OLFACTORY DYSFUNCTION IN EARLY PD SUGGESTS THAT THE DISEASE IS CAUSED BY A TOXIN

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Introduction: According to the British Brain Bank criteria Parkinson's disease (PD) is characterized by motor symptoms such as bradykinesia, rigidity, tremor and postural instability (Hughes et al. 1993). The clinical diagnosis of this disease is based on these cardinal symptoms. Nowadays, it is well known that PD patients also suffer from non-motor symptoms, which considerably impair their quality of life. Non-motor symptoms comprise disturbances of olfaction, sleep and the autonomic nervous system. Although James Parkinson reported in 1817 in his report "An Essay on the Shaking Palsy" that "the senses and the intellect are uninjured" (Parkinson 1817), many PD patients present with neuropsychiatric symptoms such as anxiety, depression and dementia. More recently, we became aware of gambling and sexual abnormalities induced by dopaminergic treatment and most probably overstimulation of the nc. accumbens.

Enteric malfunction in PD: It was Braak et al. who showed that the first morphological abnormalities such as Lewy bodies and α-synuclein deposition do not occur in the substantia nigra, but in the olfactory bulb and in the vagal and glossopharyngeal nuclei. (Braak et al. 2003). The same authors claim that even before this the first Lewy bodies (LB) or a-synuclein inclusions may be found in the enteric nervous system, i.e. gastric, myenteric and submucosal plexuses (also known as Auerbach and Meissner Plexus) (Braak et al. 2005). Diagnosis of PD is only rarely made at this time, therefore these so-called stages 1 and 2 according to the Braak classification may be considered as preclinical stages. Recognizing these preclinical stages may offer the possibility to administer disease modifying or neuroprotective substances at an even earlier time.

Olfactory dysfunction: As mentioned above, Braak stage 1 is defined by the occurrence of Lewy bodies and α-synuclein aggregates in the olfactory bulb and the anterior olfactory nucleus, and therefore it is not surprising that impairment of olfaction is a very common feature of idiopathic PD. More than 90% of PD patients present with hyposmia and anosmia (Doty et al. 1992, Müller et al. 2002). Whilst Doty and colleagues used a scratch test (University of Pennsylvania Smell Identification Test) we apply sniffing sticks to ensure standardization of odour threshold, discrimination, and identification.

With our test battery, controls can attain a maximum score of 48 points. If PD patients score less than 30 points they are considered hyposmic, and if they score less than 15 they are considered anosmic. In our first study we analysed 50 patients with typical idiopathic PD (Müller et al. 2002). All patients scored less than 30 points and half scored less than 15 points in the sniffing sticks test. In a further study, we analysed olfaction over a prolonged period of time and found only a slight decrease in olfactory function in some of our patients. We believe that most patients develop olfactory malfunction many years prior to the onset of motor symptoms.

The concept of toxic origin of PD: Thus, both olfactory dysfunction and enteric malfunction affect organs, which are exposed to the environment. One may therefore speculate that pathogens such as toxins, viruses or bacteria may be responsible for the development of Parkinson disease (PD). Although the findings of Braak and colleagues are based on only a limited number of patients, they may support a search for the etiology of PD away from genetics and back to environmental, i.e. extrinsic, factors. They claim that the uptake of exogenous substances from the extraneuronal space occurs preferentially at the axon terminal. This hypothesis is supported by the observation of receptor-mediated endocytosis, which has been shown by several authors for neurotropic viruses (Helke et al. 1998, Mufson et al. 1999, Siegel and Chauhan 2000, Murer et al. 2001). Braak et al. (2003) could also prove the existence of neuronal pathways connecting the Auerbach plexus and the vagal nerve (i.e. Hornby and Abraham, 2000). It has already been shown in 1993 (Wakabayshi et al.) that the stomach may be particularly vulnerable to the invasion of pathogens because of its thin epithelial layer, the prolonged contact with the chymus, and the remarkably large number of Lewy bodies in the enteric nervous system of the stomach. To the best of my knowledge, there is no direct link between the vagal nerve and the olfactory bulb or anterior olfactory bulb.

Thus, it is most attractive to speculate that the pathogen of interest enters the body both via the nose and the gastric wall culminating in a double-crush and inducing Parkinson disease. The idea of a pathogen (e.g. toxin) entering via the stomach is not only supported by the presence of LB in the enteric nervous system, but also by the frequently encountered constipation in PD. Even James Parkinson himself remarked about this in his assay when he said that the bowels "which had been all along torpid, now, in most cases, demand stimulating medicines of very considerably power". This is further supported by the "Honolulu-Asia Aging Study" where men with infrequent bowel movements were more prone to develop PD (Abbot et al. 2001).

There are several examples which may support the concept of nasal and/or enteric entry of a so far unknown pathogen in symptomatic PD. Bringmann and colleagues could demonstrate that a toxin, which we called TaClo could induce Parkinson disease. We also found some patients who developed symptomatic PD after the intake of chloral hydrate (sleeping pill) and exposure to the industrial solvent trichloroethylene which resulted in a spontaneous ring closure reaction and formation of TaClo (Bringmann et al. 1995, Bringmann et al. 1999; Riederer et al. 2002). It is also generally accepted that pesticides, fungicides and herbicides are riskfactors for the development of a symptomatic Parkinson syndrome (Priyardarshi et al. 2001). Viral infections are also known to cause PD, the most important infection being "von Economo encephalitis". It could be shown that the substantia nigra is a major target for the neurovirulent influenza A virus (Takahashi et al. 1995). Bacteria also may play a role which is illustrated by the observation that bacterial vaginitis during pregnancy caused by *Gardnerella vaginalis* may have induced a reduction in the number of dopaminergic cells in the substantia nigra (Carvey et al. 2003). In addition, metals such as manganese, carbon monoxide, rotenone and other substances cause a symptomatic Parkinson syndrome (Uversky et al. 2004). Another intriguing example is the observation that in Guadeloupe the use of annonaceae in tea caused a Parkinson Syndrome (Lannuzel et al. 2002).

In summary, both the neuroanatomical findings and the above cited examples may indicate that another, so far undetected, toxin may cause the so-called idiopathic Parkinson syndrome. In particular, Braak's findings of the early involvement of enteric and nasal neurons imply that the entry sites of this unknown pathogen are the nose and gastro-intestinal tract.

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