Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: U Madhusudhan, Hage N, et al., 2024. Zinc Deficiency: A Harbinger of Vestibular Dysfunction? Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5210

DOI
https://doi.org/10.18103/mra.v12i4.5210

ISSN: 2375-1924

RESEARCH ARTICLE

Zinc Deficiency: A Harbinger of Vestibular Dysfunction?

Dr Madhusudhan U [1*], Dr Neemu Hage [2], Dr Kalpana M [3], Dr Vidya G [4], Dr Archana Gaur [4], Dr Vidya Singaravelu [5], Dr Anand Pyati,[5] Dr Nitin Ashok John[7], Dr Madhuri Taranikanti [8]. Dr Parag Patil[9]

[1*]Assistant professor, Department of Physiology, AIIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.
[2] Assistant Professor, Department of ENT, AIIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.
[3] Associate Professor, Department of Physiology, IIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.
[4] Assistant professor, Department of Physiology, AIIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.
[5] Professor, Department of Pediatrics, Malla Reddy Institute of Medical Sciences, Hyderabad, Telangana
[6]Associate Professor, Department of Biochemistry, AIIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.
[7] Professor & Head, Department of Physiology, AIIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.
[8] Additional professor, Department of Physiology, AIIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.
[9]Assistant Professor, Department of Pathology, AIIMS (All India Institute of Medical Sciences), Bibinagar, Hyderabad 508126, Telangana.

***Corresponding author:** drmadhuaiimsbbn@gmail.com

ABSTRACT:

Background: Role of zinc in the maintenance of redox homeostasis have been explored & is established to have antioxidant effects in the body. Presence of zinc in auditory system & its role in deafness & tinnitus is well established. Zinc supplementation has shown to not only improve tinnitus but also dizziness associated with it which marks the presence of zinc in vestibular system [4]. The possible role of zinc in modulating neurotransmission across the glutaminergic synapses in vestibulo cerebellar, vestibulo-occular pathways are established. So, this study aims to assess serum zinc levels in vestibular disorder patients & correlate with severity of the vestibular dysfunction

Methodology: This was Cross sectional comparative study, 40 patients with vestibular disorders & 40 subjects without vestibular dysfunction were included in the study. After thorough history taking, these patients were subjected to Dix Hallpike test, Head Impulse test Romberg test on foam with eyes closed /The Clinical Test of Sensory Interaction and Balance (CTSIB) to confirm vestibular dysfunction. After that, Dizziness handicap inventory (DHI) to assess the severity of the vestibular dysfunction. Serum zinc levels along with other, micronutrients like magnesium, calcium & Serum vitamin B12 & vitamin D were also assessed. Serum zinc levels were compared with age matched controls.

Results: Out of 40 patients, 24 had mild & 16 had moderate scores according to DHI. Serum zinc levels in study group was **60.63**±10.10 which was significantly ($p<0.005$) lower than compared control group **70.50**±19.1. Also, Serum zinc levels were corelated with the severity of the vestibular dysfunction, ($r=0.89$, $p<0.00$) which shows that more severe the dysfunction lesser the serum zinc levels.

Conclusion: Role of zinc as an antioxidant is well established and deficiency of zinc is linked with the pathogenesis of various diseases. Since evidences suggest involvement of zinc in vestibular system, zinc supplementation in vestibular disorder patients can be considered as add on therapy, which might have a beneficial role with respect to cognitive function as well.

Introduction

Vestibular system generates our sense of balance. Vestibular sensation operates constantly while we are awake & communicates to the brain about the head's orientation & changes in head's motion which has vital role in reorienting the body to adjust the posture by vestibulospinal reflexes[1].Vestibular input also projects to reticularis pontis oralis and pedunculopontine tegmental nucleus which generate theta rhythm [2,3] which has a role in cognitive functions like spatial memory, spatial orientation. Vestibular lesions tend to decrease power & frequency of theta rhythm leading to altered spatial memory[4].

Zinc's role in maintaining redox homeostasis has been investigated, and it is reported to have antioxidant effects in the body. [5]. The presence of zinc in the auditory system, and the role it plays in deafness and tinnitus, is well documented. [6]. Zinc supplementation has been demonstrated to not only relieve tinnitus but also the related dizziness, indicating the presence of zinc in the vestibular system[7]. Zinc's potential significance in altering neurotransmission across glutaminergic synapses in the vestibulo-cerebellar and vestibulo-occular pathways is also established.[8,9]

Zinc is also necessary for memory, attention, motor development, and neurological behavior. The specific method by which it impacts cognition is uncertain, although research indicates that zinc shortfall has contributed to cognitive decline [10-12]. Although the role of zinc in cognition has been thoroughly investigated, there are few studies that demonstrate that a zinc deficiency causes vestibular impairment.

So, this study aims to assess serum zinc levels in vestibular disorder patients & correlate with severity of the vestibular dysfunction.

Materials & methods

This was Cross sectional comparative study, we employed Universal Sampling with Study duration of 12 months. After obtaining IRC & IEC clearance, (*AIIMS/BBN/IEC/SEP/2021/92-A*) ,40 patients with vestibular disorders & 40 subjects without vestibular dysfunction were included in the study, informed written consent was taken from all the participant.

As it was funded project, sample collection was started from November 2022 up to December 2023

Inclusion criteria for Individuals with vestibular dysfunction

1. All patients diagnosed to have vestibular dysfunction
2. Age group 18-50 years, including both males & females

Inclusion criteria for Individuals without vestibular dysfunction (Comparative group)

1. Adults aged 18-50 years with no vestibular dysfunction or any other systemic disorders like Hypertension, Diabetes mellitus type II, severe Anemia, Thyroid Disorders, Autoimmune Disorders, Acute infective conditions like vestibulitis, labyrinthitis.

Exclusion Criteria

1. Patients with diagnosed neurological disorders like Parkinson's disease, Alzheimer's diseases.
2. Other systemic disorders like Hypertension, Diabetes mellitus type II, severe Anemia, Thyroid Disorders, Autoimmune Disorders, Acute infective conditions like vestibulitis, labyrinthitis.
3. Those unwilling to participate in the study.

Method

All patients who are diagnosed to have vestibular disorders were included in the study. After thorough history taking, these patients were subjected to the following clinical tests to confirm vestibular dysfunction. These tests were also be done in comparative group to rule out vestibular dysfunction.

1. **Dix Hallpike test:** Patient is made to lie in supine position, from sitting position, with the head turned 45 degrees to one side and extended about 20 degrees backward. Once supine, the eyes are typically observed for about 30 seconds. If there is no nystagmus, the person is brought back to sitting. 30 seconds later the other side is also tested is the same manner.[13]
2. **Head Impulse test:** The patient is made to sit comfortably on the stool and asked to fix his/her gaze on the examiner's nose or a distant target. The examiner moves the patient's head quickly and unpredictably to 10 to 15 degrees of neck rotation. Normal response is marked when eyes remain on the target after the examiner's movement. Abnormal response includes when the Eyes are dragged off the target by the turning of the head, followed by a corrective saccade back to the target after the turning of head [14]
3. **Romberg test on foam with eyes closed /The Clinical Test of Sensory Interaction and Balance (CTSIB).** The test involves the subject to stand on the floor and then a foam surface with eyes open, then eyes closed and then wearing a visual conflict

dome. The length of time the subject maintains balance is recorded. Inability to maintain balance in more than one condition point towards peripheral or central cause of imbalance [15].

4. **Timed up & go test.** Patient is made to get up from the chair, walk for 3 meters which will be marked by the examiner prior & then turn around & trace his steps back to the chair. This total time taken to get up, walk, turn & reach back to the chair is noted [16].

Further, in all patients to rule out the other causes of dizziness the following Hematological & biochemical tests are done:

1. Complete hemogram: To rule out anemia & any acute infections.
2. TSH: to rule out thyroid disorders.
3. FBS: To rule out diabetes mellitus.
4. Blood pressure check after 10 mins of resting, to rule out Hypertension.

Those found to be having anemia, thyroid disorders, diabetes and hypertension are excluded from the study.

Patients are further given a questionnaire, Dizziness handicap inventory (DHI) to assess the severity & degree of handicap due to vestibular dysfunction.

- **Dizziness handicap inventory (DHI)** [17]**:** It is a standard questionnaire to quantify the degree of handicap in the daily lives of patients with vestibular disorders. It consists of 25 questions. The total score ranges from 0 (no disability) to 100 (severe disability).

Serum zinc levels was assessed by colorimeter method, micronutrients like magnesium, calcium & Serum vitamin B12 & vitamin D were also assessed in individuals with vestibular disorders & comparative group.

Statistical Tests:

The data were entered in MS excel 2019 and SPSS Version 22 was used for analysis of data. The outcome variables namely DHI, Serum zinc levels, were summarized using mean (SD). Serum zinc levels in individuals with VD & without VD will be compared using t' test of Mann Whitney U test. Pearson / Spearman correlation was used to assess the correlation between DHI scores & S.zinc levels. p value < 0.05 was considered statistically significant.

Results:

Parameters compared between study & comparative group is summarized in table 1, thyroid profile, hematological profile & BP readings in both the groups show no significant difference. Table 2 shows micro nutrients levels in study & comparative group, Zinc levels were significantly($p<0.001$) reduced in study group when compared to comparative group. Serum zinc levels were corelated with the severity of the vestibular dysfunction, ($r=0.89$, $p<0.00$) which shows that more severe the dysfunction lesser the serum zinc levels. Depicted in FIG 1. DHI scores & their correlation with zinc levels are summarized in Table 4.

Table 1: Various parameters compared in both the groups

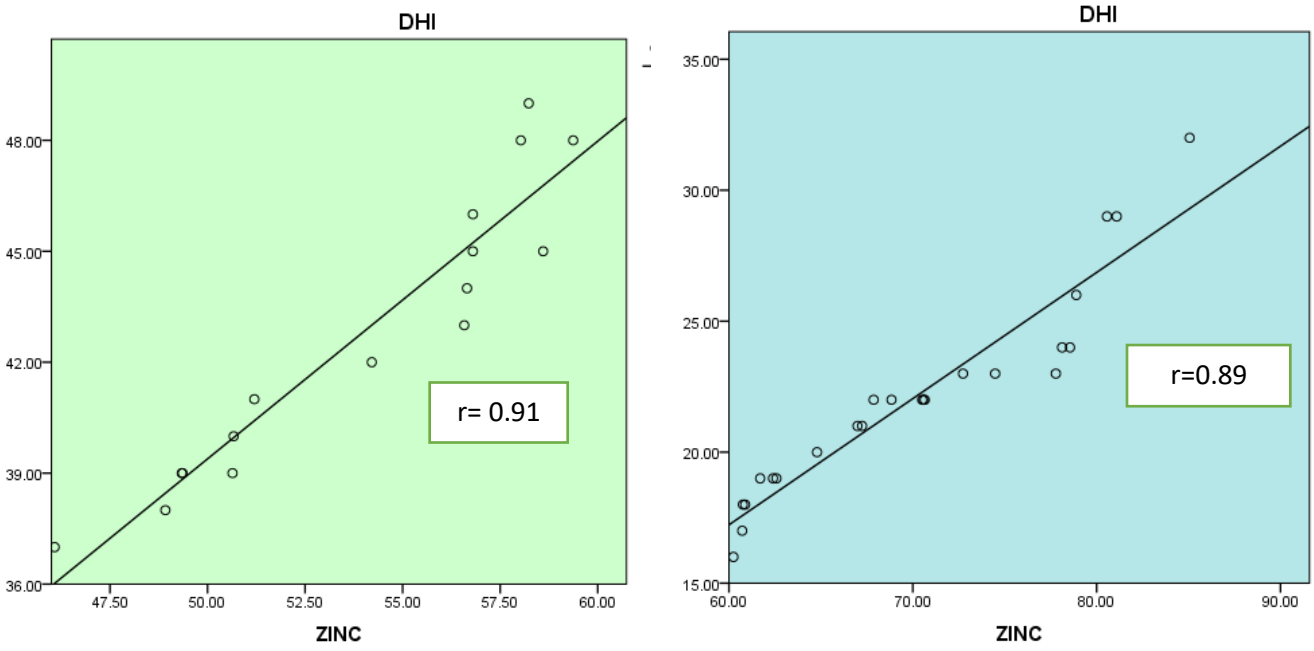
Parameter	Study group (Mean & SD)	Comparative group (Mean & SD)	T value	P value
Age (in years)	35.5± 6.76	36.2±7.92	0.454	0.6505
FBS (mg/dl)	95.03 ± 8.33	95.45 ±9.09	0.681	0.4980
HbA1c	5.53 ±0.325	5.44 ±0.280	1.2412	0.2188
TSH (µIU/ml)	1.91±0.876	1.86±0.823	0.3538	0.7244
SBP (mmHg)	122.85±9.71	124.84±5.87	1.1092	0.2707
DBP (mmHg)	79.17±7.28	79.37±7.07	0.1246	0.9011
HB (g/dl)	13.1±1.35	13.8±2.34	1.6388	0.700
RBC millions/cumm	4.65±0.420	4.79±0.50	1.3560	0.1790
WBC Cells/cumm	6673.2±1905.29	6163.93±2176.3	1.1136	0.2689
Platelet count Cells/cumm	2.75±0.44	3.10±0.70	2.6773	0.009
ESR (mm/hr)	13.1±10.31	12.01±10.11	0.4774	0.6344

Table 2: Micronutrients in both the groups

	Study group (Mean & SD)	Comparative group (Mean & SD)	T value	P value
S. zinc	**60.63**±10.10	**70.50**±19.1	**2.889**	**0.004** *
S. Magnesium	**2.13**±0.34	**2.27**±0.19	**2.768**	**0.022**
Vitamin D	**22.53**±**12.2**	**16.86**±7.43	**2.923**	**0.014**
Vitamin B12	**216.38**±158.10	**198.3**±87.8	**0.6323**	**0.529**
Folic acid	**10.60**±5.59	**8.78**±6.43	**1.3510**	**0.1806**

Table 3: DHI scores in study group

DHI scores		Number of subjects
Mild Handicap	22.12±3.74	24
Moderate Handicap	42.14±3.53	16



A (MILD) B (MODERATE)

Fig 1: Correlation of s. Zinc levels with severity of vestibular dysfunction

Table 4: Serum zinc levels in Mild & moderate severity of vestibular dysfunction.

Degree of handicap (DHI)	MILD	MODERATE	t value	P value
SERUM ZINC (µg/dl)	51.5 ± 2.00	49.42 ± 2.59	3.760	0.0004*

Table 5: Cognition Tests Scores Comparison Between study group & comparative

Cognition test	Study (n=40)	Comparative (n=40)	T VALUE	P value
Trail making test –A	110.85 ± 5.27	50.91±13.69	24.1736	0.000*
Trail making test –B	288.57± 12.32	192.62 ± 39.18	13.821	0.000*
DSST	21.57 ± 3.83	40.37 ± 7.96	12.59	0.000*

Discussion

This research study was aimed to assess serum zinc levels in patients with vestibular dysfunction & to corelate zinc levels with the severity of the dysfunction

The key points from the results we obtained are

1. Serum zinc levels in patient with vestibular dysfunction is significantly lower when compared with age matched comparative group.
2. As the severity of vestibular dysfunction increases, serum zinc levels significantly decrease.

LET US UNDERSTAND THE ROLE OF ZINC IN CNS

The exact role played by zinc in CNS is poorly understood, Zinc is hypothesized to affect glutamatergic synapses because it inhibits the binding of glutamate to its receptors [18]. Many authors have linked zinc physiology to the early onset of tinnitus[19,20]. Systemic zinc administration has been proposed as an alternative treatment for this condition [21]. Zinc also plays an essential role in the production of carbonic anhydrase, a protein that eliminates free radicals from the cochlear vascular stria[22]. Hypozincemia could impact this enzyme's role in carbon dioxide metabolism in the cochlea.

Changes in zinc content may have an impact on hair cell structure and function. These authors demonstrated that administering ototoxic doses of gentamicin produces impaired hearing, a large rise in peri lymphatic zinc concentration, and a drop in serum zinc levels [23].

Glutamate and GABA are two neurotransmitters that regulate afferent and efferent vestibular terminals, as well as synapses between the vestibular nerve and the vestibular nucleus [24]. Since zinc has been consistently detected in glutamatergic synapses, these synapses have been labelled as gluzinergic synapses[25]. Additionally, zinc modulates GABAergic and glutamatergic synapses.

Especially when zinc levels are low glutamate secretion across the synapse increases it may be due to two reasons

- Due to enhanced activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased corticosterone levels, under zinc-deficient or stressful conditions, cortisol/corticosterone may mediate the inhibition of glutamate transporter action, resulting in an accumulation of excess glutamate.[26]
- By interfering with NMDA receptors, zinc hinders the glutamate response When zinc levels are low, this inhibitory action is eliminated, leading to prolonged intracellular Ca2+ release and excitotoxic damage. [27] (Fig 2)

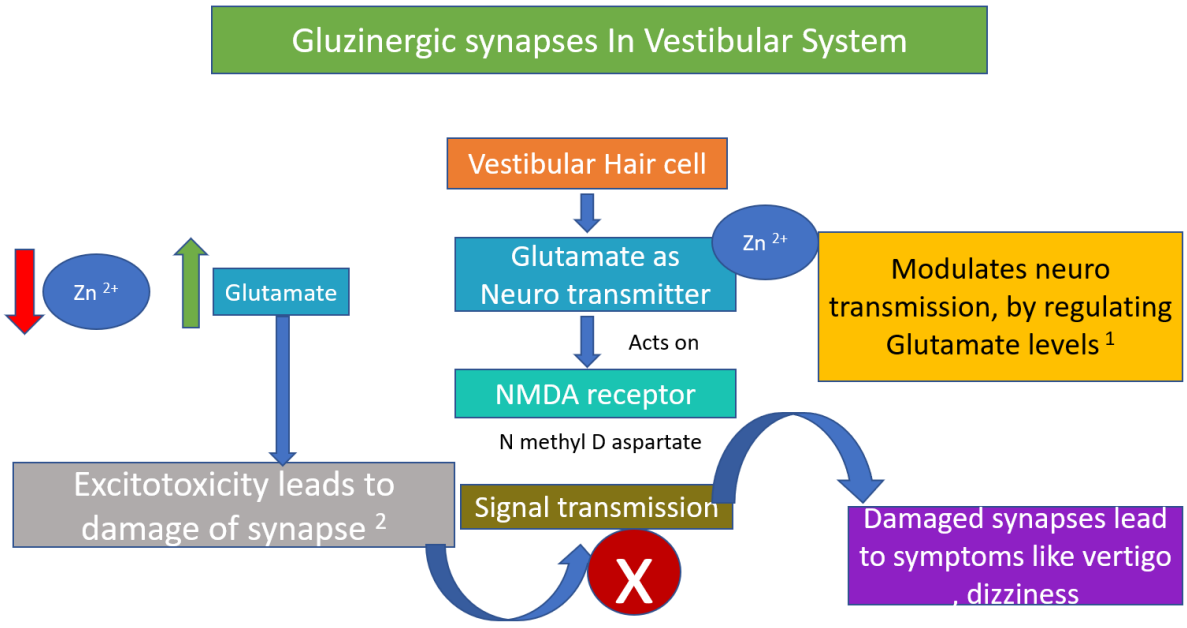


Fig 2: Events following zinc deficiency in gluzinergic synapse

In the present study, patients with vestibular dysfunction were identified by routine bedside clinical testing [28]. Following this, all other potential causes of giddiness, such as acute ear infections, diabetes, hypertension, thyroid problems, and severe anemia, were ruled out by biochemical, hematological & clinical examination.

We further ensured that the patient's giddiness was not the result of a micronutrient deficit by conducting folic acid, magnesium, vitamin B12, and vitamin D assays. The vitamin B12 and D levels in the study group were found to be higher than the desirable values when compared to the comparative group that did not have vestibular dysfunction (table 2). This observation may be explained by the fact that patients who experience vertigo or dizziness typically visit a pharmacy and take multivitamin supplements on their own, which over time would have corrected any deficiencies.

So, plectrum to this, we can conclude that zinc may have an important part in the pathophysiology of vestibular dysfunction, but only theoretically. We need to still research at the molecular level to understand the exact mechanism involved, may be by detecting zinc levels in vestibular neurons in individuals with vestibular dysfunction would be relevant in future studies.

In this study we also assessed the cognitive functions in study subjects using Trail making test & Digit symbol substitution test which showed significant decline in cognitive functions in comparison with the comparative group.

In peripheral vestibular disorders like BPPV and Vestibular neuritis, there is no unequivocal evidence to identify the type of cognition affected (table 5) Studies have demonstrated poor performance on spatial memory & mental rotation tasks, driving difficulties, decreased numerical cognition & executive functions in peripheral vestibular disorder patients [29,30].

Conclusion

Role of zinc as an antioxidant is well established and deficiency of zinc is linked with the pathogenesis of various diseases. Since evidences suggest involvement of zinc in vestibular system, zinc supplementation in vestibular disorder patients can be considered as add on therapy, which might have a beneficial role with respect to cognitive function as well.

Conflict of interest: None

Financial disclosure: This project was funded by AIIMS, Bibinagar

References

1. Walter F Boron, Emile L Boulpaep. Medical Physiology. third edition. Philadelphia: Elsevier;2017
2. Pignatelli, M., Beyeler, A., and Leinekugel, X. (2012). Neural circuits underlying the generation of theta oscillations. J. Physiol. Paris 106, 81–92. Doi: 10.1016/j.jphysparis.2011.09.007
3. Angelaki, D. E., and Cullen, K. E. (2008). Vestibular system: the many facets of a multimodal sense. Annu. Rev. Neurosci. 31, 125–150. Doi: 10.1146/annurev.neuro.31.060407.125555
4. Neo, P., Carter, D., Zheng, Y., Smith, P., Darlington, C., and McNaughton, N. (2012). Septal elicitation of hippocampal theta rhythm did not repair cognitive and emotional deficits resulting from vestibular lesions. Hippocampus 22, 1176–1187. Doi: 10.1002/hipo.20963
5. Oteiza PI. Zinc and the modulation of redox homeostasis. Free Radic Biol Med. 2012;53(9):1748-1759. Doi:10.1016/j.freeradbiomed.2012.08.568
6. Gustavo Duarte Paiva Ferreira, Maria Cristina Lancia Cury, José Antônio de Oliveira, Alessandra Kerli Manfredi, Hélio Vannucchi, Vestibular Evaluation Using Videonystagmography of Chronic Zinc Deficient Patients Due to Short Bowell Syndrome,Brazilian Journal of Otorhinolaryngology,Volume 75, Issue 2,2009,Pages 290-294,
7. Person O.C. Avaliação dos Potenciais Evocados Auditivos de Tronco Cerebral em Portadores de Tinnitus antes e após Tratamento com Administração Sistêmica de Compostos com Zinco [Dissertação]. Ribeirão Preto (SP): Universidade de São Paulo 2003.
8. MK Christensen, FA Geneser Distribution of neurons of origin of zinc-containing projections in the amygdala of the rat.Anat Embryol., 191 (Pt. 3) (1995), pp. 227-237
9. GABA receptor subunit in the rat hippocampus: Imunocytochemical distribution of 13 subunits.Neuroscience, 80 (1997), pp. 897-1000
10. Bhatnagar S, Taneja S. Zinc and cognitive development. Br J Nutr. 2001 May;85 Suppl 2:S139-45. Doi: 10.1079/bjn2000306. PMID: 11509102.
11. Warthon-Medina, M., Moran, V., Stammers, AL. et al. Zinc intake, status and indices of cognitive function in adults and children: a systematic review and meta-analysis. Eur J Clin Nutr **69**, 649–661 (2015). https://doi.org/10.1038/ejcn.2015.60.
12. Sugaya, N., Arai, M. & Goto, F. Changes in cognitive function in patients with intractable dizziness following vestibular rehabilitation. Sci Rep 8, 9984 (2018). https://doi.org/10.1038/s41598-018-28350-9
13. Hain TC, Cherchi M (2021) Vestibular Testing. Continuum. Neurology. 331-337
14. I.S. Curthoys & L. Manzari (2017) Clinical application of the head impulse test of semicircular canal function, Hearing, Balance and Communication.15:3, 113-26 DOI: 10.1080/21695717.2017.1353774
15. Cohen H. S. (2019). A review on screening tests for vestibular disorders. Journal of neurophysiology, 122(1), 81–92. https://doi.org/10.1152/jn.00819.2018
16. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Physical therapy. 2000 Sep 1;80(9):896-903
17. Jacobson, G. P. & Newman, C. W. The development of the Dizziness Handicap Inventory. Arch. Otolaryngol. Head Neck Surg. 116, 424–427 (1990).
18. Frederickson CJ, et al. Zinc - containing fiber system in the cochlear nuclei of the rat and mouse. Hearing Research. 1998;36:203–212.
19. Peters S, Koh J, Choi DW. Zinc selectively blocks the action of N-Metil-D-Aspartate on cortical neurons. Science. 1987;236:589–593
20. Rubio ME, Juiz JM. Chemical anatomy of excitatory endings in the dorsal cochlear nucleus of the rat: differential synaptic distribution of aspartat amins transferase glutamate and vesicular zinc. J Comp Neurol. 1998;339:341–358
21. Gersdorff M, et al. A clinical correlation between hypozincemia and tinnitus. Arch Otorhinolaringol. 1987;244:190–193.
22. Hewett ED, Tashian RE. Functional diversity conservation and convergence in the evolution of the alfa beta and gama-carbonic anhydrase gen families mol. Phylogenet Evol. 1996;5:50–77.
23. Min X, Yuling F, Zhengzhong G, Jie C, Jianzhong L. Hearing loss and trace elements Fe2 and Zn2 in the perilymph and related specialties. J Oto Rhino Laryngol. 1995;57:245–249.
24. Smart TG, Xie X, Krishek BJ. Modulation of inhibitory and excitatory amino acid receptor ion channels by zinc. Prog Neurobiol. 1994;42:393–441.
25. Christensen MK, Geneser FA. Distribution of neurons of origin of zinc-containing projections in the amygdala of the rat. Anat Embryol. 1995;191(Pt. 3):227–237

26. Takeda A., Tamano H., Itoh H., Oku N. Attenuation of abnormal glutamate release in zinc deficiency by zinc and Yokukansan. Neurochem. Int. 2008;**53**(6-8):230–5. Doi: 10.1016/j.neuint.2008.07.009.
27. Grønli O., Kvamme J.M., Friborg O., Wynn R. Zinc deficiency is common in several psychiatric disorders. PLoS One. 2013;**8**(12):e82793. Doi: 10.1371/journal.pone.0082793.
28. Tarnutzer AA, Dieterich M. Bedside examination of the vestibular and ocular motor system in patients with acute vertigo or dizziness. Clinical and Translational Neuroscience. 2019;3(2). Doi:10.1177/2514183X19886158
29. Gallardo-Flores, MA . Spatial memory deficits in patients with Meniere's disease. Neuroscience. (2022) 10:95–101. Doi: 10.11648/j.ajpn.20221003.13
30. Eraslan Boz, H , Kırkım, G , Koçoğlu, K , Çakır Çetin, A , Akkoyun, M , Güneri, EA, et al. Cognitive function in Meniere's disease. Psychol Health Med. (2023) 28:1076–86. Doi: 10.1080/13548506.2022.2144637