Brief report

Risk of Parkinson’s disease in patients with neovascular age-related macular degeneration

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Abstract

Purpose: To examine the risk of developing Parkinson's Disease (PD) in patients who are newly diagnosed with neovascular age-related macular degeneration (nAMD).

Methods: This was a cohort study using the British Columbia (BC) Retinal Disease Database. Data from 2009 to 2013 was accessed. Rates of PD in patients prior to the diagnosis of nAMD were computed and compared to the rates of patients newly diagnosed with PD after the diagnosis of nAMD.

Results: The rate of PD prior to the diagnosis of nAMD was 1.42 per 100,000 person-years. The rate of PD after the diagnosis of nAMD was 2.88/100,000 person-years. The rate ratio was 2.03 (95% CI; 1.31–3.16).

Conclusions: The findings suggest that patients who are diagnosed with nAMD are at a significantly higher risk of developing PD later in life. More studies are needed to identify the pathological mechanism between the two diseases.

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Keywords: Parkinson's disease; Population based databases; Macular degeneration; Epidemiologic studies

Introduction

Age-related macular degeneration (AMD), a leading cause of blindness among adults over the age of 65 in Western countries, is a common visual condition in patients with Parkinson's disease (PD). PD is a progressive neurodegenerative disorder that results in the loss of dopaminergic neurons in the substantia nigra and manifestations of Parkinsonian motor abnormalities include bradykinesia, resting tremor, and postural imbalance. A multitude of non-motor symptoms, including depression, autonomic dysfunction and visual disturbances, are frequently present during the early, prodromal stages of PD, prior to the cardinal motor signs of the disease. As such, it is imperative for clinicians to better understand the clinical features that appear during this latent phase of neurodegeneration in PD so that diagnosis and treatment can be provided as early as possible. One large cohort study showed that patients with neovascular AMD (nAMD) had a higher risk of developing PD, with a rate ratio of 2.57 (95% CI; 1.42–4.64). In this study, patients with nAMD were followed for three years to the first PD event. However, the researchers did not control for PD latency, the time period in which non-motor indicators emerge prior to the hallmark motor signs that are used for clinical diagnosis.
of PD. The purpose of our study is to determine whether patients diagnosed with nAMD are at a higher risk of developing PD while controlling for PD latency.

Methods

This was a cohort study using the British Columbia (BC) Retinal Disease Database and includes all patients in BC, Canada who were newly diagnosed with nAMD from 2009 to 2013. The BC Provincial Retinal Disease Treatment Program was developed in 2009 by the BC Ministry of Health and the Provincial Health Services Authority (PHSA) to offer anti-VEGF therapies (bevacizumab or ranibizumab) for patients in BC with nAMD. The retina specialists who administer the treatment were responsible for collecting the relevant patient health information, including age, gender, clinic location, date of treatment, injection type and visual acuity (VA). The patient data were then submitted to a comprehensive database that includes all intravitreal injections given from 2009 to 2013. These data are subject to regular quality control through frequent electronic data edits and are linkable to other BC Ministry of Health Databases, which capture all hospitalizations through the Discharge Abstract Database and all physician visits obtained through the Medical Services Plan (MSP) data file. As all residents of BC have access to universal healthcare, all diagnoses are completed through physician billings (MSP) and entered into the MSP database. This includes any BC residents who are diagnosed with PD (including those with nAMD), and thus it is unlikely for the PD diagnosis of a subject (before or after nAMD diagnosis) to not be captured into the MSP. Diagnosis of PD was made by physicians using the first ICD-9 code for PD (ICD-9332) and was ascertained through the MSP database. PD cases were required to have an additional PD code after the first to be qualified as a case. Rates of PD in patients prior to the diagnosis of nAMD (the date of injection for bevacizumab or ranibizumab) were calculated and compared to the rates of patients newly diagnosed with PD after the diagnosis of nAMD (after the first intravitreal injection). Both of the PD rates were extracted from the same MSP database. Since the duration of the prodromal phase in PD is long and can range between 2 and 10 years prior to the actual diagnosis of PD, we allowed for a 300-days lag period in order to control for PD latency. This was based on the hypothesis that PD events occurring within the first 300 days after the diagnosis of nAMD were probably not related to the nAMD disease itself and could thus be excluded. We computed age-adjusted rates for both pre- and post- AMD periods. Ethics approval was granted for the study by the University of British Columbia's Clinical Research Ethics Board.

Statistical analysis

Incident rates and rate ratios for PD were computed (adjusting for age) for the period before diagnosis of nAMD and compared to the period after diagnosis of nAMD.

Results

From the BC Retinal Disease Database that we used in our study, a total of 13,124 subjects were newly diagnosed with nAMD. Rates of PD before initiating injection and rates of new PD after the diagnosis of nAMD (one-year period after the 300 days lag period) were calculated to see how many of the nAMD patients were diagnosed with PD before and after the diagnosis of nAMD. PD was ascertained by linking the nAMD patients to the MSP database. There were 110 cases of PD prior to the diagnosis of nAMD for a rate of 1.42 cases per 100,000 person-years. This is in contrast to the 24 new cases of PD (accounting for a 300-day latency period) that were diagnosed after the diagnosis of nAMD, translating to a rate of 2.8 cases per 100,000 person-years. The two rates yielded a rate ratio of 2.03 (95% CI; 1.31–3.16).

Discussion

The results we obtained from our study are consistent with that by Chung et al. in which patients newly diagnosed with nAMD had a higher risk of developing PD. The major difference in our study to their study however is the added advantage of controlling for PD latency.

The underlying pathological mechanism between PD and nAMD is still unclear, although it is widely recognized that depletion of dopamine levels in the basal ganglia and the retina result in clinical manifestations of motor and visual symptoms respectively. Recent studies have also suggested other possibilities, including a potential genetic association between the degeneration of the retinal pigmented epithelium (RPE) and PD. In that study, mice with ablation of the Ran-binding Protein 2 (Ranbp2) in the RPE experienced RPE degeneration and secondary leakage of choriocapillaris, similar to the clinical features seen in nAMD. One-third of those mice eventually developed Parkinsonian tremors. Similarly, another study found that toxic accumulation of iron, which is known to play a role in PD, was two-folds higher among patients with AMD compared to that of controls. Patients with AMD also have a notably thinner retinal nerve fiber layer (RNFL), and various studies using optical coherence tomography (OCT) have found a significantly reduced RNFL thickness in patients with PD as well. Specifically, it has been found that PD patients with a longer duration of the disease had a greater thinning of the inner retinal layers, including the RNFL, ganglion cell layer (GCL) and inner plexiform layer (IPL). The same study also found that the thickness of the GCL was predictive of axonal damage in PD, noting an inverse relationship between the thickness of the GCL and the severity and duration of PD. The objectivity of OCT measurements has also led another group to derive a formula that can give a near approximation of the Unified Parkinson's Disease Rating Scale (UPDRS) score based on the duration of the disease and the average thickness of the peripapillary RNFL, thereby allowing for early diagnosis and prediction of the severity of PD. Altogether, it is believed that
the visual deficits (i.e., reduced contrast sensitivity and color vision) among PD patients are due to loss of retinal dopaminergic amacrine cells and damage to the ganglion cell axons as a consequence of the neurodegenerative process in PD.\(^\text{18}\)

The establishment of an association between nAMD and PD may allow for an earlier diagnosis of PD, and therefore earlier therapeutic interventions to slow down the neurodegeneration process. The strengths in our study include having a sufficiently large sample size to generate a meaningful statistical analysis in understanding the link between nAMD and PD, and allowing for a lag period to control for PD latency. One limitation of our findings is that we did not have data on other risk factors such as smoking or family history in our study. Future studies are needed to validate these data and to examine the risk of PD in relation to the duration of nAMD.

In conclusion, the implications of our study suggest that nAMD may be a predictive factor for the onset of PD. However, more research is needed to elucidate the pathomechanism between neovascular AMD and PD, and to verify whether there is in fact a causal relationship between the two pathologies.

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**References**

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Global Health*. 2017;5(12):e1221–e1234.

2. Chung S, Ho J, Hu C, Lin H, Sheu J. Increased risk of Parkinson disease following a diagnosis of neovascular age-related macular degeneration: a retrospective cohort study. *Am J Ophthalmol*. 2014;157(2):464–469, e1.

3. Kalia LV, Lang AE. Parkinson’s disease. *Lancet*. 2015;386(9996):896–912.

4. Khoo TK, Yarnall AJ, Duncan GW, et al. The spectrum of nonmotor symptoms in early Parkinson disease. *Neurology*. 2013;80(3):276–281.

5. Mahlknecht P, Seppi K, Poewe W. The concept of prodromal Parkinson’s disease. *J Parkinson’s Dis*. 2015;5(4):681–697.

6. Maberley DAL, Zhang R, Ding L, Flatt AH, Emtinan M, Hewitt M. One-year effectiveness study of intravitreous bevacizumab in neovascular age-related macular degeneration: a population-based retrospective cohort study. *Can J Ophthalmol*. 2018 [In press] https://doi.org/10.1016/j.jcjo.2018.01.013.

7. British Columbia Ministry of Health & nbsp; british columbia ministry of health. *Medical Services Plan (MSP) Payment Information File*; 2012. Available from: Ministry of Health Web site http://www.health.gov.bc.ca/data/. Updated 2012. Accessed 2 November 2015.

8. Etemin M, Maberley DA, Babik DW, Carleton BC. Risk of myocardial infarction and stroke with single or repeated doses of intravitreal bevacizumab in age-related macular degeneration. *Am J Ophthalmol*. 2016;163:53–58.

9. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson’s disease in primary care: a case-control study. *Lancet Neurol*. 2015;14(1):57–64.

10. Harnois C, Di Paolo T. Decreased dopamine in the retinas of patients with Parkinson’s disease. *Invest Ophthalmol Vis Sci*. 1990;31(11):2473–2475.

11. Patil H, Saha A, Senda E, et al. Selective impairment of a subset of ran-GTP-binding domains of ran-binding protein 2 (Ranbp2) suffices to recapitulate the degeneration of the retinal pigment epithelium (RPE) triggered by Ranhps2 ablation. *J Biol Chem*. 2014;289(43):29767–29789.

12. Aydin TS, Umit D, Nur OM, et al. Optical coherence tomography findings in Parkinson’s disease. *Kaohsiung J Med Sci*. 2018;34(3):166–171.

13. Lee EK, Yu HG. Ganglion Cell Innerplexiform layer and peripapillary retinal nerve fiber layer thicknesses in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2015;56(6):3976–3983.

14. Garcia-Martin E, Larrosa JM, Polo V, et al. Distribution of retinal layer atrophy in patients with Parkinson disease and association with disease severity and duration. *Am J Ophthalmol*. 2014;157(2):470–478, e2.

15. Satue M, Rodrigo MJ, Obis J, et al. Evaluation of progressive visual dysfunction and retinal degeneration in patients with Parkinson’s disease. *Invest Ophthalmol Vis Sci*. 2017;58(2):1151–1157.

16. Satue M, Serai M, Otin S, et al. Retinal thinning and correlation with functional disability in patients with Parkinson's disease. *Br J Ophthalmol*. 2014;98(3):350–355.

17. Jiménez B, Ascaso FJ, Cristóbal JA, López del Val J. Development of a prediction formula of Parkinson disease severity by optical coherence tomography. *Mov Disord*. 2013;28(1):68–74.

18. Obis J, Satue M, Alarcía R, Pablo LE, Garcia-Martin E. Update on visual function and choroidal–retinal thickness alterations in Parkinson’s disease. *Arch Soc Esp Ophtalmol*. 2018 May;93(5):231–238 [Article in English, Spanish].