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Split hand and minipolymyoclonus in spinocerebellar ataxia type 3: a case report

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Abstract

Background Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease, is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansion in exon 10 of *ATXN3*. Extra-cerebellar manifestations, including external ophthalmoplegia, dystonia, Parkinsonism, and peripheral neuropathy, are predominantly present in SCA3 cases. Here, we report a case of SCA3 presenting with a split hand and minipolymyoclonus.

Case presentation A 73-year-old female patient presented with a 5-year history of ataxic gait. Neurological examination revealed cerebellar ataxia and minipolymyoclonus in the digits on both sides and muscle atrophy in the right hand, consistent with the split hand pattern. Electrodiagnostic studies demonstrated decreased amplitude of compound muscle action potentials and neurogenic motor unit potentials, indicating lower motor neuron involvement.

Conclusions Our patient's case indicated a split hand and minipolymyoclonus in SCA3. Clinicians should consider these extra-cerebellar manifestations in patients with SCA3. Although neither split hand nor minipolymyoclonus are likely to directly result in a specific etiological diagnosis, a common pathophysiological mechanism for both may be lower motor neuron involvement. This extracerebellar manifestation contributes to narrowing down the diagnostic possibilities for cases presenting with progressive cerebellar ataxia.

Keywords Myoclonus, Spinocerebellar ataxias, Multiple system atrophy, Short-interval intracortical inhibition, Voxel-based morphometry

Background

Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease, is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansion in exon 10 of *ATXN3* [1]. The most consistent clinical manifestation of SCA3 is cerebellar ataxia, but SCA3 demonstrates a high frequency of extra-cerebellar manifestations, including progressive external ophthalmoplegia, dystonia, Parkinsonism, peripheral neuropathy, pyramidal signs, and sleep disorders [2, 3].

Miniploymyoclonus (also known as polyminimyoclonus) is a hyperkinetic movement disorder phenomenology characterized by intermittent, low-amplitude, irregular hand movements, prevalently of digits [4]. This clinical feature has been a supportive motor sign in diagnosing multiple system atrophy (MSA), which shares a degenerative nature, and cerebellar ataxia as a primary symptom with SCA3 [5, 6]. Split hand, which is another

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distinctive feature, is a dissociated atrophy characterized by preferential atrophies in the thenar and first dorsal interosseous (FDI) muscles, with relative hypothenar muscle sparing. This sign has been specific to amyotrophic lateral sclerosis (ALS) [7].

Reports of SCA3 cases with such minipolymyoclonus and split hands are rare to date. Here, we report a genetically confirmed SCA3 case presenting with both minipolymyoclonus and split hand and discuss the pathophysiology behind these distinct features.

Case presentation

A 73-year-old female patient presented with a 5-year gait disturbance history. Initially, she noticed instability while performing routine tasks, such as putting on and taking off her pants while standing, as well as difficulty descending stairs without a handrail. Her gait progressively became more unsteady, accompanied by a decrease in walking speed, over the subsequent years. Her medical history included diabetes mellitus, hypertension, osteoporosis, and clavicle fracture. Her family history indicated a progressive unsteady gait in her mother during her 70s, with difficulty maintaining a sitting position in her 80s, and passed away at 88 years of age, without a spinocerebellar degeneration diagnosis (Fig. 1).

A cranial nerve examination revealed normal findings but with smooth pursuit eye movements interrupted by saccades and mild cerebellar dysarthria. Thenal eminence and FDI muscle wasting were observed, with relative abductor digit minimi (ADM) preservation in the right hand (Fig. 1). Outstretching the arms and extending the fingers demonstrated jerky, irregular, and small amplitude involuntary movements of the digits, indicating minipolymyoclonus. Manual muscle strength was low in the following muscle groups based on the Medical Research Council grad (right/left): deltoid (5/5), biceps (5/5), triceps (5/5), wrist extensors (5/5), wrist flexors (5/5), abductor pollicis brevis (APB) (4+/5), ADM (5/5), iliopsoas (5/4+), quadriceps (5/5), hamstrings (5/5), tibialis anterior (5/4+), and gastrocnemius (5/5). Additionally, deep-tendon reflexes were normal in the upper extremities but absent in the lower extremities. Additionally, the finger chase test revealed mild dysmetria and the heel-shin test demonstrated lower limb incoordination. Her gait was somewhat unsteady, and her tandem gait was impaired. The Assessment and Rating of Ataxia Scale [8] was 8.5 out of 40. Sensory examination revealed intactness across all modalities.

Brain magnetic resonance imaging (MRI) revealed pons and cerebellar atrophy (Fig. 2). Nerve conduction studies (NCS) indicated a reduced amplitude of compound muscle action potential and sensory nerve action potential (Table 1). The split hand index calculated based on the nerve conduction studies was 3.4 (cut-off value of 6.4) [9], indicating an electrophysiologic split hand pattern. Needle electromyography in the right FDI revealed 2+fibrillations and high amplitude muscle unit potential, indicating neurogenic changes. Surface electromyography exhibited irregular, short duration, and asynchronous muscle bursts in the second and third dorsal interosseous muscles (Fig. 3). Threshold tracking transcranial magnetic stimulation revealed averaged short-interval intracortical inhibition (SICI) [10] with 6.6% and 5.2% in the right and left sides, respectively. Family history, progressive cerebellar ataxia with split hand and minipolymyoclonus, atrophy of the pons and cerebellum on brain MRI, and the NCS findings led us to consider autosomal dominant cerebellar ataxia with lower motor neuron involvement as possible diagnosis. Because split hand can be observed in SCA3 [11], SCA3 was specifically considered. Ataxia panel testing for SCA diagnoses, including SCA1, 2, 3, 6, 7, 8, 12, 17, and 31 and dentatorubral-pallidoluysian atrophy, revealed 14/56 CAG repeats in *ATXN3*; thus, the patient was diagnosed with SCA3.

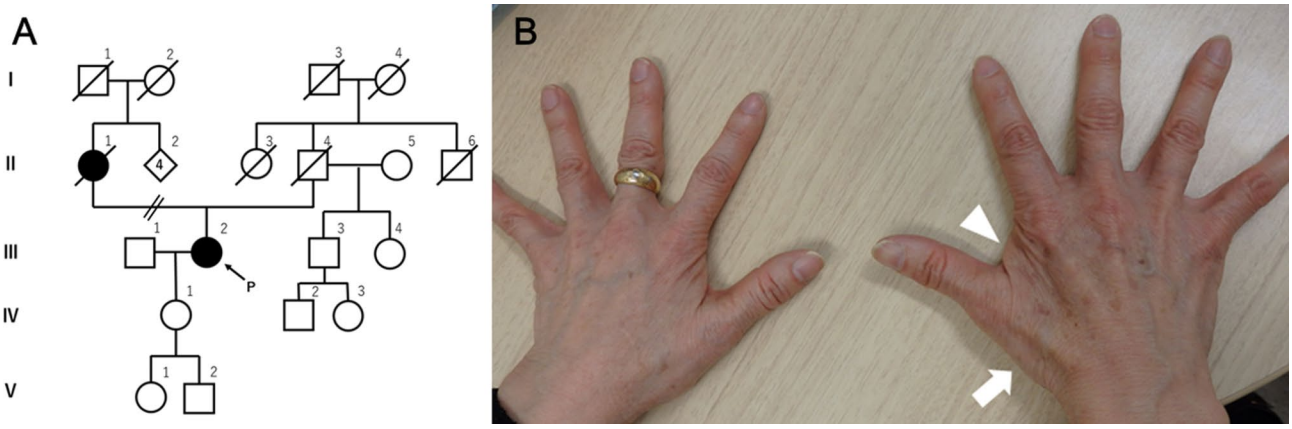

Fig. 1 Pedigree of the family and split hand of the right hand. (**A**) Pedigree is slightly modified to maintain confidentiality. (**B**) The first dorsal interosseous exhibited clear wasting (white arrowhead) and the right hand demonstrated thenar eminence (white arrow)

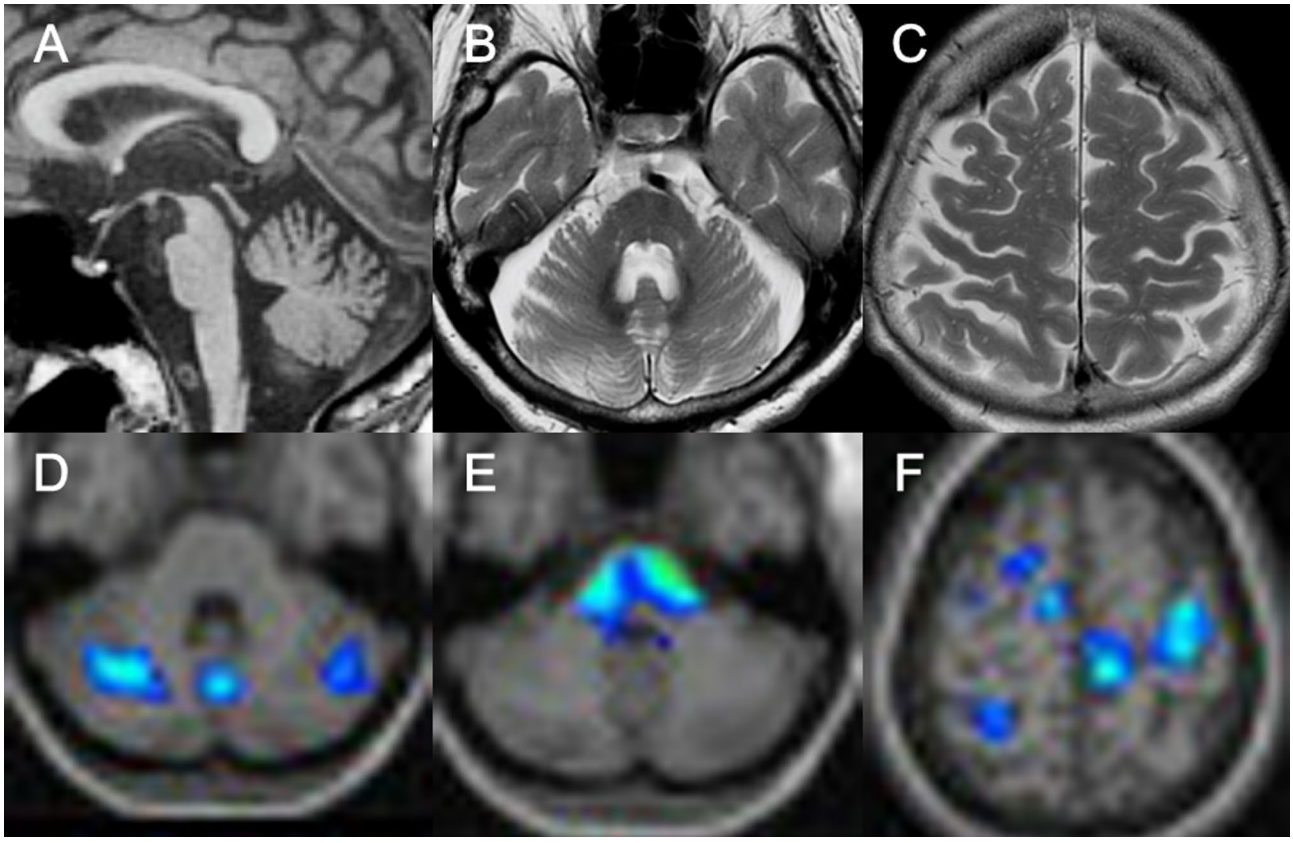

Fig. 2 Brain MRI and the VSRAD advance analysis. Sagittal T1-weighted (**A**) and axial T2-weighted (**B**, **C**) images illustrate atrophy in the pons and cerebellum. The VSRAD advance analysis of gray matter (**D**) reveals a significant decrease in cerebellar volume. The VSRAD advance analysis of white matter (**E**, **F**) indicates a significantly decreased pons and left precentral gyrus volume. Colored areas with z scores of > 2 denote significantly atrophied regions overlaid on the MRI

Table 1 Nerve conduction studies

	Motor nerve				Sensory nerve	
	Distal latency (ms)	**Conduction velocity (m/s)**	**CMAP amplitude (mV)**	**F-wave latency (ms)**	**Conduction velocity (m/s)**	**SNAP amplitude (μV)**
Median nerve	3.8 (< 4.5)	*47 (> 48)*	*3.0 (> 5.0)*	25.2 (< 31.4)	60 (> 43)	*2 (> 11.3)*
Ulnar nerve (ADM)	3.0 (< 3.6)	64 (> 46)	5.7 (> 4.7)	24.1 (< 31.7)	43 (> 40)	*2 (> 8.8)*
Ulnar nerve (FDI)	4.0	NA	4.9	NA		
Peroneal nerve	*7.3 (< 6.2)*	40 (> 37)	*0.34 (> 0.7)*	NR		
Tibial nerve	4.4 (< 5.9)	41 (> 36)	*1.74 (> 5.6)*	52.4 (< 56.8)		
Sural nerve					49 (> 37)	*3 (> 3.4)*

All studies were performed in the right extremities.

CMAP: compound muscle action potential; SNAP: sensory nerve action potential; ADM: abductor digit minimi; FDI: first dorsal interosseous; NA: not applicable; NR: not recorded. Sensory studies were performed antidromically.

Abnormal values are indicated with underline. Normal limits are indicated in parentheses (our laboratory data).

CMAP recording of FDI is not routinely done in our laboratory, so normal limits are not available.

Single-case voxel-based morphometry (VBM) was performed using three-dimensional T1-weighted images to evaluate the structural brain changes in the gray and white matter volume. Our single-case VBM analysis used the software "voxel-based specific regional analysis system for Alzheimer's disease advance" (Eisai, Tokyo, Japan) equipped with SPM8 (The Welcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK) and Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra based on VBM [12], providing statistical z score images for gray and white matter atrophy in each of the patients relative to that of the normal database. The z score is calculated as ([control mean] − [individual value])/(control standard deviation), and the z score values are overlaid on the standardized brain MRI of each patient as a color scale

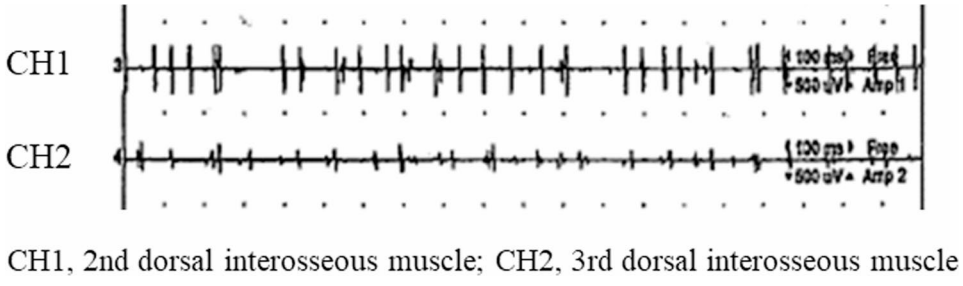

Fig. 3 Surface electromyography. Surface electromyography reveals irregular, short-duration, and asynchronous muscle bursts in the second and third dorsal interosseous muscles

map. This single-case VBM analysis for gray and white matter revealed volume reductions in the cerebellum and the pons and left precentral gyrus, respectively (Fig. 2).

Discussion and conclusion

Here, we described a case of genetically confirmed SCA3 with split hand and minipolymyoclonus as extra-cerebellar manifestations detected on neurological examinations and confirmed by electrophysiological testing. The phenotype of the patient described here is consistent with the SCA3 subtype (subtype III), which is characterized by late onset and cerebellar ataxia with peripheral involvement [3].

In this case, lower motor neuron involvement was the primary pathophysiological mechanism underlying both the split hand and minipolymyoclonus observed. Muscle weakness with atrophy and nerve conduction study and needle electromyography results in the present case indicate lower motor neuron involvement. Although split hand has been considered a pathognomonic sign in ALS [7], this sign has recently been demonstrated in other diseases as well. For instance, it has been observed in spinal and bulbar muscular atrophy (SBMA) [9] and *GARS1*-associated neuropathy [13], indicating that lower motor neuron involvement alone could contribute to the split hand. A study on patients with SCA3 who exhibited split hands revealed lower motor neuron dysfunction due to involvement of anterior horn cells as the pathophysiological background, based on nerve conduction studies [11]. Further, minipolymyoclonus has also been described in disorders with anterior horn cell involvement, including spinal muscular atrophy, SBMA, and brachial monomeric amyotrophy [4].

In this case, there was no evident involvement of upper motor neuron dysfunction in the background pathophysiology of split hand. Threshold tracking transcranial magnetic stimulation and single-case VBM demonstrated a relative reduction in SICI on the left side compared to the contralateral side, along with a reduced volume of the left precentral gyrus, indicating the possible presence of upper motor neuron impairment in the current case. Split hand is frequently observed in ALS, and both upper and lower motor neuron involvement have been considered underlying mechanisms of split hand in ALS [7]. Previous excitability studies have exhibited that motor axonal excitability is physiologically higher in APB than in ADM, and altered motor axonal excitability in ALS is more prominent in APB than in ADM [14, 15]. A previous study using transcranial magnetic stimulation revealed the preferentially impaired corticomotoneuronal input to the thenar spinal pool than the hypothenar spinal pool in ALS [16]. Another study demonstrated that cortical hyperexcitability, as indicated by a significant SICI reduction, was most prominent when recorded from the APB and FDI muscles in ALS [17]. Upper motor neuron involvement can occur in patients with SCA3. Pyramidal signs among the common extra-cerebellar manifestations of SCA3 [18, 19]. Furthermore, radiological studies in these patients have shown cortical thinning in the primary motor cortices and diffusion abnormalities in the corticospinal tract [20–22]. A study utilizing threshold tracking transcranial magnetic stimulation found motor-cortical disinhibition in both presymptomatic and symptomatic patients with SCA3 [23]. However, in this case, no left-sided pyramidal tract signs corresponding to the split hand in the right hand were observed, and there was no clear evidence of upper motor neuron involvement. To better understand the background pathophysiology of split hand in SCA3, further studies assessing both split hand and upper and lower motor neuron deficits in a larger SCA3 cohort are needed.

Minipolymyoclonus is not necessarily unique in distinguishing between SCA3 and MSA. MSA, particularly the cerebellar type (MSA-C), shares cerebellar ataxia as the primary motor symptom, degenerative nature, and characteristic findings on brain MRI with SCA3 [24], and it is difficult to distinguish from SCA3 without a clear family history. Therefore, the use of extra-cerebellar manifestations, such as minipolymyoclonus, in distinguishing between MSA and SCA3 is of clinical significance. Minipolymyoclonus has been a “red flag” or a warning sign that increases the clinical suspicion of MSA [5, 25] and is one of the supportive motor signs in the latest diagnostic

criteria [6]. Minipolymyoclonus is highly specific for parkinsonism predominant type MSA (MSA-P) in differentiating MSA-P from Parkinson's disease and progressive supranuclear palsy [5, 25], but its usefulness in differentiating MSA-C from SCA, including SCA3, has been unknown. Among SCAs, other than SCA3, minipolymyoclonus was reported in SCA21 [26].

In conclusion, split hand and minipolymyoclonus are extra-cerebellar manifestations present in SCA3. Although split hand and minipolymyoclonus unlikely result in a specific etiological diagnosis, their common pathophysiological mechanism may involve lower motor neuron involvement. As an extracerebellar sign, this involvement contributes to narrowing down the diagnostic possibilities for cases presenting with progressive cerebellar ataxia.

Abbreviations

SCA	Spinocerebellar ataxia
MSA	Multiple system atrophy
FDI	First dorsal interosseous muscles
ALS	Amyotrophic lateral sclerosis
ADM	Abductor digit minimi
APB	Abductor pollicis brevis
MRI	Magnetic resonance imaging
SICI	Short-interval intracortical inhibition
VBM	Voxel-based morphometry

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Author contributions

E.A.: Writing – original draft; A.S.: Conceptualization and Writing – original draft; K.S.: Writing – review & editing; Y.K.: Writing – review & editing; T.I.: Conducted the genetic analysis and Writing – review & editing; T.S.: Writing – review & editing; R.O.: Writing – review &editing; S.K.: Conceptualization and Final approval. All authors listed have significantly contributed to the development and writing of this article. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The patient signed written informed consent for the publication of this report.

Consent for publication

The patient provided her written informed consent for the publication of this case report. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Competing interests

The authors declare no competing interests.

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