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Response to Parkinnen et al. and Jellinger

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Response to Parkinnen et al.

We welcome the thoughtful letter from Parkinnen et al. We feel, however, that the ultimate role of medical scientific inquiry is to improve patient care and therefore it is by no means radical to bring suggested improvements in patient care before the scientific community for debate. Published literature indicates that deep brain stimulation (DBS) surgery is not without risk for serious complications and that the success of this intervention depends on the patient having PD. If this is so, olfactory bulb biopsy may prove useful and beneficial in this setting. A percentage of surgical candidates could be spared a greater surgical risk (e.g. DBS) by undergoing a lesser surgical risk (olfactory bulb biopsy). Our comments regarding (olfactory bulb biopsy) are simply meant to stimulate dialogue on this topic.

The authors question whether olfactory bulb biopsy could distinguish PD from MSA or PSP, especially since Lewy bodies may be present in sparse numbers in both of the latter two conditions. We have utilized olfactory bulb α -synuclein stains in six MSA cases, and found all had numerous and characteristic flame-shaped glial cytoplasmic inclusions, unambiguously identifying these as MSA. It may be more difficult to distinguish PD from PSP. Our data show that 15 of 45 PSP cases had olfactory bulb Lewy bodies. Of these 15, the majority also had Lewy bodies in the brainstem and limbic region, suggesting that these subjects had both PD and PSP. Whether or not these subjects would differ in surgical outcome from those with pure PD or pure PSP is not known at this time. We are currently testing methods for detecting glial tauopathy to determine whether these might positively identify PSP subjects from olfactory bulb material. In any case, accurate histological typing of DBS candidates would undoubtedly lead to beneficial refinements in surgical selection criteria.

Aside from PSP and MSA, one might also question whether olfactory bulb biopsy could distinguish PD subjects from those with dementia with Lewy bodies (DLB) and from asymptomatic incidental Lewy body disease (ILBD). However, distinguishing between these disorders and PD is based on clinical presentation, not histopathology.

The correlation coefficients we reported between clinical measures and olfactory bulb synucleinopathy density scores are admittedly low but do not impact on diagnostic accuracy as we were employing a simple positive or negative dichotomy for those calculations.

The accuracy of the clinical diagnosis of PD only rises above 80% after several years of observation and a clinical trial of levodopa, i.e. when PD is “end-stage”. As literature reports and our own data indicate that a large fraction of subjects with ILBD have olfactory bulb Lewy bodies (23/32 from our data), it appears probable that olfactory bulb Lewy bodies would be present in early clinical stages of PD and that olfactory bulb biopsy would extend a high clinical diagnostic accuracy, currently available only to those with advanced PD, to those at a much earlier stage. This is relevant in view of recent publications that may lead to early stage DBS or gene therapy for PD [4–6]. As early diagnosis and therapy is a major goal for all of the neurodegenerative diseases, olfactory bulb biopsy may offer a practical route to achieving this in the future, but only after careful and open consideration of the risk-benefit ratio in an appropriate setting such as that afforded here by *Acta Neuropathologica*.

Response to Prof. Jellinger

We thank Dr. Jellinger for his interesting remarks. The correlation between olfactory bulb and other CNS sites, in terms of synucleinopathy density, has been shown to be statistically significant, as Dr. Jellinger points out, not only for our study, but also for his own data and that of Hubbard et al. [2]. Additionally, similar confirmations have come from Fujishiro et al., reporting recently in *Acta Neuropathologica* (116:17–24, Epub 2008 April 30) and from Sengoku et al. [7]. We did not assess synucleinopathy density in the hippocampus and so cannot compare our experience with that of Dr. Jellinger’s for this region. However, our diagnostic accuracy figures for olfactory bulb synucleinopathy were calculated on the basis of their simple presence or absence and so the correlations, while interesting from the point of view of pathogenesis, do not directly bear on the issue of olfactory bulb synucleinopathy as a diagnostic marker for clinically evident Lewy body disorders. We are in agreement with Dr. Jellinger that the available data on nasal olfactory epithelium synucleinopathy, which also include an earlier publication by Duda et al. [1], makes it unlikely that olfactory epithelium biopsy would be useful. The possibility of skin biopsy for PD, as suggested by Dr. Jellinger’s citation of Ikemura et al. [3], is intriguing, but the reported low sensitivity (70%) does not really improve much on the present clinical diagnostic accuracy. Also, we have not been able to confirm this, as we have stained for α -synuclein in abdominal skin blocks of 20 autopsied cases of PD and failed to find positive staining in any of these. We did not, however, stain multiple sections of these blocks, as apparently done by Ikemura et al.

References

1. Duda JE, Shah U, Arnold SE, Lee VM, Trojanowski JQ. The expression of alpha-, beta-, and gamma-synucleins in olfactory mucosa from patients with and without neurodegenerative diseases. *Exp Neurol* 1999;160:515–522. [PubMed: 10619569]
2. Hubbard PS, Esiri MM, Reading M, McShane R, Nagy Z. Alpha-synuclein pathology in the olfactory pathways of dementia patients. *J Anat* 2007;211:117–124. [PubMed: 17553102]
3. Ikemura M, Saito Y, Sengoku R, Sakiyama Y, Hatsuta H, Kanemaru K, Sawabe M, Arai T, Ito G, Iwatsubo T, Fukayama M, Murayama S. Lewy body pathology involves cutaneous nerves. *J Neuropathol Exp Neurol* 2008;67:945–953. [PubMed: 18800013]
4. Kaplitt MG, Feigin A, Tang C, Fitzsimons HL, Mattis P, Lawlor PA, Bland RJ, Young D, Strybing K, Eidelberg D, During MJ. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson’s disease: an open label, phase I trial. *Lancet* 2007;369:2097–2105. [PubMed: 17586305]
5. Marks WJ Jr, Ostrem JL, Verhagen L, Starr PA, Larson PS, Bakay RA, Taylor R, Cahn-Weiner DA, Stoessl AJ, Olanow CW, Bartus RT. Safety and tolerability of intraputamin delivery of CERE-120

(adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. *Lancet Neurol* 2008;7:400–408. [PubMed: 18387850]

6. Schupbach WM, Maltete D, Houeto JL, du Montcel ST, Mallet L, Welter ML, Gargiulo M, Behar C, Bonnet AM, Czernecki V, Pidoux B, Navarro S, Dormont D, Cornu P, Agid Y. Neuro-surgery at an earlier stage of Parkinson disease: a randomized, controlled trial. *Neurology* 2007;68:267–271. [PubMed: 17151341]
7. Sengoku R, Saito Y, Ikemura M, Hatsuta H, Sakiyama Y, Kanemaru K, Arai T, Sawabe M, Tanaka N, Mochizuki H, Inoue K, Murayama S. Incidence and Extent of Lewy Body-Related alpha-Synucleinopathy in Aging Human Olfactory Bulb. *J Neuropathol Exp Neurol* 2008;67:1072–1083. [PubMed: 18957894]