PRION-LIKE SPREADING IS A RELEVANT THEORY FOR ALL NEURODEGENERATIVE DISEASES: YES

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"Is Alzheimer's contagious? Condition 'could be infectious like mad cow disease'" titled the *Daily Mail* in 2011, formulating a fear that has haunted the public now and then. So, what is the scientific basis of a prion-like character of neurodegenerative diseases other than veritable prion diseases? Two sets of data are available for analysis, one voluminous from experimental studies, the other from comparably sparse epidemiological studies.

In numerous experimental studies of what has been called "seeded nucleation", mainly oligomeric species have been convincingly shown to seed their own growth analogously to the self-propagating activity of prions and thus have been called "prionoids" (Aguzzi & Calella, *Physiol Rev.* 2009) or "the expanding universe of prions" (Watts & Prusiner, *J Biol Chem* 2014). They have been shown to be transmissible between individuals and to propagate within the body. Implicated neurodegeneration-related proteins include Abeta, tau, alpha-synuclein, SOD-1, TDP-43, FUS, and those with polyglutamine inserts. Usually development or acceleration of a neurologic disease is absent in such transmission experiments (with alpha-synuclein as exception). Most important is a systemic spread within the brain along preformed anatomical pathways, apparently by neuron-to-neuron propagation along neurites and transsynaptically. More recently, another exciting finding was the discovery of "strains" that may faithfully replicate in the seeded host the distinctive pathologies seen in the donor organism. This is another analogy with prions.

However, in contrast to the "prionoids", prions *sensu stricto*, composed by PrP^{Sc}, are disease-causing infectious agents that have a full infectious cycle, are infectious in diverse species by various routes and traceable by microbiological techniques (e.g. titration).

In contrast with the plethora of experimental data, epidemiological data are sparse, in particular because it is debatable how a hypothetical risk of exogenous induction of non-prion proteinopathies could best be assessed epidemiologically. Several case-control studies did not find evidence of transmissibility of Alzheimer's disease (AD). The most relevant epidemiological assessment studied the potential infectivity of AD- and Parkinson disease (PD)-related proteins in recipients of cadaver-derived human growth hormone (Irwin et al. *JAMA* 2013) and showed no elevated risk for AD and PD, although the prion disease risk was markedly elevated.

In conclusion, there is now ample experimental evidence that misfolded proteins involved in neurodegeneration may invasively propagate in susceptible hosts (mostly, but not exclusively transgenic mice); however, there is no epidemiological evidence so far that human-to-human transmission has occurred in cases other than prion diseases. The main importance of "prionoids" is in systemic and organ-specific propagation of misfolded proteins: so YES, prion-like spreading IS a relevant theory for all neurodegenerative diseases.