MND – Chorea: a new entity?

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Background and Methods

Motor Neuron Diseases (MNDs) are a group of neurodegenerative disorders affecting upper and/or lower motor neurons, leading to muscle weakness, atrophy, spasticity, and bulbar symptoms. **Amyotrophic Lateral Sclerosis** (ALS) is the most common type. A small percentage of MNDs are genetic. Rarely, MNDs may present with **extrapyramidal features** or overlap with movement disorders like Parkinson's disease or chorea. **Chorea** is a hyperkinetic disorder characterized by involuntary, random movements.

An extremely rare **overlap of ALS and chorea** has been reported (2–6 cases per billion). This may involve chorea in ALS patients or MND symptoms in HD patients, even without a known genetic mutation.

We reviewed clinical data from over 700 patients seen at the University Hospital of Padova (2010–2025), focusing on MND cases with atypical features. This report presents three male patients showing a suspected MND–chorea overlap syndrome.

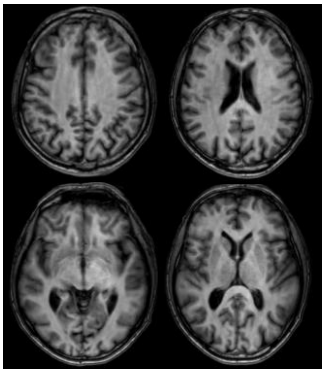

Fig. 1 – Brain MRI of patient 1.

Patient 1 (M, 70 aa)

At the age of 59, the patient began to experience generalized asthenia and episodic memory disturbances. One year later, episodes of confusion and **dysarthria** emerged. In this context, the patient underwent an EEG (unremarkable), a brain MRI which showed only minimal enlargement of the cerebrospinal fluid spaces (see fig. 1), blood tests including negative acetylcholine receptor antibodies, and an electromyography (EMG), which was also negative and repeated in 2015 with the same result. Given the clinical picture, a muscle biopsy was performed, revealing **neurogenic atrophy**. Based on these findings, a diagnosis of **atypical motor neuron disease** with bulbar onset was made. Subsequently, respiratory involvement and a progressive decline in overall muscle strength developed, although the motor deficits remained notably variable. Due to the suspicion of seronegative Myasthenia Gravis, the patient was treated with intravenous **immunoglobulin (IVIG) cycles**, which led to partial clinical improvement. In 2017, **resting cramps** in all four limbs and **left foot dystonia** were observed. A repeat muscle biopsy confirmed the presence of **chronic neurogenic atrophy**, supporting the diagnosis of motor neuron disease. Over the following years, the patient's condition remained relatively stable, except for a few episodes of accidental falls, and no significant changes were noted on follow-up neuroimaging. At the follow-up in January 2023, the patient reported **worsening gait**, requiring bilateral support, and deterioration of **speech**, along with occasional episodes of dysphagia and **sialorrhea**, with minimal drooling. In January 2024, the patient presented to the Emergency Department after a fall that had occurred approximately one week earlier, due to weakness in the lower limbs, which led to further decline in ambulation. On this occasion, involuntary, **choreiform movements of all four limbs** were observed. The patient reported having these movements for approximately one year. They were significantly disabling, leading to the initiation of treatment with **Tetrabenazine**.

Genetic testing for Huntington's Disease (HD) and spinocerebellar ataxias (SCA) was performed and returned negative. Unfortunately, due to the emergence of behavioral disturbances, the patient became uncooperative with further follow-up investigations.

Patient 2 (M, 55 years)

The patient, initially diagnosed in 2018 with a **motor neuron disease predominantly affecting lower motor neuron**s, later developed new-onset **choreic movements**. In 2023, he was evaluated at our Movement Disorders Clinic due to the emergence of generalized chorea, most pronounced **distally** and in the **left lower limb**, and exacerbated by voluntary tasks and cognitive effort. Examination also revealed severe **diffuse muscle atrophy and hypotonia**, with preserved tendon reflexes. **Genetic testing** for Huntington's disease, Kennedy's disease, C9orf72, and other motor neuron disease-related mutations was negative; broader genetic analysis for movement disorders is ongoing. Follow-up was discontinued at our center, limiting assessment of clinical progression.

Patient 3 (M, 56 years)

At the age of 48, the patient began to experience progressive gait disturbances, with particular difficulty in moving the **left lower limb**. Subsequently, the patient developed episodes of **coughing during deglutition**, along with **pseudobulbar affect**, characterized by inappropriate or exaggerated episodes of laughing and crying disproportionate to the emotional context. In 2019, the patient underwent brain and cervico-dorsal spine MRI, along with electromyography (EMG), all of which yielded results within normal limits. A DAT-SCAN was also performed, showing minimal relative hypouptake of the right putamen. During a neurological examination in 2021, **left-sided spastic hemiparesis** and increased deep tendon reflexes on the left side were observed, raising the suspicion of Mills Syndrome. In January 2023, the patient was admitted to our Day Hospital, where further investigations were carried out: electromyography (normal results), motor evoked potentials (abnormal on the left side), PET-MRI (mild hypometabolism in the medial portion of the right supplementary motor area), muscle biopsy (signs of chronic motor unit remodeling). Based on these findings, the diagnosis of **Mills Syndrome** was confirmed. During a follow-up neurological examination in June 2024, **dyskinetic movements of the left hand** and **bilateral toe movements** were observed. Given the suspicion of chorea, a **genetic panel** for Huntington's Disease (HD) and other movement disorders was ordered and is currently under evaluation. At the most recent neurological assessment in August 2025, involuntary movements of the left hand, suggestive of alien hand syndrome, were still present and were exacerbated during gait. Involuntary elevation of the left shoulder and dyskinetic flexion movements of the toes, predominantly on the left side, were also noted. Additionally, **left ideomotor apraxia** was observed. Taken together, the clinical picture appeared more consistent with an **overlap syndrome between motor neuron disease and corticobasal syndrome**. The patient will remain under clinical follow-up to monitor disease progression.

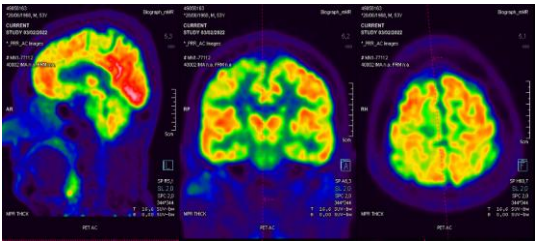

Fig. 2 - PET/MRI of patient 3. We can observe mild hypometabolism of the medial portion of the right supplementary motor area compared to the contralateral side.

Conclusions

The MND–chorea overlap syndrome remains a rare, heterogeneous, and poorly characterized condition. It remains unclear whether this presentation represents an atypical manifestation of MND/ALS or constitutes a distinct clinical entity.

1. Zhang A, Xu H, Huang J, Gong H, Guo S, Lei X, He D. Coexisting amyotrophic lateral sclerosis and chorea: A case report and literature review. Medicine (Baltimore). 2022 Dec 30;101(52):e32452. doi: 10.1097/MD.0000000000032452. PMID: 36596053; PMCID: PMC9803431