Homer-3 antibody disease:
a potentially treatable MSA-C mimic

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Multiple system atrophy (MSA) is a neurodegenerative disorder characterised by poorly levodopa-responsive parkinsonism alongside variable degrees of autonomic, cerebellar and pyramidal dysfunction[1]. Its in-vivo diagnosis (which remains largely clinical) is challenging, even for experienced physicians, and mis-diagnoses frequent- only 18% meet criteria for probable MSA at presentation, and in nearly 40% of patients ascribed a diagnosis of MSA during life, that diagnosis is incorrect[2, 3].

Although the most common disorders masquerading as MSA are other neurodegenerative pathologies such as Parkinson's disease, progressive supra-nuclear palsy (PSP) and dementia with Lewy bodies,[2] a panoply of antibody-associated neurological disorders also enter the differential diagnosis[4, 5]. These potentially treatable MSA mimics, whose outcomes critically depend on early initiation of immunotherapy, mandate that movement disorder physicians familiarize themselves with the burgeoning field of neuro-immune movement disorders, including clues to their presence, approaches to investigation and treatment[5].

In this paper, Liu et al. further characterised the clinical phenotypes and treatment response of a recently described immune-mediated cerebellar syndrome associated with anti Homer-3 antibodies[6]. They examined the serum and/or cerebrospinal fluid of 750 patients with insidious or subacute-onset cerebellar ataxia, identifying 6 cases with Homer-3 antibodies. One third of antibody-positive cases demonstrated clinical and radiologic features of the cerebellar sub-type of MSA (MSA-C), including autonomic symptoms (dysuria, postural hypotension), rapid eye movement sleep behavior disorder (RBD) and cerebellar/pontine atrophy with 'hot cross bun sign' on MRI brain, alongside cerebellar ataxia. Most (though not all) had abnormal cerebrospinal fluid parameters.

This series highlights the important syndromic overlap between Homer-3 antibody related disease and 'classic' degenerative MSA-C. Alongside clinico-radiologic similarities, its occurrence in older adults (mean age 54.5 years) and occasional insidious onset with normal CSF parameters may produce further diagnostic confusion. In fact, the cases reported here likely met current clinical criteria for a diagnosis of 'probable' MSA-C[1].

Immune-mediated neurological disease mimicking degenerative atypical parkinsonism is increasingly recognised. Arguably the best known culprit is anti-IgLON5 disease, an unusual syndrome at the interface of autoimmunity and neurodegeneration which can clinically mimic all three classically defined atypical parkinsonian syndromes- MSA, PSP and corticobasal syndrome(CBS)- though numerous other immune-mediated disorders, associated mostly with antibodies targeting intracellular epitopes, can also be at fault (table 1). Response to immunotherapy varies depending on the culprit antibody. In anti Homer-3 disease, corticosteroids, intravenous immunoglobulin(IVIG), plasma exchange and mycophenolate mofetil have been tried, resulting in partial improvement or stabilisation in some patients. However, many relapsed during corticosteroid or IVIG weaning, and most remained significantly disabled[6]. Thus far, small case numbers and frequent delays in treatment initiation (often many months/years after symptom onset) make drawing definite conclusions about response to immunotherapy in this condition difficult.

In addition to highlighting a novel immune-mediated mimic of MSA-C, this manuscript raises numerous clinical practice issues, which should give pause for reflection. It underscores the pitfalls of heuristic decision-making in neurological practice. A case in point is the facile assumption that the presence of RBD denotes an underlying synucleinopathy, when in fact, sleep disturbances including dream enactment behavior and RBD are frequent in autoimmune encephalitides[7]. Similarly, the 'hot cross bun sign' on MRI brain is highly non-specific, and well described in neuro-immune disorders (table 1)[8]. Further, the manuscript once again challenges classic concepts of a clear clinical dichotomy between 'indolent' neurodegenerative disorders and 'rapidly progressive' antibody-associated conditions. Acute/sub-acute onset, rapid progression and imaging/CSF abnormalities are just some examples of pointers which historically guided one to think of neuro-immune aetiologies. Clearly, this is too simplistic. Phenotypic manifestations of antibody-mediated disorders are highly diverse, may evolve insidiously over years, and especially in elderly populations may not be accompanied by evidence of an inflammatory CNS response[9].

Homer-3 antibody mediated disease should be added to the growing list of potentially treatable auto-immune MSA mimics. Careful attention to subtle clinical clues e.g. cerebral or nerve root involvement, or CSF abnormalities, may help to avoid mis-diagnosis. Further research is also required to determine the frequency of Homer-3 antibody positivity in MSA-C cohorts. Prior to that, however, some methodological

issues deserve further attention. For instance, despite typical somato-dendritic immunofluorescence patterns on fixed monkey cerebellum, Homer 3 antibodies were detected in the CSF of only 1/6 patients in this study[6]. This suggests that the sensitivity of the Homer-3 antibody assay may need to be improved, either targeting higher sensitivity, or better specificity in case of cross-reactivity with other, as yet un-identified, antigens.

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Table 1 : summary of antibody-associated disorders reported to mimic atypical parkinsonian syndromes

	Typical clinical syndrome †	PSP-mimic	MSA-mimic	CBS-mimic	Neuroimaging	CSF	Malignancy	Treatment outcomes
Anti-CASPR2[10]	M>F 6th-7th decade of life Limbic encephalitis; cerebellar ataxia; pain; Morvan syndrome; Isaac syndrome; seizures; autonomic dysfunction	+	+	-	Often normal. Medial temporal lobe T2 hyperintensities (LE)	Often normal	Uncommon (20%) : usually thymoma	Partial or complete response in most
Anti-CRMP5[11, 12]	M=F 6th-8th decades of life Limbic encephalitis; chorea; uveitis; optic neuropathy; cerebellar ataxia; peripheral neuropathy Commonly co-exist with other paraneoplastic antibodies e.g. anti-Hu	+	+	-	Usually abnormal : medial temporal lobe/ basal ganglia T2 hyperintensities	Variable: often mildly abnormal (pleocytosis , increased protein)	Common : Small cell lung cancer	Partial improvement with immunotherapy+/- treatment of primary malignancy
Anti-DPPX[13, 14]	M>F 5th-7th decades of life Cognitive decline; neuropsychiatric symptoms; CNS hyperexcitability syndrome: myoclonus, hyperekplexia, tremor, seizures, PERM; weight loss; diarrhoea	+	-	-	Often normal/non-specific	Abnormal in roughly 50% of cases	Identified in 25-30% : usually B-cell neoplasm	Partial improvement common
Anti-GAD[15-18]	F>M 3rd-4th decade (LE); 6th-7th decades (SPSD, ataxia) SPSD; LE; seizures; Type 1 diabetes mellitus	+	+	+	Variable, depending on syndrome: -SPSD: usually normal -Ataxia: cerebellar atrophy -LE: normal(early) or temporal lobe T2 hyperintensities	Oligoclonal bands v. common Mild pleocytosis and protein elevation in roughly half	Uncommon	Variable
Anti-glycine receptor[19, 20]	F>M 6th decade of life SPSD	+	+	+	Often normal Occasionally, temporal lobe hyperintensities evident	Abnormal in 50%	Uncommon (<20%): thymoma, lymphoma, brast, melanoma	Generally good response to treatment
Anti-Homer 3[6]	M=F 4th-5th decade of life Cerebellar ataxia; encephalopathy; myeloradiculopathy; autonomic dysfunction; REM sleep behaviour disorder	-	+	-	Cerebellar/ ponting atrophy with HCBS T2-hyperintense lesions	Usually abnormal	Uncommon	Poor- transient incomplete response in some

Anti-Hu[21, 22]	M>F 6th-7th decade of life Sensory neuropathy/neuronopathy; cerebellar ataxia; limbic encephalitis; autonomic failure	+	+	-	Often normal-may show limbic T2 hyperintensity	Often normal Mild pleocytosis /protein elevation possible	Common : Small cell lung cancer	Partial improvement in some. Better prognosis with earlier diagnosis/treatment
Anti-IgLON5[23-26]	M=F 6th-7th decade of life REM+non-REM sleep disorder; autonomic dysfunction; bulbar symptoms; neuropsychiatric changes; chorea; supranuclear palsy	+	+	+	Usually normal - may show brainstem/cerebellar atrophy	Abnormal in roughly 50% of cases - CSF protein elevation most common abnormality	Uncommon	Immunotherapy-responsive in some patients (may be higher in non-classical phenotypes, and with combined immunotherapies)
Anti-Kelch like protein 11[27-29]	M>F 4th-5th decade of life Rhombencephalitis (Ataxia, diplopia nystagmus, seizures) >>Limbic encephalitis; vertigo; hearing loss; tinnitus	+	+	-	Usually abnormal: limbic, brainstem, cerebellar T2-hyperintensities ; brainstem/cerebellar atrophy with HCBS reported	Usually abnormal	Common : testicular or ovarian tumours	Stabilisation/improvement common
Anti-LGI1[30]	M>F 5th-6th decade of life Cognitive decline; seizures (facio-brachial dystonic); dysphrenia; hyponatremia	+	+	-	Usually abnormal - temporal lobe and hippocampal T2 hyperintensity	Often normal Mild pleocytosis /protein elevation possible	Uncommon	Generally good response to treatment
Anti-Ma2[31]	M>F 4th decade (male); 7th decade (female) Limbic/brainstem encephalopathy; hypothalamic/pituitary dysfunction; weight gain; narcolepsy/cataplexy; sleep disorder; vertical gaze palsy	+	-	-	Usually abnormal : Thalamic/hypothalamic T2-hyperintensities	Usually abnormal	Common : usually testicular	variable
Anti-Ri[32, 33]	F>M 5th-7th decades of life Brainstem predominant symptoms: Diplopia; vertigo; ataxia; skew deviation; supranuclear gaze palsy; opsoclonus-myoclonus syndrome	+	+	-	Often normal - may show brainstem T2 signal change	Generally abnormal: Oligoclonal bands +ve>pleocytosis/protein elevation	Common :Breast + small cell lung cancer	Variable
Anti-Sez6l2[34]	6th-7th decades of life Rapidly progressive cerebellar syndrome; retinopathy	+	+	-	Cerebellar atrophy	Usually normal	No malignancy reported in the small number of cases thus far	Partial improvement

*Though these antibody-associated disorders may closely mimic 'classic' neurodegenerative atypical parkinsonism, usually there are additional clinical (e.g. sub-acute onset, altered level of consciousness, memory decline, seizures, behaviour change or other neurological signs incompatible with atypical parkinsonian disorders), radiological (e.g. medial temporal lobe FLAIR/T2 hyperintensities) or biochemical (e.g. hyponatremia in anti-LGI1 encephalitis; abnormal CSF constituents) abnormalities which suggest the diagnosis. In stiff person spectrum disorders, stiffness and rigidity may mimic parkinsonism, while true bradykinesia is very rare.

† Ages given in the table denote the typical median age of onset for given syndromes. The age range is of course, much broader.

CBS: corticobasal syndrome; CNS: central nervous system; CSF: cerebrospinal fluid; F: female; HCBS: 'hot cross bun' sign; LE: limbic encephalitis; M: male; MSA: multiple system atrophy; PERM: progressive encephalomyelitis, rigidity and myoclonus; PSP: progressive supranuclear palsy; REM: rapid eye movement; SPSD: stiff-person spectrum disorder