Editorial comment for jnnp-2012-303808 Alves et al. Amyloid-beta and phenotypic heterogeneity in de novo Parkinson's disease

Motor deficits that associate with changes in β-amyloid in Parkinson's disease

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β-Amyloid (Aβ) deposition in the brain is one of the main pathologic hallmarks of Alzheimer's disease (AD) with dominant gene mutations significantly increasing the amount of this protein in the brain and heralding an early onset of dementia [1]. Deposition of Aβ in the brain identified by PET imaging is closely associated with decreased CSF levels of the protein, tools that are now used clinically to assist with the diagnosis of AD.

There is considerable ongoing debate regarding the overlap of AD pathology and its contribution to Parkinson's disease (PD), but there are few studies that have assessed CSF levels of AD proteins for correlations with motor impairments in sporadic PD. The study by Alves and colleagues in this issue of JNNP assesses 99 *de novo* PD patients with either tremor-dominant (PD-TD) or postural instability/gait disorders (PD-PIGD) for relationships to CSF levels of Aβ proteins [2]. It is deficient in assessing the other major AD protein tau, but their findings of reduced CSF Abeta levels in the *de novo* PD-PIGD group compared with PD-TD and controls is significant. The CSF Abeta levels correlated with the severity of PIGD and lower limb bradykinesia but not other motor features. The study was well controlled for age of onset, MRI white matter hyperintensities and cognition, and could therefore show a clear biological difference underpinning this type of motor impairment in PD. It will be important to know if the correlate extends to CSF tau levels as well, and therefore typical AD rather than Aβ dysfunction alone.

The association of Aβ proteins to motor dysfunction in PD has not been previously considered, although recent studies using preclinical LRRK2 mutation carriers considerably strengthen the concept of early Aβ changes in PD. In particular, reduced striatal dopamine function strongly correlates with reduced CSF Aβ proteins [3] rather than CSF α-synuclein levels [4] in these preclinical LRRK2 cases. In sporadic PD, many studies have shown correlations between reduced CSF Aβ and cognitive impairment and more rapid cognitive decline [5-8], particularly with deficits in verbal fluency which may have a motor component. Interestingly, patients with PD dementia often have no Aβ on PET imaging despite cortical atrophy and hypometabolism [9], suggesting that significant compact Aβ deposition may not underlie these deficits, findings consistent with pathological studies [10 11]. However, other pathological studies assessing AD proteins in addition to α-synuclein have identified non PD-TD patients as having higher grades of α-synuclein pathology, more cortical Aβ and cerebral amyloid, and dementia at end-stage, with similar levels of pathology observed in patients with the dominant dementia syndrome of dementia with Lewy bodies [12-15]. In pathological studies, there is evidence that additional Aβ deposition in the brain increases the rate of disease progression [13 16], consistent with the increased progression observed in the PD-PIGD subtype [17]. It is difficult to reconcile these end-stage pathologies with the *de novo* data in the Alves et al paper [2], but it clear that, rather than just concentrating on the role Aβ plays in dementia in PD, the biological role Aβ may play in motor circuits to produce the motor phenotypes of PD also needs further assessment. Importantly, the early biological differences identified by Alves and colleagues [2] could be used to monitor effective treatments for these deficits in the future.

Advancing knowledge on the biology underlying the clinical heterogeneity in patients with PD can not be underestimated. While patients with PD-PIGD are known to differ from those patients with PD-TD in several clinical factors, they also have more marked dopamine deficiency and greater cortical impairments than other motor subtypes of PD [17]. Whether any

of these differences also relate to their Aβ dysfunction awaits further studies. However, it has recently been shown that PD-PIGD have increased susceptibility for motor impulsivity [18] and that non PD-TD patients have greater visual processing impairments [19]. Such neuropsychological findings are likely to directly contribute to falls risk and could also relate to Aβ dysfunction in PD. In addition, myocardial sympathetic degeneration correlates with hypokinesia in non PD-TD patients [20], a non Aβ pathology that may also contribute to the PD-PIGD subtype. While more work is now required, the study by Alves and colleagues in this issue highlights an important piece of the biological puzzle concerning why patients with PD may have such diverse clinical phenotypes.

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