Corticobasal degeneration with pallido-nigro-luysial degeneration, axonal dystrophy, and TDP-43 pathology: a distinct clinicopathologic variant

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Background

Corticobasal degeneration (CBD) is a progressive neurodegenerative 4R-predominant tauopathy with distinct neuronal and glial p-tau positive aggregates in the cortex, basal ganglia, diencephalon, and brainstem. Classically, CBD presents with asymmetric rigidity, levodopa-unresponsive parkinsonism, apraxia, aphasia, dystonia, cortical sensory loss, and cognitive dysfunction; collectively termed corticobasal syndrome (CBS). Pallidonigroluysial degeneration and axonal dystrophy (PNLA) is characterized by severe neuronal loss, gliosis, and numerous axonal spheroids in the globus pallidus, substantia nigra, and subthalamic nucleus (Luys). In the setting of PSP, PSP-PNLA accounts for roughly 10% of all PSP cases and is associated with a distinct clinical phenotype, PSP-pure akinesia gait freezing (PSP-PAGF). Since PNLA has never been reported to coincide with CBD, we sought to perform a comparative analysis of clinical and pathological features of CBD cases with and without PNLA, and compare this data to PSP cases with and without PNLA.

Characterization of Pallido-nigro-luysial Neuronal Loss

- Severe astrogliosis can be seen in all three sections in CBD-PNLA cases, as well as degeneration of the neuropil.
- Axonal dystrophy, as noted by the abundance of axonal spheroids, can be seen in the GPi and the SNc.
- Compared to CBD cases, very few neurons are preserved; and there is no longer extracellular neuromelanin in the SNc.
- In the GPi, STN, and SNc, CBD-PNLA cases had significantly fewer surviving neurons compared to CBD cases.
- In the SNc, there were also fewer surviving neurons in CBD-PNLA cases compared to PSP cases.

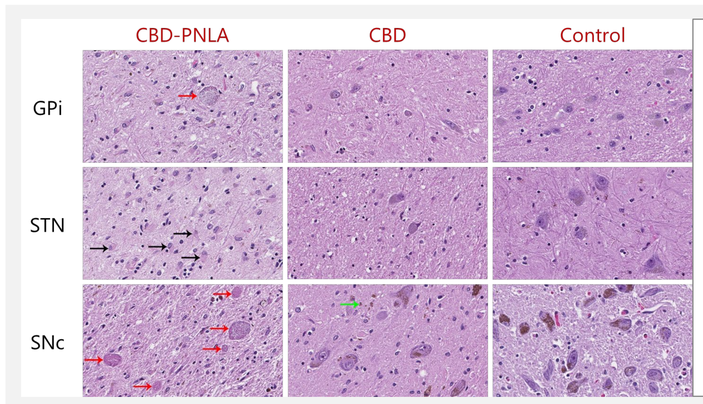


Fig.1 Comparison of neuronal loss in the globus pallidus interna (GPi), subthalamic nucleus (STN), and substantia nigra pars compacta (SNc) in CBD-PNLA, CBD, control cases (Red arrows = pigmented axonal spheroids; black arrows = reactive astrocytes; green arrows = extracellular neuromelanin).

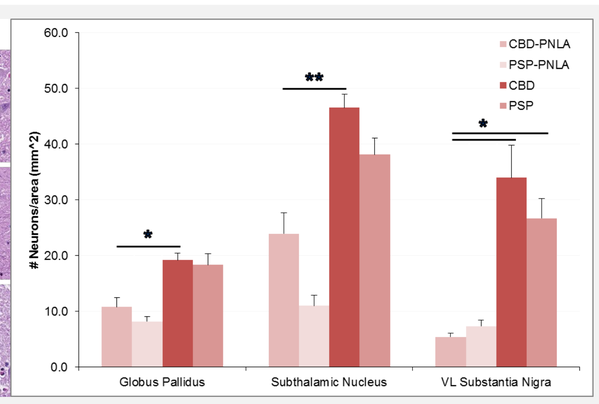


Fig.2 Neuronal loss via the number of surviving neurons per area (mm^2) in the globus pallidus, subthalamic nucleus and ventrolateral group of the substantia nigra in CBD-PNLA compared to PSP-PNLA, CBD, and PSP (N = 20 for CBD-PNLA, N = 40 for comparison groups; * = $p < 0.01$; ** = $p < 0.001$)

Materials & Methods

Case selection

Twenty CBD-PNLA cases were identified from a series of 193 CBD cases submitted for review or consultation to the Mayo Clinic Brain Bank in Jacksonville between 1998 and 2018. These three cases are compared to a set of control cases, including CBD, PSP, PSP-PNLA, and neurologically normal controls (n = 40 for each group).

IHC + semiquantitative assessment

5-µm sections of formalin-fixed and paraffin-embedded specimens were immunostained with p-tau mouse monoclonal antibody (CP13). Also, the globus pallidus, substantia nigra and subthalamic nucleus were screened for pTDP-43 mouse monoclonal antibody (pS409/410, 1:5000), then a further 24 regions were screened for pTDP-43 pathology and graded for severity semiquantitatively.

Neuronal loss

To assess neuronal loss between 20 CBD-PNLA and 40 CBD, PSP, and PSP-PNLA cases, three non-overlapping images were randomly captured from H&E-stained sections of the globus pallidus, ventrolateral substantia nigra, and subthalamic nucleus (0.6mm x 0.6mm), and the mean value of surviving neurons was counted manually.

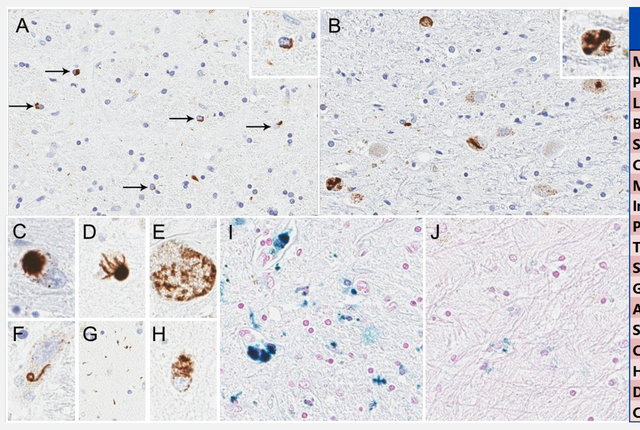
Tau burden

Three non-overlapping images were randomly captured from tau-immunostained sections of the frontal cortex grey matter, globus pallidus, subthalamic nucleus, and the substantia nigra (0.6 mm x 0.6 mm each image). The captured images were processed with image analysis software (ImageScope v12.4.0; Aperio, Vista, CA). A ratio of the immunoreactive pixels to the total pixels of the whole field was calculated to yield an estimate of lesion burden (%) and the mean value was calculated for each case.

Review of clinical records

Demographic and clinical information was gathered from medical records and a brain bank questionnaire filled out by a close family member. The information included age at symptom onset, age at death, sex, race, primary clinical diagnosis, and clinical symptoms and signs (asymmetric apraxia, rigidity, dystonia, myoclonus, alien limb phenomenon, cortical sensory loss, downward gaze palsy, cognitive impairment, and behavioral symptoms, falls, extrapyramidal symptoms, L-dopa response, and whether the onset of motor symptoms was asymmetric or not). If a symptom or sign was not specifically mentioned in the medical records or questionnaire, it was not considered to be absent and removed from the cases evaluated for that symptom.

pTDP-43 Immunoreactivity in CBD-PNLA



Location	Frequency	Median score (25,75)
Midbrain tegmentum	94%	3 (2,3)
Pontine tegmentum	94%	2 (1,3)
Locus Ceruleus	83%	1 (1,1)
Basal nucleus of Meynert	81%	1 (1,1)
Substantia nigra	81%	2 (1,3)
Caudate nucleus	80%	2 (1,3)
Midbrain tectum	80%	1 (1,3)
Inferior olivary nucleus	80%	1 (1,2)
Putamen	75%	2 (1,3)
Thalamus	75%	1 (1,3)
Subthalamic nucleus	75%	2 (1,3)
Globus pallidus	69%	1 (0,2)
Amygdala	63%	1 (0,2)
Superior frontal gyrus	56%	1 (0,2)
Cingulate gyrus	44%	0 (0,1)
Hippocampus	38%	0 (0,1)
Dorsal motor nucleus	31%	0 (0,1)
Cerebellar Dentate nucleus	31%	0 (0,1)

Fig.3 pTDP-43 positive lesions in CBD-PNLA cases. Numerous glial cytoplasmic inclusions in the globus pallidus (A); Pleomorphic skein-like neuronal cytoplasmic inclusions in the subthalamic nucleus (B). Pick body-like inclusion in the substantia nigra (C); Comet inclusion in the inferior olivary nucleus (D). pTDP-43 (+) axonal spheroid in the globus pallidus (E); skein-like inclusion in the medullary tegmentum (F). An astrocytic plaque in the head of the caudate nucleus (G); a pretangle in the posterior hippocampus/subiculum (H). Prest iron stain of the globus pallidus in CBD-PNLA (I) and CBD (J) cases.

Fig.4 Distribution and frequency of semiquantitatively scored pTDP-43 immunoreactive lesions in pTDP-43 positive CBD-PNLA cases. Scoring was based on GCIs, NCIs, and axonal spheroids cumulatively. Not included but analyzed: posterior and anterior hypothalamus, parahippocampal gyrus, corpus callosum, cerebellar white matter, dentate gyrus, pontine base, and the nucleus accumbens.

- The pTDP-43 inclusions in CBD-PNLA spanned many brain regions; but were most frequent predominantly in brainstem regions, like the midbrain tegmentum, pontine tegmentum, and locus ceruleus.
- The substantia nigra, subthalamic nucleus and the globus pallidus are more frequently effected than regions associated with other TDP-43 proteinopathies like FTLD-TDP or LATE.
- The morphology of the pTDP-43 inclusions was pleomorphic with some appearing skein-like, as preinclusions, or as more dense pTDP-43 deposits.
- TDP-43 (+) axonal spheroids were noted frequently in the globus pallidus, a feature also seen in Perry syndrome.
- There were highly frequent TDP-43 (+) GCIs in the globus pallidus of CBD-PNLA cases.
- Iron deposition in the globus pallidus was seen more often and more densely in CBD-PNLA cases compared to CBD cases.

Clinical Features

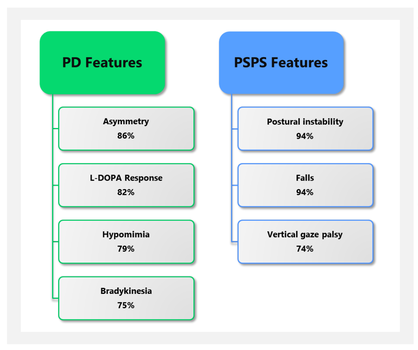


Fig.5 Frequent clinical features in CBD-PNLA cases

- Many of CBD-PNLA cases presented with an asymmetric onset of motor symptoms and responded to levodopa-carbidopa treatment.
- PSPS features were frequently noted as well, including supranuclear gaze palsy, falls, and postural instability.
- CBS features were not commonly present in CBD-PNLA cases; some suggestive features including stimulus-sensitive myoclonus were not frequently tested for on examination.

- CBD-PNLA cases did not present with resting tremor.
- The clinical features of PSP-PAGF were not frequently present.
- CBD-PNLA did not often present with typical CBS clinical symptoms.

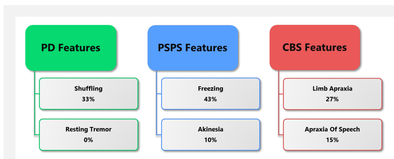


Fig.6 Infrequent clinical features in CBD-PNLA cases

Tau Image Analysis

- Percent tau burden was higher in the frontal cortex and to a greater degree in the subthalamic nucleus in CBD-PNLA cases compared to CBD cases.
- The percent tau burden was slightly, yet not significantly higher in the globus pallidus and substantia nigra in CBD-PNLA cases compared to CBD cases.

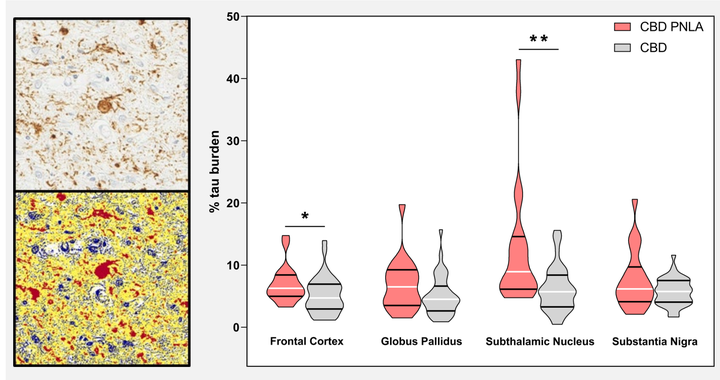


Fig.6 Percent tau burden presented as violin plots from digital image analysis of CP13 stained sections. (White bar = median; black bars = 75th and 25th quartiles; * $p < 0.03$; ** $p < 0.001$). Representatively sized image of a CP13 stained section of the subthalamic nucleus at the level of the mammillothalamic tract using ImageScope v12.4.0.

Demographics

- Disease duration was significantly shorter in CBD-PNLA cases compared to PSP-PNLA and PSP cases.
- Age at death was younger in CBD-PNLA cases compared to all other comparison groups.
- There was not a gender bias in CBD-PNLA or the comparison groups.
- CBD-PNLA presented more often with PSPS compared to CBD cases.

Features	CBD-PNLA N = 20	CBD N = 40	PSP-PNLA N = 40	PSP N = 40	P value
# Female (%)	10 (50%)	21 (53%)	18 (45%)	19 (48%)	ns
Age at death (years)	65 ± 1*	68 ± 1	74 ± 1	73 ± 1	<0.001
Disease duration (years)	5.7 ± 0.3	6.2 ± 0.4	9.3 ± 0.6	7.3 ± 0.5	<0.001
Brain weight (g)	1195 ± 30	1132 ± 24	1197 ± 30	1109 ± 22	ns
Argyrophilic grains disease	14/20 (70%)*	18/40 (45%)	8/40 (20%)	6/40 (15%)	<0.001
Lewy-related pathology	1/20 (5%)	2/40 (5%)	0/40 (0%)	0/40 (0%)	ns
Braak NFT stage	II (I, III)	II (I, III)	II (II, III)	II (II, III)	ns
Thal amyloid stage	0 (0,1)	0 (0,1)	1 (0,2)	0 (0,1)	ns
Clinical diagnosis of PSPS	14/20 (70%)	9/40 (23%)	37/40 (93%)	33/40 (83%)	<0.001
Clinical diagnosis of CBS	5/20 (25%)	22/40 (55%)	0/40 (0%)	4/40 (10%)	<0.001

Conclusions

- **10%** of CBD cases had severe neuronal loss, gliosis, and numerous axonal spheroids in the globus pallidus, substantia nigra, and subthalamic nucleus (CBD-PNLA).
- Higher tau burden in subthalamic nucleus and frontal cortex in CBD-PNLA compared to CBD.
  - No difference in globus pallidus and substantia nigra.
- The brainstem-predominant distribution of pTDP-43 inclusions in CBD-PNLA is different to LATE or FTLD-TDP.
  - pTDP-43(+) axonal spheroids and GCIs.
- Clinically, CBD-PNLA often did not present with CBS symptoms, instead CBD-PNLA cases presented with features resembling typical parkinsonism or PSPS.

Future Directions

- Tau biochemical analyses via sarkosyl insoluble tau immunoblotting to characterize possible unique banding patterns of tau isoforms and 4R versus 3R tau ratios.
- TDP-43 biochemical analyses via immunoblot to determine whether the TDP-43 pathology in CBD-PNLA is like known FTLD-TDP subtypes or ALS.
- Factoring or hierarchical clustering analysis of CBD, CBD-PNLA, PSP, and PSP-PNLA clinical features to determine whether CBD-PNLA cases present with a unique clinical syndrome.

References

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Acknowledgements

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