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Differentiating Between Parkinson's Disease Subtypes

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Abstract

Parkinson's disease (PD) is a terrible affliction without a known cure. It's a neurodegenerative disorder that causes death of neurons in the brain and eventual problems with motor and cognitive skills. The symptoms, however, can be treated, and in the process of said treatment, patients are often divided into subtypes based on their symptoms: tremor dominant (TD) or postural instability and gait difficulty (PIGD) based on the symptoms they have. Often this division can be criticized for not creating two true subtypes of PD, and it regularly becomes difficult for clinicians to distinguish what really sets these two groups apart. To help solve this problem, I investigated how exactly these two groups differ when it comes to gait, turning, cognition, and measures of the disease itself. The data found showed that TD and PIGD were quite different with respect to these measures, with PIGD patients, as hypothesized, having overwhelmingly worse motor and non-motor attributes than TD patients. This shows that these two groups truly are different subtypes of the disease, not just divided parts of a ratio.

Differentiating Between Parkinson's Disease Subtypes

Parkinson's disease (PD), a neurodegenerative condition mostly impacting neurons that produce dopamine, is a massive worldwide problem, affecting more than 10 million people worldwide (0.13% of the world's population) and promising to affect many more in the future. No cure currently exists, but treatment for the symptoms of PD is well-developed and is becoming increasingly effective. Medication, such as levodopa, is efficacious at improving quality of life for many patients. Rating scales, such as the commonly used UPDRS (Unified Parkinson's Disease Rating Scale), are very valuable tools that enable researchers and caregivers to effectively measure the progression of a patient's disease. However, much more work still remains in the development of treatment for symptoms of PD. Many different phenotypes of PD exist (Stebbins et al., 2013), and no singular treatment approach can be used for all patients.

That being said, the different manifestations of PD can, for the most part, be grouped into two different phenotypic subgroups, known as tremor dominant (TD) and postural instability/gait difficulty (PIGD) to help predict the disease's progression in a patient both in the short and long term. These groupings have been used in clinical research for quite some time. However, the complete differentiation of these two groups cognitively and in terms of gait has not been explored completely. In our research, we hope to see how patients in these subgroups really are different and how the differences we find can be used to better treat the symptoms of each subgroup.

Historical Overview

An important standard to set forth before we begin our testing of the differences between TD and PIGD is how these groups have generally differed in studies of the past, and how they've been accepted to be different. Generally, patients exhibiting PIGD have "shorter strides, less smoothness, and excessive instability" (Herman, Weiss, Brozgol, Giladi, & Hausdorff, 2014) than those showing symptoms of TD, in addition to greater rigidity and falling much more. This makes sense, considering that phenotype is distinguished by postural instability, and greater balance problems. Patients with TD, however, mostly

just have a consistent tremor, and that will usually remain the most significant symptom as the disease progresses.

In the study of Parkinson's disease, these two subgroups have most always been determined by a ratio score derived from averages of certain item scores derived from the UPDRS of the patient. The UPDRS, a scale rating the disease's progression in a patient based on disease-specific symptoms, has existed since the 1980s, and soon after it became the most widely used PD rating scale (Goetz et al., 2008). It was acclaimed by many researchers, but in the early 2000s it was revised due to its many issues with encapsulating pertinent PD problems (Goetz et al., 2008). The presence of both yes/no responses and 0 to 5 ratings to determine item scores also made calculations with and applications of the scale more difficult (Stebbins et al., 2013), further adding to the necessity of the impending revision. This revised scale was termed the MDS-UPDRS, named after the organization (the Movement Disorder Society, or MDS) that commissioned the scale's revision. It was designed to keep all the strengths of the original UPDRS while making calculations and applications more convenient. The new scale consisted of 65 rating items (from 55 in the original UPDRS), all formatted to the 0-4 rating scale rather than how the previous scale mixed that with yes/no items (Goetz et al., 2008). All in all, this revision was a landmark event in the study of PD and paved the way for more accurate and precise studies to be conducted in the future.

However, this left a specific problem in its wake. The subtypes of TD and PIGD had always been derived with two respective algorithms using calculations on specific items found in the UPDRS. With the revision of said scale into the MDS-UPDRS, new algorithms needed to be developed (Stebbins et al., 2013) to derive the TD and PIGD phenotypic groups. Five years after the publication of the MDS-UPDRS, two new algorithms for calculating the subgroup ratio score were established for use alongside the MDS-UPDRS, each utilizing more items than the originals. "A validated method for calibrating UPDRS TD/PIGD scores to MDS-UPDRS usage" (Stebbins et al, 2013) was in place.

Current Trends and Practices

Currently, the research community generally still uses the MDS-UPDRS and the corresponding algorithms used to determine if a patient has the TD or the PIGD phenotype. Which one the patient has can determined by dividing the mean of the item scores designated for TD by the mean of the scores for PIGD. If this ratio score is ≥1.15 (for MDS-UPDRS), then the patient is classified as TD; if the score is ≤0.9, then they're classified as PIGD, with those in between classified as indeterminate (Stebbins et al., 2013). The items in both the UPDRS and MDS-UPDRS exist exclusively in Parts II and III of said scales for both TD and PIGD. However, it is important to note that these algorithms and ratio cutoffs set forth by Stebbins et al. are not used by all researchers with the MDS-UPDRS.

Going back to the statement at the beginning, the work on gait and balance relating to the TD and PIGD subgroups is far from finished. Some gait aspects that haven't been well studied include "stride length, variability, smoothness, and the dual task effect" (Herman et al., 2014). In addition, there is a problem in that the TD and PIGD subtype cutoffs are not always exclusive enough to yield fully distinctive groups; sometimes patients in both groups will still exhibit some symptoms of the other group. This research group at Tel Aviv University took a novel approach to fixing this issue by creating two purer groups of classification by employing stricter measures, called predominantly-TD and predominantly-PIGD (p-TD and p-PIGD). When these two groups were compared, they were found to be significantly different in terms of gait, falls, PD subgroup-related data. These results were found using a body sensor while the patient was walking, and additional "tests of mobility, balance, and fall risk" (Herman et al., 2014). This is a prime example of how many PD researchers test gait and balance, and it likely will be included in how we test the differences of the TD and PIGD subgroups.

Controversies and Debates

Not everyone in the research community is so convinced of the usefulness of the TD and PIGD subtypes. Some, including Dr. Vikas Kotagal at the University of Michigan, propose that PIGD

specifically should be thought of as a “multidimensional continuum influenced by several overlapping age-related pathologies” and other concurrent diseases and/or disorders. This is mainly because the different subtypes don’t always act as they theoretically should: that is, they have distinct, unique symptoms easily distinguishable from those of other subtypes (Kotagal, 2016), which we have already seen an example of in the study done by Herman et al., in which the p-TD and p-PIGD purer groups were created to create minimum overlap.

Researchers also argue that PIGD isn't a valid subtype because it is mainly used as an opposite type to the tremor dominant type, and isn't necessarily its own district, recognizable phenotype. Following this line of logic, Kotagal reasons that many researchers use different definitions of the PIGD subtype for their individual studies. While this is useful, it hurts the broader community because there isn’t a set standard that everyone can use and compare for the most part (Kotagal, 2016). According to him, cluster analyses continually fail to produce a constant, defined, and unchanging PIGD subtype that can be used as a standard. This parallels the inconsistency of standards used by researchers mentioned earlier. In addition, one of the most important points made by Kotagal is that PIGD is neither a mutually exclusive subtype or a path presenting a unique course of pathogenesis, which any PD subtype ideally should (Kotagal, 2016). In conclusion, the phenotype of TD is accepted by most researchers as an unchanging, accepted, reproducible standard, but that of PIGD is much more variable and may need greater refinement and research to show how ideal and helpful it may be.

Conclusion

As researchers continue to look for a cure for Parkinson’s disease, the groupings of TD and PIGD have become very helpful implements in the current treatment of the symptoms of PD. While there are concerns that the definitions for each sublevel should be revised and that the PIGD sublevel may not be legitimate at all, these subgroups will likely remain vital tools in the care of PD patients in the near future. With the development of the MDS-UPDRS, the occasional refinement of the TD and PIGD phenotypic

groups into more concentrated, pure groups for testing, the field of PD treatment has come a very long way, and we would like to keep the good work moving forward. With our study of the complete differences between the TD and PIGD phenotypes, we hope to uncover more of what separates these two groups and help to eventually make each type individually and specifically treatable.

Materials and Methods

My study's objective was to determine if and how the PD phenotypes of TD and PIGD were different in terms of cognition, turning, gait, and the disease itself. Given that PIGD patients generally have more gait difficulty among other motor issues (this is implied in the name, which is Postural Instability and Gait Difficulty), we hypothesized that PIGD patients would have worse cognition and gait than those with TD. The investigation was conducted using data collected from gait, turning, and cognition evaluations.

For this study, we used data collected from the UDALL study, a massive assessment of PD patients from Stanford University (SU), University of Washington (UW), and Oregon Health and Sciences University (OHSU) using the same variables and metrics for cognition, turning, and gait study among patients. During my visit to OHSU, I observed several analyses of patients for the UDALL study. To analyze the cognition of each patient, they were given attention and memory tests, and also the MoCA (Montreal Cognition Assessment), which assesses those cognitive domains and many more. To test motor characteristics, patients were fitted with inertial sensors on the chest, hands, feet, and waist. Gait and turning characteristics were tested using a two-minute long walk back and forth between two lines at the patient's normal, comfortable pace. We tested patients under both single task conditions, where they just walked back and forth, and dual task conditions, where they were asked to do a cognitive task simultaneously, such as counting down by some number, like 7, from a certain large number, like 742, or saying the alphabet using every other letter starting from A and then B. All of these methods of testing gait, turning, and cognitive characteristics are from the UDALL clinical core, used at all 3 universities.

To analyze data and calculate differences, we used a spreadsheet of various cognitive and motor-related data from many different tests for all the patients tested in the study. For cognition variables, we used a test derived from a small part of the MoCA and two different, unrelated cognition tests. For disease characteristics, we looked at disease progression, a test for how much drug would be

needed to achieve a certain effect, and disease duration. For gait variables, we looked at the angle the patient's foot hit the ground, the duration of their gait cycle, their gait speed, and their stride length. And finally, for turning, we looked at how many steps they took to make a turn, and how fast their turns were. Another notable thing we had to do with the data was separating the patient data into TD and PIGD phenotypes using the MDS-UPDRS scores of patients. The MDS-UPDRS is a PD rating scale used by many clinicians to evaluate patient health relating to PD, and the patient's phenotypic subtype (TD, PIGD, or indeterminate, which means they have some of both) among other things. Once we had separated the participant data into their respective subtypes, we were ready to begin our statistical analysis.

We determined whether the TD and PIGD subgroups were different from one another in terms of each of the test variables by running t-tests on them. That would show if the two groups were significantly different from one another in terms of a given variable, given that the calculated p-value was less than a certain number (0.05 for the cognitive and disease variables, we called these variables the nonmotor group; 0.01 for the gait and turning variables, this is the motor group). For each motor variable, we ran tests separately for the single task and the dual task data, and also the standard deviations for both (a total of four sub-variables, if you will). We also ran descriptive statistics on each variable to see how they were different. In addition to doing this, we also inspected histograms and box plots for each variable to see to check distribution normality.

Results

Many of the variables that we tested were significantly different between the TD and PIGD subgroups (differences were significant if p-value was below a certain constant). Of the non-motor variables tested, the ones where the two groups were significantly different were disease duration, the subtest derived from a part of the MoCA (F-Words MoCA Score), the dose of levadopa needed to achieve a certain effect (Levadopa Equivalent Dose, or LED), the Hoehn and Yahr stage, and two measures from

other cognition tests, stroop interference and trails (Stroop Interference Correct and Trails Time B minus A). For the motor variables, all the variables tested had at least two sub-variables that were significant out of the four that were tested, (single task and dual task measures, along with their respective standard deviations, abbreviated ST, DT, std ST, and std DT) as shown by Figure 2.

Non-Motor Variables (p<0.05)	**TD** mean(std)	**PIGD** mean(std)
Disease Duration (yrs)	7.07(4.97)	9.87(6.08)
F-Words Moca Score	15.80(4.99)	14.38(4.58)
LED	380.27(385.18)	704.47(585.73)
Modified Hoehn Yahr	1.30(0.96)	2.17(0.63)
Stroop Interference Correct	37.32(8.58)	32.43(10.62)
Trails Time B minus A (s)	44.71(26.69)	63(49.43)

Figure 1: Mean and standard deviation for both groups on all significant non-motor variables

As can be seen in both figures, we compared the two groups based on mean, with the standard deviation also listed for reference. Starting with the non-motor variables, the PIGD patients had longer disease duration, lower f-words scores, higher LED, a greater Hoehn and Yahr stage, less stroop interference correct, and a longer trails time; this is shown in detail in Figure 1. For the motor sub-variables, many sub-variables were significant, so they were listed by parent variable. For angle the patient's foot hit the ground, the PIGD patients had a smaller striking angle in both single and dual task, with a higher standard deviation in dual task. With the duration of their gait cycle, they had a larger standard deviation in both single and dual task. For gait speed, PIGD patients were slower in both single and dual task and had a larger standard deviation in dual task. For steps in a turn, PIGD patients took more in both single and dual task, with larger standard deviations for both as well. They had shorter stride lengths in both single and dual task, and a larger standard deviation in dual task. And finally, PIGD

patients had lower turn velocity in both single and dual task. Further detail on these differences can be found in Figure 2.

Discussion

My hypothesis was supported by all of the data. According to the data found in Figures 1 and 2, PIGD patients always had worse nonmotor characteristics and worse motor characteristics than TD patients. Also, the PIGD group data always had greater standard deviations than the TD group when it came to motor characteristics. This fits very well with my hypothesis that the PIGD subtype would have worse gait, turning, cognitive, and disease characteristics, which was overwhelmingly supported by the data, where every single variable and sub-variable gave better marks to TD patients. This trend is also supported by the literature discussed earlier. This is specifically true where Herman et al. (2014) discussed the problems that patients with the PIGD phenotype had with stride length and stability. This is precisely true with my data, where the PIGD patients had a shorter stride length than the TD patients in both dual task and single task. The instability mentioned is shown in all of the non-motor variables tested, where the PIGD patients always had worse attributes than those with TD.

In terms of the methodology used, there were many strengths. For one, we had access to spreadsheet data from hundreds of PD patients, so our sample size was quite large. We also used a plethora of different measures for each of the characteristics tested, (gait, turning, cognition, and disease), which gave convincing evidence for each. The inertial sensors used for non-motor testing also provided a lot of input on what exactly was going on with the patient's body during gait and turning. However, our methodology wasn't perfect by any means. We only had two different ways of testing cognition during the dual task motor tests; if we had more it would have certainly helped with giving more for the patient to focus on during said tests. Also, we weren't able to test heel cord length in patient gait, which would've been more helpful than the foot strike angle variable we tested. This is because it would tell us whether

the striking angle was as small as it was because of how they walk, or simply because they couldn't lift the foot any higher because of their heel cord.

In terms of what these results mean for the study of Parkinson's disease as a whole, they are quite important. These two groups are quantitatively different when it comes to non-motor and motor characteristics, to say the least. This shows that the TD and PIGD aren't just groups divided by a ratio from the MDS-UPDRS--they actually are different types of PD that express themselves in very different ways and might possibly be treatable in their own specific ways as well. This is something that has been shown many times before in other past studies, but this simply adds more support to that hypothesis. A specialization of treatment, when and if it were possible, would greatly contribute to the treatment of Parkinson's disease. In the future, we might test heel cord length and other new motor variables to see if they also support this hypothesis and show why the foot strike angles of most patients are the way they are.

Conclusion

My research has shown that TD and PIGD really are two different types of PD, not just on paper but in reality. The data shows that PIGD was worse than TD in all cases of motor and non-motor characteristics, clearly supporting this hypothesis. This conclusion particularly mirrors that of what was shown in the literature review, with PD patients with PIGD having greater trouble with stability and gait than TD patients, precisely what was demonstrated in this study. It also shows that TD and PIGD may be able to be recognized without determination through the ratio calculated from the MDS-UPDRS. It may be possible to identify subtypes solely through the non-motor and motor characteristics of a patient, which would be a very helpful method of determination and also a more efficient one. For future research, it would be interesting to look at other tests of motor and anatomy, like heel cord length and possibly some upper body tests as well, outside the realm of gait and balance. These results are of use in the real world in that caregivers and clinicians alike may be able to conclusively identify PD subtypes through observation

of non-motor and motor characteristics alone, without the help of the MDS-UPDRS. They are also useful in that treatment for PD may be able to be specialized to the subtype of the patient in the future.

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