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Research Article

Phenotypic and Radiological Correlation of Clinical Presentation and Outcome of Patients with Cerebral Small Vessel Disease (CSVD)

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Abstract

Background: Cerebral small vessel disease (CSVD) is associated with two clinical subtypes; 1) acute stroke and 2) chronic progressive cognitive decline or gait disorder. Radiological markers of CSVD are; lacunar stroke, lacunes, white matter hyperintensity (WMH), enlarges perivascular spaces (EPVS), and cerebral microbleeds (CMBs).

Aims and Objectives: This study was aimed to find out the various clinical types of CSVD and association with demographic and radiological parameters.

Methods: all patients with acute stroke, progressive gait disorder or cognitive decline having CSVD changes on MRI were evaluated for various clinical, demographic and radiological parameters at admission and after 3 months. At the end of 3 months patient's quality of life, activity of daily living, cognitive scores and modified Rankin scores were calculated.

Results: Study performed on 80 patients of cerebral small vessels disease (CSVD) showed few interesting observations. In our cohort, chronic progressive disease was more frequent and was found in 45 (56.25%) patients and rest 35 (43.75%) presented as acute stroke. Among chronic progressive group, progressive cognitive decline was more frequent as compare to progressive gait abnormality (64% versus 36%).

Conclusions: The chronic progressive disease is commoner with progressive cognitive decline as most common type of CSVD. Poor control of hypertension, diabetes, drug compliance and quality of sleep were the most common risk factor found for worsening of CSVD patients. Radiological markers like worsening WMH, EPVS, and high total CSVD scores were associated with poor outcome and high dependency of patients at 3 months follow-up.

Keywords: Cerebral Small Vessel Disease (CSVD); White Matter Hyperintensity (WMH);

Introduction

According to CDC, 87% of stroke are of ischemic type and can be subclassified into three subtypes; lacunar, embolic and thrombotic. Lacunar stroke is most commonly associated with cerebral small vessel disease (CSVD) which is caused by different pathophysiological processes then large vessel stroke [1-6].

CSVD was considered to be slowly progressive insult of frontal-subcortical network, leading to problems in executive functions,

motor performance and mood regulation [1-6]. It has been seen that globally; but Chinese people have highest prevalence of CSVD [3-6].

CSVD is a heterogenous cerebrovascular disease characterized by a chronic progressive disorder of brain arterioles, capillaries and veins of 50-400 µm, supplying the white and deep grey matter characterized by diverse clinical picture and specific radiological and pathological biomarkers. CSVD is responsible for about 20% of stroke, 25% of ischemic stroke and 45% cases of vascular dementia [3-6].

Etiologically, CSVD can be divided in two major types; Genetic and Sporadic. 1) Genetic CSVD: Most common genetic form of CSVD is CADASIL, described first time by Van Bogaert in 1955 as familial form of Binswanger disease. Other genetic disorders are CARASIL (autosomal recessive), Fabry disease and HANAC (Hereditary Angiopathy with Nephropathy Aneurysms and Muscle cramps [3]. 2) Sporadic CSVD: There are two pathological subtypes of sporadic CSVD; 1) Amyloid form which is known as cerebral amyloid angiopathy (CAA) and 2) non-amyloid form which is related to risk factors like diabetes, hypertension, smoking, obstructive sleep apnoea, and chronic kidney disease [4-8]. Various vascular, genetic and inflammatory process shown to be important in causation of disease progression of CSVD [7-14].

Clinically, CSVD can be either silent (covert) or symptomatic (overt). Silent CSVD is a larger group of disorder which is 6-10 times more common than symptomatic stroke and about 25% people of age above 80 years found to have silent stroke and it was estimated that for each one symptomatic stroke over 10 asymptomatic cases. Subtle clinical presentation in CSVD can be of three types silent stroke, subtle neurological symptoms and stuttering TIA [3-6].

Symptomatic CSVD on the other hand can be of two types; 1) Acute CSVD and Chronic progressive CSVD. Acute CSVD further can be divided into acute ischemic CSVD and acute haemorrhagic (ICH) CSVD. Acute Ischemic CSVD: According to the classification of Oxfordshire Community Stroke Project, 5 common lacunar syndromes are; 1) pure motor stroke (PMS), which account for about 50-70% of LC; 2) pure sensory stroke (PSS); sensorimotor stroke (SMS); ataxic hemiparesis (AH) and Dysarthria-Clumsy hand syndrome (DCHS) [1-6,15-19].

Acute Haemorrhagic CSVD: Second acute CSVD presentation is associated with non-hypertensive intra cerebral hemorrhage (ICH) due to Cerebral Amyloid angiopathy (CAA). CAA is a form of CSVD is accounted for 2nd most common cause of ICH and is associated with recurrent ICH along with ischemic stroke and cognitive impairment. CAA might be genetic or sporadic form, which results in beta amyloid deposit in media and adventitia of small and medium-size vessels along with cortical vein. CAA account for about 30% of spontaneous ICH cases. Microscopically, the most common pathology is Lipohyalinosis and fibrohyalinosis with endothelial dysfunction. These two pathological processes can lead to BBB disruption and inflammatory response which results into a chronic progressive disease [1-6,15-19].

Chronic CSVD: Associated with either progressive cognitive impairment or progressive gait disorder. Vascular dementia with CSVD: It can range from mild cognitive impairment (MCI) to severe subcortical dementia. Progressive gait disorder with CSVD: Another chronic form of CSVD is progressive extrapyramidal syndrome with prominent gait and posture disorder, early symmetrical lower limb involvement, pseudobulbar involvement and sphincter dysfunction as well as depression. This condition was previously named as "lower body parkinsonism" and clinically mimic to normal pressure hydrocephalus (NPH). These syndromes are commonly associated with social withdrawal and repeated falls [1-6,20-22]. Treatment guideliens for both covert and overt types of CSVD are available for clinical practice [23,24].

There are 5 classical radiological markers of CSVD, which are lacunar stroke (LS) also known as recent small subcortical infarctions (RSSI) and lacunes, white matter hyperintensities (WMH), enlarged perivascular space (EPVS), cerebral microbleeds (CMBs) and cortical atrophy (CA) [1-3,15-17].

Recently, a "total CSVD score" term has been proposed which composite four established neuroimaging markers of CSVD, that is, WMH, lacunes, PVS, and CMB and estimate overall burden of CSVD. Total CVD burden of visually scored 0-4, based on radiological parameters [25].

The current study was aimed to find out the frequency of various clinical types of CSVD and association of various demographic and radiological parameters with the clinical type and outcome of patients of CSVD.

Methods

It was a cross- sectional follow up study on all patients presenting with Cerebral Small Vessel disease (CSVD). Sample size was calculated with standard formula considering the prevalence of CSVD of 5-10% and total sample size estimated was 80.

Patients Selection: All patients who presented with either acute lacunar stroke, progressive cognitive decline or progressive gait disorder and who had radiological changes of CSVD on MRI brain (according to Strive Criteria 2013) were included in the study.

Grouping of patients: After inclusion, the patients were classified in two categories on the basis of clinical presentation; Group1: Presentation as acute stroke; and 2) Presentation as chronic progressive CSVD. Group 1 patients were further divided in two subgroups; 1a: Acute ischemic lacunar stroke and 1b: Acute small cerebral hemorrhage. Likewise, patients of chronic progressive CSVD were also classified into two sub groups; 2a; who presented with progressive cognitive decline and 2b: who presented with progressive gait disorder.

Radiological parameters and Total CSVD score calculation: Total CSVD score was calculated as proposed by Staals., *et al*. (2014); one point was allocated to each of the following, 1) presence of lacunas; 2) presence of CMBs; 3) moderate to severe (>10) basal ganglia PVS; and 4) severe periventricular or moderate to severe deep white matter hyperintensity (WMH). Lacunes were defined as > 3 mm and < 20 mm rounded or ovoid lesion of CSF density on T2W & FLAIR image and no increased signals on DWI, in BG, internal capsule, centrum semiovale, or brain stem. CMBs were defined as rounded hypodense (black) lesion up to 10 mm in size on T2W, at least half surrounded by brain parenchyma, and distinct from other potential mimics like iron/calcium deposits or flow voids. PVS was defined as small (< 3 mm) punctate or linear hyperintensities on T2 images in BG. The severity of WMH was determined for periventricular versus deep areas according to Fazekas score [25].

Assessments at the time of first interaction for each patient presenting with stroke, included: 1) All demographic and clinical parameters were recorded on predefined printed proforma (Age, Gender, education, diet pattern, type of work or occupation, body mass index, sleep duration and quality, hypertension, diabetes, hyperlipidaemia, coronary artery disease, renal failure, hypothyroidism, vitamin B12 level, alcohol and smoking, and drug compliance were recorded).

Target cases of CSVD for the study were diagnosed according to STRIVE criteria. Grading of CSVD with radiological FAZEKAS system at 0 month was done. Number of Cerebral Microbleed (CMB) on MRI scan were assessed and were classified according to number (0-2, 2-10, and > 10) at the time of first interaction. Assessment of cognitive scoring was done with Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA) Scores at 0 and 3 months. Activity of daily living (ADL) was calculated at the end of three months and patients were classified into 4 categories; 1) independent (score 90-100); 2) partially dependent (score 60-89); 3) severely dependent (score 20-59); and 4) totally dependent (score < 20). Final outcome was based on Modified Rankin score (MRS) which was calculated at the end of 3 months and patients were classified in seven categories; 1) score 0 (no symptom); 2) score 1 (symptoms but no disability); 3) score 2 (impairment only in social role); 4) score 3 (impairment in IADL tasks); 5) score 4 (impairment in ADL tasks); 6) score 5 (impairment in mobility) and 7) score 6 (death).

The data were entered into an excel sheet and analysed with the help of IBM SPSS Version 25. Test of Association in Categorial variables was done by cross tab analysis of chi square test and for Continuous variable with Student t test. Univariate and Multivariate regression analysis was done for risk factor association of cognitive status. Qualitative variables were expressed as proportion and test of significance was tested by Chi square or Fisher Exact Tests, and p value of < 0.05 was labelled as statistically significant.

Results

Total 80 patients were enrolled and analysed during period of one year (2025-26). Among 80 patients, 35 (43.75%) were enrolled due to acute stroke like presentation (Group 1) and rest 45 (56.25%) presented with chronic progressive dysfunction (Group 2). Among group 1, total 5 patients (14%) had small intracerebral hemorrhage while rest 30 (86%) had lacunar stroke. Among those who presented with chronic progressive dysfunction, 29 (64%) presented due to progressive cognitive decline and rest 16 (36%) presented due to walking difficulty or falling tendency.

Mean age of presentation in group 1 was 66.3 years (range 46-85 years) and 69.5 years (range 33-90 years) in group 2, with male predominance as 71.42% in group 1 and 66.2% patients in group 2 were male. The education status was significantly different in two groups (P value = 0.0314) and more patients with progressive

disease rather than acute stroke had higher education. With respect to dietary habits in group 1, 15 patients (42.85%) were vegetarians while in group 2, 27 patients (60%) were vegetarians. According to MOCA assessment in group 1, 28 patients (80%) had scores below 24 and in group 2, 33 patients (73%) had MOCA scores below 24. Details of demographic findings are shown in table 1.

Parameter	Group 1 (Acute stroke) n = 35	Group 2 (chronic Progressive) n = 45	P value	Odd Ratio	CI
Age < 70 years	22 (62.85%)	19 (42.22%)	0.067	0.431	0.175-1.07
Age > 70 years	13 (37.15%)	26 (57.78%)			
Male	25 (71.43%)	28 (62.22%)	0.387	0.659	0.255-1.70
Female	10 (28.57%)	17 (37.78%)			
Below 12th class	24 (68%)	20 (44%)	0.0314	0.367	0.145-0.924
12th class and above	11(32%)	25(56%)			
Occupation: service	10 (28.57%)	16 (35.55%)	0.508	1.379	0.531-3.58
Occupation: non-service	25 (71.43%)	29 (64.45%)			
Diet habit: Vegetarian	15 (42.85%)	27 (60%)	0.127	2	0.815-4.90
Diet Habit: Mixed diet	20 (57.15%)	18 (40%)			
MMSE: below 26	21(60%)	29 (64%)	0.683	1.21	0.486-3.00
MMSE: ≥ 26	14 (40%)	16 (36%)			
MOCA: below 26	31 (88.6%)	37 (82.2%)	0.431	0.596	0.210-1.96
MOCA: ≥ 26	4 (11.4%)	8 (17.8%)			

Table 1: Demographic features of patients in both groups of patients with cerebral small vessel disease (CSVD).

Different radiological findings in both the groups are shown in table 2. 20 patients (57.14%) had a total CSVD score of 3-4, while in group 2, 35 patients (77.77%) had CSVD score of 3-4. Group 2 patients had significantly higher proportion of total CSVD score (p value = 0.0482).

Parameter	Group 1 (Acute stroke) n = 35	Group 2 (chronic Progressive) n = 45	P Value	Odd Ratio	CI
Lacunes present	30 (85.72%)	32 (71.11%)	0.120	0.410	0.131-1.29
Lacunes absent	5 (14.28%)	13 (28.89%			
White matter hyperintensities (WMH) of Fazekas grade 3-4: Yes	22 (62.86%)	39 (86%)	0.013	3.84	1.28-11.5
White matter hyperintensities (WMH) of Fazekas grade 3-4: No	13 (37.14%)	6 (14%)			

Enlarged perivascular space (EPVS): Yes	25 (71.4%)	42 (93.33%)	0.008	5.6	1.41-22.3
Enlarged perivascular space (EPVS): No	10 (28.6%)	3 (6.67%)			
Cerebral Microbleeds (CMBs): Yes	20 (57.14%)	29 (64.44%)	0.506	1.36	0.549-3.36
Cerebral Microbleeds (CMBs): No	15 (42.86%)	16 (35.56%)			
Patients having CSVD of 3-4 score on MRI	20 (57.14%)	35 (77.77%)	0.0482	2.63	0.995-6.93
Patients not having CSVD of 3-4 score on MRI	15 (42.86%)	10 (22.23%)			

Table 2: Radiological findings in patients of cerebral small vessel disease.

Different proportion of risk factors, like hypertension, diabetes, renal dysfunction, smoking, alcohol, sleep disorder and obesity are shown in table 3.

	Group 1 (Acute stroke) n = 35	Group 2 (chronic Progressive) n = 45	P value	Odd Ratio	CI
Diabetes: Yes	15 (42.85%)	25 (55.55%	0.259	1.67	0.684-4.063
Diabetes: No	20 (57.15%)	20 (44.45%)			
Hypertension: Yes	32 (91.42%)	43 (95.55%)	0.449	2.01	0.318-12.78
Hypertension: No	3 (8.58%)	2 (4.45%)			
Renal Dysfunction: Yes	8 (22.85%)	6 (13.33%)	0.266	0.519	0.162-1.67
Renal Dysfunction: No	27 (77.15%)	39 (86.67%)			
Smoking: Yes	12 (34.28%)	13 (28.88%)	0.605	0.779	0.301-2.01
Smoking: No	23 (65.72%)	32 (72.12%)			
Alcohol: Yes	14 (40%)	13 (28.88%)	0.297	0.609	0.239-1.55
Alcohol: No	21(60%)	32 (71.12%)			
Low Vitamin B12 level	9 (25.71%)	8 (17.77%)	0.389	0.625	0.213-1.83
Normal Vitamin B12 level	26 (74.29%)	37 (82.23%)			
Depression present	11 (31.42%)	16 (35.56%)	0.698	1.20	0.470-3.07
Depression absent	24 (68.58%)	29 (64.44%)			
Body mass index > 30	14 (40%)	21(46.66%)	0.551	1.31	0.537-3.21
Body Mass Index < 30	21(60%)	24 (53.37%)			
Good Sleep quality	22 (62.85%)	16 (35.55%)	0.015	0.326	0.130-0.816
Poor Sleep quality	13 (37.15%)	29 (64.45%			
Good Drug compliance	15 (42.85%)	20 (44.44%)	0.887	1.07	0.438-2.60
Poor drug compliance	20 (57.15%)	25 (55.56%)			

Table 3: Risk factors in all patients in different groups.

At three months, among patients in group 1, 21 patients (60%) were independent in activities of daily living, while 14 patients (40 %) remained dependent. Based on the Modified Rankin Scale, 26 patients (74.28%) had a score of 0-2, whereas 9 patients (25.72%) had a score of 3-5. Overall quality of life improvement was observed in 28 patients (80%), while 7 patients (20%) showed no improvement.

Similarly, in group 2, only 16 patients (35.56%) were independent in activities of daily living, while 29 patients (64.44%) remained dependent (p value 0.0296). Based on the Modified Rankin Scale, 21 patients (46.67%) had a score of 0-2, whereas 24 patients (53.33%) had a score of 3-5 (p value 0.0128). Overall quality of life improvement was observed in 19 patients (42.22%), while 26 patients (57.78%) showed no improvement (p value = 0.0007) (table 4).

	Group 1 (Acute stroke) n = 35	Group 2 (chronic Progressive) n = 45	P value	Odd Ratio	CI
Independent on activity of daily living (ADL) at 3 months	21(60%)	16 (35.56%)	0.0296	0.368	0.148-0.918
Dependent on activity of daily living (ADL) at 3 months	14 (40%)	29 (64.44%)			
Modified Rankin scale = 0-2	26 (74.28%)	21(46.67%)	0.0128	0.303	0.116-0.789
Modified Rankin scale = 3-5	9 (25.72%)	24 (53.33%)			
Improved Quality of life	28 (80%)	20 (44.4%)	0.001	0.2	0.072-0.522
No improvement in Quality of life	7 (20%)	25 (55.6%)			

Table 4: Outcome at 3 months follow-up based on stroke specific quality of life scale.

According to stroke specific quality of life score (SS-QOL), total 48 patients (60%) had improvement in QOL after 3 months of treatment while 32 (40%) had poor outcome with deterioration in QOL. Various demographic and clinical parameters were analysed to see for the association with final outcome. Results of association of final outcome with various factors is shown in table 1.

Type of clinical presentation, cognitive status at admission, total CSVD score, drug compliance and sleep quality related factors were significantly associated with the final outcome. Chronic progressive disease, abnormal MMSE score at admission high total CSVD scores, poor drug compliance and poor sleep quality were associated with poor quality of life score at 3 months (Table 5). While, on multivariate regression analysis only age group more than 70 years and cognitive status at admission were significant variable associated with poor outcome (Table 6).

	Status at 3 months: Improved (n = 48)	Status at 3 months: Not improved (N = 32)	P value	Odd Ratio	CI
Age < 70 years	28 (58.33%)	13 (40.63%)	0.120	2.05	0.82 – 5.08
Age ≥ 70 years	20 (41.67%)	19 (59.37%)			
Gender: Male	33 (68.75%)	20 (62.5%)	0.562	0.758	0.296-1.94
Gender: Female	15 (31.25%)	12 (37.5%)			
Education: Basic	24 (50%)	20 (62.5%)	0.270	0.600	0.241 -1.49
Education: High	24 (50%)	12 (37.5%)			
Occupation: Service	16 (33.33%)	10 (31.25%)	0.845	1.10	0.422-2.87
Occupation: Non-service	32 (66.37%)	22 (68.75%)			
Diet: Vegetarian	22 (45.83%)	20 (62.5%)	0.143	1.97	0.790 -4.91
Diet: Mixed	26 (54.17%)	12 (37.5%)			

Clinical presentation as CVA	28 (58.33%)	7 (21.88%)	0.0013	5.0	1.81 -13.8
Clinical presentation as non-CVA	20 (41.67%)	25 (78.12%)			
MMSE: Normal	23 (47.9%)	7 (21.88%)	0.037	NA	NA
MMSE: Abnormal	25 (52.1%)	25 (78.12%)			
CSVD Score = 0-2	21 (43.75%)	4 (12.5%)	0.0031	0.184	0.056-0.605
CSVD Score = 3-4	27 (56.25%)	28 (87.5%)			
Good Drug compliance	26 (54.2%)	7 (21.88%)	0.0041	4.22	1.53 -11.6
Poor Drug Compliance	22 (45.8%)	25 (78.12%)			
Good Sleep quality	29 (60.4%)	9 (28.1%)	0.0046	3.90	1.49 – 10.2
Poor Sleep quality	19 (39.6%)	23 (71.9%)			

Table 5: Association of different parameters with outcome at 3 months follow-up.

Variable	Estimate	Std error	T-value	P value	Significance
Total CSVD score	0.4854	0.2997	-0.6802	0.4988	Not significant
Drug Compliance	0.1853	0.2723	0.6804	0.4987	Not significant
Age Group	0.636	0.2811	2.2628	0.027	Yes
Gender	0.0912	0.5338	0.2578	0.7974	Not significant
Education	0.4416	0.2784	-1.5863	0.1175	Not significant
Occupation	0.4256	0.2956	1.4397	0.1547	Not significant
Diet pattern	-0.0347	0.2819	-0.1232	0.9023	Not significant
Clinical type	0.5618	0.2894	1.9065	0.061	Not significant
Poor cognitive status at admission	-1.2014	0.3841	-3.1281	0.0026	Yes
Poor sleep quality	0.3128	0.2787	1.122	0.266	Not significant

Table 6: Showing multivariate regression analysis for outcome measures.

Discussion

Two clinical types of CVSD is described in literature, 1) Covert or Silent CSVD and 2) Overt or symptomatic CSVD. Covert CSVD was further classified as acute CSVD and chronic CSVD. Acute CSVD present with acute lacunar stroke which are of five types; 1) Pure motor stroke (PMS) which is most common type; 2) Pure sensory stroke (PSS); 3) Sensory motor stroke (SMS); 4) Ataxic Hemiparesis (AH) and 5) Dysarthria-Clumsy hand syndrome (DCHS). On the other hand, chronic CSVD can present either as progressive cognitive impairment or progressive extrapyramidal syndrome with gait abnormality [2].

This study performed on 80 odd patients of cerebral small vessels disease (CSVD) showed few interesting observations. In our cohort of 80 CSVD patients, chronic progressive disease (group 2) was more frequent and was found in 45 (56.25%) patients and rest 35 (43.75%) presented as acute stroke (group 1). Moreover, among chronic progressive group, progressive cognitive decline was more frequent as compare to progressive gait abnormality (64% versus 36%). Likewise, acute lacunar stroke was commoner as compared to cerebral hemorrhage (86% versus 14%).

Age is important denominator in disease progression of CSVD. The frequency, severity and radiological findings are to the tune of

5 % at age around 50 years which rises up 100% by age 90 years (26). In our study, 35 (43.75%) patients were > 70 years age and 31 (38.75%) patients were between 60-70 years. Interestingly, 14 patients (17.5%) were below 60 years, 50% of which were having chronic progressive disease. Our data is matching with large cohort of CSVD patients in three Asian countries [27]. Poor lifestyle, advancing age and hypertension are risk factors for high prevalence of CSVD in Asian population. In another study on 48 CSVD patients from India, the mean age of presentation was 58.9 ± 5.9 years and 72.9% were male in accordance with our study [28].

CSVD population in our study was male predominant and in both the groups > 2/3rd were males. In one large meta-analysis on 36910 subjects of CSVD, hospital-based study showed male predominant trends and male also had higher number of cases with moderate to severe disease. There is no sufficient data to stratify difference in risk factors for CSVD in male and females [29].

Previous study has seen the evidence of early life factor can affects the small vessel disease and cognitive status. Early life effects like; prenatal nutrition, cognitive ability, education, socio-economic status in childhood, brain resilience and reserve, and health behaviour were evaluated for any association of future CSVD or dementia. Early-life factors particularly education are found to be associated with dementia but less likely to be associated with small vessel disease or vascular cognitive impairment [30]. Same study showed that higher educational attainment is associated with a lower risk of cerebral small vessel disease and helps build cognitive reserve to buffer against symptoms. More years of schooling correlate with fewer brain microbleeds, less white matter damage, and better preservation of overall brain volume in later life [30]. About 55% patients in our cohort were in low education group (high school or lesser) and only 10% patients were postgraduate.

Recent evidences also suggested that cognitive dysfunction at the time of admission are associated with poor outcome of these patients [31]. The clinical outcome of cerebral small vessel disease (CSVD) strongly correlates with baseline cognitive status at admission, with normal cognition predicts for good functional recovery, and admission cognitive impairment pointing toward progressive vascular dementia, higher dependency, and increased long-term mortality [32]. Both the groups had lower cognitive scores at the time of admission as assessed by mini mental status examination or Montreal cognitive assessment scale. Total 31 patients had MMSE score of 18 or less at admission of which 18 (58%) had poor outcome with ADL dependent while only one patient out of 49 was dependent with MMSE score of > 19 at admission.

Covert cerebral small vessel disease (cSVD) is a silent, highly prevalent microvascular brain condition often found incidentally on MRI scans in people without major neurological signs. While not a traditional infectious epidemic, its surging detection among aging populations positions it as a massive public health threat, driving up to 30% of strokes and 40% of dementia cases globally [33]. Nearly, two third of our patients had presented without symptoms of dementia and out of these about 50% already had cognitive impairment at admission and 32 (71%) out of 45 patients who presented with chronic progressive disease had silent lacunes. This finding is suggestive of silent nature of disease. Silent or Covert SVD has been recently evaluated globally to find out proportion of preventable dementia in community-based study. According to one estimate at least one-third of healthy populations have silent lacunes due to CSVD, but actual prevalence can be higher [34]. That is why European Stroke Organization (ESO) had published separate treatment and prevention guidelines for covert CSVD [23]. The importance of detecting and managing the asymptomatic CSVD in populations is posing multiple challenging issue for health worker. Moreover, after identifying covert CSVD, management strategies are poorly established, posing a further challenge for neurologists and primary care physicians. Key controversial issues are: (i) the advantages of screening asymptomatic individuals concerning reduced adverse health events or cost-effectiveness, (ii) effective community screening strategies, including the development of non-imaging biomarkers, and (iii) the clinical and therapeutic implications of covert CSVD [35].

Imaging markers of CSVD are Lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS) and cerebral microbleeds (CMBs). Total CSVD score on brain MRI is also based on presence or absence of these four findings.

In our study WMH of grade 3 or 4 according to Fazekas score were significantly higher in progressive disease group (group 2). Likewise, group 2 also had significantly higher proportion of EPVS and total CSVD scores. WMH can be found in 20% of adults at age 60 years which increases with age and reaches > 90% in 80 years

and above and it is associated with progressive decline in motor and mental functions [1-6].

WMH was regarded as an ischemic demyelination of white matter due to blood brain barrier disruption and endothelial dysfunction, which can manifest as symptomatic or silent parenchymal lesions. This silent manifestation of CSVD commonly reported as incidental findings on brain imaging in asymptomatic individuals and also considered as prognostic marker in symptomatic patients who suffered from lacunar stroke. The key difference between silent and symptomatic variant is size and location of silent brain infarcts (SBI). About 95% of asymptomatic manifestation of CSVD are related to SBI, which can evolve to WMH with advancement in age and due to uncontrolled hypertension. Silent forms of SBI are usually located in periventricular region (Periventricular lesion) or in central semiovale (Deep subcortical lesions), whereas, symptomatic SBI affects sensory or motor tracts which is better diagnosed by diffusion tensor imaging (DTI). Overall, about 30% of healthy subjects over 60 years of age found have silent WMH [1-6].

WMH is the main determining factor for progressive deterioration of clinical symptoms of SVD patients, although the mechanism of sever WMH and cognitive deterioration is not well understood. Currently, size and progressive ischemic demyelination of surrounding penumbra is supposed to be the main mechanism of worsening WMH [36].

Age and hypertension were two most common risk factors found responsible for causing and worsening of CSVD specially WMH. Persistent and abnormal circadian blood pressure variation is the most important risk factor for CSVD [4]. Hypertension was the commonest risk factor in more than 90% patients in our cohort.

Other risk factors were diabetes in 50% patients, renal dysfunction, smoking and high alcohol consumption. Family history of stroke was found only in 11% of patients. Low levels of vitamin B12, hypothyroidism, coronary artery disease and depression were associated comorbidities in one third patients. About 40-50% patients were obese (BMI > 30), loud snoring and had sleep of less than 6 hours in each group. Bad quality of sleep was significantly higher in progressive disease group (Group 2). Poor drug compliance and poor control of diabetes or hypertension were positive in more than 50% of patients.

Total 50% of our patients were having type 2 diabetes. Both type1 and type 2 diabetes is associated with higher risk of CSVD and depends on duration of diabetes. One third of our patients had depression with CSVD. In previous study depressive symptoms were found to be more common in CSVD patients with diabetes [8]. Type 2 DM is established risk factor for CSVD and vascular dementia [8]. Definitive role of persistent hyperglycaemia and worsening of WMH is still needs to be established, but out of many molecular mechanisms of CSVD, advanced glycation endproducts (AGEs) and activation of receptors for AGE (RAGE) is also important. AGEs accumulation in advance age with hypertension leads to vascular stiffness and inflammation to cause CSVD and worsening of WMH [8].

About 17.5% patients of CSVD in our study found to have renal dysfunction. It is known that CVSD is a multi-system disease and involve other vascular bed like retina and kidney. The most common explanation of renal dysfunction in CSVD is due to shared link with diabetes and hypertension [9].

Moreover, about 50% of our CVSD patients had poor quality of sleep which was significantly higher in group 2 patients. Regular exercise, healthy diet, avoiding smoking and alcohol, and good quality of sleep found to be protective for progression of CSVD. Night time sleep disorders, bad sleep habits and poor quality of sleep are largely overlooked risk factors of CSVD, which leads to brain atrophy and EPVS [4]. Another study shown that alteration in glymphatic system plays a crucial role between CSVD burden, cognitive decline and sleep quality [37]. The association of dietary factors had been studied in one study and in our study there was no significant association of diet in two groups [38].

In our study, low levels of cognitive scores at admission, high total CSVD score, poor drug compliance and poor sleep quality were significant factors that were associated with final poor outcome of disease at 3 months in spite of treatment. Life style modification, strict drug compliance and control of primary risk factors like hypertension is the only way to prevent progression of CVSD [39].

Dependency on activity of daily living (ADL), high scores on modified Rankin scale (MRS) of > 3, and poor quality of life score at 3 months was significantly higher in patients of progressive disease (group 2). Total 53.75% of our patients were dependent on family for their activities of daily living (ADL). Other studies

had delineated that about 56.8% can have moderate to severe dependency and 45% patients ultimately develops dementia in follow-up [40].

Treatment and prevention of progression of CSVD is important once diagnosis is confirmed. Lifestyle modification and behaviour interventions are associated with potential benefits on CSVD. Mediterranean diet, good quality of sleep, aerobic exercises, and good drug compliance was associated with reduction in WMH. Cessation of smoking and low dietary sodium intake is a stroke predictor of positive impact on CSVD. Mediterranean diet with folic acid and B12 supplementation is good for CSVD protection. Currently, single antiplatelet is best recommended for prevention of recurrent lacunar stroke. DAPT and anticoagulation is associated with high risk of ICH specially in presence of CMBs. Intensive BP lowering (< 120 mmHg) was found to be associated with reduced WMH progression and risk of MCI in CSVD patients. The effect of statin on progression and recurrence of CSVD related changes is still controversial and studies showed mixed results. Cilostazol, a PDE-3 (phosphodiesterase -3) inhibitor was found to be beneficial in CSVD accumulation through endothelial stabilization specially in Asia-Pacific region. Cilostazol found to be effective in prevention of recurrent stroke, intracerebral hemorrhage and death when given for longer duration (> 6 months). Nitrous oxide (NO) donor like glyceryl nitrate and isosorbide nitrate might be beneficial in CSVD if used within 4 hours of stroke onset. Regarding vitamin (B6, B12 and folic acid) supplementation, one study VITATOPS suggested patients with severe WMH, who received vitamin supplementation for > 2 years can slower the progression. Allopurinol, a xanthin inhibitor, found to have multiple positive effects on CSVD when used for one year. Remote ischemic conditioning by using transient ischemia in upper limb by inflating BP cuff shown to be neuroprotective in pre-clinical model [4,23,24,38]. Our study confirmed that patients who had poor life style factors and poor compliance had been associated with disease progression.

Conclusions

Major conclusions form this study are; that CSVD is having multiple clinical presentations like lacunar stroke, small intracerebral bleed, vascular cognitive impairment and progressive gait disorder. Our study found the chronic progressive disease is commoner then acute stroke and presentation with progressive cognitive decline is the most common type of CSVD.

Poor control of hypertension, diabetes, poor drug compliance and poor quality of sleep were the most common risk factor found for worsening of CSVD patients. Radiological markers like worsening WMH, EPVS, and high total CSVD scores were associated with poor outcome and high dependency of patients at 3 months follow-up. About 50% patients were dependent for their ADL on family members. Cognitive status at the time of admission was found to be a significant risk factor for disease progression.

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