Editorial Commentary

Is serotonin pathology a good biomarker *in vivo* for early Parkinson's disease?

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Parkinson's disease (PD) is a neurodegenerative disorder characterized pathologically by the aggregation of alpha-synuclein (SNCA), which is the main component of Lewy bodies, and the loss of dopaminergic neurons in the substantia nigra (1). Although progressive dopaminergic denervation is the cardinal pathology in PD, in the last decades several studies have shown that other systems are affected as well. The serotonergic system, originating from the brainstem raphe nuclei, is known to be disrupted in PD. Multiple preclinical and *in vivo* works provide evidence for this. Neuropathologic studies have shown a loss of serotonergic cell bodies with Lewy aggregates in the raphe nuclei (2) along with reduced serotonergic markers in striatum (3,4), hypothalamus and frontal cortex (4), although not to the same degree as dopamine loss. Molecular imaging studies using the second generation PET ligand [^{11}C]-3-Amino-4-(2-dimethylaminomethylphenylsulfaryl)-benzonitrile (DASB) have demonstrated *in vivo* changes of presynaptic 5-HT transporter (SERT) and postsynaptic serotonergic receptors targets in sporadic (5) and genetic PD patients (6). Other studies, mainly using neuroimaging techniques, have linked serotonin deficiency with some common non-motor symptoms such as depression, sleep disorder and fatigue (7-9) in Parkinson patients at different stages of disease. Additionally, several works have associated levodopa induced dyskinesia to non-physiological release of dopamine leaded by an imbalanced dopaminergic to serotonergic terminal ratio, with the later playing a main key role (10).

In the study of Wilson *et al.* published in The Lancet Neurology in June 2019, once again the importance of serotonin in PD is highlighted. This study assesses serotonergic and dopaminergic pathology in carriers of the A53T SNCA gene mutation. The A53T SNCA point mutation is a rare but relevant cause of autosomal PD, with a high penetrance (11), similar parkinsonian symptoms to idiopathic Parkinson's disease (iPD) (12) but with earlier onset age, more cognitive and neuropsychiatric symptoms and high frequency of atypical signs (13). Lewy pathology characterized by extensive burden of Lewy neurites but only few Lewy bodies has also been described (14). All these features could make this population a good model for the study of the premotor phase and progression in PD. This cross-sectional multicenter study recruited 14 A53T SNCA carriers (7 with manifest PD and 7 with no motor symptoms or premotor), 25 age matched healthy controls (HC) and two cohorts (cohort 1 and cohort 2) of patients with iPD (25 and 40 subjects, respectively). All A53T SNCA carriers, the iPD patients from cohort 1 and the HC underwent [^{11}C] DASB PET to detect serotonin transporters and [^{123}I]FP-CIT SPECT to detect presynaptic dopamine transporters in Erlangen (Germany). They also underwent MRI to assess

volumetric analyses in London, UK. iPD cohort 2 was used as comparator and retrieved from an electronic database acquired in a different PET scanner.

Despite using up to four different SPECT gamma cameras and different PET devices with not identical acquisition protocols in the iPD cohort 2, the results of the study were consistent. They found that [^{11}C] DASB PET was able to disclose decreased serotonergic uptake in the raphe nuclei, caudate, putamen, thalamus, hypothalamus, amygdale and brainstem of premotor A53T SNCA carriers before PD clinical diagnosis was made and even in advance of [^{123}I]FP-CIT SPECT dopaminergic abnormalities. Interestingly [^{11}C]-DASB PET of premotor A53T carriers was even more pathological than that of iPD, despite the later having longer disease duration. Later on, they investigated if serotonergic dysfunction spread was associated to histopathologic Braak's stages (15) where SNCA immunoreactive Lewy pathology is spread in a caudo-rostral way, affecting the dorsal raphe nuclei before the substantia nigra. Their results showed that all A53T SNCA carriers had decreased [^{11}C]DASB PET uptake in brain areas corresponding to Braak stages 1–3 (medulla oblongata, pontine tegmentum and midbrain) when comparing with HC. However, brain areas corresponding to 4–6 Braak's stages (meso and neocortex) were largely preserved in premotor A53T SNCA carriers whereas A53T SNCA carriers with PD had extended loss of serotonin transporters to these subcortical and cortical areas, suggesting that serotonergic cells degeneration spreading follows a similar pattern that SNCA aggregates. Finally, in A53T carriers and both iPD cohorts they observed an association between serotonergic pathology in the brainstem and clinical measures of motor and functional burden disease assessed by the Unified Parkinson Disease Rating Scale.

The article shows very interesting results, favoring the use of [^{11}C]-DASB PET as an even earlier marker than [^{123}I]-F-PCIT SPECT in that subgroup of patients with A53T SNCA mutation and suggesting homologous results in iPD. Finding markers capable of identifying patients with an increased risk of developing PD at a prodromal stage is a paramount. These prodromal tracers could grant earlier diagnosis and treatment not only improving patient's quality of life but also allowing enrollment into clinical trials with potential neuroprotective medications.

However, there is still not enough evidence to support the extension of these [^{11}C]-DASB PET results to iPD. Even though some studies have found significantly reduced serotonin transporter binding in patients with advanced iPD, imaging studies in early PD have been less consistent, with reports of serotonin transporter levels being mildly reduced or even normal (16-18). The study by Qamhawi *et al.* (19), performed in a large cohort of early drug-naïve PD patients (365 patients from the Parkinson's Progression Markers Initiative cohort), showed a significant reduction of [^{123}I]-FP-CIT binding in the brainstem raphe nuclei compared to healthy controls, suggesting reduced levels of serotonin transporters on the somatodendritic compartment of serotonergic neurons of the raphe complex. However, analysis of individual cases showed that serotonin transporter binding only was decreased in 12.5% of the parkinsonian patients whereas the majority of PD patients had raphe serotonin transporter availability comparable to that of healthy controls. In this study serotonergic abnormalities were associated with the severity of resting tremor but not with non-motor symptoms. Although the use of different neuroimaging techniques and serotonin markers can account for these discrepancies, another possible explanation is that in contrast to the dopaminergic degeneration seen in all PD cases, the brainstem raphe complex is affected only in a subgroup of patients with specific phenotype and underlying pathophysiology or genetic background. In this sense, a recent published article studied a cohort of asymptomatic carriers of familial dominant *LRRK2* that showed not only absence of decrement but even an increment of serotonin transporter binding in the striatum, brainstem and hypothalamus, perhaps reflecting compensatory changes in serotonergic innervation preceding the motor onset of PD (6).

In conclusion, this study shows that serotonergic abnormalities highlighted by molecular imaging are present in premotor A53T SNCA patients, a very uncommon cause of PD, at a very early stage of the disease and suggests that [^{11}C]-DASB PET can be useful to identify patients with this mutation who can benefit from potential neuroprotective treatments. Nonetheless, further investigation is needed to determine if these serotonergic abnormalities are specific of the A53T SNCA phenotype or can be extrapolated to premotor or prodromal iPD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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