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Two Siblings Diagnosed with Microcephalic Osteodysplastic Primordial Dwarfism, Type II (MOPDII), Inherited with Compound Heterozygous Variant. Case Series with Suggested Management Approach

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Abstract

Microcephalic Osteodysplastic Primordial Dwarfism, Type II (MOPDII) is the most common type of microcephalic primordial dwarfism (MPD), reported cases worldwide are about 150 cases [1] and the number is increasing. The disease is caused by biallelic loss-of-function mutations in the pericentrin gene (PCNT1), which is inherited in an autosomal recessive manner [2]. It manifests as the other MPD types with severe pre and postnatal growth retardation associated with marked microcephaly. In addition to these features, individuals with MOPDII specifically have characteristic facies, skeletal dysplasia, abnormal dentition, and an increased risk for cerebrovascular disease and insulin resistance [3]. All features might not appear until later in life, hence there is a current consensus to follow these patients for the first few years. The reported life expectancy is up to three decades [4].

In the following text, we are reporting two siblings from Qatar, in whom the mode of inheritance was identified to be of the compound heterozygous variant. We are presenting their clinical, radiological, and laboratory findings, in addition to summary of their course of diagnosis and management approach.

Keywords: *Two Siblings; Microcephalic Osteodysplastic Primordial Dwarfism, Type II (MOPDII); Heterozygous Variant*

Introduction

Microcephalic Osteodysplastic Primordial Dwarfism, Type II (MOPDII) is the most common type of microcephalic primordial dwarfism (MPD), reported cases worldwide are about 150 cases [1] and the number is increasing.

Family history

Mother is 23 years old healthy lady with no underlying medical condition, she is not on any medical treatment and does not smoke. She had no history of miscarriages. There is a maternal aunt who suffers from growth problem and mental disability which has not been specified or definitively diagnosed. Father is healthy with no significant illnesses. Parents are non-consanguineous, although they both come from the same extended family or tribe.

Case Series

First twin (case 1)

A male neonate was born at late preterm 36+0 weeks gestational age. He was the second part of twins delivered by spontaneous vaginal delivery. These twins were conceived spontaneously to the primigravida mother and the antenatal US showed dichorionic diamniotic twins with Intrauterine growth restriction (IUGR) of the second twin. He was born vigorous with no need for respiratory support and good APGAR scores with a birth weight of 1500 grams.

Initial examination revealed low birth anthropometric measures including weight, height, and head circumference all were below the 3rd percentile (WHO standard growth chart).

Apart from the low anthropometric measures and unilateral undescended testicle there was no obvious dysmorphic features at birth.

This baby was admitted to the neonatal unit because of low birth weight and poor sucking. He required naso-gastric tube (NGT) feeding for 3 weeks after which was discharged home in a good condition with a discharge weight of 2000 grams.

TORCH screening, chromosomal microarray, cranial and abdominal US were done among other investigations as part of symmetric IUGR workup and all came normal. Routine hearing screening was normal as well. After discharge and in the follow up visits he was noticed to have a poor growth. Despite exclusion of nutritional causes, celiac disease, thyroid pathology or any underlying endocrine diseases, all growth parameters remained below the 3rd centile. Up to 18 months of age his growth parameters and developmental domains like gross motor, fine motor, posture, vision, hearing, language, social and behavioral development were appropriate for age. However, at 2 and half years of age, his mother reported excessive eye blinking especially when focusing on objects, and soon he was reported to have hyperactivity and disruptive behavior with limited attention span. Furthermore, at the age of 3 and half years his speech delay and cognitive impairment became evident and the genetic team reported synophrys, low set ears, broad nasal tip and low-lying kidney in the abdominal ultrasound and they requested whole exome sequencing. At the age of 4 years the whole exome sequencing (WES) result showed: PCNT gene with 2 heterozygous variants confirming the diagnosis of autosomal recessive microcephalic osteodysplastic primordial dwarfism type II (MOPD II). Parents genetic test showed the inheritance of one pathogenic gene from his mother and other different pathogenic deletion from his father. A multidisciplinary team including occupational therapist, speech therapist, child psychiatrist and educational support team is taking care of the child.

Chronological summary of findings

- **Antenatally:** IUGR.
- **At birth:** Weight, height and head circumference all below the third percentile (wight and height - 4 SD). undescended left testes. No body asymmetry, hands and feet are normal. Normal skin with no congenital lesions. Normal hearing test.
- **At 1 year:** Dysmorphic features appeared in the form of synophrys, low set ears an broad nasal tip.
- **At 2 years:** Speech delay, started first word at 2 years and 2 words sentences at 4 years, and mild delay in basic cognitive abilities, executive functioning was moderately affected.
- **At 3 years:** He had xerosis cutis, Compound Hypermetropia requiring eyeglasses.

Summary of investigations

Blood investigation

Full blood count, renal function, liver function test, Insulin like growth hormone and thyroid functions all normal.

Genetic testing:

- Comparative genomic hybridization (CGH) microarray reported normal.
- Whole Exome Sequencing (WES) showed PCNT gene with 2 heterozygous variant one likely pathogenic from his mother and other pathogenic deletion from his father which causing autosomal recessive microcephalic osteodysplastic primordial dwarfism type II.

Imaging:

- Skeletal survey (done at age of 3.5 years) showed delayed bone age, bone age according to the standards of Greulich and Pyle is around 2 year and 6 months. Several abnormalities detected as follow (Figure 1): hypoplastic iliac bones, bilateral coxa vera with the widened epiphyseal plate bilaterally and shortening of the middle phalanges of the hands. There is delay in appearance of some secondary ossification centers of the metacarpals.
- Abdominal ultrasonography showed low lying right kidney with associated malrotation, in addition to heterogeneous texture of the liver.
- Cardiac echocardiogram reported normal results.
- MRI not done for this patient.

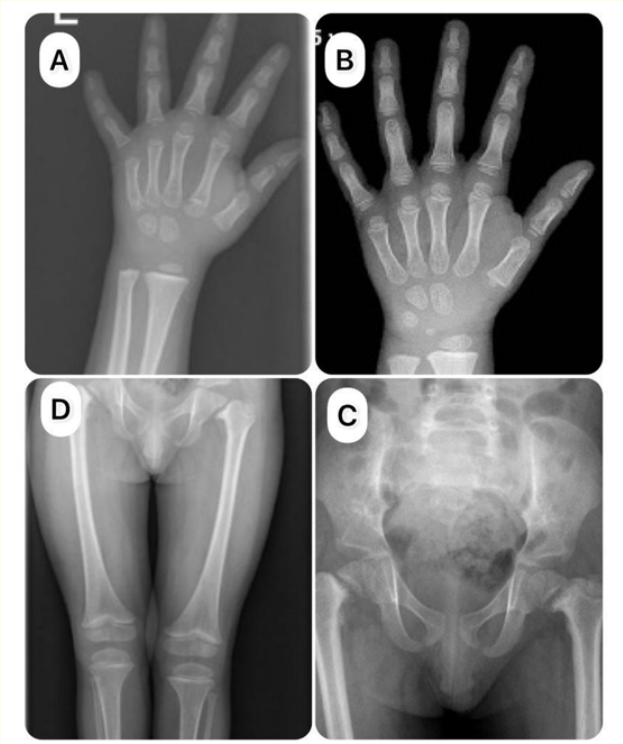

Figure 1: *a: X-ray of the left hand at the age of 3.5 years, showing delayed bone age, bone age according to the standards of Greulich and Pyle is around 2 year and 6 months. b: Normal left-hand X-ray for boys at 3.5 years from Grulich atlas. c: X-ray of the left hand at the age of 3.5 years, hypoplastic iliac bones. d: Bilateral coxa vera with the widened epiphyseal plate bilaterally.*

Second twin

A girl neonate with birth weight at the 50 percentile and normal growth and developmental milestones. She had few soft dysmorphic features in the form of pre-axial polydactyly in the lower limbs and talipes equinovarus (that resolved with physiotherapy). At age of 6 years, she developed strabismus but still having normal height and head circumference appropriate for age. Family did not agree on genetic testing and hence we are not sure if she has a carrier status.

Next delivery (Case 2)

Prenatal history

The mother conceived spontaneously after 5 year and was followed up by the Fetal Maternal Unite (FMU). At 12 weeks of gestation chorionic vellus sample (CVS) was taken and genetic testing showed the same mutation found in the previous sibling (twin 1) which is compound heterozygous mutation in PCNT gene. The fetus was diagnosed antenatally as a case of MOPDII and the diagnosis was discussed with parents and genetic counselling provided at the time.

Delivery

A male baby was born at 37 weeks + 6 days spontaneously by vaginal delivery, the baby was born vigorous and no resuscitation required. APGAR score was 9 and 10 at 1 and 5 minutes respectively. Birth weight of 1760 grams, length 45 cm, and head circumference 31 cm (all the 3 anthropometric measures were below the 3rd centile).

Birth examination

Revealed subtle features (Figure 2), Microcephaly, prominent nose with a wide nasal bridge and broad root, the columella was wide as well and the boundaries lied below the alae nasi. A mild retrognathia was documented as well.

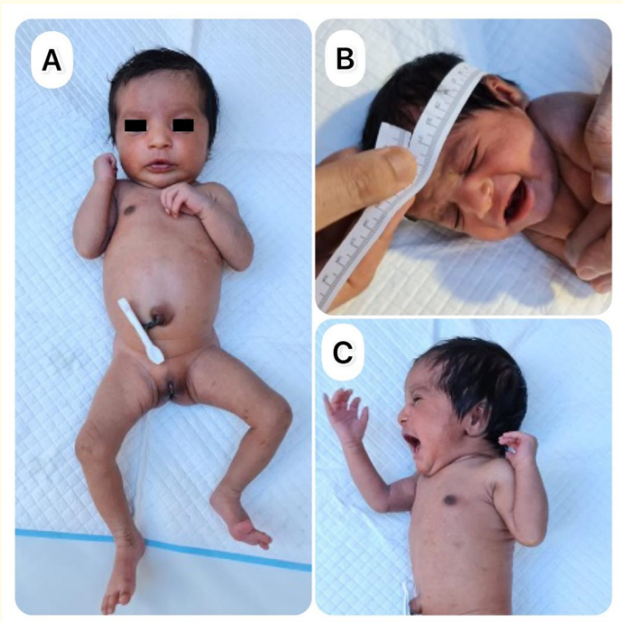

Figure 2: *a: IUGR baby with soft dysmorphic features, note the prominent nose with wide bridge and broad root. b: Microcephaly, head circumference is 33cm < 10th centile. c: full nasal tip, mild retrognathia.*

Admission

The baby was admitted to NICU because of low birth weight, to establish feeding and to complete the base line genetic workup. She remained clinically stable, vital sings including blood pressure were normal, received no specific treatment apart from routine neonatal care, baby achieved full breast feeding and gained weight. At 6 days of age, the baby was discharged home.

Investigations

Blood investigation: CBC, renal and liver function tests, electrolytes all results were within normal limits.

Imaging studies: Abdominal and hip US were normal, skeletal survey, and Magnetic resonance imaging (MRI) and Magnetic resonance angiography MRA all reported as normal. Echocardiogram showed Patent foramen ovale (PFO) with left to right shunt with otherwise normal cardiac structure and function.

Discharge plan:

- A multidisciplinary team follow up plan was arranged.
- Primary health care follows up the growth and development and for blood pressure charting.
- Speech and language team.
- Annual MRI.
- Regular follow up of the renal function, hepatic function, chemistry and metabolic panels at age of 5 years to detect any insulin resistance.
- Child psychiatrist follow up for cognitive assessment.
- Genetics and genetic counselor for future pregnancies.

Discussion

Total number of MOPDII till 2019 worldwide were only around 150 cases [1], we believe that each new case report will be a useful addition to the medical literature library. The genetic defect of the 2 cases reported in this article is a compound heterozygous, rather than being homozygous as expected in autosomal recessive (AR) disorders like MOPDII.

Historically, MOPIDII as a disease was first denoted in literature as early as 1960 by Helmut Sekel [5]. Sekel described a group of patients with unique characteristic features of short stature, prominent nose and retread head and mandible. Sekel labeled them as the Bird-Headed Dwarfs which was changed later to Sekel syndrome.

In 1982 Majewski., *et al*. described the clinical and radiological features of microcephalic primordial dwarfism (MPD) [6,7]. Majewski stated that, despite that MPD patients were sharing some similarities, those patients with MOPDII are unique and different from the group previously described by Helmut Sekel, this difference has been proven genetically later on.

Over the last 20 years, several cases have been published aiming to provide a comprehensive overview of MOPDII. MOPDII is labelled in Online Mendelian Inheritance in Man (OMIM) by the number 210720 [8].

Genetically, MOPDII is caused by biallelic loss-of-function mutations in the pericentrin gene (PCNT1) which is located in chromosome 21q22.23 [2], however there is only one case report of same disease described the genetic defect was found in chromosome number 1 [9]. MOPDII is inherited in AR manner, weather by homozygous or compound heterozygous like in our 2 reported cases.

Clinically, all types of MPD are characterized by severe pre- and postnatal growth retardation, with marked microcephaly. In addition to that individuals with MOPDII have characteristic facies, skeletal dysplasia, abnormal dentition, and an increased risk for cerebrovascular disease and insulin resistance.

We summarized the associated abnormalities as follows.

Growth: It is estimated that a term MOPDII newborn has approximately anthropometric measurements corresponding to a 28weeks preterm baby [9,10]. This growth restriction starts in fetal life and continues postnatally. It is reported in the literature that the carrier height can be affected [18]. However, the mid parental height was normal in our reported family.

Unlike babies who have specific growth charts like babies with trisomy 21 and achondroplasia for example, MOPDII patients have no specific growth charts to follow up their growth trajectory. Considering the fact that growth faltering is a universal finding among MOPDII, this should urge a collaborative effort to develop growth charts designed specifically for these group of patients. Although this might sound challenging for the time being due to the limited number of the worldwide reported cases, yet the cases are accumulating and the number is increasing and providing a growth chart seems feasible in the future.

Craniofacial features: Microcephaly is a universal finding among MOPDII. In addition, the nose is prominent, with a wide bridge and broad root. The nasal tip is full, and the columella often lies below the alae nasi. The ears may be dysplastic with attached lobules. They might have micrognathia, and the eyes usually appear prominent during childhood and become less so with age. There may be a down slanting palpebral fissure [9].

Skeletal features: Bone age is usually delayed. Upper extremity deformities include mesomelia, bowing radius and ulna, dislocation or subluxation of the radial heads, while hand might be affected with cone and ivory phalangeal epiphyses, pseudoepiphyses of the metacarpals can be seen with the first and fifth brachymetacarpalia and fifth digit clinodactyly. Back scoliosis might occur. Lower extremities deformities include small iliac wings, flat acetabulum, hip coxa vara or valga, hip dysplasia and subluxation. Acute vascular necrosis of the femoral head also been reported. Distal femoral metaphyses develop an inverted V-shape [9,11,12].

Notably, the sister of these siblings (the second part of the twin mentioned above) has some skeletal deformities in the form of polydactyly and talipes equinovarus, however, genetic testing for carrier state was denied by the family.

Dentition: MOPIDII patient tend to have deficient teeth enamel. The secondary teeth are small, dysplastic and have enamel hypoplasia. The roots of the teeth can be absent, short, or single (for molars) [9].

Central nervous system vascular anomalies: it is not uncommon for MOPDII patient to have moyamoya disease and aneurysms which might lead to stroke [9,13,14].

Insulin resistance: this is not uncommon and usually appears between 5 and 10 years, and this may cause precocious puberty and polycystic ovaries [15].

Cardiac: Usually normal at birth, rare findings include bicuspid aortic valve, atrial septal defect, and patent ductus arteriosus. However, at later life coronary arteries stenosis have been reported [9,13].

Renal disease and hypertension: The cause of hypertension is not well understood and may be due to renovascular causes or perhaps is centrally mediated or related to their short stature [16,17], they also might have proteinuria and infrequently structural renal abnormalities and nephrolithiasis [9].

Dermatologic: Different skin lesions have been described in MOPDII patients including cafe-au-lait spots, cutis marmorata and multiple creases develop on the hands and feet with aging. Later in life, areas of hypopigmentation and dry skin can also develop. The hair and eyebrows tend to be fine and thin. Acanthosis nigricans-like skin marks have been reported at school age [9].

Hematologic: Thrombocytosis, leukocytosis, and anemia all might occur in patient with MOPDII [16].

Among the above-mentioned long list of abnormalities, our reported cases have growth failure, short stature, microcephaly, typical nose characteristic, micrognathia, and delayed bone age with characteristic skeletal deformities evident by the skeletal survey.

The cases reported some abnormalities which were not reported before including undescended testicles, low lying right kidney, speech delay, cognitive, executive, and behavioral abnormalities.

Despite having normal skeletal survey at birth, our first case showed skeletal anomalies with advancing age which brings the importance to the regular follow up of MOPDII patients.

Diagnosis of MOPDII can be suspected based on the clinical features and radiographic examinations and confirmed by molecular genetic testing of PCNT1 gene.

Antenatal counselling and prenatal testing should be offered to the parents with IUGR and previous history of unexplained short stature or confirmed cases of MPD.

There is no consensus or agreement among the experts on one specific management plan, however, the management start from the fetal life if the diagnosed achieved antenatally or as soon as the diagnosed confirmed after birth.

Based on our experience with the reported case we suggest a multidisciplinary team approach involving occupational therapist, speech and language specialist, child physiatrist, social worker and physiotherapist family support with psychologist as well as special schools to be involved in the management of MOPDII patients and their families. This team might expand to involve cardiologist, neurologist and orthopedic surgeon according to the co-morbidity in each case.

After delivery, base line workup includes cardiac echocardiogram, brain MRI with MRA, abdominal ultrasound, skeletal survey, blood pressure monitoring, and some basic blood investigations which include full blood count, renal and hepatic function tests [3].

BP and protein urea to be checked regularly and if any of them became high, renal ultrasound and a urine test for proteinuria need to be done. Renal function test is usually done as well [3].

Clinical and radiological exclusion of hip dislocation, and hip with spine radiographs might need re-evaluations annually as indicated.

Counseling regarding future pregnancies and providing *In vitro* fertilization (IVF) with embryo-selection might be offered when available.

Based on the cognitive impairment and abnormal kidney position reported in our case and the renovascular abnormalities reported in the previously published cases, MRI and MRI might be considered in the management specially in patients with abnormal mental development.

MRI/MRA needs to be repeated annually up to age of 10 years [13], after that there are 2 schools, one is to continue doing MRI/MRA annually, and the other is to do MRI/MRA on alternative years, and there is no evidence to stop doing the MRI surveillance long-life [13,14]. If aneurysm or moyamoya disease found, a referral to neurosurgeon is warranted.

At around 3 to 5 years of age the, these patients need to be investigated for insulin resistance. Investigations might include basic chemistry metabolic panel, studies of lipid, hepatic function, and glucoses haemostasias.

We did not find growth hormone therapy nor vitamin D supplementation to add any benefit or cause harm in our cases.

Dental care is another point in the management of MOPDII patients as well, which need to be started soon after diagnosis [3].

The life expectancy is generally up to the 3rd decades, and the oldest age reported is 39 years [4].

Despite the lack of general consensus on how to manage babies with MOPDII, we provide a timetable that has been proposed by Michael B. Bober [3] which could be considered as reference when approaching and following up these patients especially from investigation point of view.

Recommended care guideline, Michael B. Bober [3]

Medical issues	At diagnosis	Yearly screening	Yearly screening to begin at age 5
Growth	Plot on MOPDII curves	Monitor growth on MOPDII curves	
Dental	Begin dental care[a]		
Skeletal	Hip and spine radiographs	Hip evaluation and radiographs with spine evaluation and radiographs as indicated[b]	
CNS Vascular	MRI/MRA brain	MRI/MRA brain[c]	
Insulin Resistance			Studies of lipids, hepatic function, and glucose homeostasis
Renal/blood pressure	Renal ultrasound[d] BP measurement	BP measurement	Assessments of renal function
Cardiac	Echocardiogram[d]		
Hematologic			Complete blood count

[a] As soon as teeth are present

[b] Until skeletal maturity

[c] After the age of 10 years, there is uncertainty about screening yearly vs every other year

[d] If not previously performed and there is any clinical suspicion

Figure

Conclusion

MOPDII may be considered in the differential diagnosis of unexplained symmetric IUGR specially with family history of consanguinity. More case reports and long-term follow up results are highly needed to guide our evidence-based management plans of such cases.

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