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3-M Syndrome: A Local Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 3
Final Diagnosis: 3-M syndrome
Symptoms: Severe growth retardation • dysmorphic features and skeletal abnormalities
Medication: None
Clinical Procedure: None
Specialty: Pediatric Neurology

Objective: Rare disease
Background: 3-M syndrome is an uncommon disease characterized by severe growth retardation, dysmorphic features, and skeletal abnormalities. Radiographic images may show delayed bone maturation long slender tubular bones, and tall vertebral bodies. Due to the inheritance mode of 3-M syndrome disease, early diagnosis is vital for genetic counseling.
Case Report: In this case report, we present the case of a 3-year-old male patient who was referred to our clinic for development assessment due to delayed development, particularly speech, who had clinical outcomes of 3-M syndrome.
Conclusions: The aim of the case report is to add this new patient to the literature on 3-M syndrome.

MeSH Keywords: Lead Poisoning, Nervous System, Childhood • Musculoskeletal Abnormalities • Pediatric Assistants

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Background

3-M syndrome is a rare hereditary disorder characterized by severe growth retardation, distinctive facial dysmorphic features, and skeletal abnormalities [1]. The name 3-M is derived from the initials of the 3 researchers who first identified it: Miller, McKusick, and Malvaux [1]. Mutations in any 1 of the following 3 genes – CUL7, OBSL1, and CCDC8 – are responsible for the occurrence of this disorder [1]. It is inherited through an autosomal recessive pattern [1] and is considered very rare, so far less than 100 cases worldwide have been identified.

Individuals with 3-M syndrome suffer from severe prenatal growth retardation due to growth delays during fetal development, resulting in a low birth weight. Growth delays continue after birth throughout childhood and adolescence, ultimately leading to a short stature. Many of the physical features associated with the disorder are congenital. Characteristic craniofacial abnormalities typically include a long, narrow head that is disproportionate to the body size, a broad and prominent forehead, and a triangular-shaped face with a hypoplastic midface, pointed chin, long philtrum, prominent mouth, depressed nasal bridge, fleshy-tipped upturned nose, large ears, and full lips [1–4].

Skeletal anomalies are not present at birth, but develop in the individual and include delayed bone maturation, long and slender tubular bones, and tall vertebral bodies [1,2]. Joint hyper-mobility and increased risk of hip dislocation has been reported in individuals [1,3]. Abnormal spinal curvature, either kyphoscoliosis or hyperlordosis, causing back pain can also occur in this disorder [1,3].

Additional physical abnormalities in some children include an abnormally short, broad neck and thorax, square shoulders, flared shoulder blades, unusual curving of the 5th finger, and prominent heels [1,3,4].

Mutations in the CUL7 gene cause 3-M syndrome, although genetic heterogeneity has been reported involving 2 other causative genes: OBSL1 and CCDC8 [1,3,4]. Since CUL7 is involved in chondrocyte growth and proliferation, in 3-M syndrome, reduced cell mitosis during the early gestation period could be the cause of retarded growth. In particular, these mutations disrupt the ability of the protein cullin-7 to bring together the components of the ubiquitine-proteasome system, which is involved in degradation of unwanted proteins. Therefore, impaired ubiquitination may have a role in the pathogenesis of IUGR in humans.

This is first case report from a local population and adds this new patient to the literature on 3M syndrome.

Case Report

A 3-year-old male patient was referred to the Neurodevelopment Clinic at King Fahad Specialist Hospital, Dammam for development assessment due to delayed development, particularly speech. He was born at 37 weeks of gestation by cesarian section due to failure to progress and fetal distress. He needed resuscitation and oxygen but did not need intubation. His Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores were unknown. His birth weight was 1.6 kg and he stayed in the SCBU for 3 weeks. No other neonatal or feeding problems were found. He had generalized tonic-clonic seizures, which are now under control. He had only 3 episodes of GTC. His parents are first-degree cousins and have 2 healthy children. There is no history of abortion or miscarriage and there is no similar case in the family.

On physical examination, his weight was 8.8 kg (<<3rd centile), height was 77 cm (<<3rd centile) and head circumference 51 cm (75th centile). He also had numerous characteristic dysmorphic features such as a relatively large head, frontal bossing, triangular face, mid-face hypoplasia, bushy eyebrows, depressed nasal bridge, upturned nostrils, and fleshy tip of nose, long philtrum, small pointed chin, micrognathia, prominent mouth, large and protruded ears, chubby square hands, clinodactyly, and lordosis. He also had a short broad neck and thorax, square shoulders, bilateral inguinal hernia, and hypospadias.

His development assessment showed mild global development delay, particularly speech.

Investigations

His metabolic screen, including mucopolysaccharide screen, was normal. His hormone studies, including cortisol, Growth hormones, IGF-2, IGFBP, and testosterone, were normal. MRI brain showed moderate cerebellar atrophy with brain stem and supratentorial volume loss. A skeletal maturation study showed delayed bone age about 1 year less than chronological age. but did not reveal slender long bones or tall vertebral bodies.

Genetic

CGH array showed excessive homozygosity encompassing at least 12% of the genome. By whole-exome sequencing, a homozygous variant in the CUL7 gene, c.3115-1G>C; Chr6 (GRCh37): g.43013141C>G, was detected. This has been previously described as disease-causing 3-M syndrome. Therefore, a diagnosis of 3-M syndrome was confirmed.

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Discussion

The clinical features and genetic testing in our patient confirmed the diagnosis of 3-M syndrome, but our patient did not show the radiological findings like slender long bones or tall vertebral bodies. Our patient also showed mild development delay, while patients with 3-M syndrome have normal cognitive development and intelligence. While looking for the cause of delayed development, an MRI brain showed cerebellar atrophy with brain stem and supratentorial volume loss.

3-M syndrome is characterized by a triangular-shaped face with frontal bossing, mild malar hypoplasia, depressed nasal bridge with a fleshy tip of nose, upturned nares, and full lips. Patients usually have large heads for their height, dolichocephaly, and normal intelligence. Other clinical findings are a short wide thorax, brachydactyly, clinodactyly, micromelia, and prominent heels. Both sexes are affected equally. No hormonal deficiencies are detected. Our patient had almost all of the typical clinical features, along with the above-mentioned bony abnormalities, but did not show radiological findings of slender long bones with thin diaphysis and tall vertebral bodies. These findings may appear later in some patients. The radiographic examination, although abnormal, is not diagnostic, as similar X-ray changes have been documented in other disorders.

Maksimova et al. reported on 43 patients with short stature, hydrocephaloid skull, and typical face in an isolated Yakut population. Although clinical findings were similar to 3-M syndrome but slender long bones and tall vertebral bodies have not been commonly observed in this short-stature syndrome in Yakuts (3), as in our patient [5].

Le Merrer et al. (1991) reported the cases of 9 children with primordial dwarfism and facial dysmorphism characterized as 'gloomy face.' Despite very short stature, there were no radiologic abnormalities of the skeleton and no hormone deficiency was found [6]. Le Merrer et al. (1991) suggested that this was a distinct disorder with features of 3-M syndrome [6].

Physical findings of several entities such as Silver-Russell syndrome (SRS) are similar to 3-M syndrome. Silver-Russell syndrome has many similarities with 3-M syndrome: intrauterine growth retardation, short stature, triangular face, relatively large skull, asymmetry of body or limbs, and clinodactyly. Mild mental retardation also can be found in patients with SRS, but abnormalities of the skeletal system have not been reported. Our patient showed mild developmental delay, as in SRS, but had positive homozygous variant in the CUL7 gene, which confirms 3-M syndrome. The mode of inheritance is autosomal recessive in 3-M syndrome. CUL7 mutation in 6p21.1 has been found in several families [7].

Using direct sequencing, Huber et al. (2005) found 25 distinct mutations in the cullin-7 gene (CUL7; 609577) in 29 families with 3-M syndrome [7].

In all 43 affected individuals with Yakut short-stature syndrome, Maksimova et al. (2007) identified homozygosity for a founder mutation in the CUL7 gene [5]. Delayed bone age (3) has been reported in 3M syndrome patients; our patient's was 1 year behind his chronological age.

Our patient had an incidental finding of cerebellum atrophy with volume loss of the brain stem and supratentorium, which has not been previously reported in the literature.

Conclusions

An early diagnosis is important for genetic counseling in 3-M syndrome, especially in countries like Saudi Arabia, where consanguineous marriages are common, and autosomal recessive genetic disorders leading to severe short stature should be kept in mind.

3-M syndrome should always be considered in the differential diagnosis of patients with growth retardation of prenatal onset.

Conflict of interest

None.

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