

Cerebral Small Vessel Disease—A Longitudinal 10 Years Evidence 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 cerebralsmall 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 CSVDas well be beneficial by maximizing functional independence among the subjects.

Keywords: CSV: Cerebral small vessel disease; QOL: Quality of life; ADL: Activities of daily living; NPRS: Numerical pain rating scale.

1. 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 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 geriatrics subjects developing neurodegenerative disorders like stroke, parkinson's disease, cognitive decline, psychiatric disorders, Alzheimer's. These neuroailments are found to be linked with long term healthcare affecting subjects, families, and society [1-4]. Early identification of risk factors and treatment of those 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 subjects [5-9].

One among the pathological manifestations of neurodegenerative disorders was vertigo, cerebral small vessel disease especially among subjects above 60 years. This research wherein 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 Wardlow et al 2019, increasing burden on society. Future CSVD were found to be associated with increased mortality independent of gender and preexisting vascular risk factor [8]. Genetic, environmental cultural factors were linked to cognitive decline increasing risk for SVD [9]. Low vitamin B12 (Devakumar 2019) age, hypertension, diabetes mellitus were shown to be known risk factors for CSVD [10].

Katz index was validated in the assessment with optimal reliability among subjects with or without cognitive decline (Reductive 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 [11].

Features of vascular parkinsonism like bradykinesia, rigidity, gait disturbances were associated with CSVD (Vanderholst et al 2015).

Annual plaited dizziness [12], gait, balanced dysfunction [13], falls were also recorded among CVSD subjects.

Holistic approach 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 [13-16].

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Repeated above

1.1 AimsandObjectives

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

2. MATERIALSANDMETHODOLOGY

2.1 BackgroundInformation

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 - 29kg/m²

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

Previous medical treatment for chronic neck pain with vertigo was treated by physician in tablet Vertin and NSAIDs 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.

2.2 ComplaintsoftheSubject

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

2.3 MajorMedicalConditions

- 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 CVDs since 2011

2.4 OnExamination

- Peripheral joints nil deficit restricted and range movements
- Cervical and shoulder 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.

2.5 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, teraband 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:

3. CLINICALPROGNOSISANDRESULTS

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.

TableofResultsonNprs,Hba1c,Katz,Fazekels Scale

Years	ScalesonNPRS	Hba1c	Katzindexonadl%	Fazekelsscaleon csvd
2011	8	6	69	Gradelason2011
2021	2	7	83	

Prognosis Hasnot takenMRI

AlongwithmedicationforHypertensionandDiabetes Mellitus, she was regularly treated withtwiceaweekwithphysiotherapyandherfunction alprognosiswereanalyzedalongwithfrom2011tillDecember2021.

Sheisfunctionally independentforADL,dailycare, andfinancial needs.

Pain,stiffnessofshoulders,kneepain(Right)with occasionaldizziness recorded.

Cognitively doing good as she was found to liveindependentlyliving with a good lifestyle.

4. DISCUSSION

4.1 CriticalResearchQuestionsArising

4.1.1 DoesVertigogiveacluefor SVD

Vertigowasthoughttoberelatedtocardiovascular predictor; Few researchers have relateddizzinessamongelderswithCSVDleading to neurodegenerative disorders.

Toker et al [17] in a systematic review from 1,506citationsand5studiesvertigocouldbeapredictor for cardiovascular diagnosis. Whereas this research does not give any known history orcomplaints of cardiac ailment, but a hypertensiveand on medication. FurtherFatahzadehet al 2006in clinical classification of including stroke andTransient ischemic attack to be cardiovascular diseases, which supports this subject having hadthe single - vessel disease as shown in her NMRIwith vertigo for which she was treated but SVDwasnottreatedwithmedication.

Cerchiaietal[18]withENTandNeurologicalexpertsfromItaly have shown a linkbetweencerebral small vessel white matter disease withDizziness among geriatric subjects. SVD furthercan give rise to cognitive decline [19] dementia(Tavera2016) andFalls[20].

4.1.2 Roleofphysiotherapyhere?

Karlberg et al 2004 theorized that parts of thevestibularsystemaredifferentiellysusceptibleto

global drops in pressure leading to ischemia [21].Further Newman et al [17] have added strength(this research subject having vertigo and cerebralischemicchanges)thataglobalreductionin blood pressure lead to local asymmetries in thevestibular system causing vertigo via a Transientischemicattacktypemechanism.

Tan et al [22], recorded hypertension, diabetesmellitusandgeneticsto beassociatedwithA rteriosclerosis, aging hence called hypertensiveSVD[23].

Animpairedautoregulationofinvolvedsmallvessels resultsin reduced cerebralbloodflowandchronic cerebralhypoperfusion.

Rigsbyetal[24]havenotedinmalehypertension rats spironolactone to improve thetone ofthecerebral vasculature.

Rensma et al[25]in a systematic review riskfactors such as hypertension, diabetes mellitus,smoking,dyslipidemia,infection,hereditydi seases, obesity, homocysteine concentrationforCSVD.

Pantoni[26]withneuroimagingofCSVDinvolving lacunar infarcts, subcortical infarct withmicrobleeds,brainatrophyandenlargedperivas cularspaces.

Whileresearchstudieshaveidentifiedhypertension and diabetes to be associated withCSVD, this research subject was hypertensiveanddiabeticalongwithvertigo, andmorevulnerabletodevelopingischemicchangeeofne urologicalhighercenters.

Her NMRI revealed at her age of 60 years withvertigo hasshownCSVDwithcorticalatrophy.

4.1.3 Istherealinkwithhypertensionage?

Lietal[27]havestatedmainclinicalmanifestations of CSVD include stroke, cognitive decline, dementia,psychiatricdisorders,a nabnormalgaitand Urinaryincontinence.

According to Petty et al [28], 25% of all ischemicstroke from SVD, puts patients at twice the riskforSVD [29].

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 [30] 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 Oculomotor 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 [31] as SVD is linked with the development of geriatric syndrome (Kuo et al 2004).

Dizziness Handicap Inventory Questionnaire [32].

SVD burden based on Fazekas scale [33].

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 [34].

Una et al [35] on a holistic approach in the clinical management of CSVD.

This research subject was found to have in the last ten years independent 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 [36-38].

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

Within frequent complaints with of knee pain, LBA was treated with specific physiotherapy and VD3 supplements.

As shown in the table of results, NPSS 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 research by Lira ryden et al [39]. However this research subjects did not have any known atrial fibrillation.

Hooper et al [40] have recorded that preexisting CSVD as risk factor for poor clinical outcome and predictor of 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 arteries, venules and 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 [41] 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 gloster life partner recently could further increase with CSVD.

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.

5. CONCLUSION

Less focused was geriatric research, but 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 the ten years of longitudinal

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follow up and Analysis with due evidence from 2011–2021.

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

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written ethical approval has been collected and preserved by the author(s).

REFERENCES

Alphabetic ordering is advised

1. Clancy U, Appleton JP, Arteaga C, Doubal FN, Bath PM, Wardlaw JM. Clinical management of cerebral small vessel disease: a call for a holistic approach. *Chinese Medical Journal*. 2020;134(2):127–142.
2. Fatahzadeh M, Glick M. Stroke: epidemiology, classification, risk factors, complications, diagnosis, prevention, and medical and dental management. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2006;102(2):180–191.
3. Truswell ID, Tavera Y. An Electronic Resource Handbook for CNWL Memory Services. Dementia information for Black, Asian and minority ethnic (BAME) communities, Central and North West London NHS Foundation Trust; 2016.
4. Karlberg J, Chong DSY, Lai WYY. Do men have a higher case fatality rate of severe acute respiratory syndrome among women? *Am J Epidemiol*. 2004;159:229–231.
5. Devakumar D, Bhopal SS, Shannon G. COVID-19: the great unequaliser. *Journal of the Royal Society of Medicine*. 2020; 113(6):234–235.
6. Erretti-Rebustini RE, Balbinotti MA, Jacob-Filho W, Rebustini F, Suemoto CK, Pasqualucci CA, Farfel JM, Leite RE,
7. 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;49(6):946–52.
8. Van der Holst HM, van Uden IW, Tuladhar AM, de Laat KF, van Norden AG, Norris DG, de Leeuw FE. Factors associated with 8-year mortality in older patients with cerebral small vessel disease: The Radboud University Nijmegen diffusion tensor and magnetic resonance cohort (RUNDMC) study. *JAMA Neurology*. 2016;73(4):402–409.
9. Sofla AYN, Elzey DM, Wadley HNG. Cyclic degradation of antagonistic shape memory actuated structures. *Smart Materials and Structures*. 2008;17(2):025014.
10. Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, Lu HZ. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chinese Medical Journal*. 2020;133(09):1039–1043.
11. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with life-threatening disease: a qualitative study of acute and sustained subjective effects. *Journal of Psychopharmacology*. 2015;29(1):57–68.
12. 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;17(10):639–654.
13. Ahmad H, Cerchiai N, Mancuso M, Casani AP, Bronstein AM. Are white matter abnormalities associated with unexplained dizziness? *J Neurol Sci*. 2015;358(1–2):428–31.
14. De Laat KF, van Norden AG, Gons RA, van Oudheusden LJ, van Uden IW, Bloem BR, de Leeuw FE. Gait in elderly with cerebral small vessel disease. *Stroke*. 2010;41(8):1652–1658. DOI: 10.1161/STROKEAHA.110.583229
15. Zekri, Hamid; Mokhtari, Ahmad Reza; Cohen, David R. Application of singular value decomposition (SVD) and semi-discrete decomposition (SDD) techniques in clustering of geochemical data: a environmental study in central Iran. *Stochastic Environmental Research and Risk Assessment*. 2016;30(7):1947–1960.
16. Hall CD, Herdman SJ, Whitney SL, Cass SP, Clendaniel RA, Fife TD, Furman

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- for Peripheral Vestibular Hypofunction: An Evidence-Based Clinical Practice Guideline: From THE American Physical Therapy Association Neurology Section. *Journal of neurologic physical therapy: JNPT*. 2016;40(2):124–155.
16. Pinkhardt EH, Issa H, Gorges M, Jürgens R, Lulé D, Heimrath J, Müller HP, Ludolph AC, Becker W, Kassubek J. Do eye movement impairments in patients with small vessel cerebrovascular disease depend on lesion location or cognitive deficits? A video-oculographic and MRI study. *Journal of Neurology*. 2014;261(4):791–803.
 17. Newman-Toker DE, Hsieh YH, Camargo CA, Jr, Pelletier AJ, Butchy GT, Edlow JA. Spectrum of dizziness visits to US emergency departments: cross-sectional analysis from nationally representative sample. *Mayo Clinic Proceedings*. 2008;83(7):765–775.
 18. Cerchiai N, Mancuso M, Navari E, Giannini N, Casani AP. Aging with Cerebral Small Vessel Disease and Dizziness: The Importance of Undiagnosed Peripheral Vestibular Disorders. *Frontiers in Neurology*. 2017;8:241.
 19. Jan Cees De Groot; Frank-Erik De Leeuw; Matthijs Oudkerk; Jan Van Gijn; Albert Hofman; Jellemer Jolles; Monique M.B. Breteler. Periventricular Cerebral White Matter Lesions Predict Rate of Cognitive Decline. 2002;52(3):335–341.
 20. Sibolt G, Curtze S, Melkas S, Pohjasvaara T, Kaste M, Karhunen PJ, Oksala NK, Strandberg T, Erkinjuntti T. White matter lesions are associated with hospital admissions because of hip fractures and trauma after ischemic stroke. *Stroke*. 2014;45(10):2948–2951.
 21. Bolli R, Jeroudi MO, Patel BS, DuBose CM, Lai EK, Roberts R, McCay PB. Direct evidence that oxygen-derived free radicals contribute to post-ischemic myocardial dysfunction in the intact dog. *Proc Natl Acad Sci U S A*. 1989;86(12):4695–9.
 22. Tan CS, Hassali MA, Neoh CF, Saleem F. A qualitative exploration of hypertensive patients' perception towards quality use of medication and hypertension management at the community level. *Pharmacy Practice*. 2017;15(4):1074.
 23. Ter Telgte A, van Leijen E, Wiegertjes K, Klijn C, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. *Nature reviews Neurology*. 2018;14(7):387–398.
 24. Rigsby CS, Burch AE, Ogbu S, Pollock DM, Dorrance AM. Intact female stroke-prone hypertension rats lack responsiveness to mineralocorticoid receptor antagonists. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. 2007;293(4):R1754–R1763.
 25. Rensma SP, van Sloten TT, Launer LJ, Stehouwer C. 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*. 2018;90:164–173.
 26. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet. Neurology*. 2010;9(7):689–701.
 27. Li Q, Yang Y, Reis C, Tao T, Li W, Li X, Zhang JH. Cerebral Small Vessel Disease. *Cell Transplantation*. 2018;27(12):1711–1722.
 28. Petty GW, Brown RD, Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke*. 2000;31(5):1062–1068.
 29. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhoff F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Standards for Reporting Vascular Changes on EuroImaging (STRIVE) v1. Neuroimaging standards for research into small vessel disease and its contribution to aging and neurodegeneration. *The Lancet. Neurology*. 2013;12(8):822–838.
 30. Bhattacharyya N, Gubbels SP, Schwartz SR, Edlow JA, El-Kashlan H, Fife T, Holmberg JM, Mahoney K, Hollingsworth DB, Roberts R, Seidman MD, Steiner RW, DoBT, Voelker CC, Wagstaff RW, Corrigan MD. Clinical Practice Guideline: Benign Paroxysmal Positional Vertigo (Update). *Otolaryngology--Head and Neck Surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2017;156(3_suppl):S1–S47.

31. Okroglic S, Widmann CN, Urbach H, Schelten S P, Heneka M T. Clinical symptoms and risk factors in cerebral microangiopathy patients. *PLoS One*. 2013;8(2):e53455.
32. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Archives of Otolaryngology—Head & Neck Surgery*. 1990;116(4):424–427.
33. 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. *AJR Am J Neuroradiol*. 1999;20:637–42.
34. 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;43(9):1683–9.
35. Una, C., et al. Clinical management of cerebral small vessel disease: a call for a holistic approach. *Chinese Medical Journal*; 2021.
36. Hsu-Ko Kuo, Lewis A. Lipsitz, Cerebral White Matter Changes and Geriatric Syndromes: Is There a Link?, *The Journals of Gerontology: Series A*. 2004;59;8:M818–M826.
37. Steiger, Nathan J, Steig Eric J, Dee Sylvia G, Roe Gerard H, Hakim, Gregory J. Climate reconstruction using data assimilation of water isotope ratios from ice cores. *Journal of Geophysical Research: Atmospheres*. 2017;122(3):1545–1568.
38. Dobrynina LA, Zabitova MR, Shabalina AA, Kremneva EI, Akhmetzyanov BM, Gadzhieva Z S, Krotenkova MV. MRI types of cerebral small vessel disease and circulating markers of vascular wall damage. *Diagnostics*. 2020;10(6):354.
39. Lira-Junior R, Boström EA, Gustafsson A. Periodontitis is associated to increased systemic inflammation in post myocardial infarction patients. *Open Heart*. 2021;8(2):e001674.
40. Hooper D, Nisar T, McCane D, Lee J, Ling KC, Vahidy F, Wong K, Wong S, Chiu D, Gadhaia 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;13(2):e13122.
41. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, Scratton GR. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. *Cell*. 2021;184(9):2348–2361.

References:

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- Ahmad H, Cerchiai N, Mancuso M, Casani AP, Bronstein AM. Are white matter abnormalities associated with unexplained dizziness? *J Neurol Sci*. 2015;358(1-2):428-31.
- Bhattacharya N, Gubbels SP, Schwartz SR, Edlow JA, El-Kashlan H, Fife T, Holmberg JM, Mahoney K, Hollingsworth DB, Roberts R, Seidman MD, Steiner RW, DoBT, Voelker CC, Waguespack RW, Corrigan MD. Clinical Practice Guideline: Benign Paroxysmal Positional Vertigo (Update). *Otolaryngology--Head and Neck Surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2017;156(3_suppl):S1–S47.
- Bolli R, Jeroudi MO, Patel BS, DuBose CM, Lai EK, Roberts R, McCay PB. Direct evidence that oxygen-derived free radicals contribute to post-ischemic myocardial dysfunction in the intact dog. *Proc Natl Acad Sci U S A*. 1989;86(12):4695-9.
- Cerchiai N, Mancuso M, Navari E, Giannini N, Casani AP. Aging with Cerebral Small Vessel Disease and Dizziness: The Importance of Undiagnosed Peripheral Vestibular Disorders. *Frontiers in Neurology*. 2017;8:241.
- Clancy U, Appleton JP, Arteaga C, Doubal FN, Bath PM, Wardlaw JM. Clinical management of cerebral small vessel disease: a call for a holistic approach. *Chinese Medical Journal*. 2020;134(2):127–142.
- DeLaat KF, van Norden AG, Gons RA, van Oudheusden LJ, van Uden JW, Bloem BR, de Leeuw FE. Gait in elderly with cerebral small vessel disease. *Stroke*. 2010;41(8):1652–1658. DOI:10.1161/STROKEAHA.110.583229
- Devakumar D, Bhopal SS, Shannon G. COVID-19: the great unequaliser. *Journal of the Royal Society of Medicine*. 2020;113(6):234–235.
- Erretti-Rebustini RE, Balbinotti MA, Jacob-Filho W, Rebustini F, Suemoto CK, Pasqualucci CA, Farfel JM, Leite RE,
- Fatahzadeh M, Glick M. Stroke: epidemiology, classification, risk factors, complications, diagnosis, prevention, and medical and dental management. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2006;102(2):180–191.
- 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;43(9):1683–9.
- Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al. Histopathological analysis of foci of signal loss on gradient-echo T2-weighted MR images in patients with spontaneous intracerebral hemorrhage: Evidence of microangiopathy related for peripheral vestibular hypofunction: An Evidence-Based Clinical Practice Guideline: From THE American Physical Therapy Association Neurology Section. *Journal of Neurologic Physical Therapy: JNPT*. 2016;40(2):124–155.
- Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with life-threatening disease: a qualitative study of acute and sustained subjective effects. *Journal of Psychopharmacology*. 2015;29(1):57–68.

- Grinberg LT, Nitrini R. Validity of the KatzIndex to assess activities of daily living byinformantsinneuropathologicalstudies.RevEscEnfermUSP.2015;49(6):946-52.
13. Hall CD, Herdman SJ, Whitney SL, CassSP, Clendaniel RA, Fife TD, Furman JM,GetchiusTS,GoebelJA,ShepardNT,WoodhouseSN.VestibularRehabilitation
 14. Hsu-KoKuo,LewisA.Lipsitz,CerebralWhiteMatterChangesandGeriatricSyndromes: Is There a Link?, The Journalsof Gerontology:Series A.2004;59;8:M818–M826.
 15. JacobsonGP,NewmanCW.ThedevelopmentoftheDizzinessHandicapInventory. ArchivesofOtolaryngology--Head&NeckSurgery.1990;116(4):424–427.
 16. Jan Cees De Groot; Frank-Erik De Leeuw;MatthijsOudkerk;JanVanGijn;AlbertHofman;JellemerJolles;MoniqueM.B.Breteler. PeriventricularCerebralwhiteMatter Lesions Predict Rate of CognitiveDecline. 2002;52(3):335–341.
 17. Karlberg J, Chong DSY, Lai WYY. Do menhave a higher case fatality rate of severeacuterespiratorysyndromethanwomendo?AmJEpidemiol.2004;159:229–231.
 18. Li Q, Yang Y, Reis C, Tao T, Li W, Li X,ZhangJH.CerebralSmallVesselDisease.Cell Transplantation.2018;27(12):1711–1722.
 19. LingY, Xu SB, LinYX, Tian D,Zhu ZQ,Dai FH, Lu HZ. Persistence and clearanceofviralRNAin2019novelcoronavirusdiseaserehabilitationpatients. ChineseMedicalJournal.2020;133(09):1039-1043.
 20. Newman-TokerDE,HsiehYH,CamargoCA, Jr, Pelletier AJ, Butchy GT, Edlow JA.SpectrumofdizzinessvisitstoUSemergencydepartments:cross-sectionalanalysisfromanationallyrepresentativesample. MayoClinicProceedings.2008;83(7):765–775.
 21. OkroglicS,WidmannCN,UrbachH,ScheltensP,HenekaMT.Clinicalsymptomsandriskfactorsincerebralmicroangiopathy patients. PloSOne.2013;8(2):e53455.
 22. Pantoni L. Cerebral small vessel disease:frompathogenesisandclinicalcharacteristics to therapeuticchallenges. TheLancet.Neurology.2010;9(7):689–701.
 23. PettyGW,BrownRD,Jr,WhisnantJP,SicksJD,O'FallonWM,WiebersDO.Ischemic stroke subtypes : a population-basedstudyoffunctionaloutcome,survival, andrecurrence. Stroke.2000;31(5):1062–1068.
 24. Pinkhardt EH, Issa H, Gorges M, JürgensR, Lulé D, Heimrath J, Müller HP, LudolphAC,BeckerW,KassubekJ.Doeylementimpairmentsinpatientswithsmallvesselcerebrovasculardiseasedependonlesionloadoroncognitivedeficits?Avideo-oculographicandMRIstudy. Journal of Neurology.2014;261(4):791–803.
 25. RensmaSP,vanSlotenTT,LaunerLJ,StehouwerC.Cerebralsmallvesseldiseaseandriskofincidentstroke,dementiaanddepression,andal-causemortality: A systematic review and meta-analysis. NeuroscienceandBiobehavioralReviews. 2018;90:164–173.
 26. Rigsby CS, Burch AE, Ogbu S, Pollock DM,DorranceAM.Intactfemalestroke-pronehypertensiveratslackresponsivenessstomineralocorticoid receptorantagonists. Americanjournalofphysiology.Regulatory,IntegrativeandComparativePhysiology.2007;293(4):R1754–R1763.
 27. Sibolt G, Curtze S, Melkas S, PohjasvaaraT,KasteM,KarhunenPJ,OksalaNK,Strandberg T, ErkinjunttiT. White matterlesionsareassociatedwithhospitaladmissionsbecauseofhip-fracturesandtraumaafterischemicstroke. Stroke.2014;45(10):2948–2951.
 28. Sofla AYN, Elzey DM, Wadley HNG. Cyclicdegradation of antagonistic shape memoryactuatedstructures. SmartMaterialsandStructures.2008;17(2):025014.

29. Steiger, Nathan J, Steig Eric J, Dee SylviaG,RoeGerardH,Hakim,Gregory
30. Tan CS, Hassali MA, Neoh CF, Saleem F.A qualitative exploration of hypertensive patients' perception towards quality use of medication and hypertension management at the community level. *Pharmacy Practice.* 2017;15(4):1074.
31. Ter Telgte A, van Leijsen E, Wiegertjes K, Klijn C, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal

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- to a global perspective. *Nature Reviews Neurology*. 2018;14(7):387–398.
32. Truswell ID, 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; 2016.
 33. Una, C., et al. Clinical management of cerebral small vessel disease: a call for a holistic approach. *Chinese Medical Journal*; 2021.
 34. 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;17(10):639–654.
 35. Van der Holst HM, van Uden IW, Tuladhar AM, de Laat KF, van Norden AG, Norris DG, de Leeuw FE. Factors associated with 8-year mortality in older patients with cerebrovascular small vessel disease: The Radboud University Nijmegen diffusion tensor and magnetic resonance cohort (RUNDMC) study. *JAMA Neurology*. 2016;73(4):402–409.
 36. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S. Standards for Reporting Vascular Changes on Euroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet. Neurology*. 2013;12(8):822–838.
 37. Zekri, Hamid; Mokhtari, Ahmad Reza; Cohen, David R. 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*. 2016;30(7):1947–1960.
J. Climate reconstruction using data assimilation of water isotope ratios from ice cores. *Journal of Geophysical Research: Atmospheres*. 2017;122(3):1545–1568.
 38. Dobrynina LA, Zabitova MR, Shabalina AA, Kremneva EI, Akhmetzyanov BM, Gadzhieva ZS, Krotenko va MV. MRI types of cerebrovascular small vessel disease and circulating markers of vascular wall damage. *Diagnostics*. 2020;10(6):354.
 39. Lira-Junior R, Boström EA, Gustafsson A. Periodontitis is associated to increased systemic inflammation in post myocardial infarction patients. *Open Heart*. 2021;8(2):e001674.
 40. 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.
 41. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, Sreaton GR. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. *Cell*. 2021;184(9):2348–2361.