

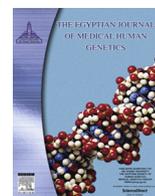
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The Egyptian Journal of Medical Human Genetics

journal homepage: www.sciencedirect.com

Case Report

Microcephalic osteodysplastic primordial dwarfism (MOPD) type I with severe anemia and MRI brain findings of MOPD type II

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ARTICLE INFO

Article history:

Received 28 March 2017

Accepted 18 April 2017

Available online 2 May 2017

Keywords:

Microcephalic osteodysplastic primordial dwarfism type I

Intrauterine growth retardation

Dilatation of internal carotid artery

Severe anemia

Skeletal anomalies

Subcutaneous fat

Superficial veins on skin

Aneurysm of internal carotid artery

ABSTRACT

We report a 4 month old male, 4th in order of birth of healthy consanguineous Egyptian parents with typical characteristics of microcephalic osteodysplastic primordial dwarfism most probably belongs to type I (MOPD I). The patient had intrauterine growth retardation, sparse scalp hair, sparse eyebrows and eyelashes, high arched palate, micrognathia, low set ears, short neck, clenched fists, groove between thumb and palm of hand, arachnodactyly, flexion contractures of elbow and knee. He also had thin dry skin with marked decreased subcutaneous fat and prominent superficial veins over chest and abdomen and mild hypertrichosis over lower back and buttocks. However, the patient had severe anemia and MRI brain findings revealed global hypovolemic brain changes in the form of dilated ventricles and widened cortical sulci, multiple old vascular insults and aneurismal dilatation of right internal carotid artery (ICA) which are consistent with MOPD II.

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1. Introduction

Primordial dwarfism is a very rare form of dwarfism beginning in early stages of intrauterine life and results in a smaller body size in all stages of life [1]. Primordial dwarfism is a very heterogeneous group of disorders and it has been classified into three main types: Seckel syndrome, microcephalic osteodysplastic primordial dwarfism (MOPD) type I/III and type II [2].

Microcephalic osteodysplastic primordial dwarfism (MOPD) is a syndrome characterized by the presence of intrauterine growth restriction, post-natal growth deficiency, microcephaly and a similar phenotype to Seckel syndrome. This condition was initially described by Majewski et al., [3] who characterized three distinct syndromes which he named microcephalic osteodysplastic primordial dwarfism types I, II and III. Majewski et al. also established the difference between these and Seckel syndrome due to the severity in the growth retardation, the presence of bone abnormalities and mild or absent mental retardation [4–7].

We report a case with the typical features of microcephalic osteodysplastic primordial dwarfism type I who had in addition

some unreported features most probably belongs to MOPD II after taking consent of the parents.

1.1. Case report

A 4 month old male, 4th in order of birth of 1st cousin consanguineous marriage. The patient was delivered at full term by cesarean delivery after uncomplicated pregnancy with no history of fever, drug intake or smoking by the mother. His birth weight was 1.6 kg (<5th percentile). The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of poor weight gain. At birth the patient was admitted to neonatal intensive-care unit (NICU) for 23 days for jaundice. At the age of 1.5 month he developed vomiting with every breast feeding not associated with fever or diarrhea. The mother added artificial milk formula without improvement. At the age of 75 days, he was readmitted to NICU for dehydration and blood transfusion was given once for anemia. At the age of 3 months, he was readmitted to hospital for refusal of oral intake and vomiting and a nasogastric tube was applied for feeding. He developed anemia and blood transfusion was given once more during admission. He also had attacks of convulsions and started Tiratam therapy. Gradually there was improvement of oral intake and the patient was discharged from hospital and he could gain 400 g within one month.

Peer review under responsibility of Ain Shams University.

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Family history revealed previous sib death at the age of 40 days with the same condition who also developed anemia. He had two other healthy sibs. Both parents were normal.

On examination, his weight was 2.600 kg (below 5th percentile), his length was 41 cm, (below 5th percentile), his span was 41 cm, and his skull circumference was 31.5 cm (below 5th percentile). The patient had sparse hair on the posterior part of the scalp and absent hair on anterior part of the scalp, sparse eyebrows and eyelashes, high arched palate, micrognathia, low set posteriorly rotated ears, short neck, clenched fists with a groove between thumb and palm of hand, arachnodactyly, flexion contractures of elbow and knee joints, thin dry skin with marked decreased subcutaneous fat and prominent superficial veins over chest and abdomen (Figs. 1, 2). He also had mild hypertrichosis over lower back and buttocks and thin wrinkled skin (Fig. 3).

Abdominal examination revealed bilateral inguinal hernia (Fig. 4). Cardiac, genital and neurologic examinations were normal.

Abdomino-pelvic ultrasonography and ECHO cardiography were normal. Extended metabolic screen, Karyotype and barium swallow were also normal.

Complete blood picture revealed HGB 10 g/dL, platelets 478 000/cm, serum iron 87 µg/dl (normal range 50–120), serum total

iron binding capacity 266 (normal range 250–450), serum transferrin 32 (normal range 20–50). Kidney and liver function tests were normal.

Plain X-ray of the chest revealed bell-shaped thoracic cage with eleven pairs of ribs. Lateral view of the spine revealed mild lumbar kyphosis. The lumbar vertebrae are oval in shape with small central peaking. Plain X-ray of the left wrist revealed absence of carpal ossific centres (Fig. 5).

MRI brain revealed aneurysmal dilatation of the internal carotid artery associated with multiple old infarcts. Ventricular dilatation is also seen indicating atrophic brain changes (Fig. 6).

2. Discussion

Microcephalic osteodysplastic primordial dwarfism (MOPD) has three subtypes I, II, III. Although MOPD I and III were originally described as two separate entities on the basis of radiological criteria mainly in long bones and pelvic bones, later reports confirmed that the two forms represent different expression of the same syndrome. MOPD I commonly has hair thinness in scalp, eyelashes and eyebrows, protruding eyes, prominent nose with a flat nasal bridge, small low-set ears, micrognathia, small chin and short



Fig. 1. a) Marked decreased subcutaneous fat, micrognathia and low set ears b) Sparse scalp hair, sparse eyebrows and eyelashes with loss of hair in anterior two thirds of scalp c) High arched palate and short neck.



Fig. 3. a) Prominent superficial veins over chest and abdomen b) Groove between thumb and palm of hand c) Arachnodactyly and clenched fist d) Thin dry skin over both legs and deviated toes.



Fig. 3. Mild hypertrichosis over lower back and buttocks with thin wrinkled skin and loss of subcutaneous fat.



Fig. 4. Bilateral inguinal hernia.

neck. They suffer from short vertebrae, elongated clavicles, bent femora, hip displacement, corpus callosum agenesis and microcephaly [8]. MOPD II often has additional problems as squeaky voice, microdontia, widely spaced primary teeth, poor sleep patterns especially in early years, normal or near normal mental

development, eating and breathing problems, hyperactivity, far sightedness, brain aneurysms, dislocated joints, scoliosis and delayed bone age [8–10].

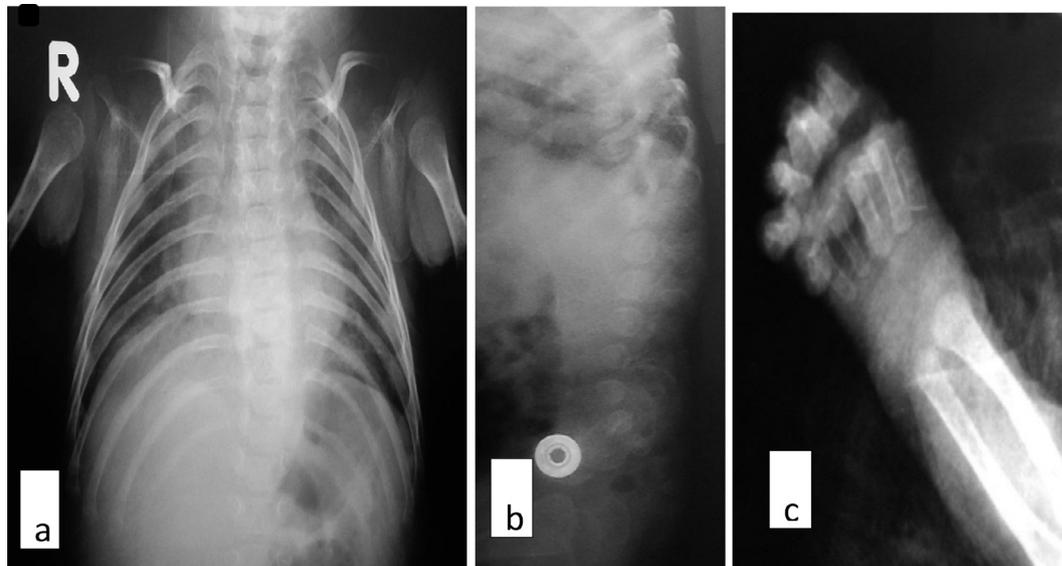


Fig. 5. a) Plain X-ray of the chest shows bell-shaped thoracic cage with eleven pairs of ribs; b) Plain X ray lateral view of the spine shows mild lumbar kyphosis. The lumbar vertebrae are oval in shape with small central peaking. c) Plain X-ray of the left wrist reveals absence of carpal ossific centres.

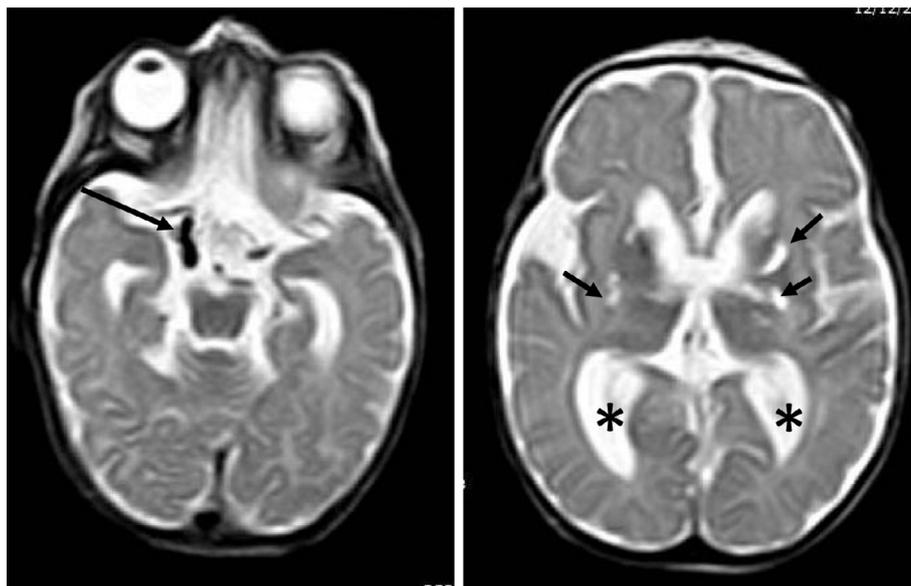


Fig. 6. MRI of the brain (axial T2-WI) shows aneurysmal dilatation of the internal carotid artery (long arrow), associated with multiple old infarcts (multiple short arrows). Ventricular dilatation (*) is also seen indicating atrophic brain changes.

We report a 4 month old male with MOPD most probably belongs to type I. At present, only around 40 patients with MOPD I have been reported according to the Human Gene Mutation Database [11]. MOPD I is usually severe and the patients do not generally live beyond the age of 3 years [2]. The patients present with severe intrauterine and postnatal growth retardation, microcephaly and facial dysmorphism [2]. Our patient was delivered at full term; however, his birth weight was below 5th percentile. He also had high arched palate, micrognathia and low set posteriorly rotated ears. Our patient had fine dry and sparse scalp hair in posterior third of the scalp with loss of hair in anterior two thirds, sparse eyebrows and eyelashes. The skin of our patient is dry with loss of subcutaneous fat as usually detected in MOPD I. Sigaudy et al. reported cases of microcephalic osteodysplastic primordial dwarfism I characterized with skin abnormalities, and sparsity of hair and eyebrows [12].

Our patient suffered poor suckling and frequent vomiting which necessitated application of a nasogastric tube for feeding at the age of 3 months. He also had severe normochromic normocytic anemia which required blood transfusion. Also his old similarly affected brother died from severe anemia as reported by the mother. Several infants with MOPD II had anemia and one patient had severe anemia which required bone marrow transplantation [1]. However, this anemia was not reported in MOPD type I.

Our patient had slender body, decreased subcutaneous fat and prominent superficial veins over chest and abdomen. He also had clenched fists, groove between thumb and palm of hand, arachnodactyly and flexion contractures of elbow and knee joints. Affected individuals with MOPD I had short limbs with brachydactyly and joint contractures [13]. In addition, bilateral preaxial polydactyly with bilateral hypoplastic thumbs were reported in MOPD I [4].

Coarctation of aorta, Tetralogy of Fallot, atrial septal defect and small ventricular septal defect [12] were reported in patients with MOPDI [13]. Our patient had normal echocardiography. Renal abnormalities, which were not detected in our patient, have been detected in MOPD I including unilateral polycystic dysplastic kidney, renal hypoplasia and renal cysts [12,13]. Males with MOPDI have cryptorchidism and micropenis [12]. Our patient had normal male genitals and bilateral inguinal hernias. Endocrine abnormalities in MOPDI, which were not detected in our patient, include central hypothyroidism, diabetes insipidus, and increased aldosteronism [14].

In our patient skeletal survey revealed absence of carpal ossification centres, bell-shaped thoracic cage with eleven pairs of ribs, mild lumbar kyphosis and the lumbar vertebrae are oval in shape with small central peaking. Radiologic abnormalities in MOPDI include delayed bone age, retarded epiphyseal maturation, cleft vertebral arches, platyspondyly, horizontal acetabular roofs, short long bones with enlarged metaphyses, 11 pairs of ribs and Long clavicles [4,13]. Joint dislocations have been also described in these patients [15].

Neurological findings in MOPDI typically include profound developmental delay, blindness, hearing deficits, central nervous system malformations, early-onset epilepsy and neuroendocrine dysfunction [14]. Brain anomalies reported in these patients are hypoplasia/agenesis of corpus callosum, abnormalities of migration, heterotopias, hypoplastic frontal lobes and vermis agenesis and lissencephaly [9], hypoplastic cerebrum, paucity of cortical gyri, pachygyria, periventricular heterotopia, thin corpus callosum, cerebellar hypoplasia, and delayed myelination [14]. Our patient MRI brain revealed aneurysmal dilatation of the internal carotid artery associated with multiple old infarcts, which were not reported before in MOPDI. Ventricular dilatation is also seen indicating atrophic brain changes. Enlarged ventricles were seen in MOPD II which may imply that there are relatively fewer neurons present than expected for relative head size, or possibly atrophy in some cases. Imaging in MOPD II has revealed abnormalities of arterial structure described as Moya Moya disease, tortuous vessels, or multiple cerebral aneurysms and affected patients have a high risk of stroke secondary to progressive cerebral vascular anomalies [16].

MOPDI is caused by homozygous or compound heterozygous mutation in the RNU4ATAC gene, encoding a small nuclear RNA (snRNA) component of the U12-dependent (minor) spliceosome, on chromosome 2q14.2 and is inherited in an autosomal recessive manner [13]. Mutations in the pericentrin (PCNT) gene cause MOPDII. PCNT has a role in cell division, cytokinesis, and proper chromosome segregation [17,18]. The disruption of pericentrin would induce mislocalization of proteins, which is crucial for microtubule nucleation or organization, and subsequently cause mitotic spindle defects, mitotic failure, chromosome missegregation, cell arrest, and/or cell death. This overall reduction in the number of cells leads to short bones, microcephaly, and the other signs and symptoms of MOPDII [19].

Consanguinity rate is high in Egypt [20]. There is consanguinity between the parents and there was a history of a similarly affected previous sib which is in favor of autosomal recessive inheritance as is usually reported [4].

At this time there are no specific treatments for MOPD1. Treatment is generally supportive and the prognosis is poor for affected individuals [2].

To conclude:

We report a patient with typical characteristics of microcephalic osteodysplastic primordial dwarfism most probably belongs to type I. MOPD I phenotype consists of severe IUGR,

microcephaly, neuronal migration abnormalities, absent/sparse hair including scalp hair, eyebrows and eyelashes, dry and aged-appearing skin, multiple joint contractures and skeletal anomalies. Our case had classical features of MOPD I described above and in addition had unusual association with severe anemia, multiple old vascular insults and fusiform dilatation of right internal carotid artery which were described in MOPDII. Molecular diagnosis is essential to confirm our diagnosis of MOPD I. If proved to be type 1, this will widen the MRI findings of type 1 and occurrence of severe anemia.

Conflict of interest

None.

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