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Predominant motor neuron involvement as a manifestation of pathogenic (full range) *ATXN3* mutations

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Dear Editor-in-Chief,

Weread with great interest the recent paper by Dong and colleagues on *ATXN3* gene mutations manifesting as amyotrophic lateral sclerosis (ALS) mimics [1]. The paper reported three patients from two different pedigrees with intermediate-length CAG expansion in the *ATXN3*. We want to illustrate that pathogenic (full range) *ATXN3* mutation may also present with the ALS-like phenotype.

A 30-year-old female presented with distal weakness of the left hand that gradually progressed and involved the forearm, arm, and shoulder. In the next 2 years, her left hand became paralyzed, and she also noticed a worsening of the fine movements in her right hand. At 35 years, she noticed progressive weakness of the legs that was more prominent on the left side, and she became wheelchair-bound 2 years later. She also noticed mild swallowing problems with only occasional choking. Her cognition and autonomic system were not affected. However, she was diagnosed with mild reactive depression that was treated with citalopram and insomnia that improved on melatonin, cannabidiol, and pregabalin. Neurophysiological studies at 32 and 34 years showed progressive neurogenic changes more pronounced on the left side and no evidence of sensory neuropathy. Brain MRI at 33 showed incidental, asymptomatic lacunar infarction in the right caudate nucleus and mild cerebellar atrophy but otherwise was normal (Fig. 1A, B). On neurological evaluation at 37, she had nystagmus in horizontal and vertical planes with rotatory component on the upgaze,

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Consent to participate Written informed consent was collected from the patient.

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mild dysarthria, polyclonic jaw jerk, palmomental reflex present on the right side, tongue fasciculations, severe flaccid four-limb weakness that was more prominent distally and on the left side, atrophy of the fine hand and forearm muscles more pronounced on the left side, brisk tendon reflexes in the upper and lower limbs that were more prominent on the right side, absent Achilles reflexes bilaterally, downgoing plantar reflexes, normal sensation to light touch, pinprick, vibration, position, and temperature. Due to muscle weakness, ataxia was impossible to test, and she could not stand up. Follow-up brain MRI (Fig. 1C, D) was stable and did not reveal progression. She died of respiratory failure at 38.

She had a positive history of gait difficulty and imbalance in her mother and many other family members (Fig. 2), which were diagnosed with spinocerebellar ataxia type 3 (SCA3; Machado-Joseph disease). The age of onset in the family members was similar to that of the patient; however, none of them displayed an ALS-like phenotype. The patient's genetic testing revealed abnormal expansion (75 and 14 CAG repeats) in the ATXN3 gene. Further extensive genetic work-up for ALS-related genes (including *ALS2, ANG, ANXA11, CHCHD10, C9orf72, DCTN1, ERBB4, FUS, HEXA, KIF5A, OPTN, PFN1, SETX, SOD1, SPG11, SQSTM1, TARDBP, TBK1, TFG, UBQLN2, VAPB, VCP*) was unrevealing.

Dong et al. reported three patients with progressive limb weakness and without ataxia. Two patients, who were siblings and had a positive family history of similar symptoms, were diagnosed with lower motor neuron loss and sensory neuropathy. The third patient had a sister with cerebellar ataxia and sensory neuropathy, yet the other family history was unremarkable. He was diagnosed with both upper and lower motor neuron loss and sensory neuropathy. The three patients had CAG expansion in *ATXN3* in the intermediate range (53, 57, and 57 repeats).

In contrast, our patient presented symptoms consistent with upper and lower motor neuron loss; however, the neurophysiological studies done twice did not demonstrate neuropathy. Although ataxia could not be appreciated, the nystagmus indicated cerebellar involvement [2]. Additionally, she had a remarkable family history of typical SCA3 symptoms and CAG repeats in the pathogenic (full penetrance) range.

The pathomechanism underlying ALS remains not well understood. It is hypothesized that oxidative stress may contribute to the development of neurodegeneration. The antiglutamergic and potentially antioxidative drug riluzole has been approved in ALS, whereas another antioxidant, edaravone, showed only modest effects [3]. Interestingly, riluzole was effective in some SCA3 patients, and a clinical trial with its derivative, troriluzole, has shown promising preliminary results in SCA3. However, in ALS and SCA3, the primary treatment remains symptomatic, including multidisciplinary care that aims to improve quality of life [4, 5].

Previous studies suggested that intermediate-length polyQ expansion may selectively affect motor neurons. Our case illustrates that pathogenic ATXN3 mutations may also manifest with predominant motor neuron involvement. The precise mechanism of atypical presentation of our patient compared to the other family members warrants further investigation.

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Availability of data and materials

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

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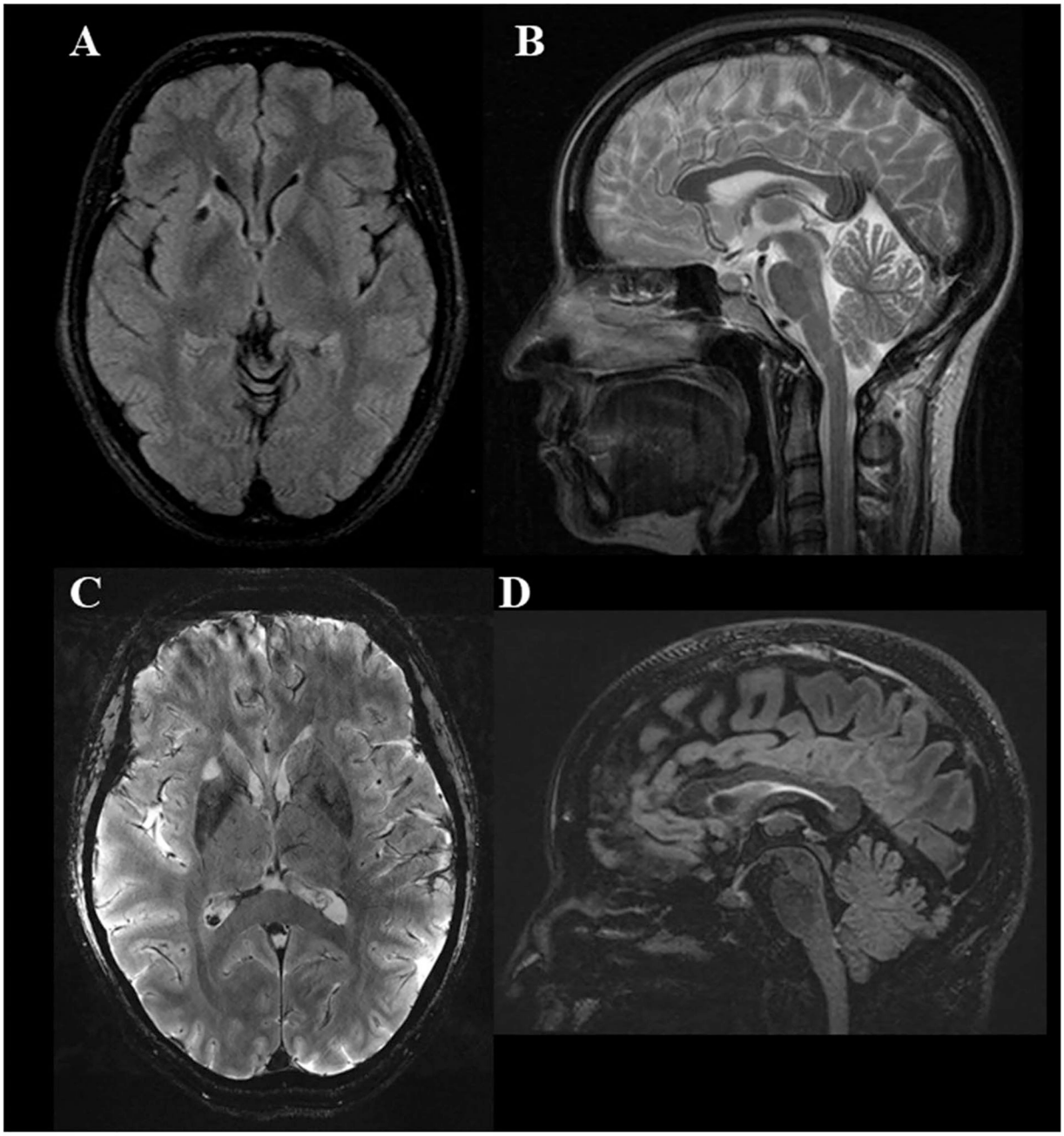

Fig. 1.

Brain 3 Tesla MRI at 33 years showing lacunar infarction in the right caudate nucleus on axial T2 turbo inversion recovery magnitude dark fluid (**A**); mild cerebellar atrophy on sagittal T2 turbo spin echo sequences (**B**). Follow-up brain 7 Tesla MRI at 37 years revealed no significant progression on axial T2 (**C**) and sagittal T2 fluid-attenuated inversion recovery sequences (**D**)

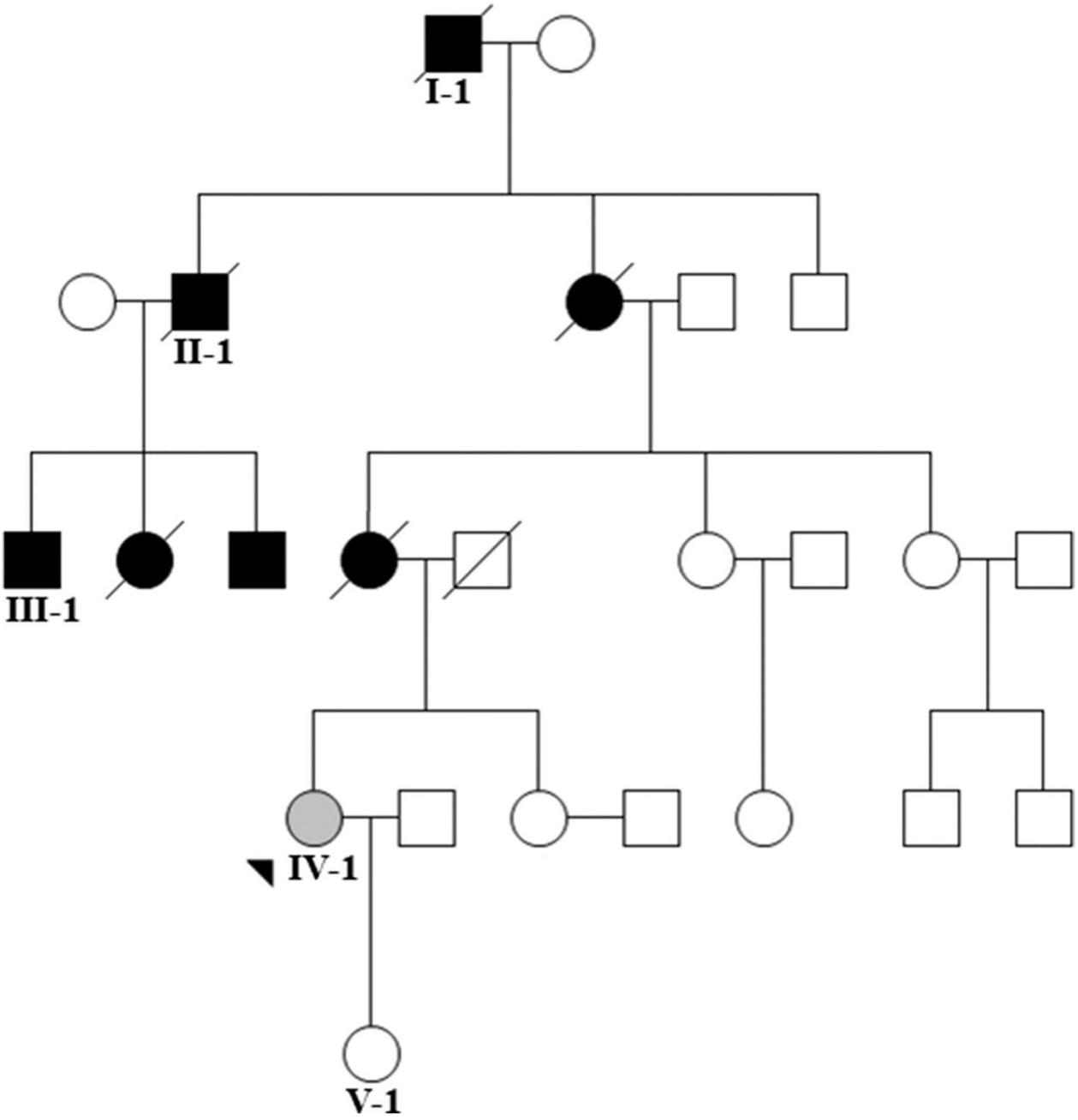

Fig. 2.

Pedigree. For family pedigree, standard pedigree symbols are used; arrow indicates the proband; circles indicate females; squares indicate males; slash through symbols indicate diseased individuals; black symbols indicate individuals with a typical phenotype of spinocerebellar ataxia type 3; gray symbol indicates affected individual with phenotype mimicking amyotrophic lateral sclerosis