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Multiple System Atrophy and Repeat Expansions in *C9orf72*

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In Reply We appreciate the comments by Schottlaender and colleagues concerning our article¹ published in *JAMA Neurology*. We agree that the importance of our article was to highlight the variable phenotypes that are associated with *C9orf72* expansions. To date, the reported *C9orf72* expansion– associated phenotypes have been frontotemporal dementia, amyotrophic lateral sclerosis (ALS), frontotemporal dementia/ ALS, Huntington disease– like disorders,² psychiatric disorders, dementia of Lewy bodies,³ parkinsonism,⁴ and multiple system atrophy (MSA).¹

The case presented in our article met clinical, not pathological, criteria for MSA, which included dysautonomia (neurogenic bladder and orthostatic hypotension), cerebellar syndrome (dysarthria, imbalance, and ataxic gait), parkinsonism,⁵ and the hot-cross-bun sign in the brain imaging. Especially early in disease progression, the symptoms of MSA may overlap with certain inherited conditions such as Fragile X–associated tremor and ataxia syndrome and spinocerebellar ataxias. In fact, we reported a case with ataxia and spinocerebellar ataxia type 2 repeat expansions, who also had a family history of ALS.⁶ These disorders differ pathologically from MSA yet may involve the same brain areas, leading to similar clinical presentations.

We agree that autopsy will be very helpful to delineate the ultimate pathological diagnosis in this case. To our knowledge, all pathology of *C9orf72* expansions showed the characteristic ubiquitin, p62–positive, TDP-43–negative neuronal cytoplasmic and intranuclear inclusions. Therefore, it is reasonable to expect that both the patient and her brother could have typical *C9orf72* pathology. Another possibility is the coexistence of synucleinopathy with *C9orf72* expansions because MSA synucleinopathy has been reported to occur with other neurodegenerative changes such as tau pathology.⁵

Until we can confirm the pathology of MSA with *C9orf72* expansions, clinicians should be aware that many possible clinical phenotypes are associated with *C9orf72* expansions and should consider genetic testing in the presence of family history of a related neurologic disease.

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References

1. Goldman JS, Quinzii C, Dunning-Broadbent J, et al. Multiple system atrophy and amyotrophic lateral sclerosis in a family with hexanucleotide repeat expansions in C9orf72. *JAMA Neurol.* 2014; 71(6):771–774. [PubMed: 24733620]
2. Hensman Moss DJ, Poulter M, Beck J, et al. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. *Neurology.* 2014; 82(4):292–299. [PubMed: 24363131]
3. Robinson A, Davidson Y, Snowden JS, Mann DM. C9ORF72 in dementia with lewy bodies. *J Neurol Neurosurg Psychiatry.* [published online March 19, 2014] doi:10.1136/jnnp-2014-307622.
4. Lesage S, Le Ber I, Condroyer C, et al. French Parkinson's Disease Genetics Study Group. C9orf72 repeat expansions are a rare genetic cause of parkinsonism. *Brain.* 2013; 136(pt 2):385–391. [PubMed: 23413259]
5. Uchikado H, DelleDonne A, Uitti R, Dickson DW. Coexistence of PSP and MSA: a case report and review of the literature. *Acta Neuropathol.* 2006; 111(2):186–192. [PubMed: 16456665]
6. Tazen S, Figueroa K, Kwan JY, et al. Amyotrophic lateral sclerosis and spinocerebellar ataxia type 2 in a family with full CAG repeat expansions of ATXN2. *JAMA Neurol.* 2013; 70(10):1302–1304. [PubMed: 23959108]