(2%). Other less common forms of ARCA represented 13% of the cases, including AOA type 1, *ANO10*, and *STUB1* (Supplemental Material).

This is the first multicentric study that provides information about epidemiology and frequency of ARCA in South America, and the largest ARCA frequency study worldwide. Our data are compatible with the literature regarding the most common forms of ARCA, but highlight the fact that ARSACS and NPC1 might be more common than previously thought, and provide the first real-world frequency estimates for the fairly recently identified RFC1 ARCA.[5]

This study is limited by its retrospective nature. Also, it is possible that patients with undetermined ataxia are still poorly investigated through exome sequencing in South America. This, however, renders our population an interesting opportunity to identify new genes and knowledge on epidemiological features in ARCA. Moreover, our observations are relevant to the current planning of upcoming gene therapy and clinical trials in ARCAs.

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References

1. Synofzik M, Puccio H, Mochel F, Schols L. Autosomal recessive cerebellar ataxias: paving the way toward targeted molecular therapies. Neuron 2019;101:560–583.
2. Beaudin M, Matilla-Dueñas A, Soong BW, et al. The classification of autosomal recessive cerebellar ataxias: a consensus statement from the Society for Research on the Cerebellum and Ataxias Task Force. Cerebellum 2019;18:1098–1125.
3. da Graça FF, Peluzzo TM, Bonadia LC, et al. Diagnostic yield of whole exome sequencing for adults with ataxia: a Brazilian perspective. Cerebellum 2021;21:49–54;
4. Rangel DM, Nobrega PR, Saraiva-Pereira ML, Jardim LB, Braga-Neto P. A case series of hereditary cerebelar ataxias in a highly consanguineous population from Northeast Brazil. Parkinsonism Relat Disord 2019;61:193–197.
5. Synofzik M, Nemeth AH. Recessive ataxias. Handb Clin Neurol 2018;155:73–89.

Supporting Data

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

A *De Novo* Missense *NPTX1* Variant in an Individual with Infantile-Onset Cerebellar Ataxia

Most recently, three different missense variants in the *NPTX1* gene were described to cause late-onset cerebellar

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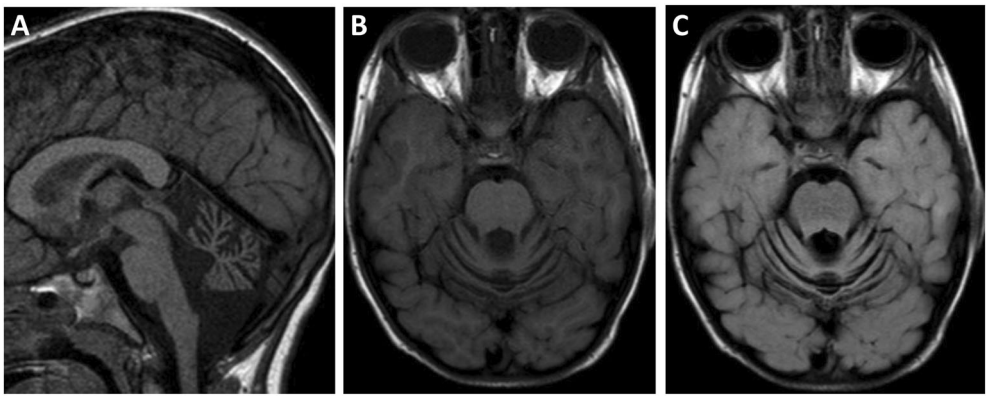

FIG. 1. Neuroimaging at the age of 40 months. (**A**) Sagittal T1-weighted image demonstrating markedly enlarged fissures of the cerebellar vermis and preserved pontine protuberance. (**B**) Axial T1-weighted image showing enlarged fissures in vermis and cerebellar hemispheres. (**C**) Axial FLAIR sequence with evidence of mild hyperintensity of the cerebellar cortex (compared with cerebral cortex). FLAIR, fluid-attenuated inversion recovery.

ataxia with an autosomal dominant inheritance pattern.[1,2] Here, we report on a child affected by early-onset ataxia and cerebellar atrophy since infancy, who carries a novel heterozygous de novo missense variant in *NPTX1*, affecting a highly conserved residue of pentraxin (Gln370Arg).

The patient, a currently 6-year-old girl, is the second child of nonconsanguineous parents with an unremarkable family history. After an uneventful pregnancy and uncomplicated delivery, developmental progress (walking, speech, and social skills) was reported normal until the age of 21 months. At this time, unsteadiness, irritability, and sleeping problems were noted, and a neurological assessment was initiated. By the age of 2 years, she developed truncal and limb ataxia with an inability to walk and loss of acquired speech skills. The first magnetic resonance imaging (MRI) was performed at the age of 25 months, demonstrating enlarged fissures of cerebellar vermis and hemispheres, suggestive of cerebellar atrophy. The cerebellar cortex had increased fluid-attenuated inversion recovery hyperintensity, compared with the cerebral cortex. A second MRI, performed at 40 months, showed the cerebellar vermis atrophy mildly more accentuated (Fig. 1); however, this is a common nonspecific finding in many pediatric-onset ataxias.[3] At the age of 6 years generalized epileptic seizures with electroencephalographic correlate were diagnosed and treated with lacosamide.

Based on the clinical diagnosis of suspected genetic ataxia and vermis atrophy on MRI, exome sequencing (using Agilent SureSelect Human All Exon V6 and Illumina HiSeq 150 bp paired-end sequencing technology) was performed at the age of 30 months in 2017 but failed to identify (likely) pathogenic variants in any gene known to be associated with ataxia or childhood-onset neurological disorders at that time. Following the publication of variants in a novel gene (*NPTX1*) to be associated with ataxia,[1] the archived exome data were reevaluated by querying for variant calls in this gene. We indeed identified a hitherto-unreported missense variant within exon 5 of the *NPTX1* gene, NM_002522.4: c.1109A>G(hg19_chr17:g.78444803T>C), predictably leading to the substitution of a highly conserved amino acid residue within the pentraxin domain: p.(Gln370Arg). Subsequent confirmation by conventional DNA sequencing and targeted segregation analysis in parental DNA revealed that the variant occurred de novo (see Appendix S1), suggestive of parental germline mosaicism. This missense variant was absent from more than 250,000 control alleles in gnomAD and more than 3400 alleles from in-house-sequenced individuals affected with various clinical conditions. In silico evaluation predicted a likely pathogenic effect of the variant (CADD phred score of 27.1, DANN score of 0.999, and ClinPred score of 0.994), with consistent results across different algorithms.[4-6]

Overall, our results support the notion that de novo variants in *NPTX1* might also be implicated in pediatric-onset ataxia. This case underlines the importance of holistic diagnostic approaches in neurologic conditions with suspected hereditary disease. Finally, this case also demonstrates how continuous reevaluation of next-generation sequencing data after publication of novel relevant disease-causing genes can shorten the path to a genetic diagnosis for individuals affected by rare diseases and their families.

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Data Availability Statement

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

References

1. Coutelier M, Jacoupy M, Janer A, et al. NPTX1 mutations trigger endoplasmic reticulum stress and cause autosomal dominant cerebellar ataxia. Brain 2021 2021. https://doi.org/10.1093/brain/awab407
2. Deppe J, Deininger N, Lingor P, Haack TB, Haslinger B, Deschauer M. A Novel NPTX1 de novo variant in a late-onset ataxia patient. Mov Disord 2022. https://doi.org/10.1002/mds.28985
3. Poretti A, Wolf NI, Boltshauser E. Differential diagnosis of cerebellar atrophy in childhood: an update. Neuropediatrics 2015;46(6):359–370. https://doi.org/10.1055/S-0035-1564620
4. Kircher M, Witten DM, Jain P, O'roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet 2014;46(3):310–315. https://doi.org/10.1038/NG.2892
5. Alirezaie N, Kernohan KD, Hartley T, Majewski J, Hocking TD. ClinPred: prediction tool to identify disease-relevant nonsynonymous single-nucleotide variants. Am J Hum Genet 2018;103(4):474–483. https://doi.org/10.1016/J.AJHG.2018.08.005
6. Quang D, Chen Y, Xie X. DANN: a deep learning approach for annotating the pathogenicity of genetic variants. Bioinformatics 2015;31(5):761–763. https://doi.org/10.1093/BIOINFORMATICS/BTU703

Supporting Data

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Glia Imaging Shows Clinical Utility in Differentiating Parkinson's Disease from Multiple System Atrophy

We recently presented a multicenter positron emission tomography (PET) study on the glia biomarker translocator protein (TSPO) in patients with multiple system atrophy (MSA) and Parkinson's disease (PD).[1] We found a distinct TSPO pattern for MSA with an elevated signal in the striatum (lentiform nucleus in particular) and cerebellar white matter (with 96% sensitivity and 100% specificity against a clinical MSA diagnosis). However, in the imaging data analysis, we observed a single patient with MSA who deviated in glia pattern across both visual and machine-learning assessment approaches. Following this observation, we now review this case in detail.

The patient is a 50-year-old woman (Fig. 1B, patient 9) diagnosed with possible MSA based on clinical symptoms of bradykinesia, stiffness, dysautonomia (segmental left-sided hyperhidrosis), and collapse attacks (thought to be attributed to orthostatism). At that time, single-photon emission computed tomography showed reduced dopamine transporter in the right striatum, especially in the posterior putamen. Brain magnetic resonance imaging (MRI) did not show any remarkable findings. Levodopa treatment was started, and she has had good and sustained response and the dysautonomic features have diminished. She has had no cerebellar or pyramidal signs. At 8 years after the diagnosis, she was included in a clinical trial as a patient with MSA. A two-level diagnostic procedure was undertaken: MSA diagnosis was established by an investigator at a specialized movement disorders clinic, and the assurance of diagnostic accuracy was performed by blinded independent expert review.[1] The patient is a mixed-affinity binder by *TSPO* genotype. However, at the baseline PET examination, the glia pattern (Fig. 1A) did not resemble that of other patients in the MSA group (Fig. 1C), and she was the only patient identified as misclassified compared with the clinical diagnosis. At follow-up 11 years after the initial diagnosis, the patient was rediagnosed with PD.

Based on the clinical course, that is, good levodopa response 15 years after the diagnosis, ability to walk well, diminished dysautonomic features, no pyramidal or cerebellar signs, no antecollis or stridor, and life longevity, this patient with MSA is now confirmed as PD.

Discussion

This case is an example of the challenge faced by clinicians in the differentiation of early MSA with parkinsonian symptoms from PD. The distinct triad of tremor, bradykinesia, and muscle rigidity describing motor impairment in PD may not always be present. Today, PD is known as a heterogenous disease, presenting in different disease variants. Clinical subtypes can range from a mild subtype, for example, a combination of motor phenotype, response to dopaminergic treatment, and slow progression, to a malignant subtype with broader symptom spectrum, poor response to treatment, and fast progression.[2] The latter may closely resemble possible MSA. In this case presentation of disease onset with dysautonomia, the symptoms led to a suspicion of MSA.

Clinical diagnostic criteria of MSA have been supported with characteristic signs observed at imaging, for example, patterns of glucose metabolism, changes in dopamine transporter levels, and specific structural changes detected on MRI.[3] Notably, these imaging modalities have provided evidence on the significant differences between patient groups with PD and MSA. However, they have limitations in the individual case diagnostics, for example, by the need of comparison of individual patient data against group threshold levels ([^{18}F]fluorodeoxyglucose[4]) or less applicable for the MSA cerebellar subtype (dopamine transporter imaging[5]).

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