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Original Article

Vitamin D deficiency in type 1 narcolepsy: a reappraisal

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ABSTRACT

Objectives: Narcolepsy type 1 (NT1) is considered to be an immune-mediated disease in which environmental factors, such as vitamin D, might play a major role. The association between NT1 and vitamin D deficiency has previously been reported. The aim of this case–control study was to reassess vitamin D levels in a large clinic-based adult and paediatric population of patients with NT1 by considering several potential confounding factors.

Methods: The serum level of 25-hydroxyvitamin D (25OHD) was measured in 174 Caucasian patients with NT1 and 174 controls. Demographic and clinical features, body mass index (BMI), Pandemrix® vaccination, age, and season at the time of blood sampling were recorded. Between-group comparisons were made using univariate and multivariate logistic regression analyses. When appropriate, interaction terms were tested using the Wald Chi-squared test.

Results: Age, BMI, and season of blood sampling were different between groups. Conversely, the 25OHD level and fraction of subjects with vitamin D deficiency (serum level <75 nmol/L: 46.6% of patients vs 48.3% of controls; <50 nmol/L: 20.7% vs 17.2%) did not differ between patients with NT1 and controls. Overall, vitamin D deficiency was more frequent in men, obese subjects, and in samples collected in winter, without any association with NT1. In the patients group, no significant association was found between vitamin D deficiency, NT1 duration and severity, treatment, and Pandemrix® vaccination.

Conclusions: Vitamin D levels were not associated with NT1 in a large case–control population when potential demographic and clinical confounding factors were taken into account.

1. Introduction

Narcolepsy with cataplexy, which was recently renamed narcolepsy type 1 (NT1), is a sleep disorder with symptom onset mostly in childhood and adolescence [1,2]. Narcolepsy type 1 is caused by the loss of hypocretin (HCRT)-producing neurons in the hypothalamus [1]. Although the precise aetiology remains unknown, NT1 is strongly associated with HLA-DQB1*06:02 [3] and also other HLA-DPB1 and HLA Class I alleles [4], polymorphisms in the T-cell receptor α locus [5], and the purinergic receptor subtype 2Y11 [6]. Environmental factors also play a significant role, and associations have been reported with streptococcal infections [7], the 2009–2010 H1N1 influenza pandemic [8], and vaccination with the AS03 adjuvant H1N1 pandemic Pandemrix® vaccine [9–12]. These findings suggest that NT1 could be an immune-mediated disorder leading to the selective loss of HCRT-containing neurons [13,14]. However, the evidence that these triggers are causative agents for NT1 remains indirect and relatively weak [13,14]. The precise immune-related mechanisms in NT1 remain poorly understood and little is known about the key environmental factors.

Vitamin D is a steroid hormone, and its active metabolite 1,25-(OH)2D is the ligand for a transcription factor and intracellular receptor that is called 'vitamin D receptor' and is expressed by brain (microglia) and circulating immune cells [15,16]. It has been suggested that vitamin D is a major environmental factor implicated in the aetiology of many autoimmune diseases, including those restricted to the central nervous system (CNS) [17]. Vitamin D regulates the expression of major histocompatibility complex (MHC) class II genes, modulates the activity of regulatory T

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lymphocyte cells, and modifies the balance between Th2 and Th1 lymphocytes [18–20]. Robust associations between sunlight and vitamin D in multiple sclerosis and type 1 diabetes suggest that vitamin D has a key role in the development of autoimmune diseases [16,21,22] that share potential T-cell-mediated mechanisms with NT1 [14,23]. In multiple sclerosis, lower vitamin D levels increase the disease risk, the relapse rate, and the specific disease activity and disability measures [22,24,25]. Moreover, in a small-size, case–control study, it was found that vitamin D deficiency was more frequent in adult patients with NT1 than in healthy controls in crude and adjusted models [26]. However, there was no association with NT1 duration and severity or treatment intake.

The aim of the present study was to confirm and extend these results in a larger clinic-based case–control population of adults and children with a definite diagnosis of NT1. Using the same method of measurement as before, the serum level of 25-hydroxyvitamin D (25OHD) was analysed in patients with NT1 and control subjects by taking into account the main factors that might influence vitamin D levels, NT1 clinical features, and the impact of vaccination with the Pandemrix® vaccine.

2. Methods

2.1. Subjects

This study included 174 European Caucasian patients with NT1 (108 males and 66 females, median age 32.5 years, range 6–68 years). Diagnosis of NT1 was based on the following criteria: history of clear-cut cataplexy and mean multiple sleep latency test (MSLT) ≤8 minutes with ≥2 sleep onset REM periods (SOREMPs) [27,28] or cerebrospinal fluid (CSF) HCRT-1 deficiency (<110 pg/mL), according to the revised International Classification of Sleep Disorders (ICSD-3) [29]. Sixty-seven patients had a lumbar puncture, including the patients with atypical MSLT results ($n = 7$) or without typical cataplexy ($n = 3$), and all had CSF HCRT-1 levels <110 pg/mL. None of the patients presented with a psychiatric disorder, based on the DSM-V criteria, or any other significant comorbid conditions. Age, sex, body mass index (BMI) (normal: <25 kg/m^2; overweight: ≥25 kg/m^2; obese: ≥30 kg/m^2) [30], season of blood sampling, NT1 clinical data (age at onset, disease duration, Epworth Sleepiness Scale [ESS] score for adults or Adapted Epworth Sleepiness Scale [AESS] score for children, cataplexy frequency scale [2], hypnagogic hallucinations, and sleep paralysis), polysomnographic data (mean sleep latency and number of SOREMPs in the MSLT, and apnoea/hypopnoea index, AHI), and treatment at the time of the study were recorded for all patients. Fifteen patients (8.62%) were vaccinated with the Pandemrix® vaccine before narcolepsy onset.

Controls (174 European Caucasian subjects, 119 males and 55 females, median age 36.0 years, range 5–87 years) were recruited from the general population in the same area in the South of France via advertisement, during the same period. Controls were community-dwelling subjects without any significant medical, neurological, or psychiatric disease. Demographic data (age and sex), BMI, season of blood sampling, and ESS/AESS scores were collected. Among the controls, 17.3% had an ESS >10, but further investigations (polysomnography, even prolonged for 24 hours, and MSLT) ruled out the diagnosis of central hypersomnia. None of the subjects included in the previous study on NT1 and vitamin D [24] were enrolled in the present study.

All subjects and the parents of children aged <18 years signed a written informed consent to participate in the study, which was approved by the local ethics committee. According to French law, the biological sample collection was registered at the 'Ministère de l'Enseignement Superieur et de la Recherche' (Number DC-2008- 417).

2.2. Blood analysis

Venous blood was sampled between 07:00 and 08:00 after overnight fasting, according to standardised procedures. Serum samples from patients and controls were handled similarly and frozen immediately for further analysis. The serum 25OHD level, which is representative of the overall vitamin D stored in the body (25-hydroxyvitamin D ergocalciferol [D2] plus cholecalciferol [D3]) [15], was measured by radioimmunoassay (25OH Vitamin D RIA, IDS, Immunodiagnostic Systems, Boldon, UK). The inter-assay coefficient of variation was <8.2% and the intra-assay variation coefficient was <6.1%. Samples were run in separate, single assays. Two commonly accepted international clinical thresholds for vitamin D deficiency and insufficiency, respectively, (serum 25OHD level <50 and <75 nmol/L) were used [22,31].

2.3. Statistical analysis

Percentages were used for categorical variables and medians and ranges for quantitative variables; the distribution of continuous variables was mostly skewed, according to the Shapiro–Wilk test. Univariate comparisons between controls and patients with NT1 were made using logistic regression analysis and quantified with odds ratios (OR) and their 95% confidence intervals (CI). The serum 25OHD levels (continuous variable) were divided into quartiles and tertiles, and were also based on the clinical thresholds of 50 and 75 nmol/L. Multivariate logistic regression analyses were performed on clinical and demographic variables with $p < 0.1$ in univariate analysis. When appropriate, interaction terms were tested using the Wald Chi-squared test given by the logistic regression model. Significance level was set at $p < 0.05$. Statistical analyses were performed using the SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

The median age at disease onset in the NT1 group was 18 years (range 4–61 years) and disease duration was 10.5 years (range 0–73 years). Among the patients with NT1, 65.9% reported hypnagogic hallucinations, 55.1% sleep paralysis, 34.3% REM sleep behaviour disorder, and 8.9% severe obstructive sleep apnoea syndrome (AHI >30/hours). At the time of blood sampling, 34% of patients with NT1 were treated with psychostimulants or anti-cataplectic drugs.

Compared with the controls, patients with NT1 were significantly older and more overweight/obese (BMI >30 kg/m^2: 15.9% vs 9.3% of controls) (Table 1). As expected, patients with NT1 had higher ESS/AESS scores (95.6% of NT1 patients had a score >10 compared with 17.3% of controls). Blood sampling in winter was significantly more frequent in the control group than in the patient group.

The serum level of 25OHD was not significantly different between patients with NT1 and controls in crude association or after adjustment for age, BMI, and season of blood sampling (Table 2, Fig. 1). No significant between-group difference was observed when vitamin D deficiency was defined according to the two thresholds (<75 nmol/L: 46.6% of patients vs 48.3% of controls; <50 nmol/L: 20.7% of patients vs 17.2% of controls), or when serum 25OHD levels were divided into quartiles and tertiles of the whole sample (Table 2). A very low vitamin D concentration (<25 nmol/L) was found in five patients with NT1 and two controls.

A comparison of all subjects (patients and controls) with low (<75, $n = 165$) and normal vitamin D levels (≥75, $n = 183$) indicated that vitamin D deficiency was more frequent in men and obese individuals, and in blood samples taken in winter (Table 3). No