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3M Syndrome, Unprecedented Variants in the CUL7 Gene: In Barranquilla - Colombia: Case Report

William Quessep – Mendoza[1], Angelica Mendoza – Caballero[1], Ronil Mercado[1], Maria Maestre[2], Jorge Ordoñez[3]

[1, 2, 3]Pediatric Fellow of Simon Bolivar University; Barranquilla, Colombia
Email id: *william.quessep[at]unisimon.edu.co*

[4]Pediatric Fellow of Libre University; Barranquilla, Colombia

[5]Pediatric Endocrinologist; Barranquilla, Colombia

Abstract: ***Miller, MacKusich, Malvaux, name 3M Syndrome, an autosomal recessive disorder expressed mainly by pathogenic variants in 3 genes (CUL7, OBS 1, CCDC8), characterized by growth retardation that can occur from prenatal stages to adult life associated with clinical characteristics such as osteoarticular alterations, craniofacial dysmorphisms, intellectual capacity and normal endocrine function, the diagnosis initially clinical and always associated with low height in the patients who consult, with findings in the genetic profile that show pathogenic variants in genes, CUL7, OBS 1, CCDC8, with the CUL7 gene being the one that reports the most cases. There is no specific treatment for these patients and management is carried out according to associated alterations. We probably describe a unique case of 3M syndrome worldwide found in Barranquilla. Colombia***

Keywords: 3M syndrome, CUL7 gene mutation, Phenotype, Recombinant growth hormone, ClinVar.

1. Introduction

The 3M syndrome, named after the initial of its 3 authors (Miller, MacKusich, Malvaux), is an autosomal recessive disorder expressed mainly by pathogenic variants in 3 genes (CUL7, OBS 1, CCDC8) [1,2] , is characterized by a growth delay that can occur from prenatal stages with IUGR (intrauterine growth restriction) to adult life; It is associated with clinical characteristics such as osteoarticular alterations, craniofacial dysmorphisms, intellectual capacity and normal endocrine function [1]. Currently without a specific treatment, but the use of exogenous growth hormone may be useful to achieve a final height close to the ideal for age [3,4]. The present study reports the discovery of de novo variants of the CUL7 gene not reported in the ClinVar database, associated with the clinical and phenotypic characteristics of the patient that lead to the 3M syndrome.

2. Clinical Case

Male schoolboy, 10 years and 3 months old, product of first pregnancy, at 38 weeks term; mother with a prenatal history of chickenpox infection in the first trimester, born by cesarean section due to acute fetal distress, Apgar score unknown, (Birth weight: 2,300g – Birth size: 37cm – Head circumference at birth: 32cm) with birth restriction intrauterine growth (IUGR); pathological history of morbid obesity, short stature, and childhood asthma; They do not report a family history. Patient with inadequate eating habits, no physical activity and good school performance. At the time of the pediatric endocrinology evaluation, the family member reported disproportionate weight gain in recent months in addition to having short height compared to his classmates; Physical Examination: Vital signs within normal parameters, Height: 116cm for 6 years 2 months outside -3 S.D. Zscore: -3.47, Weight: 53kg (Ideal weight/height 21kg), BMI: 39.4, BMI/Age: -3.47 , Head circumference: 51cm; dolichocephaly is evident, triangular face, almond-shaped eyes, depressed nasal bridge, pointed chin, large ears, long nasolabial fold, wide and short neck, kyphoscoliosis, square shoulders, hyperlordosis, gynecomastia, globose abdomen due to adipose tissue, infantile penis with 2-sized testicles cc volume, pubic hair in taner 2, extremities with hands and feet small for their size, clinodactyly of the fifth finger, short little finger, prominent heels, bilateral cubitus valgus, skin with acanthosis nigricans in folds of the neck, armpits, waist, crotches , knuckles of hands and feet; Skin stretch marks on the abdomen, shoulders, buttocks and thighs (See Figure 1). Requested paraclinics are reviewed and report blood count without alteration of cell lines, normal liver, kidney and pancreatic function, normal lipid profile, normal blood glucose, normal coagulation times with respect to controls, Hormonal profile (levels of somatomedin C, IGF-2 (Insulin growth factor type 2), IGFBP (Insulin-like growth factor binding protein) and Cortisol with normal results for their age, free testosterone levels, LH (Luteinizing Hormone), FSH (Follicle Stimulating Hormone) low for age); Likewise, imaging studies are performed with a contrast-enhanced abdominal CT report that shows hepatic steatosis, testicular ultrasound with atrophy and bilateral cryptorchidism, Carpogram that reports a bone age of 9 years 6 months with a chronological age of 10 years, it is evident in a lumbosacral radiograph that It shows lumbar hyperlordosis with a Cobb angle of 51.23º (See Figure 2). It is subsequently evaluated by genetics who consider performing individual complete exome sequencing to define genetic syndrome associated with obesity and short stature, which reports that two probably pathogenic variants

were identified in the CUL7 gene in a heterozygous state; the c.2428C>T variant; p.(Arg810*) c and the variant c.2398.2A>G; p.(?) which has been associated with 3M Syndrome. To date, no functional analyzes of this variant have been published, nor has it been reported in individuals with pathology related to the gene. A complete exome report is received in consultation, due to phenotypic and clinical characteristics and based on the genetic study, the presence of 3M Syndrome is confirmed.

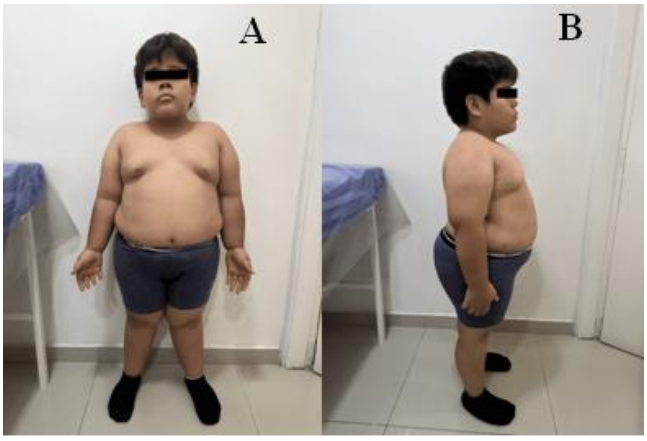

Figure 1: Photographs of a patient with 3M syndrome A) Dolichocephaly, triangular face, depressed nasal bridge, pointed chin, large ears, long nasolabial fold, wide and short neck, gynecomastia, globose abdomen due to adipose tissue, extremities with hands and feet small for their size, bilateral cubitus valgus. B) Hyperlordosis, skin with acanthosis nigricans in waist folds, skin stretch marks on shoulders, breasts, abdomen.

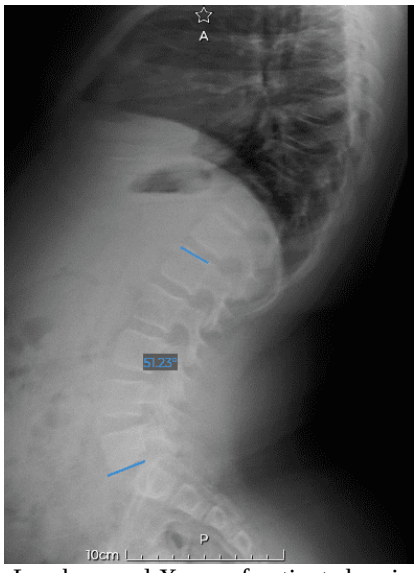

Figure 2: Lumbosacral X-ray of patient showing lumbar hyperlordosis with Cobb angle at 51.23º

3. Discussion

3M syndrome is an autosomal recessive disorder first described in the 1970s by Miller, MacKusich, and Malvaux, named after the initials of their last names. Its origin is due to the expression of specific mutations in three different genes (CUL7, OBS1, CCDC8); CUL7 representing 77.5% of the genetically confirmed pathogenic variants [2,3,4].

The main clinical characteristics are characterized by delayed growth from the prenatal and postnatal stages, childhood and/or adolescence, associated osteoarticular alterations, craniofacial dysmorphisms, intellectual capacity and normal endocrine function. There have been very few cases that have currently been reported in the medical literature, with a prevalence that is not clearly identified, with an approximate estimate of 200 cases reported to date [1,5].

There is no specific treatment for 3M-S, some data reported on the usefulness of growth hormone (GH), mainly in the prepubertal period, would show better results than after this stage to reach a height close to the ideal for age; However, other studies contradict the benefit of the use of exogenous GH [2], with multidisciplinary follow-up with the specialties of Endocrinology, Genetics, Orthopedics and Child Psychology.

It is considered that there is an under-reporting of the 3M syndrome due to the inadequate clinical and therapeutic approach to short stature, a fact reflected in the scarcity of reports published in the world literature [6]. Although we do not have a segregation analysis of the variant identified in the patient's relatives to determine the de novo and/or inherited origin, we can affirm that our patient is a unique case due to the variants found in the CUL7 gene, not previously reported in the ClinVar database.

The clinical phenotype and the genetic report confirm the diagnosis of our patient, in addition, we found typical radiological findings of the condition, likewise, we have postnatal histories with a diagnosis of IUGR that coincides with the vast majority of reports described in the literature.

Although the reason for consultation due to short stature and age at which the patient presented to the pediatric endocrinology team at our institution was 10 years old, we recognize a major limitation that is the lack of knowledge of the historical growth pattern; However, we agree with Khaoula K et al [6], who reported in 2022 a series of seven cases of 3M syndrome in Tunisia, specifically in patient 1 of family A, where the reason for consultation, age of presentation, birth weight and physical examination are practically similar, except that hypogonadism was not reported, a fact that was identified in our patient during the physical examination and due to low testosterone levels for age; finding that is not present in all male patients as described by PelinOzlem [7] in two male individuals with 3M syndrome and Cristina Meazza [8] in her report of 3M syndrome, associated with hormone deficiency of growth.

Our patient also has obesity, a fact not related to the 3M syndrome; Ming Yang [9] reports a case that presents with the development of morbid obesity after treatment with rhUGF-1 (Recombinant human insulin-like growth factor 1), associated with acanthosis nigricans, elevated insulin levels and obstructive sleep apnea; case discordant with our patient who has never received treatment with exogenous GH, no reports were found to date that associate morbid obesity and 3M syndrome.

Treatment with recombinant human growth hormone is not standardized with a specific utility, so there is no growth hormone deficiency but there is insensitivity to it. GulinKaracan et al [3] describe the experience of a single center that evidence the response to GH treatment in 3M syndrome, and indicate that there is a good growth rate during the first stages of long-term treatment, however, the effect decreases in the following years and the desired improvement is not achieved. in patients who reach final height, but they can speculate that starting treatment with GH in the prepubertal period provides better results than after it, a fact that we believe would benefit our patient taking into account the hypogonadism documented on the physical examination and low hormone levels, sexual characteristics that reflect prepubertal status, bone age of 9 years, dysmorphic findings on physical examination and genetic alteration in the CUL7 gene, it is considered that he could be a candidate for treatment with recombinant human growth hormone, requiring periodic, multidisciplinary and long-term follow-up to evaluate therapeutic response.

4. Conclusions

The 3M syndrome is a rare genetic disorder associated with short stature, with no more than 200 cases reported in the medical literature worldwide; in which great variability is observed in clinical, phenotypic and genetic characteristics expressed by three described pathogenic variants (CUL7, OBS 1, CCDC8). Currently without a specific therapeutic strategy, however, we present this case to raise awareness of the need for multidisciplinary management of short stature from the early stages of life and to highlight the importance of adequate genetic counseling to initiate timely behaviors; Furthermore, always take into account the 3M Syndrome as a diagnostic probability in patients who present with intrauterine growth restriction, short stature in childhood/adolescence and bone alterations.

5. Future Scope

Our legacy regarding this research is to continue researching this type of genetic syndromes associated with short stature; Concerning the 3M syndrome is to see the real usefulness of the use of exogenous growth hormone and whether the effects on a higher final target size are promising for this type of patient.

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Author Profile

William Alejandro Quessep Mendoza, Physician graduated from the Universidad del Sinú, third-year resident of the Universidad Simon Bolivar of Barranquilla, has been awarded the Institutional Program of Academic Excellence Award of the Universidad Simon Bolivar in the years 2022, 2023, He is currently pursuing a Diploma in Article Writing scientists at the Pontifical Javeriana University.

Angelica Maria Mendoza Caballero, Doctor graduated from the Simon Bolivar University, currently studying the Third Year of Specialization in Pediatrics at the same institution, where he works as Chief Resident for the period 2023-2024.

Ronil Jose Mercado Lopez, Physician graduated from the Metropolitan University, third-year Resident of Pediatrics at the Simon Bolivar University, has been awarded the Outstanding Resident award from the Colombian Society of Pediatrics in 2023.

Maria Consuelo Maestre Vargas, Medical graduate from the Universidad Libre section of Barranquilla, currently studying the third year of Specialization in Pediatrics at this same institution.

Jorge Luis Ordoñez Hernandez, Physician graduated from the Universidad del Norte, Specialist in Pediatric Endocrinology from the Mexican Institute of Social Security, Founding member of the Colombian Association of Pediatric Endocrinology (ACCEP), Postgraduate professor in pediatrics at the Libre and Simón Bolívar universities.