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CALcium Ionisé et troubles du COmportement chez la personne âgée : Étude CALICO

Ionized calcium and behavioral disorders in older Adults : Results from the CALICO Study

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Liste des abréviations

25OHD	25-hydroxyvitamin D
BMI	Body Mass Index
BP	Blood Pressure
Ca	Calcemia
CI	Confidence Interval
CNS	Central Nervous System
DBP	Diastolic Blood Pressure
EPIDOS	Epidémiologie de l'Ostéoporose
ER	Endoplasmic Reticulum
EDF	Echelle de Dysfonctionnement Frontal
FBS	Frontotemporal Behavior Scale
eGFR	Estimated Glomerular Filtration Rate
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
NMDA	N-methyl-d-aspartate
ORs	Odds Ratio
PTH	Parathyroid Hormone
ROC	Receiver Operating Characteristic
SBP	Systolic Blood Pressure
SD	Standard Deviation
Se	Sensitivity
Sp	Specificity
TSH	Thyroid Stimulating Hormone

Plan

Ionized calcium and behavioral disorders in older adults : Results from the CALICO study

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ABSTRACT

Introduction. Calcium may be involved in brain health and function. Ionized calcium concentration is usually better correlated to clinical impact than measured and corrected calcium values. The objective of this case-control study was to determine whether older patients with severe behavioral disorders had higher serum ionized calcium concentration than those without behavioral disorders, but no difference in serum measured or corrected calcium concentrations.

Material and method. Twenty-nine cases with severe behavioral disorders (mean±SD, 86.4±5.8years; 24.1% female) and 58 age- and gender-matched controls were enrolled in a geriatric acute care unit between 2016 and 2017. Severe behavioral disorders were defined as any behavioral disorder justifying the use of neuroleptics prior to hospitalization or as a Frontotemporal Behavior Scale (FBS) score ≥3 at hospital admission. Serum calcium, corrected calcium and ionized calcium concentrations were measured locally in a single center. Age, gender, BMI, mean arterial pressure, number of drugs daily taken, use of calcium supplements, serum concentrations of TSH, parathyroid hormone and 25-hydroxyvitamin D, and the estimated glomerular filtration rate were used as potential confounders.

Results. Cases with severe behavioral disorders exhibited higher serum ionized calcium concentration than matched controls (1.29±0.07mmol/L versus 1.25±0.07mmol/L, p=0.047), but no difference in measured (p=0.173) and corrected calcium concentrations (p=0.819). Increased ionized calcium concentration was associated with increased FBS score (β=4.91 [95CI: 1.30;8.53] per mmol/L of ionized calcium, p=0.009). The concentration distinguishing between cases and controls with the best sensitivity-specificity was found at 1.27mmol/L. Ionized hypercalcemia >1.27mmol/L was associated with more frequent severe behavioral disorders (OR=11 [95CI:1.75;63.36], p=0.011).

Conclusion. Increased serum ionized calcium concentration was associated with more severe behavioral disorders in acute geriatric inpatients. The threshold

concentration distinguishing between cases and controls was around 1.27mmol/L.

INTRODUCTION

Increasing attention is being paid to the effects of calcium on neurological and cognitive health and function. Although essential for neuronal homeostasis and signaling (1), recent evidence also suggests a possible toxicity of calcium on the central nervous system (CNS) (2); with excessive elevation of intracellular calcium leading to neuronal death by necrosis or apoptosis (3). This phenomenon could contribute to the development of neural diseases (4) such as neurodegenerative diseases (5,6). For example, an analysis of the Rotterdam study (7) showed that, in older adults, high calcium concentrations were associated with more rapid and severe cognitive decline. Delirium and neuropsychiatric behavioral disturbances have also been reported in various studies of hypercalcemia in older adults (8–10). Conversely, other studies found no link between calcium concentration and neurocognitive manifestations (11). For instance, in France, an analysis of the EPIDOS study did not find any association between calcium concentration and cognitive performance (12). Thus, further studies are needed to conclude as to the existence of a link between calcium and neurocognition.

It is interesting to note that previous studies all used the determination of calcemia and/or corrected calcemia, but not the concentration of ionized calcium, which could explain the discrepancies between previous results. Ionized calcium makes up about 50% of total serum calcium (13,14). It is considered to be the most tightly regulated, and the measure of ionized calcium is more reproducible, more sensitive, and better correlated to clinical impact than other forms of calcium (15).

We hypothesized that the concentration of ionized calcium, but neither the measured serum calcium concentration nor the corrected serum calcium concentration, influences neurocognitive functioning. The objective of this case-control study was to determine whether older patients with severe behavioral disorders had higher serum ionized calcium concentration than those without behavioral disorders, but no difference in serum measured or corrected calcium concentrations.

MATERIALS AND METHODS

1. Design and settings

The case-control CALICO (CALcium and COgnition) study was conducted in the geriatric acute care unit of the University Hospital of Angers, France, between June 2016 and April 2017. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983) and was approved by the local ethics committee (number 2016-36). The study protocol was declared to the National Commission for Information Technology and civil Liberties (CNIL) under the number 2016-040 (ClinicalTrials.gov Identifier: NCT02909491).

2. Participants

All older adults aged 75 years and over consecutively hospitalized in the geriatric acute care unit during the study period were screened for possible inclusion in the CALICO study. Patients who objected to the use of their data for research purposes were not included in the study.

Cases were geriatric inpatients exhibiting severe behavioral disorders defined either as a behavioral disorder in progress having justified the use of neuroleptics prior to hospitalization, or as a Frontotemporal Behavior Scale (FBS) score ≥ 3 (/4) at hospital admission (16).

Controls were recruited during the same study period within the geriatric acute care unit, were matched on age (± 3 years) and gender, had no severe behavioral disorders and were taking no antipsychotics.

Because the main objective of the study was descriptive, no calculation of number of subjects was required. However, in order to match a normal distribution of the data and to use parametric statistical tests, at least 40 participants were required. Twenty-nine cases with severe behavioral disorders and 58 controls without behavioral disorders were finally included (ratio 1:2).

3. Outcomes

Serum ionized calcium concentration was measured in mmol/L at hospital admission using a potentiometer (ABL800 Flex, Radiometer) locally at the University Hospital of Angers, France. Serum calcium concentration was determined in mmol/L by colorimetry and absorbance measurement (Advia Chemistry XPT, Siemens). Corrected serum calcium concentration in mmol/L was estimated using the following formula: 'corrected calcium = calcium + 0.02 x (40 – albumin in g/L)' (17).

Behaviour was assessed at the time of the blood test using the FBS (16). The FBS indicates the presence of symptoms of 4 domains of behavioral disturbances (i.e., self-control disorder, physical neglect, mood disorders and loss of general interest). Each domain is scored 1 if at least 1 symptom is present, and 0 if no symptoms are present. The total FBS score ranges from 0 (normal) to 4 (worst). The FBS is easy to perform and has demonstrated good test-retest reliability (16). Severe behavioral disorders were defined either as a FBS score ≥ 3, or as a behavioral disorder requiring the use of neuroleptics prior to hospitalization.

4. Covariables

Age, gender, body mass index (BMI), mean arterial pressure (MAP), the number of drug taken per day, the use of calcium supplements, the serum concentrations

of thyroid-stimulating hormone (TSH), parathyroid hormone (PTH) and 25-hydroxyvitamin D (25OHD), and the estimated Glomerular Filtration Rate (eGFR) were used as potential cofounders. Blood pressure was measured at rest in a quiet environment by trained nurses according to a standardized protocol (18) using a sphygmomanometer placed on the brachial artery with arm at heart level. The MAP (i.e., the average BP over the entire course of the BP cycle) was calculated in mmHg from systolic (SBP) and diastolic blood pressures (DBP) using the following formula: 'MAP = (SBP + 2 DBP)/3'. BMI was calculated using the formula: 'BMI = weight (kg)/height^2 (m^2)'. eGFR was calculated in mL/min/1,73m² using the Modification of Diet in Renal Disease (MDRD) Study equation (19).

5. Statistical analysis

The participants' characteristics were summarized using means and standard deviations (SD) or frequencies and percentages, as appropriate. Firstly, comparisons of cases and controls were performed using Wald's test. Secondly, univariate and multiple linear regressions were used to examine the associations of serum ionized calcium concentration (independent variable) with the FBS score (dependent variable) while adjusting for potential confounders. Thirdly, the serum ionized calcium threshold value that best distinguished between cases and controls was determined by sensitivity analysis. Finally, univariate and multiple logistic regressions were used to determine whether ionized hypercalcemia (defined with the threshold value calculated with the sensitivity analysis) was associated to severe behavioral disorders. P-values < 0.05 were

considered significant. All statistics were performed using SAS (V9.4 SAS Institute Inc.).

RESULTS

Twenty-nine cases with severe behavioral disorders (mean±SD, 86.4±5.8 years; 24.1% female) and 58 age- and gender-matched controls without behavioral disorders (86.8±5.1 years; 48.3% female; mean serum ionized calcium concentration, 1.27±0.08 mmol/L; mean measured calcium concentration, 2.21±0.14mmol/L; mean corrected calcium concentration, 2.38±0.11) were included in the CALICO study.

As illustrated in Table 1, cases had higher serum ionized calcium concentration than controls (respectively, 1.29 ±0.07mmol/L versus 1.25±0.07mmol/L, p=0.047). In contrast, there were no between-group differences regarding measured calcium concentration (respectively, 2.23±0.13mmol/L versus 2.20±0.14mmol/L, p=0.173) and corrected calcium concentration (respectively, 2.37±0.11mmol/L versus 2.38±0.12mmol/L, p=0.819).

Results of the multiple linear regression model were reported in Table 2. We observed a positive association between serum ionized calcium concentration and the FBS score (β=4.91 [95% confidence interval (CI): 1.30-8.53], p=0.009).

Figure 1 consistently illustrates the increase in the severity score of behavioral disorders with the increase in the serum concentration of ionized calcium.

Finally, we found that the best compromise between sensitivity and specificity to predict severe behavioral disorders (i.e. FBS score ≥3) was calculated for a serum ionized calcium threshold of 1.27 mmol/L (Se=0.69, Sp=0.64). Multiple logistic regression models showed that ionized hypercalcemia > 1.27 mmol/L was positively associated to severe behavioral disorders (OR=5.80 [95CI: 1.47-

22.93], p=0.012), even after adjusting for potential confounders (OR=11 [95CI: 1.75-63.36], p=0.011) (Table 3).

DISCUSSION

The main finding of the present case-control study was that older patients with severe behavioral disorders had higher serum ionized calcium concentration than those without behavioral disorders, irrespective of all studied potential confounders. The serum concentration of 1.27 mmol/L ionized calcium best distinguished between cases and controls. In contrast, there was no between-group difference regarding the measured and corrected calcium concentrations. These results are consistent with previous epidemiological evidence on the adverse effect of excess calcium on cognitive functions (7–10). Previous studies reported converging elements illustrating poorer neurological health and various clinical manifestations including neurocognitive and psychiatric disorders related to excessive calcium intake. Compared to previous literature, our study provides novel information by examining three different measures of serum calcium, in particular ionized calcium, and thanks to its case-control design which made it possible to specify the ionized calcium threshold concentration of 1.27 mmol/L that best distinguished between older patients with severe behavioral disorders and those without behavioral disorders.

Only one study had examined ionized serum calcium in relation to neurocognition previously (20). This cohort study, aimed at identifying the modifiable risk factors for cognitive decline after 75 years, found that ionized hypercalcemia > 1.29 mmol/L was linked to a greater risk of cognitive decline after 10 years ($p=0.048$), which is consistent with the present results. In contrast, other studies based on measured and corrected calcium concentrations did not find any association with neurocognition (11,12). This could be explained

by the fact that, in older adults, the measured and the corrected calcium concentrations tend to misclassify a significant proportion of patients with pathological conditions (kidney failure, subclinical hyperparathyroidism, cancer, undernutrition, among others). In contrast, ionized calcium is not subject to changes in albumin concentration or inflammation, and should be used as a gold standard (21).

How ionized calcium and neurocognitive function are related and whether this relationship is causal is not yet fully understood. First, it is recognized that calcium regulates fundamental neuronal functions such as synaptic plasticity and transmission (1) through the intracellular endoplasmic reticulum (22) and plasma membrane calcium channels such as the NMDA (N-methyl-d-aspartate) receptor (2). The increase in intracellular calcium leads to several calcium-activated cascades causing neuronal dysfunction, the extreme effect of which is cell death either by necrosis or by apoptosis (3). Second, while mitochondria usually regulate the increase in calcium by sequestering it (23) and thus limit oxidative stress (24), they tend to be less efficient with advancing age due to increased oxidative stress. Thus, aged neurons under persistent calcium neuronal stress may become unable to prevent the dysregulation of intraneuronal calcium homeostasis. This may partly explain the greater sensitivity of older adults to calcium variations, in particular to hypercalcemia. An acute increase in calcium could be responsible for delirium, while a chronic increase in calcium, for example due to calcium supplements or primary hyperparathyroidism, could be responsible for neurodegenerative and/or neurovascular diseases (25).

The strengths of our study include the originality of the research question on a highly common condition in older adults, the standardized collection of data from a single research center, the assessment of three different calcium serum measures, the assessment of behaviour using a validated tool, and the detailed description of the participants' characteristics allowing the use of regression models to measure adjusted associations.

Regardless, a number of limitations should be acknowledged. First, this is a single-center study with a relatively small number of participants who may not be representative of the general population of older patients with severe behavioral disorders. Second, the observational design of the case-control study precludes any causal reasoning compared to an interventional study and prevents determining whether hypercalcemia precipitates behavioral disorders or whether adults with behavioral disorders are more at risk of hypercalcemia. Third, although we were able to control for important characteristics that could modify the associations, residual potential confounders might still be present such as the ApoE genotype (26). Fourth, measurement of ionized serum calcium concentration might be affected by variability in measurement conditions and pH (27), but this has been limited by the use of only one standardized measurement method in a single laboratory. Fifth, limitations include the use of FBS tool, which may exhibit ceiling effects and limited sensitivity to subtle abnormalities but which was chosen here because it is particularly usable in acute care units compared to more complex and time-consuming tests such as the Neuropsychiatric Inventory (28). In future studies, the screening for behavioral disorders should use other outcomes, e.g., comparing the different

behavioral subdomains, both disruptive or apathetic, according to ionized calcemia.

CONCLUSION

We were able to report an association between serum ionized calcium concentration and severe behavioral disorders in older adults hospitalized in a geriatric acute care unit, especially above 1.27 mmol/L, a relatively low value usually neglected by clinicians in routine practice. Such association was not found with measured or corrected calcium concentrations. This result should be confirmed in larger longitudinal studies, preferentially on a variety of adult populations. Nevertheless, it provides new clues for better understanding the involvement of calcium in neurocognitive decline and behavioral consequences. It also provides a scientific basis for conducting clinical trials to test the efficacy of interventions aimed to reduce ionized calcium concentration -based either on surgery or medical treatment (29–32)- to prevent or improve behavioral disorders in older patients with initial serum ionized calcium concentration >1.27 mmol/L and to limit the use of psychotropic drugs.

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LISTE DES FIGURES

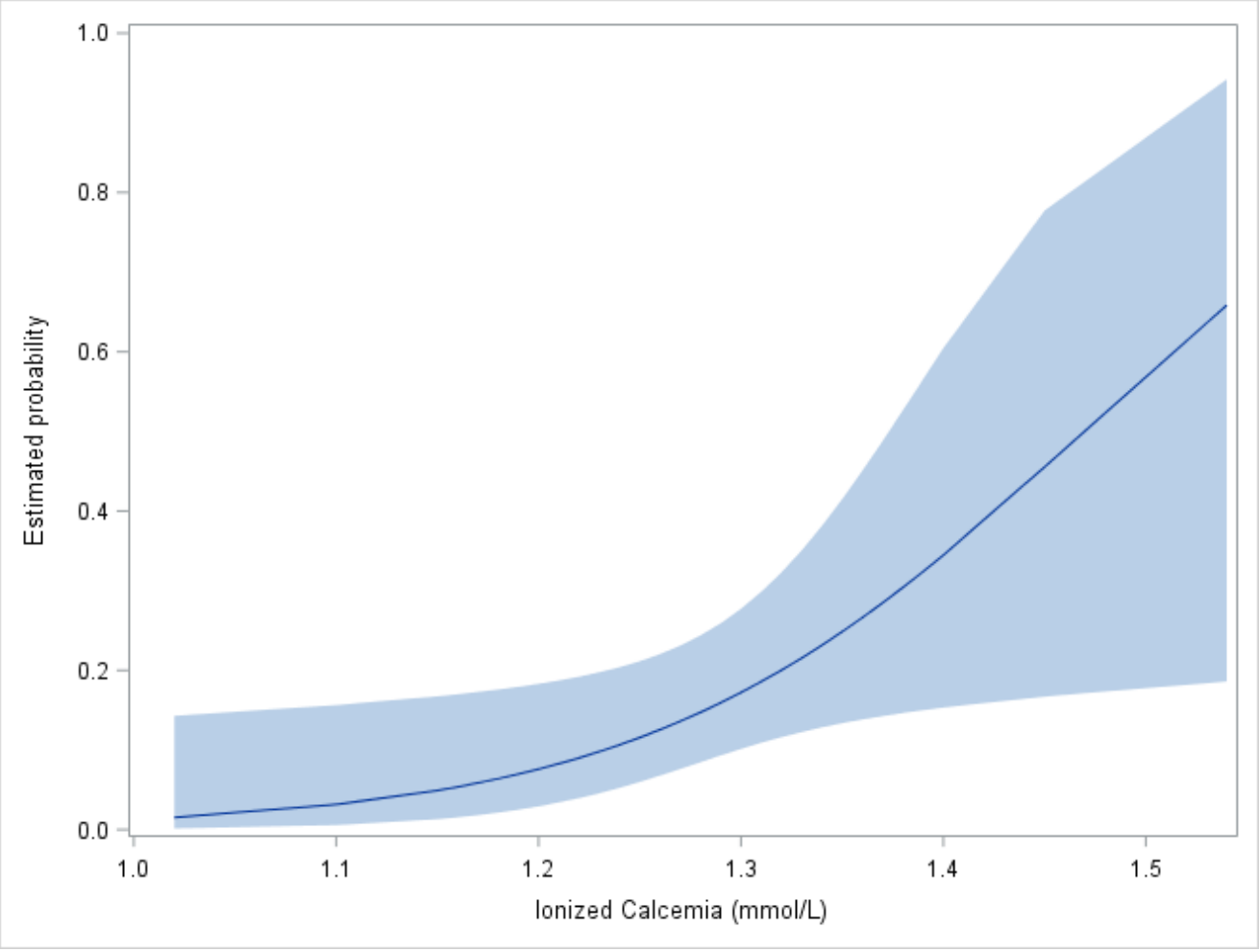

Figure 1. Estimated probability of severe behavioral disorders based on serum ionized calcium concentration.

LISTE DES TABLEAUX

Table 1. Characteristics of participants (n=87).

	Total cohort (n=87)	Cases (n=29)	Controls (n=58)	p-value
Demographical measures				
Age, years	86.6 ± 5.3	86.4 ± 5.8	86.8 ± 5.1	-
Female gender, n (%)	63 (72.4)	21 (24.1)	42 (48.3)	-
Clinical measures				
Body mass index, kg/m²	26.7 ± 5.6	26.5 ± 5.1	26.9 ± 5.8	0.733
Mean arterial pressure, mmHg	96.1 ± 13.5	97.4 ± 13.1	95.4 ± 13.7	0.489
Number of drugs taken per day	7.0 ± 2.9	7.5 ± 2.9	6.7 ± 2.8	0.232
Use of calcium supplements, n (%)	7 (8)	2 (7)	5 (9)	0.790
FBS score, /4	0.99 ± 1.25	2.10 ± 1.32	0.43 ± 0.75	**<0.001**
Serum measures				
Ionized calcium, mmol/L	1.27 ± 0.08	1.29 ± 0.07	1.25 ± 0.07	**0.047**
Measured calcium, mmol/L	2.21 ± 0.14	2.23 ± 0.13	2.20 ± 0.14	0.173
Corrected calcium, mmol/L	2.38 ± 0.11	2.37 ± 0.11	2.38 ± 0.12	0.819
TSH, mUI/L (n=78) *	1.82 ± 2.23	1.58 ± 1.30	1.95 ± 2.56	0.535
25OHD, ng/mL (n=78) *	60.5 ± 33.5	61.8 ± 36.6	59.9 ± 32.2	0.795
PTH, pg/mL (n=66) *	37.4 ± 25.3	35.0 ± 18.1	35.5 ± 28.3	0.612
eGFR, mL/min/1.73m²	79.24 ± 63.03	85.79 ± 99.04	73.61 ± 33.65	0.403

Data presented as mean±standard deviation when applicable; 25OHD: 25-hydroxyvitamin D; eGFR: estimated glomerular filtration rate; FBS: frontotemporal behavior scale; PTH: parathyroid hormone; TSH: thyroid-stimulating hormone; *: only triads (i.e. 1 case and 2 controls) without missing data were taken into account; p-values significant (i.e., $p < 0.05$) indicated in bold.

Table 2. Univariate and fully adjusted linear regressions examining the associations between the serum ionized calcium concentration (independent variable) and the Frontotemporal Behavior Scale (FBS) score* (dependent variable) adjusted for potential confounders (n=87).

	Frontotemporal Behavior Scale score					
	Univariate model			Fully adjusted model		
	β	95% CI	p-value	β	IC 95%	p-value
Ionized calcium concentration	4.13	[0.65 ; 7.61]	**0.020**	4.91	[1.30 ; 8.53]	**0.009**
Age	0.02	[-0.03 ; 0.07]	0.453	0.04	[-0.01 ; 0.10]	0.104
Female gender	-0.13	[-0.73 ; 0.47]	0.666	-0.25	[-0.88 ; 0.38]	0.435
Body mass index	-0.02	[-0.07 ; 0.03]	0.402	-0.04	[-0.10 ; 0.01]	0.103
Mean arterial pressure	0.005	[-0.01 ; 0.03]	0.592	0.005	[-0.02 ; 0.02]	0.646
Number of drugs taken per day	0.03	[-0.07 ; 0.12]	0.594	0.05	[-0.002 ; 0.20]	0.055
Use of calcium supplements	-0.61	[-1.59 ; 0.37]	0.220	-0.56	[-1.62 ; 0.49]	0.292
Serum TSH concentration	-0.07	[-0.19 ; 0,04]	0.219	-0.06	[-0.18 ; 0.07]	0.349
Serum 25OHD concentration	-0.006	[-0.01 ; 0.002]	0.158	-0.01	[-0.017 ; -0.001]	**0.030**
Serum PTH concentration	-0.00	[-0.01 ; 0.01]	0.771	0.00	[-0.01 ; 0.01]	0.996
eGFR	0.002	[-0.001 ; 0.001]	0.176	0.002	[-0.01 ; 0.01]	0.365

25OHD: 25-hydroxyvitamin D; β: coefficient of regression corresponding to a change of FBS score; CI: confidence interval; eGFR: estimated glomerular filtration rate; PTH: parathyroid hormone; TSH: thyroid-stimulating hormone; p-values significant (i.e., $p < 0.05$) indicated in bold.

Table 3. Univariate and multiple logistic regressions models examining the association between ionized hypercalcemia* (independent variable) and severe behavioural disorders (dependent variable), adjusted for potential confounders† (n=87).

	Severe behavioral disorders					
	Univariate model			Fully adjusted model		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Ionized hypercalcemia*	5.80	[1.47; 22.93]	**0.012**	11.0	[1.75 ; 63.36]	**0.011**
Age	1.05	[0.94 ; 1.18]	0.420	1.05	[0.89 ; 1.23]	0.207
Female	0.83	[0.23 ; 3.01]	0.781	2.18	[0.25 ; 18.92]	0.482
Body mass index	0.97	[0.87 ; 1.09]	0.632	0.85	[0.70 ; 1.05]	0.132
Mean arterial pressure	0.99	[0.95; 0.685]	0.685	0.96	[0.89 ; 1.04]	0.318
Number of drugs taken per day	1.06	[0.87 ; 1.31]	0.557	1.19	[0.87 ; 1.62]	0.290
Serum TSH concentration	0.89	[0.56 ; 1.42]	0.636	0.96	[0.60 ; 1.53]	0.854
Serum 25OHD concentration	0.98	[0.96 ; 1.00]	0.115	0.98	[0.95 ; 1.01]	0.111
Serum PTH concentration	1.00	[0.97 ; 1.02]	0.801	1.01	[0.98 ; 1.04]	0.635
eGFR	1.01	[0.99 ; 1.02]	0.152	1.01	[0.99; 1.03]	0.203

25OHD: 25-hydroxyvitamin D; CI: confidence interval; eGFR: estimated glomerular filtration rate; OR: odds ratio; PTH: parathyroid hormone; TSH: thyroid-stimulating hormone; *: defined as serum ionized calcium concentration > 1.27 mmol/L; †: not adjusted for the use of calcium supplements since none of the participants with severe behavioral disorders were using calcium supplements; p-values significant (i.e., $p < 0.05$) indicated in bold.

TABLE DES MATIERES

ANNEXES

Acknowledgments

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Conflicts of Interest

The authors report no conflicts of interest.

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Authors Contributions

CA has full access to all data in the study, takes responsibility for the data, the analyses and interpretation, and has the right to publish any or all data, separate and apart from the attitudes of the sponsors. All authors have read and approved the final version of the manuscript.

Study concept and design: JB and CA.

Acquisition of data: RO, JB and CA.

Analysis and interpretation of data: RO, JB and CA.

Drafting of the manuscript: RO, JB and CA.

Critical revision of the manuscript for important intellectual content: not applicable.

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Statistical expertise: CA.

Administrative, technical, or material support: CA.

Study supervision: CA.

Data availability policy

Patient level data are freely available from the corresponding author at Cedric.Annweiler@chu-angers.fr. There is no personal identification risk within this anonymized raw data, which is available after notification and authorization of the competent authorities. Data requests may be sent to the following address: Centre Hospitalier Universitaire, Délégation à la recherche clinique et à l'innovation (DRCI), 4 rue Larrey, F-49933 Angers cedex 9 France.

ORDONEZ Romain

CALcium Ionisé et troubles du COmportement chez la personne âgée : étude CALICO

RÉSUMÉ

Introduction. Le calcium pourrait être impliqué dans le bon fonctionnement du cerveau. La concentration de calcium ionisé est généralement mieux corrélée à l'impact clinique que les concentrations de calcium mesurées et corrigées. L'objectif de cette étude cas-témoins était de déterminer si les patients âgés souffrant de troubles sévères du comportement avaient une concentration sérique de calcium ionisé plus élevée que ceux qui n'avaient pas de troubles du comportement, sans différence de concentrations sériques de calcium mesurée ou corrigée.
Matériel et méthode. Vingt-neuf cas présentant des troubles sévères du comportement (moyenne±SD, 86,4±5,8 ans; 24,1% de femmes) et 58 témoins appariés sur l'âge et le sexe ont été inclus dans une unité de gériatrie aigue entre 2016 et 2017. Les troubles sévères du comportement ont été définis comme tout trouble du comportement justifiant l'utilisation de neuroleptiques avant l'hospitalisation ou comme un score à l'échelle de dysfonctionnement frontale (EDF) ≥3 lors de l'admission. Les concentrations de calcium sérique, de calcium corrigé et de calcium ionisé ont été mesurées dans un même centre. L'âge, le sexe, l'IMC, la pression artérielle moyenne, le nombre de médicaments pris quotidiennement, la supplémentation calcique, les concentrations sériques de TSH, d'hormone parathyroïdienne et de 25-hydroxyvitamine D, ainsi que l'estimation du taux de filtration glomérulaire ont été utilisés comme potentiels facteurs de confusion.
Résultats. Les cas présentant des troubles sévères du comportement avaient une concentration sérique de calcium ionisé plus élevée que les témoins appariés (1,29±0,07mmol/L contre 1,25±0,07mmol/L, p=0,047), sans différence de concentrations de calcium mesurée (p=0,173) ou corrigée (p=0,819). L'augmentation de la concentration sérique de calcium ionisé était associée à une augmentation du score EDF (β=4,91 [95CI : 1,30;8,53] par mmol/L de calcium ionisé, p=0,009). La concentration de calcium ionisé permettant de distinguer les cas des témoins, avec la meilleure spécificité et sensibilité, était de 1,27 mmol/L. L'hypercalcémie ionisée > 1,27 mmol/L était associée à des troubles sévères du comportement plus fréquents (OR=11 [95CI:1,75;63,36], p=0,011).
Conclusion. L'augmentation de la concentration sérique de calcium ionisé était associée à une augmentation des troubles du comportement sévères chez les patients gériatriques hospitalisés. La concentration seuil permettant de distinguer les cas des témoins était d'environ 1,27 mmol/L.

Mots-clés : Comportement, calcium, cognition, neuroendocrinologie, sujet âgé

Ionized calcium and behavioral disorders in older adults: Results from the CALICO Study

ABSTRACT

Introduction. Calcium may be involved in brain health and function. Ionized calcium concentration is usually better correlated to clinical impact than measured and corrected calcium values. The objective of this case-control study was to determine whether older patients with severe behavioral disorders had higher serum ionized calcium concentration than those without behavioral disorders, but no difference in serum measured or corrected calcium concentrations.
Material and method. Twenty-nine cases with severe behavioral disorders (mean±SD, 86.4±5.8years; 24.1% female) and 58 age- and gender-matched controls were enrolled in a geriatric acute care unit between 2016 and 2017. Severe behavioral disorders were defined as any behavioral disorder justifying the use of neuroleptics prior to hospitalization or as a Frontotemporal Behavior Scale (FBS) score ≥3 at hospital admission. Serum calcium, corrected calcium and ionized calcium concentrations were measured locally in a single center. Age, gender, BMI, mean arterial pressure, number of drugs daily taken, use of calcium supplements, serum concentrations of TSH, parathyroid hormone and 25-hydroxyvitamin D, and the estimated glomerular filtration rate were used as potential confounders.
Results. Cases with severe behavioral disorders exhibited higher serum ionized calcium concentration than matched controls (1.29±0.07mmol/L versus 1.25±0.07mmol/L, p=0.047), but no difference in measured (p=0.173) and corrected calcium concentrations (p=0.819). Increased ionized calcium concentration was associated with increased FBS score (β=4.91 [95CI: 1.30;8.53] per mmol/L of ionized calcium, p=0.009). The concentration distinguishing between cases and controls with the best sensitivity-specificity was found at 1.27mmol/L. Ionized hypercalcemia>1.27mmol/L was associated with more frequent severe behavioral disorders (OR=11 [95CI:1.75;63.36], p=0.011).
Conclusion. Increased serum ionized calcium concentration was associated with more severe behavioral disorders in acute geriatric inpatients. The threshold concentration distinguishing between cases and controls was around 1.27mmol/L.

Keywords : behavior, calcium, cognition, neuroendocrinology, older adults

FACULTÉ DE SANTÉ
UNIVERSITÉ D'ANGERS

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