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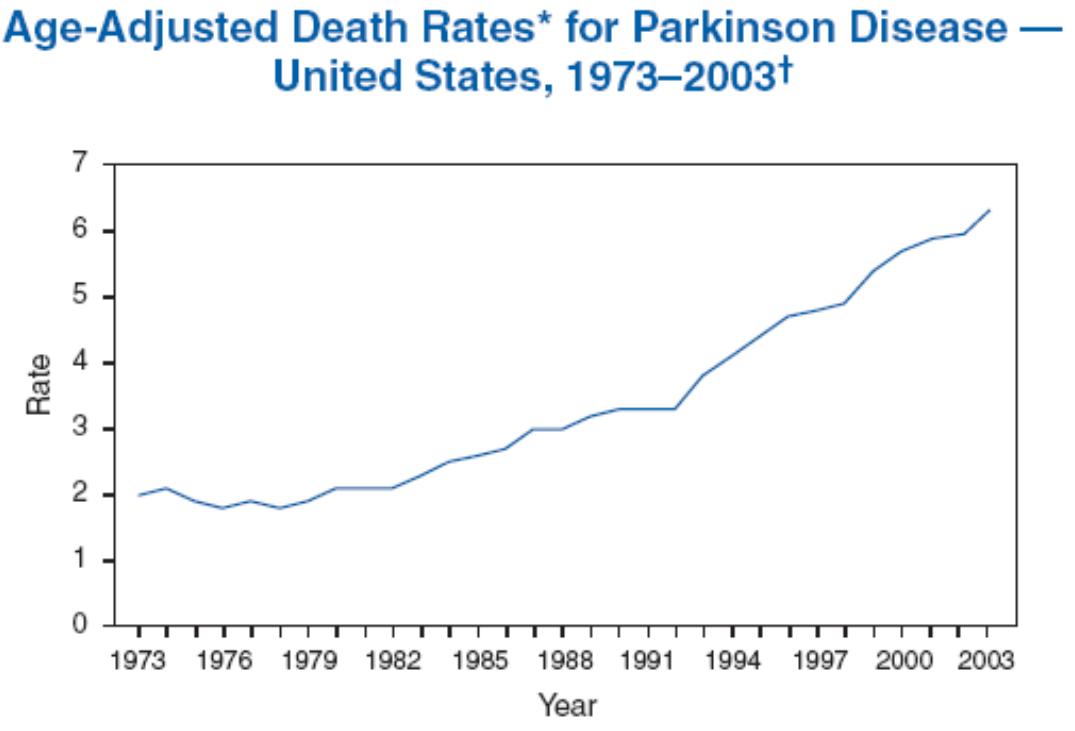
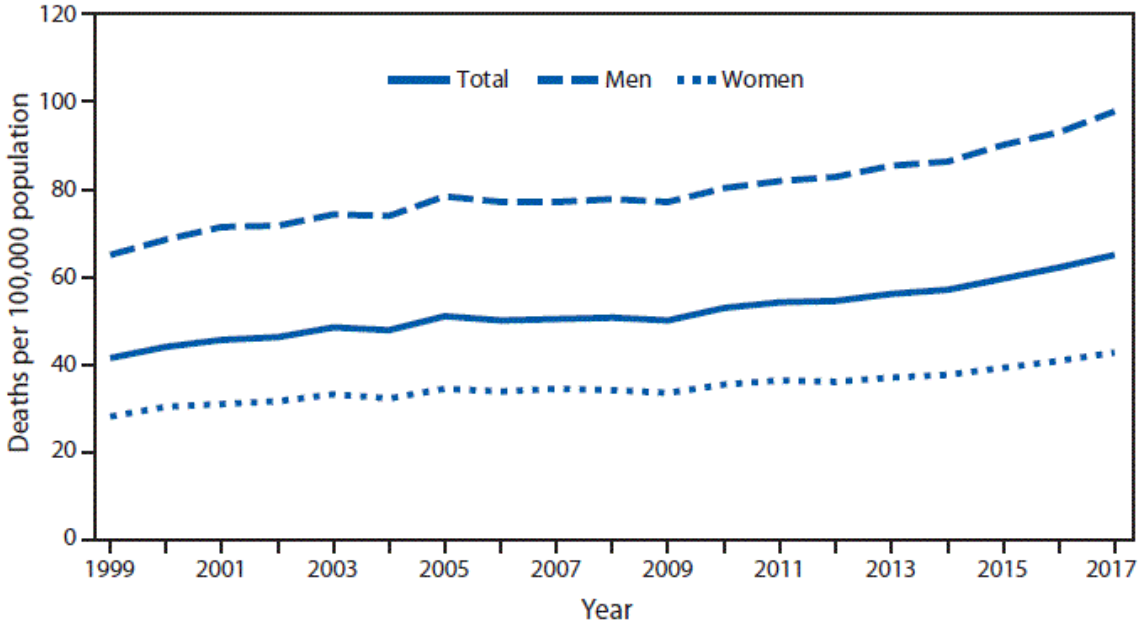
The Effectiveness of Early Biomarkers and Varying Diagnosing Methods in Indicating Parkinson's Disease

Introduction

One of the most prominent neurodegenerative diseases today is Parkinson's disease. Parkinson's disease (PD) is a neurodegenerative disorder featuring progressive loss of midbrain dopaminergic (DA) neurons that leads to motor symptoms. Parkinson's disease is an age-related neurodegenerative disorder with increasing prevalence, disability, and deaths worldwide due to the rise of the aging population (Beck 1). Approximately 60,000 Americans are diagnosed with PD each year. From 1999 to 2017, age-adjusted death rates for Parkinson's disease among adults aged ≥65 years increased from 41.7 to 65.3 per 100,000 population. Moreover, the estimated total economic burden of PD in 2017 was $51.9 billion, including a direct medical cost of $25.4 billion and an additional $26.5 billion in indirect and non-medical costs (Han 1).



(Han 1)



(Han 1)

Additionally, the death rate for Parkinson's disease patients is depicted above, emphasizing the increase in cases as well as deaths of the disease in recent years. As a result, there is a continuous effort to slow down these deaths and manage the recovery of these patients.

Background

In recent years, there has been a focus on determining biomarkers that indicate the early onset of Parkinson's disease. Many studies look into potential biomarkers that could prove the state of progression of the disease such as if it is early-onset or late-onset. These include blood-based characteristics as well as the differential expression of miRNAs in patients (Liu 1).

In addition, there has been a focus on increasing the success rate of diagnosing Parkinson's disease as a whole as research of the specific genetic traits linked with the disease

has increased. For example, the use of electroencephalogram (EEG) signals has been looked at in order to diagnose the disease. While these studies are in their early stages and have to undergo revisions and further testing, they have prompted many other studies into Parkinson's disease regarding treatment options and methods to slow the disease down. Studies are being performed on PD patients to determine if there is any potential for these methods (Yuvaraj 1).

Proposition

As I research this topic, I plan to find and gather data on multiple research articles and studies that detail the methods in which Parkinson's disease can be diagnosed and potential early biomarkers/causes for the disease. I will research the properties of different causes and diagnosing methods that make them significant. Finally, with this data, I will be able to determine ways in which Parkinson's disease can be diagnosed earlier and more efficiently which in the long run may lead to a decrease in deaths. With the findings of my research, many patients may be able to get an earlier diagnosis and be treated earlier before later stages of the disease.

Procedure

1. Use online web-based research and peer-reviewed published studies in scientific journals
2. Compile a detailed study and analysis of the studies/articles
3. Formulate conclusions about the effectiveness of varying diagnosing methods from these studies

Research

The research that was conducted can be divided into two categories. The first category explores various biomarkers used to potentially indicate the existence of early-onset Parkinson's disease. The biomarkers in the research include blood-based characteristics, differential transcript usage in a genome, and the expression of circulating miRNAs in a patient (Posavi 1). Using a trial system these treatments were compared with a control on various patients to determine if they were viable biomarkers.

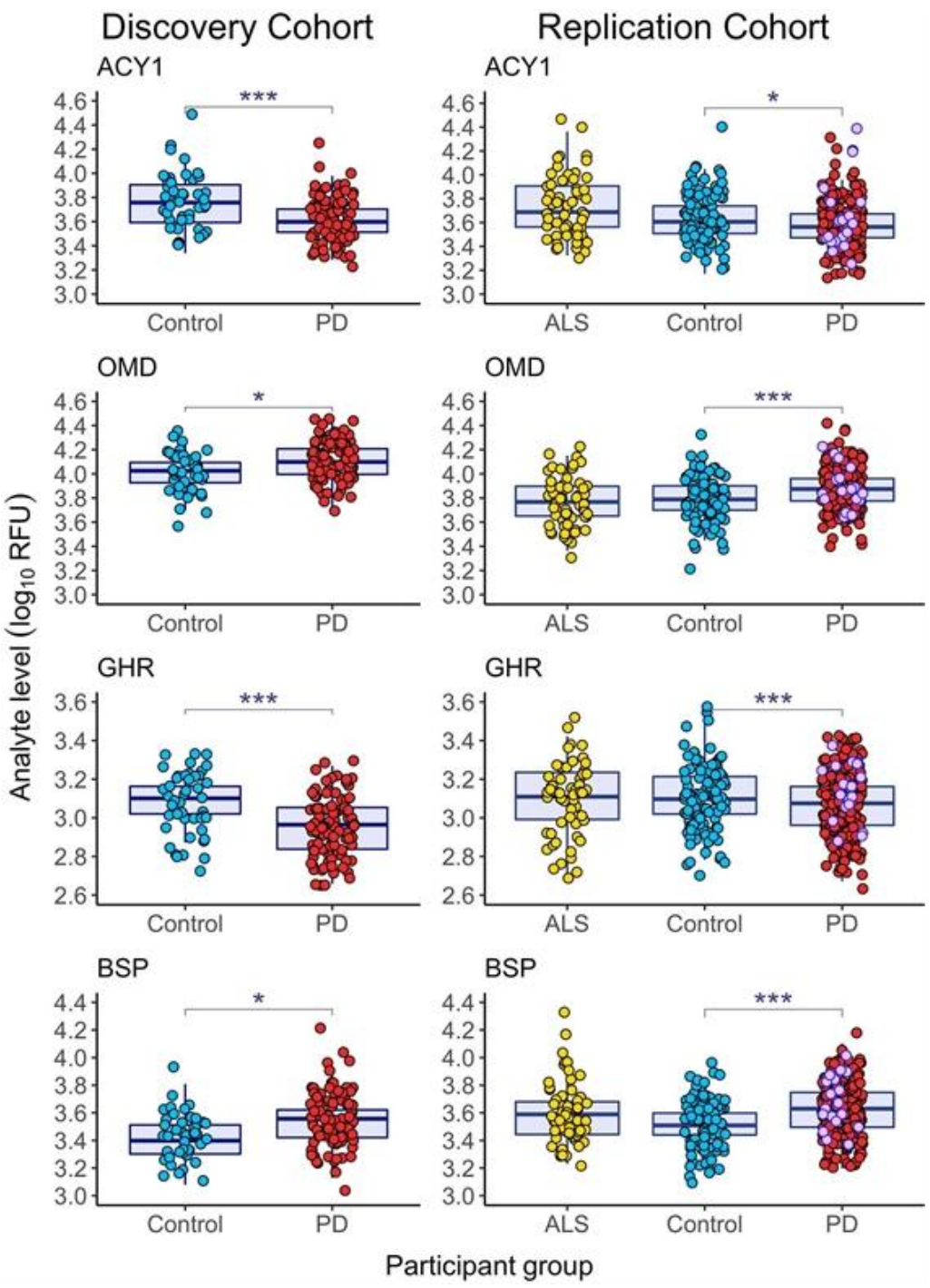
The second category of research looks into possible methods of diagnosis as well as the genetic factors that have an impact on the progression of the disease and its diagnosis. The research examined elevated COUP-TFII gene expression in dopaminergic neurons and its ability to progress the disease; electroencephalogram signals were also observed in order to determine its effectiveness at correctly diagnosing the disease (Kao 2).

Potential Biomarkers

The first potential biomarker looked at was a blood-based biomarker. A blood-based biomarker was used in order to provide a molecular characterization of individuals with PD for diagnostic confirmation and prediction of progression; if it yields results, the tests can diagnose as well as determine how late-onset the disease is in a patient. In the study, 141 plasma samples (96 Parkinson's disease patients, 45 neurologically normal individuals(control); 45.4% female, mean age 70 years) were used in which 1,129 proteins were examined using an aptamer-based platform. The protein plasma concentration was examined in relation to the respective

treatment group (Parkinson's disease versus control group), age at plasma collection, sex, and the levodopa(Parkinson's disease medicine) equivalent daily dose, in order to derive potential biomarkers that varied between the Parkinson's group and the control group. These candidate proteins were then ranked by Stability Selection. Of the top 10 proteins ranked by Stability Selection, four associations were recognized. These blood-based biomarkers were bone sialoprotein(BSP), osteomodulin(OMD), aminoacylase-1(ACY1), and growth hormone receptor(GHR). Plasma measures of OMD, ACY1, and GHR differed in PD versus the control group but did not differ between individuals with amyotrophic lateral sclerosis versus the control group. Individuals with baseline levels of GHR and ACY1 in the lowest percentile were more likely to progress to mild cognitive impairment (Liu 2).

The findings suggest that biomarkers based on a peripheral blood sample may be developed for both disease characterization and prediction of future disease progression in PD. No blood tests currently exist that distinguish people with Parkinson's disease from neurologically normal individuals or that predict the rate of disease progression in people who have already been diagnosed with PD (Posavi 2). Blood tests that distinguish people with PD would be helpful for confirmation of diagnosis, whereas blood tests that predict the rate of disease progression would be helpful for clinical trials and clinical care.



Blood-based biomarkers found in both Discovery and Replication Cohorts (Liu 1)

The second potential biomarker in the study was the varying expression of circulating miRNAs in a person's blood and its correspondence to Parkinson's disease. MicroRNA is a single-stranded non-coding small RNA capable of negatively regulating the mRNAs expression by binding to the 3'-untranslated region. Since miRNAs are stably expressed in circulating biofluids, their expression could be used as biomarkers in various stages of Parkinson's Disease development and clinical manifestation (Sulaiman 2).

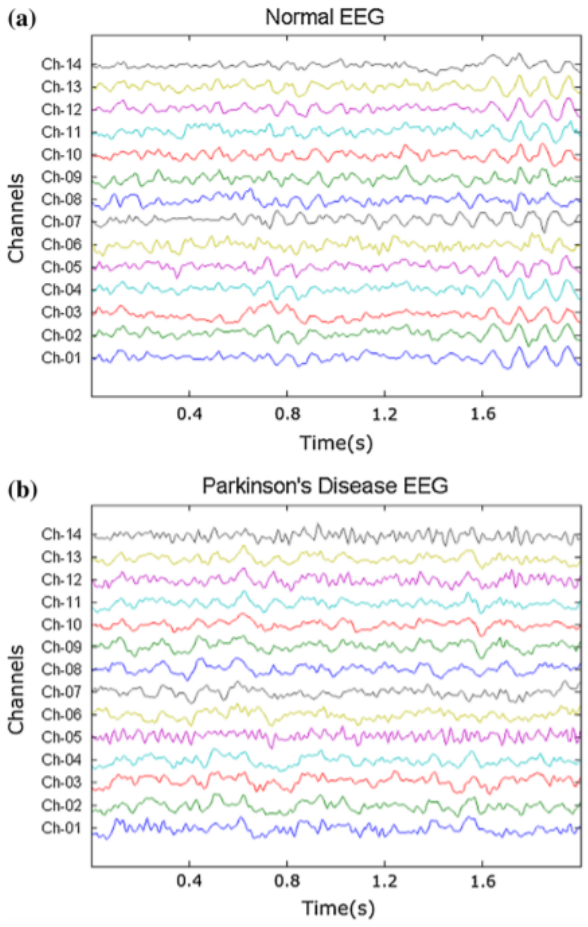
In order to test if miRNA is a biomarker in determining the chance to develop Parkinson's Disease, this study incorporated a total of 28 idiopathic Parkinson's Disease patients attending the neurology clinic at Hospital Chancellor Tunku Muhriz UKM. Following recruitment, PD patients were divided into two groups: EOPD if their age of onset was less than 50 years (14 participants) and LOPD if their age of onset was greater than 50 years (14 participants). Healthy patients, aged between 24 to 60 years with no symptoms or family history of neurodegenerative diseases or Parkinsonism were recruited as healthy controls (11 participants) and were stratified into two groups according to age. Those aged less than 50 years became early-onset controls (5 participants), while those aged greater than 50 years became late-onset controls (6 participants) (Sulaiman 3).

As a result of this study, it was found that the mean onset age for the early onset patients was 42.3 years, while the mean onset age of late-onset patients was at 61.4 years. There were no differences in gender, ethnicity, and disease distribution between the two groups. Comparison between Parkinson's Disease cases and healthy controls showed that among the 273 differentially expressed miRNAs, three miRNAs and their predicted target genes were associated with Parkinson's disease. Moreover, several AKT1 genetic variants have been

reported in PD patients. In Han Chinese PD patients, the variant rs2498799 was significantly associated with PD, as the G allele of rs2498799 was shown to decrease the risk of developing Parkinson's Disease (Sulaiman 4). This shows that there are multiple possible genetic factors that are in play with Parkinson's disease.

Diagnosing Methods

A varying approach to conventional diagnosing of Parkinson's disease is the use of electroencephalogram (EEG) signals. These signals are incorporated into an automated detection system for Parkinson's disease employing the convolutional neural network (CNN). The convolutional neural network is one of the most popular forms of deep learning that researchers adopted (Oh 2). It allows the learning of higher-level features without human intervention through training of the data, unlike most traditional machine learning algorithms. The basic layers of the CNN include the convolution, max-pooling, and fully connected layer. Typically, the network tends to learn better as the network gets deeper (Hagiwara 3). The EEG signals of 20 PD patients (10 women and 10 men) with an age range



(Oh 3)

between 45 and 65 years old were involved in the study. The proposed CNN model yielded an accuracy of 88.25%, sensitivity, and specificity of 84.71% and 91.77%, respectively. Based on these positive results, the presented model may be able to serve as a trusted and long-term tool to assist clinicians in PD diagnoses (Oh 6).

Conclusion

Parkinson's disease continues to have a significant impact on worldwide health. There is ongoing research to find more effective management and recovery options. The current diagnosing and treatment systems are beneficial to patients with later-onset stages of the disease, but it could be improved through the incorporation of treatments during earlier stages. Diagnosing PD is essential so that patients can receive the proper treatment and advice regarding care. In addition, diagnosing PD early is vital because treatments such as levodopa/carbidopa are more effective when administered early on in the disease. Through the research completed in this analysis, improvisations to both the diagnosing and treatment systems could be adopted to yield a more beneficial and earlier recovery process.

With the adoption of the new systems incorporated in these studies as well as future studies, there could be a dramatic improvement in the recovery and quality of life of patients with Parkinson's disease.

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