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Is levodopa response a valid indicator of Parkinson disease?

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Abstract

Objective/background—The clinical diagnosis of Parkinson disease (PD) requires the presence of parkinsonism and supportive criteria that include a clear and dramatic beneficial response to dopaminergic therapy. Our objective was to test the diagnostic criterion of dopaminergic response

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by evaluating its association with pathologically confirmed diagnoses in a large population of parkinsonian patients.

Methods—We reviewed clinical data maintained in an electronic medical record from all patients with autopsy data who had been seen in the Movement Disorders Center at Washington University, St. Louis between 1996 and 2018. All patients with parkinsonism who underwent postmortem neuropathologic examination were included in this analysis.

Results—There were 257 unique parkinsonian patients with autopsy-based diagnoses who had received dopaminergic therapy. Marked or moderate response to dopaminergic therapy occurred in 91.2% (166/182) of those with autopsy-confirmed PD, 52.0% (13/25) of those with autopsy-confirmed multiple systems atrophy, 44.4% (8/18) with autopsy-confirmed progressive supranuclear palsy, and one (1/8) with autopsy-confirmed corticobasal degeneration. Other diagnoses were responsible for the remaining 24 individuals, 9 of whom had a moderate response to dopaminergic therapy.

Conclusion—A substantial response to dopaminergic therapy is frequent but not universal in PD. An absent response does not exclude PD. In other neurodegenerative disorders associated with parkinsonism, a prominent response may also be evident but this occurs less frequently than in PD.

Keywords

Parkinson disease; parkinsonism; levodopa; diagnostic specificity

INTRODUCTION

Parkinsonism is a clinical syndrome consisting of bradykinesia with either rest tremor, rigidity, or both. The most common cause of parkinsonism, Parkinson disease (PD), affects at least 1% of the population over age 60. Other neurodegenerative disorders, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are less common causes of parkinsonism. While the differentiation of these conditions can present a diagnostic challenge to clinicians, their delineation is important for treatment and prognostication.

The clinical diagnosis of PD is based on its characteristic motor manifestations of parkinsonism plus supportive criteria that include “clear and dramatic beneficial response to dopaminergic therapy”.[1] In a review of autopsy confirmed patients, Hughes et al provide evidence that not all PD cases have this degree of response to therapy.[2] Initial response to levodopa was reported as “nil to poor” in about 6% of patients. Furthermore, studies indicate that dopaminergic responsiveness may not be specific for a PD diagnosis.[3–5] Post-mortem neuropathological evaluation remains the only definitive test to differentiate PD from other neurodegenerative disorders associated with parkinsonism.

Research on these syndromes is often limited by a lack of pathological confirmation of the clinically established diagnosis. We aim to address this limitation and test the current clinical diagnostic criterion of dopaminergic response by evaluating its association with pathologically confirmed diagnoses in a large population of parkinsonian patients seen in the Movement Disorders Center at Washington University School of Medicine in St. Louis.

METHODS

We reviewed clinical data maintained in an electronic medical record (EMR) from all patients seen in the Movement Disorders Center at Washington University, St. Louis between 1996 and 2018 (n=17,575). All patients seen at this Center are routinely invited to participate in our brain donation program, regardless of clinical diagnosis. All those with parkinsonism (n=8249) from this population who had subsequent autopsy confirmation of diagnosis underwent further analysis (n=297). Each patient was examined by a subspecialty-trained movement disorders neurologist who recorded clinical status in the EMR at each visit. Medication response was based on previously established clinically important differences in motor scores[6] and determined from the historical narrative supplemented by UPDRS scores obtained in on- and off-medication states when available. Response was classified as marked if there was a >10 point change in the motor UPDRS associated with the use of dopaminergic medication or if the narrative indicated a marked symptomatic improvement, or moderate for a 5–10 point change in motor UPDRS or corresponding narrative. Response was considered nil in the absence of objective benefit, i.e. improvement ≤3 points on the motor UPDRS (as suggested in the MDS clinical diagnostic criteria[1]) or corresponding narrative description. Dyskinesias and wearing off, occurring at any time in the disease course, were recorded. Medication intake, expressed as levodopa equivalent dose (LED),[7] was recorded at the time of peak benefit early in the disease course estimated from the clinical record. Age of onset was defined as the patient's age at the first symptom of disease. Disease duration was defined as the interval between onset and death. The Washington University in St. Louis (WUSTL) Human Research Protection Office approved this study. All participants or their next-of-kin provided written informed consent.

Thorough neuropathologic examinations were performed at WUSTL as described in Franklin et al;[8] however, immunohistochemistry (IHC) for alpha-synuclein using the LB509 monoclonal antibody was introduced in 1998, and was supplanted by IHC using phosphorylation-specific anti-alpha-synuclein antibodies in 2009 (167/257 (65%) autopsies were done with the phosphorylation-specific antibodies).

Autopsy diagnoses were based on standard pathological criteria.[9–14] The diagnosis of Parkinson disease (PD) was based on the presence of Lewy bodies within and the loss of pigmented neurons from the substantia nigra. Cortical alpha-synuclein-positive inclusions consistent with Lewy bodies, although not required for the diagnosis of PD, were present in many of these patients. PSP patients had phospho-tau-immunoreactive astrocytes with 'tufted' morphology neurofibrillary tangles, and oligodendroglial inclusions ('coiled bodies') in the typical distribution in cortex and subcortical nuclei. Those with multiple system atrophy (MSA) had alpha-synuclein immunoreactive glial cytoplasmic inclusions with neurodegenerative changes in striatonigral or olivopontocerebellar structures. The diagnosis of corticobasal degeneration (CBD) was based on the presence of several forms of tau-immunoreactive lesions, including astrocytic plaques, characteristic neuronal cytoplasmic inclusions ('corticobasal bodies'), coiled bodies, swollen achromatic 'ballooned' neurons, and neuronal loss in cortex and basal ganglia.

Cases with multiple pathologies were identified, looking specifically for PD, PSP, CBD, and MSA as well as a high likelihood of AD based on NIA-Reagan diagnostic criteria[15], nonvascular amyloid plaque deposits not meeting these criteria for an AD diagnosis, TDP43 neuronal immunoreactivity[16], and primary age-related tauopathy (PART).[17] Those with multiple pathologies were arbitrarily classified for further analysis by the non-PD movement disorder pathology.

Quantitative clinical data were compared with non-parametric tests, namely Kruskal-Wallis followed by a post hoc pairwise multiple comparison procedure, or with a Student t-test as appropriate. Categorical measures were compared using χ^2 test.

RESULTS

A total of 297 patient records, all with formal autopsy reports and a clinical diagnosis of parkinsonism, were reviewed. From this total, 257 patients had a trial of dopaminergic therapy and sufficiently detailed clinical records to be analyzed further. Pathological diagnoses of excluded patients were PD (21), Alzheimer disease (4), MSA (2), vascular disease (2), PSP (1), CBD (1), argyrophilic grain disease (1), neurodegeneration with brain iron accumulation (1), Huntington disease (1), Creutzfeld-Jakob disease (1), primary lateral sclerosis (1), and unexplained (4). Basic demographics and medication response are summarized in Table 1. Pathological diagnoses included PD in 182 participants (70.1%), MSA in 25 (9.7%), PSP in 18 (7%), and CBD in 8 (3.1%). This distribution is comparable to the general patient distribution in our Center. A separate review of 3883 patients with parkinsonism showed a clinical diagnosis of MSA in 6%, PSP in 6%, and CBD in 1.7% and with the remainder being clinically diagnosed with PD (unpublished). The remaining 24 participants (9.3%), including 5 in whom the movement disorder remained unexplained after autopsy, had other pathological diagnoses, summarized in Table 2. These 24 participants were excluded from the statistical analyses.

Multiple pathologies were often present. In participants diagnosed with PD, AD was also present in 6, nonvascular amyloid deposition that did not meet criteria for AD in 127, TDP43 immunoreactivity in 17, and primary age-related tauopathy (PART) in 16. In participants with MSA, nonvascular amyloid was noted in 9 with no other co-pathologies evident. In participants with PSP, a co-diagnosis of PD was present in 4, AD in 1, nonvascular amyloid in 10, TDP43 in 1, and PART in 2. One PSP case had a co-diagnosis of NBIA. In CBD, a co-diagnosis of PD was present in 1; nonvascular amyloid was noted in 5.

Mean age of onset (Table 1) differed amongst the diagnostic groups as determined by the Kruskal–Wallis test ($H = 11.708$, df 3, $p = 0.008$). A post hoc pairwise multiple comparison procedure (Dunn) showed significant differences in age of onset as follows: MSA < PSP ($p < 0.05$) and PD < PSP ($p < 0.05$). Comparisons of other pairs were non-significant. Mean disease duration also differed amongst groups ($H = 56.029$, df 3, $p < 0.001$). Post hoc pairwise comparisons showed significant differences in disease duration as follows: PD > CBD ($p < 0.05$), PD > MSA ($p < 0.05$), and PD > PSP ($p < 0.05$ with other pairwise comparisons being non-significant. There was no significant sex difference amongst groups ($\chi^2 = 7.03$).

Levodopa equivalent doses at peak benefit in individual patients varied widely, ranging from 150 to 2843 mg/day (mean 795 mg/day) in those with PD who exhibited a marked response to dopamine replacement. There was no significant difference in mean LED between responders (marked/moderate) and non-responders in any of the major patient groups. Few of the non-responding patients received an LED < 600 mg/d (PD 2 patients, MSA 1 patient, PSP 2 patients, CBD 1 patient). In the group of participants with other diagnoses, 9 individuals had a moderate response to dopaminergic therapy (mean dose 1045 ± 424 mg) including 2 in whom the movement disorder remained unexplained after autopsy. LEDs are summarized in Table 1.

The presence of multiple pathologies did not correlate with medication response. In PD, age of onset correlated significantly with medication response (Kruskal–Wallis; H = 15.597, df 2, $p<0.001$) with marked response < no response. Disease duration also correlated with medication response (Kruskal–Wallis; H = 16.639, df 2, $p<0.001$) with marked response > no response.

DISCUSSION

A clear and dramatic beneficial response to dopaminergic therapy is considered to be a supportive criterion for the clinical diagnosis of PD.[1] In our study, approximately 91% of PD participants had a marked or moderate response to dopaminergic medication. Unequivocal wearing off was present in 23/41 of our patients with a clinically moderate response, consistent with MDS criteria defining a dramatic response for these patients.[1] Using this definition, at least 81.3% of PD patients have a dramatic response to dopaminergic medication. The absence of observable response to high-dose levodopa (defined in the MDS criteria as ≥ 600mg/day) despite at least moderate clinical severity of disease is considered to be an absolute exclusion for the diagnosis.[1] After excluding patients receiving <600 mg/day and ensuring appropriate disease severity, approximately 7.7% of our autopsy-proven PD patients would have been misdiagnosed clinically suggesting that this criterion for absolute exclusion should be used with caution. None of the non-responders developed dyskinesias or motor fluctuations in response to dopaminergic treatment, supporting our impression that these are true non-responders.

This study also confirms observations from previous studies that a response to dopaminergic therapy is not specific for PD. We found that, in other neurodegenerative disorders associated with parkinsonism, a marked or moderate dopaminergic response was often present although not as frequently as in PD. In MSA, the second most common confirmed diagnosis, 52% had a marked or moderate response to dopaminergic medication whereas in PSP 44% had this degree of response. In CBD, there was only one dopaminergic responder although the number of patients in this group was relatively low in comparison to the other groups. A marked response was present in 7/51 non-PD patients. Disease duration in all groups was comparable to literature reports.[18] These results are similar to those previously reported by Rajput et al from a 22 yr study of 59 patients with parkinsonism of which 37 received an adequate trial of levodopa (defined as at least half of the usual dose for at least 2 months).[19] In this study, symptomatic improvement was evident in 94% of patients with pathologically confirmed PD and in 33% of MSA cases.

An important caveat to our observations is that we are not addressing primarily the accuracy of a clinical diagnosis of PD but the spectrum of pathological entities underlying the clinical manifestation of parkinsonism. The range of pathological diagnoses is comparable to that in previous reports that also found MSA to be the second most common pathological diagnosis after PD in patients with parkinsonisim.[20] Hughes et al have reported that the accuracy of clinical diagnosis of PD can be as high as 90%.[21] Others have emphasized the importance of long term follow-up in establishing an accurate clinical diagnosis.[22,23]

Interestingly, in the 24 patients with other diagnoses, there were still 9 with a moderate response (including 5 with wearing off) to dopaminergic therapy including 2 in whom the movement disorder remained unexplained after autopsy, providing further evidence of the lack of diagnostic specificity of dopaminergic response.

Average LEDs at the time of peak benefit early in the disease course were comparable in all groups making it unlikely that the group difference in medication response was related to dose. While it is possible that some patients would respond to a higher LED than was administered, this is not likely to be a major issue in our patient population since only 2 non-responders in each of the PD and PSP groups and one in each of the MSA and CBD groups received <600 mg LED/day. Our routine practice is to administer dopaminergic medication with an escalating dose until there is adequate symptomatic benefit or dose-limiting side effects. With the exception of one patient with PSP and two with MSA, all of the non-responders in this study received treatment for more than 6 months.

Notwithstanding the 600 mg/day recommendation from the MDS Clinical Diagnostic Criteria for Parkinson's Disease noted above, an unresolved challenge in clinical practice relates to the dosage of levodopa that must be administered before concluding that the patient is non-responsive.[24] Hauser et al reported that a substantial percentage of patients receiving up to 600 mg/day of levodopa fail to exhibit a robust response in a cohort of previously untreated PD patients enrolled in the ELLDOPA study.[25] At 24 weeks after starting medication, 26.3% of levodopa treated participants in this study experienced a 10% or less improvement compared with baseline. These patients, however, had clinically diagnosed PD without autopsy confirmation. In a review of autopsy confirmed patients, Hughes et al[2] reported initial response to levodopa to be "nil to poor" in 6 of 95 patients receiving a dose of "usually 1000 mg/d" which is consistent with our findings. In contrast, in a study of 1007 patients with clinically diagnosed PD, a limited response to levodopa challenge was evident in 39% of participants.[26] The levodopa dose in those displaying a limited response was relatively low at 485 ± 215 mg/d. Mark et al. reported 2 cases of autopsy confirmed PD who were non-responsive to carbidopa/levodopa (75/750 mg/d, 100/1,000 mg/d), further emphasizing that PD cannot be excluded by a lack of levodopa response.[27]

Dopamine responsiveness in MSA similar to the 52% that we observed has been reported previously. Wennig et al reported a beneficial response in 42% of autopsy proven MSA patients vs 77% of those with PD.[28] These authors acknowledge that clinicians may sometimes not increase levodopa doses sufficiently to gain a response but do not state what doses their patients were receiving. A similar degree of response was reported by the North

American MSA Study Group but dose issues were not provided.[29] Hughes et al reported an initial response to levodopa of >50% in approximately 43% of autopsy proven MSA patients who had received a mean dose of 580 mg/d.[30] The consensus statement regarding MSA diagnosis recommends escalating doses of levodopa to at least 1 g/d (if necessary and tolerated).[31]

While a poor or absent response to LD has previously been one of the clinical diagnostic criteria for PSP, several papers have reported a beneficial response similar to the 44% that we observed. This can potentially lead to an incorrect diagnosis of PD in patients with PSP, particularly in view of our previous observation that supranuclear gaze palsy is not uncommon in people with PD.[32] Lang suggests that the overall response rate to LD in PSP is about 26%.[33] A retrospective review of 87 clinically diagnosed PSP patients reported a benefit from LD in 38% of patients.[34] A clinicopathological study involving 103 cases of PSP reported that a trial of LD or dopamine agonist was undertaken in 88%.[35] No patient had an “excellent” response but 32% had a modest or good response although the dosage was not reported. In this study, individuals with the parkinsonism-PSP subtype were more likely to show a benefit than those with the Richardson syndrome subtype (50% vs 14.3%). Current diagnostic criteria for PSP include levodopa resistance while receiving at least 1,000 mg of levodopa for at least 1 month.[36] Our study suggests that this approach would misclassify about a third of people with PSP.

CBD as a cause of parkinsonism is seen less frequently than the other disorders described. Only 8 of our participants (3.1%) had autopsy confirmed CBD, one of which had a moderate response to dopaminergic medications. Kompiliti et al. suggest a higher rate of response in a review of 147 individuals clinically diagnosed (confirmed by autopsy in only 7) with CBD from 8 centers.[3] Symptomatic improvement was noted in 24% of cases who were receiving dopaminergic medications. Median levodopa dose in these patients was 300 mg/d.

Dementia with Lewy bodies (DLB) is not represented in our patient population in large part because DLB does not have a disease-specific pathological marker. Substantial pathological overlap exists between DLB and PD with dementia. Most of our PD patients had not only brainstem changes but also cortical alpha-synucleinopathy, the characteristic pathology of both PD with dementia and DLB. Pathologically these two conditions are indistinguishable. In fact, both conditions represent the same synucleinopathy with clinicopathologic diagnosis assigned according to the timing of onset of the dementia with respect to onset of motor parkinsonism. Additionally, our brain bank reflects the bias of those patients referred to a movement disorder center. By definition, patients with DLB have cognitive changes that precede or occur within one year of the onset of the movement disorder; these individuals are more likely to seek evaluation at a dementia center.

Neuropathological changes consistent with AD were present in 6/182 PD patients. Nonvascular amyloid deposition not meeting criteria for AD was present in another 127 patients. This is comparable to previous observations of Aβ deposition with at least moderate neocortical tauopathy (compatible with the presence of neurofibrillary tangles and/or neuritic plaques) in only 1/32 autopsied patients with PD and dementia, corresponding to a high likelihood of AD based on NIA-Reagan diagnostic.[37] In contrast,

this study found Aβ deposition with minimal or no cortical tau in 19/32 patients suggesting that Aβ deposition alone does not necessarily indicate AD in the context of PD. Irwin et al reported autopsy studies of 140 patients with a clinical diagnosis of PD, 48 of whom were cognitively normal vs 92 with dementia.[38] A total of 28.6% of all PD cases had sufficient pathology for comorbid AD, of whom 89.5% were demented. However, these investigators used a less stringent criterion for a neuropathological diagnosis of AD, namely an intermediate or high probability of AD vs the high likelihood used in our study. Because our objective was to evaluate the dopaminergic motor response and its association with pathologically confirmed diagnoses, we did not assess cognition in the present study and cannot address dementia prevalence in our patients.

Why do some patients who are ultimately shown pathologically to have PD show no response to levodopa? Age may be an important factor. In our study, the non-responders had a significantly greater age of onset than did those with a marked response. Non-responders also had a shorter disease duration. LED did not differ between these groups. While it is possible that at least some of the non-responders may have responded to a higher dose, these patients were not treated differently in the clinic where all patients with parkinsonism receive an escalating medication dose based on individual patient tolerance.

Our study does have some limitations. As a retrospective chart review, it is dependent on the accuracy of clinical information available within the medical record. Not all patients had clinical findings recorded in the form of a UPDRS motor rating and, for practical reasons, assessments were not always done in both the ON and OFF states. However, subspecialty trained movement disorders neurologists were responsible for all assessments and the narrative record provided a good indication of the degree of response to dopaminergic medications. The history of medication use and medication dose was available for all patients. Selection bias is unlikely to be a major issue. All patients in our Center are routinely invited to participate in our brain donation program early in the course of their clinic involvement, regardless of clinical diagnosis. Furthermore, the distribution of pathological diagnoses in this study is comparable to the distribution of clinical diagnoses in our Center. While we acknowledge that there are other important measures relating to the clinical diagnosis of PD and listed in the MDS clinical diagnostic criteria[1], our intent was to assess the dopaminergic response specifically and not to evaluate the overall accuracy of the criteria. Similarly, we have not addressed the accuracy of the clinical diagnosis itself in our patients or the evolving nature of clinical diagnoses as disease progresses.

These observations provide useful information regarding the sensitivity and specificity of the response to dopamine replacement medications as a disease marker. Our data indicate that a substantial response is frequent but not universal in PD. An absent response does not exclude PD. In other neurodegenerative disorders associated with parkinsonism, a significant response may also be evident although less frequently than in PD. Our data in addition to previously published data on medication response suggest that using the absence of an observable response to a levodopa dose ≥ 600mg/day as an exclusion for the diagnosis of PD as recommended in the MDS Clinical Diagnostic Criteria for Parkinson's Disease[1] merits reconsideration.

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Table 1.

Demographics and Medication Response

	Total Group	Medication Response		
		marked	moderate	nil
PD				
subjects (% total PD)	182	125 (68.7%)	41 (22.5%)	16 (8.8%)
% female	29.1%	30.4%	31.7%	12.5%
onset age (yr; mean±SD)	60.8±11.9	58.8±12.5	61.7±13.2	70.6±9.1
disease duration (yr; mean±SD)	16.2±7.7	17.8±9.1	14.6±8.5	10.4±6.0
LED median/mean±SD	650/766±410	700/795±438	600/639±322	825/845±308
LED range	150–2843	150–2843	190–1600	400–1500
dyskinesia	121 (66.5%)	101 (80.8%)	20 (48.8%)	0
wearing off	129 (70.9%)	106 (84.8%)	23 (56.1%)	0
MSA				
subjects (% total MSA)	25	4 (16%)	9 (36%)	12 (48%)
% female	56.0%	75.0%	44.4%	58.3%
onset age (yr; mean±SD)	58.6±11.1	49±11.3	60.9±10.8	60.1±9.4
disease duration (yr; mean±SD)	6.9±3.9	8.5±5.3	7.8±4.7	5.7±2.9
LED median/mean±SD	900/922±377	775/849±409	826/964±423	938/915±363
LED range	200–1900	450–1397	600–1900	200–1500
dyskinesia	6 (24%)	3 (75%)	3 (33.3%)	0
wearing off	9 (36%)	4 (100%)	5 (55.6%)	0
PSP				
subjects (% total PSP)	18	3 (16.7%)	5 (27.8%)	10 (55.6%)
% female	33.3%	66.7%	40%	40%
onset age (yr; mean±SD)	69.3±7.9	71.3±6.7	76.9±7.6	65.0±5.3
disease duration (yr; mean±SD)	9.1±5.6	17.0±4.9	8.2±6.3	7.2±3.3
LED median/mean±SD	875/924±373	851/934±236	750/810±272	1050/978±455
LED range	300–1630	750–1200	451–1200	300–1630
dyskinesia	5 (27.8%)	1 (33.3%)	4 (80%)	0
wearing off	5 (27.8%)	2 (66.7%)	3 (60%)	0
CBD				
subjects (% total CBD)	8	-	1 (12.5%)	7 (87.6%)
% female	25.0%	-	100%	14.3%
onset age (yr; mean±SD)	63.9±9.0	-	66.8	63.5±9.6
disease duration (yr; mean±SD)	6.9±4.6	-	6.9	6.9±4.9
LED median/mean±SD	975/943±336	-	1064	900/926±359
LED range (median)	450–1500	-	1064	450–1500

	Total Group	Medication Response		
		marked	moderate	nil
dyskinesia	1 (12.5%)	-	1	0
wearing off	1 (12.5%)	-	1	0

PD: Parkinson disease

MSA: multiple system atrophy

PSP: progressive supranuclear palsy

CBD: corticobasal degeneration

LED: levodopa equivalent dose (mg)

Table 2.

Other Pathological Diagnoses and Medication Response

Diagnosis	Patients	Female	Onset Age (yr; mean ±SD)	Duration (yr; mean±SD)	Medication Response			Dyskinesias	Wearing off
					marked	moderate	nil		
vascular disease	7	2	74.2±4.8	10.7±5.3	-	3	4	-	2
Alzheimer disease	2	1	60.5±3.5	7.7±2.5	-	-	2	-	-
NBIA	2	-	63.8±10.2	7.1±5.6	-	1	1	-	-
PART	2	1	70.5±0.7	16.8±6.4	-	1	1	-	1
CJD	1	-	75.1	7.5	-	-	1	-	-
AGD	1	-	72.0	13.6	-	-	1	-	-
Huntington disease	1	-	24.0	18.1	-	1	-	-	-
mitochondrial mutation	1	1	51.0	11.7	-	1	-	-	-
HIE	1	-	67.0	18.7	-	-	1	-	-
NPH	1	1	70.0	13.5	-	-	1	-	-
unexplained	5	3	64.4±17.1	11.8±4.4	0	2	3	2	2

NBIA: neurodegeneration with brain iron accumulation

PART: primary age-related tauopathy

CJD: Creutzfeld-Jakob disease

AGD: argyrophilic grain disease

HIE: hypoxic-ischemic encephalopathy

NPH: normal pressure hydrocephalus