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Assessing Medication Role on Neuropathologic Findings in Parkinson's disease

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The relationship between medication treatment and possible effects on neuropathological findings in Parkinson's disease (PD) has not been well studied. Most PD patients who come to autopsy have had long disease duration, have been treated with a variety of medications at constantly changing dosages and very variable treatment durations, resulting in a completely heterogeneous population. Because of this it is extremely difficult to make clinicopathological correlations regarding the role of any administered medications on pathological findings. In this issue of *Movement Disorders* Yarnall et al.¹ discuss whether treatment with apomorphine, a dopamine agonist requiring injection or infusion, correlated with amyloid pathology in brains of patients with PD.

The authors report the neuropathological findings from 36 pathologically proven PD cases who never took apomorphine and 35 cases that were treated at some point in time. They divided the subjects into those with dementia (PDD) and those without dementia. In PD subjects without dementia those treated with apomorphine had reduced amyloid- β deposition while this effect of apomorphine was not seen in the PDD cases. These results are provocative although must be put in context.

First, a major confounding factor regarding potential drug effects on brain pathology is the variability of PD pathology regardless of medication treatment. The neuropathological diagnosis of PD is made based on the finding of Lewy bodies in the substantia nigra along with loss of dopamine neurons.² However, the presence and density of Lewy bodies in other brain regions may vary as can the presence of plaques, tangles, hippocampal sclerosis,

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argyrophilic grains, cerebral white matter infarction, etc.³⁻⁵ This variability occurs with or without treatment for PD. The patients in the Yarnall et al. study had disease durations averaging > 20 years with marked heterogeneity in pathological findings (see Table 1 in Yarnall et al.¹). Controlling for this tremendous heterogeneity is extremely difficult in neuropathological studies, especially in a small study such as this.

In reviewing their paper for treatment effects, the variability in treatment duration with apomorphine, as well as dose and duration with other medications, was difficult to assess.¹ As expected in retrospective chart reviews, quantifying treatment with apomorphine and other medications is difficult and therefore, confounding effects of other medication must be considered. While the authors found a correlation between maximum dose of apomorphine and amyloid- β burden the data regarding cumulative dose of apomorphine was questioned, and that would likely have been the better measure to use. Many other calculations related to apomorphine dose and timing did not correlate with any of the pathology scores in either the cognitively normal or dementia groups. As discussed by the authors, the data was not corrected for multiple comparisons, which makes the single positive correlation more speculative.¹ It would have been interesting to have known the actual number of subjects on the different medications as patients on higher doses or longer duration treatment with certain medications may have skewed the results.

Another very interesting topic that must be considered is the role medication for dementia may play in the pathological findings. It is likely that patients with PDD were taking acetylcholinesterase inhibitors or memantine, and these may have influenced the results in the PDD group. One could also speculate that some non-demented patients who had mild cognitive impairment may have taken these drugs which could influence the results. Yarnall et al. do not mention the role concomitant diseases may have played. It is important that future studies of neuropathological effects of medication consider the presence of hypertension, diabetes, cardiac or other systemic diseases which may well influence both AD and PD pathology in the brain.

Could there be other explanations for the published finding? Could the apomorphine-treated group differ from the apomorphine-untreated group in some way that might have resulted in a difference in plaque load regardless of drug treatment? From Table 1,¹ it seems that the apomorphine treated, non-demented group had an earlier age of onset, longer disease duration and longer treatment duration with 4 of the 5 drug classes. Could any of these differences, or a combination of them, somehow explain the difference in plaque load, independent of apomorphine treatment? Which patients receive apomorphine may be influenced by their response to other dopamine agonists. If a patient on oral dopamine agonist did not tolerate the drug, or developed side effects such as impulse control disorders, the use of apomorphine may have been contraindicated, potentially influencing results from the pathology analysis.

Finally, stratification by cognitive impairment at death may not be appropriate because the variable of interest, amyloid accumulation, is related to cognitive impairment. The authors likely did not have the data to stratify by cognitive impairment at the time apomorphine was initiated. As presented, in the PDD subgroup, diffuse plaques were higher in the

apomorphine treated group than the untreated group.¹ Yet, in the non-demented group the difference was in the opposite direction. That would suggest that treatment with apomorphine improves plaques in cognitively normal patients, but worsens plaques in cognitively impaired patients. Plaques did not differ if the groups are combined. The role that A β plays in dementia may not be as great as the role of α -synuclein in PDD^{2, 6-10} and thus apomorphine's role in reducing cognitive impairment will remain unclear.

Despite these limitations, the Yarnall et al.¹ paper does raise the interesting question of whether apomorphine alters brain pathology. The authors do an excellent job of discussing the numerous limitations to their study. Clearly, a huge unmet need in the treatment of neurodegenerative disorders is finding disease-modifying treatments, and these findings with apomorphine certainly warrant further investigation. Unfortunately, we are unaware of published data to use for comparison purposes. As apomorphine treatment is not tremendously widespread, those centers and countries where it is more commonly used should be encouraged to increase enrollment of subjects in autopsy programs. Other autopsy programs should determine if other medication/pathology interactions exist.

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