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Vitamin D-related changes in intracranial volume in older adults: A quantitative neuroimaging study

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ABSTRACT

Objectives: Vitamin D is involved in skeletal and brain health. Recently, serum 25-hydroxyvitamin D (25OHD) concentration was found to be inversely correlated with intracranial volume in younger adults. Since hypovitaminosis D is most common in older adults, our objective was to determine whether this inverse correlation between 25OHD concentration and intracranial volume also occurred in older adults.
Study design: Cross-sectional study.
Main outcome measures: One hundred and ten Caucasian older community-dwellers (mean, 71.7 ± 5.7 years; 45.5% female) received a blood test and an MRI of the brain at the same period. The intracranial volume and the subvolumes of cerebrospinal fluid, total brain, infratentorial brain, supratentorial brain, total white matter, total gray matter, cortical gray matter and subcortical gray matter were measured using FreeSurfer volumetry on T_1-weighted images. Vitamin D insufficiency was defined as serum 25OHD < 50 nmol/L. Age, gender, body mass index, education level, use of vitamin D supplements, season of evaluation, serum concentrations of calcium and thyroid stimulating hormone were used as covariables in the analysis.
Results: We found that participants with vitamin D insufficiency ($n=41$) had greater intracranial volume than those without (1555.0 ± 1379.2 cm^3 versus 1488.0 ± 167.4 cm^3, $P=0.033$). Serum 25OHD concentration was cross-sectionally associated with decreased intracranial volume in mm^3 (unadjusted $\beta=-1194.4$, $P=0.028$), even after adjustment for covariables (adjusted $\beta=-994.3$, $P=0.048$). We found an inverse correlation of serum 25OHD with intracranial volume ($r=-0.21$, $P=0.028$) and the volume of white matter ($r=-0.20$, $P=0.033$). The other subvolumes did not correlate with serum 25OHD concentration.
Conclusions: Serum 25OHD concentration was independently and inversely associated with intracranial volume in older adults.

1. Introduction

Vitamin D is not only a fat-soluble vitamin, but primarily a secosteroid hormone involved in the regulation of various biological targets including skeletal and non-skeletal organs such as the brain [1]. Serum 25-hydroxyvitamin D (25OHD) concentration is a measure of individual vitamin D status [1]. It is generally accepted that the higher the 25OHD, the fewer the adverse events [2]. However at least 1 billion people have insufficient 25OHD concentrations worldwide [1], and older adults are at particular risk with prevalence between 40 and 90% [1]. Vitamin D insufficiency exposes older adults to various adverse health events [1,2], including brain changes, cognitive decline, Alzheimer disease and dementia [3,4].

Intriguingly, a recent study reported that the intracranial volume inversely correlated with serum 25OHD concentration in a cohort of healthy younger women; the participants with high

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25OHD concentrations exhibited smaller intracranial volume than those with low 25OHD concentrations [5]. This finding seems to contradict the neuropsychological literature since it is commonly accepted that the intracranial volume is positively correlated with the intelligence quotient (IQ) and inversely associated with the risk of Alzheimer disease [6]. However the relationship between vitamin D and cognition has been found thus far only in older adults but not in younger ones [7], and hypovitaminosis D is a condition mostly faced by seniors [1], therefore the latter finding should be evaluated in older adults. We had the opportunity to examine the association of serum 25OHD concentration with intracranial volume among older adults recruited in the 'Gait and Alzheimer Interactions Tracking' (GAIT) study [8]. Our objective was to determine whether serum 25OHD concentration was inversely associated with intracranial volume in a cohort of community-dwelling older adults.

2. Materials and methods

2.1. Participants

We studied 110 older community-dwellers followed in the Memory Clinic of the University Hospital of Angers, France, and consecutively recruited in the GAIT study in 2009–2011. The GAIT study is an observational cross-sectional study designed to examine gait in older community-dwellers reporting subjective memory complaint. The sampling and data collection procedures have been described elsewhere in detail [8]. In summary, subjective memory complaint was documented using the Subjective Memory Complaints Questionnaire [9] and the main exclusion criteria were age below 60 years, Mini-Mental State Examination (MMSE) score < 10 [10], inability to walk independently, a history of stroke, history of any acute medical illness within the preceeding 3 months, current delirium, severe depression, and inability to understand or answer the study questionnaires. All study participants received a full medical examination, consisting of structured questionnaires and standardized clinical examination, a cerebral MRI scan and a blood test.

2.2. MRI data acquisition

Imaging of the brain was performed with a 1.5-Tesla MRI scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) using a standard MRI protocol [8] including T_1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) axial images (acquisition matrix = 256 × 256 × 144, FOV = 240 mm × 240 mm × 187 mm, TE/TR/TI = 4.07 ms/2170 ms/1100 ms).

2.3. Intracranial volume and other cranial subvolumes analysis

T_1-weighted MRI data were processed by an operator (CA) using the FreeSurfer version 5.1.0 morphometric analysis tools to evaluate intracranial volume. FreeSurfer is a highly automated image analysis suite that segments, labels and quantifies brain tissue volumes, and is available for download online (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer uses a probabilistic atlas generated from manually segmented MR scans to perform the segmentation. The probabilistic information for each tissue type has been mapped into Talairach space. Given a specific location and tissue type, the probabilities are given as (i) a Gaussian intensity distribution, (ii) probability of occurrence, and (iii) probability of neighboring tissue types. During segmentation, a number of processing steps occur including motion correction, intensity normalization, removal of nonbrain tissue, Talairach registration, and labeling of voxels into tissue types. Initially, each voxel is assigned its most probable tissue type. An iterative algorithm then uses the tissue probabilities to calculate new probabilities for the voxel labels. This process continues until no changes in tissue types occur. Manual edits were made by the operator (CA) to reduce inaccuracies in white matter (WM) and gray matter (GM) classification. The segmentation process has been described in detail elsewhere [11,12]. The intracranial volume was estimated according to the methods by Buckner et al. [13] based on the determinant of the affine transform matrix used to align the image with a reference atlas produced from 40 subjects spanning from young to old and including 10 cases with Alzheimer disease [14]. The intracranial volume calculated with Freesurfer does not differ with time ($r = 0.995$) [15]. For the present analysis, the subvolumes of cerebrospinal fluid (CSF), total brain, infratentorial brain, supratentorial brain, total WM, total GM, cortical GM and subcortical GM were also measured automatically [11,12].

2.4. Serum vitamin D assessment

Venous blood was collected from resting participants at the same time as the brain imaging acquisition. Serum 25OHD concentration was measured by radioimmunoassay (*DiaSorin* Inc., Stillwater, MN) in nmol/L (to convert to ng/mL, divide by 2.496). With this method, there is no interference of lipids, which is often observed in other non-chromatographic assays of 25OHD. The intra- and interassay precision was 5.2% and 11.3% respectively. Vitamin D insufficiency was defined as 25OHD concentrations < 50 nmol/L according to the definition of the World Health Organization [16]. All measurements were performed at the University Hospital of Angers, France.

2.5. Covariables

The following covariables were included as potential confounders in the statistical models: age, gender, body mass index (BMI), high education level, use of vitamin D supplements, season of evaluation, serum concentrations of calcium and thydroid stimulating hormone (TSH).

Demographical and clinical covariables were obtained from a physical examination and a standardized comprehensive geriatric assessment. The BMI was calculated in kg/m^2 as $weight_{kg}/height_{m^2}$. Education level was self-reported with a structured standardized questionnaire. Participants who did graduate studies were considered to have a high level of education compared to those who did not. The regular use of vitamin D supplements was collected from the primary care physician's prescriptions and sought by questioning the patient. The season of evaluation was recorded as follows: spring from March 21 to June 20, summer from June 21 to September 20, fall from September 21 to December 20, and winter from December 21 to March 20. Finally, serum concentrations of calcium, albumin, and TSH were determined using automated standard laboratory methods at the University Hospital of Angers, France. Because of the high prevalence of hypoalbuminemia in older adults, serum concentrations of albumin and calcium were used to correct the calcium value: corrected $calcium_{mmol/L}$ = uncorrected $calcium_{mmol/L} + ([40 - albumi_{g/L}] \times 0.02)$.

2.6. Statistical analysis

The participants' characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Normality of the data distribution was checked using skewness-kurtosis test. As the number of observations was higher than 40, comparisons were not affected by the shape of the error distribution and no transform was applied [17]. Firstly,