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Review

SIALORRHEA AND XEROSTOMIA IN PARKINSON'S DISEASE PATIENTS

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SUMMARY – Parkinson's disease (PD) is generally considered as a primary movement disorder, but the majority of patients also suffer from non-motor oral, salivary symptoms. The most common salivary symptoms, sialorrhea and xerostomia, have a considerable negative impact on the quality of life. Although these symptoms are completely opposite ones, both significantly impair oral health of patients. Sialorrhea is defined as an increased amount of the retaining saliva. It is related to salivary overproduction, or it may be associated with impaired clearance of saliva. Opposed to sialorrhea, xerostomia is subjectively defined as dryness of mouth and it is related to insufficient salivary secretion. Xerostomia promotes imbalance of oral microflora and oral pathology that often leads to malnutrition in PD patients. It is mostly related to autonomic dysfunction, or it might be considered as a side effect of dopaminergic or anticholinergic medication. In PD, different assessments are used for evaluation of sialorrhea and xerostomia, including validated scales for non-motor symptoms and standardized questionnaires on oral health. Consequently, treatment of salivary symptoms includes pharmacological and nonpharmacological approach, and surgical interventions. A multidisciplinary approach in clinical neurology and dental medicine, which includes accurate evaluation of salivary symptoms and effective treatment, indicates successful management of PD patients.

Key words: *Parkinson's disease; Sialorrhea; Xerostomia*

Introduction

Idiopathic Parkinson's disease (PD) is a progressive neurodegenerative disease that affects around 1% of adults over age 60, with the annual growth rate of 7.9% worldwide[1-3]. It is related to a significant loss of dopamine neurons in substantia nigra and dysfunction of nigrostriatal neural pathways, both important for the initiation and control of motor movements. Tremor, rigidity, hypokinesia, and postural instability generally occur as cardinal symptoms of PD. Motor impairment in later stages of PD leads to poor oral hygiene, mostly due to impaired function and limited daily activities[4,5]. Dysfunction of mesolimbic pathways affects motivation for oral hygiene and lowers decision making regarding dental treatment. Although PD is generally considered as a primary movement disorder, the majority of patients suffer from non-motor symptoms that may be related to oral pathology[6,7]. The aim of this mini review is to underline the importance of salivary symptoms in the management of PD patients in order to minimize poor health outcomes. The most common oral pathology in PD comprises diurnal and

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nocturnal sialorrhea, xerostomia, gingivitis and periodontitis, caries and edentulous oral cavity, orofacial pain, burning mouth syndrome, and bruxism. Concomitantly, patients are affected by behavioral and cognitive disorders. Clinical implications of oral health (OH) in PD are heterogeneous. Dental and periodontal diseases are associated with impaired oral hygiene due to hypokinesia or involuntary movements such as tremor, facial dyskinesias, and dystonia[8]. PD patients often report dysphagia combined with sialorrhea or xerostomia, or they might complain of painful conditions such as burning mouth syndrome and orofacial pain. In general, sialorrhea and xerostomia have unfavorable effect on OH and dental treatment[9,10]. Patients often report these symptoms together, which may seem contradictory, as they present completely divergent salivary symptoms. Sialorrhea is described as an increased amount of retaining saliva in the oral cavity. It occurs either due to salivary overproduction or impaired clearance of saliva. It is commonly caused by swallowing impairment. Salivary continence is usually established by the first 15-36 months of life, and after the age of 4 years, sialorrhea is considered pathologic. In severe cases, sialorrhea can end up as drooling, defined as the presence of saliva beyond the margin of the lip[13]. Drooling is a common symptom in PD, with the prevalence ranging from 10% to 80%[11,12]. It often becomes a main health concern, with negative impact on the quality of life (QoL) and possible social isolation. Differentiation between sialorrhea and hypersalivation is important, as the latter refers to the objective finding of increased salivary production[13-15]. It is accepted that drooling develops due to dysphagia in advanced stages of PD, with a prevalence ranging from 9% to 77%, but it may also occur early, even as a presenting feature[16,17]. In contrast, xerostomia is defined as abnormal subjective dryness of mouth that mostly occurs due to insufficient salivary secretion. It is important not to misdiagnose it as hyposalivation, which is defined as an objective finding of decreased salivary production. If salivary flow decreases by 50%, it will result in xerostomia, although this symptom may occur in patients with normal salivary flow rates[18,19]. Among healthy subjects, xerostomia is often associated with salivary gland dysfunction. Age, gender, depression, diabetes mellitus, head and neck radiotherapy are contributing factors that increase the risk of xerostomia among healthy population[18-20]. In PD, xerostomia develops either due to reduced saliva production and autonomic dysfunction, or as a side effect of dopaminergic or anticholinergic medication. It may cause imbalance of oral microflora and lead to periodontitis and caries, which may further promote neuroinflammation and neurodegeneration in PD. The interaction of non-motor salivary symptoms and their subjective burden on QoL is still unclear[21,22].

Sialorrhea

Sialorrhea (uncontrollable salivation, leaking of saliva) or drooling are frequently reported non-motor symptoms that affect 30%-80% of PD patients[10,21,22]. Although the precise pathophysiological mechanism is unknown, it is commonly associated with ineffective swallowing, reduced oral motor control, and dysphagia. It is still unclear how sialorrhea influences oral pH and microflora, but clinical experience shows that edentulous PD patients often have problems with dentures, which negatively affects their masticatory function and QoL. In the early course of PD, different factors are associated with sialorrhea, e.g., male gender, motor symptom severity, excessive daytime sleepiness, or impaired sleep quality. Sialorrhea and drooling are associated with reduced bolus formation, dehydration, loss of antibacterial features of saliva, perioral dermatologic changes, and speech difficulties[23]. In general, drooling in PD appears to be primarily related to reduced swallowing efficiency rather than to increased salivary production. Further contributing factors are reduced lip closure as part of hypomimia, postural changes, particularly anteflexion, and unawareness of drooling. Different data show that drooling is generally not an early symptom of the disease because it takes three years on average to develop diurnal hypersalivation[22]. Diurnal salivary leaking commonly appears in the later course of PD and is associated with involuntary mouth opening and swallowing dysfunction. Diurnal and nocturnal sialorrhea were compared in order to evaluate sialorrhea severity, and facial and oral motor deficit, considering reduced facial expressions, involuntary mouth opening, and swallowing problems[23]. Diurnal drooling was present in 28%, and nocturnal drooling in 58% of PD patients. Patients with sialorrhea were older, had severe form of the disease and longer disease duration, worse dysphagia score, and reduced facial expression as compared with those without sialorrhea. Among PD

patients with sialorrhea, one-third reported frequent swallowing to avoid speech difficulties, in comparison with less than 5% of PD patients without sialorrhea[23]. The difference was detected in the frequency of drooling and swallowing, at rest and during the task, implying that participants swallowed less frequently and more often drooled during the distraction task[13,23]. Retrospective analysis of 728 patients, as part of the Non-motor International Longitudinal Study (NILS), was performed to determine the prevalence of drooling, dysphagia, and QoL in PD patients[12,23]. The NILS was a prospective, international longitudinal study with over 1600 PD patients included, which assessed correlation of non-motor symptoms and treatment response. Non-motor symptoms in PD were evaluated by the Non-Motor Symptoms Scale (NMSS) including the presence and severity of drooling, and by using the Non-Motor Symptoms Questionnaire (NMSQ). NMSS commonly classifies non-motor symptoms in PD by the following areas: cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention and memory, gastrointestinal, urinary, sexual function, and miscellaneous[24]. The NILS sub analysis of drooling presence and frequency was based on the scores for question 19 of NMSS, at baseline and at follow-up. Regarding the presence of drooling, it was scored as either absent (score 0) or present (1-12), and concerning the severity of drooling, scores were as follows: absent to mild (0-3), moderate (4-7), and severe (8-12). The baseline prevalence of drooling (PD duration 5.6 years) increased from 37.2% to up to 40.1% at 3-year follow-up. The prevalence of drooling increased with age, but the severity of drooling did not change. In advanced PD, drooling occurred in over one-third of patients and was significantly associated with decreased QoL, social distancing and stigmatization of PD patients. The prevalence of dysphagia was evaluated with 8-item Parkinson's Disease Questionnaire (PDQ-8) scale. At baseline, only 16% of PD patients without drooling and 34.3% of those with drooling reported dysphagia. At follow-up, the number of patients with dysphagia without drooling increased by 20.4% and of those with drooling by up to 43.6%[12,23-25]. The frequency of swallowing and severity of drooling in PD patients were also assessed during computer-based language task, at rest and during activation. Results showed that there was no significant difference in the severity of drooling in either parameter. Dental care and oral health in PD are commonly self-assessed through different questionnaires that comprise performance of oral hygiene, xerostomia, drooling and dysphagia, and QoL. The Oral Health Impact Profile (OHIP-14)[19,20] is a questionnaire most commonly used for the evaluation of oral health. The results are expressed as the sum of scores, with maximum score of 70 for 14 questions. The OHIP-14 assesses the occurrence and severity of pain, physical, psychological and social limitations, and other disabilities related to oral symptoms, ranging from never (score 0), hardly ever (1), occasionally (2), fairly often (3), very often (4) to always (5). Specific elements of OHIP-14 are more important to PD patients because of the symptoms of xerostomia, salivation and drooling, and dysphagia. The compound questionnaire that evaluated oral health and dental care, comprised of the OHIP-14 score, the levodopa equivalent daily dose, and the Movement Disorder Society Unified Parkinson's Disease Rating Scale-II (UPDRS-II), was completed by 100 PD patients. Patients reported drooling (70%), xerostomia (49%), dysphagia (47%), and limited performance of oral hygiene (29%). Results showed that subjects suffered from oral health related symptoms that impaired their QoL. Participants felt that dental advice regarding management of PD-related oral health problems was often lacking. Not only that sialorrhea has a negative impact on patient QoL, but it also affects caregivers[25].

Treatment of sialorrhea includes pharmacological and nonpharmacological methods, and rarely surgical interventions on salivary glands. Short-term treatment of sialorrhea in PD may include the anticholinergic agent ipratropium bromide (a derivative of atropine) and glycopyrrolate, whereas for long-term treatment botulinum toxins A and B are considered effective. The application of botulinum is associated with the risk of transient swallowing difficulties and dysphagia, and therefore it requires specialized monitoring. Nonpharmacological interventions that include speech therapy and orofacial regulation modify swallowing and reduce drooling in PD patients, but not many of them have really been applied to PD patients. Surgical treatment options include neurectomy (sectioning of the chorda tympani nerves), and salivary gland excision, or salivary duct ligation and salivary duct relocation. The last three mentioned procedures are combined or performed individually and have been performed mainly

in neurologically impaired children. These procedures are also more invasive than pharmacological and non-pharmacological methods and may cause complications such as xerostomia and dental caries.

Xerostomia

Xerostomia is considered as abnormal subjective feeling of dry mouth and a quite common non-motor PD symptom. Data show that almost half of PD patients report xerostomia[26,27]. It may be considered as an early non-motor PD symptom since recent data support neuropathological evidence for salivary gland involvement in PD and in Lewy body disease[16,18,28]. Although being completely opposite symptoms, xerostomia and drooling are perpetuated in a vicious circle. Drooling is promoted by dysphagia, but the excess of saliva cannot relieve dry mouth symptoms. Additionally, xerostomia can worsen dysphagia, potentially leading to further drooling[28]. The presence of both xerostomia and drooling in the same patient reflects the different pathophysiological basis for the two symptoms. Further on, xerostomia promotes imbalance of oral microflora and might initiate the pathologies such as caries and periodontal disease, both relevant for developing malnutrition. Evidence shows that oral and systemic inflammation underlying periodontal disease may trigger neuroinflammatory processes and contribute to further neurodegeneration in PD. Considering the impact of medications on QoL in PD, it is important to ask the patients about xerostomia and provide available therapy[29,30]. In most PD cases, xerostomia is induced by the specific medical therapy and it usually appears as a side effect of dopaminergic or anticholinergic medication, tricyclic antidepressants, antipsychotics (e.g., clozapine), antihypertensives and antihistamines, but it might also be due to reduced saliva production or autonomic dysfunction[30]. Although different treatment options are utilized in PD (L-dopa, dopamine agonists or dopamine-reuptake inhibitors), it is not clear what influences the salivation rate most. PD patients with xerostomia often report poor QoL, corresponding to patient-reported outcome questionnaires. In the compound questionnaire completed by 100 PD patients, xerostomia was reported by 49% of patients, 64.3% of female patients and 43.7% of male patients[19,29,30]. The median PD duration in patients with xerostomia was 8 years. Further on, participants had self-assessed xerostomia by the OHIP-14 survey. According to the results of the survey, dental counseling about dry mouth symptoms was received by only 6.1% of patients that suffered from xerostomia and only 4.1% used symptom-relieving hygiene products. It might be due to the fact that only 12% of patients reported dry mouth. In patients with self-reported xerostomia, 53.1% had no dysphagia, 24.5% had slight impairment, 4.1% reported mild impairment and 18.4% moderate dysphagia problems. Interestingly, dry mouth was reported by 60.8% of PD patients and 27.9% of controls, while dry mouth and drooling coexisted in 30% of cases. Xerostomia is rarely mentioned as an autonomic symptom of PD despite the evidence that it might be due to autonomic involvement of the salivary gland[31-33] related to reduced salivary secretion in PD patients. On the opposite side, drooling results from the impaired automatic oropharyngeal phase of swallowing. Consequently, levodopa improved drooling in 34.7% of patients, but had no effect on dry mouth in most of the cases[34-36]. Autonomic dysfunction in PD concomitantly affects a wide range of QoL elements, e.g., daily living activities, cognitive functions, and social support. In a study that evaluated autonomic dysfunction in more than 100 PD patients, the Scales for Outcomes in Parkinson's disease-Autonomic Dysfunction (SCOPA-AUT) were applied. Results of the study revealed that 84% of patients complained of autonomic symptoms. The severity of autonomic symptoms was associated with advanced age, extended disease duration, pronounced disease severity, and higher doses of dopaminergic medication[37,38]. However, in another study on 40 patients with PD, autonomic dysfunction did not correlate either with age or motor symptoms. Generally, SCOPA-AUT is more specific for the evaluation of gastrointestinal and urinary dysfunction but quite deficient in the assessment of xerostomia or sudomotor function, so many autonomic syndromes in PD are often evaluated by the Survey of Autonomic Symptoms (SAS), commonly used in patients with diabetic neuropathy. SAS consists of questions that evaluate the presence and severity of autonomic symptoms regarding orthostatic, sudomotor and vasomotor, gastrointestinal and urinary, and sexual dysfunction. The maximum number of symptoms, occurring in the 6-month period prior to SAS administration, ranges from 0-12 for men and 0-11 for women. It is scored as one point for the answer yes

or zero point for the answer no and determines SAS A sub score. The severity of autonomic symptoms is commonly rated from 1 (least severe) to 5 (most severe), and the sum of all scores (0-60 for men and 0-55 for women) defines the total autonomic symptom burden (SAS total)[33,34]. Sicca symptoms in PD (xerostomia and dry eyes) frequently occur together with other non-motor symptoms, e.g., urine urgency, orthostatic problems, and diminished concentration. The association of autonomic and sicca symptoms was assessed in more than 90 PD patients along with other non-motor symptoms and QoL[20,37,38]. Autonomic symptoms were evaluated by SAS, motor function was estimated by the standard MDS-UPDRS III, non-motor symptoms were assessed by the Non Motor Symptoms Questionnaire (NMSQ)[39,40] patient-based survey that provides comprehensive assessment of non-motor symptoms in all PD stages, and QoL was evaluated by the standard 39-item PDQ (PDQ-39). Multivariable and multivariate analyses were performed to determine the association between clinical parameters and PDQ-39 survey that commonly includes activities of daily living, social situations, and communication. Sicca symptoms were the most commonly reported (69%) autonomic symptoms, followed by sexual dysfunction in men, vasomotor dysfunction, constipation, sudomotor dysfunction, and orthostatic symptoms. Overall, 75% of the subjects were under treatment by at least one medication that might cause sicca symptoms (anti-PD medication, antidepressants, antihypertensive drugs, antipsychotic drugs, antimuscarinic drugs, and analgesics). SAS total score correlated well with the NMSQ and Hoehn and Yahr scores, but did not correlate with age, levodopa daily dose, disease duration, and MDS-UPDRS III. Thus, the SAS total score was determined as an independent predictor of the PDQ-39 summary index and mainly affected cognition and emotional well-being areas[41].

Treatment of xerostomia includes pharmacological and nonpharmacological methods. Pharmacological alternatives for xerostomia management include cholinergic agonists such as pilocarpine hydrochloride or cevimeline hydrochloride, which stimulate the production of saliva. Nevertheless, studies regarding these agents in PD are lacking. Recently, orally administered ubiquinol or coenzyme Q10 was shown to remarkably improve salivary secretion (up to 80%). Nonpharmacological methods include frequent gum chewing and using various salivary substitutes, as PD patients that suffer from xerostomia have a natural tendency to frequently consume liquids to relieve their symptoms.

Conclusion

Patients with advanced PD often suffer from salivary symptoms, xerostomia and sialorrhea, which significantly impair their oral health and QoL. Oral symptoms of PD that appear as combined or isolated non-motor symptoms are still underreported. Salivary symptoms are often associated with non-motor PD subtypes and disease progression. Considering non-motor, especially salivary symptoms in PD, it is evident that multidisciplinary approach to oral pathology is warranted. This implies active interaction between clinical neurology and dental medicine, and further research into treatment modalities for salivary symptoms in PD.

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Sažetak

SIJALOREJA I KSEROSTOMIJA U BOLESNIKA S PARKINSONOVOM BOLEŠĆU

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Parkinsonova bolest (PB) općenito se smatra primarnim poremećajem pokreta, ali većina bolesnika pati i od ne-motornih oralnih salivarnih simptoma. Najčešći salivarni simptomi, sijaloreja i kserostomija, imaju značajan negativan utjecaj na kvalitetu života bolesnika. Iako su navedeni simptomi potpuno suprotni, oboje značajno narušavaju oralno zdravlje bolesnika. Sijaloreja se definira kao povećana količina zadržavajuće sline, a povezana je s prekomjernim lučenjem sline ili nedostatnim odstranjivanjem sline. Za razliku od sijaloreje, kserostomija se subjektivno definira kao suhoća usta i povezana je s nedovoljnim lučenjem sline. Kserostomija potiče neravnotežu oralne mikroflore i oralnu patologiju koja često dovodi do pothranjenosti kod bolesnika s PB. Povezana je s autonomnom disfunkcijom ili se može smatrati nuspojavom dopaminergičkih ili antikolinergičkih lijekova. U PB se za procjenu sijaloreje i kserostomije primjenjuju različite metode procjene, uključujući standardizirane ljestvice za procjenu ne-motoričkih simptoma i upitnike oralnog zdravlja. Slijedom toga, liječenje salivarnih simptoma uključuje farmakološki i ne-farmakološki pristup te kirurške intervencije. Multidisciplinarni pristup u kliničkoj neurologiji i dentalnoj medicini, koji obuhvaća preciznu procjenu salivarnih simptoma te učinkovito liječenje, ukazuje na uspješno liječenje bolesnika s PB.

Ključne riječi: *Parkinsonova bolest; Sijaloreja; Kserostomija*