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View point: Etiology in Parkinson's disease. Dual hit or spreading intoxication

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ABSTRACT

Parkinson's disease is not only a movement disorder: non-motor symptoms such as loss of smell, constipation, depression, cognitive impairment, sleep problems and disturbances of the autonomic nervous system also feature. The etiology is still unknown, although an increasing number of gene-related Parkinsonian syndromes have been identified. It is intriguing to speculate that PD starts by the intake of a toxin, bacteria or virus. This idea stems from the fact that pathological abnormalities such as Lewy neuritis, Lewy bodies and alpha-synuclein accumulation are first found in the enteric nervous system of the gut and in the olfactory bulb. There is increasing evidence that the disease may spread out from the enteric nervous system of the gut via the vagal nerve up to the brain. Here we present data from animal work which supports this assumption.

1. Introduction

According to the UK Brain Bank Criteria [1] Parkinson's disease (PD) is characterized by motor symptoms such as bradykinesia, rigidity, tremor and postural instability. Nowadays, it is well known that PD patients also suffer from non-motor symptoms [2,3] which considerably impair their quality of life [4]. Non-motor symptoms comprise disturbances of olfaction, vision, sleep and the autonomic nervous system [5]. Although James Parkinson claimed in 1817 in his essay that "the senses and the intellect are uninjured" [6], many PD patients present with neuropsychiatric symptoms such as anxiety, fatigue, apathy, anhedonia, depression and dementia. Taking this into account, it is obvious that PD does not only result from a loss of dopaminergic neurons in the substantia nigra, although this is most probably the reason for the motor symptoms which gave rise to the term "shaking palsy."

2. The pre-motor phase of Parkinson's disease

There have been more and more reports in recent years about symptoms that occur in the so-called premotor phase of PD. Olfactory impairment [7], REM sleep behavior disorder [8], constipation [9,10] and depression [11] are the most prominent of these symptoms. These findings further support the idea that the disease does not begin in the substantia nigra.

In the current view point, the so called Braak hypothesis that PD starts in the olfactory bulb and spreads via the enteric nervous system of the gut and the stomach towards the vagal nucleus [12], is considered.

3. Enteric malfunction

Braak et al. [12] showed that the first morphological abnormalities associated with PD, i.e. Lewy bodies, Lewy neurites and alpha-synuclein deposition, occur in the olfactory bulb and the vagal and glossopharyngeal nuclei rather than in the substantia nigra. It is even suggested that the first Lewy bodies or alpha-synuclein inclusions are to be found in the enteric nervous system i.e. the gastric, myenteric and submucosal plexuses (also known as Auerbach and Meissner plexus) [13,14]. Recently, Lewy bodies were detected in the enteric nervous system of the colon in PD patients [15]. Diagnosis is rarely made in the early stages of the disease, the so called stages 1 and 2 according to the Braak classification, and hence these stages may be considered to be preclinical stages. In a more recent paper, Del Tredici et al. [16] showed that Lewy pathology can also be found in the submandibular glands from patients who died with Parkinson's disease. Each of the 9 PD patients in this study had positive α-synuclein immunohistochemistry, while 2 individuals with multisystem atrophy did not.

We recently showed in mice that intragastrically administered rotenone, a commonly used pesticide that inhibits complex I of the mitochondrial respiratory chain, was able to reproduce the PD pathology staging found in patients [17]. Chronically administered low doses of rotenone induced alpha-synuclein accumulation in the enteric nervous system, followed by the dorsal motor nucleus of the vagus, the intermediolateral nucleus of the spinal cord and finally, the substantia nigra. In addition, we observed inflammation and α-synuclein phosphorylation in the enteric nervous system and

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the dorsal motor nucleus of the vagus. Since we could not detect rotenone in the blood or in the central nervous system, and mitochondrial complex I activity in brain and muscle was not decreased, a spreading process, starting in the enteric nervous system and involving only synaptically connected structures of the nervous system, had to be involved. Thus, by using this pesticide in mice, we were able to mimic the progression hypothesized to occur in PD patients [12]. Li et al. [18] and Kordower et al. [19] showed that Lewy bodies were detectable in grafted neurons in subjects with PD, which implies spreading of the neuropathological abnormality from host cells to the grafted tissue. Of particular note, Li and colleagues investigated a PD patient who had undergone two separate grafts, 12 and 16 years prior to investigation, [20], and found that up to 5% of the neurons in the 16 year old graft had Lewy body pathology, whereas 2% of the neurons in the 12 year old graft had Lewy bodies [20]. The authors speculate that this implicates a gradual development of Lewy body pathology in transplanted tissue, and hypothesize that PD may well be a prion-like disorder [21,22].

Such findings are in line with our observations in mice and support this view point of a spreading disorder.

4. 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 [7]. More than 90% of PD patients present with hyposmia and anosmia [7,23,24]. When questioned about their sense of smell, many PD patients report that they had noticed that this function was impaired years before they developed motor symptoms. PD patients who believe that their sense of smell remains intact should be investigated with the University of Pennsylvania Smell Identification Test (scratch test, 23), or, as we do, by the use of sniffing sticks, so that a quantitative method is used to identify any unrecognized loss of olfaction [7].

5. View point

Both olfactory dysfunction and enteric malfunction affect organs which are exposed to the environment. One may therefore speculate that pathogens such as toxins, viruses and/or bacteria may be responsible for the development of PD. Although the findings of Braak and colleagues are based on a restricted number of autopsies, 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 our study in mice and the observation that receptor-mediated endocytosis is involved in the infectious process of neurotropic viruses [25]. Braak et al. [12] also showed the existence of neuronal pathways connecting the Auerbach plexus and the vagal nerve. It had already been proposed in 1988 [13] 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 [13]. Water from wells located in areas of high pesticide usage would be a good example of a possible source of exogenous toxin [26].

But what connects the olfactory bulb and the enteric nervous system in the stomach? There is no direct nervous connection between both systems. Lately, Braak showed that the salivary glands also contain Lewy bodies [16] and this may lead to the hypothesis that it is the mucus which connects the olfactory system, the salivary glands and finally the stomach [27]. From the ENS of the stomach and gut it is a spreading affection of the nervous system.

In my view, we still don't have a clue as to the possible pathogen or pathogens involved, but it may well be a toxin, swallowed only once or perhaps over several years, which starts PD pathology. The same might be true for a bacterial or virus infection.

As much as the new genetic findings explain the basic cell mechanisms of cell death in monogenetic PD and idiopathic PD [e.g. 28], it is my view that they do not explain the existence of PD in the majority of PD patients. We should certainly once again start to search for pathogens from the environment which can enter via the nose, or swallowing, and then start the disease process from the enteric nervous system in the stomach and the gut. Support for this view comes from various studies which show environmental factors such as herbicides, pesticides, metal emissions related to the occurrence of Parkinson's syndrome [29–32].

Conflict of interest

None.

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