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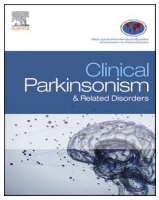

Short Communications

The potential role of chronic pain and the polytrauma clinical triad in predicting prodromal PD: A cross-sectional study of U.S. Veterans

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ABSTRACT

Introduction: The research criteria for prodromal Parkinson disease (pPD) depends on prospectively validated clinical inputs with large effect sizes and/or high prevalence. Neither traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), nor chronic pain are currently included in the calculator, despite recent evidence of association with pPD. These conditions are widely prevalent, co-occurring, and already known to confer risk of REM behavior disorder (RBD) and PD. Few studies have examined PD risk in the context of TBI and PTSD; none have examined chronic pain. This study aimed to measure the risk of pPD caused by TBI, PTSD, and chronic pain.

Methods: 216 US Veterans were enrolled who had self-reported recurrent or persistent pain for at least three months. Of these, 44 met criteria for PTSD, 39 for TBI, and 41 for all three conditions. Several pain, sleep, affective, and trauma questionnaires were administered. Participants' history of RBD was determined via self-report, with a subset undergoing confirmatory video polysomnography.

Results: A greater proportion of Veterans with chronic pain met criteria for RBD (36 % vs. 10 %) and pPD (18.0 % vs. 8.3 %) compared to controls. Proportions were increased in RBD (70 %) and pPD (27 %) when chronic pain co-occurred with TBI and PTSD. Partial effects were seen with just TBI or PTSD alone. When analyzed as continuous variables, polytrauma symptom severity correlated with pPD probability ($r = 0.28$, $P = 0.03$).

Conclusion: These data demonstrate the potential utility of chronic pain, TBI, and PTSD in the prediction of pPD, and the importance of trauma-related factors in the pathogenesis of PD.

1. Introduction

Evidence of substantial neurodegeneration is already present at the time of Parkinson disease (PD) diagnosis suggesting that a prodromal period precedes manifest disease [1]. This prodromal period is characterized by various non-motor symptoms. But these symptoms express themselves variably; not all are present in any one individual who later develops PD. In fact, the strongest predictive marker, REM Behavior Disorder (RBD), which portends a phenoconversion rate of up to 96 % to any synucleinopathy within 14 years [2], is present in no more than 25 % of newly diagnosed PD patients. To accommodate this heterogeneity in presentation, the international Parkinson and Movement Disorder Society (MDS) research criteria have been developed to combine prodromal symptoms with known risk factors to predict whether individuals are likely to have prodromal PD (pPD) [3].

Currently unaccounted for in this algorithm are trauma-related factors, principally, traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). However, evidence for their inclusion is mounting. One

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meta-analysis of 22 association studies indicates that a history of head injury with loss of consciousness had a statistically significant association with a higher risk of developing PD [4]. Larger more recent case-control studies of TBI in community [5] and Veteran [6] populations affirmed this association. Fewer studies have been performed reporting direct associations between PTSD and PD, one in a US Veteran cohort [7] and one based on national medical records in Taiwan [8]. A general limitation of these studies were incomplete controlling of important confounders and shorter lag times which could indicate reverse causation. Our own large retrospective case-control study of US Veterans showed significantly higher rates of both PTSD and TBI individually among Veterans who later developed PD compared to controls, even as far back as 60 years [9]. Moreover, these data do not support the view that PTSD and TBI confer redundant risk; in fact, the combination of both PTSD and TBI further increased the odds of PD beyond either factor alone. Since PTSD and TBI are increasingly recognized to be linked with chronic pain – a distinct nosological entity termed the 'polytrauma clinical triad' (PCT)[10] known to carry greater morbidity [11] – we next explored this subgroup of Veterans and found they had the highest rates of later PD diagnosis, even more so than established conditions of the MDS prodromal criteria [9]. Despite these findings and the observation of high prevalence of pain complaints in manifest PD [12], there is a paucity of evidence exploring chronic pain in pPD. In fact, the concept of pain in the prodromal period comes largely based on a case report [13] with more recent association studies further supporting this contention [14,15]. And while sensory detection abnormalities have been demonstrated in RBD patients, no differences have been found in pain thresholds [16,17]. This backdrop sets the stage for the question posed by the current study, which fills a focused gap in the scientific premise described above about the role of chronic pain in prodromal PD.

To test the hypothesis of whether chronic pain, and the PCT, increases the risk of prodromal PD, we performed a retrospective analysis of an ongoing cross-sectional study of chronic pain in US Veterans with and without TBI [18]. We explored the association of chronic pain with RBD and with pPD. Finally, we attempted to determine if severity of their chronic pain and comorbid TBI and PTSD symptoms influenced pPD probability.

2. Methods

2.1. Overview

The VA Portland Healthcare System Institutional Review Board approved this study (VA IRB #3988), and all participants provided informed consent. Participants (n = 246) were enrolled in this sub-study if they were Veterans with accessible electronic health records (EHR). Individuals with eye diseases (e.g., glaucoma, macular degeneration) or taking eye medications were excluded.

2.2. Polytrauma clinical triad characterization

TBI was defined by search of the EHR for TBI, head injury, brain injury, head trauma, brain trauma, concussion, loss of consciousness, and blast. If present, the Head Trauma Events Characteristics was used to determine recency, severity, and recurrence rates of TBI recurrence. Presence of likely PTSD was assessed using the PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, PCL-5, 20 items; range = 0–80), using a standard cutoff of a PCL-5 score $\geq$ 33. Chronic pain was defined as self-reported recurrent or persistent pain affecting any body part for $\geq$ 3 months. Self-reported pain severity and impact were evaluated using the Defense Veterans Pain Rating Scale (DVPRS), the Symptom Impact Questionnaire-Revised (SIQR), the National Institutes of Health Patient-Reported Outcomes Measurement Information System (NIH PROMIS) Pain Interference (PROMIS-PI), and the Neurobehavioral Symptom Inventory (NSI). These scales evaluated the impact of pain over a 24-hour, 7-day, 7-day, and 14-day time period, respectively. The Michigan Body Map (MBM) was used to identify the presence of pain over 35 different locations persisting for $>$ 3 months. Pressure algometry was performed as a quantitative assessment of somatic pain. Finally, a composite score representing PCT symptom severity, which combined the NSI, PCL, and PROMIS, was created and normalized to 100.

2.3. RBD, sleep, and depression outcomes

Participants' self-reported history of RBD was assessed via the REM Sleep Behavior Disorder Single-Question Screen (RBD1Q) [19]. All participants who underwent confirmatory video polysomnography (PSG) as part of routine clinical care within 5 years of study entry (n = 67) were retrospectively reviewed to define REM sleep without atonia (RSWA). Additional sleep specific questionnaires and self-reported depression scores, via the Patient Health Questionnaire-9 (PHQ-9), were also collected.

2.4. Prodromal PD calculator

We employed the prodromal PD calculator per published guidelines [3]. Eight out of the 10 risk factors (pesticide and solvent exposure, caffeine intake, smoking status, first degree relatives with PD, diabetes mellitus type 2, physical activity, and serum uric acid levels) and 9 out of the 11 prodromal symptoms (RBD (based on RBD1Q or PSG), a Movement Disorder Society Unified Parkinson Disease Rating Scale, Part 3 (MDS-UPDRS3) score $>$ 6 (exclusive of action tremor), constipation, excessive daytime sleepiness, orthostatic hypotension, erectile dysfunction, urinary dysfunction, depression, and global cognitive deficit) were collected from the questionnaires and electronic medical record review. Information on PD risk genes, substantia nigra echogenicity, hyposmia and tracer uptake of the presynaptic dopaminergic system were not available. Each variable was assigned a positive or negative likelihood ratio, with missing values scored as 1.0. Total likelihood ratio was calculated by multiplying the corresponding markers. This was then transformed into pPD probability, which was employed as a continuous variable. We used a cut-off of 80 % to indicate probable pPD, as suggested previously [3].

2.5. Statistical analyses

Analyses were performed using GraphPad Prism v10. Statistical significance was defined *a priori* as $p < 0.05$. When analyzing continuous variables, one-way ANOVA with Tukey's post-hoc tests were performed unless failing tests of normality and inhomogeneity, in which case the non-parametric Kruskal-Wallis test was performed with Dunn's post-hoc test and Bonferroni correction. Chi-square tests were used when analyzing categorical variables. Spearman's correlation coefficients of different groups were compared based on their confidence intervals, due to the non-normality of data.

3. Results

3.1. Study population

Data from a total of 216 Veterans with chronic pain (CP), defined as self-reported recurrent or persistent pain affecting any body part for a minimum of three months duration, were analyzed, along with 30 control Veterans (i.e. without chronic pain, TBI, or PTSD) (Table 1). Of these 216 Veterans with CP, 92 met criteria for chronic pain but not TBI or PTSD. An additional 44 met criteria for both chronic pain and PTSD, 39 met criteria for chronic pain and TBI, and 41 met criteria for all three conditions, termed the polytrauma clinical triad (PCT). The CP + PTSD and CP + TBI participants were analyzed together as a single group (CP + 1). These participants were predominantly middle-aged (54.3 ± 14.0 years of age), male (79 %), and white (76 %). Of those with TBI, 28/39

Table 1
Demographic and Polytrauma Clinical Triad Symptom Characterization.

	Controls	CP	CP+1	PCT	P value
	n=30	n=92	n=83	n=41	
Sex					0.21
Male	28 (93.3%)	76 (82.6%)	61 (73.5%)	30 (73.2%)	
Female	2 (6.7%)	16 (17.4%)	21 (25.3%)	10 (24.4%)	
Non-binary	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (2.4%)	
Age, years	54.1 ±19.2	57.6 ±12.8	52.3 ±12.8	50.3 ±13.0	0.06
Race					0.51
American Indian/Alaskan Native	0 (0.0%)	3 (3.3%)	1 (1.2%)	3 (7.3%)	
Asian	2 (6.7%)	1 (1.1%)	1 (1.2%)	1 (2.4%)	
Black/African American	1 (3.3%)	4 (4.3%)	6 (7.2%)	1 (2.4%)	
Native Hawaiian/ Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
White	22 (73.3%)	75 (81.5%)	60 (72.3%)	31 (75.6%)	
Mixed	3 (10.0%)	5 (5.4%)	11 (13.3%)	1 (2.4%)	
Other	2 (6.7%)	4 (4.3%)	1 (1.2%)	0 (0.0%)	
Not Reported	0 (0.0%)	0 (0.0%)	3 (3.6%)	4 (9.8%)	
Education					0.67
Prior to High School	0 (0.0%)	0 (0.0%)	1 (1.2%)	2 (4.9%)	
High School or GED	3 (10.0%)	9 (9.8%)	8 (9.6%)	4 (9.8%)	
Some College or Associate Degree	16 (53.3%)	45 (48.9%)	50 (60.2%)	21 (51.2%)	
Bachelor's Degree	6 (20.0%)	20 (21.7%)	16 (19.2%)	8 (19.5%)	
Master's Degree	4 (13.3%)	16 (17.4%)	5 (6.0%)	6 (14.6%)	
Doctorate's Degree	1 (3.3%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	
Not Reported	0 (0.0%)	1(1.1%)	2 (2.4%)	0 (0.0%)	
Symptom Severity					
NIH PROMIS Pain Intensity	3.79 ±1.19	7.80 ±2.68	8.62 ±2.58	9.63 ±2.66	**<0.0001**
NIH PROMIS Pain Interference	4.45 ±1.07	9.85 ±4.82	10.99 ±4.80	14.00 ±4.98	**<0.0001**
PCL-5	7.00 ±7.05	14.88 ±10.50	35.51 ±18.02	50.83 ±10.98	**<0.0001**
NSI	8.07 ±7.08	18.49 ±11.83	31.73 ±15.42	44.98 ±13.64	**<0.0001**
Psychotropic Medication Usage					
SSRI	4 (13.3%)	15 (16.3%)	23 (27.7%)	15 (31.3%)	**0.003**
SNRI	1 (3.3%)	5 (5.4%)	14 (16.9%)	4 (8.3%)	0.06
TCA	0 (0.0%)	1 (1.1%)	3 (3.6%)	1 (2.1%)	0.26
Other Psychotropic	1 (3.3%)	0 (0.0%)	3 (3.6%)	3 (6.3%)	0.08
Multiple	1 (3.3%)	4 (4.4%)	3 (3.6%)	1 (2.1%)	0.73
Total REM-active drug usage	6 (20.0%)	25 (27.2%)	43 (51.8%)	21 (43.8%)	**0.0001**

Data are mean ± standard deviation, or n (% of total). Subjects who endorsed multiple races demographic were marked Mixed. CP = chronic pain; CP + 1 = chronic pain and either TBI or PTSD; PCT = polytrauma clinical triad; NIH PROMIS = National Institutes of Health Patient-Reported Outcomes Measurement Information System; PCL-5 = Post-traumatic stress disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; NSI = Neurobehavioral Symptom Inventory. SSRI = Selective serotonin reuptake inhibitor; SNRI = Serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant. Other Psychotropic = dopamine receptor blocking agents, selegiline, valproic acid, bupropion, and lamotrigine. P values represent tests for trend.

(71.8 %) and 28/41 (68.3 %) were mild TBI (defined as duration of loss of consciousness of less than 30 min) in the CP + 1 and PCT groups, respectively. Each group was also similar in terms of mean duration of loss of consciousness (18.4 v. 16.5 h), recurrence rates (74 % v. 86 %), age of first head injury (27.9 v. 29.4 years), and years since most recent TBI (13.0 v. 15.0 years). Greater serotonergic drug usage was identified among the CP + 1 and PCT groups ($p < 0.0001$, post hoc pairwise comparisons) compared to the controls and those with chronic pain alone.

3.2. Proportion of RBD is increased in those with chronic pain

Using the RBD1Q, 36 % of CP, 46 % of CP + 1, and 71 % of PCT reported RBD (Fig. 1**A**), compared to 10 % of controls. The overall trend was statistically significant ($p = <0.0001$) with all pairwise comparisons showing significance post hoc, with the exception of CP:CP + 1. When considering only participants with confirmatory PSG ($n = 67$), the same pattern of increasing RBD frequency with accumulating neurotrauma persisted ($p = 0.04$), but post hoc pairwise comparisons were not statistically significant (Fig. 1**B**).

3.3. Prodromal Parkinson disease calculations

While RBD is specific for the subsequent development of a synucleinopathy, not all inevitably progress to PD, and the absence of a reliable bed partner can make ascertainment of RBD challenging. To evaluate whether chronic pain, PTSD, and TBI are associated with biological evidence of disease activity, i.e. prodromal disease, we utilized the pPD calculator [3]. Because the calculator is only considered valid for those participants aged 50 and above, 79 participants below age 50 were excluded from this portion of the analysis. Paralleling the prior significant trends, the highest proportion of participants with pPD were identified among the PCT group (17 %) compared to the control group (0 %), the CP group (6 %), and the CP + 1 group (10 %; $p = 0.03$; Fig. 1**C**). Similarly, we found a significant increase in mean pPD probability across the four groups ($p = 0.02$; Fig. 1**D**).

One potential concern with this approach is that these trauma-related conditions may not represent unique, independent inputs. In order to address this potential concern, the distribution of each input in the pPD calculator across the four comparison groups was examined. Statistically significant group differences did not survive post-hoc testing for any input, with the exception of depression, where the PCT group showed significantly higher rates than Control, CP, and CP + 1 (Supplementary Table 1). When depression was eliminated as a variable from the calculator, there was no change in the proportion of pPD across groups. A second potential concern is that the pPD calculator could be heavily influenced by presence or absence of PSG-confirmed RBD, given its relative weight (RBD confers a positive likelihood ratio of 130); however, even after eliminating this variable, those participants previously defined as probable pPD still showed a 3-fold increase in probability compared to those without PSG-evidence of RBD (36.6 % versus 12.4 %; $p < 0.0001$).

3.4. Association of pain with pPD probability

We next examined whether extent and severity of pain were predictive of pPD. A Spearman correlation analysis was performed to compare pain severity, measures of impact on daily function over various time ranges (24 h, 7 days, and 14 days prior to survey), and body distribution of pain with probability of pPD. Using a Bonferroni adjusted p value of 0.005 as a cutoff for statistical significance, we found that the reports of impact of pain over the preceding 7 days (PROMIS-PI and SIQR) showed statistically significant associations with pPD probability

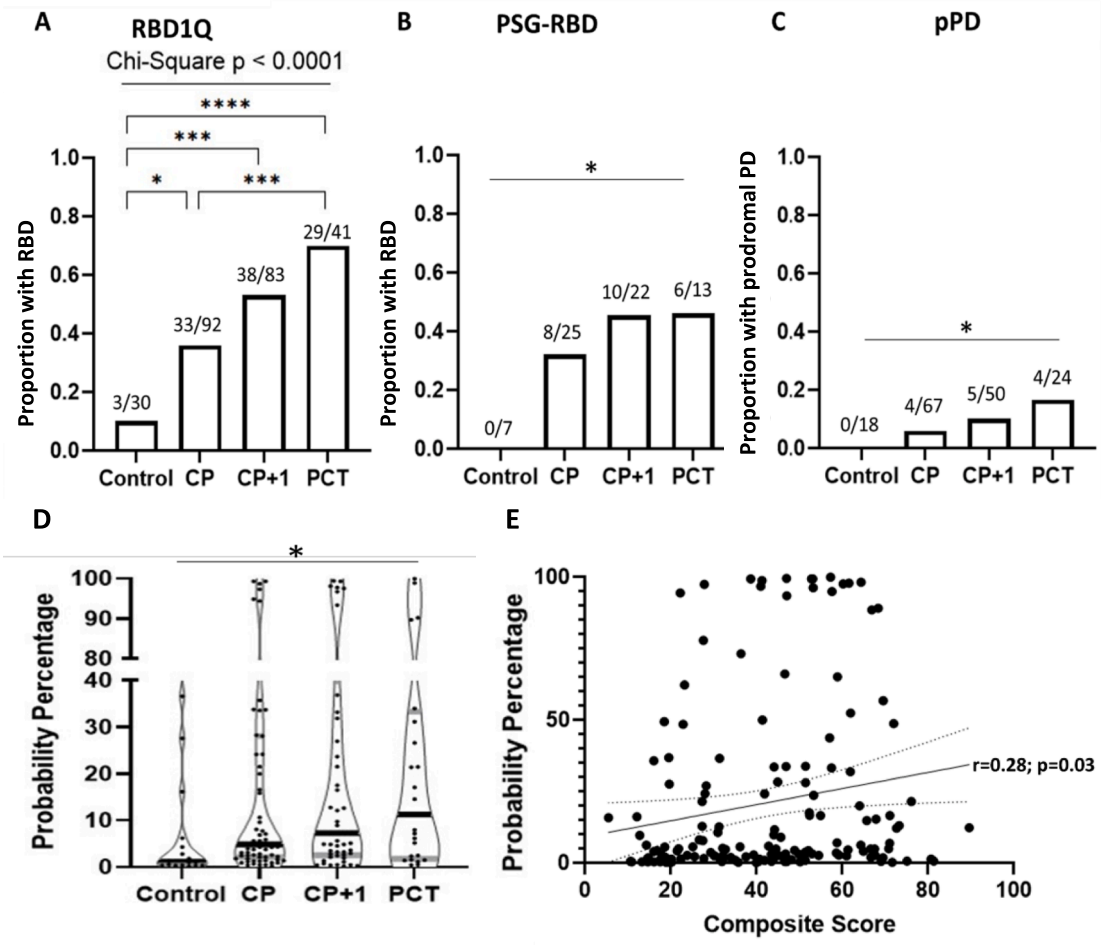

Fig. 1. Association between trauma factors with prodromal Parkinson Disease (pPD). A) Proportion of participants screening positive for REM Sleep Behavior Disorder (RBD) on the RBD1Q (chi square, $p < 0.0001$). B) Proportion of participants with polysomnography-confirmed RBD ($P = 0.04$). C) Proportion of participants defined as probable pPD based on the prodromal calculator ($P = 0.03$). D) Mean pPD probability percentage plotted for each group. Mean probability indicated by thick line: 8.4 %, 18.1 %, 23.7 %, and 27.1 % for the Control, CP, CP + 1, and PCT groups, respectively. Thick gray lines indicate 25 %-75 % interquartile range. E) Composite score of PCT severity (comprised of NIH PROMIS pain intensity and pain interference, PCL-5, and NSI; normalized to 0–100 %) plotted against probability percentage of pPD ($P = 0.03$; r = 0.28; n = 159). CP = chronic pain; CP + 1 = chronic pain + either TBI or PTSD. PCT = polytrauma clinical triad (chronic pain + TBI + PTSD); NIH PROMIS-PI = National Institutes of Health Patient-Reported Outcomes Measurement Information System; PCL-5 = Post-traumatic stress disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; NSI = Neurobehavioral Symptom Inventory. * $P < 0.05$; **** $P < 0.0001$.

(p = 0.004 and p = 0.003, respectively). Other survey instruments (DVPRS and MBM) and somatic pressure pain measures did not show significant associations. Finally, we examined the association of pPD probability with the NSI, a measure of TBI symptom type and severity, and the PCL-5, quantifying PTSD symptoms. Both correlations were statistically significant (r = 0.19; p = 0.004 and r = 0.16; p = 0.004, respectively). Finally, the composite score representing PCT symptom severity was positively correlated with pPD probability (r = 0.28; P = 0.03; Fig. 1**E**).

4. Discussion

An urgency in the field of PD is improved recognition of the disease in the prodromal state. In addition to improving patient care, it is also critical for PD clinical trials, which are increasingly aimed at early-stage disease. This has led to the development of pPD research criteria. Lacking from this are trauma-associated conditions: chronic pain, PTSD, and TBI. Since these neuropsychiatric conditions are prevalent, are commonly found in combination [10], and may influence future neurodegenerative risk [9], it is essential they are thoroughly characterized in the prodromal period.

Not only did Veterans with chronic pain show increased rates of screening positive for RBD, but we also showed that increasing trauma burden is associated with PSG-confirmed RBD and increased rates of pPD using the established pPD research criteria. While chronic pain is highly prevalent once PD is manifested – present in as many as 95 % of PD cases [20] – our study suggests that chronic pain may precede the clinical motor impairments in PD patients. Furthermore, we found that the mere presence of chronic pain, and not any specific feature, is associated with prodromal PD in individuals prior to motor symptom onset. These findings are perhaps unsurprising given that strong evidence suggests chronic pain is a hypodopaminergic state and PD is the canonical disease of reduced dopamine transmission. Evidence for this comes from rodent models of neuropathic pain which have demonstrated upregulation – and consequently increased dopamine reuptake – of dopamine transporters [21], and reduced striatal dopamine content [22]. When looking in the opposite direction – taking a lesional approach to the mesostriatal dopamine system – rodents exhibit decreased nociceptive thresholds, aggravation of chronic pain, and development of allodynia [23,24], some of which can be rescued by dopamine replacement [24,25]. Further evidence comes from human patient data. A small PET study of individuals with fibromyalgia showed reduced presynaptic dopamine release [26] and a second study of individuals with chronic low back pain showed reduced dopamine

receptor availability within the striatum and a reduced dopamine release in response to a pain challenge when compared to controls [27]. This line of evidence is further reinforced when examining PD patients, as they are demonstrably more sensitive to noxious stimuli compared to controls when tested in the off-medication state, and rescued when administered dopamine replacement [28]. Moreover, as the disease progresses, and as motor function declines, pain threshold and pain tolerance decline further [29].

This study did not address whether chronic pain is a risk factor for PD – causally contributing to PD pathogenesis – or whether it is a consequence of early structural changes that occurs in prodromal disease. In support of the former, some studies show that morphological changes (e.g. reduced striatal gray matter density) pre-exist and predispose to later development of chronic pain [30,31]. In contrast, a separate longitudinal study in patients transitioning from subacute to chronic back pain demonstrated that morphological changes only developed when the pain became chronic [32]. And some hypothesize that pain is simply a manifestation of subclinical rigidity [33]. While difficult to disentangle, either case has important implications for care of patients with chronic pain. If chronic pain contributes to PD pathogenesis, therapeutic interventions that target improvements in measures of chronic pain may also be effective at lowering patient's later risk of PD development. The identification of such could also trigger more aggressive screening or lifestyle modification to attenuate this risk [34]. If instead chronic pain is driven by reduced dopaminergic tone, medications correcting this dopamine loss may prove more effective than current standard pain management strategies without dopamine replacement therapies.

Further limiting our conclusions is the lack of precise timing information and other comparator groups. Ascertainment of TBI could be insensitive using EHR review, but it is likely to have been more specific for symptomatic TBI [35], and was confirmed with follow-up HTEC interviews. It is also unclear precisely when in life chronic pain began. While the CP + 1 and the PCT groups clearly report taking more serotonergic medications, it is unknown when these were started relative to the PSGs and it is unknown what effect these drugs may have had on dream enactment behavior. While these drugs may underlie secondary RBD [36], other reports suggest these drugs may potentially unmask a pre-existing vulnerability to RBD in a subset of individuals with pre-existing risk for synucleinopathy [37,38]. Further, due to the nature of this being a secondary analysis, we did not have groups of participants with TBI or PTSD alone to examine. The inclusion of these groups would permit logistic regression analysis, more precise timing information could permit retrospective survival analysis, or a longer follow up would permit determination of true incidence of manifest PD.

Finally, we evaluated chronic pain in the context of other trauma-related risk factors – PTSD and TBI – which represent the nosological entity known as the Polytrauma Clinical Triad (PCT). The Veteran population is an ideal population to explore these risk factors. While mostly studied in the context of Veterans, it is plausibly generalizable beyond this group. The PCT has also been described in civilian car accident survivors [39]. Moreover, we have shown that these individuals are at the highest risk of pPD. It would be ideal to follow this and similar cohorts prospectively to capture PD incidence and obtain a true measure of risk, and to assess whether those patients who are effectively treated for these PCT conditions are less likely to convert to clinical PD.

5. Conclusion

Our study evaluated a large group of Veterans with chronic pain and varying degrees of comorbid, acquired neurotrauma – PTSD and TBI. Chronic pain was associated with RBD, a powerful predictive marker of future synucleinopathy. Chronic pain was also associated with prodromal PD as measured by the MDS prodromal research criteria. Both associations were strengthened in the subpopulation that also exhibited comorbid TBI and PTSD. Finally, we showed that, as these symptoms increased in severity, the probability percentages of pPD increased. While perhaps not yet ready for inclusion within the criteria until large, long-term studies have been carried out, these data do implicate trauma-related risk factors in PD pathogenesis and may offer opportunities to potentially mitigate disease progression through early identification and intervention.

6. Disclosures

None. The interpretations and conclusions expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, the National Institute of Health, or the United States government.

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CRediT authorship contribution statement

Lee E. Neilson: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Nadir M. Balba:** Writing – review & editing, Methodology, Formal analysis. **Jonathan E. Elliott:** Writing – review & editing, Formal analysis. **Gregory D. Scott:** Writing – review & editing. **Scott D. Mist:** Funding acquisition, Data curation. **Matthew P. Butler:** Funding acquisition, Data curation. **Mary M. Heinricher:** Writing – review & editing, Investigation, Funding acquisition. **Miranda M. Lim:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The United States Veterans Affairs legally restricts access to Veteran health care data, which includes sensitive and identifying patient information. The data used for this study are not permitted to leave the Veterans Affairs firewall without a Data Use Agreement.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2024.100253.

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