














What a Neurosurgeon Should Know About the Endolymphatic Sac: Part 1–Anatomy and Physiology

O que um neurocirurgião deve saber sobre o saco endolinfático: Parte 1–Anatomia e Fisiologia

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Abstract

Objective To describe the microsurgical anatomy and the physiology of the endolymphatic sac (ES) that a neurosurgeon should know.

Methods Review of previous studies from 1927 to 2021, from basic and translational research using human and animal ES tissue or cells, as well as previous reviews about the subject. The present article is divided into three parts. In this first part, we review the microsurgical anatomy and physiology of the ES.

Results The ES is a structure situated in the inner ear, together with the cochlea, the vestibular system, and other structures. Differently from its adjacent structures, the ES does not have a specialized epithelium; instead, it has mitochondria-rich cells and ribosomal-rich cells, which are responsible for ionic transportation and secretory activity. Apart from these functions, the ES is also responsible for homeostasis regulation of the inner ear, endolymphatic fluid volume control, immune response, elimination of inner ear cellular debris and floating otoconia, regulation of membranous labyrinth pressure, acid/basic transport, and secretion of substances. Its anatomy is not very variable, since in most studies no more than 20mm separates the location of the ES in the samples, in any direction.

Keywords

- endolymphatic sac
- anatomy
- physiology
- neurosurgery

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Resumo

Palavras-chave

- Saco Endolinfático
- Anatomia
- Fisiologia
- Neurocirurgia

Conclusion The human ES has vital functions in the inner ear, and its anatomy is rarely variable. Knowing that, and the importance of this area for neurosurgery, the present study elucidates the exact location of the ES and the lost functions that a lesion in this structure must cause.

Objetivo Descrever a anatomia microcirúrgica e a fisiologia do saco endolinfático (SE) que um neurocirurgião deve saber.

Métodos Revisão de estudos prévios de 1927 até 2021, de pesquisa básica até translacional usando tecidos ou células do SE humanas e animais, além de revisões sobre o assunto. O presente artigo é dividido em três partes. Nesta primeira, nós revisamos a anatomia microcirúrgica e a fisiologia do SE.

Resultados O SE é uma estrutura situada no ouvido interno, junto da cóclea, do sistema vestibular e outras estruturas. Diferentemente das estruturas adjacentes, o SE não tem um epitélio especializado; ao invés disso, possui células ricas em mitocôndrias e outras ricas em ribossomos, que são responsáveis por transporte iônico e atividade secretória. Além dessas funções, o SE é responsável por regulação homeostática do ouvido interno, controle do fluido endolinfático, resposta imune, eliminação de detritos e otólitos livres, regulação da pressão da membrana labiríntica, transporte ácido/básico e secreção de substâncias. Sua anatomia não é muito variável, já que na maior parte dos estudos a máxima diferença de localização entre as amostras do SE foi dada em 20 mm, em todas as direções.

Conclusão O SE humano tem uma função vital no ouvido interno e sua anatomia não é muito variável. Sabendo disso, e da importância dessa região para a neurocirurgia, o presente estudo elucida a localização exata do SE e as funções perdidas em uma eventual lesão dessa estrutura.

Introduction

The endolymphatic sac (ES) is a structure situated in the inner ear, together with the cochlea and the vestibular system.¹ These two have the responsibility of, respectively, detecting sound frequencies and capturing angular and linear acceleration, therefore, acting in hearing and balance. To do that, the cochlea and the vestibular system have a specialized epithelium, which transforms external stimuli into electrical signals that will be interpreted by the brain.^{1–4}

Differently from its adjacent structures, the ES does not have a specialized epithelium; instead, it has mitochondria-rich cells and ribosomal-rich cells, which are responsible for ionic transportation and secretory activity.¹ This way, the ES has a very different function if it is compared with the cochlea and the vestibular system.³

The ES, despite being only 3 mm in diameter, does not have a very variable location inside the inner ear.^{2,5} Almost any alteration in this structure can cause a massive problem to the hearing, including its loss.¹

In the present review, our goal is to elucidate the anatomy and the physiology of the ES.

Methodology

The present article is divided into three parts. In this first part, we review the microsurgical anatomy and physiology of

the ES. We focused on evidence of PubMed (from 1927 to 2021) from basic and translational research using human and animal ES tissue or cells, as well as previous reviews about the subject, using the following terms individually and combined: *Endolymphatic sac*, *anatomy*, *physiology*, and *neurosurgery*. Literature inclusion criteria were articles in English; individual case studies and long-term follow-up studies were not excluded. duplicate studies were excluded. First, we made a detailed explanation of the ES anatomy, followed by a briefing of the endolymph circulation prioritizing their relationship with the ES, and in the end, we discussed the physiology of the ES.

Results

Endolymphatic Sac History

The discovery of the ES was made by Neapolitan Domenico Felice Antonio Cotugno in 1760, on his famous dissertation *De Aquaeductibus Auris Humanae Internal* (On the Aqueducts of the Human Internal Ear).⁶ He described the presence of labyrinthine fluid in the various cavities of the inner ear and the existence of two aqueducts: the cochlear aqueduct and the vestibular aqueduct. As well as the structures, Cotugno described the path taken by the aqueduct from the posterior cranial fossa to the inner ear, the two leys of dura enclosing the ES, and that this sac is a continuation of the vestibular aqueduct.⁷



Fig. 1 Domenico Cotugno (1736–1822) by C. Nalli (wood engraving). Portrait no. 689. (Courtesy of the United States National Library of Medicine: Image ID172387)

Cotugno, despite having described the anatomy, was not the one that named the structure as an ES. This credit goes to German Hasse, who introduced the term in 1873, which has remained in use until today (►Fig. 1).⁸

Endolymphatic Sac Anatomy

The ES is divided into three regions. The proximal part, closer to the vestibule, is revested by an epithelium like the endolymphatic duct,⁹ that is, epithelial cells with the cellular membrane folded, creating fingerlike cytoplasmic protrusions.¹⁰ The middle region is revested by a high cylindrical epithelium with many papillae and crypts. The distal part is in a dura mater duplication, that is, connective tissue, with its surface all covered by the same type of simple pavement epithelium.⁹ The vascularization of each part of the ES is made by the same vessels that irrigate its adjacent structures, proximal being the same of the endolymphatic duct, and middle and distal being the same of the dura mater vessels.^{5,11–13}

The location of the ES stands in a dura mater duplication posteriorly to the petrous pyramid, thus ending up being a surgical area for many neurosurgical procedures in the posterolateral part of the skull base.⁵ The average measurements in a study conducted by Ammirati et al. were 15.7 mm posterosuperior (superolateral) to the 11th nerve in the jugular foramen (range, 11.0–18.5 mm), and 13.3 mm posterior (lateral) to the internal auditory meatus (range, 10.0–18.0 mm). The center of the sac was 24.1 mm (mean value) (range, 20.0–28.0 mm) ahead of the petrosigmoid

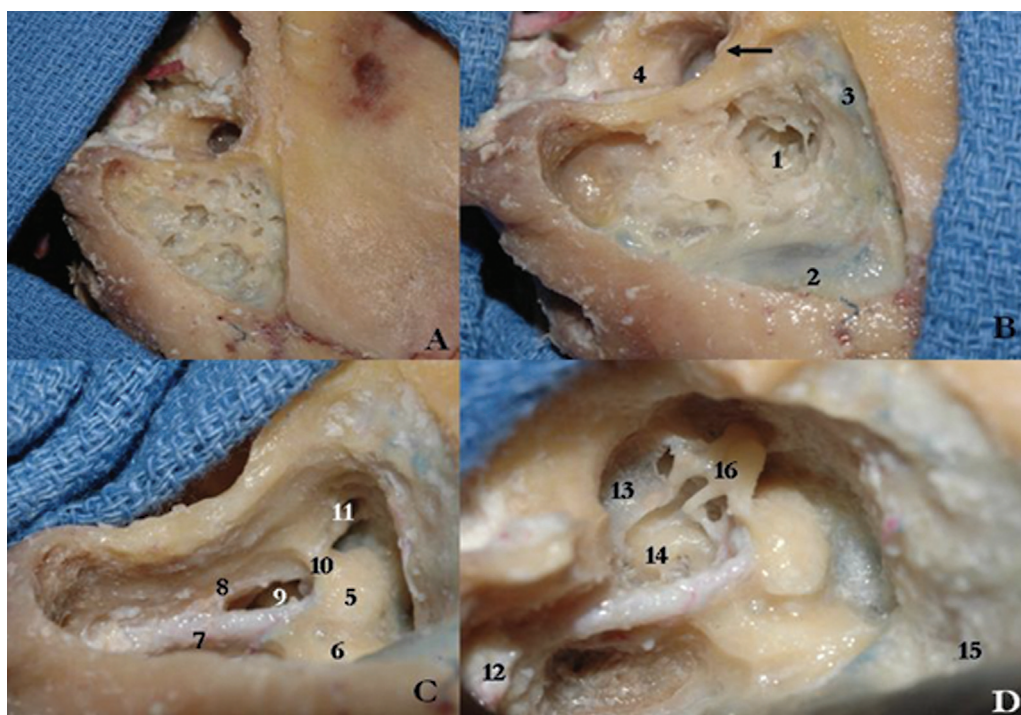


Fig. 2 Pictures of the inner ear showing: 1. Antrum, 2. Sinus Sigmoideus, 3. Mastoids segment of the dura mater, 4. External auditory meatus inferior wall, 5. Lateral semicircular canals, 6. Posterior semicircular canals, 7. Mastoids portion of the facial nerve, 8. Chorda tympani, 9. Facial recess, 10. Buttress, 11. Anvil, 12. Jugular bulb, 13. The tympanic membrane, 14. Promontory, 15. Citelli angle, 16. Ossicles. Mastoidectomy performed by Gustavo Isolan, MD, PhD.

intersection at a point 11.5 mm (mean value) (range, 8–17 mm) below the petrous ridge. The width and height of the sac were 3.83 (range, 2–6 mm) and 3.80 mm (range, 2.5–8 mm), respectively (**Fig. 2**).⁵

There are some named structures that delimit the ES space. The Donaldson line is a surgical line that is parallel to the lateral semicircular canal (LSC) whereas it is vertical to the posterolateral semicircular canal (SSC) and divides it into superior and inferior portions, from its most posterior point. Below this line, medial to the labyrinth, the endolymphatic sac is situated⁵—the Trautmann triangle is another important anatomic mark, bounded by the superior petrosal sinus (SPS) superiorly, the sigmoid sinus (SS) posteriorly, and a solid angle, which is formed by the bony labyrinth, anteriorly. In this triangle, the retrolabyrinthine tract from the mastoid antrum (MA), the ES, and the vestibular aqueduct are located.¹³ Probably because of the bone limitation, the exact location of the sac is rarely variable.² In 85% of the cases studied by Ammirati, the sac was located between 10 and 15 mm posterior (lateral) to the internal auditory meatus. Similarly, the ES was never located < 11.5 or > 18.5 mm posterolateral (superolateral) to the 11th nerve in the jugular foramen; in 80% of cases, the sac was located between 11 and 17 mm posterolateral (superolateral) to the 11th nerve in the jugular foramen (**Fig. 3**).⁵

The ES is attached to the endolymphatic duct, which is responsible for making the transit between the endolymph in the utricular saccular duct and in the endolymphatic sac.¹⁴ The endolymphatic duct is vascularized by the accessory canal of the vestibular aqueduct, but there are no arteries in this structure.⁹ The irrigation of the endolymphatic duct is made by adjacent capillaries that are in contact with the tissue through the lumen invagination of the duct.⁹

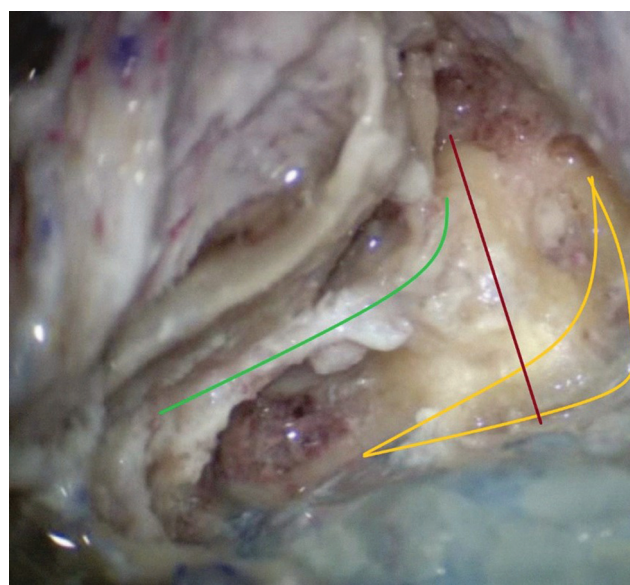


Fig. 3 Image showing the microanatomy of the inner ear. In red: Donaldson line. In yellow: Margins of the Trautmann triangle, in green: facial nerve. Mastoidectomy performed by Joel Lavinsky, MD, PhD.

Endolymph Way to the Endolymphatic Sac

The endolymph is a fluid with a composition very similar to the intracellular liquid.¹ The formation of this fluid is not a responsibility of one single structure; instead, all the blood capillaries in the membranous labyrinth work together in this goal.⁹ Therefore, there is no unique way to the endolymph, as it can freely transit in the lumen of the canals. The orientation of the liquid will depend on the head orientation, the angle of the body, etc.¹⁴ In this system, the ES is accountable, among other things, for storing the excess of endolymph.¹

As said before, the endolymph does not have a single way to transit.¹⁵ However, to explain the membranous labyrinth, let us take a portion of endolymph that is on the semicircular canals and go all the way to the ES. For that, we will always suppose that the endolymph heads to its next named structure. In the semicircular canals, the possibilities of the endolymph are to stay in it or reach the membranous ampullae of the semicircular canals. In the ampullae, the endolymph can return to the semicircular canals, stay in the ampullae, or move forward to the utricle. After reaching the utricle, the endolymph can stay in it, go back to the membranous ampullae of the semicircular canals, or proceed to the utricular saccular duct. In this stage, the endolymph is able to stay in the utricular saccular duct, flow back to the utricle, move to the saccule, or maintain itself in the way to the ES and go through the endolymphatic duct in the vestibular aqueduct. Once in the endolymphatic duct, which is sheltered by the vestibular aqueduct, the endolymph can only stay, go back to the utricular saccular duct, or move in the way to the ES (**Fig. 4**).^{14,16–18}

Starting from the cochlea, the differences are only at the beginning. The endolymph, if not remaining in the cochlea, can only go to the saccule through the canalis reuniens. In the saccule, the endolymph can stay, flow back to the cochlea by the canalis reuniens or move to the utricular saccular duct, and from there the way is the same if starting in the semicircular canals.^{14,16–18}

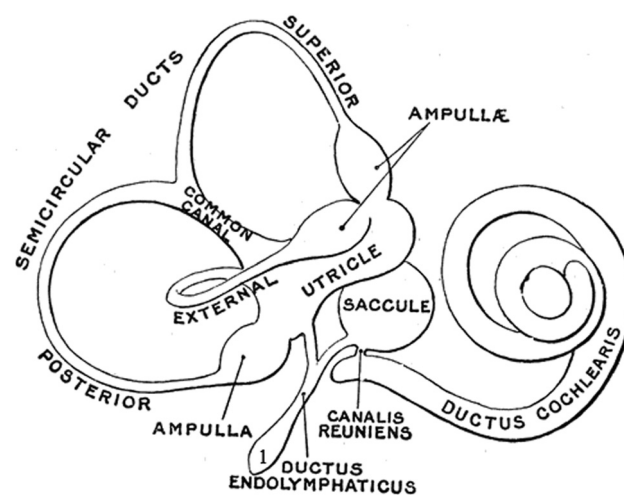


Fig. 4 Image showing the endolymphatic system. 1. Endolymphatic sac. Taken from the public domain: GRAY, H., & LEWIS, W. H. (1918). *Anatomy of the human body*. Philadelphia, Lea & Febiger, page 1052.

Endolymphatic Sac Physiology

The cochlea and semicircular canals or the vestibular system have the function of, respectively, detecting sound frequencies as well as angular and linear acceleration, acting therefore in hearing and balance. To do that, the cochlea and the vestibular system are provided with a sensorial epithelium, which transforms external stimulus in electric signals that will be interpreted by the brain.¹⁻⁴

Differently from its adjacent structures, the ES does not have a specialized epithelium; instead, it has mitochondria-rich cells and ribosomal-rich cells, which are responsible for ionic transportation and secretory activity.¹ In this way, the ES has a very distinct function if compared with the cochlea and the vestibular system.³

In animals, it is suggested that the ES has an important role in the ionic homeostasis regulation of the internal ear and in the endolymphatic fluid volume control. Besides that, its involvement in immune response, elimination of inner ear cellular debris and floating otoconia, membranous labyrinth pressure, acid/basic transport, and substances secretion has been studied (► Fig. 5).^{1,2,11,19-26}

Ionic Homeostasis

In the study by Mori et al.,²⁴ they show that mitochondria-rich cells in the ES intermediate portion have a

higher activity of Na^+ , K^+ -ATPase, and higher Na^+ permeability than other types of cells, implying that molecules related to Na^+ transport, such as epithelial sodium channel, Na^+ - K^+ -2Cl cotransporter 2 (NKCC2) and thiazide-sensitive Na^+ -Cl cotransporter (NCC), may be present in mitochondria-rich cells.²⁴ Because of that, it is possible to suggest that the ES epithelium plays a role in the ionic transportation and composition of the endolymph.

Volume Regulation and Pressure Regulation

Also, in the study by Mori et al.²⁴ and supported by the study by Furuta et al.,²⁷ it is said that aldosterone may regulate Na^+ transport in ES, resulting in endolymph volume regulation. Based on that, we can suggest that the ES is also a crucial part of the pressure regulation in the membranous labyrinth.^{24,27}

Acid/Base Transportation

In the same study,²⁴ Mori suggests that the presence of molecules related to acid/base transport, such as H^+ -ATPase, Na^+ - H^+ exchanger (NHE), pendrin (SLC26A4), Cl^- - HCO_3^- exchanger (SLC4A2), and carbonic anhydrase in ES epithelial cells may be a reason for the acid/base transport be another important role of the ES.

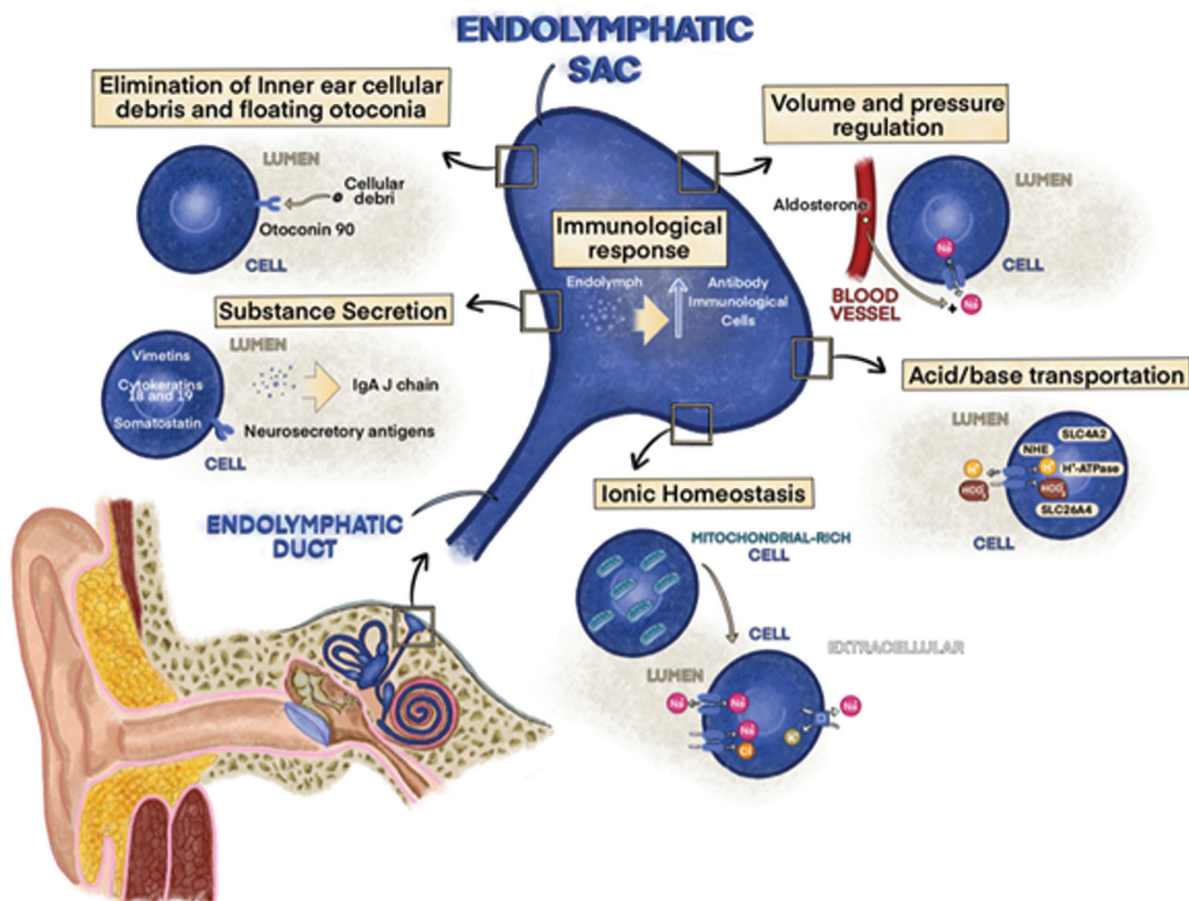


Fig. 5 Schematic representation of the endolymphatic sac physiology. “Created by Lia Grub Becker”.

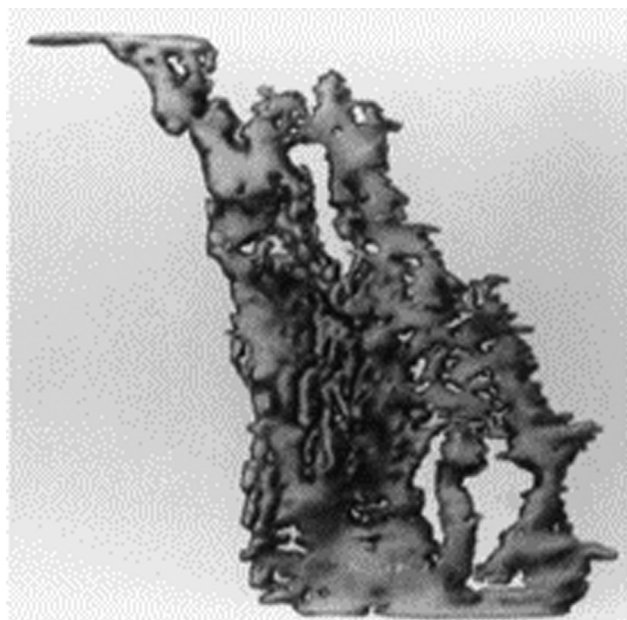


Fig. 6 3D image of the endolymphatic sac. Taken from: Oehler MC, Chakeres DW, Schmalbrock P. Reformatted planar 'Christmas tree' MR appearance of the endolymphatic sac. *AJNR Am J Neuroradiol.* 1995 Aug;16(7):1525-8. **FIG 1B.**

Immunologic Response

Recent studies demonstrated the presence of immunocompetent cells in the ES and its capability to respond to local primary and secondary antigen challenges.^{3,21-23}

Measurements of serum and perilymph antibody levels, followed by inner ear immunization with keyhole limpet hemocyanin in guinea pigs with normal or obliterated ES, suggested that the ES plays a crucial role in the generation of local humoral immune responses.^{25,26}

Also, these studies have searched for different types of cells in the ES and several, related to the immunologic system, have been found.^{3,21-26}

Elimination of Inner Ear Cellular Debris and Floating Otoconia

According to the study by Ignatova et al.,²⁸ Otoconin-90 is the main otoconial matrix protein, and the endolymphatic sac of

the embryonic chicks and guinea pigs contain otoconia. Otoconin-90 is also localized at the surface and inside epithelial cells lining the endolymphatic sac and is also incorporated into free-floating cells. Thus, the study concludes that the presence of these proteins can only be explained if there is an elimination process linked to it.²⁸

Secretion of Substances

The presence of immunoglobulin A (IgA), secretory components like Cytokeratins 18 and 19, vimentins, as well as the J chain, was described within epithelial cells and in the lumen of the human ES.^{19,20} Thus, the expression of these substances in the human ES epithelium supports the assumption that the ES is metabolically active and functionally related to a mesothelium that has both secretory, resorptive, and elimination capabilities.^{10,19,20}

A positive reaction for neuron-specific enolase and neurosecretory antigens was demonstrated in a few epithelial cells of the rugose part of the human ES.^{19,20} In addition, neurosecretory granules and somatostatin were observed in cells of the human ES.^{10,19,20} All this information contributes to the hypotheses of the secretory capacity of the ES.

Radiological Anatomy of the Endolymphatic Sac

The ES is a complex structure in terms of microscopic anatomy, which makes it difficult to visualize it in magnetic resonance imaging (MRI).²⁹ However, Oehler et al.²⁹ made a high-resolution three-dimensional Fourier transform technique and prototype bilateral dual phased-array surface coil technique, obtaining a 3D image of the ES (►Fig. 6).

Based on the results, it is possible to ensure that instead of a large confluent cavity, the ES is composed of multiple small channels that are interconnected, that in the study by Oehler et al is called by "Christmas tree" appearance.²⁹ However, Connor et al.³⁰ have shown that some ES pathologies can change its anatomy on MRI and computed tomography (CT). Individuals who have been diagnosed with large endolymphatic sac anomaly (LESA) and large vestibular aqueduct (LVAS) syndrome will probably have alteration on the scans, like the enlargement of the extra-osseous ES (►Fig. 7).³⁰

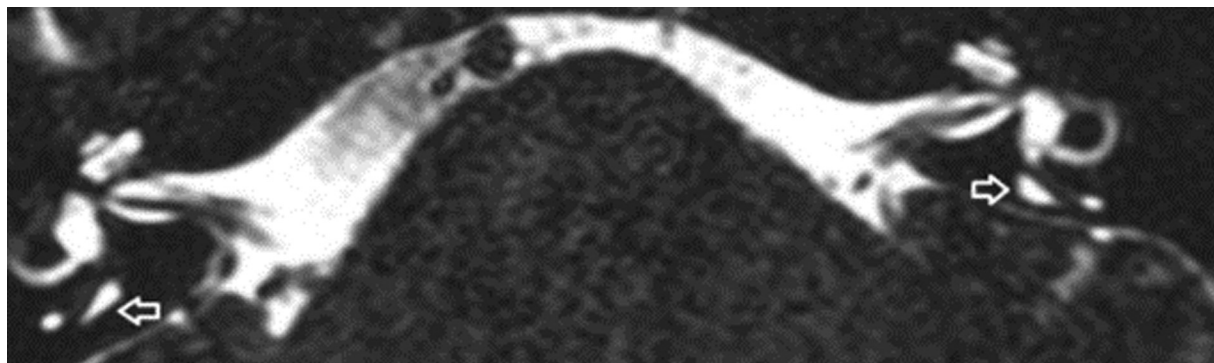


Fig. 7 T2 DRIVE axial images show an enlarged extra-osseous sac on the left. Taken from: Connor SEJ, Dudau C, Pai I, Gaganasiou M. Is CT or MRI the optimal imaging investigation for the diagnosis of large vestibular aqueduct syndrome and large endolymphatic sac anomaly? *Eur Arch Otorhinolaryngol.* 2019 Mar;276(3):693-702. ►Figure 3.

Conclusion

The human ES has vital functions in the inner ear, such as homeostasis regulation of the internal ear, endolymphatic fluid volume, immune response, elimination of inner ear cellular debris, and floating otoconia, membranous labyrinth pressure, acid/based transport, and secretion of substances.

The anatomy of the ES is rarely variable, since in > 80% of the cases, in the reviewed studies, the maximum difference in the samples was < 20 mm in any direction. Knowing that, and the importance of this area for neurosurgery, the present study elucidates the exact location of the ES and the function that a lesion in this structure must cause.

Conflict of Interests

The authors have no conflict of interests to declare.

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