Corticobasal degeneration with TDP-43 pathology presenting with progressive supranuclear palsy syndrome: A distinct clinicopathologic subtype

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Background & Aim

Corticobasal degeneration (CBD) shows various clinical phenotypes, such as corticobasal syndrome (CBS), progressive supranuclear palsy (PSP) syndrome, frontal behavioral-spatial syndrome, and non-fluent aphasia.[1] Several studies have demonstrated that the severity and distribution of tau pathology may contribute to the different clinical phenotypes;[2,3] however, the clinicopathologic correlation of CBD is not fully understood. We hypothesized that concomitant pathology other than tau, such as TDP-43, may also affect clinical phenotypes of CBD. The objective of this study was to examine whether TDP-43 contributes to clinicopathological heterogeneity of CBD.

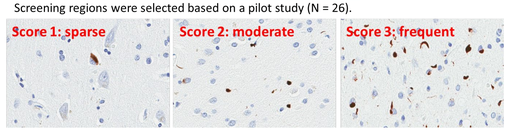
Materials & Methods

Case selection and diagnosis: Between 1998 and 2017, 211 cases in the Mayo Clinic brain bank have been given a neuropathologic diagnosis of CBD. Of those, 187 cases with available paraffin-embedded tissue were included in this study.

Screening of TDP-43 pathology: We screened TDP-43 pathology using sections as shown below and the pilot study. The sections were immunostained with anti-phospho-TDP43 antibody (pS409/410, mouse monoclonal, 1:5000, Cosmo Bio) using a DAKO Autostainer. All slides were reviewed simultaneously by two observers (D.W.D., S.K.) who agreed on the presence of TDP-43 immunoreactivity, defined as neuronal cytoplasmic inclusions (NCIs), glial cytoplasmic inclusions (GCIs), dystrophic neurites, neuronal intranuclear inclusions, spheroids, or perivascular inclusions in any region. The severity of TDP-43 pathology was graded semi-quantitatively on a four-point scale.

Screened in all cases		Additional regions
Amygdala	If TDP-43 (+)	Superior frontal gyrus
Hypothalamus		Cingulate gyrus
Subthalamic nucleus		Precentral gyrus
Thalamus		Hippocampus
Midbrain		Medulla
Pons		Cerebellum

Screening regions were selected based on a pilot study (N = 26).



Cluster analysis: Hierarchical cluster analysis using Euclidean distance and average linkage clustering was performed on patients and region-specific variables reflecting the severity of TDP-43 pathology.

Genetic analysis: For genotyping, genomic DNA was extracted from cerebellum of frozen brain tissue using standard procedures. Genotyping for *GRN* (SNP rs5848 C/T SNPs, T minor allele), *TMEM106B* (rs3173615 C/G SNPs, G minor allele), and *MAPT* H1/H2 (SNP rs1052553 A/G, A = H1, G = H2) was assessed with TaqMan SNP genotyping assays.

Pilot study

Pilot ID	Midbrain	Subthalamic nucleus	Amygdala & basal forebrain	Pons	Medulla	Sup Front gyrus	Precentral gyrus	Hippocampus	Cerebellum
1	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-
5	-	-	-	NA	NA	-	-	-	-
6	-	-	-	-	-	-	-	-	-
7	+	+	+	+	+	+	-	+	-
8	-	-	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-
11	-	+	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-
13	+	+	+	+	+	+	+	-	-
14	+	+	+	+	+	-	-	-	-
15	-	-	-	-	-	-	-	-	-
16	+	+	+	+	+	-	-	+	-
17	+	+	-	-	-	-	+	-	-
18	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	-	-
20	+	+	+	+	+	-	-	-	-
21	+	+	+	-	-	+	-	-	-
22	-	-	-	-	-	-	-	-	-
23	-	-	-	-	-	-	-	-	-
24	+	-	-	-	-	-	+	-	-
25	-	-	-	+	-	-	-	-	-
26	+	+	+	+	+	+	-	+	-
Total	9/26	9/26	7/26	7/26	6/26	4/26	3/26	3/26	0/26

Table 1: Nine sections are screened for TDP-43 immunohistochemistry using most recent 26 CBD cases. The result suggest that the sections of midbrain, subthalamic nucleus, amygdala & basal forebrain, and pons have most frequently have TDP-43 pathology.

Results: TDP-43 screening

In total, **45%** of CBD had TDP-43 pathology

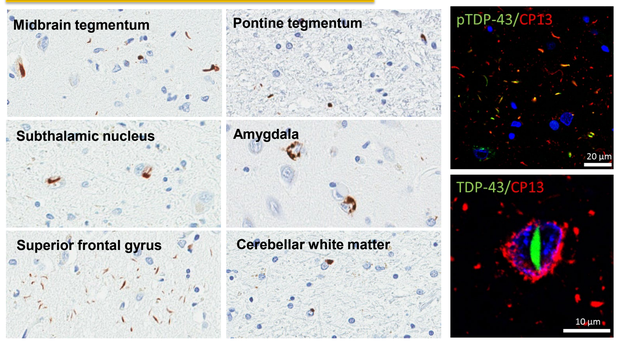


Fig. 1: TDP-43 pathology showed various morphology: NCIs, GCIs, dystrophic neurites, neuronal intranuclear inclusions, spheroids, and perivascular inclusions. Double-labeling immunofluorescence staining revealed that TDP-43 aggregates were observed in astrocytic plaques and pretangles (right column).

Vulnerable regions		Less vulnerable regions	
Brainstem		**Limbic structures**	
Midbrain tegmentum	36%	Amygdala	19%
Substantia nigra	28%	Hippocampus	16%
Pontine tegmentum	29%	**Neocortices**	
Inferior olivary nucleus	23%	Superior frontal gyrus	19%
Subcortical nuclei		Motor cortex	13%
Subthalamic nucleus	31%	**Cerebellum**	
Hypothalamus	27%	Cerebellar white matter	7%
Thalamus	23%		

Results: Cluster analysis

Cluster analysis based on the extent and severity of TDP-43 pathology

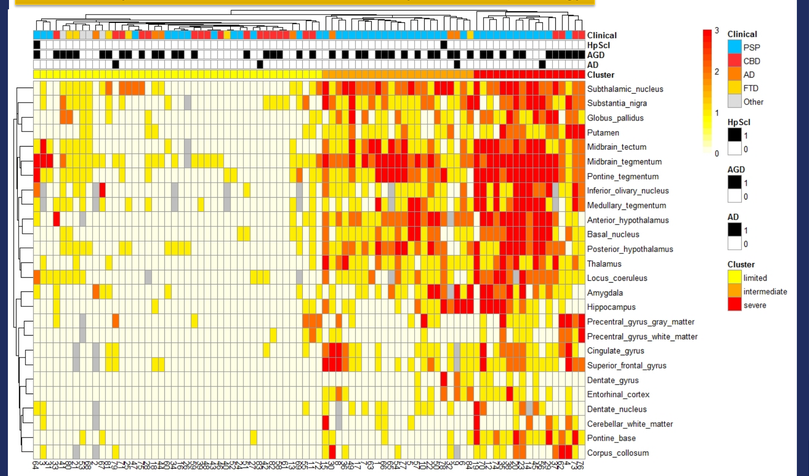


Fig. 2: Hierarchical cluster analysis suggested potentially three distinct clusters (i.e. limited, intermediate, and severe). We combined intermediate and severe into a single group; thus, we divided TDP-43 positive CBD cases into TDP-limited (N = 44) and TDP-severe (N = 40) groups. Concomitant pathologies (Alzheimer's disease [AD], argyrophilic grain disease [AGD], and hippocampal sclerosis [HpScl]) and clinical diagnosis of each case is also shown as annotation labels.

Clinical features	TDP-negative N = 103	TDP-limited N = 44	TDP-severe N = 40	P value
Sex, %male	52%	48%	38%	0.284
Age, years	69 ± 8	70 ± 7	72 ± 9	0.226
Disease duration, years	6 ± 3	7 ± 2	7 ± 4	0.396
Clinical diagnosis of CBS	47%	39%	10%	<0.001
Clinical diagnosis of PSP syndrome	30%	32%	80%	<0.001
Downward gaze palsy	34%	35%	85%	<0.001
Asymmetrical parkinsonism	74%	69%	65%	0.766

Table 2: Clinical features are compared between the three groups: TDP-negative, TDP-limited, and TDP-severe CBD. Only 10% of TDP-severe CBD was clinically diagnosed with CBS. Instead, 79% of them were diagnosed with PSPS. This can be explained by the fact that 85% of TDP-severe CBD presented with downward gaze palsy, a characteristic feature of PSP.

Explanatory variables	Odds ratio	95% CI	P value
Age at death, years	1.02	0.97-1.08	0.385
Sex (0 = female, 1 = male)	1.04	0.44-2.46	0.928
Disease duration, years	0.88	0.73-1.06	0.181
TDP-43, midbrain tectum	**9.77**	**1.75-54.7**	**0.010**
TDP-43, midbrain tegmentum	0.79	0.31-2.02	0.618
Tau, oculomotor complex	1.51	1.09-2.08	0.012
Tau, midbrain tectum	0.79	0.59-1.06	0.120

Table 3: A multivariate logistic regression model shows that TDP-43 pathology in the midbrain tectum is strongly associated with the downward gaze palsy.

	TDP-negative N = 103	TDP-limited N = 44	TDP-severe N = 40	P value Overall
TMEM106B, Minor	12%	15%	11%	0.861
GRN, Minor	6%	7%	14%	0.420
MAPT, H1/H1	91%	89%	**65%**	**0.002**

Table 4: The frequencies of TMEM106B minor allele and GRN minor allele were not different, suggesting these variant may not associate with TDP-43 pathology in CBD. MAPT H1/H1 haplotype was significantly lower in TDP-43 severe CBD than other CBD

Discussion

- It is well known that TDP-43 pathology is frequently observed in Alzheimer's disease or hippocampal sclerosis. As shown in Fig. 2, however, the concomitant Alzheimer's disease or hippocampal sclerosis did not affect the TDP-43 pathology in CBD (the frequency of these pathologies was not different between the groups).
- TDP-severe CBD cases present frequently with PSP syndrome, but it is still unclear that TDP-43 pathology cause characteristic features of PSP.
- TDP-43 pathology is rare in PSP; thus, the TDP-43 may be useful to distinguish CBD and PSP.
- The results of the genetic analysis suggest that the mechanism of TDP-43 pathology may differ from that of frontotemporal lobar degeneration with TDP-43, in which *TMEM106B* and *GRN* are the risk modifier for TDP-43 pathology.

Summary

- TDP-43 pathology is frequent (45%) in CBD, mainly in the brainstem and subcortical nuclei.
- TDP-severe CBD were commonly diagnosed as PSP syndrome because of the downward gaze palsy.
- The severity of TDP-43 pathology in the midbrain tectum was strongly associated with the presence of downward gaze palsy.
- MAPT H1 frequency is significantly low in TDP-severe CBD compared with other CBD.
- TMEM106B and GRN variants may not be a risk factor for TDP-43 pathology in CBD.

References

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