Endocrinología, Diabetes y Nutrición 72 (2025) 101537

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

Alterations in *MORC2* gene and DIGFAN syndrome: A rare cause of short stature

Alteraciones en el gen *MORC2* y síndrome DIGFAN: una causa infrecuente de talla baja

The association among short stature, developmental delays, facial dysmorphisms, and axonal neuropathy has been characterized as DIGFAN syndrome (developmental delay, impairment growth, dysmorphic facies, axonal neuropathy), which is caused by heterozygous mutations in the *MORC2* gene located on chromosome 22q12. This condition represents a rare cause of short stature, which may lead to delayed diagnosis if there is not a high index of suspicion. We present the case of a patient referred for short stature, early puberty, and associated neurological signs.

This is the case of an 8-year and 11-month-old girl with thelarche and pubarche since the age of 8½. Growth charts show a height consistently below the 3rd percentile since the first year of life, with preserved growth velocity. She had previously been diagnosed with global developmental delay, hypotonia, fine motor clumsiness, intentional tremor, and non-epileptic paroxysmal disorder associated with limb myoclonus, along with cerebellar vermis hypoplasia on neuroimaging. Additionally, she was under follow-up by Ophthalmology for hypermetropia and astigmatism. Family history includes a father with a height of 155 cm and associated sensorineural hearing loss, as well as a paternal cousin under follow-up for short stature and psychomotor delay.

On initial physical examination, her height was −2.85 standard deviations according to the 2010 Spanish Growth Studies reference values, with no disproportion between body segments. Mild cognitive deficit was noted without neurological focal signs, and facial inspection revealed symmetrical enophthalmos and a broad nasal root. Pubertal development showed Tanner stage 2 with bilateral thelarche and pubarche, without other abnormalities.

Initial lab test results revealed normal blood count, biochemistry, thyroid function, and baseline androgens, negative anti-transglutaminase antibodies, baseline LH > 5 mIU/mL with an LH/FSH ratio > 0.6, normal IGF-1 and IGF-BP3 for her age, a 46XX karyotype, and no abnormalities in the *SHOX-PAR1* gene study. Bone age at the first visit was 10 years according to the Greulich and Pyle atlas, with a predicted adult height of 141.3 ± 5 cm using the Bayley-Pinneau method. Given her short stature, early puberty, and poor adult height prognosis relative to her target height (156.5 cm), treatment with gonadorelin 3.75 mg every 28 days via parenteral administration was initiated to halt pubertal progression.

With these findings, the etiological diagnosis was reconsidered, and an exome sequencing was requested, revealing the heterozygous variant c.1271A > G; p.(Thr424Lys) in the *MORC2* gene, associated with DIGFAN syndrome.

During follow-up, there was no progression of secondary sexual characteristics, and growth velocity remained above the 25th percentile for her age. After 1½ years of treatment, it was discontinued due to a bone age of 13 years according to the Greulich and Pyle atlas. Subsequently, pubertal progression was observed, with menarche occurring at 12 years of age. A progressive slowing of growth was noted, culminating in an adult height of 130.5 cm.

The first cases of neurological abnormalities related to *MORC2* gene mutations were described in the scientific literature in 2016, primarily in patients diagnosed with Charcot-Marie-Tooth disease.[1,2] In patient series with *MORC2* gene mutations, significant clinical variability has been observed[3–6]: most present with axonal neuropathy involving motor and/or sensory impairment, others exhibit symptoms similar to spinal muscular atrophy, and a final group shows signs of peripheral neuropathy, intellectual disability, growth delay, and facial dysmorphisms,[7] collectively termed DIGFAN syndrome, with very few cases being reported.[3,7,8] The girl described in this article presents findings suggestive of peripheral neuropathy, such as hypotonia and motor clumsiness, along with cognitive and growth delays, which, along with her facial characteristics, align her within the clinical spectrum attributed to *MORC2* gene mutations.

Regarding short stature, which this patient exhibited since infancy and maintained throughout childhood with preserved growth velocity, its severity is notable, with an adult height significantly below her genetic target. Additionally, other endocrine abnormalities associated with this syndrome, such as hypothyroidism and precocious puberty, have been described, though their frequency and progression remain unclear due to the limited number of cases reported. In our case, thyroid function was normal, and pubertal development began around 8½ years, corresponding to early puberty. Similarly, of note, the association with ophthalmopathies (the most severe being retinitis pig-

mentosa, in up to 83%), sensorineural hearing loss (up to 58%), neuroimaging abnormalities (up to 66%), and less frequent conditions: swallowing disorders, gastroesophageal reflux, and kyphoscoliosis.[3] Given the documented frequency of these abnormalities, including endocrine ones,[3,7,8] it seems reasonable to conduct thorough clinical monitoring for screening in these patients.

Although most *MORC2* gene mutations are de novo, and a broad clinical spectrum has been observed,[3–7] it is highly likely that both the father and the cousin share the same mutation as our patient, given their similar phenotypes. However, genetic testing was not possible in these relatives, so this possibility could not be confirmed.

In conclusion, this case illustrates a very rare cause of short stature, which may be accompanied by other endocrine abnormalities such as hypothyroidism or precocious puberty, whose clinical behavior is not well understood in these patients. Its association with psychomotor delay and facial abnormalities should prompt consideration of DIGFAN syndrome and screening for the various described complications. Furthermore, the phenotypic variability observed in *MORC2* gene abnormalities poses a diagnostic challenge for the future,[4] necessitating the characterization of different mutations in affected patients and relatives, as well as correlating them with clinical outcomes.

References

1. Hyun YS, Hong YB, Choi BO, Chung KW. Clinico-genetics in Korean Charcot-Marie-Tooth disease type 2Z with MORC2 mutations. Brain. 2016;139:e40.
2. Sevilla T, Lupo V, Martínez-Rubio D, Sancho P, Sivera R, Chumillas MJ, et al. Mutations in the MORC2 gene cause axonal Charcot-Marie-Tooth disease. Brain. 2016;139:62–72.
3. Hanada K, Osaki Y, Miyamoto R, Muto K, Haji S, Nazere K, et al. Intermediate phenotype between CMT2Z and DIGFAN associated with a novel MORC2 variant: a case report. Hum Genome Var. 2024;11:29.
4. Jacquier A, Ribault S, Mendes M, Lacoste N, Risson V, Carras J, et al. Expanding the phenotypic variability of MORC2 gene mutations: from Charcot-Marie-Tooth disease to late-onset pure motor neuropathy. Hum Mutat. 2022;43:1898–908.
5. Ando M, Okamoto Y, Yoshimura A, Yuan JH, Hiramatsu Y, Higuchi Y, et al. Clinical and mutational spectrum of Charcot-Marie-Tooth disease type 2Z caused by MORC2 variants in Japan. Eur J Neurol. 2017;24:1274–82.
6. Duan X, Liu X, Wang G, Gu W, Xu M, Hao Y, et al. Characterization of genotype-phenotype correlation with MORC2 mutated Axonal Charcot-Marie-Tooth disease in a cohort of Chinese patients. Orphanet J Rare Dis. 2021;16:244.
7. Guillen Sacoto MJ, Tchasovnikarova IA, Torti E, Forster C, Andrew EH, Anselm I, et al. De novo variants in the ATPase module of MORC2 cause a neurodevelopmental disorder with growth retardation and variable craniofacial dysmorphism. Am J Hum Genet. 2020;107:352–63.
8. Xie B, Fan X, Wei X, Gui B, Wei X, Ma Y, et al. Analysis of a child with DIGFAN syndrome due to variant of MORC2 gene. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2024;41:234–8.

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