



## Case Reports

## Dystonia: A novel sign of the Smith-Magenis syndrome – A three-case report

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## ARTICLE INFO

## Keywords:

Dystonia  
Smith-Magenis syndrome  
Case report  
Genetic disorder

The Smith-Magenis syndrome (SMS) is a rare genetic disorder caused by a microdeletion in the 17p11.2. region or a pathogenic variant of the *RAI1* (retinoic acid-induced), which is located in the 17p11.2 area [1]. In most cases, SMS is caused by a heterozygous de novo deletion. Sometimes inherited mutations of the *RAI1* are described, suggesting an autosomal dominant inheritance [2]. There is a broad spectrum of symptoms, including distinctive facial features, skeletal malformations, varying intellectual disability, speech, motor skills delay, sleep disturbances, and self-injurious or attention-seeking behaviors [1,3]. Despite an extensive literature review, the manifestation of dystonia remains absent from documented cases. Dystonia represents a notable clinical symptom, the recognition of which may prompt the initiation of genetic testing and facilitate precise diagnostic assessment.

## 1. Case report 1

A 31-year-old male (See [video](#): Patient 1) diagnosed with cerebral palsy since early childhood, was referred to our center with a progressive and complex neurological syndrome. The family history was negative, and the prenatal and perinatal periods were uneventful. Since early childhood, a delay in psychomotor development was reported. Metabolic screening showed no abnormality. The first signs of slowly progressing truncal dystonia emerged after the age of two, affecting his

gait. Apart from that, craniofacial dysmorphism, onychophagy, and hearing loss were reported. There was no chronic medication before the onset of the dystonic symptoms. Subsequently, during adolescence, he exhibited multiple behavioral changes, including aggressiveness and lack of cooperation with the need for depot typical antipsychotics – zuclopenthixol at a dose of 400 mg every 4 weeks. Following the initiation of neuroleptics, the dystonia worsened, and hypokinetic-rigid syndrome emerged. After the withdrawal of antipsychotics and anticholinergics (biperiden) administration, all motor symptoms improved within 6 months. However, dystonia remained present. At the age of 28 years, the patient experienced a generalized tonic-clonic epileptic seizure. Subsequent EEG analysis revealed epileptiform activity, leading to the initiation of valproate therapy. A further neurological examination reported an intellectual disability with dysarthria, truncal dystonia with hyperlordosis and right truncal deviation, spasticity of all extremities, and sialorrhea. A brain MRI revealed no pathology. Given the progressive nature and complex phenotype, we suggested comprehensive genetic testing. The genome sequencing uncovered a heterozygous pathogenic 17p11.2 deletion, chromosomal position GRCh38: 17:16732537-20314064, containing 119 genes including *RAI1* (3.6 MB in size). A genetic analysis of the parents was not available. A multidisciplinary treatment approach including antidepressants, atypical antipsychotics, anticholinergics, and anticonvulsants showed favorable

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<https://doi.org/10.1016/j.prdoa.2024.100267>

Received 19 April 2024; Received in revised form 24 June 2024; Accepted 5 August 2024

Available online 6 August 2024

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outcomes. At the most recent visit, the patient, along with his family and nursing staff, reported an improvement in his condition including dystonia.

## 2. Case report 2

Patient 2 is a 5-year-old female with a normal prenatal and perinatal history, born in the 36th week. Patient 2 was referred to our center due to a neurodevelopmental delay affecting speech, limb postures, and eye movements. Postnatally, an ultrasound examination revealed symmetrically enlarged lateral ventricles, and a cardiovascular examination identified a minor ventricular septal defect. Metabolic screening revealed several nonspecific abnormalities (mild lactaciduria with mild excretion of lactose and raffinose). Despite the age of 5, only basic vocalizations were achieved. During further neurological evaluations, patient 2 exhibited severe expressive aphasia, mild truncal hypotonia, dystonic foot positioning (tiptoeing) which was accentuated when walking, a slightly widened gait, and convergent strabismus. Based on the development of clinical symptoms and the complexity of the disability, genetic testing was indicated.

Genome sequencing revealed a heterozygous pathogenic 17p11.2 deletion, chromosomal position GRCh38: 17:16831407-20314064, containing 112 genes including *RAI1* (3.5 Mb in size). The deletion was not detected in the healthy parents, suggesting that it is a *de novo* mutation. Patient 2 remains under the care of an outpatient specialist, with no significant deterioration noted recently.

## 3. Case report 3

A 24-year-old male (see [video](#): Patient 3) was born in term with a Caesarean section due to fetal hypoxia. Since early childhood, a psychomotor development delay was observed. Patient 3 has been under the care of a psychiatrist due to Asperger syndrome, attention deficit hyperactivity disorder, and Tourette syndrome. The medication history consisted of atomoxetine and aripiprazole. A neurological examination at the age of 12 years revealed craniofacial dysmorphism, cognitive impairment, sialorrhea, clumsiness, hypotonia with hyporeflexia, and lumbar hyperlordosis with trunk deviation to the left (very likely unrecognized dystonia). The EMG examination and metabolic screening showed no abnormalities. Preceding the final diagnosis of dystonia, he underwent spinal surgery including stabilization of the Th1-L3 region due to a worsening left truncal deviation. Initially, the intervention exhibited a moderate effect, but the condition deteriorated over time. We observed generalized dystonia with gait-associated dystonic left foot posturing, worsened left truncal deviation, camptocormia, and neck dystonia. It became evident that there was a positive family history, with the patient's father also being afflicted by similar symptoms. A brain MRI under anesthesia was recommended; however, due to complicated anesthesia during the surgery, the procedure was declined.

Exome sequencing in the family identified a novel variant *RAI1* (NM\_030665.4): c.3218del (p.Gly1073AlafsTer2) inherited from the father. The variant is not present in the GnomAD v4.0.0 database and is classified as likely pathogenic based on meeting the PVS1 and PM2 ACMG criteria.

Due to trunk anteflexion affecting posture and gait, ultrasound-guided botulinum toxin injections for iliopsoas muscles were indicated with only a mild therapeutic effect. He continues to receive a regimen comprising of atomoxetine, aripiprazole, and baclofen. Apart from that, rehabilitation therapy was recommended.

In this report, we present the first three cases of patients manifesting dystonia associated with the Smith-Magenis syndrome. The goal is to emphasize dystonia as a novel and potentially prominent sign, extending the already diverse phenotypic spectrum of the SMS.

Our patients manifested some of the typical features of SMS including neurodevelopmental delay, speech disturbances, and craniofacial dysmorphism [2,3]. However, certain symptoms characteristic of

SMS, such as sleep disorders, were not observed. This absence may have contributed to diagnostic delays. 17p11.2 deletions are more associated with cardiac anomalies, speech and motor delay, cognitive impairment, hypotonia, short stature, and hearing loss than intragenic variants [4].

Although fetal hypoxia was reported in patient 3, he does not meet the diagnostic criteria of the Surveillance of Cerebral Palsy in Europe (SCPE) network (progressive character, appearance of new clinical signs) [5].

The dystonia observed in all three patients has not been previously documented in SMS. However, in one previous patient with SMS [4], scoliosis has been described among non-specific signs, which could have been unrecognized truncal dystonia. The initial onset of dystonia occurred at an early age in the first two patients (patient 1: 24 months, patient 2: 26 months, patient 3: 12 years). The dystonia remained relatively stable in these cases, aside from an expected worsening following the initiation of depot neuroleptics in patient 1, with partial improvement upon their discontinuation. In patient 3, the dystonic symptoms worsened and extended to other body regions, likely as a consequence of the spinal surgery.

It is questionable whether dystonia is also common among other patients with SMS but is not recognized [2,4] and reported by attending physicians due to the presence of other significant neurological disabilities. This issue warrants attention in future follow-up studies involving larger cohorts of SMS patients.

The exact cellular mechanism of the disease onset remains unclear. Some studies have demonstrated a disorder at the lysosomal level (with impaired lipid metabolism, accumulation of toxic products, and membrane dysfunction), autophagy/mitophagy disorders with an increase in reactive oxygen species (ROS), and a dysbalance in pro-inflammatory substances. The combination of these factors led to increased cell death [6,7]. These pathological mechanisms are also described in the development of dystonia, which may be their common denominator. [7,8]

In individuals manifesting dystonia, SMS can be classified as a complex dystonic syndrome, characterized by the presence of additional neurological and non-neurological symptoms. In these cases, a scoring algorithm for predicting the utility of whole exome sequencing (WES) was designed. [9,10] The algorithm counts with several phenotypic aspects and proves itself a useful tool for determining the WES success rate [10].

**Video:** Patient 1: Truncal dystonia with hyperlordosis and right truncal deviation affecting the gait as a prominent symptom. Craniofacial dysmorphism and obesity observed in the [video](#) are recognized as common symptoms within the broad spectrum of manifestations.

Patient 3: Generalized dystonia with left truncal deviation, camptocormia, and lumbar hyperlordosis affecting the posture and gait. Secondary findings include craniofacial dysmorphism, obesity, and a scar on the back from spinal surgery.

## 4. Funding Sources, grant/award info

LK, PH, IP, KP, and RJ were supported by The project National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107) - Funded by the European Union – Next Generation EU; Charles University: Cooperation Program in Neuroscience.

LK, PH, IP, KP, MT, TH, and RJ were supported by the institutional research: General University Hospital in Prague project MH CZ-DRO-VFN64165.

MZ receives research support from the German Research Foundation (DFG 458949627; ZE 1213/2-1) and acknowledges grant support by the European Joint Programme on Rare Diseases (EJP RD Joint Transnational Call 2022), and the German Federal Ministry of Education and Research (BMBF, Bonn, Germany), awarded to the project PreDYT (PREdictive biomarkers in DYsTonia, 01GM2302), by the Federal Ministry of Education and Research (BMBF) and the Free State of Bavaria under the Excellence Strategy of the Federal Government and the

Länder, as well as by the Technical University of Munich – Institute for Advanced Study.

LN was supported by a grant AZV NU23-07-00281 from by the Ministry of Health of the Czech Republic.

MZ's research is also supported by a "Schlüsselprojekt" grant from the Else Kröner-Fresenius-Stiftung (2022\_EKSE.185).

MS received funding from the EU Renewal and Resilience Plan „Velké projekty pre excelentných výskumníkov“ under No. 09I03-03-V03-00007 and from the Slovak Research and Development Agency under no. APVV-22-0279.

#### CRedit authorship contribution statement

**Lukáš Kunc:** Writing – original draft, Project administration, Investigation, Data curation. **Petra Havráňková:** Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Matěj Škorvánek:** Writing – review & editing, Investigation, Data curation. **Iva Příhodová:** Writing – review & editing, Investigation, Data curation. **Kamila Poláková:** Writing – review & editing, Investigation. **Lenka Nosková:** Methodology, Investigation. **Markéta Tesařová:** Writing – review & editing, Methodology, Investigation. **Tomáš Honzík:** Writing – review & editing, Methodology. **Michael Zech:** Writing – original draft, Methodology, Investigation. **Robert Jech:** Writing – review & editing, Writing – original draft, Methodology.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgments

We are profoundly grateful to our patients and their families. Additionally, we extend our gratitude to Jan Roth for the revision of the manuscript and for providing valuable advice.

#### Ethical approval information

The authors confirm that approval from institutional review boards was obtained for this project. All patients signed a written consent for print and online publication, including all [video](#) recordings.

We also 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.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.prdoa.2024.100267>.

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