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Short communication

Hyposialorrhea as an early manifestation of Parkinson disease

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ABSTRACT

We sought to determine whether hyposialorrhea is an early manifestation of Parkinson disease (PD). We measured basal and citric acid stimulated secretion of whole saliva in 20 patients with early stage (Hoehn–Yahr I–II) PD who had motor symptoms for less than 1 year and were on no medication and 11 age matched controls. Compared to controls, PD patients had significant reduction of both basal (0.0964 ± 0.08 vs 0.293 ± 0.112 ml/min, $p<0.001$) and reflex (0.263 ± 0.213 vs 0.537 ± 0.313 ml/min, $p<0.001$) salivary secretion. Our findings confirm that hyposialorrhea is an early autonomic manifestation of PD.

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1. Introduction

Reduced salivary secretion is a manifestation of autonomic failure in patients with advanced Parkinson disease (PD) (Proulx et al., 2005; Tumilasci et al., 2006). In PD patients with motor fluctuations, hyposialorrhea is present both on the "off" and "on" conditions and improves with dopaminergic stimulation (Tumilasci et al., 2006). Whereas gastrointestinal motility disorders constitute early autonomic manifestations of PD (Pfeiffer, 2003), whether exocrine secretion, such as salivation, is also affected early in the disease has not yet been explored. We sought to determine whether impaired salivary secretion was an early manifestation of PD, as this could provide insight into the pathodynamics of autonomic involvement in this disorder.

2. Methods

This study was approved by the Institutional Review Board at the "Hospital de Clinicas", University of Buenos Aires. Subjects receiving anticholinergic drugs or affected by disorders that may alter autonomic or salivary gland functions, such as diabetes or Sjögren disease were excluded. We studied 20 PD patients (12 women, 8 men, and age 67 ± 11 years, range 40–81) and 11 age- and sex matched controls. In PD patients, disease duration was 8 ± 3 months (range, 4–12) average Hoehn and Yahr stage was 1.7 ± 0.44 (range, 1–2), and the unified Parkinson Disease rating scale (UPDRS)-III score was 13.8 ± 5.7 (range 6–26). PD patients had never received pharmacological treatment for their disease. None of the PD patients or control subjects complained of xerostomia.

We measured basal and citric acid-stimulated (reflex) secretion of whole saliva according to a standardized method (Navazesh and Christensen, 1982; Tumilasci et al., 2006). Saliva was collected after at least 10 h fasting, excluding water, and all studies were conducted between 8:00 and 9:00 AM. A discharged dental saliva ejector tip, attached to a water vacuum pump via a plastic tube was placed on the floor of the mouth and saliva was collected in a graduated centrifuge tube. Saliva collected during the first 5 min was discarded and only that obtained in the last 5 min was used for measurement of basal salivary secretion. Reflex salivary secretion was determined 10 min after obtaining basal samples. Secretion was stimulated by means of filter paper disks soaked in 2% citric acid and placed on the dorsum of the tongue every minute. The collection period was 3 min (three consecutive stimuli of 1 min each). The volume of saliva was measured by means of a microliter syringe (Hamilton, Reno, NV) and the flow rate calculated in ml/min. All determinations were performed once in each subject.

Data were expressed as means ± SD. Statistical analysis was performed using one- and two-way ANOVA, followed by posthoc Duncan test to compare means data. The differences were considered significant when $p<0.05$.

3. Results

Both basal and reflex salivary secretion were significantly reduced in early PD patients compared to controls (Fig. 1). Basal secretion was 0.0964 ± 0.08 ml/min in PD and 0.293 ± 0.112 ml/min in control subjects ($p<0.001$). Citric-acid stimulated salivary flow was $0.263 \pm$

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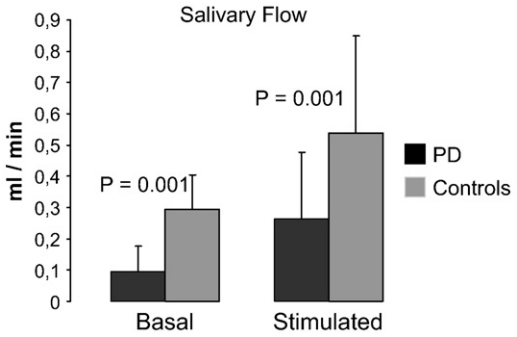

Fig. 1. Basal and acid-citric stimulated salivary flow in patients with early Parkinson disease (PD, $n=20$) and age-matched controls ($n=11$). Results are expresses as mean ± SD.

0.213 ml/min in PD and 0.537 ± 0.313 ml/min in control subjects ($p<0.001$). (Fig. 1)

4. Discussion

Our results indicate that hyposialorrhea is an early autonomic manifestation in PD. Not only basal secretion but also reflex secretion activated by citric acid were affected, suggesting that there is a reduction in neural input to the salivary glands. Unlike previous studies (Proulx et al., 2005; Tumilasci et al., 2006), our study focused on patients with early PD and not receiving dopaminergic medications. This allows excluding effect of disease severity, fluctuations, or dopaminergic receptor stimulation on salivary secretion. Whereas gastrointestinal motility disorders are frequent and may be an early manifestation or precede the motor symptoms of PD (Pfeiffer, 2003), our findings suggest that impaired exocrine gland function, including salivary secretion, may also be an early autonomic manifestation of this disorder. Gastrointestinal dysmotility in PD reflects early involvement of the enteric nervous system (ENS) (Wakabayashi and Takahashi, 1997) (Wakabayashi et al., 1993) and the dorsal motor nucleus of the vagus (DMV) (Braak et al., 2006a) by a-synuclein pathology, including Lewy neurites and Lewy bodies. According to Braak et al. (Braak et al., 2006b; Braak and Del Tredici, 2008), a potential pathogen present at the intestinal lumen may trigger α-synuclein accumulation in enteric neurons and, via retrograde mechanisms, in preganglionic neurons of the DMV. The presence of Lewy bodies and neurites in the submucous plexus of Meissner (Braak et al., 2006a; Braak et al., 2006b), which contains secretomotor neurons, and the finding that Lewy bodies are present in neurons synthesizing vasoactive intestinal polypeptide (VIP) (Wakabayashi et al., 1990), which is a marker of secretomotor neurons in the ENS (Costa et al., 1986) suggest that impairment of exocrine gland function in the digestive system may occur at early stages of PD (Costa et al., 1986), (Yazawa et al., 1994). Our present finding that impaired salivary secretion is an early autonomic manifestation of PD is consistent with this possibility. Salivary glands are innervated by cranial parasympathetic ganglion neurons that, like enteric neurons, are located close to their targets. These salivary ganglion neurons receive preganglionic inputs from pontomedullary neurons of the salivary nucleus (Gai and Blessing, 1996), which, like the DMV is part of the brainstem general visceral efferent column and contains cholinergic neurons with long, small diameter myelinated axons, which may predispose to Lewy body pathology (Braak et al., 2003). Our results suggest that involvement of salivary ganglion neurons, the brainstem salivary nucleus, or both, by a-synuclein pathology may be an early feature in PD. If the intriguing possibility proposed by Braak (Braak et al., 2006b; Braak et al., 2003) is correct, our results may raise the possibility that an environmental pathogen may access the nervous system via neurons that innervate the salivary glands. Further studies are necessary to explore this possibility.

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