ORIGINAL ARTICLE

Does calcemia influence the onset of myringosclerosis after myringotomy with the insertion of ventilation tubes?

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Received 20 October 2016; accepted 21 February 2017
Available online 15 May 2017

KEYWORDS
Calcium;
Ventilation tubes;
Myringosclerosis

Abstract
Introduction: Myringosclerosis is one of the most frequent late complications of the insertion of ventilation tubes, and its aetipathogenesis remains unknown. The calcification that occurs in the formation of myringosclerosis plaque raises the hypothesis of the presence of a calcium metabolism disorder. The objective is to determine whether calcemia contributes to the development of myringosclerosis after insertion of ventilation tubes.

Material and methods: A longitudinal, prospective, analytical cohort study was conducted in patients undergoing myringotomy with the insertion of ventilation tubes due to otitis media with effusion. Calcemia was evaluated pre-operatively and in the follow-up the appearance of myringosclerosis and the percentage of the tympanum involved were evaluated.

Results: The study included 156 patients (297 ears), with calcemia values ranging from 7.6 to 10.2 mg/dl. Myringosclerosis was identified in 35.4\% of the operated ears. No relationship was found between the appearance of myringosclerosis and calcemia $p = .596)$. It was found, however, that the greater the percentage of the tympanum affected by myringosclerosis, the lower the calcemia values ($p = .014$).

Conclusion: The population studied had calcemia values within the normal range, which allows us to infer that no changes in calcium metabolism are required for the development of myringosclerosis. Moreover, unlike in previous studies, higher calcium levels are not associated with more myringosclerosis. Calcemia did not influence the appearance of myringosclerosis after myringotomy with the insertion of ventilation tubes.

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http://dx.doi.org/10.1016/j.otorri.2017.02.003
0001-6519/© 2017 Elsevier España, S.L.U. and Sociedad Española de Otorrinolaringología y Cirugía de Cabeza y Cuello. All rights reserved.
¿Influye la calcemia en la aparición de miringoesclerosis después de miringotomía con inserción de tubos de ventilación?

Resumen

Introducción: La miringoesclerosis es una de las complicaciones tardías más frecuentes de la inserción de tubos de ventilación pero su etiopatogenia sigue siendo desconocida. La calcificación que se produce en la formación de la placa miringoesclerótica plantea la hipótesis de la presencia de un trastorno en el metabolismo del calcio. El objetivo es determinar si la calcemia contribuye al desarrollo de miringoesclerosis después de la inserción de tubos de ventilación. Material y métodos: Se realizó un estudio longitudinal, prospectivo, de cohorte analítica en pacientes tratados con miringotomía con inserción de tubos de ventilación, debido a otitis media con efusión. Se evaluó la calcemia antes de la operación y en el seguimiento se evaluó la presencia de miringoesclerosis y el porcentaje de afectación del tímpano. Resultados: El estudio incluyó a 156 pacientes (297 oídos), con valores de calcemia comprendidos entre 7,6 y 10,2 mg/dl. Se identificó miringoesclerosis en el 35,4% de los oídos operados. No se encontró relación entre la aparición de miringoesclerosis y calcemia (p = 0,596). Se encontró, sin embargo, que cuanto mayor es el porcentaje de afectación del tímpano por miringoesclerosis, menores son los valores de calcemia (p = 0,014). Conclusión: La población estudiada tuvo valores de calcemia dentro del rango normal, lo que nos permite inferir que no se requieren cambios en el metabolismo del calcio para desarrollar miringoesclerosis. Por otra parte, al contrario que en estudios anteriores, los niveles de calcio superiores no se asociaron a un incremento de miringoesclerosis. La calcemia no influye en la aparición de miringoesclerosis después de miringotomía con inserción de tubos de ventilación. © 2017 Elsevier España, S.L.U. y Sociedad Española de Otorrinolaringología y Cirugía de Cabeza y Cuello. Todos los derechos reservados.

Introduction

Myringosclerosis that occurs after myringotomy is one of the most frequent late complications of the procedure, the incidence of which varies between 17.1 and 56%. Although several studies have been dedicated to researching the pathogenesis of myringosclerosis and tympanosclerosis, there is still no specifically defined theory regarding their origin.

Various hypotheses have been proposed to explain its development, including changes in the metabolism of collagen, an excessive inflammatory response with consequent tissue damage, increased formation of free radicals, trauma caused by myringotomy and the insertion of ventilation tubes and genetic predisposition.

It is known, however, that the development of myringosclerosis plaque involves the evolution of three consecutive phases: initial lesion of the collagen fibres with destruction of the layer of connective tissue; the invasion of fibroblasts causing a process in which excessive collagenisation and hyalinisation occurs and irreversible calcification and ossification.

This pathological calcification raises the hypothesis that there is a disorder of calcium metabolism which might contribute to the development of myringosclerosis.

Material and methods

A longitudinal, prospective, analytical cohort study was conducted in patients undergoing myringotomy with the insertion of short-term transtympanic tubes due to chronic otitis media with effusion.

The study included all patients with otitis media with effusion undergoing myringotomy with insertion of unilateral or bilateral transtympanic tubes between February 2013 and May 2014 who agreed (or whose legal representatives agreed) to participate in the study by signing an informed consent form.

The exclusion criteria considered were: the presence of tympanosclerosis prior to surgery; in the case of indication of unilateral surgery, the contralateral ear having any chronic condition other than otitis media with effusion; inability to attend the follow-up appointments; refusal of the patient, or legal representative, to participate in the study.

All patients included were evaluated for calcemia preoperatively.

The surgical procedure was performed under balanced general anaesthesia. The myringotomy (radial or non-radial) was performed with micro-scalpel/Politzer-type myringotomy knife, from Storz, in the posterior-inferior or anterior-inferior quadrant. In all cases, a 1.14-mm Shepard fluoroplastic ventilation tube, from Xomed, was inserted. At the end of operation, around 4 drops of topical ofloxacin were applied.

Objective

The objective of the study is to determine whether plasma calcium levels contribute to the development of myringosclerosis after myringotomy with the insertion of ventilation tubes.
Postoperatively, the follow-up of the patients was performed every six months until extrusion of the tubes. On the last visit, a micro-otoscopy was performed to identify myringosclerosis and determine the percentage of the tympanum affected.

For statistical analysis, the programme SPSS for Windows (version 21) was used. The following tests were used: Kendall correlation coefficient and Pearson correlation coefficient. A result of $p < .05$ was accepted as significant.

The protocol of this study was approved by the Ethical Committee.

### Results

Between February 2013 and May 2014, 179 patients underwent myringotomy with insertion of transtympanic tubes. Of these, a total of 23 were excluded from the study, due to refusal to participate (2 patients), the presence of tympanosclerosis prior to surgery (10 patients) and abandonment of the follow-up appointments (11 patients).

Thus, 156 patients were included. In 15 the procedure was unilateral, which corresponds to a total of 297 ears operated on.

The age of the patients included at the time of the surgery ranged from 2 to 36 years of age, only two patients were adults (mean: 5.5 ± 3.65 years), and 89 were male and 67, female.

Calcemia values ranged from 7.6 to 10.2 mg/dl (mean: 9.26 ± 0.52 mg/dl) (Table 1). Associated with the myringotomy with insertion of tubes, a tonsillectomy was performed in 78 patients and an adenoidectomy in 76.

A radial incision was performed in 51.5% of the ears and a non-radial in the remaining ears. The antero-inferior quadrant was the location for myringotomy in 52.9% of the cases, and the remaining cases had a posterior-inferior incision. Aspiration was performed in 60.3% of the cases.

Bleeding during myringotomy occurred in 35.7% of the cases. Effusion in the middle ear was detected in 62.2% of the ears, 80% was mucoid and the remaining was serous.

Myringosclerosis was identified in 35.4% of the operated ears ($n = 105$). Concerning tube extrusion, 21.9% of the operated ears showed a complete extrusion in less than 6 months. In 49%, the tube was present for 6 months to 12 months, in 20.5% from 13 to 18 months, in 7.9% from 19 to 24 months and in .7% for more than 24 months.

### Discussion

The calcemia values of the study population ranged from 7.6 to 10.2 mg/dl, and were therefore considered normal. This fact allows us to infer that altered calcemia values are not required for the appearance of myringosclerosis, and therefore this assessment is clinically irrelevant.

In the present study, no association was found between serum calcium concentration and the appearance of myringosclerosis. Indeed, a seemingly paradoxical result was obtained, because patients with lower calcemia values demonstrated a higher percentage of tympanic involvement by myringosclerosis. It is known that the calcification of myringosclerosis comes from the release of cytoplasmic vesicles filled with calcium crystals, present in fibroblasts and inflammatory and epithelial cells, it does not come directly from the peripheral blood. Eventually, intracellular calcium is higher in patients with low levels of calcemia.

Patients with calcium metabolism disorders were not evaluated, so it was not possible to rule out the hypothesis that a change in those levels may contribute to the onset of myringosclerosis.

Leal et al.,[20] conducted a study in mice that compared the appearance of myringosclerosis, after inoculation of
Streptococcus pneumoniae, between a calcium dietary supplement group and a control group with normal calcium content in their diets. The results, although not statistically significant, suggest that hypercalcemia is a factor in the development of tympanosclerosis.

Another study in which diltiazem, a calcium channel blocker, was used demonstrated that topical application of this product prevents the development of tympanosclerosis in animals. This reduction in the formation of sclerotic plaque may be attributed to the preventive effect of diltiazem in the accumulation of calcium. However, when studying patients with chronic renal insufficiency (who typically have disturbances in calcium homeostasis), Caldas Neto et al. concluded that serum calcium (whether hypo- or hypercalcemia), phosphorus or PTH levels had no influence in the occurrence of tympanosclerosis.

In the light of these contradictory results, more studies will be required to clarify the influence of calcemia in the development of myringosclerosis. However, we know that, as identified in other forms of pathological calcification, particularly in dystrophic calcifications, the occurrence of hypercalcemia is not a determining factor for calcification.

Conclusion

Plasma calcium levels did not influence the appearance of myringosclerosis after myringotomy with the insertion of tubes.

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding

This work has not received any contribution, grant or scholarship.

References

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