

TITLE: CEREBRAL SMALL VESSEL DISEASE – A LONGITUDINAL 10 YEARS EVIDENCED STUDY

ABSTRACT

A Cluster of geriatric health issues which can lead to many neurodegenerative disorders including Parkinson's disease, Alzheimer's, and dementia. All these carry along with it a potential decline in quality of life, health care expenses; a larger amount of disability. An early identification of risk factors, along with treatment using due medication coupled with non – pharmacological treatment using physiotherapy were analyzed with evidence in a Ten year follow up of a subject with cerebral small vessel disease. Outcome of the research can be beneficial for geriatric subjects and to further the continuation of the findings of the research.

Cerebral small vessel diseases, with risk arising from ageing, hypertension, and diabetes can better be medically diagnosed treated and duly followed up as it could lead to cognitive decline, dementia, falls physical dysfunctions resulting physical and psychological challenges lowering an elderly subjects quality of life. A holistic intervention, including regular physiotherapy can do a larger extent can minimize progression CSVD as well be beneficial by maximizing functional independence among the subjects.

INTRODUCTION

There is an increasing longevity found to be associated with various health ailments, especially geriatric subjects vulnerable to psychosocial, physical, financial issues leading to a diminished dignity, larger dependence and different degrees of disabilities. Systemic illnesses like hypertension, diabetes, atherosclerosis, can along with genetic factors play a vital role in global geriatric subjects developing neurodegenerative disorders like stroke, parkinsons disease, cognitive decline, psychiatric disorders, Alzheimer's. These neuro ailments are found to be linked with long term health care affecting subjects, families, and society. Early identification of risk factors and treatment of that were to be more focused medically. Another key

factor from literature recorded was an early onset of these said risk factors can more be critical on living days of affected subject.

One among the pathological manifestations of neurodegenerative disorders was vertigo, cerebral small vessel disease especially among subjects above 60 years. This research where non - pharmacological ways with specific physiotherapy were discussed using evidence on geriatric females on a longitudinal analysis from 2011 - 2021.

CSVD Accounts for 25% of strokes and contributes for future risks of stroke and dementia ward low et al 2019,increasing burden on society .Futures CSVD were found to be associated with increased mortality independent of gender and preexisting vascular risk factor (*Ayn et al 2008*) Genetic ,environmental cultural factors were linked to cognitive decline increasing risk for SVD (*ling et al 2020*) Low vitamin B 12 (*Devakumar 2019*) age ,hypertension ,diabetes mellitus were shown to be known risk factors for CSVD (*Gasser et al 2015*)

Katz index was validated in the assessment with optimal reliability among subjects with or without cognitive decline (*Rebustive et al 2015*)

While neuro imaging studies demonstrate higher cortisol levels in neural activity as diffuse white matter hypertension intensity were related to atrophy, cognitive decline, dementia (*Ungvari et al 2021*).

Features of vascular parkinsonism like bradykinesia,rigidity, gait disturbances were associated with CVSD (*Van der holst et al 2015*)

Annual plaited dizziness (*Ahmad et al 2015*),gait ,balance dysfunction (*De Laat et al 2010*),falls were also recorded among CVSD subjects .

Holistic approach in effective assessment any clinical management of patients him CSVD including experts in stroke neurology ,cognitive ,physical dysfunction ,life style intervention and pharmacological treatment were emphasized for CSVD by Clancy et al 2020 ,as this being common global brain disease mat causes cognitive impairment ,ischemic or hemorrhagic stroke ,problems with mobility ,neuropsychiatric symptoms with focal white and deep gray matter lesion in NMRI.

Cerebral small Vessel Disease (CSVD) Accounts for 25% of strokes and contributes for future risks of stroke and dementia (*Wardlow et al 2019*), increasing burden on society. CSVD were found to be associated with increased mortality independent of gender and preexisting vascular risk factor (*Ayn et al 2008*) Genetic ,environmental cultural factors were linked to cognitive decline increasing risk for SVD (*ling et al 2020*) Low vitamin B 12 (*Devakumar 2019*) age ,hypertension ,diabetes mellitus were shown to be known risk factors for CSVD (*Gasser et al 2015*).

Katz index was validated in the assessment with optimal reliability among subjects with or without cognitive decline (*Rebustive et al 2015*).

While neuro imaging studies demonstrate higher cortisol levels in neural activity as diffuse white matter hypertension intensity were related to atrophy, cognitive decline ,dementia (*Ungvari et al 2021*).

Features of vascular Parkinsonism like bradykinesia, rigidity, gait disturbances were associated with CVSD (*Van der holst et al 2015*)

Unexplained dizziness (*Ahmad et al 2015*), Gait , balance dysfunction (*De Laat et al 2010*),falls were also recorded among CVSD subjects.

Holistic approach in effective assessment any clinical management of patients with CSVD including experts in stroke neurology ,cognitive ,physical dysfunction ,life style intervention and pharmacological treatment were emphasized for CSVD by Clancy et al 2020 ,as this being common global brain disease that causes cognitive impairment ,ischemic or hemorrhagic stroke ,problems with mobility ,neuropsychiatric symptoms with focal white and deep gray matter lesion in NMRI.

KEY WORDS:

CSVD - Cerebral small vessel disease, QOL - Quality of life, ADL - Activities of daily living, NPRS - Numerical pain rating scale

AIMS AND OBJECTIVES:

1. To understand the pathogenesis of vertigo
2. To find the role of physiotherapy as a prophylactic therapeutics.

MATERIALS AND METHODOLOGY:

BACKGROUND INFORMATION:

Mrs. XXX aged 78 years, known hypertensive on Amlodipine 10mg for twenty years, Type 2 diabetes for 15 years taking Glycomet 500 SR, had hysterectomy at her age of 43 years, mother of two female adults, literate and retired as a Tamil Nadu State Government official, India.

Physical examination as on 2011: BMI - 29 kg/m²

Waist circumference - 98 cm, Blood pressure in sitting - 150/93 mm/Hg

Previous medical treatment for chronic neck pain with vertigo was treated by physician tablet Vertin and NSAID since 2010.

INVESTIGATION:

YEAR	HbA1c
2011	6
2013	7.5
2021	7

NMRI in 2011 has revealed cortical atrophy, small vessel disease with white matter hyperintensity of Fazekas Grade I.

COMPLAINTS OF THE SUBJECT:

Neck pain, vertigo, unexplained dizziness, fatigue, stiff shoulders, occasional low back and knee pain.

MAJOR MEDICAL CONDITIONS:

- a. Hysterectomy at her age of 45
- b. Covid 19 tested positive in July 2020, has recovered with due medical treatment, but in December 2021 had hypertonicity of both extremities with mild rigidity, was treated by physician with tablet pre Gabapentin.
- c. Hypertensive for 20 years

- d. Diabetic for 15 years
- e. Having CSVD since 2011

ON EXAMINATION:

- Peripheral joints nil deficit restricted end range movements
- Cervical and shoulders movements painful and mild restricted
- ADL - Independent reasonably
- Gait - Ambulant and functionally independent to a larger extent

Last decade she has made adequate life style changes with regular walking, good sleeping pattern, along with regular adherence to specific physiotherapy.

PROCEDURE:

This Research was carried in longitudinal means from May 2011 to 2021 December with weekly twice physiotherapy sessions for 25-30 minutes at an exercise intensity of 60-70% of her maximal heart rate.

Cervical spine strengthening, shoulder bracing, core strengthening and inversion therapy were carried in sitting, standing, supine, side and prone positions. A set of 15 exercises were used with 5-6 repetitions. Gadgets including physio ball, tera band were used. With no untoward incidents she was regularly treated during this period.

Pain, activities of daily living were taken in 2011 and 2021 were analysed and presented with due literature evidence as below:

CLINICAL PROGNOSIS AND RESULTS:

Major functional problems faced by this research subject were neck pain, dizziness who has retired from Government service, being the mother of two adult girls becoming a widow at the age of 76 years.

She was treated for hypertension and diabetes, but mesomorph. She was infected with SARS Covid 19, developed cerebral hypoxia, and was medically treated.

Along with medication for Hypertension and Diabetes Mellitus, she was regularly treated with twice a week with physiotherapy and her functional prognosis were analyzed along with from 2011 till December 2021.

She is functionally independent for ADL, daily care, and financial needs.

Pain, stiffness of shoulders, knee pain (Right) with occasional dizziness recorded.

Cognitively doing good as she was found to live independently living with a good life style.

TABLE OF RESULTS ON NPRS,HbA1c, KATZ, FAZEKELS SCALE

YEARS	SCALES ON NPRS	HbA1c	KATZ INDEX ON ADL %	FAZEKELS SCALE ON CSVD
2011	8	6	69	Grade I as on 2011
2021	2	7	83	
PROGNOSIS	Has not taken MRI			

DISCUSSION

Critical Research Questions arising:

I. Does Vertigo give a clue for SVD

Vertigo was thought to be related to cardiovascular predictor; Few researchers have related dizziness among elders with CSVD leading to neurodegenerative disorders.

Toker et al 2008 in a systematic review from 1,506 citations and 5 studies vertigo could be a predictor for cardiovascular diagnosis. Whereas this research does not give any known history or complaints of cardiac ailment, but a hypertensive and on medication. Further *Fatahzadehet al 2006* in clinical classification of including stroke and Transient ischemic attack to be cardiovascular diseases, which supports this subject having had the single - vessel disease as shown in her NMRI with vertigo for which she was treated but SVD was not treated with medication.

Cerchiali et al 2017 with ENT and Neurological experts from Italy have shown a link between cerebral small vessel white matter disease with Dizziness among geriatric subjects. SVD further can give rise to cognitive decline (*De Groot 2002*) dementia (*Tavera 2016*) and Falls (*Sibolt 2014*).

II. Role of physiotherapy here?

Karlberg et al 2004 theorized that parts of the vestibular system are differentially susceptible to global drops in pressure leading to ischemia (*Bolli et al 1989*). Further *Newman et al 2008* have added strength (this research subject having vertigo and cerebral ischemic changes) that a global reduction in blood pressure lead to local asymmetries in the vestibular system causing vertigo via a Transient ischemic attack type mechanism.

Tan et al 2017, recorded hypertension, diabetes mellitus and genetics to be associated with Arteriosclerosis, aging hence called hypertensive SVD (*TerTelgte 2018*).

An impaired auto regulation of involved small vessels results in reduced cerebral blood flow and chronic cerebral hypoperfusion.

Rigsby et al 2007 have noted in male hypertension rats spironolactone to improve the tone of the cerebral vasculature.

Rensma et al 2018 in a systematic review risk factors such as hypertension, diabetes mellitus, smoking, dyslipidemia, infection, heredity diseases, obesity, homocystenine concentration for CSVD.

Pantoni 2010 with neuro imaging of CSVD involving lacunar infarcts, subcortical infarct with micro bleeds, brain atrophy and enlarged perivascular spaces.

While research studies have identified hypertension and diabetes to be associated with CSVD, this research subject was hypertensive and a diabetic along with vertigo, and more vulnerable to developing ischemic changes of neurological higher centers.

Her NMRI revealed at her age of 60 years with vertigo has shown CSVD with cortical atrophy.

III. Is there a link with hypertension age?

Li et al 2018 have stated main clinical manifestations of CSVD include stroke, cognitive decline, dementia, psychiatric disorders, an abnormal gait and Urinary incontinence.

According to *Petty et al 2000*, 25% of all ischemic stroke from SVD, puts patients at twice the risk for SVD (*Warldlow et al, 2013*).

The leading cause of functional loss, cognitive decline and disability in elders.

Subtle gait and postural abnormalities were recorded among SVD subjects (*Ahmad et al, 2016*).

BPPV (*Bhattacharya et al 2017*) to be prevalent among 9 % of elders can reduce ADL and depression.

Vestibular rehabilitation programs were shown to be effective (*Herdman 2013*).

Gait and posture can get altered in CVSD which are physical components involved.

Pinkhardt et al 2014 recorded Occulomotor and cognitive functioning probably depend more on which fibers are hit by SVD than the amount of fibers affected.

White matter lesions burden positively correlates with age (*Okroglic et al 2013*) as SVD is linked with the development of geriatric syndrome (*Kuo et al 2004*).

Dizziness Handicap Inventory Questionnaire (*Jacobson et al 1990*).

SVD burden based on Fazekas scale (*Fazekas et al 1999*).

White matter hyper intensities on T2 weighted on MRI are the radiological expression of SVD and known marker of a higher risk cerebral, cerebellar and brainstem stroke (*Fazekas et al, 1993*).

Una et al 2021 on a holistic approach in the clinical management of CSVD.

This research subject was found to have in the last ten years independant for ADL, reasonable cognitive abilities going for regular walking for 30 minutes weekly five times.

Having been infected with SARS Covid -19, she has recovered with bilateral hypertonicity (could be cerebral hypoxia) but with good functional recovery. She was complaining of a stiff neck, shoulders which were treated with physiotherapy.

With regular adherence to specific physiotherapy findings of this longitudinal research can be vital for larger RCTs as a prophylactic therapy for CSVD.

With infrequent complaints with of knee pain, LBA was treated with specific physiotherapy and VD3 supplements.

As shown in the table of results, NPRS reduced but glycemic control varied but remained functionally independent for all his daily activities, which were worth noting.

Cognitive decline and dementia were proven with cerebrovascular pathology on MRI findings to be associated with symptomatic stroke including silent stroke and markers of cerebral small vessel diseases especially among subjects with atrial fibrillation as evidence in a birth cohort researched by *Lira ryden et al 2021*. However this research subjects did not have any known atrial fibrillation

Hooper et al 2021 have recorded that preexisting CSVD as risk factor for poor clinical outcome and predictor for mortality in patients with asymptomatic ischemic stroke , despite successful recanalization with endovascular thrombectomy for large vessel occlusion , the probable reason could be pathological changes with chronic cerebral hypo perfusion and ischemia affecting small perforating cerebral arterials ,venules ad capillaries in CVD as recorded by *Streifer et al 2017* but this research findings where the subject was conservatively treated him holistic approach of meditation and physiotherapy and lifestyle modification.

Zhou et al 2021 among 158 CVD patients with mean age of 60 years measured with elevated serum cortisol level and concluded that cortisol can be a promising biomarker in CVD as cortisol is concerned with anxiety and depression. This research subject having lost her life partner recently could further increase with CVSD.

Lariza et al 2020 having carried out MRI among 96 CSVD Russian subjects of both sex above 60 years recorded heterogeneity of CVSD and variations in clinical manifestations observed in Fazekas stage 3 of this disease but this research subject had a fazekas stage 1.

CONCLUSION

Less focused was geriatric research, but as it necessitates their right to lead their life well, prophylactic means where especially with physiotherapy, a non – pharmacological means can along with due treatment with medication can be a boon in elderly care with an increasing elders worldwide, this unfocussed area of preventing neurodegenerative disorders gets more highlighted in this ten years of longitudinal follow up and Analysis with due evidence from 2011 – 2021.

Further studies on other measurable variables such as NMRI, specific parameters like gait, including other disciplines into the research are highly recommended.

AUTHOR CONTRIBUTION:

NAME OF THE AUTHOR: Dr S.S .Subramanian PhD ,

The principal , sree balaji college of physiotherapy ,
BIHER, Chennai, 600073 .

ORIGINAL RESEARCH ARTICLE

The author having treated this subject research continuously 10 years using non-pharmacological means using physiotherapy having conceived this manuscript and written with due scientific evidence.

Discloses no conflicts of interests towards publication.

ARTICLE INFORMATION: Single case experimental design

SPECIALITY: Field of Geriatrics and Physiotherapy

REFERENCES

1. Sofla, A. Y. N., Elzey, D. M., & Wadley, H. N. G. (2008). Cyclic degradation of antagonistic shape memory actuated structures. *Smart Materials and Structures*, 17(2), 025014.
2. Ling, Y., Xu, S. B., Lin, Y. X., Tian, D., Zhu, Z. Q., Dai, F. H., ... & Lu, H. Z. (2020). Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chinese medical journal*, 133(09), 1039-1043.
3. Devakumar D, Bhopal SS, Shannon G. COVID-19: the great unequaliser. *Journal of the Royal Society of Medicine*. 2020;113(6):234-235.
4. Gasser, P., Kirchner, K., & Passie, T. (2015). LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *Journal of Psychopharmacology*, 29(1), 57-68.
5. Erretti-Rebustini RE, Balbinotti MA, Jacob-Filho W, Rebustini F, Suemoto CK, Pasqualucci CA, Farfel JM, Leite RE, Grinberg LT, Nitrini R. Validity of the Katz Index to assess activities of daily living by informants in neuropathological studies. *Rev Esc Enferm USP*. 2015 Dec;49(6):946-52.
6. Ungvari Z, Toth P, Tarantini S, Prodan CI, Sorond F, Merkely B, Csiszar A. Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nat Rev Nephrol*. 2021 Oct;17(10):639-654.
7. Van der Holst, H. M. , van Uden, I. W. , Tuladhar, A. M. , de Laat, K. F. , van Norden, A. G. , Norris, D. G. , ... de Leeuw, F. E. (2016). Factors associated with 8-year mortality in older patients with cerebral small vessel disease: The Radboud University Nijmegen diffusion tensor and magnetic resonance cohort (RUN DMC) study. *JAMA Neurology*, 73(4), 402-409.
8. Ahmad H, Cerchiali N, Mancuso M, Casani AP, Bronstein AM. Are white matter abnormalities associated with "unexplained dizziness"? *J Neurol Sci*. 2015 Nov 15;358(1-2):428-31.
9. De Laat, K. F. , van Norden, A. G. , Gons, R. A. , van Oudheusden, L. J. , van Uden, I. W. , Bloem, B. R. , ... de Leeuw, F. E. (2010). Gait in elderly with cerebral small vessel disease. *Stroke*, 41(8), 1652-1658.
- 10.1161/STROKEAHA.110.583229

10. Clancy, U., Appleton, J. P., Arteaga, C., Doubal, F. N., Bath, P. M., & Wardlaw, J. M. (2020). Clinical management of cerebral small vessel disease: a call for a holistic approach. *Chinese medical journal*, 134(2), 127–142.
11. Newman-Toker, D. E., Hsieh, Y. H., Camargo, C. A., Jr, Pelletier, A. J., Butchy, G. T., & Edlow, J. A. (2008). Spectrum of dizziness visits to US emergency departments: cross-sectional analysis from a nationally representative sample. *Mayo Clinic proceedings*, 83(7), 765–775.
12. Fatahzadeh, M., & Glick, M. (2006). Stroke: epidemiology, classification, risk factors, complications, diagnosis, prevention, and medical and dental management. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*, 102(2), 180–191.
13. Cerchiai, N., Mancuso, M., Navari, E., Giannini, N., & Casani, A. P. (2017). Aging with Cerebral Small Vessel Disease and Dizziness: The Importance of Undiagnosed Peripheral Vestibular Disorders. *Frontiers in neurology*, 8, 241.
14. Jan Cees De Groot; Frank-Erik De Leeuw; Matthijs Oudkerk; Jan Van Gijn; Albert Hofman; Jellemer Jolles; Monique M. B. Breteler (2002). Periventricular cerebral white matter lesions predict rate of cognitive decline. , 52(3), 335–341.
15. Truswell, D. & Tavera, Y. An Electronic Resources Handbook for CNWL Memory Services. Dementia information for Black, Asian and minority ethnic (BAME) communities, Central and North West London NHS Foundation Trust, Feb. 2016.
16. Sibolt, G., Curtze, S., Melkas, S., Pohjasvaara, T., Kaste, M., Karhunen, P. J., Oksala, N. K., Strandberg, T., & Erkinjuntti, T. (2014). White matter lesions are associated with hospital admissions because of hip-fractures and trauma after ischemic stroke. *Stroke*, 45(10), 2948–2951.
17. Karlberg J, Chong DSY, Lai WYY (2004) Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? *Am J Epidemiol* 159:229–231.
18. Bolli R, Jeroudi MO, Patel BS, DuBose CM, Lai EK, Roberts R, McCay PB. Direct evidence that oxygen-derived free radicals contribute to postischemic

myocardial dysfunction in the intact dog. *Proc Natl Acad Sci U S A*. 1989 Jun;86(12):4695-9.

19. Tan, C. S., Hassali, M. A., Neoh, C. F., & Saleem, F. (2017). A qualitative exploration of hypertensive patients' perception towards quality use of medication and hypertension management at the community level. *Pharmacy practice*, 15(4), 1074.
20. TerTelgte, A., van Leijsen, E., Wiegertjes, K., Klijn, C., Tuladhar, A. M., & de Leeuw, F. E. (2018). Cerebral small vessel disease: from a focal to a global perspective. *Nature reviews. Neurology*, 14(7), 387–398.
21. Rigsby, C. S., Burch, A. E., Ogbi, S., Pollock, D. M., & Dorrance, A. M. (2007). Intact female stroke-prone hypertensive rats lack responsiveness to mineralocorticoid receptor antagonists. *American journal of physiology. Regulatory, integrative and comparative physiology*, 293(4), R1754–R1763.
22. Rensma, S. P., van Sloten, T. T., Launer, L. J., & Stehouwer, C. (2018). Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neuroscience and biobehavioral reviews*, 90, 164–173.
23. Pantoni L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet. Neurology*, 9(7), 689–701.
24. Li, Q., Yang, Y., Reis, C., Tao, T., Li, W., Li, X., & Zhang, J. H. (2018). Cerebral Small Vessel Disease. *Cell transplantation*, 27(12), 1711–1722.
25. Petty, G. W., Brown, R. D., Jr, Whisnant, J. P., Sicks, J. D., O'Fallon, W. M., & Wiebers, D. O. (2000). Ischemic stroke subtypes : a population-based study of functional outcome, survival, and recurrence. *Stroke*, 31(5), 1062–1068.
26. Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R. I., O'Brien, J. T., Barkhof, F., Benavente, O. R., Black, S. E., Brayne, C., Breteler, M., Chabriat, H., Decarli, C., de Leeuw, F. E., Doubal, F., Duering, M., Fox, N. C., Greenberg, S., ... STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1) (2013). *Neuroimaging*

standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet. Neurology*, 12(8), 822–838.

27. Zekri, Hamid; Mokhtari, Ahmad Reza; Cohen, David R. (2016). Application of singular value decomposition (SVD) and semi-discrete decomposition (SDD) techniques in clustering of geochemical data: an environmental study in central Iran. *Stochastic Environmental Research and Risk Assessment*, 30(7), 1947–1960.
28. Bhattacharyya, N., Gubbels, S. P., Schwartz, S. R., Edlow, J. A., El-Kashlan, H., Fife, T., Holmberg, J. M., Mahoney, K., Hollingsworth, D. B., Roberts, R., Seidman, M. D., Steiner, R. W., Do, B. T., Voelker, C. C., Waguespack, R. W., & Corrigan, M. D. (2017). Clinical Practice Guideline: Benign Paroxysmal Positional Vertigo (Update). *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, 156(3_suppl), S1–S47.
29. Hall, C. D., Herdman, S. J., Whitney, S. L., Cass, S. P., Clendaniel, R. A., Fife, T. D., Furman, J. M., Getchius, T. S., Goebel, J. A., Shepard, N. T., & Woodhouse, S. N. (2016). Vestibular Rehabilitation for Peripheral Vestibular Hypofunction: An Evidence-Based Clinical Practice Guideline: FROM THE AMERICAN PHYSICAL THERAPY ASSOCIATION NEUROLOGY SECTION. *Journal of neurologic physical therapy: JNPT*, 40(2), 124–155.
30. Pinkhardt, E. H., Issa, H., Gorges, M., Jürgens, R., Lulé, D., Heimrath, J., Müller, H. P., Ludolph, A. C., Becker, W., & Kassubek, J. (2014). Do eye movement impairments in patients with small vessel cerebrovascular disease depend on lesion load or on cognitive deficits? A video-oculographic and MRI study. *Journal of neurology*, 261(4), 791–803.
31. Okroglic, S., Widmann, C. N., Urbach, H., Scheltens, P., & Heneka, M. T. (2013). Clinical symptoms and risk factors in cerebral microangiopathy patients. *PloS one*, 8(2), e53455.
32. Hsu-KoKuo, Lewis A. Lipsitz, Cerebral White Matter Changes and Geriatric Syndromes: Is There a Link?, *The Journals of Gerontology: Series A*, Volume 59, Issue 8, August 2004, Pages M818–M826.

33. Jacobson, G. P., & Newman, C. W. (1990). The development of the Dizziness Handicap Inventory. *Archives of otolaryngology--head & neck surgery*, 116(4), 424-427.
34. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2-weighted MR images in patients with spontaneous intracerebral hemorrhage: Evidence of microangiopathy-related microbleeds. *AJNR Am J Neuroradiol*. 1999;20:637-42.
35. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*. 1993 Sep;43(9):1683-9.
36. Una, C., et al. (2021) Clinical management of cerebral small vessel disease: a call for a holistic approach. *Chinese Medical Journal*.
37. Lira-Junior, R., Boström, E. A., & Gustafsson, A. (2021). Periodontitis is associated to increased systemic inflammation in post myocardial infarction patients. *Open heart*, 8(2), e001674.
38. Hooper D, Nisar T, McCane D, Lee J, Ling KC, Vahidy F, Wong K, Wong S, Chiu D, Gadhia R. Severe Cerebral Small Vessel Disease Burden Is Associated With Poor Outcomes After Endovascular Thrombectomy in Acute Ischemic Stroke With Large Vessel Occlusion. *Cureus*. 2021 Feb 4;13(2):e13122.
39. Steiger, Nathan J.; Steig, Eric J.; Dee, Sylvia G.; Roe, Gerard H.; Hakim, Gregory J. (2017). Climate reconstruction using data assimilation of water isotope ratios from ice cores. *Journal of Geophysical Research: Atmospheres*, 122(3), 1545-1568.
40. Zhou, D., Dejnirattisai, W., Supasa, P., Liu, C., Mentzer, A. J., Ginn, H. M., ... & Sreaton, G. R. (2021). Evidence of escape of SARS-CoV-2 variant B. 1.351 from natural and vaccine-induced sera. *Cell*, 184(9), 2348-2361.
41. Dobrynina, L. A., Zabitova, M. R., Shabalina, A. A., Kremneva, E. I., Akhmetzyanov, B. M., Gadzhieva, Z. S., ... & Krotenkova, M. V. (2020). MRI types of cerebral small vessel disease and circulating markers of vascular wall damage. *Diagnostics*, 10(6), 354.

