

Variations in the patterns of prevalence and therapy in Australasian Parkinson's disease patients of different ethnicities

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease in the elderly after Alzheimer's disease. It is expected that PD cumulative incidence will increase in the future, as there are far more people surviving into late age than there ever used to be. While most commonly idiopathic, rare forms of PD can be familial/genetic. In addition, socioeconomic, cultural and genetic factors may influence the way in which anti-parkinsonian medications are prescribed, and how patients respond to them. This review aims to highlight the potential impact of genetic variation on the epidemiology and therapeutics of PD, focusing on data from New Zealand and Australia.

INTRODUCTION

Parkinson's disease (PD) is a degenerative disorder that primarily affects the nervous system. While the pathophysiology underlying idiopathic PD has long been elusive to pinpoint, mounting evidence is implicating neuroinflammation as a central, although not exclusive, precipitating and perpetuating culprit.¹ PD is the second most common neurodegenerative disease in the elderly after Alzheimer's disease.² Since PD is an age-related disorder, it is expected that PD cumulative incidence will increase in the future, as there are far more people surviving into late age than there ever used to be. The increase may not be continuous, however, as PD incidence appears to decline in persons surviving past 85 years of age.³ The present review aims to highlight the impact of genetic variation on the epidemiology and therapeutics of PD, focusing on data from New Zealand and Australia.

ETHNIC VARIATION IN PD EPIDEMIOLOGY

General remarks

PD is often quoted to have a global prevalence rate of 0.3%, although this figure increases substantially when populations are age-stratified.⁴ For example, the prevalence of PD may reach 1.9% (1903 per 100 000) of persons 80 years and older, while persons under 40 years of age represent only 5% to

10% of all PD patients.⁴ Among all neurological disorders, PD is the only one to have exhibited increased age-standardised prevalence between 1990 and 2015.⁴

As evident from the literature, prevalence rates can vary considerably according to, for example, the diagnostic criteria used in a particular study or the methodology of screening.⁵ In addition, it is likely due to ethnic and sociodemographic differences and time since publication, reported prevalence rates of PD vary widely in the published literature.⁶

PD in Māori and New Zealand Europeans

Recent studies have shed some light on the prevalence and incidence of PD in New Zealand.^{3 7} Using national health data sets, the total adult population of the country was studied, with case identification through the use of anti-parkinsonian medications, and diagnostic information gained from both national and local databases. The 2013 age-standardised and sex-standardised incidence was estimated to be 31 per 100 000 person-years, and the age-standardised and sex-standardised prevalence to be 210 per 100 000 people.³

Given that New Zealand is a multicultural society, PD within the major ethnic groups represented in the population (New Zealand European, Māori, Pasifika (Polynesian) and Asian) was also assessed.⁷ Māori—the indigenous people of New Zealand—had substantially lower age-standardised and sex-standardised incidence and prevalence rates compared with New Zealand Europeans. The incidence of PD in Māori was 20 per 100 000 per year (compared with 33 in New Zealand Europeans), and PD prevalence was 114 per 100 000 in Māori (compared with 223 in New Zealand Europeans).⁷

The underlying causes of such a low incidence in Māori are unknown, but a number of factors may be contributing. Such potential factors include inequitable access to healthcare, differential treatment within the healthcare system



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once it is accessed, differing rates of both potentially protective and risk-increasing lifestyle and co-morbidity factors and possible genetic differences among ethnic groups. Furthermore, one ought to be cognisant of potential methodological flaws in studies reporting PD incidence in Māori based on surrogate markers. For example, a study that estimates PD prevalence among Māori from drug prescription data may overlook Māori patients with PD who do not take medications or never fill their prescriptions.

Māori are known to face a number of health disparities in terms of access to and treatment within the healthcare system.⁸ There are no data specific to neurological disorders, but there is no reason to suspect that healthcare services encountered by people with PD, or neurological disorders in general, are achieving greater engagement with Māori compared with services for other conditions.

Māori are known to have comparatively high rates of smoking⁹ and hyperuricaemia,¹⁰ both of which have often been shown to be associated with lower rates of PD.^{11 12} Māori are also known to have high rates of hypertension.¹³ Hypertension can be treated with calcium channel blockers, which have the potential to protect against the development of PD,¹⁴ although a recent phase III clinical trial did not show isradipine (a calcium-channel blocker) to slow the progression of the disease.¹⁵

Māori also have high rates of type 2 diabetes which has been associated with an increased risk of PD in prospective population studies,¹⁶ but not case-control studies.¹⁷ Glitazones¹⁸ and dipeptidyl peptidase-4 inhibitors¹⁹ used as a treatment of type 2 diabetes have been associated with reduced risk of PD. Another treatment for type 2 diabetes, metformin, may also be offering some protection from PD. Animal studies have indicated that metformin is capable of preventing dopamine neuron death in rodent models of the disease,^{20 21} although population level have had mixed results.^{16 22} Although these same factors (ie, hyperuricaemia, hypertension and type 2 diabetes) also hold true for the Pasifika group, Māori were found to have lower incidence and prevalence compared with Pasifika.⁷

No data are available on the expression of potential PD genetic risk factors within the Māori population, but it is possible that differential expression of risk alleles across ethnic groups could be present, as this has been shown for alleles associated with multiple sclerosis.²³ As a population, Māori also have a substantially lower incidence of multiple sclerosis and motor neuron disease compared with New Zealand Europeans.²⁴

PD in other ethnic groups in New Zealand

The incidence and prevalence of PD in the Asian and Pasifika groups in New Zealand were intermediate between rates in Māori and New Zealand Europeans (Asian: incidence 28, prevalence 174; Pasifika: incidence 27, prevalence 160).⁷ The lower incidence and prevalence in the Asian group compared with the New Zealand Europeans follow international literature, where Asian populations have generally been shown to develop PD at rates lower than populations of Caucasian/European

descent.^{25 26} Although often these comparisons have been made across studies conducted in different countries, and using different methodology, a similar pattern has been evident when comparing ethnic groups within the American population.^{4 27}

PD in Australia

The most recent nationwide estimate of PD in Australia is from a Deloitte report on the economic cost of the disease.²⁸ This report used prescription data and estimated a prevalence of 294 per 100 000 population as at 2014. The report did not, however, consider individual ethnic groups represented within the Australian population.

There is growing recognition that more detailed Australian-specific data are required and that special consideration should be given to obtaining estimates for the indigenous Aboriginal and Torres Strait Islander populations of Australia.²⁹ The best indication of PD in those indigenous groups comes from a burden-of-disease-and-injury report, specifically targeted at these populations, in the state of Queensland.³⁰ This report indicated that PD is ranked as the 10th leading cause of non-fatal burden of disease or injury for indigenous groups aged 60–74 years (contributing to 2.3% of total burden) and ≥75 years (contributing to 3.1%). This is compared with PD being the 6th leading cause of non-fatal burden in the non-indigenous population for the group aged 60–74 years (contributing to 4%), and the 10th leading cause in the group aged ≥75 years (contributing to 3.7%).³⁰ Although burden of disease and prevalence are not synonymous, one might infer from this report that Australian indigenous populations also experience PD at lower rates than the non-indigenous population.

PD outside Australasia

In the 2015 GBD study on burden of neurological disorders,³¹ the prevalence of PD was found to be the lowest in sub-Saharan Africa and Eastern Europe. Similarly, lower prevalence of PD has been reported among Asian and Latin American populations.³¹ Although the limited life expectancy may have played a factor, it is unlikely to fully explain the discrepant prevalence. In a recent review of PD prevalence among Arabs,³² the reported rates were found to vary widely (from 27 to 557.4 cases per 100 000 people). Arab families generally tend to be large units with a high rate of consanguineous marriages, thereby increasing the risk of genetic and familial disorders, including genetic forms of PD.³²

ETHNIC VARIATION IN PD THERAPY

Use of anti-parkinsonian medications among various ethnic groups

Accurate assessment of racial and ethnic differences in PD management is hampered by a multitude of factors. These may be grouped into prediagnosis factors (eg, differences in PD prevalence), postdiagnosis factors (eg, choice of medication and lower access to specialist neurologists) and treatment-related factors (eg, ethnicity-specific

response to medications and lower recruitment into clinical trials).

Factors that may influence racial differences in treatment prior to PD diagnosis include the observed variation in disease incidence and prevalence among the various ethnic groups. For example, the use of anti-parkinsonian medications has been found to be lower in PD patients of African-American descent compared with white Americans. The authors attributed such discrepancy to the possible lower prevalence of PD in African Americans.³³

Once a diagnosis of PD is established, other factors may come into play which contribute to ethnic variations in PD therapy. Racial disparities in healthcare access (including access to specialist neurologists) may influence the type of treatment, patient adherence to management plans, as well as referrals for more advanced treatment options (eg, deep brain stimulation).³⁴ How cultural beliefs vis-à-vis advanced and potentially invasive PD therapies among indigenous populations influence access to such treatments is yet to be determined.

Moreover, the choice and dosing of anti-parkinsonian medications were shown to vary by the patient's ethnicity. Within the analyses by Myall *et al*³ and Pitcher *et al*,⁷ it was noted that many of the Māori cases, identified by receiving anti-parkinsonian medications, were ultimately classified as having a low probability of PD. This was due to anticholinergics being the sole anti-parkinsonian medication prescribed to these people. For most of these people, only mental health diagnoses, rather than neurological ones, were identified.⁷

Māori who were assigned a high probability of PD tended to start on higher-than-usual doses of medication (unpublished observations). Whether this reflects a more rapid progression of the disease in Māori or that they are diagnosed later in the disease process (potentially related to access to, and treatment within, the healthcare system) remains unclear.

Finally, treatment-related factors may exacerbate observed differences in treatment among PD patients of different ethnicities. Lower health literacy in disadvantaged racial groups often translates to suboptimal management of chronic conditions, including PD.³⁴ Furthermore, fewer patients from these disadvantaged racial groups tend to be recruited into clinical trials.³⁴

Expert opinion: does the efficacy of anti-parkinsonian medications vary among different ethnicities?

There is no published information regarding efficacy of anti-parkinsonian therapies stratified by ethnicity in Australasia. Indeed, only scant such literature relating to ethnicity in other world regions exists. In a study of pramipexole treatment in PD, there was no significant difference in efficacy by race or ethnicity.³⁵ Although one might expect such variations, not only in efficacy, but also in adverse effects—because of genetic (including epigenetic) or socioeconomic factors—very little is known about this. The concept of variations in drug responsiveness relating to ethnicity has been controversial. In 2001, a

study published in the *New England Journal of Medicine* suggested that enalapril was more effective in white than black American patients, at least in preventing hospitalisation.³⁶ The publication, in turn, led to some practitioners in the USA not to prescribe ACE inhibitors to black Americans.³⁷

Response to medications may be affected by polymorphisms in genes influencing drug metabolism, and polymorphism frequency can vary among populations with different ancestries. Although this factor might suggest that differences in response to medications, including anti-parkinsonian drugs, could be ascribed to genetic differences among ethnic groups, there are many other explanations, including the influence of lifestyle, socioeconomic status and general health.³⁸ There are no data to date that examine the prevalence and/or effect of genetic polymorphisms among Australasian indigenous populations in the magnitude of response to anti-parkinsonian medications (eg, Val158Met COMT polymorphism) or probability of developing side effects (eg, impulse-control disorders in response to dopamine replacement therapies).

It also needs to be recognised that with increasing diversity of populations in Australasia, allelic frequency will vary considerably within each ethnic group. While it is true that, overall, there may be some differences in genetic influences on anti-parkinsonian drug response among ethnic populations in both Australia and New Zealand, there will be much overlap, and such differences will almost certainly be very small. As genes that contribute to anti-parkinsonian drugs response are increasingly identified, clinicians will be better informed to take genotype—and certainly not ethnicity or racial group—into account when prescribing one medical class over another.³⁹

CONCLUSIONS

The prevalence of PD is likely to increase with the ageing population, although affecting patients of various ethnicities differently. Accurate assessment of the response to PD medications among patients of different ethnic backgrounds is stifled by a range of factors, including the general lack of studies in the area. While some of the ethnic differences are unavoidable (eg, genetic predilections), other discrepancies ought to be addressed and rectified (eg, equitable access to timely diagnosis, treatment options and community supports). Finally, as finer clinical tools (eg, genetic markers and panels) are made available, personalised (cf. ethnic) medicine will be the way forward.

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