Comparison of 25-hydroxyvitamin D and bilirubin levels between patients with essential tremor and Parkinson's disease

Comparação dos níveis de 25-hidroxivitamina D e bilirrubina entre pacientes com tremor essencial e doença de Parkinson

Celmir de Oliveira Vilaça, Marco Antônio Araujo Leite

ABSTRACT

Introduction: Differential diagnoses between essential tremor and Parkinson's disease is challenging in some individuals, with both disorders sharing similarities. Considering these links, we hypothesized that both conditions have a similar profile for some antioxidant molecules, including 25-hydroxyvitamin D and bilirubin. **Methods:** We performed a cross-sectional study comparing serum levels of 25-hydroxyvitamin D and bilirubin in 31 ET patients, 38 PD, and 65 controls matched for age. We used the Fahn-Tolosa-Marin scale for the severity of tremors in the ET group. We used Hohen-Yahr and MDS-UPDRS part III scales in the PD group. In addition, we evaluated sociodemographic characteristics, including age, sex, ethnicity, years of study, duration of disease, and use of primidone. **Results:** We found no differences in serum levels for 25-hydroxyvitamin D or bilirubin subtype levels between the ET and PD groups. We found low levels of indirect bilirubin in the PD group compared to the controls. We did not find differences between ET and controls in all biomarkers of the study. **Conclusion:** ET and PD patients have similar profiles for 25-hydroxyvitamin D and bilirubin serum levels. The discovery of differences in oxidative stress biomarkers in both conditions, mainly low-cost substances available clinically, can assist in the differential diagnosis and, in the future, prognostication and better therapy management.

Keywords: Essential tremor, Parkinson's disease, 25-hydroxyvitamin D, Indirect bilirubin

RESUMO

Introdução: O diagnóstico diferencial entre tremor essencial (TE) e a doença de Parkinson (DP) é desafiador em alguns indivíduos com ambas as afecções apresentando algumas similaridades. Assim sendo, hipotetizamos que ambas têm perfil similar de algumas moléculas antioxidantes, incluindo 25-hidroxivitamina D e bilirrubina. **Métodos:** Realizamos um estudo transversal comparando os níveis séricos de 25-hidroxivitamina D e bilirrubinas em 31 indivíduos com TE, 38 com DP e 65 controles pareados por idade. A escala de Fahn-Tolosa-Marin foi usada para avaliação da gravidade do tremor no grupo com TE e Hohen-Yahr e UPDRS parte III na avaliação do grupo com DP. Também foram avaliadas as características sociodemográficas. **Resultados:** Não encontramos diferenças nos níveis séricos de 25-hidroxivitamina D ou bilirrubina entre os grupos TE e DP. Encontramos baixos níveis de bilirrubina indireta no grupo DP comparado aos controles. Não encontramos diferenças entre os grupos com TE e controles em nenhum dos biomarcadores do estudo. **Conclusão:** Pacientes com TE e DP apresentam níveis séricos semelhantes de 25-Hidroxivitamina D e bilirrubinas. Diferenças nos biomarcadores de estresse oxidativo em ambas as condições, principalmente substâncias de baixo custo disponíveis na clínica, pode auxiliar no diagnóstico diferencial e, futuramente, no prognóstico e otimização terapêutica.

Palavras-chave: Tremor essencial, Doença de Parkinson, 25-hidroxivitamina D, Bilirrubina indireta

INTRODUCTION

Essential tremor (ET) is considered the most frequent movement disorder in the general population. ET presents a bimodal distribution, with the first peak of incidence in adolescence and a second in those older than 40. The prevalence in individuals over 40 years is approximately 4 to 5.6%[1] Clinically characterized by an action tremor in the upper limbs with more than

Universidade Federal Fluminense, Departamento de Medicina Clínica. Programa de Pós-Graduação em Neurologia/Neurociências, Niterói-RJ, Brasil.

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three years duration, a tendency to symmetry and associated or not with tremor in other locations, without signs of parkinsonism, ataxia, or dystonia.[2]

On the other hand, Parkinson's disease (PD) is the second most frequent degenerative neurological disease. Clinically, it is characterized by the obligatory presence of bradykinesia associated with resting tremor or rigidity. Postural instability, a common feature in parkinsonism, is not part of the PD criteria of the Movement Disorder Society (MDS) because it occurs in the later stages of the disease. The onset of PD is usually unilateral or asymmetric, with progressive evolution and loss of independence.[3]

Essential tremor and Parkinson's disease share some links in several studies.[4,5] In epidemiological studies, relatives of patients with ET have a higher risk of developing PD and vice versa. Clinically, individuals with ET who later develop PD usually present the onset of PD tremor on the side of the body most affected by the ET. Moreover, the action tremor component of PD may respond to treatment with propranolol or primidone, as it does in ET.[4] Histologically, some patients with ET or PD have intraneuronal inclusions called Lewy bodies, which are composed of α-synuclein protein aggregates in the brainstem. Regarding radiological findings, single photon-emission-computed tomography (SPECT) shows reduced dopamine uptake in the striatum in both diseases. In addition, genetic mutations in genes with elevated risks of PD have also been associated with ET occurrence.[5]

Despite these similarities, both diseases represent different pathologies, with difficulty in the differential diagnosis, especially in the initial stages of PD motor symptoms beginning with tremor.[6]

Vitamin D (VD), or its measurable form 25-hydroxyvitamin D, is an essential hormone in calcium and phosphorus homeostasis.[7] More recently, it has been suggested as a substance active in oxidative damage protection mechanisms directly or indirectly by activating enzymatic pathways of other free radical scavengers.[8] Reduced Vitamin D levels are associated with increased risk or accelerated evolution in several neurodegenerative conditions such as multiple sclerosis, Alzheimer's disease, and lateral amyotrophic sclerosis. Considering PD, most authors found reduced VD levels in this condition.[9]

Bilirubin, once considered a waste product of metabolism, represents the principal lipophilic antioxidant molecule, acting through its indirect form.[10] However, there are discrepant data on bilirubin levels in individuals with PD and variable studies considering the staging of disease and bilirubin subtypes.[11]

ET and PD are progressive diseases, with probable participation of oxidative stress. We hypothesize that both conditions present similar profiles for several antioxidant molecules, and the differences could help in the differential diagnosis. Therefore, we compared serum levels of 25-hydroxyvitamin D and bilirubin subtypes in individuals with ET and PD.

METHODS

We performed an analytical cross-sectional study among non-demented patients, including three samples of volunteers with ET, PD, and a control group. The groups were composed of 31 volunteers with ET (18 men and 13 women), 38 individuals with PD (28 men and 10 women), and 65 controls (34 men and 31 women) aged between 60 and 80 years. The recruitment sites were three tertiary hospitals in the metropolitan region of Rio de Janeiro, Brazil. We diagnosed patients with ET using the 2018 tremor criteria from the International Parkinson's Movement Disorders Society (IPMDS).[2] We assessed ET volunteers for tremor severity using the Fahn-Marin-Tolosa tremor scale (FMT) without treatment withdrawal.[12] We diagnosed PD patients using the IPMDS 2015 Parkinson's disease criteria. We assessed the PD group for clinical severity of symptoms by the MDS-UPDRS- part III scale under antiparkinsonian medication ("on state") and disease staging using the Hoehn and Yahr scale (H-Y).[3,13]

We measured the serum levels of 25-hydroxyvitamin D using the chemiluminescence method. In addition, we evaluated serum levels for bilirubin total, indirect and direct, by the colorimetric method. We excluded conditions with interference in the metabolism of vitamin D and bilirubin. We excluded patients with body mass

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indices (BMI) higher than 30 kg/m^2, a history of vitamin D replacement therapy, hemolytic anemia, granulomatous diseases, renal failure, liver failure, alcoholism, or use of corticoids. We also excluded individuals with a clinical suggestion of overlap between ET and PD and PD volunteers in later stages, with Hoehn and Yahr stage above III. PD patients in later stages may present severe disability, interfering in outdoors and sunlight exposure for vitamin D synthesis. In addition to serum 25-hydroxyvitamin D and bilirubin levels, we included sociodemographic data such as age, gender, ethnicity, years of study, and disease duration for statistical analysis. We described the results in frequencies, percentages, medians, and standard deviations. For multiple comparisons of non-parametric quantitative data, we used Kruskal-Wallis and Dunn's test for post-hoc comparison. We used the Spearman test for correlation analysis and Ancova for covariance analysis. P-values lower than 0.05 were considered statistically significant. We performed statistical analyses using Microsoft® Excel 2010 and IBM version 20® SPSS software. The Research Ethics Committee approved the three units of the study.

RESULTS

Table 1 shows the results of the sociodemographic and scale punctuations by groups. Considering sociodemographic data, we did not

Table 1

Description of socio-demographic data and scales by groups

	Essential tremor (n=31)	Parkinson (n=38)	Controls (n=65)	Total (n=134)	p-value[1]
Age	M=70 P25=64.5 P75=76	M=67 P25=64.0 P75=70	M=66 P25=62 P75=69	M=67 P25=62 P75=72	0.058
Gender					0.100
Female	13 (42%)	10 (26%)	31 (48%)	54 (40%)	
Male	18 (58%)	28 (74%)	34 (52%)	80 (60%)	
Ethnicity					0.630
White	20 (64%)	22 (58%)	35 (54%)	77 (58%)	
Black	3 (10%)	2 (5%)	9 (14%)	14 (10%)	
Brown	8 (26%)	14 (37%)	21 (32%)	43 (32%)	
Years of study					0.600
< 5	08 (26%)	09 (24%)	22 (34%)	39 (29%)	
6–9	08 (26%)	13 (34%)	15 (23%)	36 (27%)	
10–12	08 (26%)	12 (32%)	21 (32%)	41 (31%)	
>12	07 (22%)	04 (10%)	07 (11%)	18 (13%)	
BMI	M=26.6 P25=25.2 P75=28.7	M = 24.5 P25=23 P75=26.7	M = 27 P25=25,2 P75=28.7	M = 26.4 P25=24.2 P75=28.3	<0.001
Years of disease	M=17 P25=4.50 P75=40	M=8.5 P25=5.25 P75=15.5	—	M=10 P25=5 P75=20	0.055
FMT Score	M=28 P25=19.5 P75=35	—	—	—	
UPDRS-III	—	M=41.5 P25=31.8 P75=53.3	—	—	
Hoehn-Yahr Scale	—	M=2 P25=2 P75=3	—	—	

Summary measures (M=median. P25= 25th percentile, P75=75th percentile for quantitative variables). Frequency and relative percentage to qualitative variables. [1]Kruskal-Wallis for comparison of quantitative variables and chi-square for qualitative variables. BMI: Body Mass Index in Kg/m^2.

find differences between groups in age, gender, ethnicity, or years of schooling. In addition, we did not find differences in the duration of the diseases between ET and PD groups (p=0.055). The median FMT score in ET volunteers was 28%. PD patients show a median of 31.8 points in MDS-UPDRS part III. The median of the H-Y stage in PD groups was 2.0 (20 individuals in H-Y II and 18 in H-Y III). Considering the BMI, we found differences in the groups in Kruskal-Wallis multiple comparisons. The PD group had a low BMI (median 24.5 Kg/m^2) compared to ET (26.6 Kg/m^2) and controls (26.4 Kg/m^2) (P<0.001).

Figure 1 shows the comparison of the results for serum levels of biomarkers of the study in the three groups.

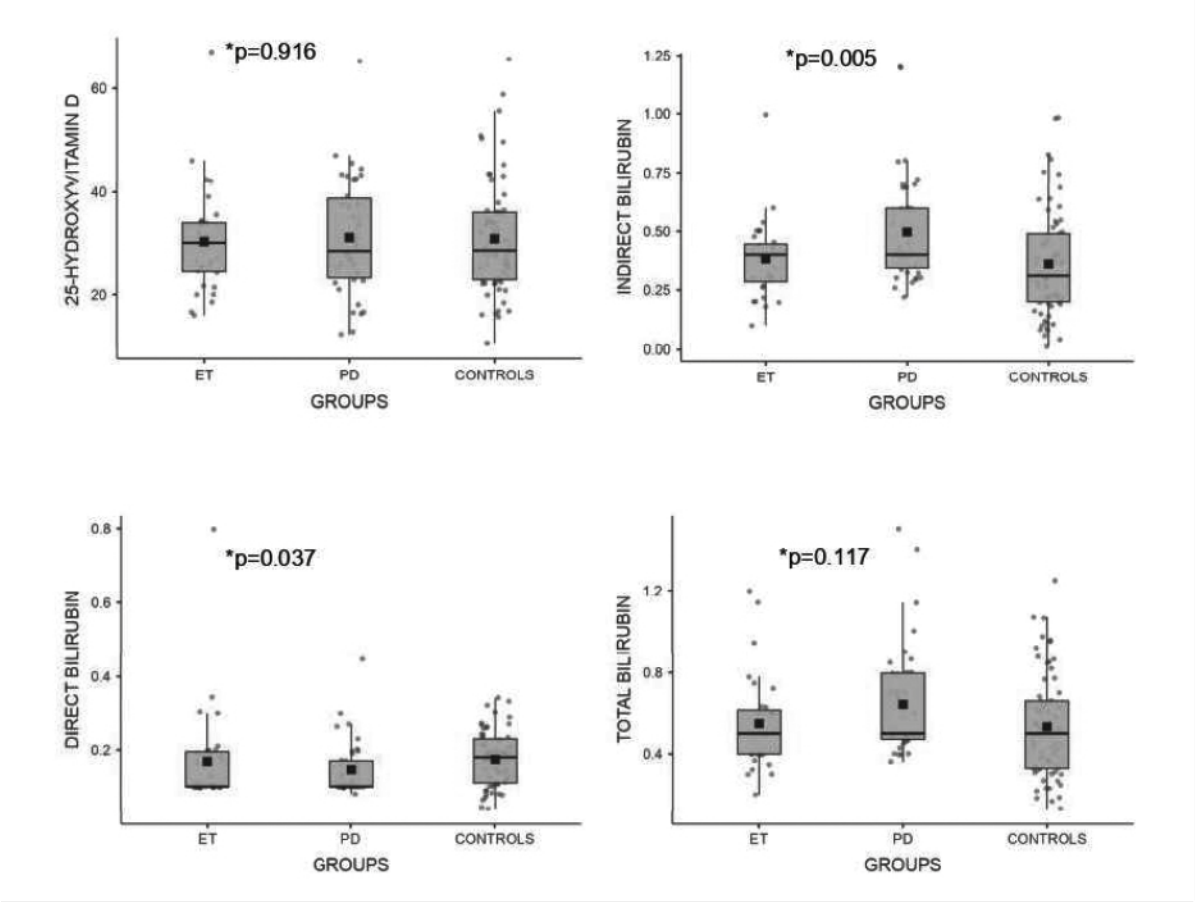

Figure 1: Serum levels of biomarkers and comparison between groups.
*Nonparametric Kruskal-Wallis test for comparison of three groups. Results of 25-hydroxyvitamin D in ng/ml. Results of bilirubin in mg/dl. ET: essential tremor. PD: Parkinson's disease.

We found indirect bilirubin differences between groups in the Kruskal-Wallis multiple analysis (p=0.005). In post-hoc analyses using Dunn's test (not shown in Tables), we found higher serum levels of indirect bilirubin in the PD group compared to controls (p<0.003), without differences in comparison between TE and PD (p>0.187) groups or TE versus controls (p>0.95).

Considering direct bilirubin, we found differences between groups in multiple analyses (p=0.037). However, despite these differences,

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we did not find differences between groups in post-hoc analysis using Dunn's test (p>0.05).

We did not find differences in the 25-hydroxyvitamin D (p=0.916) or total bilirubin (p=0.117) between groups in the Kruskal-Wallis multiple analysis.

Using the Spearman test, we found an inverse correlation between the severity of the FMT scale in the ET group and serum levels of indirect bilirubin (p=0.023, rho= -0.407) and total bilirubin (p=0.018, rho= -0.422) but no correlation with direct bilirubin levels (p=0.052). Considering the PD group, we did not find a correlation between punctuation in the MDS-UPDRS part-III scale and serum levels of biomarkers of study (p>0.05).

In the second stage of the study, Table 2 shows the results for the serum levels of biomarkers in the three groups, excluding ET patients in treatment with primidone (21 individuals). Primidone treatment, through phenobarbital, a product of primidone metabolism, could affect bilirubin levels by stimulating indirect bilirubin conjugation in the liver.[14] Primidone could also reduce vitamin D levels by stimulating its metabolism.[15] Results of Kruskal-Wallis show differences in indirect bilirubin between groups (p=0.005). However, we found in the post-hoc analysis only differences between PD groups and controls (p=0.04). We did not find differences in indirect bilirubin levels in other comparisons or between other biomarkers of study in this second stage.

Table 2

Median, percentile 25 and 75 of serum levels of biomarkers between groups excluding ET patients in primidone use

	Essential tremor (without primidone) (n=21)	Parkinson (n=38)	Controls (n=65)	p-value[1]
	Median (P25-P75)	Median (P25-P75)	Median (P25-P75)	
25-hydroxyvitamin D	30.0 (25.3 – 31.9)	28.3 (23.2–38.8)	28,5 (22.9 – 36.0)	0.853
Indirect Bilirubin	0.40 (0.30 – 0.48)	0.40 (0.34 – 0.60)	0.31 (0.20 – 0.49)	0.005
Direct Bilirubin	0.10 (0.10 – 0.20)	0.10 (0.10 – 0.17)	0.18 (0.11 – 0.23)	0.057
Total Bilirubin	0.50 (0.40 – 0.64)	0.50 (0.47 – 0.80)	0.50 (0.33 – 0.66)	0.128

[1]*Nonparametric Kruskal-Wallis test for comparison of three groups. P25= 25th percentile, P75=75th percentile. Results of 25-Hydroxyvitamin* D *in ng/ml. Results of bilirubin in mg/dl.*

DISCUSSION

Our results demonstrated similar serum levels for 25-hydroxyvitamin D and bilirubin subtypes between ET and PD patients. Furthermore, these results were similar when we excluded patients with ET in primidone use.

We did not find differences between ET and controls for any biomarkers in this study (25-hydroxyvitamin D or subtypes of bilirubin), regardless of treatment with primidone in the ET group. However, considering comparisons between PD and the control group, we found higher indirect bilirubin levels in the PD group.

Our results for VD serum levels were not as expected, considering the comparison of the PD group with the controls. Most authors found decreased 25-hydroxyvitamin D levels in patients with PD compared to the general population.[9] Explanations for our results may be the more significant concern of relatives of the PD group, with insertion of them in rehabilitation activities in these tertiary units, resulting in higher sun exposure and stimulation of VD synthesis by the skin. Another factor in explaining our results may be the lower H-Y staging in our sample compared to other studies, resulting in less motor disability to outdoor activities and higher sunlight exposure.

Considering the ET group, studies indicate lower social interaction in individuals with ET due to the mood disorders associated with the condition, regardless of the severity of the tremor.

In addition, tremors of the upper members can affect manual activities and decrease sociability with low exposure to sunlight.[16] We do not suppose this explanation in our results. The subitems of the FMT scale that assess social or work activities were not impacted in the individuals with ET in our sample compared to other subitems of the scale.[12]

Hypovitaminosis D in patients with ET may indicate the need to include ET in the screening for deficiency of this vitamin, like PD and other clinical conditions. Also, patients with ET have higher annual fall rates than the general population. ET patients with low vitamin D levels were at an increased risk of fractures due to reduced bone mineralization, and the regular use of primidone can improve this problem.[17]

We found only one study comparing serum levels of VD in people with ET and controls in war veterans.[18] However, this study was retrospective, did not describe the serum levels of vitamin D, and did not consider adjustments for confounders, including elevated BMI or drug therapy with primidone. In addition, some authors found VDR gene variations and increased risk of ET, but they did not assess 25-hydroxyvitamin D levels in participants.[19]

Our results for the higher serum levels of indirect bilirubin in patients with low H-Y stages of PD compared with the control group were similar to those of another author.[20] Most authors have measured only total bilirubin with higher serum levels in the PD group than controls, mainly in the early stages of PD.[11] One author observed higher direct bilirubin levels in PD patients than in controls. The author speculates a possible action of direct bilirubin as an antioxidant molecule, considering the low affinity for albumin.[10]

Indirect bilirubin is a product of hemoglobin degradation in red blood cells. In addition, there is increased bilirubin production in the SN from increased induction of heme-oxygenase I (HO-I) under inflammatory conditions or excess free radical production in the SN. Increased HO-I activity in the early stages of PD could elevate BI production to counter oxidative damage in PD. Genetic variations in HO subtypes correlate with an increased risk of PD. [21] Although SN represents a small group of neurons, this region is the region of highest oxidative stress in the CNS from dopamine metabolism, and, in PD, oxidative stress is also occurring in other locations, albeit to a lesser extent.[22]

Considering the ET group, one study demonstrates no association between polymorphisms of the subtypes of HO and the risk of ET.[23] We found two studies evaluating the differences in bilirubin levels between ET and PD patients. Unlike our study, neither used the new 2018 IPMDS tremor classification and did not separate bilirubin subtypes, and one of the studies was retrospective.[24,25]

Experimental data reinforces the joint action of the VD and indirect bilirubin pathways in oxidative stress. Both molecules can act in oxidative stress by synthesizing glutathione (GSH). GSH is a tripeptide formed by cysteine, glycine, and glutamate and is the principal intracellular hydrophilic antioxidant molecule, participating in several defense mechanisms against free radicals.[26] In this case, while indirect bilirubin would stimulate cysteine uptake by neurons, vitamin D enables the enzymes responsible for synthesizing glutathione with the accumulated cysteine.[27]

Another link between the VD and bilirubin pathways may be the activation of the Nrf2 protein gene. VD stimulates the synthesis of Nrf2, an oxidative stress protein that elevates HO-1 levels and thus may secondarily elevate indirect bilirubin levels.[28]

We used the new IPMDS 2018 classification for ET diagnosis but did not subdivide individuals between essential tremor and essential tremor-plus (ET-plus). This approach is due to the existing controversies in the new tremor classification and the criteria for differentiating individuals with ET or ET-plus.[2]

One limitation of the study was the small number of participants, who were not naïve drug patients. In addition, despite our results and exclusion criteria, the participants were recruited in tertiary centers, increasing the possibility of polypharmacy for multiple comorbidities interfering with our results, especially in the control group.

The PD group showed a higher number of male participants than female participants. However, when we performed covariance analysis, the gender differences did not interfere with the results of biomarkers between groups ($p>0.05$).

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It is difficult to attribute changes in the serum levels of a substance to its participation as a biomarker in neurodegenerative diseases. However, some are reduced in size and easily pass through the brain-blood barrier. Furthermore, the CNS is responsible for the consumption of 20% of cardiac output, being one of the areas with the most significant oxidative stress and possibly the consumption of antioxidant molecules.[22]

Finally, as with any cross-sectional analysis, we cannot establish whether the changes in 25-hydroxyvitamin D or bilirubin levels found in the results of the study are a causal factor or a consequence of the diseases evaluated (ET or PD).

Our results must be reproduced in research with VD and bilirubin measures in larger samples assessing volunteers without treatment for both conditions.

CONCLUSION

We found similar serum levels of 25-hydroxyvitamin D and bilirubin levels in ET patients compared to individuals with PD. These results were independent of treatment with primidone in ET individuals. Studies of low-cost molecular biomarkers available clinically for ET and PD may serve as a tool for differential diagnosis between both conditions and, in the future, can assist in assessing the progression and therapeutic response in these diseases.

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Contributions

COV: conceptualization, data curation, formal analysis, research, methodology, and original draft writing. MAAL: conceptualization, formal analysis, methodology, project management, supervision, writing, proofreading, and editing.

Conflicts of Interest:

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Corresponding Author:
Celmir de Oliveira Vilaça
celmir@gmail.com

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