and mild cervical dystonia were also present. Brain magnetic resonance imaging (age 7 years) disclosed T2 white matter hyperintensity at the posterior limb of the internal capsule. Twenty-four years later, T2* hypointensities of the pallida, substantia nigra, and dentate nucleus were also identified (Fig. 1). An exhaustive investigation was performed (Supporting Information Data S1), with genetic diagnosis being achieved by a next-generation sequencing multigene panel based on whole-exome sequencing (WES).

This case consubstantiates the complexity of de novo *SPAST* variants, broadening their phenotype spectrum to include delayed motor milestones, together with early cerebellar signs, fulfilling criteria for nonprogressive congenital ataxia,[2] her initial clinical diagnosis. After a period of slow (although ongoing) motor acquisitions, as seen in nonprogressive congenital ataxia, it was only in the eighth year of life that pyramidal signs emerged. In most series, spastic paraplegia occurred at a much earlier age.[1,3] Further reports will be important to clarify whether this was an anecdotal clinical feature in our patient or if HSP-*SPAST* is being underrecognized in case late-emergent pyramidal signs. Interestingly, despite a severe phenotype, normal imaging has usually been described.[1,3,4] In our patient, magnetic resonance imaging initially suggested a metabolic disorder and, later, brain iron accumulation, posing an additional challenge. The WES-based multigene panel was crucial for diagnosis, after three decades of investigation. Interestingly, the p.Arg499His variant found in our patient was also frequent (16/40 cases) in the cohort reported by Mo et al.[1] Given the genomic context, deamination of a methylated CpG may constitute a suitable explanation for this recurrent de novo variant.

To conclude, we wish to highlight the atypical features and emphasize the observation by Mo et al[1] of de novo HSP-*SPAST* as a complex disorder, with p.Arg499His being the most frequent de novo variant and advanced paternal age a possible risk factor. Use of WES-based panels in clinical practice shortens time to diagnosis, decreases unnecessary investigation, and contributes to phenotypic expansion of neurological disorders.

Ethical Compliance Statement

This study was approved by the ethics committee of Centro Hospitalar Universitário do Porto, and informed consent was obtained from the patient and her parents for case and video publication. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Acknowledgments: We would like to acknowledge the patient and the patient's family.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Joana Damásio, MD,[1,2,3*] Clara Barbot, MD, PhD,[2] Rui Felgueiras, MD,[1] Ana Filipa Brandão, MSc,[3] José Barros, MD, PhD,[1,4] Jorge Oliveira, MSc, PhD,[2,3] and Jorge Sequeiros, MD, PhD[2,3,4]

[1]*Neurology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal,* [2]*Unidade de Investigação Genética e Epidemiológica em Doenças Neurológicas, Institute for Molecular and Cell Biology, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal,* [3]*Centre for Predictive and Preventive Genetics, Institute for Molecular and Cell Biology, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal, and* [4]*ICBAS School of Medicine and Biomedical Sciences, Universidade do Porto, Porto, Portugal*

References

1. Mo A, Saffari A, Kellner M, et al. Early-onset and severe complex hereditary spastic paraplegia caused by De novo variants in SPAST. Mov Disord 2022;37(12):2440–2446.
2. Bertini E, Zanni G, Boltshauser E. Nonprogressive congenital ataxias. Handb Clin Neurol 2018;155:91–103.
3. Schieving JH, de Bot ST, van de Pol LA, et al. De novo SPAST mutations may cause a complex SPG4 phenotype. Brain 2019; 142(7):e31.
4. Nan H, Shiraku H, Mizuno T, Takiyama Y. A p.Arg499His mutation in SPAST is associated with infantile-onset complicated spastic paraplegia: a case report and review of the literature. BMC Neurol 2021; 21(1):439.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Reply to: Early-Onset and Severe Complex Hereditary Spastic Paraplegia Caused by De Novo Variants in *SPAST*

We thank Damásio et al for their contribution and agree that their case likely expands the phenotypic spectrum associated with de novo variants in *SPAST*.

***Correspondence to:** Dr. Darius Ebrahimi-Fakhari, Movement Disorders Program, Department of Neurology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02215, USA; E-mail: darius.ebrahimi-fakhari@childrens.harvard.edu

Relevant conflicts of interest/financial disclosures: Nothing to report.

Funding agencies: This work was supported by Deutsche Forschungsgemeinschaft (German Research Foundation; SA 4171/1–1 to A.S.), The Tom Wahlig Foundation (D.E.-F.), CureAP4 Foundation (D.E.-F.), CureSPG50 Foundation (D.E.-F.), Spastic Paraplegia Foundation (D.E.-F.), Manton Center for Orphan Disease Research (D.E.-F.), and National Institute of Neurological Disorders and Stroke, National Institute of Health (1K08NS123552–01 to D.E.-F).

Received: 22 February 2023; **Accepted:** 24 February 2023

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29384

TABLE 1 *Ten additional children and young adults with de novo variants in* SPAST

Case, Sex, Age	De Novo *SPAST* Variant[a]	Age at Molecular Diagnosis (y)	DD/ID	Nonverbal	Motor Regression	Spasticity	Pyramidal Signs	Contractures	Dysarthria	Dysphagia	SPRS	Level of Ambulation[b]	CADD Score	ACMG Classification
No. 1, F, 3.8 y	c.1496G>A; p.Arg499His	2.8	GDD	No	No	LL/UL	Yes	No	No	No	40	IV	31	P
No. 2, F, 4.1 y	c.1496G>A; p.Arg499His	2.2	GDD	No	No	LL	Yes	Yes	No	No	24	III	31	P
No. 3, F, 5.9 y	c.1250G>A; p.Gly417Glu	5.4	Mild ID	No	Yes	LL	Yes	Yes	Yes	No	28	IV	28	P
No. 4, M, 7.5 y	c.1168A>G; p.Met390Val	7.3	Mild ID	No	No	LL	Yes	No	No	No	9	III	25.5	P
No. 5, F, 7.7 y	c.1360G>A; p.Glu454Lys	4.6	Severe ID	Yes	Yes	LL/UL	Yes	Yes	–	Yes	47	IV	29.5	P
No. 6, M, 8.9 y	c.1130G>A; p.Gly377Glu	4.8	Mild ID	No	Yes	LL	Yes	No	No	No	13	II	28.2	P
No. 7, F, 10.2y	c.1348A>G; p.Arg450Gly	7.8	Moderate ID	No	Yes	LL	Yes	Yes	No	No	25	III	28	P
No. 8, M, 11.0 y	c.1219A>T; p.Ser407Cys	7.5	Moderate ID	No	Yes	LL	Yes	Yes	Yes	No	–	III	27.7	P
No. 9, M, 14.1y	c.1494G>C; p.Arg498Ser	12.8	Motor delays but no ID	No	No	LL	Yes	Yes	No	No	19	I	32	P
No. 10, F, 32.8y	c.1163A>G; p.Lys388Arg	31.6	Severe ID	No	Yes	LL/UL	Yes	Yes	Yes	Yes	46	IV	31	P

Abbreviations: ACMG, American College of Medical Genetics and Genomics; CADD, combined annotation dependent depletion; DD, developmental delay; F, female; GDD, global developmental delay; ID, intellectual disability; LL, lower limbs; M, male; P, pathogenic; SPRS, spastic paraplegia rating scale; UL, upper limbs.

[a]*SPAST*: NM_014946.4.

[b]Level of ambulation: I = mild symptoms but walking without an aid; II = walking without aid but unable to run; III = walking with aid; and IV = wheelchair dependent.

Since the publication of our report,[1] we have evaluated 10 additional children and young adults with de novo variants in *SPAST* (Table 1). The rapid detection of these cases, some through reanalysis of existing cohorts, supports the observation that de novo *SPAST* variants are likely underrecognized in children with early-onset complex hereditary spastic paraplegia (HSP). The case presented by Damásio et al highlights the important notion that atypical symptoms, including ataxia and other cerebellar signs, can precede pyramidal signs in children with complex HSP. This has been noted in multiple cases and cohorts of autosomal dominant[2,3] and recessive forms,[4,5] and it underscores the phenotypic pleiotropy seen in HSP. These findings demonstrate the importance of careful phenotyping through longitudinal natural history studies.

Notably, our follow-up cohort spans a broader age range and includes older individuals (3.8–32.8 years). All individuals received an initial diagnosis of cerebral palsy, usually before referral to a tertiary care center, underlining that *SPAST*-associated HSP is a common genetic mimic of cerebral palsy.[6]

The neuroimaging findings in the case discussed by Damásio et al deserve further exploration in well-characterized cohorts of older individuals with de novo *SPAST*-HSP. Although abnormalities on brain magnetic resonance imaging were found only in a small subset of the initial cohort,[1] and none of the additional 10 patients, our studies are limited because of the unavailability of serial imaging for most patients, and the fact that almost all brain magnetic resonance scans were obtained during early childhood. Longitudinal imaging studies in adults with de novo *SPAST*-HSP are needed.

We thank Damásio et al for their observation and agree that careful phenotyping is crucial to establishing the phenotypic spectrum of HSP caused by de novo variants in *SPAST*.

Acknowledgments: We thank the patients and their families for supporting this study.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Afshin Saffari, MD and
Darius Ebrahimi-Fakhari, MD, PhD*
Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

References

1. Mo A, Saffari A, Kellner M, et al. Early-onset and severe complex hereditary spastic paraplegia caused by De novo variants in SPAST. Mov Disord 2022;37(12):2440–2446.
2. Alecu JE, Saffari A, Jumo H, et al. Novel CAPN1 missense variants in complex hereditary spastic paraplegia with early-onset psychosis. Ann Clin Transl Neurol 2022;9(4):570–576.
3. Alecu JE, Saffari A, Jordan C, Srivastava S, Blackstone C, Ebrahimi-Fakhari D. De novo variants cause complex symptoms in HSP-ATL1 (SPG3A) and uncover genotype-phenotype correlations. Hum Mol Genet 2023;32(1):93–103.
4. Saffari A, Kellner M, Jordan C, et al. The clinical and molecular spectrum of ZFYVE26-associated hereditary spastic paraplegia: SPG15. Brain 2022:awac391.
5. Ebrahimi-Fakhari D, Teinert J, Behne R, et al. Defining the clinical, molecular and imaging spectrum of adaptor protein complex 4-associated hereditary spastic paraplegia. Brain 2020;143(10):2929–2944.
6. Srivastava S, Lewis SA, Cohen JS, et al. Molecular diagnostic yield of exome sequencing and chromosomal microarray in cerebral palsy: a systematic review and meta-analysis. JAMA Neurol 2022;79(12):1287–1295.

Cholinergic Nucleus 4 Degeneration in Isolated Rapid Eye Movement Sleep Behavior Disorder: One Piece of the Puzzle

We read with interest the article by Tan et al.[1] that describes how patients with isolated REM sleep behavior disorder (iRBD) have reduced gray matter density in the cholinergic nucleus 4 (Ch4) compared with healthy individuals. This atrophy was linked to a lower performance in working memory, which agrees with a previous study from our group that found that only patients with iRBD with concomitant mild cognitive impairment (MCI) had left Ch4 atrophy compared with healthy individuals,[2] although no correlation was found between Ch4 atrophy and cognitive functions.

Most patients with iRBD will develop a manifest synucleinopathy, with approximately half being diagnosed first with Parkinson's disease and the other half being diagnosed first with dementia with Lewy bodies (DLB).[3] MCI affects more than a third of patients with iRBD and is related to a higher risk of developing DLB in this population.[3,4] The heterogeneous clinical presentation and progression of symptoms in patients with iRBD suggest that different neurodegenerative pathways are involved.

***Correspondence to:** Dr. Shady Rahayel, The Neuro (Montreal Neurological Institute-Hospital), McGill University, 3801 University Street, Montreal, QC H3A 2B4, Canada; E-mail: shady.rahayel@mcgill.ca

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 14 February 2023; **Accepted:** 16 February 2023

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29400