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Case report on Microcephalic Osteodysplastic primordial dwarfism- A rare autosomal recessive skeletal dysplastic disorder

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Abstract
Microcephalic osteodysplastic primordial dwarfism(MOPD) is a rare autosomal recessive disorder characterised by severe cause of microcephaly, facial dysmorphism, central nervous system , skeletal,skin and limb abnormalities. Recently mutations in RNU4atac SnRNA ,have been recognised as the cause of MOPD. Less than 50 cases have been reported worldwide.We are reporting a case of a 18week- old female fetusdiagnosed with MOPD.

Keywords: Microcephaly, Osteodysplasty, skeletal dysplastic disorder

INTRODUCTION

Microcephalic osteodysplastic primordial "dwarfism" (MOPD) is a group of disorders similar to Seckel syndrome. Three subtypes (types I-III) have been reported. The manifestations included severe intrauterine and postnatal growth failure, microcephaly, a distinctive facial appearance, micromelia, brachytelephalangy, coxa vara, and V-shaped metaphyses of the distal femora. Other than small cerebral hemispheres, no neuropathological abnormalities were found. Chondro-osseous histology showed thinning of the growth plate, ballooned chondrocytes, reduced cellularity, lack of zonal and columnar formations, and poor formation of primary trabeculae. These findings suggest that impairment of chondrocytic formation and differentiation is the major pathogenesis of MOPD .

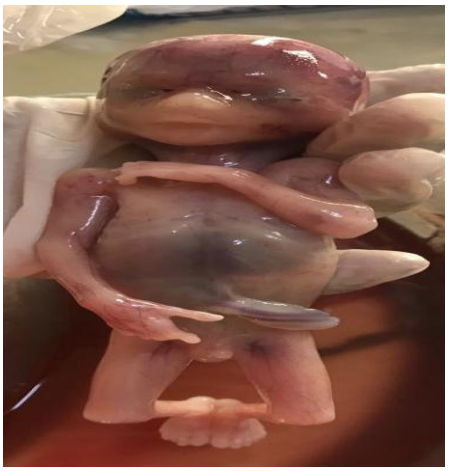
CASE PRESENTATION

26yrs, third degree consanguineous marriage, primigravida, gestational age-18weeks came to SBMCH OPD with complaints of spotting per vaginum and pain abdomen ;
Per abdomen – uterus corresponds to 16 weeks, fetal parts felt, nontense and nontender;
Per speculum examination- cervix,vagina healthy.
Mild brownish discharge noted.
Per vaginal examination – Cervix -pointing downwards ,os closed, uterus 16weeks size, mobile ,fornices free , nontender.

Anomaly scan showed Single gestation corresponding to a gestational age of 16weeks 4 days

Growth:BPD and HC fall at <4SD ,AC and FL fall at <2SD – SUGGESTIVE OF SYMMETRIC IUGR, MICROCEPHALY

and BILATERAL CONGENITAL TALIPES EQUINO VARUS.
Patient spontaneously expelled a female fetus weighing 163gm , placenta and membranes delivered intoto.
Gross examination revealed microcephaly , symmetrical IUGR:Advised to do fetal autopsy and TORCH SCREENING.



Fetal autopsy done revealed

→intrauterine growth restriction corresponding to 16- 17weeks

- ➔ Microcephaly
- ➔ DYSMORPHIC FACIES:
  a) NARROW FOREHEAD
  b) PROTUBERANT EYES
  c) LOW SET EARS WITH SMALL PINNAE
  d) LARGE NOSE
  e) SHORT PHILTRUM
  f) OPEN MOUTH
  g)

→SHORT NECK
→BROAD THORAX
→ANTERORLY PLACED ANUS
→UPPER LIMB: RIGHT HAND -HITCH HIKER THUMB
→LOWER LIMB: LEFT TALIPES EQUINOVARUS
→CNS:
MICROCEPHALY WITH SECONDARY CRANIOSTENOSIS
OBLITERATED LATERAL AND THIRD VENTRICLES
AGENESIS OF CORPUS CALLOSUM
FUSED THALAMI

LARGE CEREBELLUM
→HYPOPLASTIC THYMUS AND ADRENALS
→FETOGRAM:

- GENERALISED POOR MINERALISATION
- MICROCEPHALY
- BONY HYPOTELORISM
- ROUNDED ORBITAL MARGINS
- BROAD AND SQUARE THORACIC CAVITY WITH THIN RIBS
- PAIR OF CERVICAL RIBS
- OVERTUBLATED LONG BONES WITH MOTH EATEN APPEARANCE
- STRAIGHT SPINE POORLY OSSIFIED AND HYPOPLASTIC VERTEBRAE
- SACRAL DYSGENESIS

IMPRESSION: Features suggestive of Microcephalic Osteodysplastic Primordial Dwarfism (MOPD)

DISCUSSION

MOPD a rare condition with an unknown incidence, but is likely <1 in 10,000 live birth .
This disorder is autosomal recessive and is diagnosed with an RNU4ATAC mutation on chromosome 2q14.2.
In 2008, Rauch et al. and Griffith et al. concurrently recognized that biallelic loss-of-function mutations in the pericentric gene (PCNT) cause MOPD. Rauch et al. suggested MOPDII as the form caused by these mutations while phenotypically similar cases were classified by Griffith et al. as a form of Seckel syndrome . In subsequent work by Willems in 2010, all patients with a clinical diagnosis of MOPD (8 of 8) were

identified to have PCNT mutations and 5 of 16patients with a clinical diagnosis of Seckel syndrome were identified to have PCNT mutations . Retrospective analysis of the five Seckel patients with PCNT mutations suggested that they all belong to the MOPDspectrum . It is now recognized that MOPD is genetically homogeneous and caused by loss-of-function mutations in PCNT .

The PCNT gene is located on 21q22.3 and encodes PCNT protein, a giant coiled-coil protein (~370 kDa) that localizes to centrosomes throughout the cell cycle. The centrosome organizes cytoplasmic organelles and primary cilia in interphase cells , mitotic spindles and microtubules to ensure proper chromosome segregation during cell division . PCNT anchors regulatory and structural molecules to centrosomes, specifically the γ-tubulin ring complex which initiates the assembly of the mitotic spindle apparatus . Absence of PCNT results in disorganized mitotic spindles andmis-segregation of chromosomes .

The classic presentation of MOPD is intrauterine and postnatal growth retardation,microcephaly,partial or complete agenesis of the corpus callosum,short limbs, dislocation of hips and elbow,sparse hair including eyebrows, seizures and facial abnormalities.This presentation should lead the healthcare provider to seek further imaging and genetic testing for early diagnosis.

Cardinal brain MRI features in MOPD include gyration abnormalities , callosal body malformations and interhemispheric cysts.While physical examination and imaging studies are important in determining the severity of dysfunction, genetic testing is currently the only definitive way to diagnose MOPD .

Other physical findings in MOPD1 include cerebellar vermis hypoplasia, lack of retinal pigmentation and polymicrogyria. These variations in presentation of MOPD and an overall paucity of information regarding the syndrome can lead to a delayed diagnosis. While early diagnosis does not change the outcome of this fatal genetic disease, early detection is essential to raise awareness and educate the parents on the risk of future children having a similar outcome.

CONCLUSION

The purpose of this case is to both identify and describe some common physical findings related to MOPD.

The rarity of this disease and overlapping features with other forms of primordial dwarfism make definitive diagnosis challenging.

MOPD has 25% recurrence risk in every pregnancy hence,

Both parents were advised for genetic counseling and further genetic testing to identify if they were carriers for this particular genetic mutation.

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