Traumatic Brain Injury and Age at Onset of Cognitive Decline in Corticobasal Degeneration, Corticobasal Syndrome, and Progressive Supranuclear Palsy

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Abstract

Importance: Traumatic brain injury (TBI) has been repeatedly shown to be a risk factor for several neurodegenerative diseases. However, no studies have yet examined TBI as a risk factor for corticobasal degeneration (CBD) or corticobasal syndrome (CBS), and few have examined progressive supranuclear palsy (PSP) in relation to TBI.

Objective: Determine TBI's relation to the age at onset (AAO) of cognitive decline in PSP, CBS, and CBD and to the prevalence of PSP and CBD neuropathology.

Design: This is a retrospective observational study using the National Alzheimer's Coordinating Centers (NACC) database. The most recent assessment of participants was used as of June 2018, including participant visits which occurred between 2005 and 2018.

Setting: NACC is a multicenter dataset with standardized data collection procedures.

Participants: The NACC dataset includes a total of 38,249 participants. 101 (14 TBI+) participants were included with clinical (antemortem) diagnoses of PSP and 137 (16 TBI+) with CBS. It also includes 2,743 autopsy samples, including 120 (14 TBI+), 58 (7 TBI+), and 11 (1 TBI+) with neuropathological (autopsy) diagnoses of PSP, CBD, or both, respectively. 181 (21 TBI+) of the participants with autopsy diagnosed PSP or CBD had antemortem cognitive decline.

Exposure: Self-reported history of TBI.

Main Outcomes: Clinician estimated AAO of cognitive decline and prevalence of neuropathological diagnosis of CBD and PSP.

Results: TBI is associated with a significant 4-year earlier AAO of cognitive decline among participants with an antemortem diagnosis of CBS and a 6-year earlier AAO in participants with autopsy diagnosed PSP. Additionally, TBI among participants with autopsy diagnosed CBD without concomitant Alzheimer's disease (AD) neuropathology was associated with a 7-year earlier AAO of cognitive decline (p=.066). History of TBI was not significantly associated with the prevalence of PSP and/or CBD pathology postmortem.

Conclusions and Relevance: This is the first report linking TBI with an earlier onset of cognitive decline in CBS and in neuropathologically defined PSP.

Methods

Database: The NACC database is comprised of data from 32 NIH supported Alzheimer's disease centers. History of TBI is collected through participant and informant interviews and AAO of cognitive decline is estimated by the clinician. Diagnosis of CBS and PSP are made by clinician judgement. For neuropathological examinations, diagnoses of PSP and CBD are made based on diagnostic criteria from Dickson[1] and Dickson et al.[2] As has been seen in past reports[3], there was very poor diagnostic overlap between clinical and postmortem diagnoses of CBD/CBS and PSP (e.g. <20% of those with a CBS diagnosis had CBD on postmortem evaluation). Clinical and postmortem diagnoses were therefore treated separately throughout this report. For all NACC participants, the most recent clinic visit was used. Inclusion criteria required participants to have data on relevant demographic variables and no reported TBI <1 year prior to assessment.

Antemortem Diagnosed Sample: The NACC dataset is comprised of 38,249 participants. 238 (30 TBI+) of these participants had antemortem diagnoses of PSP and/or CBS, including 101 (14 TBI+) diagnosed with PSP and 137 (16 TBI+) diagnosed with CBS.

Autopsy Diagnosed Sample: Of the 38,249 participants in the NACC dataset, 2,743 (322 TBI+) are included in the postmortem analyses, including 2,554 (300 TBI+) with neither PSP nor CBD, 120 (14 TBI+) with only PSP, 58 (7 TBI+) with only CBD, and 11 (1 TBI+) with both PSP and CBD as postmortem diagnoses. Of the 189 (22 TBI+) participants with PSP and/or CBD (postmortem), 181 (21 TBI+) were deemed to have cognitive decline at their most recent visit. These participants are therefore included in analyses examining AAO of cognitive decline among participants with these neuropathologies.

Analyses: Demographic differences were compared using t-tests and Chi-square tests. A generalized linear model was used to predict AAO after adjusting for education, sex, history of alcohol abuse, history of smoking, history of drug abuse, education, race, and APOE e4 status. Odds ratios (ORs) for likelihood of postmortem diagnosis of PSP and/or CBD were calculated based on binary logistic regressions and the above covariates and age at death were included in the model.

Results

Antemortem Diagnoses: TBI was associated with a significantly earlier AAO among participants diagnosed antemortem with PSP and/or CBS by 3.5 (0.37-6.7) years, and among participants diagnosed antemortem with CBS by 4.1 (0.0-8.2) years. TBI-related AAO differences among participants with antemortem PSP did not reach significance, likely due to its smaller sample size, but TBI was associated with a sizeable effect of a 2.2 (-2.7-7.0) year earlier AAO (see table below).

		AAO TBI-	N_{TBI-}	AAO TBI+	N_{TBI+}	Raw AAO Difference	Adjusted AAO Difference
Ante-mortem Diagnosis	PSP+ CBS	63.8 (8.1)	208	60.3 (8.8)	30	3.5 (0.4-6.7)	3.5 (0.4-6.7)
	PSP	64.8 (9.0)	87	61.6 (8.5)	14	3.2 (-1.8-8.2)	2.2 (-2.7-7.0)
	CBS	63.1 (7.4)	121	59.1 (9.2)	16	4.0 (0.0-7.9)	4.1 (0.0-8.2)
Post-mortem Diagnosis	PSP+ CBD	67.4 (9.6)	160	64.3 (11.0)	21	3.0 (-1.4-7.5)	4.3 (-.2-8.8)
	PSP	69.4 (9.9)	110	65.1 (11.5)	14	4.3 (-1.4-10.0)	5.9 (0.4-11.5)
	CBD	63.4 (7.7)	60	65.0 (11.4)	8	-1.6 (-7.8-4.5)	-2.2 (-8.4-4.0)

AAO: TBI predicted a younger AAO of cognitive decline among participants diagnosed at autopsy with PSP (5.9 years) but not among those with autopsy diagnosed CBD (non-significant 2.2-year older AAO), as shown in the table above.

AAO in 'Pure CBD/PSP': 47 (5 TBI+) and 23 (4 TBI+) participants were diagnosed at autopsy with PSP and CBD (respectively) and had no concomitant AD pathology ('pure' CBD/PSP). TBI was associated with a 9.2 (2.4-16.0) year younger AAO of cognitive decline in these participants, with a 7.0 (-0.5-14.4) year younger onset in those with 'pure' CBD (p=.066) and a 10.5 (1.7-19.4) year younger onset in those with 'pure' PSP.

Neuropathology: TBI+ and TBI- participants had nearly identical rates of postmortem defined CBD (2.5% vs. 2.5%) and PSP (4.7% vs. 4.8%), with no significant difference in regression models (table below).

Outcome	TBI- (n=2421)	TBI+ (n=322)	OR_{TBI}
PSP+CBD (n=189)	167 (6.9%)	22 (6.8%)	0.88 (0.55-1.41)
PSP (n=131)	116 (4.8%)	15 (4.7%)	0.87 (0.50-1.53)
CBD (n=69)	61 (2.5%)	8 (2.5%)	0.86 (0.40-1.84)

Discussion

Summary: We found TBI to be associated with a younger AAO of cognitive decline among participants with antemortem diagnosed CBS or postmortem diagnosed PSP, making TBI the first discovered environmental risk factor for CBS and one of the first for PSP. The non-significant relation between TBI and the AAO of cognitive decline in participants with antemortem diagnosed PSP was likely due to misdiagnoses decreasing our power for detecting true effects. We interestingly found TBI to be associated with a non-significant 2-year older AAO of cognitive decline among participants with autopsy diagnosed CBD which reversed to a trend toward significant 7-year earlier AAO for TBI+ participants when cases with concomitant AD pathology were excluded. Further work and replication is needed to explain this finding. Lastly, we did not find TBI to be significantly associated with neuropathological prevalence of PSP or CBD.

Implications: The neuropathological changes seen in PSP and CBD overlap considerably with the neuropathological criteria for chronic traumatic encephalopathy (CTE).[4] These similarities have likely led to misdiagnoses of PSP and CBD as CTE and extant reports have prematurely excluded PSP and CBD in favor of CTE diagnoses.[5,6] Future work is needed to understand the commonalities and differences underlying PSP, CBD, and CTE's patterns of tau deposition and their relations to TBI and care should be taken in differentiating cases of CTE from PSP and CBD.

Limitations: Limitations of this study include our inability to look at the AAO of non-cognitive symptoms, ou reliance on self-report of TBI history, our inability to examine number of TBIs suffered or TBI severity, and our reliance on clinician estimates for AAO of cognitive decline. Additionally, we could not exclude TBIs which occurred after the onset of cognitive decline but >1 year prior to visits, likely biasing our AAO analyses toward null results. Lastly, despite working in a large dataset which included 189 postmortem cases of PSP and CBD and 238 antemortem cases of PSP and CBS, making this one of the largest studies on these disorders to date, several analyses suffered from small sample sizes.

Refrerences

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