

International Neuropsychiatric Disease Journal

16(4): 1-8, 2021; Article no.INDJ.80507 ISSN: 2321-7235, NLM ID: 101632319

# Cerebral Small Vessel Disease – A Longitudinal 10 Years Evidenced Study

# S. S. Subramanian <sup>a\*≡</sup>

<sup>a</sup> Sree Balaji College of Physiotherapy, Constituent to Bharath Institute of Higher Education and Research Institute University, Chennai -73. India.

Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

### Article Information

DOI: 10.9734/INDJ/2021/v16i430184

**Open Peer Review History:** 

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/80507

Original Research Article

Received 20 October 2021 Accepted 23 December 2021 Published 26 December 2021

# 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.

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

<sup>■</sup> The Principal;

<sup>\*</sup>Corresponding author: E-mail: subramanian.sbcp@bharathuniv.ac.in, subramanian.podhigai1968@gmail.com;

#### **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 a diminished dignity, larger dependence and different degrees of disabilities. Systemic like hypertension, diabetes. illnesses 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 [1-4]. 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 5-9].

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 Genetic ,environmental cultural [8] linked to cognitive factors were decline increasing risk for SVD [9] Low vitamin B 12 (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 CVSD (Van der holst et al 2015).

Subramanian; INDJ, 16(4): 1-8, 2021; Article no.INDJ.80507

Annual plaited dizziness [12] gait, balance dysfunction [13], 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 [13-16].

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 [8] Genetic ,environmental cultural factors were linked to cognitive decline increasing risk for SVD [9] Low vitamin B 12 *(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 (*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 [11].

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 [13], 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.

Subramanian; INDJ, 16(4): 1-8, 2021; Article no.INDJ.80507

### 1.1 Aims and Objectives

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

#### 2. MATERIALS AND METHODOLOGY

#### 2.1 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/m<sup>2</sup>

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.

### 2.2 Complaints of the Subject

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

### 2.3 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

#### 2.4 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.

#### 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, 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:

### 3. 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.

#### 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			

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.

#### 4. DISCUSSION

#### 4.1 Critical Research Questions Arising

#### 4.1.1 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* [17] 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.

*Cerchiai et al* [18] 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 [19] dementia (Tavera 2016) and Falls [20].

#### 4.1.2 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 [21]. Further Newman et al [17] 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 [22], recorded hypertension, diabetes mellitus and genetics to be associated with Arteriosclerosis, aging hence called hypertensive SVD [23].

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

Rigsby et al [24] have noted in male hypertension rats spironolactone to improve the tone of the cerebral vasculature.

Rensma et al [25] in a systematic review risk factors such as hypertension, diabetes mellitus, smoking, dyslipidemia, infection, heredity diseases, obesity, homocystenine concentration for CSVD.

Pantoni [26] 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.

#### 4.1.3 Is there a link with hypertension age?

Li et al [27] 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 [28], 25% of all ischemic stroke from SVD, puts patients at twice the risk for SVD [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 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 [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 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 [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 for mortality in patients with asymptomatic ishemic 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 [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 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 heterogenecity 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 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.

## 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).

# **COMPETING INTERESTS**

Author has declared that no competing interests exist.

# REFERENCES

- 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.
- 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 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; 2016.
- 4. Karlberg J, Chong DSY, Lai WYY. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? 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.
- 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;49(6):946-52.

- 7. 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 (RUN DMC) study. JAMA Neurology. 2016;73(4):402–409.
- 8. Sofla AYN, Elzey DM, Wadley HNG. Cyclic degradation of antagonistic shape memory actuated structures. Smart Materials and Structures. 2008;17(2):025014.
- 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.
- Gasser P, Kirchner K, Passie T. LSDassisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. Journal of Psychopharmacology. 2015;29(1):57-68.
- 11. 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.
- 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.
- 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
- Zekri, Hamid; Mokhtari, Ahmad Reza; Cohen, David R. Application of singular value decomposition (SVD) and semidiscrete 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.
- Hall CD, Herdman SJ, Whitney SL, Cass SP, Clendaniel RA, Fife TD, Furman JM, Getchius TS, Goebel JA, Shepard NT, Woodhouse SN. 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. 2016;40(2):124–155.

- 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 load or on 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 a nationally representative sample. Mayo Clinic Proceedings. 2008;83(7):765–775.
- 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.
- 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.
- 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.
- 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;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. TerTelgte A, van Leijsen 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, Ogbi S, Pollock DM, Dorrance AM. Intact female stroke-prone hypertensive 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 metaanalysis. 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.
- Petty GW, Brown RD, Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes : a populationbased 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, 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 nEuroimaging (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.
- 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, Do BT, 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.

Subramanian; INDJ, 16(4): 1-8, 2021; Article no.INDJ.80507

- Okroglic S, Widmann CN, Urbach H, Scheltens P, Heneka MT. 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.
- Fazekas F, Kleinert R, Roob G, Kleinert G, 33. Schmidt Kapeller Ρ, R. et al. Histopathologic analysis of foci of signal loss on gradient-echo T2-weighted MR images in patients with spontaneous intracerebralhemorrhage: Evidence of microangiopathyrelated microbleeds. AJNR Am J Neuroradiol. 1999;20:637-42.
- 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-KoKuo, 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 usina data assimilation of water isotope ratios from ice cores. Journal of Geophysical Research: Atmospheres. 2017;122(3): 1545-1568.
- Dobrynina LA, Zabitova MR, Shabalina AA, Kremneva EI, Akhmetzyanov BM, Gadzhieva ZS, 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, 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.
- Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, Screaton GR. Evidence of escape of SARS-CoV-2 variant B. 1.351 from natural and vaccineinduced sera. Cell. 2021;184(9): 2348-2361.

© 2021 Subramanian; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history: The peer review history for this paper can be accessed here: https://www.sdiarticle5.com/review-history/80507