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Association between hypovitaminosis D and cognitive inhibition impairment during major depression episode

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ABSTRACT

Background: Major depressive episode (MDE) has been associated with cognitive functioning alteration and hypovitaminosis D (hypoVD), but the relationship between hypoVD, depression, and cognition is not well understood. We aimed to compare patient with MDE with or without hypoVD in regard of cognitive functioning.
Methods: 91 patients (38.5 years old, 65.9% female) with MDE were included in a cross-sectional study and were evaluated with a complete cognitive battery. None of the participants were medicated at the time of the inclusion. Serum 25-hydroxyvitamin D was measured using LC-MS/MS method, and hypovitaminosis was defined as 25OHD < 50 nmol/L. Covariates were gender, season of dosage, first MDE onset, age, body mass index and depression severity
Results: Patients with hypoVD demonstrated a higher stroop intereference index time underscoring that means low cognitive inhibition ability. Mutiple logistic regression confirmed that hypoVD was significantly associated with high stroop interference time index after controlling by gender, season of dosage, first MDE onset, age, body mass index and depression severity.
Conclusion: Our results suggest that patient with MDE having hypoVD may be more prone to cognitive impairment.

1. Introduction

Hypovitaminosis D (hypoVD) is frequent among adults, notably among those with chronic conditions, with an estimated prevalence of more than 1 billion people worldwide (Holick, 2007). Besides its classical function of bone metabolism regulation, vitamin D exhibits multiple biological targets mediated by its nuclear hormone receptor, the Vitamin D Receptor (VDR) (Annweiler et al., 2011). Specific actions on the central nervous system have been described (Kalueff et al., 2007, Annweiler et al., 2010): VDR are present in neurons and glial cells of the limbic system (Walbert et al., 2001), hippocampus, hypothalamus, and other cortical and sub-cortical regions (Eyles et al., 2005; Drevets et al., 2008) with possible consequence on mood, behaviour and cognition.

Observational studies have indeed reported that serum concentration of 25-hydroxyvitamin D (25OHD) was lower among people with depression when compared to controls (Hoogendijk et al., 2008; Walbert et al., 2001) and to patients with other psychiatric disorders

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(Belzeaux et al., 2015; Boerman et al., 2016). Previous interventional studies have found a benefit of vitamin D supplements on symptoms of depression, thus strengthening the plausibility of a causal relationship (Shaffer et al., 2014; Gowda et al., 2015; Sarris et al., 2016; Annweiler et al., 2013). However, whether hypoVD is associated with specific depressive phenotypes remains to be elucidated. In particular, hypoVD has been repeatedly linked to cognitive decline and executive dysfunction (Annweiler et al., 2013) while cognition is classically impaired during major depressive episode (MDE). The clinical relevance is that cognitive dysfunction during MDE is associated with increased suicide risk (Richard-Devantoy et al., 2014) and predicts poor response to antidepressant drugs (Sneed et al., 2007a) as well as for recurrence of MDE (Alexopoulos et al., 2009). However, to the best of our knowledge, no study has examined yet the relationship between cognitive functioning and hypoVD during MDE. We hypothesized that hypoVD could be associated with greater cognitive dysfunction during MDE. The present study aimed to compare MDE patients with or without hypoVD in regard of cognitive functioning.

2. Methods

2.1. Population

Ninety-one participants aged 18–65 were recruited. All patients suffered from a MDE at the time of the inclusion. Only outpatients with a major depressive disorder were recruited. None of the participants were medicated at the inclusion. All participants were English- or French-speaking natives of Québec, Canada. Informed written consent was obtained from all participants. This study was conducted at the Douglas Mental Health University Institute in Montréal and was approved by the local ethics committee.

Exclusion criteria were a lifetime history of schizophrenia or bipolar disorder, a history of alcohol/substance abuse or dependence spanning the previous six months, a major general medical condition requiring ongoing pharmacological treatment, a lifetime history of severe head trauma or central nervous system disorder.

2.2. Evaluation

Diagnoses were made using the Structured Clinical Interview for Axis I DSM-IV (SCID I) (First et al., 2002). Level of severity of depressive symptoms was rated using the 21-item Hamilton Rating Scale for Depression (HAMD-21) (Hamilton, 1960). Level of anxiety was assessed using the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959). Number of MDE, age at the onset of depressive disorder and Body Mass Index were also collected.

Twenty-five (33.3%) had never received any antidepressant medication before. It was their first major depressive episode. For those who received an antidepressant just before starting the study, the washout period, in days, was 7.65 ± 3.4, 7.56 ± 3.14 for patients with hypoVD and 7.69 ± 3.52 for patients with no hypoVD ($p = 0.89$). No patient took lithium or fluoxetine before the study. Vitamin D was measured at the time of inclusion in the same laboratory using Liquid chromatography–mass spectrometry (LC-MS/MS) method. HypoVD was defined following the definition of the World Health Organization (WHO) and of the American Institute of Medicine as serum 25OHD concentration lower than 50 nmol/L (20 ng/mL) (Anglin et al., 2013). Also, as serum 25OHD concentration may vary according to season and sun exposure, the season of assay was collected as a covariate, and classified as “winter” from November to March or “summer” from April to October, according to publication of statistics Canada (http://www.statcan.gc.ca).

Patients were evaluated using a large cognitive battery by an experimented neuropsychologist. Cognitive inhibition was assessed using the Stroop Color Test (Stroop, 1935; Godefroy et al., 2008), the Trail Making Test (Godefroy et al., 2008), and the Hayling Sentence Completion Test (Burgess et al., 1996). The Iowa Gambling Task (IGT) was used to assess decision-making (Bechara et al., 1999), Verbal Fluency Test (Godefroy et al., 2008) to assess verbal fluency, the WAIS-IV (Wechsler, 2008), Digit Span Test (forward and backward) to assess working memory, and the National Adult Reading Test (NART) (Beardsall et al., 1990; Mackinnon et al., 2005) to assess verbal IQ. The order of the tasks was randomized.

2.3. Statistical analyses

Comparisons of quantitative data between the two groups (HypoVD vs. non hypoVD) were made by a Student's *t*-test. Associations between qualitative variables and groups were calculated with a Chi-square test.

An univariate logistic regression analysis was first conducted to determine group differences. Variables with a p-value < 0.1 and available covariables previously found to influence vitamin D concentrations (i.e. BMI, age, gender, season, and depressive symptom severity) were then added in a multivariate model.

An alpha threshold of 0.05 was set *a priori*. SPSS 21.0 (IBM Corporation, Chicago, Illinois) was used to conduct statistical analysis.

3. Results

In total, 91 outpatients successfully completed the clinical assessment (65.9% female, n = 60), the neuropsychological testing and had a serum 25OHD measure. The mean age of our population was 38.5 (SD = 12.15). The mean level of depression was 32.6 (SD = 6.0; range = 21–48).

Twenty-eight patients (30.8%) had hypoVD. Comparison between depressed patients with and without hypoVD is presented in Table 1. Patients with hypoVD were significantly older at onset of depressive disorder. Age and gender tend to be significantly different, while there were no significant differences between patients with and without hypoVD for all other socio-demographic and clinical measures in univariate analyses. Moreover, patients with hypoVD showed a higher Stroop intereference index time in univariate analyses. No other neuropsychological measure differed between groups.

Using logistic regression, we found that hypoVD remains associated with higher Stroop interference time index after controlling by age, gender, season, age at first MDE, age at inclusion, BMI and depression severity (Table 2). Including level of education did not alter the findings (data not shown). Using the same potential confounding variables (gender, season of dosage, first MDE onset, age, body mass index and depression severity), conducting a linear regression with VD concentration as continuous variable did not alter our results, VD concentration remaining associated with Stroop interference time index (beta = − 0.288, p = 0.028).

4. Discussion

The present study revealed impairment in cognitive inhibition process as measured by Stroop test, in patients with hypoVD, during MDE. This association remained significant after controlling for several potential confounding factors. Otherwise, we found no association between depressive symptoms severity or other clinical variables and hypoVD. To the best of our knowledge, no previous study examined association between cognitive functioning and hypoVD in MDE.

However, previous studies suggest an association between hypoVD and cognitive functioning in several different populations. In healthy adults (mean age = 56.3 (SD = 14)), a study demonstrated an association between vitamin D status and verbal fluency performance (Pettersen, 2016). In another study focusing on old subjects with memory complaint, hypoVD was associated with poorer mental flexibility based on TMT-B performance (Annweiler et al., 2013). In a study including prefrail and frail elderly, hypoVD was also associated with executive impairment (Brouwer-Brolsma et al., 2013). In the present