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Research Article

Neurological and Behavioral Sequelae of Ischemic and Hemorrhagic Cerebrovascular Accidents in a Developing Country

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Abstract

We have clinically studied 27 adult and old patients with one or multiple cerebral accidents. The hot weather and poor socio-economic environment were considered important risk factors for cerebrovascular accidents. We have found the following risk factors for patient age ranging from 39 to 89 years old: blood hypertension, senil demencia, diabetes mellitus, migraine, hyperlipidemia, cardiovascular pathology, tobacco smoking and alcoholic habits.

Blood hypertension was a risk factor in all cases examined (100%). Diabetes was found in eight patients associated with cerebrovascular accidents (28%). On case of myocardial infarction was found as risk factor for ischemic and hemorrhagic stroke. Preceding depression was associated with an increased risk of stroke and vascular dementia. We found just one case with associated Alzheimer Disease (4%). We found epilepsy in two patients with cerebrovascular accidents (7%). Migraine, especially with aura was a risk factor for both ischemic and hemorrhagic stroke. Fifteen patients presented left or right hemiparetic gait (70%), three cases with sleep disorders: somnolence

and /or imsomnia (11%). Dysphagia, dysarthria and aphasia occurred in 7% of cases following stroke. Cerebrovascular accidents lead to decreased visual acuity and visual field loss. Somnolence and insomnia was observed in nineteen cases (29%). Depression, anxiety, senil demencia, familiar stress, disturbance of emotional state, irritability and aggression were found in 28% of examined patients. We reported two cases with Migraine (7%). Most patients develop signal intensity changes in the subcortical white matter and periventricular region, generalized brain atrophy and presence of brain infarcts on MRI, specifically associated with decline in information processing speed and executive function. Two patients were associated kidney disease, such as renal lithiasis and renal insufficiency (7%). Gastrointestinal disease were found in 11% of cases studied. The relationship of gut microbiota with cerebrovascular accidents, kidney and gastrointestinal diseases is discussed.

Introduction

The major modifiable risk factors of stroke are arterial hypertension, diabetes mellitus, tobacco smoking, and hyperlipidemia, as well as lifestyle factors, such as obesity, poor diet/nutrition, and physical inactivity [1,2]. Preclinical hypertensive lesions in most target organs are left ventricular hypertrophy for the heart, microalbuminuria for the kidney, fundus abnormalities for the eye, and intima-media thickness and pulse wave velocity for the vessels [3-5].

Deep perforator arteriopathy and cerebral amyloid angiopathy are the commonest known cerebral small vessel diseases, which cause ischemic stroke, intracerebral haemorrhage and vascular cognitive impairment [6].

The prognostic impact of depression and the role of heart failure as a risk factor for dementia and stroke are not fully understood. The heart failure cohort have a 21% increased rate of all-cause dementia, mainly driven by increased hazards of vascular dementia and other dementia. [7].

Non-valvular atrial fibrillation (AF) carries an increased risk of stroke mediated by embolism of stasis-precipitated thrombi originating in the left atrial appendage [8].

Diabetes causes various microvascular and macrovascular changes often culminating in major clinical complications, 1 of which, is stroke. Although gains have been made over the last 2 decades in reducing the burden of stroke, the recent rise in rates of diabetes threatens to reverse these advances. Of the several mechanistic stroke subtypes, individuals with diabetes are especially susceptible to the consequences of cerebral small vessel diseases.

Hyperglycemia confers greater risk of stroke occurrence. This increased risk is often seen in individuals with diabetes and is associated with poorer clinical outcomes (including higher mortality), especially following ischemic stroke [9].

In the present study we analyze the neurological and neurobehavioral sequelae of 27 patients with neurological and neurobehavioral disorders who suffered one or several ischemic or hemorrhagic cerebrovascular accidents.

Material and Methods

We have clinically studied 27 adult and old patients, ranging from 39 to 92 years old, with cerebrovascular accidents to examine post neurological and behavioral pathological changes. These patients were examined at the Neuroscience Outpatient Clinic of Clinical Neuroscience Institute of San Rafael Home Clinic of Maracaibo, Venezuela. The principles of Helsinki declaration for research in human being were taking into account.

Results

Case Report Summary

Case 1. DC. 77 years old. F. Blood hypertension. Hypertensive crisis and hemorrhagic cerebrovascular accident. Demencia senil post stroke and miocardial infarction, gait disorders, aggressive behavior, speech disturbances and insomnia.

Case 2. AH. 69 years old. M. Rupture of brain aneurism 15 years ago and subarachnoidal hemorrhage. NMR images showed blood collections in basal and supraselar cisterns, severe brain edema and ventricular enlargement. After neurosurgery developed temporo-spatial disorientation, loss of memory and senil demencia featured by irritability and aggression.

Case 3. LL, 77 years old, F. Blood hypertension and ischemic cerebrovascular accident. Senil demencia featured by visual and auditive hallucinations, night terror, and loss of memory.

Case 4. NS.73 years old, M. Blood hypertension and two ischemic cerebrovascular accidents, one in 2017 and another in 2019. Speech disturbance, right hemiparesis, insomnia, and, loss of sphincter control.

Case 5. NM. 75 years old, M, Blood hypertension and and occipital cerebral infartion 5 years ago. Loss of consciousness, loss of language. Convulsive syndrome with aura, blindness of right eye. NMR images showed occipital brain infarct.

Case 6. MF. 58 years old, F. Severe blood hypertension, Patients with 6 ischemic strokes in the last ten years, Diabetes. Woman with smoking habit during 40 years, insomnia, blurred vision, gait disturbances. RMN images showed cerebral atrophy, deep cortical sulcus, hypodense lesion in left parieto-occipital region, ventriculomegaly, scarce differentiation between white matter and gray matter.

Case 7, MJC, 55 years old, F. Blood hypertension, Ischemic cerebrovascular accident six years ago and convulsive syndrome.

Case 8. MP.63 years old, F. Blood hypertension, Ischemic cerebrovascular accident right hemiparesis, seizures, loss of speech, ptosis palpebral, intentional tremor, loss of memory, headache.

Case 9. YC, 47 years old, F. Blood hypertension. Hemorrhagic cerebrovascular accident and right hemiparesis, facial paralysis, headache, speech disorders. NMR images showed hemorrhagic focus at the temporo-occipital region of left hemisphere.

Case 10. ZE, 48 years old, F. Blood hypertension, migraine, ischemic cerebrovascular accident two years ago.

Heart failure, atheromatosis, urinary infection, patient with dizziness, vomits, diarrhea, pain in right eye and temporal region, weight loss, paleness of skin and anaemia.

Case 11, JV, 58 years old, M. Blood hypertension, migraine, ischemic cerebrovascular accident one year ago. Left hemiparesis, insomnia, Dizziness, behavioral changes, alcoholic and smoking habits, NMR images showed subarachnoid hemorrhage, atrophic changes at temporo-parietal region and prominent cortical sulcus.

Case 12. CH, 51 years old, F. Blood hypertension, migraine, ischemic cerebrovascular accident and right hemiparesis since one year ago, language and sleep disorders and dizziness.

Case 13. JC, 66 years old, F. Blood hypertension, Hemorrhagic stroke right hemiparesis. Diabetes, cardiac failure. NMR image showed left fronto-temporal hemorragic infarction.

Case 14, EG, 39 years old, F. Blood hypertension, Diabetes. Ischemic cerebrovascular accident and left hemiparesis two years ago, tonic-clonic convulsive syndrome, facial paralysis, headache, blurred vision, ptosis palpebral, familiar stress, neurobehavioral disorders, and speech disturbances.

Case 15, EM, 85 years old, M. Blood hypertension. Two ischemic cerebrovascular accidents five years ago, right hemiparesis, dizziness, daytime and night somnolence, and tic left eye.

Case 16, YN, 52 years old, F. The patient presented an hemorrhagic cerebro-vascular accident and cerebral infart 7 year ago, At the present time presents blood hypertension headache, dizziness and lumbar pain, irritable bowel syndrome. CAT images showed calcified aortic valve, renal and bilateral pielocalectasy.

Case 17. ZE, 51 years old, F. Two years ago suffered ischemic cerebrovascular accident. Tremor in left leg, and loss of weight. Eco Doppler showed arteriosclerosis in both carotid system. NMR images showed hyperintense area in the cerebellum, cerebral atrophy and deep cortical sulcus.

Case 18. MQ, 86 years old, F. Ischemic cerebrovascular accident, paresis of left arm, and seizures. Alzheimer disease featured by loss of memory, lack of personal recognition and somnolence.

Case 19. FS. 76 years old, M. Four years ago the patient suffered ischemic cerebrovascular accident, right hemiparesis gait disturbances, disorders of language, intense headache and diminution of vision.

Case 20. OU, 56 years old, M. Blood hypertension. Diabetes. Patient suffered ischemic cerebrovascular accident. Gait disturbances, and loss of memory. Crambs in right hemifacial region, legs, feet and arms. NMR images showed irritable vowel syndrome. Eco Doppler showed segmentary stenosis of carotid system.

Case 21. NG, 49 years old, M. Patient with one ischemic cerebrovascular accident in 2016 and another in 2017. NMR images showed cerebral atrophy, ischemic infarct in right fronto-parietal region. The patient presented somnolence, vomits, loss of consciousness. Eco Doppler depicted arteriosesclerosis and myointimal complex thickening in both carotid arteries.

Case 22. JP, 72 years old, M. Patient with one ischemic cerebrovascular accident three months ago and paralysis of lower limbs, headache, dizziness, vertigo, language disorders, anorexia, prostatic hyperplasia and kidney insufficiency.

Case 23. JR, 86 years old, F. Diabetic patient suffered an ischemic cerebrovascular accident 20 years ago. Transient loss of consciousness. She exhibits severe high blood pressure, left hemiparesis and spasticity, difficult swallowing, transient loss of consciousness, and loss of sphincter control.

Case 24. JB. 59 years old, M. Diabetes. Patient suffered three ischemic cerebrovascular accidents 15, 7 and 4 years ago. In the first one presented right hemiparalysis and fall of head, in a second cerebrovascular accident left hemiparalysis, language disorders, difficult for swallowing and use of nasogastric sonda for proper nutrition, sialorrea, disorders of language, Alzheimer disease featured by loss of memory and deficit of personal recognition.

Case 25. CN, 70 years old, M. Diabetes and arterial hypertension since 10 years ago. Patient suffered ischemic cerebrovascular accident 15 days ago, showing vertigo, temporo-spacial disorientation. NMR images showed stenotic vascular changes of Willis Circle and vertebral and cerebral arteries

Case 26. LB, 59 years old. F. Patient obese suffered hemorrhagic cerebrovascular accident by rupture of aneurism of communicant anterior artery 5 years ago. Paresis of right arm, transient loss of consciousness, blurred vision, language disorder, and gait disturbances.

Case 27. SG, 68 years old, M. Patient suffered ischemic cerebrovascular accident with transient loss of consciousness and loss of sphincter control 5 years ago. Lately presents depression, anxiety and visual hallucinations.

Interpretation of Results

We have found the following risk factors for patients age ranging from 39 to 89 years old, hot weather, blood hypertension, small cerebral vessel, diabetes mellitus, migraine, hyperlipidemia, cardiovascular pathology, and tobacco smoking and alcoholic habits.

The patients exhibited some of the following neurological sequelae: right or left hemiparesis and gait disorders, speech disturbance, ptosis palpebral, transient loss of consciousness, vertigo, dizziness, insomnia, speech disturbances, language disorders, facial paralysis, facial and muscular tics, tremors, seizures, spatial disorientation, loss of equilibrium, intense headache, neurosensorial deficits, such as visual and auditive deficits, muscle weakness, muscle spasticity, somnolence, loss of implicit and explicit memory and deficit of personal recognition, difficult for swallowing, sialorrea, loss of weight, and loss of sphincter control, kidney lithiasis, anorexia, and irritable bowel syndrome.

The psychiatric diseases and behavioral changes were depression, anxiety, visual and auditive hallucinations, and night terrors.

The following neuropathological changes were found in NMR images: brain aneurism and subarachnoid hemorrhage, blood collections in basal and supraselar cisterns, severe brain edema, ventricular enlargement, occipital brain infarct, hypodense lesion in left parietal-occipital region, scarce differentiation between white matter and gray matter, brain atrophy, brain infarction, arteriosclerosis and myointimal complex thickening in both carotid arteries, and stenosis of vertebral, basilar arteries and arteries belonging the Willis Poligono, aortic valve calcifications, hemorrhagic focus at the temporo-occipital region of left hemisphere, atrophic changes at temporo-parietal region and prominent cortical sulcus, left hemorrhagic fronto-temporal hemorrhagic infart, cerebellar hyperintense area, cerebral atrophy, and ischemic infarct in right fronto-parietal region. The non-nervous diseases mainly found were renal lithiasis, bilateral pielocalectasy, irritable vowel syndrome and gastritis.

Most patients examined belong to the lowest socio-economical conditions, and contaminated environmental conditions in a country with critical sociopolitical crisis

Discussion

Blood Hypertension and Cerebrovascular Accidents

The Vascular Risk Factor

According to Schreiber *et al.* 2019 [10] deep perforator arteriopathy (DPA) and cerebral amyloid angiopathy (CAA) are the commonest known cerebral small vessel diseases, which cause ischaemic stroke, intracebral haemorrhage and vascular cognitive impairment, blood-brain barrier breakdown, endothelial damage and impaired perivascular β-amyloid (Aβ) drainage are hallmark common mechanisms connecting DPA and CAA.

Non-amyloid cerebral small vessel disease/hypertensive arteriopathy (HA) results in vessel wall injury that may promote cerebral amyloid angiopathy (CAA) [11]. In sporadic CAA, β-amyloid is deposited on the lobar intracortical and leptomeningeal vessel wall. Fibrinoid necrosis, fibrohyalinous intimal thickening, microaneurysms, luminal stenosis, and inflammatory cell infiltration of the involved vessels appear subsequent to the amyloid deposition [12].

Deposited amyloid proteins damage smooth muscle cells in blood vessel walls leading to pathological appearances calling 'double-barreled' changes, fibrinoid necrosis, and microaneurysms. These structural abnormalities result in microinfarcts and hemorrhages in the central nervous system. Recurrent hemorrhage is a common clinical manifestation in patients with CAA; however, small multiple infarctions, progressive dementia, transient neurological symptoms, and CAA-related inflammation can also occur [13].

Blood Hypertension and Stroke

We found blood hypertension in all cases examined (100%). Hypertension is the most important cardiovascular risk factor for developing both ischemic and hemorrhagic stroke, as well as small vessel disease predisposing to lacunar infarction, white matter lesions, and cerebral microbleeds. In addition, hypertension predisposes to atherosclerosis and cardiac diseases (notably atrial fibrillation), thereby promoting cerebral embolism.

Inflammatory mechanisms play a central role in the pathogenesis and progression of atherosclerosis, plaque rupture, thrombosis, and stroke. Endothelial dysfunction, in part resulting from excessive production of reactive oxygen species, is an important mechanism of cerebrovascular damage. Age and high blood pressure are responsible for silent structural and functional cerebral changes leading to white matter lesions and cognitive impairment. Hypertensive patients have more white matter lesions, which are an important prognostic factor for the development of stroke, cognitive impairment, dementia and death, than normotensive people. Over the past 10 years, strong evidence has emerged that cerebral white matter lesions in hypertensive patients should be considered a silent early marker of brain damage [14].

The severity of systolic destabilization indicates the presence of systemic vasospasm and determines the need for the correction of hypertension. Diastolic destabilization indicates a decrease in the pumping function of the heart, which requires immediate inotropic support [15] In the hyperacute phase, a majority of patients shows an elevated blood pressure at the time of presentation because of sympathetic hyperactivity or a physiological response to tissue ischemia [16].

Myocardial Infarction and Ischemic and Hemorrhagic Stroke

Myocardial infarction affects the risk of ischemic and hemorrhagic stroke and dementia. Preceding depression was associated with moderately increased mortality after myocardial infarction, and that was associated with an increased risk of stroke and vascular dementia, but not dementia from other causes [17].

Vascular Cognitive Impairment

In our study we found four cases with vascular cognitive impairment. The prevalence, morphology, and pathogenesis of vascular dementia, recently termed vascular cognitive impairment, and of mixed dementia (Alzheimer disease associated with vascular encephalopathy) are a matter of discussion and clinical diagnostic criteria for these disorders slow of low sensitivity and variable specificity. It has been related to focal, multifocal or diffuse cortical and/or subcortical microinfarcts and lacunes often affecting strategically important brain areas (thalamus, frontobasal and/or limbic systems), hemispheric white matter lesions and, less often, large brain infarcts. The pathogenesis of cerebrovascular lesions is multifactorial and their pathophysiology affects neuronal systems involved in cognition, memory, and behavior. The lesion patterns in "pure" vascular cognitive impairment with predominant multiple small subcortical lesions related to arteriosclerosis and microangiopathies, and in mixed dementia associated with vascular encephalopathy, more often showing large infarcts, suggest different pathogenesis of both types of lesions. They result from systemic, cardiac or local large or small vessel disease. The pathogenesis of cerebrovascular lesions is multifactorial and their pathophysiology affects neuronal systems involved in cognition, memory, and behavior [18,19].

Cerebral Small Vessel Disease and Cerebrovascular Accidents

In the present study we found three cases with cerebral small-vessel disease (11%).

Cerebral small-vessel disease is common in older people and may contribute to the development of dementia. Increasing severity of periventricular white matter and generalized brain atrophy, and the presence of brain infarcts on MRI were associated with a steeper decline in cognitive function. Stroke plays an intermediate

role in the relationship between cerebral small-vessel disease and cognitive decline. In older people cerebral small-vessel disease may contribute to cognitive decline by affecting information processing speed and executive function [20].

Moreover, patients with small-vessel disease have an increase in the mid- and long-term risk of death, stroke recurrence and dementia. Ischemic cerebral small-vessel disease should be regarded as a potentially severe condition prodrome of subcortical vascular dementia rather than a relatively benign disorder [21].

Cerebrovascular Accidents and White Matter Damage

With the advent of sensitive brain imaging techniques, white matter lesions are commonly observed in healthy as well as in demented elderly people. Primarily vascular risk factors have been related to the presence of white matter lesions, such as hypertension, atherosclerosis and atrial fibrillation. Subcortical white matter lesions are mainly associated with depression in the elderly, while periventricular lesions are clearly associated with cognitive dysfunction Current evidence on the relation between vascular risk factors, white matter lesions and cognition is based on cross-sectional studies [22].

Increasing severity of periventricular white matter lesions and generalized brain atrophy and the presence of brain infarcts on MRI were associated with a steeper decline in cognitive function. These structural brain changes were specifically associated with decline in information processing speed and executive function [21].

Correlative pathology may include cortical atrophy and ventricular dilatation. Loss of either cortical or subcortical tissue function is expected to be related to functional compromise. In addition, there are potential features such as the coexistence of small vessel cerebrovascular disease and Alzheimer's disease. Small vessel cerebrovascular disease might also play a contributing factor in patients susceptible to Dementia with Lewy Bodies or patients susceptible to fronto-temporal dementia or any other dementing process. The relationships between cognitive impairment, dementia and subcortical vascular lesions are poorly understood [23].

Cerebrovascular Accidents and Gait Disorders

In the present study 15 patients presented left or right hemiparesis (70%). The most common pattern of walking impairment poststroke is hemiparetic gait, which is characterized by asymmetry associated with an extensor synergy pattern of hip extension and adduction, knee extension, and ankle plantar flexion and inversion [24]. In both non-disabled and post-stroke subjects, motor control is organized on a task-oriented basis using a common set of a few muscle modules to simultaneously achieve body support, balance control, and forward progression during gait. Hemiparesis following stroke is due to disruption of descending neural pathways, usually with no direct lesion of the brainstem and cerebellar structures involved in motor automatic processes [25]. (Beyaert *et al.*, 2015). Spasticity might affect gait post-stroke [26]. Strokes commonly result in trunk impairments that are associated with decreased trunk coordination and limited trunk muscle strength. These impairments often result in biomechanical changes during walking [27].

Cerebrovascular Accident and Alzheimer Disease

In the present study we found two cases with Alzheimer Disease (7%) associated with cerebrovascular accidents. Vascular lesions often coexist with Alzheimer's disease (AD) and other pathologies. Minor vascular lesions hardly contribute to cognitive decline in full-blown AD, while both mild Alzheimer pathology and small vessel disease interact synergistically. AD pathology is less severe in the presence of vascular lesions. Cerebral amyloid angiopathy is emerging as an important marker of risk for Alzheimer disease, microinfarction, microhemorrhage and macrohemorrhage of the brain, and vascular cognitive impairmen (VCI).

The neuropathology of cognitive impairment in later life is often a mixture of Alzheimer disease and microvascular brain damage, which may overlap and synergize to heighten the risk of cognitive impairment. The complex interplay between vascular and Alzheimer disease pathologies influent the evolution of clinical VCI and Alzheimer disease. Carotid intimal-medial thickness and arterial stiffness are emerging as markers of arterial aging and may serve as risk markers for VCI [28].

Diabetes and Their Relationship with Cerebrovascular Accidents

In the present study we found diabetes in eight patients studied with cerebrovascular accidents (28%). A host of diabetes-related insults to the central nervous system (CNS) have been clearly documented in type-1 and -2 diabetic patients as well as experimental animal models. These host of neurological disorders encompass hemodynamic impairments (e.g., stroke), vascular dementia, cognitive deficits (mild to moderate), as well as a number of neurochemical, electrophysiological and behavioral alterations. The underlying causes of diabetes-induced CNS complications are multifactorial and are relatively little understood although it is now evident that blood-brain barrier (BBB) damage plays a significant role in diabetes-dependent CNS disorders. Changes in plasma glucose levels (hyper- or hypoglycemia) have been associated with altered BBB transport functions (e.g., glucose, insulin, choline, amino acids, etc.), integrity (tight junction disruption), and oxidative stress in the CNS microcapillaries. Last two implicating a potential causal role for upregulation and activation of the receptor for advanced glycation end products (RAGE). This type membrane-protein also transports amyloid-beta (Aβ) from the blood into the brain across the BBB thus, establishing a link between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD, also referred to as "type 3 diabetes" [29].

Cerebrovascular Accidents, Post Seizures and Epilepsy

We found epilepsy in two patients with cerebrovascular accidents. Stroke is associated with an increased risk of subsequent seizures and epilepsy. Cerebrovascular lesions are the leading cause of epilepsy in the elderly, ahead of degenerative disorders, brain tumors and head trauma, accounting for up to one-third of newly diagnosed seizures in this population. Early seizures are usually defined as those occurring within one or two weeks after stroke; late seizures usually occur within the first year after stroke. Several risk factors of seizures have been identified; stroke subtype and cortical location being the best-characterized predictors of seizure development [30].

Although a well-known clinical phenomenon, there still remain some questions regarding the definitions, pathophysiology and epidemiology of early and late poststroke seizures and of poststroke epilepsy. Poststroke seizures and epilepsy constitute important complications in patients surviving a stroke. Several studies of the prevalence and possible predictors of poststroke seizures and epilepsy have been undertaken during the past few decades. Unfortunately, these studies have not consistently used the established definitions [31].

Cerebrovascular accidents (strokes) are one of the main acquired causes of epilepsy in adults [32]. Stroke (infarction or haemorrhage) is an important cause of epilepsy in adulthood, especially in the elderly. Because of a high incidence and improved survival, post-stroke epilepsy (PSE) is a great contemporary challenge for physicians. Severe strokes increased the incidence of PSE five-fold compared to minor strokes. We saw almost a doubling of the incidence one year to five years after the stroke. This might be explained by a long epileptogenesis, but it could also be due to high morbidity in this age group [33].

Migraine and Cerebrovascular Accidents

In our study we have diagnosed two cases with migraine (7%). It has been difficult to differentiate migraine from headache present in some stroke cases, and to differentiate some migraine with aura with cerebrovascular accidents with hemiparesis. Population-based studies have highlighted a close relationship between migraine and stroke. Migraine, especially with aura, is a risk factor for both ischemic and hemorrhagic stroke. Interestingly, stroke risk is highest for migraineurs who are young and otherwise healthy. Spreading depolarization (SD), a slowly propagating wave of neuronal depolarization, is the electrophysiologic event underlying migraine aura and a known headache trigger. Migraine patients are at risk for particularly cardioembolic stroke. At the same time, studies suggest an increased incidence of coagulopathy, atrial fibrillation and patent foramen ovale among migraineurs, providing a possible path for microembolic induction of SD and, in rare instances, stroke in hyperexcitable brains. Recent imaging studies document an accelerated infarct progression with only little potentially salvageable brain tissue in acute stroke patients with a migraine history, suggesting an increased vulnerability towards cerebral ischemia [34].

Migraine can be both an ischemic stroke/transient ischemic attack mimic (false positive) and chameleon (false negative). Differentiating between migraine aura and transient ischemic attacks remains challenging. On the other hand, migraine is a common incorrect diagnosis initially given to patients with stroke [35]. Similar difficulties have been also faced by Lebedeva *et al.* [36] (2018.). In addition, distinct subtypes of migraine with aura exist, such as familial hemiplegic migraine, sporadic hemiplegic migraine, and nonhemiplegic migraine with aura, with phenotypic differences between the different subtypes of migraine with aura which likely are caused by different etiological mechanisms [37]. Migraine increases the risk of stroke, particularly in young and otherwise healthy adults. Being the most frequent neurological condition, migraine prevalence is on a par with that of other common stroke risk factors, such as diabetes or hypertension [38].

Migraine may directly cause an ischemic event (i.e, migrainous infarct), by inducing cerebral microcirculatory vasoconstriction (cortical spreading depression-related oligemia), intracerebral large vessels spasm, and vascular endothelium-related hypercoagulability. On the other hand, migraine may predispose to cerebral ischemia outside of a migraine attack by affecting endothelial function, alone or in combination with traditional vascular risk factors, or by interacting with pre-existent stroke susceptibility conditions (i.e, patent foramen ovale) [39].

Disorders of Sleep

We have reported three cases with sleep disorders: somnolence and /or imsomnia (11%). Disorders of sleep are an integral part of neurodegenerative diseases and include insomnia, sleep-wake cycle disruption, excessive daytime sleepiness that may be manifested as persistent somnolence or sudden onset of sleep episodes, obstructive and central sleep apnea, rapid eye movement sleep behavior disorder, and restless legs syndrome. The origin of these sleep disorders is multifactorial including degeneration of the brain areas that modulate sleep, the symptoms of the disease, and the effect of medications [40].

Disorders of Language

We have found eleven patients with languajes disorders: (40%). Dysphagia, dysarthria and aphasia occur frequently following stroke. The high incidence and co-occurrence of devastating swallowing and communication disorders post-ischemic stroke provides clear motivation for speech-language pathology involvement in the early phase of stroke rehabilitation [41-43].

Ocular Outcomes After Stroke

We found one case with blindness and two cases with decreased visual acuity (11%).The different ocular outcomes after stroke are divided into three categories: vision, ocular motility, and visual perception. Cerebrovascular accident (CVAs) can lead to decreased visual acuity, visual field loss, ocular motility abnormalities, and visuospatial perception deficits [44].

Neurobehavioral Sequelae of Cerebrovascular Accidents

In the present study we have reported depression, anxiety, senil demencia, familiar stress, disturbance of emotional state, irritability and aggression (28%).

Stroke survivors are often affected by psychological distress and neuropsychiatric disturbances. About one-third of stroke survivors experience depression and anxiety or apathy, which are the most common neuropsychiatric sequelae of stroke. The most common or relevant poststroke emotional and behavioral disturbances, include poststroke mania and poststroke depression, poststroke anxiety disorders, posttraumatic stress disorder, personality changes with focus on apathy and disturbances of emotional expression control, Lower income, cognitive dysfunctions, poor activities of daily life, poor social support, and history of hypertension and previous stroke are risk factors for the acute stroke patients to get depression. Stroke severity, stroke-related disabilities, cerebral small vessel disease, previous psychiatric disease, poor coping strategies and unfavourable psychosocial environment influence the presence and severity of the psychiatric sequelae of stroke. [45,46]. The comorbidity of psychiatric disorders and cerebrovascular disease appears to be complex with underlying bidirectional influences. Psychiatric premorbidity and its impact on stroke severity, psychiatric complications during the initial treatment phase, and the short-term functional outcome of stroke [47].

Recent evidence suggests that poststroke depression is associated with the location of the brain infarct, proximity to the frontal pole being associated with greater depression following left hemisphere injury, and an opposite relationship being seen with injury to the right hemisphere [48]. Stroke lesions involving left hemisphere prefrontal or basal ganglia structures are associated with poststroke depression [49].

Depression is associated with left-hemisphere lesion severity and proximity of the lesion to the frontal pole and related to the dysfunction of (cortico-) striato-pallido-thalamic-cortical projections. In post-stroke period (1-2 years) depression is significantly associated with right-hemisphere lesion severity and proximity of the lesion to the occipital pole. The most relevant psychosocial risk factors for PSD are described as follows: past history of depression and other mental disorders, dysphasia, functional impairment, living alone and post-stroke social isolation [50].

Left hemisphere (LHS) stroke survivors reported higher levels of depression than right hemisphere (RHS) stroke survivors, Lower income, cognitive dysfunctions, poor activities of daily life, poor social support, and history of hypertension and previous stroke were risk factors for the acute stroke patients to get depression [51]

Brain-derived neurotrophic factor (BDNF) is well known to play a critical role in cognition. Its role in mood disorders, including post stroke depression (PSD) is also recognized with more evidence surfacing. The hypoxic environment induced by stroke could possibly downregulate BDNF expression in the brain, In PSD patients, the presence of stroke may contribute to the development of depression, including affecting the expression of BDNF [52]. Schmitt *et al.* [53] postulated the hypothesis that chronic stress might induce a deregulation of the hypothalamic-pituitary-adrenal system. In the long-term it leads to sleep disturbance and depression as well as decreased BDNF levels. Brain-derived neurotrophic factor (BDNF) plays a key role in the pathophysiology of stress-related mood disorders.

Ischemic and Hemorrhagic Strokes and Chronic Kidney Diseases

In the present study we found two patients with kidney disease such as renal lithiasis and renal insufficiency (7%). Both thrombotic and hemorrhagic complications are highly prevalent in chronic kidney disease patients. Growing evidence suggests that in chronic kidney disease patients, ischemic strokes are more common than hemorrhagic strokes. Mild to moderate chronic kidney disease incites various pathogenic mechanisms such as inflammation, oxidative stress, neurohormonal imbalance, formation of uremic toxins and vascular calcification which damage the endothelium and blood vessels. Cognitive dysfunction, dementia, transient infarcts, and white matter lesions are widespread in mild to moderate chronic kidney disease patients. Uremic toxins produced after chronic kidney disease can pass through the blood-brain barrier and mediate cognitive dysfunction and neurodegeneration. Furthermore, chronic kidney disease precipitates vascular risk factors that can lead to atherosclerosis, hypertension, atrial fibrillation, and diabetes [54]. Hemorrhagic stroke is leading cause of death in Chronic Kidney Disease (CKD) population. Uremic patients are susceptible to hemorrhagic complications due to multiple reasons i.e platelet dysfunction, low platelet number, use of heparin during hemodialysis, use of anticoagulants for thromboembolic risk etc. [55].

The Relationship Gut Microbiota, Cerebrovascular Accidents, Kidney and Gastrointestinal Diseases

In our study we have found two patients with cerebrovascular accidents and kidney diseases (7%) and three patients with gastrointestinal diseases (11%).

Gut microbiota has been recognized as an important endogenous organ. The kidney-gut axis would contribute to gut dysbiosis, which might worsen chronic kidney disease (CKD). Constipation, commonly seen in CKD, was one of the clinical presentation of gut dysbiosis. Emerging evidence suggests that gut-brain-microbiota axis may play a pivotal role linking gastrointestinal and neuronal disease [56].

Gut microbiota may affect distant organs through mechanisms that include regulating the absorption of nutrients and/or the production of microbial metabolites, regulating and interacting with the systemic immune system, and translocating bacteria/bacterial products through disrupted mucosal barriers [57].

Gut microbiota-dependent metabolites, in particular trimethylamine N-oxide (TMAO), have recently been reported to promote atherosclerosis and thrombosis. Higher TMAO plasma levels were linked with an increased risk of incident cardiovascular events including myocardial infarction, recurrent stroke, and cardiovascular death. Our data support the notion that TMAO-related increase of proinflammatory monocytes may add to elevated cardiovascular risk of patients with increased TMAO levels [58].

Bacterial colonization increased cerebral expression of cytokines as well as microglia/macrophage cell counts. These findings support the concept of lymphocyte-driven protective neuroinflammation after stroke under control of the microbiome [59].

Hot Weather as a Risk Factor for Cerebrovascular Accidents

As above mentioned most patients examined in the present study were subjected to a warm climate and stress environmental conditions. A possibility exists that hypertensive and diabetic people may have external heat as potential risk factors for brain damage. Muresanu *et al.* [60] (2019) have seen brain edema and brain damage following exposure to heat stress at 38˚C for 4h.

Conclusions

The hot climate with temperatures ranging between 32 and 52 centigrade degree and poor socio-economic environment. Are considered important risk factors for cerebrovascular accidents. In addition, we have found the following risk factors for patient age ranging from 39 to 89 years old: blood hypertension, senil demencia, diabetes mellitus, migraine, hyperlipidemia, cardiovascular pathology, tobacco smoking and alcoholic habit.

Blood hypertension was a risk factor in all cases examined (100%). Diabetes was found in eight patients associated with cerebrovascular accidents (28%). On case of myocardial infarction was found as risk factor for ischemic and hemorrhagic stroke and dementia. Preceding depression was associated with an increased risk of stroke and vascular dementia. We found just one case with associated Alzheimer Disease (4%).

We found epilepsy in two patients with cerebrovascular accidents (7%). Migraine, especially with aura was a risk factor for both ischemic and hemorrhagic stroke.

Fifteen patients presented left or right hemiparesis (70%). The most common pattern of walking impairment poststroke was hemiparetic gait. We found three cases with sleep disorders: somnolence and /or imsomnia (11%). Dysphagia, dysarthria and aphasia occurred in 7% of cases following stroke. Cerebrovascular accidents lead to decreased visual acuity, visual field loss, ocular motility abnormalities, and deficits. Somnolence and insomnia was observed in nineteen cases (29%). Depression, anxiety, senil demencia, familiar stress, disturbance of emotional state, irritability and aggression in 28% of examined patients. We found two cases with Migraine (7%). Most patients develop signal intensity changes in the subcortical white matter and periventricular region, generalized brain atrophy and presence of brain infarcts on MRI, specifically associated with decline in information processing speed and executive function. We found two patients with associated kidney disease, such as renal lithiasis and renal insufficiency (7%). Gastrointestinal disease were found in 11% of cases studied. The relationship of gut microbiota with cerebrovascular accidents, kidney and gastrointestinal diseases is discussed.

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