Corneal nerve microstructure in Parkinson's disease

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Abstract

Ocular surface changes and blink abnormalities are well-established in Parkinson's disease. Blink rate may be influenced by corneal sub-basal nerve density, however, this relationship has not yet been investigated in Parkinson's disease. This case-control study examined the ocular surface in patients with moderately severe Parkinson's disease, including confocal microscopy of the cornea. Fifteen patients with moderately severe Parkinson's disease (modified Hoehn and Yahr grade 3 or 4) and fifteen control participants were recruited. Ophthalmic assessment included slit-lamp examination, blink rate assessment, central corneal aesthesiometry and in vivo confocal microscopy. The effect of disease laterality was also investigated. Of the 15 patients with Parkinson's disease, ten were male and the mean age was 65.5 ± 8.6 years. The corneal sub-basal nerve plexus density was markedly reduced in patients with Parkinson's disease (7.56 ± 2.4 mm/mm²) compared with controls (15.91 ± 2.6 mm/mm²) (p < 0.0001). Corneal sensitivity did not differ significantly between the patients with Parkinson's disease (0.79 ± 1.2 mBAR) and the control group (0.26 ± 0.35 mBAR), p = 0.12. Sub-basal nerve density was not significantly different between the eye ipsilateral to the side of the body with most-severe motor symptoms, and the contralateral eye. There was a significant positive correlation between ACE-R scores and sub-basal corneal nerve density (R² = 0.66, p = 0.02). This is the first study to report a significant reduction in corneal sub-basal nerve density in Parkinson's disease and demonstrate an association with cognitive dysfunction. These results provide further evidence to support the involvement of the peripheral nervous system in Parkinson's disease, previously thought to be a central nervous system disorder.

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1. Introduction

The hallmark motor features of Parkinson's disease are tremor, rigidity, postural instability and bradykinesia [1]. Non-motor involvement, including cognitive dysfunction, hallucinations and abnormalities of the visual system, is now also recognised as an important feature of Parkinson's disease [1,2]. Both the motor and non-motor features of Parkinson's disease are frequently asymmetric, with one side of the body more affected than the other [3].

In recent years, visual pathway changes in Parkinson's disease, including retinal thinning, reduced contrast sensitivity and colour vision defects, have been widely studied [2,4–6]. Ophthalmic involvement also extends to the anterior eye structures, and in particular the ocular surface [7].

Signs suggestive of ocular surface irritation are common in Parkinson's disease [7]. The cause of these is thought to be twofold: blink abnormalities caused by the disease itself and medical therapies used to treat the condition [7]. Blink abnormalities, including altered blink rate and blink duration, are frequently reported in patients with Parkinson's disease and are related to dopamine activity in the central nervous system [8–10].

It might be reasonably assumed that the cause of the decreased blink-rate in Parkinson's disease is simply a manifestation of bradykinesia, arising centrally. However, given that blink rate may be influenced by the nerve density in the sub-basal layer [11], this study explored whether sub-basal corneal nerve density is reduced in patients with Parkinson's disease. The hypothesis was supported by recent reports suggesting that peripheral neuropathy is a common feature of Parkinson's disease [12–16] and the observation that diabetic small fibre sensory neuropathy is strongly associated with reduced corneal sub-basal nerve plexus density and corneal sensitivity in patients with diabetes mellitus [17–19].
The objectives of this study were to examine the ocular surface in patients with moderately severe Parkinson’s disease, including in vivo confocal microscopy of the corneal sub-basal nerve plexus, and to compare findings with a control group. The relationships between sub-basal corneal nerve density, corneal sensitivity, blink rate and measures of disease severity in Parkinson’s disease were also investigated.

2. Methods

2.1. Participants

A total of 111 patients attending Auckland City Hospital (Auckland, New Zealand) with an established diagnosis of Parkinson’s disease confirmed by a consultant neurologist, were contacted about participation in this study. Exclusion criteria included: mild Parkinson’s disease (Hoehn and Yahr grades 1–2) [20], co-existing neurological disease; diabetes mellitus; previous ocular surgery; corneal trauma or scarring; corneal pathology; previous episodes of significant ocular inflammation or infection; thyroid eye disease; history of contact lens wear; and use of topical antihypertensive agents for treatment of glaucoma or ocular hypertension. Eighteen patients (N = 18) met initial inclusion criteria. Fifteen age-matched controls were recruited for comparative analysis.

Patients underwent a comprehensive ophthalmic and medical history, including current medical therapies. Participants with Parkinson’s disease on dopamine therapy were instructed to continue their medication regimen prior to ophthalmologic examination. A slit-lamp biomicroscopic examination of the anterior eye was conducted to rule out potentially confounding corneal, or other, anterior segment pathology.

The study was approved by the Northern-X Ethics Committee (NTX/11/EXP/022) and the Auckland District Health Board Research Committee (A+5185). The study followed the tenets of the Declaration of Helsinki. Written informed consent was given by all participants.

2.2. Examination of the ocular surface

The assessments of the cornea and tear film were carried out strictly in the order highlighted below in all participants.

2.2.1. Blink rate assessment

The blink rate was assessed during a two minute conversation prior to any ocular assessment. The number of complete blinks was counted by an observer while the patient had a conversation with the examiner.

2.2.2. Corneal Sensitivity

The non-contact corneal aesthesiometer (NCCA) (Glasgow Caledonian University, Glasgow, UK) [21] was used to evaluate central corneal sensitivity. The device emits a jet of air (lasting 0.9 s) directed towards the cornea. This produces a localised reduction in the surface temperature of the cornea, which is detected by the corneal nerves. The minimum force of air (in millibars) required to induce a sensation is the corneal sensitivity [22]. A higher value indicates reduced corneal sensitivity.

2.2.3. Infrared Blink Rate Assessment

The Keratograph (Oculus, Wetzlar, Germany) is a non-contact keratometer and also contains an infrared (880 nm) illumination system [23]. A one minute infrared video was captured while the subject was instructed to look straight ahead, and the number of complete blinks (full eyelid closure) was recorded. The patients were not informed that their blink rate was being assessed.

2.2.4. Confocal Microscopy of the cornea

Parallel to, and below, the corneal epithelium are nerve bundles which form the corneal sub-basal nerve plexus [24]. These nerves are derived from the ophthalmic division of the trigeminal nerve [25]. In vivo confocal microscopy (IVCM) of the cornea allows for the non-invasive acquisition of two-dimensional images of the corneal layers at a cellular level, including the sub-basal nerve plexus [24,26]. The Heidelberg retina tomograph (HRT) II Rostock Corneal Module (RCM), (Heidelberg Engineering, Heidelberg, Germany) was used to capture the images of these nerves. The focal plane is moved manually in order to scan through the layers of the cornea. Each image acquired by the HRT II RCM is 400 x 400 μm in size, with a section thickness of 4 μm and lateral resolution of 2 μm. A well-established protocol which ensures accurate assessment of corneal nerve density and also avoids sampling bias was followed for this assessment [27–29]. Duplicate and poor quality images were discarded.

The sub-basal corneal nerve density was calculated by an experienced examiner masked to the participants’ diagnosis. An electronic pen (Wacom Technology Group, Vancouver, Canada) was used to trace the visible nerves. The total length of the traced nerves, denoted as corneal sub-basal nerve density, was measured using a digital calliper (analysis 3.1, Soft Imaging System, Münster, Germany) (Fig. 1). The tracings for each participant were done in a single session.

2.3. Neurological assessment

Hoehn and Yahr scores were obtained for all Parkinson’s disease patients. Where possible, cognitive function was assessed using the Addenbrooke’s cognitive examination- revised (ACE-R), with a score of less than 88 out of a possible 100 indicating the presence of dementia with a sensitivity of 0.94 and specificity of 0.89 [30]. Autonomic dysfunction was assessed using the Survey of Autonomic Symptoms (SAS). The questionnaire consists of 12 questions for men and 11 for women. Each question is rated by an impact score (from 1 to 5) and the total symptom impact score is given by the sum of the severity scores [31].

2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism (GraphPad Software Inc., La Jolla, California) and Microsoft Excel® (Redmond, WA). All comparisons between Parkinson’s disease patients and controls were performed using right eye data only. Continuous variables are presented as mean ± standard deviation (SD). Normality of distribution was assessed by the Shapiro–Wilk test. Comparison of normally distributed variables was performed by two sample t-test. The Mann–Whitney test was used for non-parametric comparisons. Correlation analysis was performed using the Spearman test or Pearson test as appropriate. Because of asymmetry in Parkinson’s disease, corneal confocal microscopy measurements from the eye ipsilateral to the side of the body with the most severe motor symptoms were compared with the contralateral side. For within patient analysis, a paired t-test was used. A p-value of less than 0.05 was considered significant.

3. Results

3.1. Ocular assessment

Patients with Parkinson’s disease (12 males and 6 females) had a mean age of 65.5 ± 8.6 years (range 40–76 years), while the mean age was 60.2 ± 6.1 years (range 53–73 years) in the control group (8 males:7 females) (Table 1). Analysis confirmed there was no
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