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Original Research

The first study of 3-M Syndrome in Jordan and Literature Review

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Abstract

The prevalence of 3-M syndrome remains unclear owing to its rarity and the limited number of reported cases in the medical literature. To date, approximately 100 cases of the disorder have been documented in MedlinePlus Genetics. Here, we present the first case study report from Jordan of a boy diagnosed with 3-M syndrome at 9 months of age via karyotyping. The patient exhibited distinct facial features, severe prenatal and postnatal growth retardation, and normal mental development. As rare genetic autosomal recessive mutations are common where consanguineous marriages are prevalent, raising awareness of such rare genetic diseases is critical. This paper aims to provide a case report on 3-M syndrome and a literature review.

Keywords: 3-m syndrome; rare genetic diseases; autosomal recessive disease; genetics; Jordan

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INTRODUCTION

The Miller-McKusick-Malvaux (3-M) syndrome is a rare autosomal recessive disorder with fewer than 100 cases reported globally.[1] 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.[2] 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.[3,4] However, Clayton et al. (2012) imply that additional genes, most likely in the same growth regulation system, may be involved in the etiology.[5] 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.

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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

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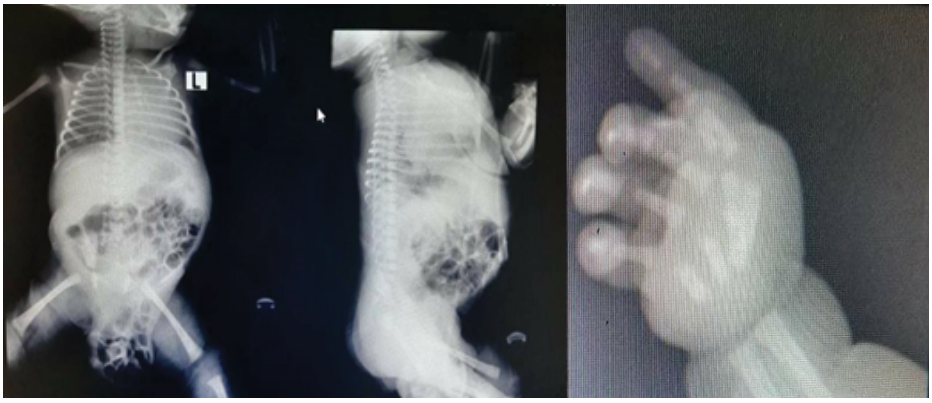

Figure 1. X-ray images, showing typical features of the 3-M syndrome: A pronounced short thighs and feet, narrow and short chest, abdomen relatively large.

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

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stature observed in individuals with 3-M syndrome, many patients are initially suspected of having storage disorders such as mucopolysaccharidoses within the first year of life. However, patients with mucopolysaccharidoses exhibit hepatomegaly, hearing loss, dysostosis multiplex, and ID, in addition to the coarse visage and short stature, which are absent in 3-M syndrome.[4] Intellectual or Developmental Disabilities is not one of the expected manifestations of 3-M syndrome, nevertheless, there have been reports of 3-M syndrome patients with moderate motor developmental delay and normal intelligence.[17, 18] 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.[19]

Radiographic findings in the 3-M syndrome may not be detected during the first 2 years of life;[5, 16] 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.[20] It has been suggested that patients with CUL7 mutations have a lower incidence of bone abnormalities.[21]

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).[22] 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.[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.[25] 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.

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References

1. 3-M syndrome. Accessed 16 April 2023, 2023. https://medlineplus.gov/genetics/condition/3-m-syndrome/#frequency
2. Mortier GR, Cohn DH, Cormier-Daire V, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. American journal of medical genetics Part A. 2019;179(12):2393-2419. https://doi.org/10.1002/ajmg.a.61366
3. Spranger JW, Superti-Furga A, Unger S. Bone dysplasias: an atlas of genetic disorders of skeletal development. Oxford University Press, USA; 2018.
4. Akalın A, Şimşek-Kiper PÖ, Taşkıran E, et al. Typical Face, Developmental Delay, and Hearing Loss in a Patient with 3M Syndrome: The Co-Occurrence of Two Rare Conditions. Molecular Syndromology. 2022;13(6):537-542.https://doi.org/10.1159/000524703
5. Clayton PE, Hanson D, Magee L, et al. Exploring the spectrum of 3-M syndrome, a primordial short stature disorder of disrupted ubiquitination. Clinical endocrinology. 2012;77(3):335-342. https://doi.org/10.1111/j.1365-2265.2012.04428.x
6. Miller JD, McKusick VA, Malvaux P, et al. The 3-M syndrome: a heritable low birthweight dwarfism. Birth defects original article series. 1975;11(5):39-47.
7. Hanson D, Murray PG, Sud A, et al. The primordial growth disorder 3-M syndrome connects ubiquitination to the cytoskeletal adaptor OBSL1. The American Journal of Human Genetics. 2009;84(6):801-806.https://doi.org/10.1016/j.ajhg.2009.04.021
8. Huber C, Dias-Santagata D, Glaser A, et al. Identification of mutations in CUL7 in 3-M syndrome. Nature genetics. 2005;37(10):1119-1124.https://doi.org/10.1038/ng1628
9. Temtamy SA, Aglan MS, Ashour AM, et al. 3-M syndrome: a report of three Egyptian cases with review of the literature. Clinical dysmorphology. 2006;15(2):55-64. https://doi.org/10.1097/01.mcd.0000198926.01706.33
10. Hanson D, Murray P, Coulson T, et al. Mutations in CUL7, OBSL1 and CCDC8 in 3-M syndrome lead to disordered growth factor signalling. Journal of molecular endocrinology. 2012;49(3):267. https://doi.org/10.1530/jme-12-0034
11. Khachnaoui-Zaafrane K, Ouertani I, Zanati A, et al. 3M syndrome: A Tunisian seven-cases series. European Journal of Medical Genetics. 2022;65(3):104448. https://doi.org/10.1016/j.ejmg.2022.104448
12. Hanson D, Murray PG, Black GC, et al. The genetics of 3-M syndrome: unravelling a potential new regulatory growth pathway. Hormone research in paediatrics. 2011;76(6):369-378. https://doi.org/10.1159/000334392
13. Hanson D, Murray PG, O'Sullivan J, et al. Exome sequencing identifies CCDC8 mutations in 3-M syndrome, suggesting that CCDC8 contributes in a pathway with CUL7 and OBSL1 to control human growth. The American Journal of Human Genetics. 2011;89(1):148-153. https://doi.org/10.1016/j.ajhg.2011.05.028
14. Huber C, Delezoide A-L, Guimiot F, et al. A large-scale mutation search reveals genetic heterogeneity in 3M syndrome. European journal of human genetics. 2009;17(3):395-400. https://doi.org/10.1038/ejhg.2008.200
15. Vishwakarma P, Dubey A, Kalo D, et al. Identification of a novel mutation (c. 1172_1181 del TGGTGCAAGC (p. Leu391fs) in the CUL7 gene in a patient of 3M Syndrome. Polymorphism. 2022;9:17-22.
16. Huber RS, Houlihan D, Filter KJ. Dubowitz syndrome: a review and implications for cognitive, behavioral, and psychological features. Journal of clinical medicine research. 2011;3(4):147. https://doi.org/10.4021/jocmr581w
17. Hu X, Li H, Gui B, et al. Prenatal and early diagnosis of Chinese 3-M syndrome patients with novel pathogenic variants. Clinica Chimica Acta. 2017;474:159-164. https://doi.org/10.1016/j.cca.2017.09.022
18. Jacob P, Girisha KM. Three M syndrome 2 in two Indian patients. American Journal of Medical Genetics Part A. 2021;185(2):614-616.https://doi.org/10.1002/ajmg.a.61949
19. HabibUllah H, Albaradie R, Bashir S. 3-M syndrome: a local case report. The American Journal of Case Reports. 2019;20:36. https://doi.org/10.12659/ajcr.912736
20. Hennekam RC, Bijlsma JB, Spranger J, et al. Further delineation of the 3-M syndrome with review of the literature. American journal of medical genetics. 1987;28(1):195-209. https://doi.org/10.1002/ajmg.1320280127
21. Maksimova N, Hara K, Miyashia A, et al. Clinical, molecular and histopathological features of short stature syndrome with novel CUL7 mutation in Yakuts: new population isolate in Asia. Journal of Medical Genetics. 2007;44(12):772-778.https://doi.org/10.1136/jmg.2007.051979
22. Dias DC, Dolios G, Wang R, et al. CUL7: a DOC domain-containing cullin selectively binds Skp1 Fbx29 to form an SCF-like complex. Proceedings of the National Academy of Sciences. 2002;99(26):16601-16606. https://doi.org/10.1073/pnas.252646399
23. Simsek-Kiper PO, Taskiran E, Kosukcu C, et al. Further expanding the mutational spectrum and investigation of genotype–phenotype correlation in 3M syndrome. American Journal of Medical Genetics Part A. 2019;179(7):1157-1172. https://doi.org/10.1002/ajmg.a.61154
24. Isik E, Arican D, Atik T, et al. A rare cause of syndromic short stature: 3M syndrome in three families. American Journal of Medical Genetics Part A. 2021;185(2):461-468. https://doi.org/10.1002/ajmg.a.61989
25. Xu X, Sarikas A, Dias-Santagata DC, et al. The CUL7 E3 ubiquitin ligase targets insulin receptor substrate 1 for ubiquitin-dependent degradation. Molecular cell. 2008;30(4):403-414. https://doi.org/10.1016/j.molcel.2008.03.009

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