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Is Multiple System Atrophy An Infectious Disease?

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Keywords

MSA

Multiple system atrophy (MSA) is a fatal neurodegenerative disorder that causes autonomic failure, parkinsonism, and cerebellar ataxia in any combination.¹ Pathological hallmarks of this condition are α -synuclein rich glial cytoplasmatic inclusions (GCIs).^{2,3} Misfolded α -synuclein aggregates can be identified also in Parkinson's disease (PD) and Lewy body (LB) dementia (DLB), therefore defining a family of diseases called α -synucleinopathies. In contrast to PD and DLB, in MSA aggregated or pathological α -synuclein selectively accumulates within glial cells and rarely within neurons.^{4,5} The etiology and the pathogenic mechanism leading to α -synuclein misfolding and deposition remain unclear.^{6,7}

Prusiner et al., recently published a series of papers^{8–11} in which they assessed whether α -synuclein aggregates may act as prions and whether MSA is a prion disease. In Prusiner's definition, *prion is a small proteinaceous infectious particle which is resistant to inactivation by most procedures that modify nucleic acids*.¹² Infectivity is broadly accepted as a core feature of prions, and is therefore required to define prion diseases. For this reason, Prusiner's hypothesis has several theoretical and practical implications.

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POTENTIAL CONFLICT OF INTEREST

The authors have no potential conflicts of interest..

Both evidence of self-templating propagation in cellular cultures and infectivity in animal models and in humans are required to define MSA as a prion disease. Furthermore, evidence that exogenous mutant α -synucleins may produce α -synuclein pathology when transmitted to healthy subjects is required to assess α -synuclein aggregates' infectivity. *There is no documented infectious spread of MSA and related synucleinopathies from human to human.*

However, there is evidence of misfolded α -synuclein self-propagating in neural cell cultures,^{9,13} and embryonic stem cells injected into the striatum of patients with Parkinson's disease showed evidence of α -synuclein associated pathology in the grafted cells, suggesting a host-to-graft self-propagation of the misfolded proteins.^{14,15} A cell-to-cell self-spreading pattern resembles prion spreading and has led to the concept of prion-like propagation for α -synuclein, β -amyloid, and tau.¹⁶ Self-propagation of α -synuclein oligomers in vitro is not sufficient to define them as prions, since the evidence of infectivity cannot be assessed at a cellular level.

Converging data suggest that misfolded α -synuclein¹⁷ and β -amyloid¹⁸ are able to propagate in a connectome-dependent manner within the central nervous system (CNS) after intracerebral inoculation in non-transgenic mice.¹⁷ Furthermore, intracerebral inoculation of misfolded α -synuclein seems to anticipate and accelerate neurodegeneration in several transgenic mice models carrying mutations that predispose animals to the development of α -synuclein-related pathology.^{19,20} These latter observations show "seeding" activity rather than infectivity of α -synuclein.

Recently, Prusiner and colleagues reported in a series of papers that both intracerebral¹¹ and peripheral²¹ inoculation of brain homogenates derived from MSA patients but not from PD patients were able to produce α -synuclein pathology in TgM83+/- but not in TgM83-/- wildtype mice. The authors hypothesize that different α -synuclein strains may show different infectivity and may determine different α -synucleinopathies' phenotypes.¹¹ Furthermore, the same group showed that α -synuclein aggregates (that the authors call "prions") exhibit stability and resistance to denaturation and can be transmitted by means of surgical devices in TgM83 +/- mice, raising the hypothesis of a risk for iatrogenic transmission of the disease (indirect, vehicle-borne transmission).^{21,22}

It should be noted that Prusiner and colleagues tested their hypothesis using a TgM83 +/- mouse model.²³ TgM83+/+ homozygous mice express mutant A53T α -synuclein and spontaneously develop α -synuclein pathology while TgM83+/- hemizygous mice do so to a lesser degree and at much older ages. A53T α -synuclein mutation has been primarily identified in PD patients, but it has never been documented in patients with MSA. TgM83 mice cannot be therefore considered a valid animal model for MSA. Furthermore, the authors were able to demonstrate inoculation-induced α -synuclein Lewy body pathology rather than GCI pathology in alpha-synuclein TgM83 +/- hemizygous mice, but not in wildtype mice suggesting that the A53T α -synuclein mutation in the *SNCA* gene plays a critical role in α -synuclein spreading and self-propagation in this model system. In addition, GCI have never been identified in wild type mouse brains inoculated with MSA-derived α -synuclein.¹¹ Hence, α -synuclein aggregates ("prions") derived from MSA patients generate a neurodegeneration pattern that is atypical for MSA.

As regards to the human spreading of MSA, no evidence of transmissibility in humans has ever been reported.²⁴ Furthermore, no epidemiological data suggests a person-to-person spreading for Parkinson's disease or for MSA even in people with close contacts or who share a living environment as life partners.²⁵ Of the estimated 30,000 patients who received cadaver-derived human Growth Hormone (c-hGH) worldwide, over 200 developed prion diseases, but the cohort had no increase risk for Parkinson's disease, Alzheimer's disease, or tau-associated disorders.²⁶ No evidence of iatrogenic transmission of α -synucleinopathies in humans has ever been reported,²⁴ even after MSA patients' brain tissue handling. In particular, no evidence of iatrogenic spreading or clinical worsening due to brain tissue surgical contamination after deep brain stimulation implantation has been reported. In addition, no evidence of animal-to-man transmission or of the existence of animal reservoirs has been documented.

Infectious spread of prions is not just through iatrogenic means, but also through the food supply, which justifies categorizing infectious prion diseases as infectious. This was dramatically evidenced by the spread of prion disease from cattle to humans which was termed "Mad Cow" disease.²⁷ Moreover, in the original population of the Foré linguistic group of Papua New Guinea in whom person-to-person spread of the infectious prion disease kuru occurred through recurrent exposure to the CNS tissues of individuals afflicted with kuru, there were never any reports that AD, PD, or other non-prion neurodegenerative tauopathies, synucleinopathies, or A β opathies were spread by ritual cannibalism. Moreover there are no epidemiological data to support the notion that there is infectious spread of AD, PD, or other tauopathies, A β opathies, and synucleinopathies through blood transfusions, organ transplants, surgical instruments, or other iatrogenic means.

Thus, despite the fact that infectious prion diseases are clearly zoonoses, there is no evidence that synucleinopathies and related A β opathies and tauopathies are infections or zoonotic diseases. Indeed, further contrast between prion and non-prion neurodegenerative disease proteins with respect to infectivity comes from the very high prevalence of readily transmissible or infectious prion diseases in sheep, cattle, moose, elk, and other animals for which there is no counterpart such as contagious tauopathies, A β opathies, or synucleinopathies in domesticated animals or animals in the wild.

All these findings seem to suggest that species or strains of endogenous misfolded α -synuclein are able to self-propagate through the central nervous system but do not show infectivity. It seems therefore reasonable to postulate that even if prion-like spreading of α -synuclein in experimental model systems may justify the view that the progression of neurodegeneration in MSA reflects the cell-to-cell spread of pathological α -synuclein, this is not sufficient to define MSA a classic prion-disease. This view underlines the interpretation of the scientific literature to-date that prion-like particles and prions are different entities, and that a more precise definition of both, which is capable of differentiating them from one another, is necessary.

In conclusion, there is currently no evidence of infectivity of α -synuclein aggregates in humans; transmissibility of misfolded α -synuclein has been reported exclusively in animal models and, in the case of MSA, it requires engineered mice (TgM83+/-). Patients should

be reassured that there is no evidence of transmissibility for MSA and other neurodegenerative proteinopathies, even in people with close contact. Standard precautions to remove and disassemble α -synuclein seeds from laboratory instruments have been published and they are different from those that are now used to eliminate prion infectivity.²⁸ These procedures should be encouraged for people handling MSA patients' brains or other patients' tissues (e.g. blood). Further studies should be encouraged to establish α -synuclein spreading pathways and to definitively rule out the risk of infectivity in humans (indirect, vehicle-born transmission). An important take home message for patients, their caregivers, and medical professionals is assurance that there is no evidence of MSA infectivity in any real life circumstance. Being in close contact with MSA patients carries no risk of developing the disorder. The focus needs to be on gaining a better understanding of the mechanism(s) underlying α -synuclein misfolding, aggregation, and self-propagation; which could pave the way to disease modifying strategies that are now unfortunately missing in MSA.

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