Abstract
Ménière’s disease (MD) is a chronic illness of the inner ear. It is characterised by intermittent episodes of vertigo lasting from minutes to hours, with sensor neural, usually fluctuating, hearing loss, tinnitus, and aural pressure. Diagnosis is mainly based on clinical course and MD is usually considered as a multifactorial disease. Thus there are not yet evidences of a specific treatment. Authors start from a particular case of MD patient that was completely healed after tonsillectomy, an absolute unusual treatment for this kind of disease. On the basis of Literature and their studies about the role of vascular, viral, allergologic and immunologic disorders in MD patients, Authors speculates about the Brain Lymphatic System as an unitary explanation of the effects of infective foci, like chronic palatine tonsils, viral infections, inner ear epitopes activation and allergo-immunologic disturbances in MD pathogenesis. This kind of approach, in the aim of the Authors, may help to better planning a tailored treatment for the patient.

Keywords: mènière disease, tonsillectomy, allergy, viral infections, brain lymphatic system

Introduction
Ménière’s disease (MD) is a chronic illness of the inner ear with an incidence, in Europe about 50-200/100,000 a year.1 It is characterised by intermittent episodes of vertigo lasting from minutes to hours, with sensor neural, usually fluctuating, hearing loss, tinnitus, and aural pressure. Diagnosis is mainly based on clinical course and MD is usually considered as a multifactorial disease, thus there are not yet evidences for a specific treatment.2,3 The inner ear comprehends hearing and balance sensory organs it is deeply embedded into the petrosus part of the temporal bone, its blood supply is provided through the labyrinthine artery, a branch of the anterior inferior cerebellar artery (>85% cases) or basilar artery (<15% cases), its drainage is formed by the labyrinthine veins that flow, via the inferior petro us sinus, into the Internal Jugular Veins (IJVs).4 The luminal compartment of the inner ear, known as the endolymphatic space, is separated by the abluminal compartment, the perilymphatic space, through highly specialized epithelial cells with tight junctions. The fluid volume within the bony labyrinth remains constant. Changes in the volumes of the endolymphatic and perilymphatic compartments are responses to osmotic gradients between the compartments themselves.5 MD is characterized by impairment of this balance between the compartments causing the so called Endolymphatic Hydrops (EH), usually considered the pathogenesis of MD. The EH associated with Ménieré’s disease has been correlated to many etiological factors able to alter the endolymphatic homeostasis, such as abnormalities in end lymph production or absorption,6 cervico-cerebro venous drainage impairment7-9, genetic anomalies, allergies,10 viral infections11 and autoimmunity or inflammatory processes.12 It has been suggested that certain cases of MD may have an altered immunological background, which may be attributable to an autoimmune mechanism that depends on humoral and/or cellular responses leading to an altered blood-labyrinth barrier.13 The underlying mechanism of EH is still debated, with some researches in favour of a purely hydraulic mechanism and others hypothesizing a control mechanism of ionic balance. Hydraulic hypothesis supports ES surgical treatment while Control hypothesis a pharmacologic and dietary approach.

An intriguing case report
We observed a particularly successfully complete resolution of MD in a young woman after tonsillectomy, an absolute atypical approach to this kind of disorder. Marta C was affected with an absolute right hearing loss occurred during infancy probably caused by a “viral” infection. When she was 21 Marta begun to manifest typical Ménière attacks with involvement of the left, healthy, ear. This condition is also called Delayed Hydrops, which is a MD that occurs many years after a sudden hearing loss.14 Generally speaking, involvement of the healthy ear is probably due to a cochlear autoimmune response activated by the initial viral infection.15 In the same period she began to alternate typical MD spells and “typical” acute tonsillitis. Antibiotics were effective during tonsillitis but they did not prove to be effective to prevent the acute episodes. Throat specimen during acute episodes and between them was always negative for a bacterial origin of chronic tonsillitis. On the other hand, an enzyme-linked immunosorbent assay (ELISA) was used to detect antibodies (IgM and IgG) to Herpes simplex type 1-2 (HSV-1, HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV) and Ebstein-Barr (EBV). The presence of high level of CMV IgG was detected. On the basis of clinical and laboratory results the patient underwent tonsillectomy. Ménière attacks immediately stopped and after more than 10 years follow-up no more vertigo attacks occur and left, health, hearing is completely normal. Evidently, tonsillectomy removed infective foci able to activate a counter-inner ear response. However, the question is which is the putative link between palatine tonsils infections and Ménière Disease?

Some further considerations about MD and immune system
A similar question regards the role of virus and the role of allergy in MD pathogenesis A viral cause of MD has been sustained by some Authors. Gacek, for instance4,5 hypotized a vestibular ganglionitis or a vestibular neuropathy induced by Herpes infections or re-activations. In our experience only in one case we could sustain a direct action...
of virus in MD when we had been able to measure anti-VZV IgM and IgG and Anti Heath Shock Protein (HSP)-70 antibodies in a patient in which both the early phase of VZV manifestation and a typical MD acute attack occurred at the same time. 18 If a viral direct action on inner ear lacks of laboratory support, the role of allergy in MD seems more evident and sustainable. Derebery and Berliner describe three theories related to allergy in MD that focus on inflammation within the endolymphatic sac. 19 First, the endolymphatic sac contains a fenestrated blood supply that may allow antigen entry leading to mast cell degranulation and inflammation. A second proposed mechanism involves circulating immune complexes that enter endolymphatic sac circulation and the stria vascularis leading to inflammation and increased permeability as well as fluid balance disruption. A final theory pertains to a viral antigen-allergic interaction. Viruses have been shown to exacerbate allergic symptoms by enhancing histamine release and can damage epithelial surfaces as well as trigger T-cell migration to the endolymphatic sac. 20

The question remains the same

How viruses may be effectively removed by the inner ear?

Both inhalant and food allergies have been associated with Di Berardino et al. 21 verified the incidence of gliadin IgE hypersensitivity 21 and the effectiveness of gluten-free diet in MD patients. 22 To sum up, also in the case of allergy a unitary explanation of damage and repair mechanisms seems to lack.

The putative role of brain lymphatic system

Brain tissues are composed of three compartments

Parenchyma (neural and glial cells), vascular system and then interstitial system (ISS). The brain ISS is an irregular, tortuous and narrow space among neural cells and capillaries and contains interstitial fluid (ISF) and extracellular matrix (ECM). 23 Cerebro Spinal Fluid (CSF) and ISF are strictly functionally connected. It has been suggested that Cerebro Spinal Fluid (CSF) formation occurs by filtration and flow of fluid through the capillary walls, and that the respective volumes of CSF and interstitial fluid mainly depend on hydrostatic and osmotic forces between the CSF and brain parenchyma created by gradients of proteins and inorganic ions across the capillary membrane. CSF and ISF are continuously interchanging and the volume occupied by each compartment depends on hydrostatic and osmotic forces. This exchange is facilitated by convective influx of CSF along the periarterial space. From the subarachnoid space, CSF is driven into the Virchow-Robin spaces. CSF works mainly during sleep and it is largely disengaged during wakefulness. 27 Nakayama et al. 26 found in 35 patients that total sleeping time was significantly higher than in controls. Nevertheless, they also showed in these patients, for the first time, a poor quality of sleep with decreased deep sleep and an elevated arousal index allowing speculating an impairment of GS at least in some patients affected with MD. However, as far as the present case report regards, in our opinion, more than GS, is the Brain Lymphatic System (BLS) that has to be taken in account to understand as un unique phenomenon direct or undirected, through the activation of inner ear epitopes, 28 the action of virus, allergic and immune reaction, and the resulting preventive actions. A true lymphatic vascular system draining brain interstitial fluids and macromolecules has been very recently described. 10 Generally speaking, BLS is formed by a network of lymphatic vessels in the dura mater of the Central Nervous System (CNS) that drains out via the foramina of the skull base itself alongside arteries, specifically the major branches of the middle and anterior meningeal arteries and the pterygopalatine artery, cranial nerves, specifically I, V, IX, X and XIIth, and veins. Lymphatic vessels have been observed in the dural lining of the cribiform plate where some vessels pass into the nose. 27

Dura mater 22, 23 lymphatic vessels drains brain ISF into deep cervical lymph-nodes. Variations in intracranial blood volume 4 may potentially influence also Brain Lymphatic System (BLS). 35 Recently, Louveau et al. 27 underlined that the presence of a lymphatic system draining the CNS potentially offers a new player and a new avenue for therapy in neurological disorders, specifically multiple sclerosis and Alzheimer’s disease. Similarly Lei Y et al. 25 emphasized the potential role of ISF to better deliver specific drugs to brain cells taking in account that neural cells occupy only 70-80% of the total brain volume, the vascular system and ISS together form the brain microenvironment and ISF alone occupies 15-20% of the total brain volume. Both Authors 30-36 suggested that neurological afflictions can be viewed as diseases with a neuro-lympho-vascular component and should be therapeutically targeted as such. This kind of approach may be extended to MD treatment, too. The lymphatic vessels run down toward the skull base also along the transverse sinus, the sigmoid sinus, the retroglossogoid vein and the rostral rhinal vein. The endolymphatic
The putative role of brain lymphatic system in ménière disease pathogenesis

References

1. James A, Thorp M. Méniére Disease. Clinical Evidence. 2007;3:505.
2. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière’s disease. Otolaryngol Head Neck Surg. 1995;113(3):181–185.
3. Lopez Escamez JA, Carey J, Chung WH, et al. Diagnostic Criteria for Ménière Disease. J Vest Res. 2015;25(1):1–7.
4. Baloh RW. Dizziness, Hearing Loss, and Tinnitus. New York, USA; 1988.
5. Merchant SN, Adams JC, Nadol JB. Pathophysiology of Ménière Syndrome: are Symptoms caused by Endolymphatic Hydrops? Otol Neurotol. 2005;26(1):74–81.
6. Schuknecht HF, Ruther A. Blockage of longitudinal flow in endolymphatic hydrops. Ear Arch Otorhinolaryngol. 1991;248(4):209–217.
7. Alpini D, Bavera PM, Hahn A, et al. Chronic Venous cerebrospinal insufficiency (CCSVI) in Meniere Disease. Case or Cause? Science Med. 2013;4:9–12.
8. Di Berardino F, Alpini DC, Bavera PM, et al. Chronic cerebrospinal venous insufficiency in Ménieère disease. Phlebology. 2015;30(4):274–279.
9. Filipo R Ciciarello F, Attanasio G, Mancini P, et al. chronic cerebrospinal venous insufficiency in patients with Ménieère’s disease. Ear Arch Otorhinolaryngol. 2015;272(1):77–82.
10. Derebery MJ. Allergic and immunologic aspects of Meniéere’s disease. Otolaryngol Head Neck Surg. 1996;114(3):360–365.
11. Bergstrom T, Edstrom S, Tjellstrom A, et al. Ménieère’s disease and antibody reactivity to herpes simplex virus type 1 polypeptides. Am J Otol. 1992;13(5):295–300.
12. Hughes GB, Barna BP, Kinney SE. Delayed endolymphatic hydrops: five-year review. Otolaryngol Head Neck Surg. 1988;98(3):221–225.
13. Tomoda K, Suzuka Y, Iwai H, et al. Ménieère’s disease and autoimmunity: clinical study and survey. Acta Otolaryngologica. 1993;500:31–34.
14. Harcourt JP, Brookes GB. Delayed endolymphatic hydrops: clinical manifestations and treatment outcome. Clin Otolaryngol Allied Sci. 1995;20(4):318–322.
15. Schuknecht HF, Suzuka Y, Zimmermann C. Delayed endolymphatic hydrops and its relationship to Ménieère’s disease. Ann Otol Rhinol Laryngol. 1990;99(11):843–853.
16. Gacek RR, Gacek MR. Meniéere’s disease as a manifestation of vestibular ganglionitis. Am J Otolaryngol. 2001;22(4):241–250.
17. Gacek RR. Ménieère’s disease is a viral neuropathy. ORL J Otorhinolaryngol Relat Spec. 2009;71(2):78–86.
18. Di Berardino F, Cesaran A, Hahn A, et al. Viral infection and serum antibodies to heat shock protein 70 in the acute phase of Ménieère’s disease. Int Tinnitus J. 2007;13(2):90–93.
19. Derebery JM, Berliner KI. Allergy and Its Relation to Ménieère’s Disease. Otolaryngol Clin North Am. 2010;43(5):1047–1058.
20. Savastano M, Giacomelli L, Marioni G. Non-specific immunological determinations in Ménieère’s Disease: any role in clinical practice? Eur Arch Otorhinolaryngol. 2007;264(1):13–19.
21. Di Berardino F, Cesaran A. Gluten Sensitivity in Meniéere’s Disease. Laryngoscope. 2012;122(3):700–702.
22. Di Berardino F, Filipponi E, Alpini D, et al. Ménieère disease and gluten sensitivity: recovery after a gluten-free diet. Am J Otolaryngol. 2013;34(4):355–356.

Citation: Carlo Alpini D, Federica DI Berardino, et al. The putative role of brain lymphatic system in Ménieère disease pathogenesis. MOJ Immunol. 2018;6(5):151–154. DOI: 10.15406/moj.2018.06.00211

The putative role of brain lymphatic system in Ménieère disease pathogenesis

Sac is placed on the posterior surface of the petrous portion of the temporal bone where is in contact with the dura mater. The endolymphatic duct and endolymphatic sac play both an absorptive and secretory role, as well as phagocytic and immunodefensive functions: the endolymphatic sac is capable of antigen recognition and processing for initiation of an immune response. Subject to the above, some brain lymphatic vessels pass through the skull into the nasal mucosa and it is well known the correlation between MD and nose disorders. Nose and deep cervical lymph nodes therefore are common stations on which converge brain and inner ear waste products both via the GS and the BLS. The case reported in this paper seems strictly connected with the experiments conducted in mice that showed how impairment of these lymph-nodes compromises CNS macromolecule clearance. The interconnection of brain lymphatics with both the nasal mucosa and the deep cervical lymph-nodes allows T-cells and viruses to easily circulate into the brain and therefore in the inner ear too. This connection between Brain Lymphatic System and deep cervical lymph-nodes seems to support the action of allergic reactions, viruses and immunological complex directly arising form the upper airways on the inner ear. Di Berardino et al. have recently shown that MD patients present also reduced nasal mucous clearance (NCS). Slowing of clearance of allergens or other potentially dangerous agents from the nose and the upper airways may reduce protective action of cervical lymph-nodes and therefore facilitate sensitization of the inner ear that becomes a hypersensitive target of the immune response to antigen, immunocomplexes and viruses, as speculated it might happen in the CNS. In other words, tonsillectomy in the reported case, accidentally, produced the removal of specific infective/irritative foci that sustained MD.

Conclusion

A Brain Lymphatic System based interpretation of MD pathogenesis leads to a specific therapeutic approach to MD patients because it allows understanding some of the factors to be known playing a significant role in MD.

As a consequence, brain lymphatic system based treatment requires

i. Prompt and accurate treatment of middle ear infections like otitis media
ii. Accurate treatment of nasal and paranasal sinus disorders particularly paying attention to restore an effective nasal mucous clearance
iii. Accurate treatment of potentially irritative or infective foci in the head or the neck, e.g tonsillitis or odontostomatological disturbances
iv. Specific allergic desensitization using vaccine for inhalants and appropriate diet for food allergies
v. Prevention of viral re-activation of cranial nerves neuritis, e.g sensor neural sudden hearing loss, vestibular neuritis or facial palsy.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.
The putative role of brain lymphatic system in Ménière disease pathogenesis

23. Lei Y, Han H, Yuan F, et al. The brain interstitial system: Anatomy, modeling, in vivo measurement, and applications. *Prog Neurobiol*. 2016;90(1):303-316.

24. Jessen NA, Munk AS, Lundgaard I, et al. The Glymphatic System: A Beginner’s Guide. *Neurochem Res*. 2015;40(12):2583-2599.

25. Wostyn P, Keller HE, De Deyn PP. Glymphatic stasis at the site of the lamina cribrosa as a potential mechanism underlying open-angle glaucoma. *Clin Exp Ophthalmol*. 2017;45(5):539-547.

26. Alpini DC, Bavera PM, Di Berardino F, et al. Bridging the gap between chronic cerebrospinal venous insufficiency and Ménière Disease. *Veins and Lymphatics*. 2016;5(2).

27. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373-377.

28. Nakayama M, Suzuki M, Inagaki A, et al. Impaired quality of sleep in Meniere’s disease patients. *J Clin Sleep Med*. 2010;6(5):445-449.

29. Platt M, Diwali S, Elackattu A, et al. Mining immune epitopes in the inner ear. *Otolaryngol Head Neck Surg*. 2014;150(3):460-463.

30. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic. *Nature*. 2015;523(7560):337-341.

31. Goldmann J, Kwidzinski E, Brandt C, et al. T cells traffic from brain to cervical lymph nodes via the cribroid plate and the nasal mucosa. *J Leukoc Biol*. 2006;80(4):797-801.

32. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *JEM*. 2015;212(7):991.

33. Raper D, Louveau A, Kipnis J. How Do Meningeal Lymphatic Vessels Drain the CNS? *Trends Neurosci*. 2016;39(9):581-586.

34. Contarino C, Toro EF. A first step towards a mathematical model for the human Lymphatic System. Paper at 6th ISNVD Annual Meeting, New York, USA; 2016. p. 991-999.

35. Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. *Science*. 2016;353(6301):766-771.

36. Louveau A, Da Mesquita S, Kipnis J. Lymphatics in Neurological Disorders: A Neuro-Lympho-Vascular Component of Multiple Sclerosis and Alzheimer’s Disease? *Neuron*. 2016;91(5):957-973.

37. Moller MN, Kirkeby S, Vikeså J, et al. Gene expression demonstrates an immunological capacity of the human endolymphatic sac. *Laryngoscope*. 2015;125(8):269-275.

38. Harris JP. Immunology of the inner ear: response of the inner ear to antigen challenge. *Otolaryngology--Head and Neck Surgery*. 1983;91(1):18-23.

39. Hall CM, Brackman DE. Eustachian tube blockage and Meniere’s disease. *Arch Otolaryngol*. 1977;103(6):355-357.

40. Zamboni P. The discovery of the brain lymphatic system. *Veins and Lymphatics*. 2015;4(2):5360.

41. Endicott JN, Stucker FJ. Allergy in Méniere’s disease related fluctuating hearing loss preliminary findings in a double-blind crossover clinical study. *Laryngoscope*. 1977;87(10):1650-1657.

42. Hsu L, Zhu XN, Zhao YS. Immunoglobulin E and circulating immune complexes in endolymphatic hydrops. *Ann Otol Rhinol Laryngol*. 1990;99(7):535-538.

43. Di Berardino F, Soi D, Alpini D, et al. Gluten Sensitivity and Meniere Disease. Paper presented at 7th Symposium on Meniere Disease and Inner Ear Disorders. Italy; 2015.

44. Sleigh MA, Blake JR, Liron N. The propulsion of mucus by cilia. *Am Rev Respir Dis*. 1988;137(3):726-741.

45. Gacek RR. A perspective on recurrent vertigo. *ORL J Otorhinolaryngol Relat Spec*. 2013;75(2):91-107.

46. Gacek RR. Recovery of Hearing in Meniere’s Disease after Antiviral Treatment. *Am J Otolaryngol*. 2015;36(3):315-323.