Movement Disorders
CLINICAL PRACTICE
LETTER: GENOTYPE AND PHENOTYPE

Myoclonus-Dystonia plus Syndrome in a Patient Carrying a Novel *TCF20* Variant

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Myoclonus dystonia (MD) is characterized by myoclonic jerks, mostly involving the upper body, associated with mild–moderate dystonic postures starting in childhood. Pathogenic variants in *SCGE* represent the most frequent genetic cause, although other genes like *KCTD17, KCNN2YY1, YY1* and *ATP1A3* have been implicated.[1] The term "myoclonus dystonia plus syndrome" (MDPS) refers to a complex phenotype, including also intellectual disability and facial dysmorphisms, generally related to SGCE deficiency due to larger chromosomic deletions involving, among others, *SGCE*.[2] Pathogenic variants in *TCF20* have been mostly described in patients with neurodevelopmental disability, behavioral problems (including autism spectrum disorders) facial dysmorphisms (like brachy-, micro- macrocephaly, low set ears, long face) and seizures.[3] Few subjects carrying *TCF20* pathogenic variants and movement disorders have been reported so far.[4]

We describe herein a patient with a MDPS carrying a novel *TCF20* variant.

A 70-year-old-man presented myoclonic jerks involving upper limbs (worsened by tactile stimuli) and the head, which started approximatively at the age of 40, associated with a cranio-cervical dystonia (antero-and right laterocollis, mild left torticollis see video 1).

Since the age of 4, his gait was mild ataxic, with stumbling walking. Furthermore, he had hyperreflexia in the lower limbs and dystonic dysarthria. The myoclonic jerks and the dystonia remained stable over the years without any specific treatment. He also presented a moderate intellectual disability (IQ 51 points) which prevented him from completing the first-degree-schools and working. Moreover, delayed language development was reported (first words at 10 months; problems in forming entire sentences and, since the age of 7–8, his speech was described as dyslalic and dysarthric). Mild dysmorphic features (micrognathia, broad forehead, thin upper lip and smooth philtrum) were present. His family history was unremarkable. No consanguinity was reported.

A brain MRI showed a mild diffuse unspecific cortical atrophy especially in the temporal lobes (See Fig. 1). An EEG displayed diffuse unspecific theta irregularities, while at the polygraphy, EMG signal revealed several myoclonic jerks in the upper limbs without a clear EEG graphic correlation as confirmed with back averaging. The absence of giant somatosensory evoked potentials and C-reflex indicated a suitable subcortical origin of the myoclonus. A CGH array was performed, which was normal, and X fragile syndrome was ruled out. Both single nucleotide variants (SNVs) and copy number variations (CNVs) in *SCGE* were not detected. A whole exome sequencing analysis showed the heterozygous c.4737dupA, p.Gln1580ThrfsTer32 variant in *TCF20*. According to the ACMG guidelines,[5] it is classified as likely pathogenic as predicts the formation of a truncated protein in a gene where the loss of function is a well-known disease mechanism (PVS1). The A insertion is predicted to cause a frameshift and the introduction of a premature stop codon, likely resulting in nonsense-mediated decay. Furthermore, the variant is absent in all population databases (PM2). Different drugs were sequentially tried (clonazepam, piracetam, levetiracetam) but all were unsuccessful. Patient's clinical condition remained stable over the years.

This represents a complex case characterized by the presence of MD, cognitive delay and mild dysmorphic features in which a novel likely pathogenic variant in *TCF20* has been identified. Pathogenic SNVs and CNVs in *TCF20* have been mostly associated with neurodevelopmental delay, behavioral abnormalities and craniofacial malformations.[6] Only few carriers of *TCF20* pathogenic variants presenting with movement disorders have been described so far. Particularly, Torti et al[3] described six patients with tremor, ataxic gait/balance problems and muscular hypo/hypertonia. Moreover, Vetrini[7] presented three patients with abnormal/jerky movements and dyskinesia. Up to now, dystonia has been reported in only two patients[4]: both cases presented a generalized, not a segmental, dystonia with head tremor in the first case and myoclonic jerks of the upper body in the second. Notably, like ours, Svorenova's cases had intellectual disability but no dysmorphic features were reported.

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Video 1. Neurological examination of the patient. The patient presents a mild ataxic, wide-based gait with a stumbling walk. He also had myoclonic jerks involving upper limbs (worsening with tactile stimuli) and the head. Furthermore, a cranio-cervical dystonia is shown characterized by antero-and right laterocollis, mild left torticollis
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14241

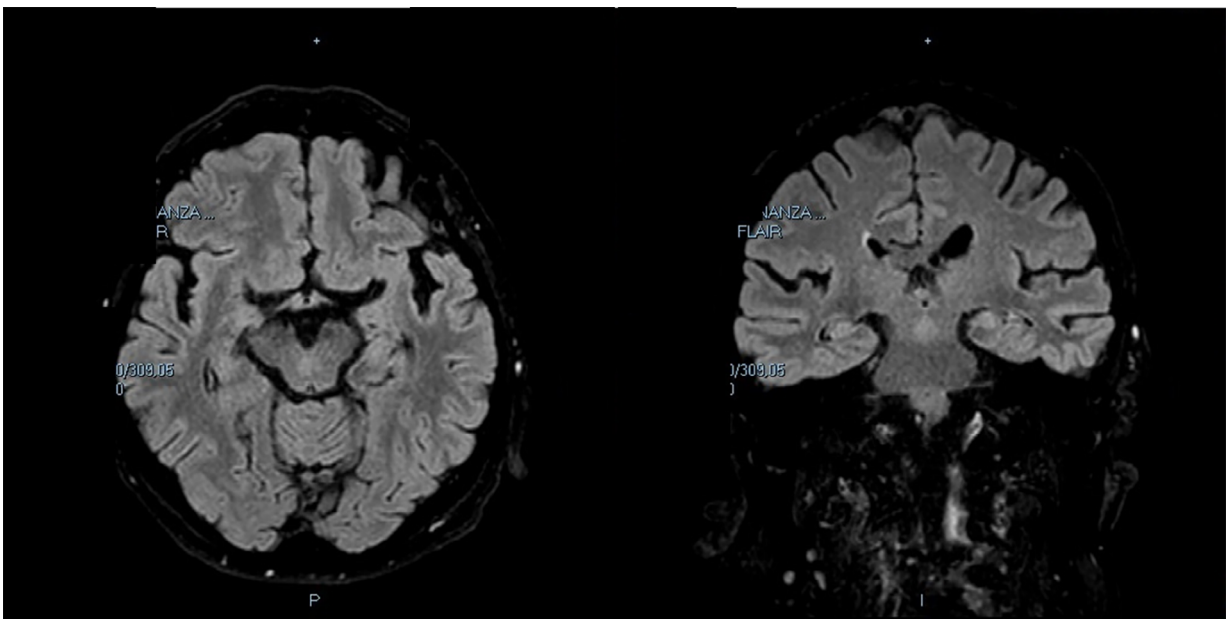

Figure 1. Brain MRI showing a mild diffuse subcortical atrophy particularly involving the temporal lobes.

Our case expands the spectrum of movement disorders related to *TCF20* variants: no other patients with a MD have been reported yet. *TCF20* variants have been linked to a heterogeneous group of neurodevelopmental disorders with various degrees of dysmorphic features that can be even mild like in our patient.[3] TCF20-related MD presents a proximal upper body myoclonus and a prominent cranio-cervical dystonia, similar to other genetic forms. Differently from other genetic MD, considered childhood diseases (with few exceptions[8]), TCF20-MD may appear in adulthood and display mild ataxic features, not

unusual in TCF20 patients, but not described in the other forms. Furthermore, this condition, tends to be stable over the years. This report widens the genetic spectrum of MDPS, up to now just linked to *SGCE* pathogenic SNVs or chromosomic deletions encompassing the gene. So far, no data on the biological pathways shared by *TCF20* and other MD genes have been reported.

A prolonged follow-up of these patients is needed to further expand the spectrum of movement disorders associated with this rare condition.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

L.M.: 1A, 3A
E.C.: 3B
S.D.A.: 1C, 3B
L.C.: 1C,3B

Disclosures

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. ■

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