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Changes in Coagulation Study and Risk of Developing Cholesteatoma: Is There a Link?

Joana Raquel Costa, Ângela Reis Rego, Teresa Soares, Cecília Almeida e Sousa, and Miguel Bebiano Coutinho

Department of Otorhinolaryngology-Head and Neck Surgery, Centro Hospitalar Universitário do Porto, Porto, Portugal

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Address for correspondence
Joana Raquel Costa, MD
Department of Otorhinolaryngology-Head and Neck Surgery,
Centro Hospitalar Universitário do Porto, Largo do Prof, Abel Salazar,
4099-001 Porto, Portugal
Tel +351918109458
Fax +351223320318
E-mail joana_cccosta@hotmail.com

Background and Objectives: The etiopathogenesis of acquired pediatric cholesteatoma has not yet been fully clarified. Recent studies and modern technologies have led researchers to look for explanations at a molecular level. This study aims to understand if the origins of cholesteatoma could be related to dysfunctions in coagulation factors, thereby emphasizing its role in angiogenesis. **Subjects and Methods**: This was a retrospective case-control study carried out at a tertiary hospital center between January 2010 and December 2020. The study included 92 children. The variables of the summary coagulation study (partial thromboplastin time, prothrombin time, and international normalized ratio) were compared among children with and without development of chronic otitis media with cholesteatoma. **Results**: The cases and controls were comparable in terms of age, type, and number of times that ventilation tubes were placed. Partial thromboplastin times tended to be higher in children who developed cholesteatoma, with a statistically significant difference between the two groups in terms of normal and abnormal partial thromboplastin times (p=0.029). **Conclusions**: The results of this case control study indicate that slight extension of partial thromboplastin times in the coagulation study may not meet the criteria for diagnosis of certain hematological pathologies or clinical significance, but at a molecular level may already have implications for activation of angiogenesis and other growth factors involved in the onset, growth, and expansion of acquired pediatric cholesteatoma.

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Keywords: Pediatric cholesteatoma; Chronic otitis media; Coagulation factors; Ventilation tubes.

Introduction

Acquired cholesteatoma is a well characterized nonneoplastic lesion in the temporal bone that arises from an abnormal growth of keratinizing squamous epithelium [1]. Despite being a benign lesion, tends to extend gradually and becomes locally destructive. Bone resorption of the ossicular chain and otic capsule may result in subsequent hearing loss, vestibular dysfunction, facial paralysis and intracranial complications [2-6].

Pediatric acquired cholesteatoma (PAC) in general seems to spread more extensively through the temporal bone than in adult disease, being more aggressive, but there is no definitive proof [7,8].

Despite substantial research into the disorder, the etiopathogenesis of acquired cholesteatoma is not yet fully clarified [9]. Four theories dominate the debate, including invagination, immigration, squamous metaplasia, and basal cell hyperplasia [9]. Recent studies and modern technologies have led researchers to search for explanations at a molecular level and having been describing angiogenesis as a crucial process [10-12].

It has been noticed in the clinical practice of the Centro Hospitalar Universitário do Porto, that children who arise with significant changes in otomicroscopy, with chronic otitis media with effusion (OME) requiring multiple placements of ventilation tubes (VT) and that culminate in the development of cholesteatoma, frequently presented prolonged coagulation values in the preoperative coagulation studies, with particular emphasis on the partial thromboplastin time (PTT) value.

In this sense, a case-control study was developed to try to understand if children with chronic otitis media with cholesteatoma (COMc) development are more likely to have prolonged coagulation values (PTT, prothrombin time [PT], and international normalized ratio [INR]) compared to children with chronic OME that resolved with growth and medical/surgical treatment (placement of VT in one or more moments) or developed noncholesteatomatous chronic otitis media (wCOMc).

Subjects and Methods

Study design and population

A retrospective case-control study was developed at Centro Hospitalar Universitário do Porto.

The study population included children followed in pediatric ENT Consultation between 2010 and 2015, with the diagnosis of chronic OME, and who have placed VT at least once. Clinical records were obtained for a period of 5 years after the first surgery to place VT.

Selection of cases and controls

During the follow-up period after placement of the VT, for one or more times, some of these children developed COMc, with indication to undergo mastoidectomy. These children were included in the case group (COMc group).

Children who had placed VT during this period, and during follow-up had their OME resolved or developed noncholesteatomatous chronic otitis media, and as such, without COMc, were included in the control group (wCOMc group).

The following inclusion and exclusion criteria were applied.

A. Case group (COMc group)

Inclusion criteria: Under 18 years old; history of Shepard Ventilation Tube (MEDTRONIC, Minneapolis, MN, USA) placement; follow-up period of at least 5 years; COMc; complete clinical record (OME documented with otomicroscopy, audiogram and tympanogram; COMc documented with otomicroscopy, audiogram and tympanogram; complete surgical records; PTT, PT and INR values in preoperative blood samples); authorization from parents/legal guardians to participate in the study.

Exclusion criteria: Congenital cholesteatoma; history of long-term tube placement; child with craniofacial dysmorphia; diseases associated with changes in mucociliary transport such as cystic fibrosis and primary ciliary dyskinesia; history of taking anticoagulant medication or some pathology (such as tumors, chronic inflammatory diseases) that can lead to changes in coagulation values.

B. Control group (wCOMc group)

Inclusion criteria: Under 18 years old; history of Shepard Ventilation Tube placement; follow-up period of at least 5 years; no cholesteatom development; complete clinical record (OME documented with otomicroscopy, audiogram and tympanogram; complete surgical records; PTT, PT, and INR values in preoperative blood samples); authorization from parents/legal guardians to participate in the study.

Exclusion criteria: Congenital or acquired cholesteatoma; history of long-term tube placement; child with craniofacial dysmorphia; diseases associated with changes in mucociliary transport such as cystic fibrosis and primary ciliary dyskinesia; history of taking anticoagulant medication or some pathology (such as tumors, chronic inflammatory diseases) that can lead to changes in coagulation values.

Coagulation tests

Venous blood samples were collected from all the participants before each surgical intervention. The values for the coagulation parameters were collected from all participants. In children who underwent more than one surgical procedure who had more than one analytical study in the preoperative period, an average of PTT, PT, and INR values was performed.

According to the data provided by hospital laboratory of Centro Hospitalar Universitário do Porto, and given that these values are extremely variable between laboratories according to the methods used, for the analysis of the coagulation study was considered, in seconds (s): 1) PTT values between 25−30 s were considered normal, between 30−35 s were considered at the upper limit of normality, ≥35 s were considered abnormal; 2) PT values ≤13 s were considered normal, >13 s was considered abnormal; 3) for the INR value between 0.08−1.00 it was considered normal, >1.00 abnormal.

Information on symptoms compatible with easy blood loss or family history of hematological disease, age, sex, number of times VT were placed, age of first placement of VT, age of mastoidectomy, number of times of mastoidectomy revision, and blood tests results was collected from clinical process and surgical database of all participants.

Data collection and data analysis

Data collection and analysis was performed using the IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

Descriptive statistics are used to describe the basic features of your study's data and form the basis of virtually every quantitative analysis of data. For the analysis of the differences between cases and controls, the Student's t-test was used. $p \leq 0.05$ was considered statistically significant.

An authorization has been obtained by Ethics Committee of

Centro Hospitalar Universitário do Porto to carry out this study and an informed consent was obtained and signed from all parents/legal guardians for the use of clinical information and complementary diagnosis exams, as well as its publication and disclosure in scientific journals.

Results

Table 1 shows descriptive data for the two groups included in the study. Ninety-two children were included in the study, aged between 8 and 19 years (average age of 11.1 years): 27 children with COMc (COMc group) and 65 children without COMc (wCOMc group).

Among children belonging to the COMc group, 59.3% were male, and the remaining 40.7% were female. In the wCOMc group, 50.8% were male and the remaining 49.2% were female.

Both groups were comparable in terms of age and sex (p=0.566 and p=0.463, respectively).

The mean age of VT placement for the first time was similar between groups, 6.56 years in the COMc group and 5.63 years in the wCOMc group, with no statistically significant difference between the two groups evaluated (p=0.077). In 51.2% of children with COMc and in 75.4% of children wCOMc, VT was placed before 6 years of age (Fig. 1).

In both groups, wCOMc and COMc, the vast majority had VT placement only once (86.2% and 85.2% of children, respectively). It was verified that there are no significant differences between the two groups regarding the number of times the tubes were placed (p=0.600).

In the COMc group, the first mastoidectomy surgery, with evidence of cholesteatoma intraoperatively, was performed more frequently at age 9, with an average age of 11.1 years old (with a minimum age of 8 years and a maximum of 16 years). The majority (66.7%) had to perform mastoidectomy revision surgery, most with disease control with a single surgical revision.

Only 3 children included in the study had a history of easy bleeding, when brushing their teeth and prolonged bleeding time when performing invasive procedures such as blood collection or accidental injuries. No child had a family history of easy bleeding or known hematological diseases.

Of the children included in the study, and after conducting the coagulation study in the preoperative period, 16 had an indication by the laboratory to repeat the coagulation study and send for hematology consultation. After investigation, 5 children showed confirmation of a factor deficiency of some clotting: in 1 case, deficit of factor VIII (FVIII), and in the remaining cases, deficit/deficiency of von Willebrand factor (vWF), confirmed by complementary exams, all belonging to the group of children who developed COMc.

The results described below refer to Table 2 and Fig. 2. In the wCOMc group, the mean value of PTT was 29.69 s, lower than that registered in the COMc group, which was in the order of 31.04 s. Thus, among the children belonging to the wCOMc group, the majority (64.6%) had normal PTT values. On the other hand, among children in the COMc group, the majority (59.3%) was in the upper limit of normality, and in 11.1% of the cases the PTT value were considered abnormally high.

Regarding the PT value, in the wCOMc group the average

Table 1. Comparison of demographic and clinical characteristics between COMc and wCOMc groups

Variables	COMc (n=27)	wCOMc (n=65)	*p*-value
Sex			0.463
Male	16 (59.3)	33 (50.8)	
Female	11 (40.7)	32 (49.2)	
Age (yr)	11.9±2.53 (9−18)	10.8±2.41 (8−19)	0.566
VT placement			
Age of the first VT placement (yr)	6.56±2.33 (3−12)	5.63±2.23 (3−13)	0.077
Times of VT placement	1.15±0.36 (1−2)	1.15±0.40 (1−3)	0.600
One time	23 (85.2)	56 (86.2)	
Twice	4 (14.8)	8 (12.3)	
Three times	0 (0.0)	1 (1.5)	
Mastoidectomy performance			
Age of mastoidectomy (yr; mean [range])	11.1 (8−16)		
Mastoidectomy revision surgery	18 (66.7)		
1	11 (40.7)		
2	5 (18.5)		
3	2 (7.5)		

Values are presented as mean±standard deviation (range) or number (%), unless otherwise indicated. COMc, chronic otitis media with cholesteatoma; wCOMc, noncholesteatomatous chronic otitis media; VT, ventilation tube

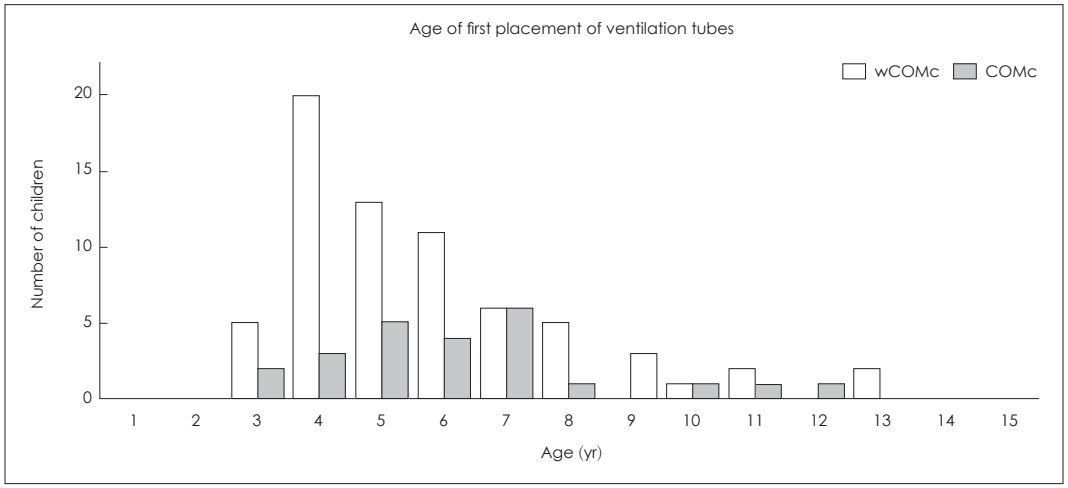


Fig. 1. Bar chart showing the age distribution of first ventilation tube placement per group. COMc, chronic otitis media with cholesteatoma; wCOMc, noncholesteatomatous chronic otitis media.

PT value was 11.58 s, which is lower than that recorded in children who developed cholesteatoma, in the order of 11.93 s. It was noticed that in the wCOMc group the majority (95.4%) of the children had normal PT values, likewise among children belonging to the COMc group, where most also had normal PT values (92.6%).

The mean INR value was similar in both groups (INR 1.03 in wCOMc group; 1.08 in the COMc group), with more than 95% of children in both groups having a normal INR value.

In order to verify whether there was a significant difference in the normal values of the PTT, between the cases and controls a Student's t-test was performed. A statistically significant difference was found between children with COMc and wCOMc when comparing PTT values (p=0.029). Moreover, children with COMc submitted to multiple mastoidectomy revisions due to disease recurrence in a short period of time, had longer values compared to children submitted to only one intervention (average of 33.0 s and 30.9 s, respectively), however, this value was not statistically significant.

Receiver operating characteristic curve (ROC) for prediction of chronic COMc based on the PTT value was performed, and can be found in Fig. 3. The ROC analysis found that PTT value was effective in showing the presence of the disease, and according to ROC analysis, the area under the curve value was calculated as 0.752 for PTT value. When 30 s (upper limit of normality) was taken as cutoff, PTT value showed 82% specificity and 35% sensitivity.

In turn, no statistically significant difference was found between the two groups in relation to PT and INR values (p=0.595 and p=0.879, respectively).

Table 2. Descriptive statistics of coagulation values

Coagulation study values	COMc	wCOMc	*p*-value*
PTT, mean±SD (range)	31.04±3.13	29.69±3.23	0.029
	(24.70−37.70)	(22.70−38.90)	
95% CI	29.80−32.28	28.83−30.43	
PT, mean±SD (range)	11.93±0.85	11.58±0.88	0.595
	(10.10−13.30)	(10.00−14.50)	
95% CI	11.59−12.26	11.37−11.80	
INR, mean±SD (range)	1.08±0.08	1.03±0.08	0.879
	(0.89−1.21)	(0.88−1.29)	
95% CI	1.05−1.11	1.01−1.05	

*Student's t-test application, considering a $p \leq 0.05$ a statistically significant result. Laboratory reference values: 1) PTT values (seconds [s]) between 25−30 s are normal, between 30−35 s are at the upper limit of normality, ≥35 s were considered abnormal; 2) PT values ≤13 s are normal, >13 s are abnormal; 3) INR value between 0.08−1.00 are normal, >1.00 are abnormal. COMc, chronic otitis media with cholesteatoma; wCOMc, noncholesteatomatous chronic otitis media; SD, standard deviation; CI, confidence interval; PTT, partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio

DISCUSSION

Chronic otitis media and eustachian tube dysfunction are two of the most common diagnoses performed by pediatric otolaryngologists. The immaturity of the eustachian tube and the negative middle ear pressure it produces, is one of the likely etiological factors for the development of cholesteatoma. The placement of VT may have an overall protective effect on cholesteatoma formation in children [13,14].

However, as we know the VT placement technique itself may result in shedding and implantation of epithelial cells into the middle ear or due to in growth of squamous epithelium from the perforation margin to the under surface of the tympanic membrane [15]. Given that the placement of the VT itself is a

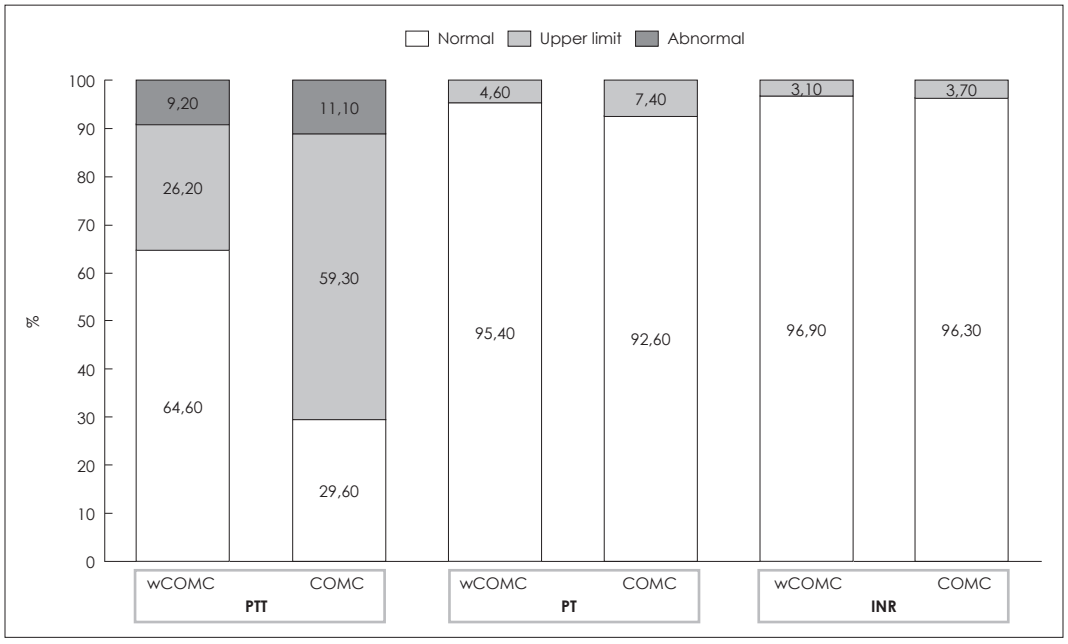


Fig. 2. Bar chart showing the distribution of partial thromboplastin time (PTT), prothrombin time (PT) and international normalized ratio (INR) values in the two groups. COMc, chronic otitis media with cholesteatoma; wCOMc, non-cholesteatomatous COMc.

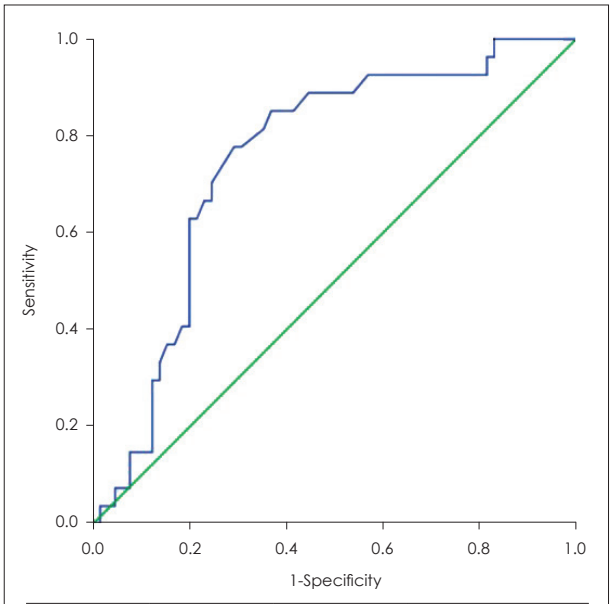
risk factor for the development of cholesteatoma.

In order to eliminate this confounding factor, all children included in this study had OME and placed VT at least one time. Most of them before 6 years of age. No significant difference was found between cases and controls regarding the age of placement of VT for the first time, the same observed in relation to the number of times they were placed.

When disease progress continues unchecked, keratinocytes can become trapped in the middle ear and result in cholesteatoma. The incidence of cholesteatoma in children is estimated at approximately 10 per 100,000 person years [16]. Surgery continues to be the mainstay of therapy, but cholesteatoma is a challenging disease process in which many factors lead to residual/recurrent disease requiring revision. Previous series have shown recurrence rates ranging from 10%−70% [17,18]. In our group of children who underwent mastoidectomy, 66.7% of the cases required mastoidectomy revision, with a report of cholesteatoma recurrence.

The middle ear acquired cholesteatoma pathogenesis is a subject of debate for decades. Although multiple studies have attempted to investigate this feature by comparing histopathological findings in pediatric and adult patients, the molecular mechanism of cholesteatoma remains controversial.

Angiogenesis is a hall mark of middle ear diseases, especially in the inflammatory granulation tissue and cholesteatoma [12,19,20]. Angiogenesis occurs in the subepithelial connective tissue of cholesteatoma, termed the perimatrix, an integral part of the middle ear inflammatory response and an important driving force for the persistent growth of the cholesteatoma matrix [12,20].



Area under the curve	Std. error*	Asymptotic Sig.†	Asymptotic 95% confidence interval
0.752	0.054	0.000	0.647−0.857

Fig. 3. Receiver operating characteristic curve (ROC) for prediction of chronic otitis media with cholesteatoma based on the partial thromboplastin time value. *under the nonparametric assumption; †null hypothesis: true area=0.5.

The association between coagulation and angiogenesis is already reported in the literature in several studies. For example,

vWF, beyond its role on hemostasis, has several others functions including angiogenesis, cell proliferation, inflammation, and tumor cell survival [21-24]. There are even studies that show that inhibition of the expression of vWF in endothelial cells causes an increase in vascular endothelial growth factor (VEGF) and, consequently, angiogenesis stimulation [22]. Gritti, et al. [25] showed to exist a substantial increase in circulating endothelial cells in patients with von Willebrand disease (vWD), as well as angiogenic cytokines and, therefore, a direct correlation between this disease and increased angiogenesis has been previously proposed.

In fact, the association between vWD and increased angiogenesis has been clinically proven in patients with both vWD and gastrointestinal angiodysplasia [26]. Reis Rego, et al. [27] hypothesized that in the vWD there is a downregulation of angiogenesis, and therefore, a greater propensity for development, maturation and expansion of cholesteatoma.

Other factors directly involved in the coagulation cascade are also involved in angiogenesis. This is the case of coagulation FVIII. Beyond its established role as a coenzyme to factor IXa to expedite thrombin generation through the intrinsic pathway of coagulation, emerging evidence for the role of FVIII across multiple systems, including the cardiovascular system, angiogenesis and maintenance of bone health [28].

FVIII protein as a coagulation replacement factor has for decades been used as the standard of care for management of people with hemophilia A [29].

Proangiogenic factors such as VEGF, stromal cell-derived factor 1, and matrix metalloproteinase 9 were found to be elevated in proangiogenic macrophage/monocyte cells in the pathogenesis of hemophilic joint disease, suggesting that angiogenesis is involved in the disease [30].

To date, there is no study that establishes causal evidence between deregulation in the coagulation cascade, or deficit/deficiency of clotting proteins and cholesteatoma etiopathogenesis, especially in those with a more aggressive and relapsing course.

With this study it was proven that there is a relationship between prolonged PTT value and the development of PAC.

Deficit/deficiency of clotting proteins are associated with hematological diseases such as vWD and Hemophilia. In these diseases, dysregulation in angiogenesis is extensively described, as mentioned before.

Prolongation of the PTT value in most cases has no clinical significance, since they do not reach the values necessary to establish a diagnosis of vWD or hemophilia, for example. However, the authors suggest that prolonged PTT values, even if slight, may already reflect and have molecular effects on the regulation of angiogenesis, despite the fact that children are healthy and often asymptomatic. It is legitimate in the future consider antiangiogenic molecules as an adjuvant therapy in patients with cholesteatoma, although surgical treatment is currently the greatest weapon to prevent the local advance of cholesteatoma and all the complications that may arise [27].

This study has some limitations that are important to mention: 1) other risk factors for OME have not been investigated, such as family history of ear pathology; 2) the risk of developing cholesteatoma after placing the VT may be higher when performed by an ENT resident, often in the early stages of his career, compared to a ENT specialist; 3) the study presents a reduced sample in the groups of cases, which makes it difficult to extrapolate the data, but which reflects the decrease in the number of children with acquired cholesteatoma over the years with the improvement of health care.

In conclusion, with this case-control study, it is hypothesized that a slight extension of the PTT value in the coagulation study may not meet the criteria for the diagnosis of certain hematological pathologies, not presenting clinical significance, but at a molecular level it may already have implications for the activation of angiogenesis and other growth factors involved in the onset, growth and expansion of acquired pediatric cholesteatoma.

Acknowledgments
None

Conflicts of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Joana Raquel Costa, Miguel Bebiano Coutinho. Data curation: Joana Raquel Costa, Ângela Reis Rego. Formal analysis: Ângela Reis Rego. Investigation: Joana Raquel Costa. Methodology: Joana Raquel Costa. Project administration: Teresa Soares, Miguel Bebiano Coutinho. Resources: Joana Raquel Costa, Ângela Reis Rego. Software: Ângela Reis Rego. Supervision: Miguel Bebiano Coutinho. Validation: Cecília Almeida e Sousa, Miguel Bebiano Coutinho. Visualization: Cecília Almeida e Sousa, Miguel Bebiano Coutinho. Writing—original draft: Joana Raquel Costa. Writing—review & editing: Ângela Reis Rego. Approval of final manuscript: all authors.

ORCID iDs
Joana Raquel Costa https://orcid.org/0000-0002-3558-6254
Ângela Reis Rego https://orcid.org/0000-0002-1905-3271
Teresa Soares https://orcid.org/0000-0003-0607-7968
Cecília Almeida e Sousa https://orcid.org/0000-0003-4822-6343
Miguel Bebiano Coutinho https://orcid.org/0000-0002-3122-4555

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