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Research Article

Dripping Down in Japanese Age-Specific Mortality of Parkinson's Disease in the Super Elderly

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Abstract

Parkinson's disease (PD) is one of the most common neurodegenerative diseases and is becoming a significant cause of death as life expectancy increases in Japan. While most of major causes of death increase nearly exponentially with age, the age-mortality curve of PD drips down in the super elderly. To explain this phenomenon, a simple model in which two sub-populations, one prone to PD and the other not, mixed in the entire population was considered. Assuming exponential age-mortality dependency of PD in the PD susceptible subpopulation, rough estimation of the proportion of PD-susceptible in the whole population was calculated about 1.12%. Estimated separately for men and women, PD susceptible subpopulations were 1.32% and 0.92%, respectively. There was no significant gender difference in the age-mortality dependency of PD between male and female PD susceptible subpopulations.

Keywords: *Parkinson's Disease; Alzheimer's Disease; Super Elderly; Lewy Body Dementia*

Introduction

Parkinson's disease (PD), like Alzheimer's disease (AD), is one of the most common neurodegenerative diseases that mainly occur in the elderly [1]. AD and PD were ranked 9th and 12th cause of death in Japan in 2019, respectively [2]. In terms of mortality, PD is more common in men, while AD is more common in women. The most notable difference, however, is that, while the death rate of AD continues to increase with age, the death rate of PD begins to decline in the super-elderly [3] (See figure 1). To explain this dripping down of the PD mortality in the super-elderly, we assumed a simple model, in which there are two subpopulations within the whole population, one is susceptible to PD and the other is not and have tried to roughly estimate the proportion of PD susceptible subpopulation.

Materials and Methods

The life table and death rates by sex, age group in 2019 in Japan were obtained from the Japanese government portal site E-Stat [2].

Assumptions

We assumed that the dripping down of the age-specific mortality of PD was due to the different susceptibility to PD among the population subgroups. As a simple model, we divided the entire population into two subpopulations: one (SPD) is prone to PD with a simple exponentially increase in the age-specific PD mortality rate, and the other (NSPD) is completely free from the risk of PD. With the exception of death of PD, SPD and NSPD were assumed to have the same age-specific mortality rate. What is unknown is the initial fraction of SPD in the entire population and the parameters of the age-specific PD mortality curve in the SPD. In this study, the shape of the age-specific PD mortality curve was assumed as the exponential function $Exp((t-d)/\tau)$, where t is age, d is the parameter indicating delay to reach the same mortality rate and τ is time constant for the rate of increase in mortality. d and τ, together with the initial SPD fraction a, are parameters to be determined.

Estimation procedure

KyPlot 6.0 (KyensLab, Japan) [4,5] was used for the data processing, model calculations and determination of the parameters by the least squares method.

The age-specific mortality rate of PD in 5-year increments was converted to 1-year increments using Kyplot.

The values of the parameters were determined by adjusting model predicted deaths using generalized least squares method to deaths of PD by age on the stationary population from 2019 life table.

Model considered is as below.

As mutual relations among parameters:

$p_{SPD}(t)=p_{NSPD}(t)+p_{PD}(t)$

$p(t) = P_{NSPD}(t)\star p_{NSPD}(t)+P_{SPD}(t)\star p_{SPD}(t)=p_{NSPD}(t)=P_{SPD}(t)\star p_{PD}(t)$

$P_{SPD}(t) = S_{SPD}(t)/ S(t)$

$P_{NSPD}(t) = S_{NSPD}(t)/ S(t)$

$S(t)= S_{SPD}(t)+S_{NSPD}(t)$

$P_{SPD}(t) = S_{SPD}(t)/ S(t)$

$P_{NSPD}(t) = S_{NSPD}(t)/ S(t)$

As time evolution formulae,

$S_{SPD}(t)=- S_{SPD}(t)* p_{SPD}(t)$

$S_{NSPD}(t)=- S_{NSPD}(t)* p_{NSPD}(t)$

Where, S(t): number of survivors at age t

$S_{SPD}(t)$: number of SPD survivors at age t

$S_{NSPD}(t)$: number of NSPD survivors at age t

$P_{SPD}(t)$: proportion of SPD at age t

$P_{NSPD}(t)=1-P_{SPD}(t)$: proportion of NSPD at age t

p(t): mortality rate of deaths at age t

p_{NSPD} (t): mortality rate of deaths in NSPD at age t

p_{PD} (t): mortality rate of PD in SPD at age t

$p_{SPD}(t)$: mortality rate of deaths in SPD at age t

As initial conditions,

S(0) = 100000: initial population

$P_{SPD}(0) = a$: initial proportion of PD susceptible subpopulation

By adopting the mortality rate of the 2019 vital statistics as p (t),

and p_{PD} (t) was assumed as $Exp((t-d)/\tau)$.

a, d and τ were to be determined by the least squares method.

The differential equation was converted to a difference equation in 0.1 year increments and calculated.

Model predicting number of deaths of PD in the age range of 75 - 90 years were adjusted to the number of deaths of PD on stationary population of 2019 using the least squares method and values of parameters were determined.

Results

Figure 1 shows age specific mortality rate of PD compared with that of AD in 2019. While mortality of AD rapidly increased with age, mortality of PD dripped down in the super elderly. Peak of mortality rate of PD was 0.108% at 88 years old in male and 0.076% at 91 years old in female. As shown in figure 2, in the entire population, only less than 0.8% people died of PD in the stationary population, both in male and in female.

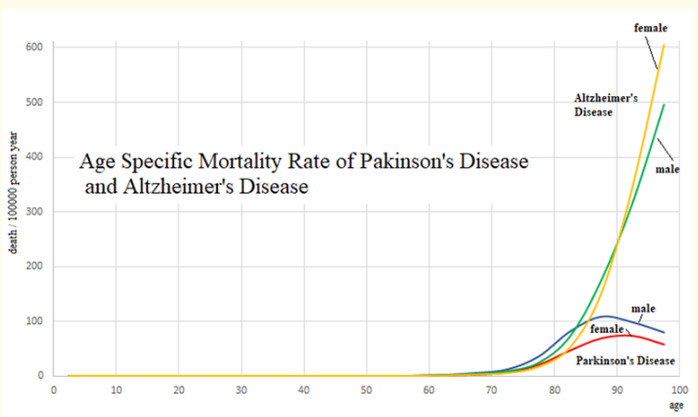

Figure 1: *Age specific mortality rate of PD and AD.*

Age specific mortality of PD and AD obtained from 2019 vital statistics of Japan were compared. The most prominent difference was monotonic increase of AD mortality with age and dripping down of PD mortality in the super elderly.

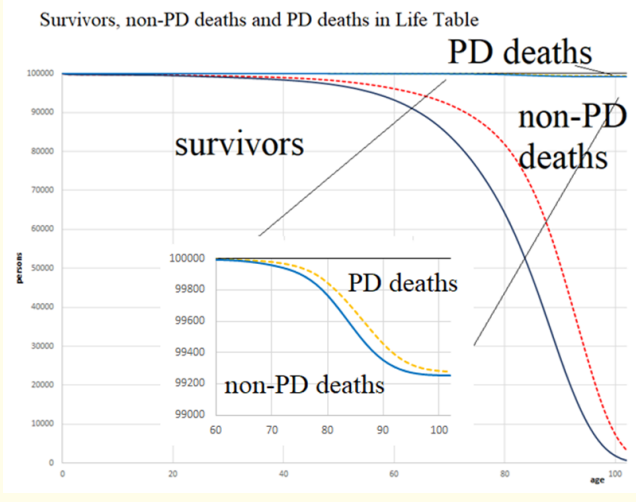

Figure 2: *Relationship between the number of survivors and the number of non-PD deaths and PD deaths with age.*
Above the survivorship curves of male (dark blue line) and female (red dashed line), the cumulative number of deaths other than PD and of PD are shown separated by light blue line (male) and yellow dashed line (female).
The inset is the vertically enlarged part that shows boundary between non-PD deaths and PD deaths over 60 years.

The model calculation was executed and the solutions obtained by the least squares method were $P_{SPD}(0) = 0.0132$ d = 94.6, $\tau = 4.96$ in male, and $P_{SPD}(0) = 0.0092$, d = 96.5, $\tau = 5.19$ in female.

Figure 3 shows the age - number of death curve of PD on the 2019 stationary population and model-calculated fit curve. In the model calculations, the climb is a little slower, the peak is a little too high and most importantly, the descent is too fast compared to the actual ones, both in men and women.

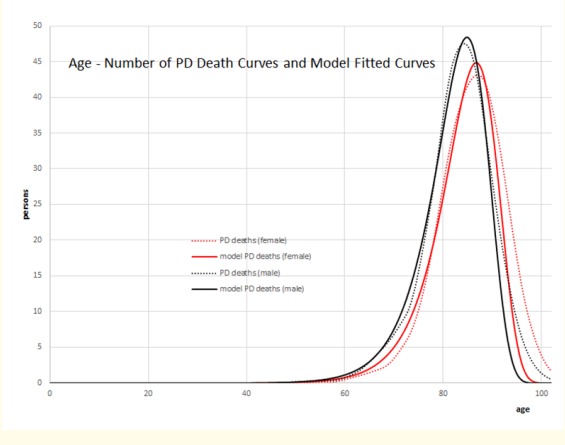

Figure 3: *Age - number of PD death curve on the 2019 stationary population and model-calculated fit curve.*
model-calculated curves were fitted to the male and female number of PD deaths on the stationary population using least squares method between age of 75 and 90 years.

As is shown in figure 4, in the assumed PD susceptible subpopulation, 53.3% of male and 70.6% of female died of PD, making expected life span 4.0 years in male and 5.6 years in female shorter than the entire population.

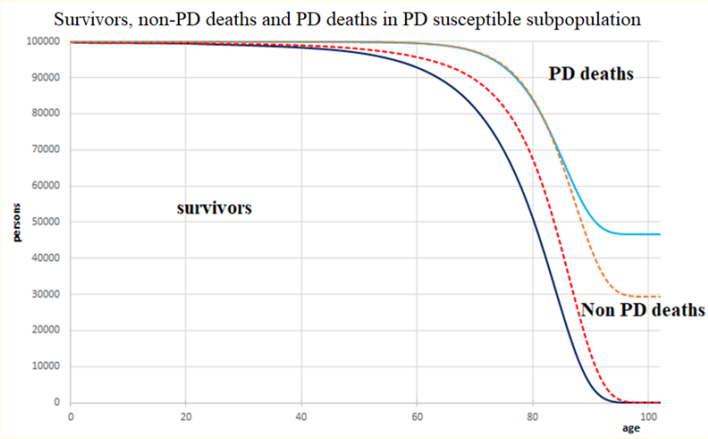

Figure 4: *Relationship between the survivors and the non-PD deaths and PD deaths with age in PD susceptible subpopulation. Dark blue line (male) and red dashed line (female) shows survivorship curves. Light blue line (male) and yellow dashed line (female) shows boundary between non-PD deaths and PD deaths.*

Model estimated cumulative PD deaths exceed 50% in male and about 70% in female in PD susceptible subpopulation (SPD). The survivorship curve in the SPD, therefore, fell after 70 years old faster than that of entire population and estimated life expectancy was shorten 4.0 years in male and 6.2 years in female.

Discussion

In developed countries, the leading cause of death shifts from lifestyle-related diseases that increase after middle age, including metabolic syndrome, to frailty syndrome caused by aging, which progresses rapidly causing death in the elderly [6]. Among these, PD has attracted attention as a typical neurodegenerative disease that develops in old age, deteriorates quality of life and causes death, and although the exact mechanism of the cause has not yet been elucidated, the various effects of heredity, environment and lifestyle have been known [7-9]. The view that the synergistic work of innate genetic factors and acquired environmental and lifestyle factors is important for the onset of Parkinson's disease is becoming influential [10,11]. It has also been suggested that an autoimmune mechanism is involved in the development of Parkinson's disease and a common genetic predisposition between autoimmune disease and Parkinson's disease is being explored [12,13].

The cause of death of the elderly is mostly linked to the aging phenomenon and it seems natural that the mortality rate increases with age. Therefore, it seems necessary to explain why the mortality rate of PD does not simply increase with age. Our model is simple, but sufficient to explain the phenomenon in a first approximation. Unsurprisingly, however, there were some inconsistency. As seen in figure 3, the descending part on the elderly side of actual deaths is gentler than the model. This disagreement may just because the increase of PD mortality in SPD deviates from simple exponential growth and increases more slowly in the very old age, as predicted by the mutation-accumulation theory [9]. The other possible explanation is that the subpopulation NSPD is not completely free of PD but has a low but residual PD mortality rate and contributes to the number of PD deaths in the super-elderly. The prevalence [3,7] and incidence [7] of PD also have been reported to show dripping down in elderly about 10 years earlier than the PD mortality.

Though our assumption is, of course, too simple, and without a solid basis, it can at least explain the dripping down in the super elderly. In more general situation, population can be separated into three or more sub populations according to difference in susceptibility to Parkinson's disease, or even to give a parameter as a probabilistic variable which determine susceptibility of each individual. However, what we wanted to reveal is that the considerable difference of susceptibility can cause a dripping down of age-specific mortality rate at the higher-age with a simple model. It is, of cause, other possibility of the dripping down. One important possibility is that among the Lewy body diseases, super-elders tend develop Lewy body dementia (LBD) [14] rather than PD and die of LBD, reducing apparent mortality rate of PD in super elder.

Conclusion

This study is a qualitative analysis rather than a quantitative one, although numerical values appear as rough estimate. As the conclusion, the decline in the age mortality curve of PD can be explained by assuming the existence of subpopulation that are prone to PD and dying early in that population. In the PD susceptible subpopulation, the mortality rate of PD may be quite high, significantly shortening life expectancy, so that early detection of susceptible person and intervention by prevention and treatment should be important.

Conflict of Interest

The authors have no conflicts of interest to declare.

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