal intelligence, spinal cord compression | - Glabellar hemangioma |
| CNS | Voice | - Hoarse voice | - Hoarse voice |
| Prenatal manifestations | Laboratory abnormalities | - Polyhydramnios, fetal hydrops | - Polyhydramnios, fetal hydrops |
| Polyhydramnios, fetal hydrops | - No cartilage staining with toluidine blue, impaired synthesis of fibroblast-sulfated proteoglycans | - Breech presentation at birth, often stillborn | - Breech presentation at birth, often stillborn |
| - Breech presentation at birth, often stillborn | - Lacunar halos around chondrocytes in skeletal cartilage | - Stillborn or death shortly after birth | - Lacunar halos around chondrocytes in skeletal cartilage |
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