PD BEGINS IN THE PERIPHERAL NERVOUS SYSTEM - NO

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Synuclein is central to the pathogenesis of Parkinson's disease (PD). It is the principal protein component of Lewy bodies (LBs). Several missense mutations and triplication and duplication mutations, that result in overexpression of wildtype protein, cause familial forms. Variations in the synuclein gene are the most important genetic risk factor for the sporadic forms. However, the precise role that synuclein plays to induce the neurodegeneration that is characteristic of PD remains unknown.

For many years, it has been known that synuclein pathology can be found not only in the central nervous system (CNS) of PD patients, but also in the peripheral nervous system (PNS) including the Auerbach plexus of the esophagus, the gastric Meissner plexus, the myenteric plexus of the colon, sympathetic neurites of the heart, neurites of bladder, prostate, skin and adrenal gland. More recently, epidemiologic evidence has suggested that peripheral autonomic involvement may precede the onset of the motor signs of PD. In a prospective study, men with infrequent bowel movements had over a fourfold increase in risk of developing PD over 12 years follow-up. The possibility that PD may universally begin the periphery, and specifically within the enteric nervous system, has been formally proposed by Braak and colleagues (see, for example, Braak et al Neurosci Lett, 2006; Braak et al J Neural Trans, 2003). These investigators have proposed that a hypothetical neurotropic pathogen infiltrates the enteric mucosa to gain access to the enteric nervous system. The pathogen then is proposed to pass retrogradely and transynaptically to the unmyelinated preganglionic fibers of the dorsal motor nucleus of the vagus nerve (DMV), and thereafter pass by retrograde axonal transport to the DMV in the CNS. A critical and essential focal point of this hypothesis is the claim by Braak that the "… very first nerve cells in the brain to display LNs [Lewy neurites] and LBs (Lewy bodies) are the neurons of the dmX [DMV]…"

For the purposes of this debate, it is important first to be clear on the full implications of this hypothesis and the ways in which it has been interpreted. Whether intended by Braak or not, the hypothesis has been interpreted by many to mean that the presence of synuclein pathology in the PNS provides sufficient evidence that the patient has PD; i.e., the individual will predictably go on to develop PD as we currently diagnose it, with motor signs. Thus synuclein pathology in the PNS is sufficient to diagnose PD, and it thereby provides a useful biomarker of the disease, before motor signs develop. This 'enteric pathogen" hypothesis by Braak has also been interpreted to mean that in <u>all</u> cases diagnosed as PD by current clinical criteria, the motor manifestations (and the underlying pathology of neuron loss and LBs in the substantia nigra pars compacta (SNPC)) are <u>universally</u> preceded by Lewy pathology in the DMV. In other words, Lewy pathology in the DMV is an essential, necessary feature of the early course of PD. We shall consider these two interpretations of the Braak proposal separately.

Let us consider first the concept that the mere presence of synuclein pathology in the PNS is sufficient evidence that the affected individual will go on to develop PD, as defined by conventional criteria of motor impairments. In order for such pathology to serve as a useful biomarker, its predictive specificity must be determined. Minguez-Castellanos and co-workers (2007) studied surgical specimens of 100 individuals (aged 44-84) without PD, and found that anti-synuclein staining revealed pathology in 9% of the whole sample and in 26% of vesicoprostatic specimens. The likelihood that all of these individuals, in their lifetimes, will go on to develop PD is unknown, but probably small. At 16 months follow-up, none had developed PD. Estimates of lifetime risk of PD would indicate that those in their 40's would have a 4.0% risk, and those in their 80's a 2.7% risk (see Elbaz et all, 2002). Thus, synuclein pathology in the PNS is unlikely to predict with compelling accuracy that an individual will go on to develop PD.

The alternate interpretation of Braak's enteric pathogen hypothesis posits that involvement of the DMV is necessary in order for PD to occur, because it is the unique portal of entry from the enteric nervous system into the CNS. However, many neuropathologists have shown that synuclein pathology in the DMV does not always occur in PD. Nor does it always occur in incidental Lewy body disease (ILBD), which is quite likely to be a precursor to clinical PD, and thereby to provide an ideal opportunity to examine the early pathology. In an important study by Parkkinen et al (2005) 904 autopsies identified 106 brains with synuclein pathology. Among these brains, if we exclude 7 with Alzheimer's disease (in which Braak synuclein staging has been shown not to hold), there were 17 (17%) in which DMV was not involved, and yet there were LBs in SN, or the nucleus basalis, or both. Most of these cases were instances of ILBD. However, even when the question is examined strictly within a population of PD patients, diagnosed by clinical and pathological criteria, there are a substantial number of instances in which the DMV lacks

synuclein pathology. Kalaitzakis and colleagues examined 71 PD brains and identified 7% in which the DMV was not involved, in spite of the clinical diagnosis of PD and the presence of synuclein pathology in the SN.

In conclusion, the available evidence indicates that synuclein pathology in the PNS is neither necessary nor sufficient for the occurrence of PD. The disease is therefore unlikely to always begin in the PNS.