



LETTER TO THE EDITOR

Complex dystonia in an adolescent male with a *MECP2* variant



Distonía compleja en un adolescente varón con una variante en el gen *MECP2*

Dear Editor,

MECP2 is the most commonly implicated gene in Rett syndrome, an X-linked dominant neurodevelopmental disorder predominantly affecting females. In males, *MECP2* mutations are infrequent but can lead to a broad range of neurological manifestations, ranging from severe congenital encephalopathy to mild mental retardation.¹ Additionally, it is a known cause of X-linked parkinsonism and spasticity.^{2,3} In this report, we present the case of a 20-year-old male exhibiting generalized dystonia, eyelid apraxia, and oculomotor apraxia, thereby broadening the spectrum of the *MECP2* phenotype.

Case report

A 20-year-old male from Morocco was referred to our Movement Disorders Unit for consideration of Deep Brain Stimulation (DBS) surgery to address dystonia. He was born to healthy, unrelated parents following an uncomplicated pregnancy and delivery. The family history revealed no neurological or psychiatric diseases. Although his psychomotor development seemed normal, his parents noted difficulties in social interaction and school performance, leading to his inability to complete secondary school. At the age of 15, he experienced a psychotic episode treated with olanzapine 20 mg bid. By 16, cervical involuntary posturing emerged, extending to his right hemibody. Due to psychiatric concerns, reducing or discontinuing the antipsychotic medication was not feasible. He had undergone botulinum toxin injections for cervical and right foot dystonia, resulting in partial improvement.

At the age of 20 (video 1), he presented with left laterocollis and more pronounced dystonic postures in the right limbs. Mild eyelid opening apraxia and oculomotor apraxia were noted, and the speech exhibited a subtly dystonic quality. While finger tapping was mildly impaired due to dystonia, there was no evident bradykinesia or rigidity. Cerebellar signs were absent. The gait was unsteady, marked by trunk and lower limb hyperextension. Notably, posture significantly improved when walking backward or from side to side, a distinctive characteristic of dystonia. Deep tendon reflexes were brisk, featuring bilateral ankle clonus, but cutaneous plantar responses were flexor.

A comprehensive laboratory investigation, including biochemistry, blood cell count, three acanthocytes determinations, serologies, autoimmunity, vitamin B12, vitamin E, TSH, alpha-fetoprotein, serum copper, ceruloplasmin, 24-h urine copper, plasma amino acids, and urine organic acids, was conducted, yielding no significant findings. Brain Magnetic Resonance Imaging (MRI) results were normal. Written informed consent was obtained for genetic analysis. Initially, dystonia genes were examined using a focused dystonia sequencing gene panel, but no results were obtained. Subsequently, due to the presence of pyramidal signs, the patient underwent analysis with a spastic paraplegia gene panel, revealing a loss-of-function mutation in *MECP2*: NM.004992.4: c.1086delC, p.Lys363Argfs*46, classified as pathogenic according to the American College of Medical Genetics (ACMG) criteria.

This patient presented with generalized dystonia involving the cervical and oromandibular regions. Tardive dystonia typically manifests as focal, segmental, or less commonly, generalized. The cranial regions are frequently affected, with retrocollis being the most characteristic manifestation. In this case, the emergence of generalized dystonia, coupled with intellectual disability, pyramidal signs, eyelid opening apraxia, and oculomotor apraxia, prompted an investigation into inherited etiologies. Oculomotor apraxia is a recognized clinical manifestation associated with various ataxia-related genes (*APTX*, *SETX*, *PNKP*, *ATM*). However, considering the presence of pyramidal signs without ataxia, an initial examination of spastic paraplegia genes was prioritized.

MECP2 mutations are the primary cause of Rett syndrome, with mutations predominantly originating during spermatogenesis, elucidating the higher incidence in females. This prevalence persists independently of the random occurrence of X-chromosome inactivation. Movement disorders are commonly associated with Rett syndrome, typically progressing from hyperkinetic to rigid-akinetic states.^{4,5} In the recent years, *MECP2* gene has been involved in milder clinical phenotypes with extrapyramidal manifestations. Torticollis and dystonic finger posturing were described in an adult female patient with mild learning disability and a pathogenic frameshift variant in *MECP2*.⁶ Parkinsonism has been observed in both males and females with Psychosis, Pyramidal signs, and Macroorchidism (PPM-X) syndrome^{2,7} and a young onset PSP-like phenotype with catatonia was also described.⁸ Additionally, an early onset infantile ataxia was reported in two brothers with a *MECP2* mutation.⁹ Genotype-phenotype studies have found that early truncating mutations in the *MECP2* gene and large indels cause the most severe phenotypes, while missense mutations and late truncating mutations cause mildest manifestations.¹⁰ Interestingly, individuals with truncating mutations exhibit a higher frequency of dystonia.¹¹ In our case, a late variant p.Lys363Argfs*46 located in the C-terminal domain was identified, contributing to delayed onset and a milder phenotype. Increasingly evidence of clinical heterogeneity among individuals with *MECP2* mutations suggests that its contribution to diverse neurological disorders may be overlooked. *MECP2* encodes

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Methyl-CpG binding protein 2 (MeCP2), a regulator of gene expression levels. Consequently, identifying the genes targeted by MeCP2 may enhance our understanding of shared pathophysiological pathways among different neurological disorders.¹²

In conclusion, we present a case of a mild *MECP2* phenotype in an adolescent male, emphasizing the importance of studying this gene in young-onset complex movement disorders, particularly when accompanied by intellectual delay or psychosis.

Ethical compliance statement

Patient provided written informed consent for clinical information and video material use for academic purposes. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.nrleng.2025.08.004](https://doi.org/10.1016/j.nrleng.2025.08.004).

Conflict of interest

The authors report no conflicts of interest.

References

1. Moog U, Smeets EEJ, Van Roozendaal KEP, Schoenmakers S, Herbergs J, Schoonbrood-Lenssen AMJ, et al. Neurodevelopmental disorders in males related to the gene causing Rett syndrome in females (MECP2). *Eur J Paediatr Neurol*. 2003;7:5–12.
2. Klauck SM, Lindsay S, Beyer KS, et al. *Am J Hum Genet*. 2002;70:1034–7.
3. Meloni I, Bruttini M, Longo I, et al. A mutation in the Rett syndrome gene, *MECP2*, causes X-linked mental retardation and progressive spasticity in males. *Am J Hum Genet*. 2000;67:982–5.
4. Kang UJ, Burke R, Fahn S. Natural history and treatment of tardive dystonia. *Mov Disord*. 1986;1:193–208.
5. Jordan CR, Li HH, Kwan HC, Francke U. Cerebellar gene expression profiles of mouse models for Rett syndrome reveal novel *MECP2* targets. *BMC Med Genet*. 2007;8:1–16.
6. Venkateswaran S, Mcmillan HJ, Doja A, Humphreys P. Adolescent onset cognitive regression and neuropsychiatric symptoms associated with the A140V *MECP2* mutation. *Dev Med Child Neurol*. 2014;56:91–4.
7. Dzinovic I, Skovráněk M, Necpal J, Boesch S, et al. Dystonia as a prominent presenting feature in developmental and epileptic encephalopathies: a case series. *Parkinsonism Relat Disord*. 2021;73–8.
8. Pollini L, Galosi S, Nardecchia F, et al. Parkinsonism, intellectual disability, and catatonia in a young male with *MECP2* variant. *Mov Disord Clin Pract*. 2020;7:118–9.
9. Zinck D, Biskup S, Vieker S. Early infantile ataxia as cardinal symptom for an X-linked *MECP2* mutation. *Neuropediatrics*. 2014;45 Suppl 1, fp015 (abstract number).
10. Kyle S, Vashi N, Justice M. Rett syndrome: a neurological disorder with metabolic components. *Open Biol*. 2018;8:170216.
11. Singh J, Lanzarini E, Nardocci N, et al. Movement disorders in patients with Rett syndrome: a systematic review of evidence and associated clinical considerations. *Psychiatry Clin Neurosci*. 2021;75:369–93.
12. Bach S, Ryan NM, Guasoni P, et al. Methyl-CpG-binding protein 2 mediates overlapping mechanisms across brain disorders. *Sci Rep*. 2020;10:1–13.

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