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The Diagnosis of Parkinson's Disease (PD)

I am sending out this communication because many of us are sharing patients or seeing each other's patients. I just want you to know how I am naming and thinking about these clinical diagnoses. It is as it has been since I started seeing Parkinson's patients in 1968 at Iowa's clinic difficult to make a correct diagnosis of PD when compared to autopsy, especially early in the journey of the disease. It is also almost impossible to make a diagnosis of co morbidity or at least the degree of the impact of the co morbidity on the clinical picture in a Parkinson patient especially later in the journey of the disease or in the older patients with Parkinsonism. This co morbidity factor is most difficult to account for in the second decade of the disease or in the older patient in their late 70's or 80's.

Why is the terminology important to us and to the patient? Most of us are or have done trials in IPD or other Parkinson syndromes. Obviously the correct diagnosis is important for the enrollment of patients and hence the conclusions of the trial. But also it can be confusing to the patient, the family and the caregivers if a patient is given various names for their clinical condition. If a doctor is aggressive or adamant about a diagnosis labeling the patient different than the prior treating doctor, several impressions to the patient and family may take place. First is that the initial or prior treating doctor does not know his or her field or secondly even worse, this difference may initiate a lawsuit for failure of diagnosis or failure of appropriate treatment format and management. An angry patient or family, a progressively worsening clinical state, an impression that the treatment was not adequate or incorrect, or a doctor with hubris, ego, coming on strong on a treatment plan and or a diagnosis, can certainly bring on a lawsuit against the prior doctor. To criticize management of a prior doctor is certainly inappropriate, when the treatment now by the current doctor is being performed in a patient with an uncertain diagnosis, (no pathology) and or the treatment used has little or no benefit documented by class I evidence. This is especially a possible law suit in an elderly patient with significant co morbidity complicating the clinical picture. The patient or family will not know or remember that the only definite way to make the diagnosis is autopsy.

We have known since the London Brain bank data (Hughes) that the accurate diagnosis, especially early in the journey is difficult and not very accurate (maybe 75% at best initially) when comparing to autopsy reports. And even late in the clinical state at best the accuracy is near only 90%. In the Hughes group the clinical diagnosis was more likely accurate when compared to autopsy if the patient had a foundation of bradykinesia, been followed for a longer period of time, had a robust maintained response to L-Dopa, hand motor fluctuations (dyskinesia's and wearing off), had a resting tremor with maintained asymmetrical signs, late appearing postural instability, and no robust atypical parkinson features. I have used this set of clinical characteristics to make a more comfortable, probably accurate diagnosis in my patients for at least 15 years. We all know that there is even sometimes different diagnosis's made among different pathologist who may use different criteria in this group of diseases. Also some of these neurodegenerative diseases have more than one disease pathology, as we all know.

Now we have a number of articles that give us even more insight into the inaccuracy of the initial diagnosis on first evaluation. Dr. Adler's accurate diagnosis in Parkinson patients, seen at different times in the evaluation compared to autopsy results, ranged with an accuracy that was on initial visit "26% in PD in untreated or not clearly therapeutically responsive subjects". Then in patients followed less than 5 year duration and considered to be

Probable Parkinson's clinically responsive to medication, the correlation with autopsy was only 53%. At greater than five years when diagnosed as Probably PD using the final diagnosis at time of death, these cases had”85% accuracy" in cases with a longer duration of disease and were followed up and they were a medication responsive group of patients. Adler goes on to relate that in the last diagnosis in the journey in autopsied cases the diagnosis of PD had a "sensitivity of 88% and a specificity of 68%" There were clinical "variables" that improved the accuracy, ones we know such as medication response, motor fluctuations, and dyskinesia's (all which I strongly believe is supportive for the diagnosis of IPD). There was greater accuracy of clinical diagnosis for PD the longer the patient was followed and the more severe the reduction in olfactory testing. We have all known that probably the last doctor to see the patient has the better chance to have greater accuracy. But also the patient, the family and caregivers are probably learning to give a better history. The Adler paper used Possible and Probable PD grouping and a group of parkinsonism not otherwise specified (ParkNOS) but like all of us had no definite way (biomarker or tissue) to separate them prior to autopsy. The pathology on autopsy was the gold standard for the diagnosis. No single biomarker for diagnosis, but some possible help from the smell test. Clinical evidence that gave a greater accuracy for making the diagnosis of IPD in the Adler paper were; younger age Parkinson patients, no atypical features, having had a chance for longer follow up, tremor and persistent asymmetry of the clinical findings, robust response to the dopaminergic medication especially L-dopa, development of motor fluctuations, especially wearing off and the development of dyskinesia's, and loss of smell. A trick I use to lower the threshold of possible dyskinesia's is to have the patient walk, or be active with AMR's or counting rapidly. This will often bring out subclinical dyskinesia's. Against getting the diagnosis of PD confirmed by autopsy was early falling, and cognitive impairment. Positive predictive values (PPV) were 91% for tremor predominant disease. At first visit, motor fluctuations cases, many were diagnosed as "parkinsonism not otherwise specified" which I am not sure how this affected the results and analysis of the study. There were 5 cases called PSP but were PD, and all 8 that were diagnosed as DLB had no pathological diagnosis of PD. Limitations of this study are selective biases, much older age groups and numbers of examiners that were movement disorder doctors. When this study results are thought to be different than we would expect, it is my opinion that it is because there are many older people in the study (they probably have more co morbidity), and many of the patients had the diagnosis of parkinsonism not otherwise specified.

Fereshtehnejad and others reported on 113 patients prospectively with the patients clinically determined to have Idiopathic Parkinson's Disease. These patients were followed for a mean of 4.5 years and 76 were reassessed. No autopsy data was given to determine accuracy of diagnosis. The authors divided the patients into three subtypes (ones I had not been familiar with or used), 1) mainly motor/slow progression; 2) diffuse/malignant; and intermediate. Their conclusion was that those patients diagnosed as having Parkinson's Disease that had cognitive impairment, orthostatic hypotension and RBD (Rapid Eye Movement Disorder) at first visit, fit into the more rapidly progressive, poorer prognosis group. Obviously this type of sub typing will need to be reevaluated by other centers and obviously autopsy data would be very helpful as the accuracy of diagnosis, which will give greater meaning to the information. I am not sure how the terminology will fit into the current concepts of IPD, APD, MSA, PSP, CBS, and the FTD syndrome.

In the article "When DLB, PD, and PSP masquerade as MSA" Koga and others came to the conclusion that in patients with clinically diagnosed MSA, at autopsy, only 62% had the correct diagnosis. DLB > PSP>PD were in that order the most common misdiagnosis confirmed by autopsy. They reviewed 134 consecutive patients with an ante mortem diagnosis of MSA and had post-partum autopsy evaluations to give a definite diagnosis. Only 62% had the correct diagnosis of MSA. Dementia with Lewy Bodies (DLB) was the most common accurate diagnosis if MSA Diagnosis was incorrect, then PSP and then PD. The diagnostic accuracy was 71% in probably MSA and 60% in possible MSA. Of interest some cases of DLB had no significant clinical dementia, and PSP was missed

because the cerebellar ataxia which often presented early in the journey was attributed to MSA and not PSP. Most frequent reason for missing the diagnosis of DLB was 17 0f 18 patients with DLB presented with autonomic failure or significant autonomic signs and symptoms. Cases missed diagnosed as MSA instead of DLB was because the patient had minimal cognitive impairment. The MSA patients commonly had incontinence, constipation, orthostatic hypotension and REM Behavior Disorder (RBD). 38% of the patients pathologically diagnosed as MSA had no abnormal MRI findings. The limits of this study are the retrospective aspects, multiple doctors, no biomarker and selection bias.

Also in these two studies and others there is evidence that there is mixed pathological findings, hence giving the possibility of a mixed clinical picture because of more than one pathological process. We have no way of giving us any measurement of how progressive WMD affects the clinical picture. We know that cerebral vascular disease, as cortical or lacunar strokes occur, (with 4 of 5 of the strokes on MRI being clinically silent) but we have no way to determine how these affect the clinical picture or how much of the clinical picture is related to these insults. Aging and other medical diseases certainly affect the clinical picture.

Some limited help for the diagnosis is from the DAT Scan which gives us about an 85% sensitivity and specificity generally for Parkinson's disease but relates more to dopaminergic deficiency and MSA, PSP, LBD, and CBS can have abnormal DAT Scans. I think the DAT Scan helps rule out drug induced parkinsonism, many of the vascular parkinsonism cases, Essential Tremor Syndromes, and psychogenic (functional) parkinsonism.

On top of all this lack of accuracy in the diagnosis and the lack of one or multiple biomarkers, our management of our PD patients is getting much more difficult and hazardous for us and the patients. The impersonalness of EMR, more difficulty in getting testing on a timely basis, doctors under more stress and anxiety because of forced performance, documentation and the vagueness and hassle of Coding, is disruptive to patient care and often leads to patient dissatisfaction and sometimes a law suit. And patients, in some cases, are definitely not as happy, nor as content with the mechanics of health care. If that is not enough we have tensions between health care centers, everyone wanting to make their group or center the best, the largest, and the most knowledgeable. We have in some cases an unhappy patient group looking for a different answer or they are very happy to have no or little real loyalty to their prior hardworking, caring doctor. Someone can or easily convince them that they can get better care with them as the new doctor and or in their center.

So adding, aggressively and adamantly, a different diagnosis that is in itself uncertain and in a disease that to this day has no biomarker, cure or way of delaying the progression (other than possibly aggressive physical exercise), only adds to difficulty for everyone.

At the movement disorder meeting in San Diego the most often used term or a name for a clinical picture other than IPD that did not fit clearly into one of the other Parkinson diseases, was APD (Atypical Parkinson's Disease). For me that is what I am using as a diagnosis for a clinical picture that probably falls out of the IPD clinical spectrum. I will code as best I can but will use a great deal of G20's. The great debate and discussion is what to call these diseases we are seeing. Many have suggested that we could use Parkinson Disease Syndrome, Parkinsonian Syndrome, Parkinson's Spectrum Disorder, Parkinsonism, Alpha Synucleinopathy Syndrome; but I will stick with the description of APD as was used most in San Diego and Stockholm Sweden.

Often in an APD case or where the diagnosis is uncertain, I will start L-dopa and see if the patient gets any non-motor and motor improvement. An important aspect to this is that the PD patient, family and caregivers have to know what to look for that would indicate improvement. I use a handout for that and have them understand the non-motor and motor signs and symptoms of wearing off or improving. If the patient improves, I increase the dose

to try to determine if the patient is suboptimal in the therapy, and often will go up to 800mg to 1000mg. If there is development of dyskinesia's or robust wearing off, the dose is most likely of benefit and you are close to where you want to be. If there is a consensus that the patient is better I keep them on the dose or lower to a dose where there are few if any adverse side effects. If later the patient, family, or caregivers do not feel the L-dopa is of benefit, I will gradually go lower and slow in the taper to see if there is worsening clinically. If there is I hold at that dose or if not I take them off the L-dopa.

One clinical feature that often helps place PD patients into the APD group is the inability to do the tandem gait test and this is very often associated with early postural instability on testing and early falling in the clinical journey. All of these suggest APD or MSA, PSP, CBS, or FTD syndrome. The one concern is that the patient may have co morbidity. I always like to relate that at Iowa, in the late 60"s, we knew patients with PD could ride a bike well into their disease. The reason was that often the farmer's family with one truck would take the PD patient out to the field to work and would take a bike in the pick up so the patient could ride the bike home from the field while the wife was in town.

When doing the AMR's mirroring of movement or tremor in the other hand and less often the foot, suggest a parkinson syndrome. This however can also be seen in ETS.

So for me I will be using IPD for the cases that I feel fit the diagnosis and which fit as best possible with the London Brain Bank criteria and the findings that are suggested by these two papers and APD as the name to the clinical picture that does not fit clearly into LBD, MSA, PSP, CBS, FTS, or ET syndrome. However I will try to high light the signs and symptoms for why I decided to choose the diagnosis I give. I will probably diagnosis some IPD patients that will not have it, and call others like MSA or PSP or CBS that will not have the diagnosis but I promise to the patient I will reevaluate the diagnosis on each visit, try to put it all together, modify treatment and prognosis as needed. And to the patient, family, caregiver, and referring doctor, I will emphasize that the journey gives us a better idea of treatment selection and prognosis and that the only absolute diagnosis is autopsy.

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