INTRODUCTION

The Miller-McKusick-Malvaux (3-M) syndrome is a rare autosomal recessive disorder with fewer than 100 cases reported globally. According to Nosology and Classification of Genetic Skeletal Diseases, 3-M syndrome is classified under the “Slender Bone Dysplasia Group.” Patients with 3-M syndrome exhibit unique facial characteristics, normal mental development, and significant intrauterine and postnatal growth retardation. Among the radiographic features is the slender look of long tubular bones, tall vertebrae with short anteroposterior diameter, and a narrow pelvis. The genetic aetiology of 3-M syndrome is heterogeneous, with CUL7 (MIM 609577), OBSL1 (MIM 610991), and CCDC8 (MIM 614145) variants found in the aetiology. The CUL7 mutations are the predominant gene deficiency associated with the disease. However, Clayton et al. (2012) imply that additional genes, most likely in the same growth regulation system, may be involved in the etiology. Therefore, given the rarity of the condition, further research is necessary to fully understand the molecular mechanisms involved in the development of 3-M syndrome.

CASE

Family history and diagnosis

A 4-year-old boy was diagnosed at the age of 9 months with the 3-M syndrome through karyotyping, which revealed a pathogenic mutation in the CUL7 gene (OMIM #273750). The patient’s parents were first-degree cousins and had previously given birth to one healthy child. Notably, there were no prior reports of 3-M syndrome within the family, though the patient’s maternal uncle exhibited short stature.

Neonatal Presentation and Dysmorphic Features

The patient was delivered via lower segment cesarean section at 39 weeks of gestation. At birth, the patient weighed 2.63 kg, which fell within the 5th percentile for weight. However, his head circumference was notably larger, measuring 37.5 cm and exceeding the 97th percentile. The patient presented with multiple characteristic dysmorphic features, as depicted in Figure 1, including short limbs, hyperlaxity (joint hypermobility), hypertelorism (increased distance between the eyes), a high arched palate, bluish discoloration around the knuckle of the right hand, simian crease, a relatively large head, disproportionate limbs, short stature, pronounced short thighs and feet. Additionally, the patient exhibited a narrow and short chest, a relatively large abdomen, bilateral club foot, and a blue sclera. A further follow up at the age of 4 reported that the patient height was 80 cm, indicating delayed development.

Coexisting Medical Conditions

At three years of age, the patient was diagnosed with steroid-dependent nephrotic syndrome, a kidney disease characterized by proteinuria and low levels of blood protein. To manage this condition, the patient is currently receiving cyclosporine.

Neurological and Radiographic Findings

The patient underwent a brain MRI which revealed that the third and lateral ventricles were prominent with no evidence of active CSF flow. The fourth ventricle was of normal calibre and...
cerebral aqueduct appeared grossly normal, Corpus callosum was slightly thinned. Upon further examination, the patient’s skull X-ray revealed the presence of multiple void areas within the skull, distinct from the fontanelles. Echocardiography showed evidence of a small patent ductus arteriosus (PDA) and mild Tricuspid Regurgitation (TR).

Operations

The patient was admitted to the neonatal intensive care with respiratory distress and had bilateral inguinal hernias operated on and a bilateral club foot treated by casts.

INFORMED CONSENT

A written consent form was obtained from the patient’s family for the publication of images and materials as part of this case report.

DISCUSSION AND REVIEW OF THE LITERATURE

This case report identified one Jordanian child with a homozygous mutation in the CUL7 gene. The patient had most of the typical clinical features for the 3-M syndrome besides mild Tricuspid Regurgitation (TR), blue sclera, and nephrotic syndrome. Genetic testing confirmed the diagnosis of the 3-M syndrome, with the detection of a homozygous mutation in the CUL7 gene (OMIM #273750), (c.2416C>T) (p.Arg806). The present case report elucidates the clinical and molecular characteristics of the patient, with the aim of contributing new information to the existing literature on 3-M syndrome.

In 1975, the 3-M syndrome was first described by Miller, McKusick, and Malvaux. The 3-M is derived from the initials of the three researchers who first identified it.6 The 3-M syndrome is characterized by severe growth retardation, low birth weight, dysmorphic facial features including macrocephaly, frontal bossing, a triangular face, a pointed and prominent chin, a fleshy and upturned nose, full lips, full eyebrows, a long philtrum, and a flattened malar region. Radiological abnormalities and abnormal skeletal features are also reported including foreshortened lumbar vertebral bodies, small pelvis and slender long bones and ribs, short neck, square shoulders, prominent trapezius, short thorax, pectus deformity, increased mobility of the joints, hyperlordosis, clinodactyly, and prominent heels. Individuals diagnosed with 3-M syndrome typically exhibit normal intelligence, as reported in previous studies.7-9

The leading cause of this condition is mutations in the coiled-coil domain containing 8 (CCDC8) proteins and genes encoding obscurin-like 1 (OBSL1) and cullin 7 (CUL7).10-13 Researchers discovered 25 distinct mutations in the cullin-7 gene in 29 families with the 3-M syndrome.14,15 These mutations lead to antenatal and postnatal growth retardation as a result of resistance to the growth hormone and insulin-like growth factor. However, the exact mechanism that causes growth impairment associated with 3-M syndrome has not been discovered till now.5, 12, 13

Approximately 100 patients with 3-M syndrome have been reported in the medical literature to date.1 As with this reported patient, many neonates with 3-M syndrome are initially diagnosed with achondroplasia. Despite similarities in presentation, clinical and radiographic features of achondroplasia can be distinguished from those of 3-M syndrome. Notably, the absence of typical radiographic findings and less severe short stature compared to 3-M syndrome can help to exclude the possibility of achondroplasia. Moreover, children with 3-M syndrome are substantially shorter at birth than those with achondroplasia. Russell Silver syndrome (RSS) is another differential diagnosis for 3-M syndrome. The characteristic limb asymmetry of RSS is absent in the 3-M syndrome, and facial features are also distinct. In Mulibrey nanism, another possible diagnosis, a J-shaped sella turcica, and hepatosplenomegaly may be distinctive. Dubowitz syndrome is another disorder that should be considered in the differential diagnosis of 3-M syndrome. Dubowitz syndrome is distinguished by microcephaly, skin lesions such as eczema, distinctive facial features (small face, sloping forehead, broad nasal bridge, road nasal tip, short palpebral fissures, telecanthus, ptosis, dysplastic ears), and intellectual disabilities (ID).4, 16

Due to the characteristic coarse facial features and diminutive
involvement of unknown gene(s). 

22 The first gene variants of CUL7, OBSL1, and CCDC8 pathogenic variants suggests the presence of 3-M syndrome patients devoid of CUL7 pathogenic variants, including frameshift, nonsense, and missense mutations, have been reported in 3-M syndrome patients to date.23, 24

The CUL7 c.418 419delAC p.(Thr140Cysfs*11) protein mutation results in an early termination codon at position 140 of the CUL7 mRNA. CUL7 is a member of the cullin family, which consists of seven cullins (CUL1, 2, 3, 4A, 4B, 5, and 7) that serve as scaffolds in the assembly of a multisubunit ubiquitin ligase (E3s).21 CUL7 interacts with other cellular proteins (SKP1, FBXW8, and ROC1) to form an E3 ubiquitin ligase complex that promotes ubiquitination. Numerous vital biological processes, including cell cycle progression, cell proliferation, apoptosis, and signal transduction pathways, depend on it for normal operation. CUL7 is essential for fetal growth and development, including lung development, endochondral ossification, and chondrogenesis. Variants in CUL7 may contribute to the disruption of the GH and IGF-I signaling pathways via IRS-1 deposition; this accumulation results in increased activation of ACT and MAPK, and overstimulation may contribute to cellular senescence. Recently, variants in OBSL1 and CCDC8 were found in 3-M patients without CUL7 variants. Importantly, the variants in these three genes occurred in a mutually exclusive manner, strongly indicating that OBSL1, CCDC8, and CUL7 are all involved in the same pathway, known as the 3-M complex.22

The dysfunction of this complex causes severe defects in microtubule dynamics, chromosome separation, cell survival, and organism growth.

CONCLUSION

In conclusion, this case report presents a patient with 3-M syndrome and a homozygous mutation in the CUL7 gene, expanding the mutational spectrum of this rare autosomal recessive disorder. The patient exhibited typical clinical features of 3-M syndrome along with mild Tricuspid Regurgitation, blue sclera, and nephrotic syndrome. This report highlights the importance of considering 3-M syndrome in the differential diagnosis of patients with short stature and characteristic facial features, despite the presence of other inconsistent findings. It is particularly crucial to raise awareness about rare autosomal recessive genetic disorders in countries with a high rate of consanguineous marriage, such as Jordan.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHORS CONTRIBUTION

Aseel Alkhawaldeh and Nancy Hakooz were responsible for the data collection of the case and original writing; Ahmad Alsayed wrote the literature review, revised and edited the manuscript; Sara Abudahab revised and edited the manuscript; Jumana Albaramiki and Dana Shibli were the physicians treating the patient.

The involvement of unknown gene(s). Nonetheless, the presence of 3-M syndrome patients with moderate motor developmental delay and normal intelligence. For instance, a case study describes a 3-year-old patient with moderate developmental delay, particularly in speech, who had a history of embryonic distress after birth, seizures, and feeding difficulties. This patient experienced embryonic distress after birth, necessitating resuscitation and a three-week neonatal intensive care unit stay. During the investigation of developmental delay, cranial MRI revealed cerebellar atrophy and volume loss in the brain stem and supratentorial regions.

Radiographic findings in the 3-M syndrome may not be detected during the first 2 years of life; however, these findings can be detected after. Typical radiological findings include thin long bones, a reduction in the posteroanterior diameter of vertebral bodies, delayed bone age, and a narrow pelvis. Kyphoscoliosis and distal ulnar shortening are uncommon in these patients. It has been suggested that patients with CUL7 mutations have a lower incidence of bone abnormalities.

The genetic etiology of the 3-M syndrome is heterogeneous. Previous research has implicated homozygous or compound heterozygous pathogenic variants in the etiology of CUL7 (MIM 609577), OBSL1 (MIM 610991), and CCDC8 (MIM 614145). Nonetheless, the presence of 3-M syndrome patients devoid of CUL7, OBSL1, and CCDC8 pathogenic variants suggests the involvement of unknown gene(s). The first gene variants linked to the 3-M syndrome were identified by Huber et al. as CUL7 pathogenic variants. More than 40 distinct CUL7 pathogenic variants, including frameshift, nonsense, and missense mutations, have been reported in 3-M syndrome patients to date.

The CUL7 c.418 419delAC p.(Thr140Cysfs*11) protein mutation results in an early termination codon at position 140 of the CUL7 mRNA. CUL7 is a member of the cullin family, which consists of seven cullins (CUL1, 2, 3, 4A, 4B, 5, and 7) that serve as scaffolds in the assembly of a multisubunit ubiquitin ligase (E3s). CUL7 interacts with other cellular proteins (SKP1, FBXW8, and ROC1) to form an E3 ubiquitin ligase complex that promotes ubiquitination. Numerous vital biological processes, including cell cycle progression, cell proliferation, apoptosis, and signal transduction pathways, depend on it for normal operation. CUL7 is essential for fetal growth and development, including lung development, endochondral ossification, and chondrogenesis. Variants in CUL7 may contribute to the disruption of the GH and IGF-I signaling pathways via IRS-1 deposition; this accumulation results in increased activation of ACT and MAPK, and overstimulation may contribute to cellular senescence. Recently, variants in OBSL1 and CCDC8 were found in 3-M patients without CUL7 variants. Importantly, the variants in these three genes occurred in a mutually exclusive manner, strongly indicating that OBSL1, CCDC8, and CUL7 are all involved in the same pathway, known as the 3-M complex. The dysfunction of this complex causes severe defects in microtubule dynamics, chromosome separation, cell survival, and organism growth.

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