Movement Disorders
CLINICAL PRACTICE

Parkinsonism, Intellectual Disability, and Catatonia in a Young Male With *MECP2* Variant

Luca Pollini, MD,[1] Serena Galosi, MD, PhD,[1] Francesca Nardecchia, MD, PhD,[1] Francesco Musacchia, PhD,[2] Raffaele Castello, PhD,[2] Vincenzo Nigro, MD,[2] and Vincenzo Leuzzi, MD[1,]*

Methyl CpG-binding protein 2 (MeCP2) deficiency is associated to Rett syndrome (RTT), an X-linked neurodevelopmental disorder affecting females, accounting for 95% to 97% of typical RTT.[1] The first male patient with *MECP2* mutation was described in 1999, overcoming the concept of lethality of MeCP2 deficiency in males, and, later on, a number of patients with early-onset severe encephalopathy were described.[2] *MECP2* is now recognized to be causative of a wide spectrum of clinical manifestations in males, including cognitive impairment, movement disorders, and epilepsy.[3]

Here we report on a new phenotypic presentation of MeCP2 deficiency characterized by intellectual disability, early-onset parkinsonism, and vertical supranuclear gaze palsy (VSGP).

This 17-year-old male was born at term without complications from nonconsanguineous healthy parents. He was able to walk at 16 months and spoke his first words at 24 months of age. At the age of 4 years, upper limb tremor was noticed, and at the age of 8, a neuropsychological evaluation revealed a borderline intellectual functioning. At that time, karyotype, *FMR1* sequencing, and single-nucleotide polymorphism array revealed no abnormalities.

At the age of 16 years, he suffered from an acute-onset psychomotor agitation, confabulation, and visual hallucinations. On examination, a few weeks later, he presented a catatonic state, with stupor, akinesia, waxy flexibility, mutism, staring, and catalepsy (Video 1, segment 1). He also had hypostaturism. A lorazepam trial (2 mg) rapidly resolved the catatonic state. Once catatonia resolved VSGP, intermediate-frequency low-amplitude postural and kinetic tremor with superimposed distal jerks and only minimal rest component, upper limb slight dystonic posturing, bradykinesia, rigidity, and anterior neck flection became evident (Video 1, segments 2–4). Finger tapping showed decrement in both rate and amplitude (Video 1, segment 3). Lower limb reflexes were brisk. A reevaluation of his cognitive function revealed moderate cognitive impairment (IQ = 40). An extensive metabolic workup, including plasma aminoacids, urinary organic acid, acylcarnitine, plasma oxysterols, lactate, pterins, and cerebrospinal fluid neurotransmitter metabolites failed to detect any specific alterations. Brain MRI and DaT-scan were both normal. A levodopa trial was ineffective. Next-generation sequencing panels for monogenic parkinsonisms and dystonias were inconclusive. Finally, whole-exome sequencing detected a novel *MECP2* c.503G>A (p.Arg168Gln) missense variant, inherited from his unaffected mother and predicted as pathogenic by different tools.[4]

Whereas MeCP2 deficiency accounts for 1.3% to 1.7% of males with cognitive impairment,[3] parkinsonian features have been reported in few patients (Table 1).[5–8]

A specific syndromic constellation encompassing psychosis, pyramidal signs, and macro-orchidism (PPM-X), as well as cognitive impairment, parkinsonism, and short stature, has been described in 6 males from the same family harboring the *MECP2* A140V variant.[9] Although *MECP2* is recognized to cause rigid-hypokinetic syndrome in Rett females in the advanced stage of the disease,[10] parkinsonism with VSGP, evoking a PSP-like phenotype,[11] has not been previously reported in males with *MECP2* variants. The tremor observed in this patient according to phenomenology has similarities with both essential tremor–like tremor of fragile X–associated tremor/ataxia syndrome[12] and cortical reflex myoclonus observed in RTT and other conditions[13]; detailed electrophysiological studies are needed for proper characterization.

The C.503G>A variant is adjacent to the c.502C>T, one of the most frequent *MECP2* alterations found in females with typical RTT.[14]

This case, expanding the phenotypic spectrum of MeCP2 deficiency, suggests that this gene may be a neglected cause of parkinsonism and intellectual disability in males, deserving to be added to the differential diagnosis of early-onset parkinsonism in males with cognitive impairment.

[1]*Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy;* [2]*Telethon Institute of Genetics and Medicine, Pozzuoli, Italy*

***Correspondence to:** Prof. Vincenzo Leuzzi, Department of Human Neuroscience, Sapienza University of Rome, Via dei Sabelli 108, 00185 Rome, Italy; E-mail: vincenzo.leuzzi@uniroma1.it
Keywords: *MECP2*, Rett syndrome, atypical parkinsonism.
Dr. Pollini and Dr. Galosi contributed equally to the manuscript.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 28 July 2019; revised 1 October 2019; accepted 16 October 2019.
Published online 21 November 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12865

TABLE 1 *Parkinsonism and associated features in male patients with* MECP2 *alterations*

Reference (Case No.)	Age (Years)	Parkinsonian features	Cognitive Functioning	Brisk Tendon Reflexes	Action Tremor	Other Clinical Findings	Genotype
Lindsay et al., 1996[5] (case 1)	11	Bradykinesia, resting tremor, shuffling gait	Moderate cognitive impairment (IQ = 49)	+	+	Psychotic bipolar disorder	c.419C>T p.Ala140Val
Lindsay et al., 1996[5] (case 2)	39	Resting tremor and shuffling gait	Moderate cognitive impairment	+	–	Psychotic bipolar disorder	c.419C>T p.Ala140Val
Orrico et al., 2000[6] (cases 1-4)	27 to 40	Bradykinesia and resting tremor	Severe cognitive impairment	–	–	–	c.419C>T p.Ala140Val
Couvert et al., 2001[7] (cases 1-3)	25 to 50	Resting tremor	Mild to moderate cognitive impairment (IQ = 50–70)	–	–	–	c.499C>T p.Arg167Trp
Chahil et al., 2018[8] (case 1)	16	Bradykinesia, resting tremor, camptocormia	Neurodevelopmental disorder	+	+	Autistic spectrum disorder	c.419C>T p.Ala140Val
Present case	18	Rigidity, hypomimia, mild camptocormia, resting tremor	Moderate cognitive impairment	+	+	Catatonia, psychotic features, vertical gaze palsy	c.503G>A p.Arg168Gln

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript: A. Writing of the First Draft, B. Review and Critique.

L.P.: 1A, 2A
S.G.: 1A, 2A
F.N.: 1B, 1C
F.M.: 1B, 1C
R.C.: 1B, 1C
V.N.: 2A, 2B
V.L.: 2A, 2B

Disclosures

Ethical Compliance Statement: We declare that the patients and/or their parents consented for video publication and provided a signed release form authorizing the offline and/or online distribution of this video material. 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.

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: Vincenzo Leuzzi has served on scientific advisory boards for Nutricia and BioMarin.

References

1. Neul JL, Fang P, Barrish J, et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. *Neurology* 2008;70:1313–1321.
2. Leuzzi V, Di Sabato ML, Zollino M, Montanaro ML, Seri S. Early-onset encephalopathy and cortical myoclonus in a boy with MECP2 gene mutation. *Neurology* 2004;63:1968–1970.
3. Villard L. MECP2 mutations in males. *J Med Genet* 2007;44:417–423.
4. Musacchia F, Ciolfi A, Mutarelli M, et al. VarGenius executes cohort-level DNA-seq variant calling and annotation and allows to manage the resulting data through a PostgreSQL database. *BMC Bioinformatics* 2018;19:477.
5. Lindsay S, Splitt M, Edney S, et al. PPM-X: a new X-linked mental retardation syndrome with psychosis, pyramidal signs, and macroorchidism maps to Xq28. *Am J Hum Gen* 1996;58:1120–1126.
6. Orrico A, Lam CW, Galli L, et al. MECP2 mutation in male patients with non-specific X-linked mental retardation. *FEBS Lett* 2000;481:285–288.
7. Couvert P, Bienvenu T, Aquaviva C, et al. MECP2 is highly mutated in X-linked mental retardation. *Hum Mol Genet* 2001;10:941–946.
8. Chahil G, Yelam A, Bollu PC. Rett syndrome in males: a case report and a review of literature. *Cureus* 2018;10:e3414.
9. Klauck SM, Lindsay S, Beyer KS, Splitt M, Burn J, Poustka A. A mutation hot spot for nonspecific X-linked mental retardation in the MECP2 gene causes the PPM-X syndrome. *Am J Hum Genet* 2002;70:1034–1037.
10. Temudo T, Ramos E, Dias K, et al. Movement disorders in Rett syndrome: an analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. *Mov Disord* 2008;23:1384–1390.
11. Stamelou M, Quinn NP, Bhatia KP. "Atypical" atypical parkinsonism: new genetic conditions presenting with features of progressive supranuclear palsy, corticobasal degeneration, or multiple systemic atrophy—a diagnostic guide. *Mov Disord* 2013;28:1184–1199.
12. Apartis E, Blancher A, Meissner WG, et al. FXTAS: new insight and the need for revised diagnostic criteria. *Neurology* 2012;79:1898–1907.
13. Guerrini R, Bonanni P, Parmeggiani L, Santucci M, Parmeggiani A, Sartucci F. Cortical reflex myoclonus in Rett syndrome. *Ann Neurol* 1998;43:472–479.
14. Townend GS, Ehrhart F, van Kranen HJ, et al. MECP2 variation in Rett syndrome—an overview of current coverage of genetic and phenotype data within existing databases. *Hum Mutat* 2018;39:914–924.

Supporting Information

Supporting information may be found in the online version of this article.

Video S1. Segment 1: clinical presentation with catatonic features including facial grimaces and mutism. Segment 2: resolution of catatonic state after lorazepam trial; severe vertical gaze palsy. Segment 3: resolution of catatonic state after lorazepam trial; persistent hypomimia, postural tremor of upper limbs with occasional distal jerks, and upper limb slight dystonic posturing. On finger tapping, reduction of both amplitude and speed rate and exacerbation of distal myoclonic jerks. Segment 4: anterior neck flection, hand-washing stereotypies, and reduced arm swing during gait.