CASE REPORT

Metatropic Dysplasia with a Novel Mutation in *TRPV4*

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Back ground: Metatropic dysplasia is a skeletal dysplasia characterized by rhizomelia, severe kyphoscoliosis and a coccygeal tail. **Case characteristics**: A 12 day-old male neonate had facial dysmorphism, short limbs and coccygeal tail and showed radiological features of metatropic dysplasia. **Observation**: A novel heterozygous variant was observed in *TRPV4* gene. **Message:** We report a novel mutation in an Indian neonate with metatropic dysplasia.

Keywords: *Coccygeal tail, Genetics, Metatropic dysplasia, TRPV4.*

Metatropic dysplasia (OMIM 156530) is a severe skeletal dysplasia characterized by rhizomelia, kyphoscoliosis and coccygeal tail, manifesting in the immediate perinatal period [1]. Based on the radiological findings and clinical features, three forms have been described, including a lethal form, and a non-lethal form with less severe radiographic manifestations. Recently, dominant mutations in *TRPV4* were identified both in severe and mild forms of metatropic dysplasia by Camacho, *et al.* [2].

We are reporting a male neonate with features of metatropic dysplasia, with a novel heterozygous mutation in *TRPV4*. This is the first mutation-proven case from India.

CASE REPORT

A 12-day-old male new born was brought for evaluation of dysmorphic facial features and short limbs. He was the first born product of non-consanguineous marriage. Antenatal ultrasonogram was normal. He was born at term, with uneventful perinatal period. He was noticed to have short limbs compared to his trunk and a flat facies (***Fig*. 1**). Parents were of normal stature.

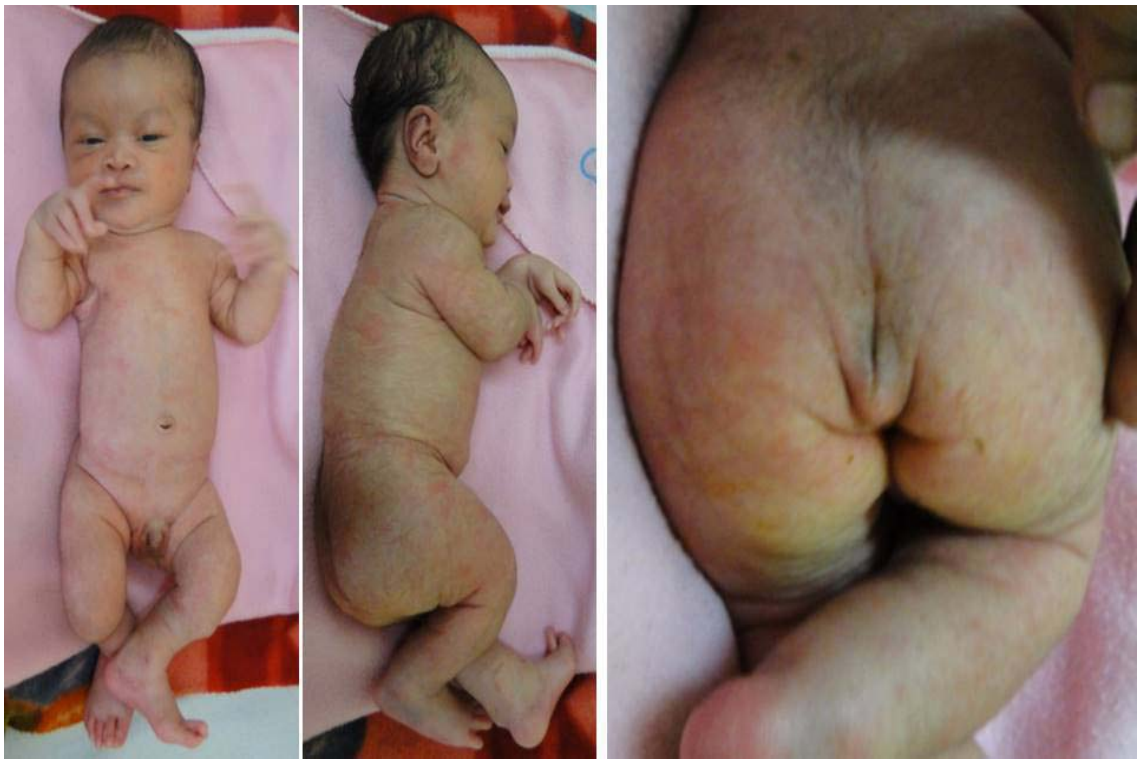
His length was 43 cm (-3 SD), with an upper segment to lower segment ratio of 1.8:1(Normal 1.7:1 at birth), indicating that he had short limbs. His head circumference was 33.5 cm (normal). Examination showed limitation of movements at both wrists, both knees and both ankles, a prominent coccygeal tail and prominent knees, with a gibbus in the thoracic spine. He had a flat facial profile (***Fig*.1**).

Radiographic evaluation showed severe platyspondyly with wafer thin vertebra, dumb bell shaped long bones, halberd shaped pelvis, narrow thorax and short ribs with cup shaped ends (***Fig*. 2**).

Mutation analysis by sequencing all the coding regions of *TRPV4* gene (GenBank accession no. NM_021625) revealed a novel heterozygous missense mutation, c.1834A>G (p.K612E), in exon 12 of *TRPV4* gene. This missense variant was not present in dbSNP and the 1000 Genome database and was predicted to be pathogenic by pathogenicity predicting software Mutation Taster. The same mutation was absent in parents.

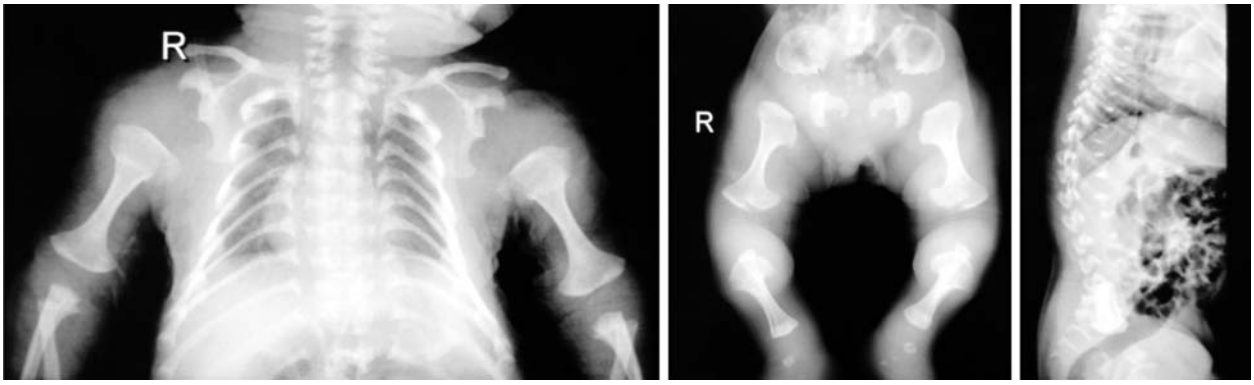
DISCUSSION

Our patient had short limbs, flat facies, prominent joints, and a coccygeal tail, which helped us to establish the clinical diagnosis of metatropic dysplasia. This condition was first described by Maroteaux in 1966 [3]. The word 'Metatropic' refers to the change in phenotype with short limbs and long trunk during neonatal period to progressive short trunk during childhood, giving the name 'changing dysplasia'. There is a broad range of clinical severity in patients with metatropic dysplasia [2]. The clinical features include short limbed dwarfism, narrow cylindrical thorax and enlarged joints which present at birth, with evolving severe kyphoscoliosis. The facial features are also distinctive with squared-off jaw, prominent forehead and mid-face hypoplasia [4]. Excessive ossification of the coccyx causing a prominent "tail" has been described in patients [5]. Cervical myelopathy, odontoid hypoplasia and spinal stenosis leading to neurological sequelae and respiratory compromise causing death are the associated serious complications [5]. Due to progressive kyphoscoliosis,



(*a*) (*b*) (*c*)

FIG. 1 *Infant with dysmorphism showing rhizomelia (a), flat facies (b), and coccygeal tail (c)*



(*a*) (*b*) (*c*)

FIG. 2 *X-rays of child showing dumb bell shaped long bones (a,b), narrow thorax and short ribs with cup shaped ends (a), Halberd shaped pelvis (b), platyspondyly and wafer thin vertebral bodies (c).*

pulmonary function may become compromised.

Radiological findings include wafer-thin vertebral bodies in newborn, halberd shaped proximal pelvis, brachydactyly with delayed carpal ossification and flared proximal and distal metaphysis of femora leading to 'dumb bell shape' of long bones [4]. Dumb bell-shaped long bones are seen in other skeletal dysplasias like Kneist dysplasia, fibrochondrogenesis and metatropic type of Spondylo epimetaphyseal dysplasia (SEMD).

Till date, 33 mutation proven cases have been described in literature [6]. Most of the mutations are missense mutations. Based on the severity of the clinical features, the disease is subclassified into a severe lethal form and a less severe non-lethal form. There are eight

allelic disorders, of which three are neurological disorders, caused by mutations in *TRPV4;* These are Charcot Marie Tooth Disease Type II C, scapuloperoneal spinal muscular atrophy and congenital distal spinal muscular atrophy. This indicates that, TRPV4, a cation channel which is selectively non-permeable to calcium, encoded by the gene *TRPV4*, on chromosome 12, is involved in many physiological processes [7]. It is now considered that *TRPV4* mutations cause a phenotypic spectrum of skeletal dysplasias ranging from mild brachyolmia to spondylometaphyseal dysplasia-Kozlowski to metatropic dysplasia on the severe end of the spectrum [2]. No definite genotype phenotype correlation could be observed [2], but degree of activation of *TRPV4* could determine the severity of the phenotype.

Metatropic dysplasia is primarily a dominant disorder. Even if the parents are unaffected, there could be recurrence in siblings due to germline mosaicism in parents. To ascertain the empiric risk, more experiments are needed [2]. But the risk of recurrence is well below the 25% attributed for a recessive disorder.

Since the clinical and radiological features are shared by other skeletal dysplasias, mutation analysis is essential to reach a conclusive diagnosis. Prenatal diagnosis can be offered to families where the mutation has been identified, by chorion villus sampling and targeted mutation analysis of the fetus.

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