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Hypovitaminosis D is associated with depression and anxiety in schizophrenia: results from the national FACE-SZ cohort.

Running title: hypovitaminosis D, depression and anxiety in schizophrenia

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Abstract

Objective: Hypovitaminosis D has been associated with respectively major depressive disorder, schizophrenia (SZ) and cognitive disorders in the general population, and with positive and negative symptoms and metabolic syndrome in schizophrenia. The objectives were (i) to determine the prevalence of hypovitaminosis D and associated factors (with a focus on depression and cognition) in a national non-selected multicentric sample of community-dwelling SZ subjects (ii) to determine the rate of SZ patients being administered vitamin D supplementation and associated factors.

Methods: A comprehensive 2 daylong clinical and neuropsychological battery was administered in 140 SZ subjects included between 2015 and 2017 in the national FondaMental Expert Center (FACE-SZ) Cohort. Hypovitaminosis D was defined by blood vitamin D level <25nM. Depressive symptoms were assessed by the Positive and Negative Syndrome Scale depressive subscore and current anxiety disorder by the Structured Clinical Interview for Mental Disorders.

Results: Hypovitaminosis D has been found in 21.4% of the subjects and none of them had received vitamin D supplementation in the previous 12 months. In multivariate analysis, hypovitaminosis D has been significantly associated with respectively higher depressive symptoms (aOR=1.18 [1.03-1.35], p=0.02) and current anxiety disorder (aOR=6.18 [2.15-17.75], p=0.001), independently of age and gender. No association of hypovitaminosis D with respectively positive and negative symptoms, cognitive scores or other biological variables has been found (all p>0.05), however, a trend toward significance has been found for metabolic syndrome (p=0.06). Vitamin D supplementation has been administered during the previous 12 months in only 8.5% of the subjects but was associated with lower depressive symptoms (aOR=0.67 [0.46-0.98], p=0.04) and lower rate of current anxiety disorder (aOR=0.06 [0.01-0.66], p=0.02) compared to patients with hypovitaminosis D.

Conclusion: Hypovitaminosis D is frequent and associated with depressive symptoms and anxiety disorders in schizophrenia. Vitamin D supplementation is associated with lower depressive and anxiety symptoms, however patients with hypovitaminosis D remain insufficiently treated.

Keywords: vitamin D, schizophrenia, depression, anxiety, metabolic syndrome

Introduction

Treating comorbid major depressive disorder (MDD) and anxiety disorders in SZ is clinically important due to the high prevalence of depression and suicidality in SZ and to its impact on functioning and quality of life (Andrianarisoa et al., 2017; Harvey, 2011). Hypovitaminosis D has been extensively associated with MDD in general population (for meta-analysis see (Ju et al., 2013) and for review see (Lerner et al., 2018)) and supplementing subjects with MDD has been found to improve depressive symptoms in another recent meta-analysis (Schefft et al., 2017). Patients with SZ are at higher risk of hypovitaminosis D (Belvederi Murri et al., 2013) and this association has been replicated in first episode psychosis in another recent meta-analysis (Firth et al., 2017) (for review see (Adamson et al., 2017)). Vitamin D deficiency may play a role in mediating hippocampal volume deficits, possibly through neurotrophic, neuroimmunomodulatory and glutamatergic effects (Shivakumar et al., 2015). A study has found high levels of hypovitaminosis in a monocentric sample of SZ inpatients in the south of France (Belzeaux et al., 2015) but no data is available to date in a national non-selected sample of community-dwelling SZ subjects. Studies exploring the association of vitamin D deficiency with psychotic symptomatology have yielded inconsistent findings (Akinlade et al., 2017; Cieslak et al., 2014; Nerhus et al., 2016; Yüksel et al., 2014). The association of vitamin D deficiency and depression in schizophrenia has been explored in only one study with positive results (Nerhus et al., 2016), and no study has explored the association between hypovitaminosis D and anxiety disorders in SZ subjects to date. Preliminary findings have suggested that vitamin D supplementation may improve cognition in schizophrenia (Krivoy et al., 2017), however the association of hypovitaminosis D with cognitive impairment has not been explored to date. Vitamin D insufficiency has been associated with metabolic syndrome in psychotic disorders (Yoo et al., 2018), with insulin resistance (Garbossa and Folli, 2017), with thyroid dysfunction (Kim, 2017; Wang et al., 2018) and high vitamin D blood levels have been suggested to reduce peripheral low-grade inflammation (Zhu et al., 2015). There is a current debate on the association between alcohol use disorder and vitamin D deficiency (Tardelli et al., 2017).

The objective were (i) to determine the prevalence of hypovitaminosis D and associated factors in a non-selected multicentric sample of community-dwelling SZ subjects

(ii) to determine the rate of vitamin D supplementation, its effectiveness in correcting vitamin D blood levels and the associated factors. Our hypotheses were that hypovitaminosis D was associated with higher depressive and anxiety disorders, higher cognitive impairment and higher biological disturbances.

Population and methods

Study design

The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles), set up by a scientific cooperation foundation in France, the FondaMental Foundation (www.fondation-fondamental.org) and pioneered by the French Ministry of Research in order to create a platform that links thorough and systematic assessment to research (Schürhoff et al., 2015).

Study population

Consecutive clinically stable patients (defined by no hospitalization and no treatment changes during the 8 weeks before evaluation) with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder were consecutively included in the study. Diagnosis was confirmed by two trained psychiatrists of the Schizophrenia Expert Centres network. All subjects were referred by their general practitioner or psychiatrist who subsequently received a detailed evaluation report with suggestions for personalized interventions.

Data collected

Patients were interviewed by members of the specialized multidisciplinary team of the Expert Center. Diagnoses interviews were carried out by two independent psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID 1.0).

All clinicians were blinded of the vitamin D status of the patient at the time of evaluation, and all technicians carrying out laboratory measurements were blinded of the diagnosis and evaluation. Information about age at illness onset, duration of untreated psychosis and illness duration was recorded. Current daily tobacco smoking was self-reported. Ongoing psychotropic treatment was recorded as well as other medication. Current alcohol and cannabis disorders were defined according to the Structured Clinical Interview for Mental

Disorders (SCID 1.0). The antipsychotic treatments were classified according to their Anatomical-Therapeutic-Clinical ATC class. First-generation antipsychotics (FGA) were defined by ATC class N05AA to AC (phenothiazines), NO5AD (butyrophenones), NO5AF (thioxanthenes). Second-generation antipsychotics (SGA) were defined by ATC class N05AH (diazepines, oxazepines, thiazepines and oxepines) and NO5AL (benzamides).

The National Adult Reading Test (Nelson and O'Connell, 1978) provides an estimate of premorbid intellectual ability. French version of the NART was used in our analysis (Mackinnon and Mulligan, 2005). Wechsler Adult Intelligence Scale – 4th Edition (Wechsler, 2008) provides a measure of general intellectual function in older adolescents and adults. Seven subtest short form (Ryan and Ward, 1999) was used to estimate the Full Scale IQ (FSIQ). Trail Making Test (Reitan, 1958) reflects the control of attention, visual exploration, speed and mental flexibility. The subject is asked to connect, by making pencil lines, encircled numbers randomly arranged on a page in proper order (Part A) and encircled numbers and letters in alternating order (Part B). A French version of the normative data was used (Godefroy, 2008). California Verbal Learning Test (Delis et al., 2000) is designed to measure verbal learning and memory using a multiple-trial list-learning task. The examiner reads the word list and records the patient's oral responses verbatim in the order in which they are given. Learning efficiency, strategies, interference management and learning bias are measured. A French version of the task was used in this study (Poitrenaud et al., 2007). Doors test (Baddeley et al., 1994) is a visual recognition memory test in which participants view photographs of 12 doors for 3 seconds each. Immediately thereafter, participants are presented with 12 arrays of four doors each, and are asked to identify the door from the previous list. In the second part new photographs of doors are displayed, but the recognition stimuli are rather similar to the key list. The Continuous Performance Test – Identical Pairs (CPT-IP) is a computerised measure of sustained, focused attention or vigilance. This version is a part of MCCB-Matrics Consensus Cognitive Battery and involves monitoring a series of multiple digits and responding with a button press each time that two stimuli in a row are identical (Nuechterlein et al., 2008)

Vitamin D measurement

Seric 25-hydroxy-vitaminD3 (25(OH)VD3) was quantified in the hospital Laboratories using a commercial radioimmuno-assay (Diasorin,Stillwater,MN, USA). Hypovitaminosis D severity was defined in 2 classes according to the French National Nutrition Health Study

2006–2007: severe to moderate (<25 nM) vs mild or no hypovitaminosis D (≥25nM)(Unité de surveillance et d'épidémiologie nutritionnelle, 2007).

Other biological measurements

Routine blood exam has been systematically performed and triglycerides, LDL, HDL and total cholesterol as well as glucose (with fasting for at least 10h), uric acid, prolactinemia, highly-sensitive C-reactive Protein (CRP) and ultrasensitive TSH (TSHus) have been measured.

Metabolic syndrome (MetS) definition

Sitting blood pressure (BP) and anthropometrical measurements were recorded. Two BP measurements were made 30 seconds apart in the right arm after the participant had sat and rested for at least 5 minutes. A third BP measurement was made only when the first two BP readings differed by more than 10 mm Hg. The average of the 2 closest readings was used in the analysis. Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects standing. This was performed with a tape equipped with a spring-loaded mechanism to standardize tape tension during measurement. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Overnight fasting blood was collected for metabolic profiles analysis. Fasting levels of serum triglyceride (TG) and fasting plasma glucose were measured by an automated system, and serum high-density lipoprotein cholesterol (HDL-C) level was measured by electrophoresis. Metabolic syndrome was defined according to the modified criteria of the International Diabetes Federation (IDF) (Alberti et al., 2006), which requires the presence of three or more of the following five criteria: high waist circumference (>94 cm for men and >80 cm for women), hypertriglyceridemia (≥1.7 mM or on lipid lowering medication), low HDL cholesterol level (<1.03 mM in men and < 1.29 mM in women), high blood pressure (≥ 130/85 mmHg or on antihypertensive medication), high fasting glucose concentration (≥ 5.6

mM or on glucose-lowering medication). High sensitivity CRP (hs-CRP) was measured with an assay using nephelometry (Dade Behring). Abnormal CRP level was defined as >3 mg/L according to the ("The Emerging Risk Factors Collaboration"; 2010). Patients with hs-CRP levels >30 mg/L, which corresponds to an acute inflammation, were not included in the analyses ("The Emerging Risk Factors Collaboration"; 2010).

Ethical concerns

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki). The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18th, 2010). All data were collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

Statistical analysis

Socio-demographics, clinical characteristics, cognitive scores, addictive behavior, treatments and biological variables are presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data were examined for normal distribution with the Shapiro-Wilk test and for homogeneity of variance with the Levene test. Comparisons between (i) individuals with or without hypovitaminosis D (table 1) and supplemented vs. non-supplemented individuals (table 2), regarding all above-mentioned characteristics were performed using the chi-square test for categorical variables. Continuous variables were analyzed with Student t-tests for normally distributed data and in case of normality violation, additional Mann-Whitney tests were performed to confirm the result.

Multiple logistic regressions were then performed to confirm the association between (i) hypovitaminosis D and respectively current anxiety disorder and depressive symptoms, after adjusting for age and gender (table 1) and (ii) vitamin D supplementation and respectively current anxiety disorders and depressive symptoms, after adjusting for age, gender and illness duration (table 2). Adjustment variables were selected based on their clinical interest (age, gender and illness duration) and on threshold P-value ≤ 0.05 as calculated from the univariate analyses statistical (none of the variables). The association of

vitamin D supplementation with cognitive scores has not been carried out because of statistical power lack (N=18). The final models included odds ratios and 95 % confidence intervals. This study was a confirmatory analysis. No correction for multiple testing has therefore been carried out, which is consistent with recommendations (Bender and Lange, 2001). Analyses were conducted using SAS (release 9.3; SAS Statistical Institute, Cary, NC). All statistical tests were two-tailed, with α level set at 0.05.

Results: Overall, 140 patients have been consecutively recruited. Hypovitaminosis D has been found in 21.4% of the subjects and none of them had received vitamin D supplementation in the previous 12 months. In multivariate analysis, hypovitaminosis D has been significantly associated with respectively higher depressive symptoms (aOR=1.18 [1.03-1.35], p=0.02) and current anxiety disorder (aOR=6.18 [2.15-17.75], p=0.001), independently of age and gender. No association of hypovitaminosis D with respectively daylight sun exposure, positive and negative symptoms, cognitive scores or other biological variables has been found (all p>0.05), however, a trend toward significance has been found for metabolic syndrome (p=0.06). Overall, 8.5% of the patients had been administered Vitamin D supplementation in the 12 previous months, none of them had hypovitaminosis D. Vitamin D supplementation has been associated with lower depressive symptoms (PANSS depressive subscore) (aOR=0.67 [0.46-0.98], p=0.04) and lower rates of current anxiety disorder (aOR=0.06 [0.01-0.66], p=0.02).

Discussion

Altogether, the present findings may be summarized as follows: in a national sample of community-dwelling stabilized SZ subjects mean aged 33 years, 21.4% were found with hypovitaminosis D. Hypovitaminosis D has been significantly associated with anxiety and depressive symptoms after adjustment for confounding factors, and vitamin D supplementation has been associated with lower depressive symptoms and lower rates of comorbid anxiety disorders. No association of hypovitaminosis D or vitamin D supplementation with other biological variables or addictive behavior has been found.

We found a prevalence of hypovitaminosis D of 21.4%, which is lower than the rate of 34% found in 202 SZ Dutch outpatients (Boerman et al., 2016). In a recent French study, a comparable rate of 34% was found for hypovitaminosis D in the French general population (Souberbielle et al., 2016), which suggests that hypovitaminosis D may be lower in SZ

patients than in general population. However, it should be mentioned that the present sample was younger (mean aged 32 years) than the general French population (mean aged 40), which may explain these discrepancies. The life expentancy of SZ subjects is 10 years lower than the general population and hypovitaminosis D is usually associated with older age (Custodero et al., 2018). A previous study has suggested that sun exposure was not sufficient to increase vitamin D blood levels (Bogers et al., 2016), which is consistent with the present results suggesting no association between number of hours outside per day and hypovitaminosis D. No information on vitamin D supplementation in the previous year was reported in Boerman et al. study (Boerman et al., 2016). These discrepancies may be due to differences in diet and complementary agent consumption that should be evaluated in further studies.

The major finding of the present study is the association of hypovitaminosis D with respectively depressive symptoms but also current anxiety disorder (with a stronger association). The association with depressive symptoms has confirmed previous preliminary results (Nerhus et al., 2016). The association with anxiety disorders has been explored for the first time in the present study. This is probably due to the fact that no specific anxiety scale has been validated for schizophrenia to date. Future studies exploring the associations between hypovitaminosis D and clinical features in schizophrenia should therefore include specific anxiety measurements. Moreover, vitamin D supplementation has also been shown for the first time to be associated with lower depressive symptoms and lower rates of anxiety disorders in SZ subjects. Due to the low rate of patients supplemented with vitamin D (8.5%), larger samples are needed to replicate these findings. Due to the cross-sectional retrospective design, no causal association may be drawn from the present findings and further clinical trials are also needed to determine if vitamin D supplementation in patients with hypovitaminosis D may definitely improve depression and anxiety. Treating depression in schizophrenia remain a challenge in the current state of the art (Guillaume Fond et al., 2018), and vitamin D may be suggested as a low-cost and high benefit/risk ratio add-on therapy in SZ patients with depressive and anxiety symptoms.

No association between positive and negative symptoms and hypovitaminosis D has been found in the present study, contrary to previous findings (Doğan Bulut et al., 2016; Graham et al., 2015). The discrepancy with Doğan Bulut et al. study may be due to the use of different scales (PANSS vs. Scale for the Assessment of Negative Symptoms SANS and Scale for the Assessment of Positive Symptoms SAPS) and discrepancies in antipsychotic treatments. The present sample was larger than other studies (N=140 vs. respectively N=80 and N=20) (Doğan Bulut et al., 2016; Graham et al., 2015). Another explanation may be that

depressive symptoms may be strongly associated with negative symptoms (Fond G., et al., 2018) and depressive symptoms have not been explored in the previous studies except one (Nerhus et al., 2016). No association of current illness severity (PANSS total score) or psychotropic drugs with hypovitaminosis D has been found in present work, which is consistent with some previous findings (Akinlade et al., 2017; Itzhaky et al., 2012). Altogether, these inconsistent results suggest the need for larger studies and for a quantitative meta-analysis.

Contrary to what could have been expected, vitamin D has not been associated with metabolic syndrome, insulin resistance (proxy by fasting blood glucose), chronic low-grade inflammation (hs-CRP blood level) and oxidative stress (proxy by uricemia). The association with metabolic syndrome was near significance (p=0.06). This association has been extensively validated in non-SZ populations (Archontogeorgis et al., 2018; Barbalho et al., 2018; Zhu and Heil, 2018), which may suggest a power lack in the present study that would be consistent with the results of Yoo et al. (Yoo et al., 2018). No association between vitamin D blood level and hs-CRP blood level has been found, while extensive works have shown the impact of vitamin D on peripheral inflammation (Garbossa and Folli, 2017). In the present study, only hs-CRP has been explored as an inflammatory marker, future studies should explore other inflammatory markers like cytokines IL1ß, IL6 and TNF α.

Limits and future directions. These results should be replicated in larger samples and confirmed in longitudinal studies. Lifestyle habits should also been explored. The dose and duration of vitamin D supplementation have not been reported.

The screening for depression and anxiety in SZ is rarely carried out. One explanation is the debate of the existence of major depression and anxiety disorders as comorbidities of schizophrenia (Guillaume Fond et al., 2018). Some authors suggest that anxiety and depressive symptoms are part of psychotic symptomatology (as measured by the PANSS depressive factor that includes anxiety and depressive symptoms) (Wallwork et al., 2012). However, major depression has been shown to be associated with lower quality of life independently of negative symptoms (Andrianarisoa et al., 2017). The other reason may be the perception of lack of effectiveness of antidepressants in SZ subjects, while a recent study has shown that antidepressants were associated with lower depressive symptoms in SZ subjects (Guillaume Fond et al., 2018). Some depressive symptoms are also associated with insight into illness and therefore not necessarily treated (Roux et al., 2018). Anxiety and depression may also be increased by addictions and sedentary lifestyle (Fond et al., 2013a; Leventhal et al., 2008). Future studies should include qualitative interviews to understand the

barriers to anxiety and depression assessment and treatment in SZ subjects. There is no reliable specific scale to measure anxiety in schizophrenia to date.

Another barrier is that vitamin D may be identified as a complementary agent by psychiatrist, despite its medical prescription. Psychiatrists may therefore be doubtful on its efficacy, as vitamin D as an extremely good tolerance. Moreover, vitamin D may still not be identified an agent with psychotropic effects, despite the existence of vitamin D receptors in the brain and the efficacy on peripheral inflammation (G. Fond et al., 2018). Vitamin D has been recently shown to maintain extracellular fluid serotonin concentrations in the brain, thereby offering an explanation for how vitamin D could influence the trajectory and development of neuropsychiatric disorders (G. Fond et al., 2018).

Strengths. The 2 daylong-standardized evaluation including comprehensive cognitive battery, the national multicentric recruitment and the multiple confounding factors taken into account in analyses may be mentioned in the strengths of the present work.

Conclusion

The present findings suggest that hypovitaminosis D is frequent and associated with anxiety disorders and depressive symptoms in SZ subjects. As these comorbidities are under diagnosed and under treated, these results may open the path to a new precision medicine strategy in the treatment of anxiety and depression in schizophrenia. Future studies should confirm that vitamin D supplementation may be effective in alleviating depressive symptoms and anxiety disorders in SZ subjects. The association of hypovitaminosis D with metabolic syndrome deserves further explorations.

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Contributors

Dr Guillaume Fond, Dr Laurent Boyer wrote the manuscript.

All authors designed the study and wrote the protocol.

Dr Guillaume Fond and Dr Ophelia Godin managed the statistical analysis.

All authors contributed to and approved the final manuscript.

Conflict of interest.

The authors report no conflict of interest.

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