Journal of Otology 18 (2023) 49–54

Contents lists available at ScienceDirect

Journal of Otology

journal homepage: www.journals.elsevier.com/journal-of-otology/

Investigation of serum calcium and vitamin D levels in superior semicircular canal dehiscence syndrome: A case control study

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ARTICLE INFO

Article history:
Received 26 June 2022
Received in revised form
22 November 2022
Accepted 24 December 2022

Keywords:
Superior semicircular canal
Dehiscence
Calcium
Vitamin D
Metabolism

ABSTRACT

Objective: It remains unknown whether calcium metabolism has any effect on the clinical presentation of superior semicircular canal dehiscence (SSCD). Our aim was to analyse the adjusted calcium and vitamin D levels in SSCD patients compared to a control group.

Methods: This was a prospective case-control study performed in a tertiary referral center, university teaching hospital in the UK. It included all new patients with SSCD seen in a dedicated skull base clinic over a 5-year period (2015–2019) compared to a gender and age matched control group. The main outcome of the study was adjusted calcium and Vitamin D levels between the two groups.

Results: A total of 31 SSCD patients were recruited with a matched number of control patients. The mean Vitamin D level on the SSCD group was 44.8 nmoL/l (SD: 20.8) compared to 47.5 nmoL/l (SD: 27.4) on the control group ($p = 0.702$). Mean Adjusted calcium level was 2.34 mmoL/l (SD: 0.7) for SSCD compared to 2.41 mmoL/l (SD: 0.11) for controls ($p = 0.01$), being within normal limits for both the SSCD and the control group.

Conclusion: Our study did not identify a link between Vitamin D levels and presence of SSCD. Normal adjusted calcium values were found in both groups. Despite that a statistically significant lower calcium level was found in the SSCD group which could indicate that suboptimal levels of calcium may affect the micro-environment of the otic capsule at the SSC region.

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1. Introduction

Superior semicircular canal dehiscence (SSCD) is a rare entity. It usually manifests with vertigo and nystagmus on exposure to loud sound or pressure changes (Minor et al., 1998). It is suggested that the superior semicircular canal (SCC) dehiscence might be present for a considerable amount of time, starting in the adolescent years, with a progression of symptoms that prompt an attendance to a physician later in life (Hegemann and Carey, 2011).

The cause of the dehiscence remains unknown, but there are several theories attempting to explain the events leading to the dehiscence. Studies have linked the SSCD with the temporal bone and middle cranial fossa anatomy as well as changes in the intracranial and inner ear pressures (Hegemann and Carey, 2011; Takahashi et al., 2012). Cases have also been documented of acquired SSCD in patients previously having normal temporal bone anatomy. Nevertheless, no mention of the thickness of the bony labyrinth covering the SCC was made prior to the development of dehiscence (Bae et al., 2013). This could be a result of osteoclastic activity in the bony labyrinth resulting in a dehiscence later in life. A study looking at the effect of calcium and vitamin D in SSCD subjects who underwent plugging, showed that the higher the calcium level the less likely the need for further corrective surgery but there was no mention of pre-operative calcium levels and the association with patients' symptomatology (Nguyen et al., 2018).

An inner ear pathology that has been found to be associated with low vitamin D levels in some studies is benign paroxysmal positional vertigo (BPPV), whereas no difference in calcium level has been noted (Inan et al., 2021; Lee et al., 2017). Osteoporosis and osteopenia are more frequently found in BPPV cases (Jeong and Kim, 2019). Following these initial results, more specific bone formation and absorption markers have been assessed, with high levels of urinary free deoxypridinoline and osteocalcin being

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Peer review under responsibility of PLA General Hospital Department of Otolaryngology Head and Neck Surgery.

https://doi.org/10.1016/j.joto.2022.12.005
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identified in BPPV cases (Lee et al., 2017). But no correlation has been seen with the other markers (Han et al., 2021). Evidence is in favor of calcium and Vitamin D supplementation for reduction of further BPPV attacks (Jeong and Kim, 2019; Yang et al., 2021).

It remains unknown whether bone metabolism markers have any association with the clinical presentation of SSCD which could be affected similarly to BPPV, being also an inner ear disease associated with bone loss or lack. As this is an area not previously researched, the main calcium metabolism markers ought to be assessed first prior to embarking in more complex research of other bone metabolism markers. Therefore, the aim of this study is to investigate the serum calcium and vitamin D levels in patients with SSCD and compare them to a controlled group of unaffected subjects. This is a question not previously been addressed in the SSCD literature.

2. Materials and methods

2.1. Basic settings and patient selection

This was a prospective case-control study performed in a tertiary referral university hospital.

All symptomatic patients diagnosed with SSCD from January 2015 to January 2019 were included in the study (n = 31). The diagnosis of SSCD was made based on clinical, audiological and Computed Tomography (CT) scan findings (Fig. 1) and through detailed vestibular assessment including cervical evoked myogenic potentials (cVEMPs). Additional oblique reconstructions on the CT scans were performed in radiologically equivocal cases.

For the disease group, patients' complaints were evaluated during history taking at time of first clinical consultation. Patients were symptomatic at the time of diagnosis with the presence of at least autophony or vertigo on exposure to loud noise or pressure changes that led to the clinical diagnosis of dehiscence of the SSC, followed further radiological and audiological assessment to lead to the SSCD diagnosis (Ward et al., 2021). The CT of the temporal bones were 0.5–0.625 mm thickness, both with reconstruction on axial, coronal, and sagittal plane. Scans with thicker sections were excluded from this study. The assessment of the temporal bone scan was performed by a dedicated skull base/head and neck radiologist. Audiometric and cVEMP assessment was performed by trained audiologists. PTA was measured using the clinical diagnostic audiometry system MADSEN Astera (GN Otometrics, Denmark). Patients were tested in a standard soundproof room after removing cerumen in the external auditory canal. Audiometry was performed according to the British Society of Audiology guidance (British Society of Audiology, 2018). The recording device for cVEMP was the audiometry system ICS Chartr EP 200 (GN Otometrics, Denmark). The reference electrode was placed between the clavicle joints, and the ground electrode was positioned between the forehead and the eyebrows. The left and right recording electrodes were placed in the middle of the left and right sternocleidomastoid muscles (electrode impedance: <5 KΩ). The air-conducted sound was presented with 500-Hz short tone bursts (1 ms rise/fall time, 2 ms plateau time, 5 Hz stimulus frequency, and 50 times superimposition). The starting stimulus intensity was 100 dB nHL, decreased by 5 dB nHL each time until the meaningful VEMP wave was undetectable. During the test, the subject was instructed to slightly raise his or her head by 30° to activate the sternocleidomastoid muscles.

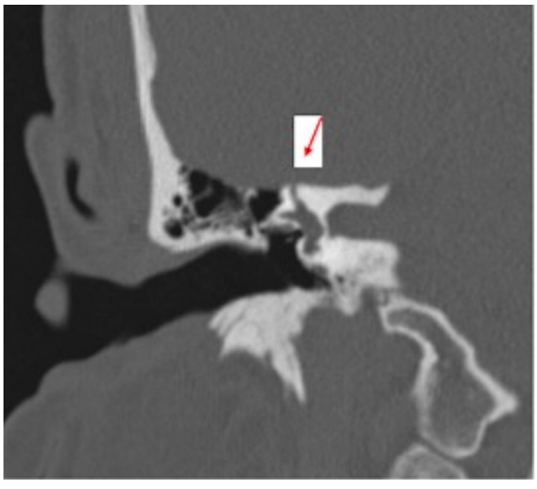

Fig. 1. High Resolution temporal bone CT scan (coronal plane) showing a right and left superior semi-circular canal dehiscence.

The control group was comprised of 31 patients, being age and gender matched to the SSCD group. The subjects were randomly selected from our regional thyroid database, as all patients in the database had Vitamin D and adjusted Calcium level recorded at the time seen in a parallel running specialized head and neck – thyroid clinic. The bloodwork taken was part of the standard practice of the head and neck surgeon. No radiological, formal audiological or cVEMP evaluation was performed in the control group. As we were interested in symptomatic SSCD population so there was no scope of radiologically screening for potentially asymptomatic patients within the control group.

Inclusion criteria in the SSCD group were: SSCD diagnosis based on the classification committee of the Barany Society (Ward et al., 2021) otherwise the patients were excluded from the study. Exclusion criteria in the control group were any known ear pathologies (hearing loss, dizziness, previous ear surgery or disease history), renal, endocrine and bone metabolism pathology including known osteoporosis and any other physiological known hormonal changes that may affect serum calcium and Vitamin D values. The past medical history of the SSCD group was also screened for the above non-auditory system conditions that may affect bone metabolism. None of the SSCD patients had any relevant past medical history, hence all cases were included in the study.

2.2. Ethical considerations

Caldicott Guardian approval was granted by the Hospital Review Board (22/02/19GGC). Ethics committee approval was not required based on assessment of the study design using the Health Research Authority (HRA) decision tool. Informed consent was obtained from all subjects prior to entering the study.

2.3. Investigations

All patients had a blood sample taken for measurement of Vitamin D and adjusted calcium levels at the time of the first clinical consultation following the diagnosis of SSCD.

The normal range of adjusted Calcium was taken at 2.2–2.6 mmol/L and for Vitamin D for levels over 25 nmol/L as per our hospital's recommended thresholds, which are in accordance with our national guidance standards. The dataset was fully anonymized at the time of data collection and analysis.

2.4. Data analysis

The vitamin D and adjusted calcium levels were treated as continuous data. The student t-test was used for comparison of the continuous data following assessment of normality with the

Kolmogorov-Smirnov test. The minimal clinically important difference (MCID) for calcium and vitamin D levels between the groups was calculated using the distribution-based method, implementing the following formula:

$$MCID = Standard\ error\ of\ measured\ difference\ (SE) \times \sqrt{2} \times 1.96$$

The MCID indicates the minimal amount of change that can be interpreted as real change/clinically important change. A small MCID indicates a more sensitive measure, equating to a smaller effect size (Mouelhi et al., 2020).

The SPSS 20 software was used for the statistical analysis.

3. Results

A total of 31 patients were diagnosed with SSCD during the study period. The majority of them were females (n = 18, 58.1%). The mean age was 47 years (SD: 12.3). Bilateral SSCD was found in seven patients, whereas 24 patients had unilateral SSCD, with a right ear predominance (n = 14, 58.3%). All patients presented primarily with sound and pressure-induced dizziness, oscillopsia and autophony with low frequency air-bone gap indicative of the third window effect. This symptomatology raised the clinical suspicion for SSCD and was the main indication for obtaining the initial imaging. As there were no differences between the presenting symptom across our group, we did not perform any further analysis of the symptoms nor attempted to correlate them with Vitamin D or calcium levels. The presenting symptoms of the SSCD group are summarised in Table 1. The control group was gender matched (18 females: 13 males) and age matched (mean age: 45.1, SD: 14.9).

The mean adjusted calcium level in the SSCD group was 2.34 mmol/L (SD: 0.7) and the Vitamin D level was 44.8 (SD:20.8). In the control group the mean value of the adjusted calcium was 2.41 (SD:0.11) and for Vitamin D the mean was 47.5 (SD:27.4). Patients in both groups had adjusted calcium levels above 2.2 mmol/L. Four patients (12.9%) in the SSCD group had Vitamin D levels below 25 nmol/L compared to six patients (19.5%) in the control group (p = 0.571).

There was no statistically significant difference on the vitamin D measurements for the SSCD compared to the control group (p = 0.702), whereas the difference in the adjusted calcium scores was statistically significant (p = 0.01), with lower values noted in the SSCD group (Table 2). Nevertheless, the calcium levels were within normal limits for both the SSCD and the control group. The distribution of values for the adjusted calcium and Vitamin D for the two groups are seen in Figs. 2 and 3 respectively. The MCID value for calcium was 0.068 and for vitamin D was 18.9. Therefore, the mean difference of vitamin D measurement between the case and the control groups was much smaller than the MCID value (Vitamin D Mean difference = 2.7 vs MCID = 18.9) showing that there is no clinically significant difference between the groups, as already shown statistically. The effect size of the difference is large enough to be appropriately assessed by the sample size of this study based on the power calculation previously mentioned.

The mean difference of the calcium level between the case and the control groups was 0.07, being only slightly higher to the MCDI calcium value of 0.068. Therefore, despite the statistically significant difference identified in the calcium level, only a marginal clinically significant difference has been identified.

Table 1
SSCD patients presenting complains.

Presenting symptom	Number (frequency)
Autophony	16 (64%)
Feeling of blocked ear	8 (28.6%)
Dizzy on pressure change	8 (28.6%)
Hypersensitivity to own body sounds	8 (28.6%)
Dizzy on loud sound	8 (28.6%)
Non specific dizziness	7 (25%)
Tinnitus	6 (21.4%)
Hyperacusis/distorted sound	3 (10.7%)

Table 2
Patients' demographics and bloodwork results.

	SSCD group	Control group	P value
Gender male	13 (41.9%)	13 (41.9%)	–
female	18 (58.1%)	18 (58.1%)	
Age mean (SD)	47 (12.3)	45.1 (14.9)	0.586[a]
Adjusted calcium (mmol/L) mean (SD)	2.34 (0.7)	2.41 (0.11)	0.01[a]
Vitamin D (nmol/L) mean (SD)	44.8 (20.8)	47.5 (27.4)	0.702[a]

[a] T-test, SD: standard deviation.

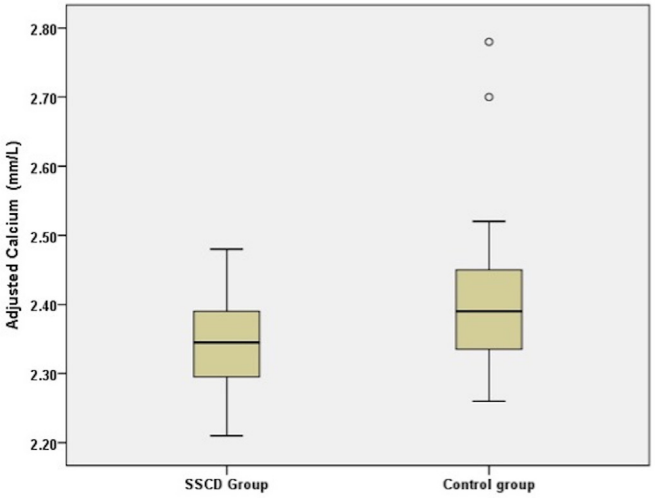

Fig. 2. Box plot chart showing the distribution of adjusted calcium levels for the SSCD and the control group. Bold line: median; end of box lines: upper (1st) and lower (3rd) quartile (interquartile range), far lines: ± 1.5 x interquartile range; circles: outliers.

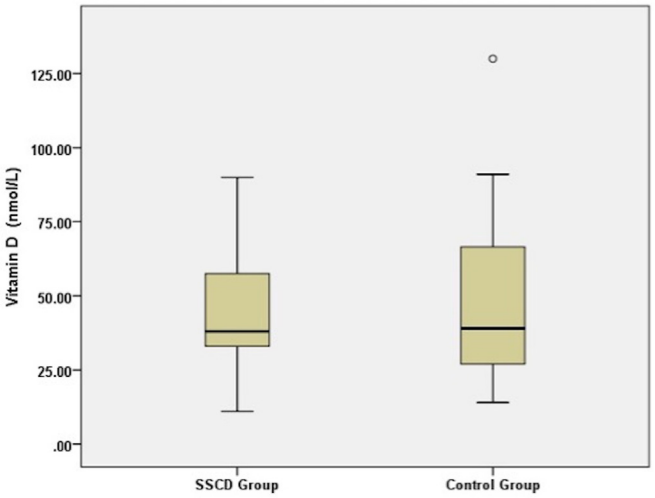

Fig. 3. Box plot chart showing the distribution of Vitamin D levels for the SSCD and the control group. Bold line: median; end of box lines: upper (1st) and lower (3rd) quartile (interquartile range), far lines: ± 1.5 x interquartile range; circles: outliers.

4. Discussion

4.1. Synopsis of key findings

Our case-control study has identified comparable results for Vitamin D levels in the SSCD and the control group. Additionally, calcium levels were within normal limits for both groups. Despite that we did identify a statistically significant lower calcium level in the SCCD group with a marginal clinically significant implication. This is the first time that bone metabolism bloodwork was measured prospectively for SSCD patients at the time of initial diagnosis and also compared to unaffected individuals. The cause of SSCD is still unknown and our study has shown that gross bone metabolism mechanisms reflected by Vitamin D and Calcium normative values does not appear to affect SSCD presentation. Nevertheless, it could be that the microenvironment of the otic capsule at the SSC territory may be affected by lower calcium levels despite still being within normal limits, which could explain the significantly lower values of calcium in the SSCD group.

4.2. Comparisons with other studies

Only one retrospective study was identified looking at bone metabolic markers in SSCD patients. Calcium level data were retrospectively available for 79 patients (Nguyen et al., 2018). In that study, the level of calcium negatively correlated with the need for revision surgery. A negative correlation was also seen for the need of calcium supplementation and dizziness improvement following surgical plugging (n = 72). Nevertheless, the levels of adjusted calcium were not taken into account when analyzing the results; hence their findings can be affected by differences in albumin levels making those findings debatable (Nguyen et al., 2018). In our study, we have addressed this issue by ensuring that the adjusted calcium readings were utilised, thus taking into account the albumin levels. This adjustment may be the reason our results are different to the Nguyen et al. (2018) conclusions.

In the same study, Vitamin D levels had a negative correlation with pre-operatively hyperacousis and a positive correlation with postoperative autophony (n = 12). Those taking Vitamin D post-operatively were more likely to have hearing decline (n = 23). Osteoporosis was found in one patient and osteopenia in nine females (Nguyen et al., 2018). The study also suggested that osmotic changes as a result of high Vitamin D could lead to hearing reduction from osmotic changes associated toxicity; thus, Nguyen et al. proposed cessation of Ca and Vitamin D supplementation post-operatively. Nevertheless, it is unclear why such effects were not noted pre-operatively while there was no detailed analysis of each biomarker and pre-operative symptoms association (Nguyen et al., 2018). Our study bridges that gap being the first research to prospectively compare the adjusted Calcium and Vitamin D of normal subjects with SCCD individuals prior to any surgical intervention, looking into the association of bone metabolism and the presence of SSCD. Unlike the data presented by Nguyen et al. (2018), in our study, all patients were symptomatic (auditory and vestibular symptoms) at time of presentation with no identifiable differences across the group to allow for analysis of symptoms in relation to calcium and Vitamin D levels.

4.3. SSC micro-environment and potential effect in SSCD pathogenesis in relation to calcium metabolism

There are several markers of bone metabolism influencing the biochemical processes in the skeletal matrix including the bones and associated cellular components. These markers are classified in enzyme activity markers, bone matrix proteins and products for: bone formation (total alkaline phosphatase, bone alkaline phosphatase, osteocalcin, c − and n-terminal propeptide of type I procollagen), bone resorption (hydroxyproline, pyridinoline, deoxypyrindoline, cross-linked c- and n-terminal telopeptide of type I collagen, bone sialoprotein, free gamma carboxyglutamin acid, tartarat − resistant acid phosphatase) as well as inorganic skeletal matrix markers (calcium, phosphorus) and calcium metabolism regulators (Vitamin D, parathyroid hormone) (Cepelak and Cvoriščec, 2009; Khundmiri et al., 2016). The former markers vary significantly depending on biological endogenous and exogenous causes but also technical causes relating to sample requirements for collection, integrity, storage, and laboratory variations. Most of them are also costly to perform and not available in all hospitals. These make universal adaptation and guidelines difficult to establish (Hlaing and Compston, 2014).

In the semicircular canals, epithelial calcium channel transport systems exist as well as calcium binding proteins. Vitamin D organizes the expression of some of these calcium binding proteins and receptors in inner ear. They are also upregulated by changes in the pH and any change in the ions balance in the endolymph. The inner ear micro-environment has naturally a low calcium concentration. It has been suggested that otoconia work as a reservoir of calcium, maintaining adequate calcium levels in the semicircular canals. Otocononia are very sensitive in the changes in the chemical consistency of the endolymph and found to be weakened in the aging population with decreased bone minerality (Han et al., 2021; Inan et al., 2021; Jeong and Kim, 2019; Lee et al., 2017; Wu et al., 2020). Therefore, even minor changes in the calcium concentration could significantly alter the micro-environment of the semicircular canals leading to increased osteoclastic activity. In BPPV, a common inner ear disease, aging, osteopenia, osteoporosis and low vitamin D has been shown to be associated with recurrent episodes of BPPV, with improved frequency of attacks following Vitamin D and calcium supplementation in some studies (Jeong and Kim, 2019; Yang et al., 2021). Similar triggers could be the reason of symptomatic SCCD, hence influenced by even small changes in calcium concentration.

The aging process has been linked to the incidence of SSCD in some studies. Nadgir and colleagues looked at 306 CT temporal bones scans, stratified by age from seven months up to 89 years of age in interval of five years. Increase in age was associated with higher change of both SSCD and bone thinning (Nadgir et al., 2011). It has been also found than the thickness of bone overlying the SCC is inversely associated with increased age, with thin (<0.6 mm) found in 7.1% of subjects younger than 45 years of age versus 13.8% in older subjects. This difference was greater in the menopausal female subgroup (Crovetto et al., 2012). This suggests that osteopenia could contribute to presence of SSCD which is supported by later research (Yu et al., 2012). The thickness of temporal bone has been found to be decreasing by 0.0047 mm for every one unit increase in age in linear regression fashion (between age 6 and 86, n = 121 subjects) and a reduced SSC roof height was seen with increased age (n = 354 bones) suggesting aging of the skull base as a cause of the SSCD (Davey et al., 2015; Klopp-Dutote et al., 2016). Additionally, Sood and colleagues, identified a progressively increased SSCD incidence with older age (84.4% in the age group 60–80 (n = 32); being 60%, 31.2% and 8.3% for the age groups: 40–60 (n = 50); 20–40 (n = 48); 0–20 (n = 24) respectively) (Sood et al., 2017). Therefore, older age, usually accompanied by osteopenia or osteoporosis, can contribute to in impaired calcium metabolism in the semicircular canals contributing to symptomatic SSCD.

Nevertheless, osteoclastic activity has been found in patients with SSCD as well as in normal subjects of all ages with or without otosclerosis hence this cannot be the sole aetiology of the

dehiscence (Kamakura and Nadol, 2017). A paediatric population study has shown the peak age of dehiscence to be at age seven years of life, with an overall SSCD incidence of 1.9% (23/1188 ears) (Jackson et al., 2015). These findings could suggest a bimodal incidence of dehiscence, that is early in life perhaps due to increased osteoclastic activity in the bony labyrinth remodeling balance which later recovers until seen again much later in life due to effects of aging and osteoporosis. It is known that the bony labyrinth bone turnover is very slow with an abnormally negative metabolism balance in favor of osteoclastic activity; it has been suggested that this fine balance can be more easily disrupted compared to other body areas. This can perhaps result in dehiscence in a background of possibly congenitally thin SCC bone labyrinth cover (Brandolini et al., 2014). Recently we showed better pneumatisation of the temporal bone and lower lying middle fossa dura in patients with SSCD, indicating a developmental component to the underlying pathophysiologic mechanisms (Tikka and Kontorinis, 2020).

It seems that the origin of SSCD is not necessarily an isolated acquired or developmental condition rather a result of a 'second event' (which could also be the lower - yet within normal limits – calcium levels) to a pre-existing thin osseous cover. Additionally, one could argue that the underlying lower calcium levels can make the otic capsule/arcuate eminence of the SCC more vulnerable to minor trauma, which could result in the presentation of SCCD. This is, based on our findings, difficult to prove but worth hypothesizing. The information presented here should be interpreted with caution, mostly due to the number of included cases; as well as the fact that if the data are interpreted solely by looking at normative values, no difference exists.

The present findings enrich our understanding of the factors that can contribute to SSCD rather than facilitate clinical outcomes. Theoretically, improving SSCD patients calcium profile could help with their symptoms or possibly with their recovery following surgery for SSCD. However, this is as yet a hypothesis, as one could argue that once the dehiscence has occurred then improving the bone profile of the patients might not have any significant impact at all. We believe that our findings can be used as the groundwork for further research on this possible association, with research on other more specific bone metabolism markers in larger cohort studies.

6.4. Study strengths and limitations

The small number of cases in the SSCD group is the main weakness of this study possibly limiting the generalizability of our findings. Nevertheless, considering the rarity of symptomatic SSCD presentation, the enrollment of 31 subjects is a relatively large representative sample of SSCD blood work measurements. Another point to note is that vitamin D and calcium levels were taken from symptomatic SSCD patients hence at a time point in life that the dehiscence has already occurred. Thus, likely missing the precise timepoint that calcium and Vitamin D levels could be perhaps having a causative effect. However, the prospective study of SSCD patients that do not yet have symptoms is not practically possible, unless the dehiscence is randomly identified on scans performed for other pathologies. The prospective methodology has eliminated presence of missing data and the sample size, age and gender matched case-control setting enabled comparison of the SSCD bloodwork findings with control subjects with same baseline characteristics. We have focused our study in symptomat4.4ic SSCD cases, hence our control group consisted of patients with no otological symptoms suggestive of SCCD. On this basis, CT, formal audiology assessment and cVEMPs were not performed for the control group as these investigations were only undertaken in the SSCD group following a clinical diagnosis of SSCD being made based on their symptoms. Unfortunately, due to the way SSCD diagnosis is being established, our data and conclusion are based at the time point when patients presented themselves to our service rather than when it first occurs.Despite the rarity of SSCD and the asymptomatic control group, a missed case of asymptomatic SCCD cannot be ruled out.

5. Conclusion

To our knowledge, this is the first study looking at serum adjusted calcium and vitamin D levels at the point of SSCD diagnosis. Calcium levels were within normal limits for both groups, nevertheless a significant association was found between adjusted calcium levels and SSCD presentation, with SSCD subjects having lower mean values compared to the control group. The possible clinical implications and pathophysiologic mechanism of these findings have been discussed. Vitamin D levels did not differ significantly between the compared groups.

Author's contribution

Concept – T.T., GK.; Design - T.T., G.K., MA.MS., T.T, A.S.; Supervision - T.T., G.K.; Resource - T.T., A.S, MA.MS.; Materials - T.T., T.T, MA.MS. A.S.; Data Collection and/or Processing - T.T., MA.MS., T.T., A.S., G.K.; Analysis and/or Interpretation- T.T., MA.MS., T.T, A.S., G.K.; Literature Search - T.T., G.K.; Writing - T.T., MA.MS., T.T., A.S., G.K.; Critical Reviews - T.T., MA.MS., T.T., A.S.,G.K.

Ethics committee approval

Caldicott guardian approval was obtained from the Hospital's Review Board. Ethics committee approval was not required based on assessment of the study design using the Health Research Authority (HRA) decision tool.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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