

Spinocerebellar ataxia type 3 (Machado–Joseph disease)

Jarosław Dulski^{1,2,3}, Rana Hanna Al-Shaikh¹, Anna Sułek⁴, Jakub Kasprzak³,
Jarosław Sławek^{2,3}, Zbigniew K. Wszolek¹

¹ Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

² Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Gdańsk, Poland

³ Neurology Department, St. Adalbert Hospital, Copernicus PL Ltd., Gdańsk, Poland

⁴ Department of Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland

Ataxia denotes impaired balance and coordination of gait, posture, limbs, and speech. It usually results from disturbances of the cerebellum and its connections (cerebellar ataxia) or sensory pathways (sensory ataxia). In most patients, it is secondary to toxic (alcohol, antiepileptics), vascular (stroke), immune (paraneoplastic, multiple sclerosis), infectious (SARS-CoV-2, HIV, cerebellar abscess), and neoplastic (metastatic or, more rarely, primary tumor) causes.^{1–3} Genetic ataxias include spinocerebellar ataxias (SCAs), with an average estimated prevalence worldwide of up to 5.6 per 100 000.¹ There are more than 40 distinct forms of SCA, among which the most common is SCA type 3 (SCA3; also referred to as Machado–Joseph disease), accounting for 20% to 50% of all SCA cases.^{1,4}

SCA3 is a progressive neurodegenerative disease first described 50 years ago in 2 families (Machado and Joseph) of Portuguese-Azorean descent.⁴ It is caused by abnormal repeat expansion in the *ATXN3* gene. Healthy individuals have up to 44 cytosine-adenine-guanine (CAG) repeats, whereas those who develop SCA3 usually have more than 60 repeats.^{1,4} The mutation causes the expression of aberrant protein with expanded polyglutamine stretch that easily aggregates and deposits in the neurons of the cerebellum and brainstem.^{1,4} This leads to the typical clinical presentation of progressive cerebellar ataxia and worsening of speech. Magnetic resonance imaging of the brain reveals atrophy of the brainstem and cerebellum (FIGURE 1). Some patients may also manifest other motor symptoms, including extrapyramidal syndromes (basal ganglia involvement), amyotrophy (brainstem and spinal cord involvement), and neuropathy (peripheral nervous system involvement).⁴ Autonomic symptoms, particularly

bladder dysfunction (nocturia and urinary incontinence), sudomotor (abnormal thermoregulation, cold intolerance, hypohidrosis), and cardiovascular disturbances (orthostatic hypotension), affect the majority of patients.^{4,5} Autonomic cardiac denervation is mostly parasympathetic and occurs in up to 60% of patients; however, sympathetic dysfunction was also demonstrated with iodine-123 metaiodobenzylguanidine cardiac scintigraphy.⁵ Psychiatric features, predominantly depressive symptoms, affect up to 60% of SCA3 patients, and their basis (organic vs reactive) is not yet understood.⁵ Cognitive impairment, particularly worsened learning abilities and memory dysfunction, was reported in many patients.⁵ Fatigue occurs in up to 61% of cases, and its severity makes it one of the most disabling symptoms in SCA3.⁵ Chronic pain, particularly in the lumbosacral region, and painful muscle cramps affect up to 80% of patients.^{4,5} The latter may be the first manifestation of the disease even in a quarter of patients.⁵ Sleep disturbances are common and include REM sleep behavior disorder, restless legs syndrome, sleep apnea, insomnia, and daytime sleepiness.⁵

Currently, there is no approved therapy for SCA3.^{1,4} The preliminary reports suggest beneficial effects of riluzole in SCA3 and other SCAs.^{1,4} The therapeutic effect of riluzole is attributed to its antiglutamatergic activity in the brain.^{1,4} Of note, close monitoring for adverse effects, particularly during the first year of treatment, is necessary, as some patients develop liver toxicity ranging from mild elevation of aminotransferases to liver failure. Troriluzole, a prodrug of riluzole with a better safety profile and promising efficacy in SCA3, is in phase III of a clinical trial (NCT03701399).

Correspondence to:

Zbigniew K. Wszolek, MD,
Department of Neurology, Mayo
Clinic, 4500 San Pablo Road,
Jacksonville, FL 32224, United
States, phone: +1 904 953 7229,
email: Wszolek.Zbigniew@mayo.edu
Received: August 5, 2022.

Revision accepted: August 16, 2022.

Published online: August 22, 2022.

Pol Arch Intern Med. 2022;

132 (10): 16322

doi:10.20452/pamw.16322

Copyright by the Author(s), 2022

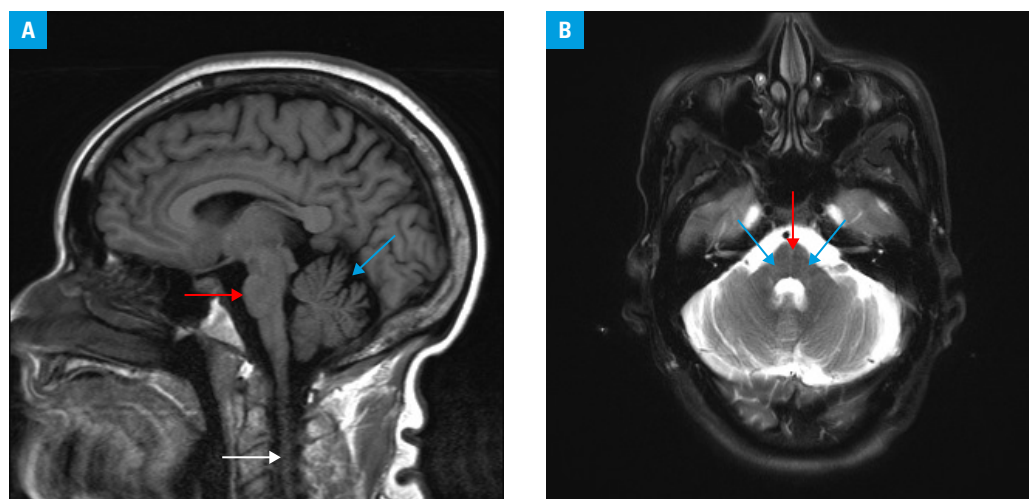


FIGURE 1 Brain magnetic resonance imaging (3 Tesla study) of a 50-year-old female patient who developed imbalance and gait difficulty at the age of 30 years. She had a positive family history for SCA type 3, and genetic testing confirmed abnormal expansion in *ATXN3* (70 and 30 CAG repeats). **A** – cerebellar (blue arrow), brainstem (red arrow), and cervical spinal cord (white arrow) atrophy on sagittal T1-weighted fluid-attenuated inversion recovery imaging; **B** – atrophy of the pons (red arrow) and middle cerebellar peduncles (blue arrows) on axial T2-weighted fat-saturated turbo spin echo imaging

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING The study was partially funded by donations from the Donald G. and Jodi P. Heeringa family.

CONFLICT OF INTEREST JD reports honoraria from VM Media Ltd., Radosław Lipiński 90 Consulting, and Ipsen, and grants from the Haworth Family Professorship in Neurodegenerative Diseases fund. JS reports consultancies, contracts, and honoraria from Allergan, Abbvie, Ipsen, Everpharma, Merz, Novartis, Biogen, Roche, TEVA, and honoraria from the Polish Neurological Society (coeditor-in-chief of *Neurologia i Neurochirurgia Polska*). Mayo Clinic and ZKW have a financial interest in technologies entitled “Identification of Mutations in *PARK8*, a Locus for Familial Parkinson’s Disease” and “Identification of a Novel *LRRK2* Mutation, 6055G>A (G2019S), Linked to Autosomal Dominant Parkinsonism in Families from Several European Populations”. Those technologies have been licensed to a commercial entity, and to date, ZKW has received royalties <USD 1.500 through Mayo Clinic in accordance with its royalty sharing policies. ZKW also serves as a consultant and member of the advisory board of Vigil Neuroscience, Inc., and reports honoraria from the Polish Neurological Society (coeditor-in-chief of *Neurologia i Neurochirurgia Polska*) and the following grants: NIH/NIA and NIH/NINDS (1U19AG063911, FAIR: U19AG063911), Mayo Clinic Center for Regenerative Medicine, Mayo Clinic in Florida Focused Research Team Program, the gifts from the Donald G. and Jodi P. Heeringa Family, the Haworth Family Professorship in Neurodegenerative Diseases fund, and The Albertson Parkinson’s Research Foundation. He serves as PI or Co-PI on Biohaven Pharmaceuticals, Inc. (BH4157-206 and BH3241-301), Neuraly, Inc. (NLY01-PD-1), and Vigil Neuroscience, Inc. (VGL101-01.001). Other authors declare no conflict of interest.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

HOW TO CITE Dulski J, Hanna Al-Shaikh R, Sulek A, et al. Spinocerebellar ataxia type 3 (Machado–Joseph disease). *Pol Arch Intern Med.* 2022; 132: 16322. doi:10.20452/pamw.16322

REFERENCES

- 1 Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers.* 2019; 5: 24. [↗](#)
- 2 Adamczyk-Sowa M, Niedziela N, Kubicka-Bączek K, et al. Neurological symptoms as a clinical manifestation of coronavirus disease 2019: implications for internists. *Pol Arch Intern Med.* 2021; 131: 54-62. [↗](#)
- 3 Hirschfeld AS. Autoimmune mediated hyperkinetic movement disorders in SARS-CoV-2 infection - a systematic review. *Neurol Neurochir Pol.* 2021; 55: 549-558. [↗](#)
- 4 Paulson H, Shakkottai V. Spinocerebellar Ataxia Type 3. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews*. Seattle (WA): University of Washington, Seattle; Copyright 1993-2022, University of Washington,

Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.

5 Moro A, Moscovich M, Farah M, et al. Nonmotor symptoms in spinocerebellar ataxias (SCAs). *Cerebellum Ataxias.* 2019; 6: 12. [↗](#)