Early biomarkers for Parkinson's disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease characterized by the onset of multiple motor symptoms, including: rigidity, tremors, and frozen facial expression. Loss of dopaminergic (DA) neurons from the substantia nigra of the brain and misfolded alpha synuclein (a-syn) protein clumps, called Lewy bodies, are also hallmarks of PD. PD is diagnosed by the onset of multiple motor symptoms, at which point significant damage to DA neurons has already taken place. Our research focuses on analyzing data from the Parkinson's Progression Markers Initiative to identify conclusive biomarkers in PD patients.

Background

The progressive degeneration of dopaminergic neurons (DA) is seen in the substantia nigra in the brain of PD patients (fig. 1). Dopamine inhibits activity in motor neuron center and plays a role in starting and stopping both voluntary and involuntary action. This can be linked to the uncontrolled trembling and stiff movements seen in PD patients.

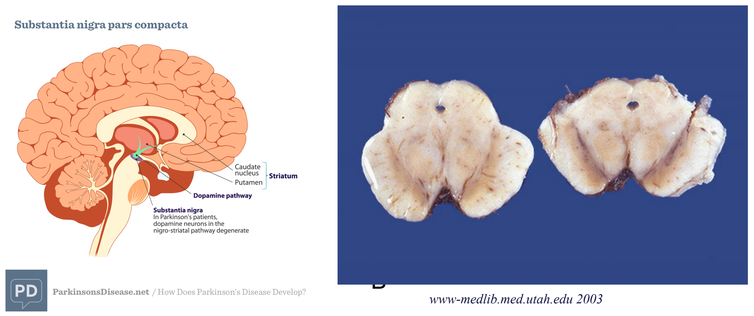
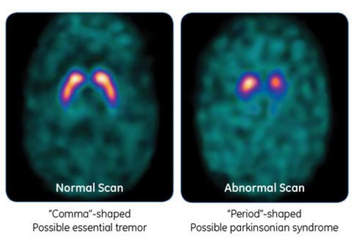


Figure 1. (A) Parts of the brain and the dissected substantia nigra from a patient with PD (B, left panel) and a control subject (B, right panel)

Figure 2. DaTscan shows PD patient dopamine activity (right) compared to control (left)

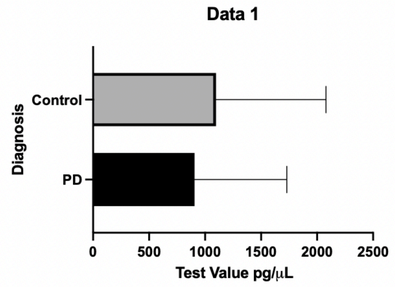


DaTscans can be used to show DA neuron activity in the substantia nigra of the brain, less activity confirming suspected PD diagnosis. However, at this point motor symptoms of PD are already presenting, these tests are not easily accessible, and lastly they are nonspecific to PD as the scan will present similarly across other neurodegenerative diseases.

Currently, biomarkers are being researched in blood, cerebrospinal fluid (CSF), saliva and tissue biopsy. There are studies identifying links between a-syn aggregation in the brain, leading to decreased a-syn present in the CSF, as well as studies showing increased presence of a-syn in the plasma.

Methods

Figure 3. A-Syn in CSF PD vs Control

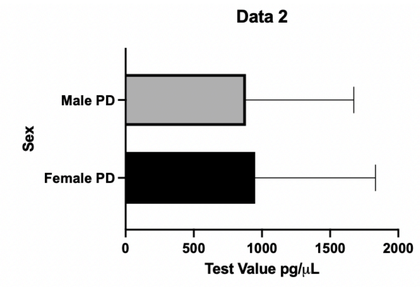


Value	PD	Control
N	2913	1305
Mean (pg/µL)	905.6	1089
Range (pg/µL)	0.60-8405.70	21.2-5153.5
Highest frequency (pg/µL)	0-200	21.2-331.2

Table 1

Data of biospecimen results from various labs are organized to compare PD to control patients. Although there are numerous types of biospecimen entries, alpha synuclein in CSF is being analyzed. Range and mean of values from PD vs control patients are compared in figure 3.

Figure 4. A-Syn in CSF PD male vs female

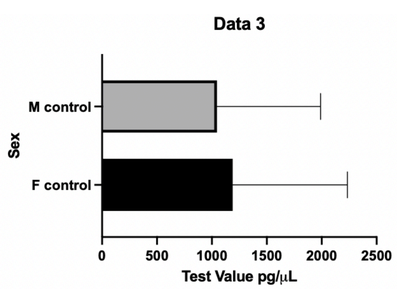


Value	Male PD	Female PD
N	1915	998
Mean (pg/µL)	882.4	950.1
Range (pg/µL)	0.6-5256.9	3.90-8405.7
Highest frequency (pg/µL)	0-200	0-301

Table 2

Levels of A-syn in CSF of PD male vs female patients is analyzed.

Figure 5. A-Syn in CSF male vs female controls



Value	Male Control	Female Control
N	837	468
Mean (pg/µL)	1046.3	1189.7
Range (pg/µL)	21.2-5034.5	27.9-5135.3
Highest frequency (pg/µL)	21.2-371.2	27.9-497.3

Table 3

Levels of A-syn in CSF of male vs female controls is analyzed.

Results/conclusion

In our analysis, the vast majority of PD patients a-syn in CSF test values were between 0-200 pg/µL, while controls were within the range of 21.2-331.2 pg/µL. Initial findings suggest that the presence of a-syn in CSF of PD patients is lower than that of controls. Both male and female controls averaged higher values of a-syn and higher frequencies compared to male and female PD patients. Female controls had the highest average of a-syn at 1189.7n pg/µL and the highest frequency at 27.9-497.3 pg/µL.

While our initial findings are broad, more research needs to be done to identify specific values for the markers. Additional research is required to cross compare a-syn values with other biomarkers or a-syn in other biospecimens.

Identifying conclusive biomarkers, not just to identify but also to track the progression, is a critical step in advancing treatment for PD. With such variation in results, there is a clear need to develop standard, easily replicable testing. This would allow earlier diagnosis, leading to the development of treatments to slow, manage, and reverse the neurodegeneration of this disease.

References

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