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Clinical and Neuroimaging Study of Thirty Three Patients with Vascular Dementia in Neurological, Psychiatric and Cardiovascular Diseases Exhibiting Microangiopathy and Leukoencephalopathy

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Abstract

We examine thirty three patients with vascular dementia or cerebral small vessel disease, and NMR images of microangiopathy and leukoencephalopathy in patients with high blood pressure, Alzheimer disease, Parkinson disease, Epilepsy, Stroke, Trigeminal neuralgia, Migraine, Diabetes, and Depression. Some of these patients showed the following symptoms: cervicalgia, language disturbances, sleep disorder, loss of short and long term memory (implicit and explicit memory), aggression, crisis of hyperexcitability, sleep, appetite and recognition disorders, headache, sinus arrhythmia, tonic-clonic convulsive syndrome with aura, visual and auditive hallucinations, temporo-spatial disorientation, impaired balance and muscle weakness, gait disorders as onward and slow march, persecution delusions, mood disorders, tachylalia, mutism, wandering, spasticity of lower limbs and loss of sphincter control or constipation. We found the following neuropathological changes: leukoaraiosis in one case, microangiopathy and arteriosclerotic leukoencephalopathy in 23 cases. Some patients exhibit subcortical white matter hyperintensive focus, ventriculomegaly, areas de encephalomalacia related with previous strokes, cortical atrophy and cortical calcifications, granulomatous in nature. We observed the following interactions leading to vascular dementia: Alzheimer disease and migraine (Alzheimer mixed dementia), migraine and Parkinson disease, Stroke and high blood pressure, stroke and migraine, epilepsy and high blood pressure.

Keywords: *Microangiopathy; Leukoencephalopathy; Vascular Dementia; Small Vessel Disease*

Introduction

In recent years, interest in vascular causes of dementia has increased and it has been proposed that vascular dementia (VAD) may be more common than previously supposed. Several vascular factors have been related to cognitive decline and dementia in the elderly, including stroke and white matter disease. Generally, risk factors for multi-infarct dementia are supposed to be the same as those for stroke and include hypertension, diabetes mellitus, advanced age, male sex, smoking and cardiac diseases [1]. The clinical distinction between

Alzheimer's disease and vascular dementia may be difficult and strict criteria (NINDS/ AIREN) have recently been adopted as standard guidelines for research studies. Vascular dementia and Alzheimer's disease can co-exist, so-called "mixed dementia", and the presence of cerebrovascular disease may worsen Alzheimer dementia. Indeed, there is often a vascular component in the pathogenesis of dementia. The pathogenesis of vascular dementia is complex. Post-stroke patients are at increased risk; some predisposing or risk factors are the volume, number and site (whether strategic or not) of cerebral injuries, distal field vascular injury with reduced cerebral blood flow, white matter ischemia due to small vessel disease, the co-existence of vascular disease and Alzheimer's dementia, and the presence of cognitive decline prior to stroke [2].

Various risk factors have been identified for microangiopathy-related cerebral abnormalities, such as white matter changes and lacunae, which are the core lesions for the development of a vascular dementia syndrome without stroke symptoms. Most consistently, arterial hypertension and diabetes mellitus have been found to be associated with such brain abnormalities. Diastolic blood pressure seems to be of particular importance as recent investigations demonstrate that this factor is related to the course of multiple lacunar strokes and the progression of white matter disease [3].

According to the Consortium for the Investigation of Vascular Impairment of Cognition the concept of mixed dementia should be extended to include vascular dementia in combination with dementias, other than Alzheimer's disease. These data suggest that an operational definition of mixed AD/VaD can be proposed on presentation and clinical/radiographic findings, but indifferent to vascular risk factors. The concept of mixed dementia should be extended to include vascular dementia in combination with dementias, other than Alzheimer's disease [4]. Both the clinical criteria and morphologic substrates of dementia resulting from cerebrovascular disease and its relation to Alzheimer disease and other age-related brain changes are controversial. In contrast to previous suggestions that vascular impairment disease (VID) was largely the result of large hemispheral infarcts, according to recent studies, it is most commonly associated with widespread small ischemic or vascular lesions (microinfarcts, gaps) throughout the CNS with predominant subcortical lesions in the basal ganglia and white matter or in strategically important brain regions (thalamus, hippocampus). The lesion pattern of rare "pure" VID, which is related to atherosclerotic and hypertensive microangiopathy, differs from that in mixed type dementia (Alzheimer disease and cerebrovascular lesions) that more often shows larger hemispheral infarcts. Another form of VID that is not infrequent in very old subjects is hippocampal sclerosis, a selective damage to the hippocampus that is often accompanied by multiple other cerebrovascular lesions. Both, mild Alzheimer type pathology and small vessel disease-associated subcortical vascular pathology appear to be common and may interact in causing cognitive decline [5].

Subcortical Vascular Encephalopathy (SVE) is an increasingly diagnosed disease with an enormous socio-economic impact. SVE leads to a progressive disability with immobilization because of gait- and postural disturbances and with a progressive subcortical vascular dementia which is composed of cognitive slowing, loss of initiative and forgetfulness. A valid diagnosis has become possible only through a clear improvement in cerebral imaging techniques developed in the eighties. The pathophysiological basis of small vessel disease is a cerebral microangiopathy leading to lacunar infarcts and to diffuse ischemic white matter lesions, often occurring side by side. Taken together, such lesions lead to an interruption of parallel functional prefrontal-subcortical circuits, which are essential for psychomotor function [6].

According to Kalvach and Gregová [7] occlusions of big vessels with a single major infarct, middle caliber vasculopathy with multiple gaps and finally microangiopathy causing leukoaraiosis-all these three entities- produce cognitive disorders

Vascular cognitive impairment, the recent modification of the terminology related to vascular burden of the brain, reflects the all-encompassing effects of vascular disease or lesions on cognition. It incorporates the complex interactions between vascular aetiologies, risk factors and cellular changes within the brain and cognition. The concept covers the frequent poststroke cognitive impairment and dementia, as well as cerebrovascular disease (CVD) as the second most common factor related to dementia. Cerebrovascular disease

(CVD) as well as vascular risk factors including arterial hypertension, history of high cholesterol, diabetes or forms of heart disease are independently associated with an increased risk of cognitive decline [8].

Knowledge about the longitudinal change of cerebral small-vessel disease-related magnetic resonance imaging abnormalities increases our pathophysiologic understanding of cerebral microangiopathy. For other small-vessel disease-related brain abnormalities including microbleeds and microstructural changes in normal-appearing white matter longitudinal change and correlations with clinical decline is not yet fully determined [9].

Small cerebral vessel disease is a relatively new group of angiopathies diagnosed more frequently thanks to common availability of neuroimaging [10]. With the development of brain MRI, it is now possible to detect small-vessel disease, whose prevalence and severity increase with age. The first types of small-vessel disease to be described were white matter hyperintensities (WMHs) [11].

In recent years, neuroimaging and pathological studies have informed on the pathogenesis of sporadic small vessel disease (SVD) and several single gene (monogenic) disorders predisposing to subcortical strokes and diffuse white matter disease. Arteriolosclerosis and diffuse white matter changes are the hallmark features of both sporadic and hereditary SVDs [12].

This decade witnessed a resurgence of interest in vascular dementia (VaD) as an increasingly important cause of senile dementia. Although definitions of dementia in general, and of VaD in particular, are still controversial recent diagnostic criteria for VaD acknowledge that pathogenetic mechanisms different from multi-infarct dementia are important in dementia causation. These include subcortical strokes, mainly lacunes, global hypoxic-ischemic events during acute stroke, and ischemic periventricular white matter lesions of the Binswanger type. These lesions tend to be manifested primarily by alterations of frontal executive function control [13].

With the advancement of technical progress, especially with respect to magnetic resonance imaging, patchy cerebral white matter lesions (WML) are being found with increasing frequency. The (differential) diagnosis between the two main dementias of old age, (senile) dementia of the Alzheimer type (SDAT) and vascular dementia (VD) is made more frequently in favor of the latter, since the detection of WML leads to support a vascular origin for dementia. As shown in some studies the neuropathologic correlates of WML have in common that the relative tissue water content is increased. This includes inflammation, gliosis, complete and incomplete infarctions, dilation of the perivascular (Virchow-Robin) spaces with myelin atrophy [14].

The prevalence, morphology, and pathogenesis of vascular dementia (VaD), recently termed vascular cognitive impairment (VCI), and of mixed dementia (Alzheimer disease associated with vascular encephalopathy) are a matter of discussion and clinical diagnostic criteria for these disorders of slow low sensitivity and variable specificity. The lesion patterns in "pure" VCI with predominant multiple small (subcortical) lesions related to arteriosclerosis and microangiopathies, and in mixed dementia (AD associated with vascular encephalopathy), more often showing large infarcts, suggest different pathogenesis of both types of lesions [15,16].

Recent data indicate that cognitive decline is commonly associated with widespread small ischemic/vascular lesions (microinfarcts, lacunes) throughout the brain with predominant involvement of subcortical and functionally important brain areas. Neuropathologic changes associated with cognitive impairment include multifocal and/or diffuse disease and focal lesions: multi-infarct encephalopathy, white matter lesions or arteriosclerotic subcortical leukoencephalopathy, multilacunar state, mixed cortico-subcortical type, borderline/watershed lesions, rare granular cortical atrophy, post-ischemic encephalopathy and hippocampal sclerosis [17]. Brain images of patients with Alzheimer's disease (AD) on magnetic resonance imaging (MRI) show white matter lesions (WML), which are attributed to degenerative changes of small vessels [18]. According to Targosz-Gajniak., *et al.* (2009). with these Authors, a significant factor correlating with the location of WML in patients with MCI and AD is the age of patient.

The present clinical and neuroimaging study of patient with vascular dementia associated to different neurological and mental diseases is an attempt to get a deeper insight into the clinical study of patients with microangiopathy and leukoencephalopathy or cerebral small vessel disease, as seen in patients with different neurological, psychiatric, metabolic and cardiovascular diseases.

Materials and Methods

We have clinically examined thirty three adult and aging patients with neurological, psychiatric and cardiovascular diseases. The patient age ranges between 28 to 92 years old. They were clinically studied at the Clinical Neuroscience Outpatient Clinic of Neuroscience Institute at Clinical Home San Rafael de Maracaibo. Venezuela. Nuclear magnetic resonance images were correlated with the clinical data. This study was carried out following the ethical principles of Helsinki Declaration for research in human beings.

Results

Summary of cases and clinical study

Case No. 1. AP. 92 years old, M. Alzheimer disease, elevated systolic blood pressure, severe dizziness, neck pain (cervicalgia), language disturbances, sleep disorder, loss of short memory and preserved long term memory, calcifications of aortic arch artery, constipation, low diastolic pressure, bradycardia. TAC showed severe cortical atrophy according to age, and cortical calcifications, periventricular hypodensity suggestive of leukoaraiosis leukoencephalopathy, granulomatous in nature. Sinusal arrythmia, and constipation.

Case No. 2. AR. 60 years old. F. Depression. Diabetes type II. NMR images showed microangiopathy and leukoencephalopathy in brain cortex and thalamus.

Case No. 3. CG. 71 years old, F. Alzheimer mixed dementia, high blood pressure, fronto-occipital headache, loss of memory, aggression, sleep, appetite and recognition disorders, NMR showed microangiopathy arteriosclerotic leukoencephalopathy, ectopia tonsillar and normal hydrocephalus.

Case No. 4. DA. 65 years old, M. Parkinson disease. Headache, onward and slow march, bradykinesia, loss of short memory and preserved long term memory. NMR images exhibited subcortical white matter hyperintense focus, arteriosclerotic microangiopathy and leukoencephalopathy, prominent cortical sulcus and cisterns, and cortical atrophy. Carotid Doppler showed myointimal thickening of bilateral carotid system and atheromatous disease.

Case No. 5. FG. 58 years old. M. Cerebral vascular accident (Stroke), left hemiparesis, high blood pressure, language disorder, epistaxis, and family stress. NMR images showed arteriosclerotic microangiopathy and leukoencephalopathy.

Case No. 6. WQ. 53 years-old, M. Epilepsy, tonic-clonic generalized seizures and auras. High blood pressure. NMR images depicted cortical hyperdense images corresponding to microangiopathy, leukoencephalopathy and moderate ventriculomegaly.

Case No. 7. VL, 51 years old. F. Vascular migraine featured by severe and analgesic resistant temporo-occipital headache irradiated to right arm, loss of consciousness, reddened eyes and dizziness. NMR images showed arteriosclerotic microangiopathy and leukoencephalopathy.

Case No. 8. TO, 80 years old, F. Alzheimer Disease (AD). High blood pressure. Familial background of AD, sleep disorders, somnambulism, visual and auditive hallucinations, NMR images showed microangiopathy and leukoencephalopathy

Case No. 9. RM, 59 years old. M. Mixed Parkinson disease and Alzheimer disease. Loss of implicit and explicit memory. Temporo spatial disorientation, sleep disorder. NMR images showed cystic leukoencephalopathy.

Case No. 10. JI, M, 68 years old. M- Parkinson disease, bradykinesia and tremors in both hands, feeling of heaviness in cervical region, insomnia, low blood pressure, dyspnoea at rest, and background of previous pancreatitis four years ago. NMR images showed microangiopathy and leukoencephalopathy.

Case No. 11. LR, 65 years old, F. High blood pressure and diabetes, dizziness, impaired balance and coordination, muscle weakness, NMR images showed microangiopathy and leukoencephalopathy and brain atrophic changes.

Case No. 12. LMP, 72 years old, M. Parkinson disease, diabetes type, gait disorders, frequently falls and right deviation of facial features. NMR images showed microangiopathy and leukoencephalopathy.

Case No. 13. JL, 54 years old, F. Migraine, Depression, Hyperthyroidism, tachycardia, familial and conjugal stress. Background history of mother and daughter with migraine. NMR images showed cerebral punctiform hyperdense focus compatible with disease of small brain vessels (microangiopathy and leukoencephalopathy), in specific gliosis and right asymmetry of lateral ventricles.

Case No. 14. JUB. 87 years old, M. Two ischemic strokes. High blood pressure. Neurobehavioral disorders, crisis of hyperexcitability, persecution delusions, aggression to family alternating with apparently normal behavior, gait disturbances, loss sphincter control. NMR images showed microangiopathy and leukoencephalopathy, ventriculomegaly, and small areas of frontal and cerebellar encephalomalacia related with previous strokes.

Case No. 15. MP, 76 years old, F. Trigeminal neuralgia, frontal headache, blood hypertension, and anaemia. NMR images showed microangiopathy and leukoencephalopathy.

Case No. 16. AA. 77 years old, F. Diabetes, left eye ophthalmoplegia, NMR images showed subcortical and periventricular microangiopathy and leukoencephalopathy.

Case No. 17. MM, 44 years old, F. Chronic headache, Depression, High blood pressure, loss of implicit and explicit memory, dyslipidemia, NMR images showed subcortical and supratentorial leukoencephalopathy, degenerative cervical and lumbar discopathy.

Case No. 18. EA, 66 years old, F, Depression, Sleep disorder, Blood hypotension, bradycardia, dyslipidaemia, hematuria. NMR images showed microangiopathy and leukoencephalopathy.

Case No. 19. EU, 28 years old, M. Epilepsy, Visual hallucinations, mutism, wandering, low blood pressure, disorders of memory, constipation, Family background of mental diseases and epilepsy. NMR images showed microangiopathy and leukoencephalopathy, frontotemporal cortical atrophy and arachnoidocele selar.

Case No. 20. FV, 74 years old, M. Epilepsy, Diabetes, high blood pressure, abnormal EEG. NMR images showed microangiopathy and leukoencephalopathy, cortical atrophic changes and prominent sulcus and cisterns, and multiple periventricular hyperintensities.

Case No. 21. DG, 32 years old, F. Migraine, Facial paralysis. Left Hemiparesis. NMR images exhibited hyperintense focus at the level of corona radiata and semi oval center, areas of in specific gliosis. Stress conjugal.

Case No. 22. GB, 43 years old, F. Headache, visual disorders, dizziness, seizures. NMR showed subcortical leukoencephalopathy, pituitary cist and prechiasmatic aneurism.

Case No. 23. AAA. 77 years old, F, Diabetes, paralysis of IV cranial nerve, left ophthalmoplegia, vascular hypotension. NMR showed subcortical and periventricular leukoencephalopathy.

Case No. 24. MF, 44 years old, F. High blood pressure, Memory disturbances, Depression, hypoacusia, and dyslipidaemia. NMR showed supratentorial subcortical leukoencephalopathy.

Case No. 25. IS, 88 years old, F. High blood pressure, Headache, gait and sleep disturbances. NMR showed arteriosclerotic microangiopathy and leukoencephalopathy.

Case No. 26. GF. 85 years old, M. Parkinson disease. Depression, High blood pressure, loss of equilibrium, sleep disorders, nightmares, hand tremor, bradykinesia. NMR showed arteriosclerotic microangiopathy and leukoencephalopathy.

Case No. 27. JV, 76 years old, M. Two Ischemic Strokes, high blood pressure, dysarthria, severe speech disorder, RMN showed arteriosclerotic microangiopathy and leukoencephalopathy and multiple hyperintense images in brain parenchyma.

Case No. 28. OP, 78 years old, M. Parkinson disease. Bradykinesia, Cardiovascular disease, low blood pressure, insomnia, acroparestesis. NMR showed arteriosclerotic microangiopathy and leukoencephalopathy.

Case No. 29, JNC, M. Brain trauma. Ischemic stroke. Headache. RMN showed left ischemic lesion fronto-temporal, microangiopathy and leukoencephalopathy, and demyelinating disease.

Case No. 30. DP, 79 years old. M. Cerebral palsy. Diabetes and dyslipidaemia, gait disturbances, body drowsiness. RMN images showed microangiopathy and leukoencephalopathy, atrophic changes of bran cortex and cerebellum, vascular atheromatosis changes, bilateral diffuse myointimal carotid thickening.

Case No. 31. ML. 79 years old, M. Traumatic cerebrovascular accident. After neurosurgery he suffered, Arnold suboccipital neuritis, hand tremor, speech disturbance. RMN mages showed microangiopathy and leukoencephalopathy, thinning of callosal body, loss of periventricular white matter substance and deep cortical sulcus.

Case No. 32. JS, 76 years old. M. Parkinson disease. Depression, Anxiety, sleep disorders, hyperactive, inclined postural body, visual hallucinations, speech disorders and suicide attempt. RMN images showed microangiopathy and subcortical and periventricular leukoencephalopathy.

Case No. 33. MM. 65 years old. F. Parkinson disease. Bradykinesia, tremor, insomnia, loss of body weight, difficult swallowing, visual hallucinations, hypoacusia and speech disorder. RMN images showed microangiopathy and leukoencephalopathy and atrophic changes of bran cortex.

Interpretation of Results

From total population examined twenty seven patients studied exhibited NMR images of leukoencephalopathy and microangiopathy (89%), eleven cases showed high blood pressure (42%) and two cases exhibited low blood pressure (2%), nine cases with Parkinson disease (27%), five cases showed migraine (21%), five cases with type II diabetes (15%), four cases with Alzheimer disease (12%), two cases with epilepsy (6%), three cases with stroke (9%), nine cases with depression (24%), one case with hyperthyroidism and one case with Arnold temporal arteritis.

We observed the following interactions leading to vascular dementia: Alzheimer disease and migraine (Alzheimer mixed dementia), migraine and Parkinson disease (Parkinson mixed dementia), stroke and high blood pressure, stroke and migraine, epilepsy and high blood pressure. The exact pathogenetic mechanisms through which these interactions cause dementia are still unknown.

High blood pressure	42%
Parkinson disease	27%
Depression	24%
Migraine	21%
Alzheimer's disease	12%
Stroke	9%
Diabetes	9%
Arnold temporal arteritis	1%
Epilepsy	6%
Hyperthyroidism	1%

Table 1: *Small cerebral vessel disease. Percentage frequency of neurological, psychiatric and metabolic diseases.*

As shown on above case reports, the patients exhibited some of the following neurobehavioral dysfunctions: severe dizziness, cervicalgia, language disturbances, sleep disorder, loss of implicit and explicit memory, aggression, crisis of hyperexcitability, sleep, appetite and recognition disorders, headache, tonic-clonic convulsive syndrome with auras, visual and auditive hallucinations, temporo spatial disorientation, persecution delusions mood disorders, tachylalia, mutism, wandering, gait disorder featured by impaired balance and coordination. muscle weakness and spasticity of lower limbs, sinusal arrhythmia, loss of sphincter control and constipation.

We found the following neuropathological changes: leukoaraiosis in one case, arteriosclerotic microangiopathy and leukoencephalopathy in twenty seven cases. Five patients exhibit subcortical white matter hyperintense focus, two cases with ventriculomegaly, one case with areas of encephalomalacia related with previous strokes, cortical atrophy, and cortical calcifications, granulomatous in nature.

Microangiopathy and leukoencephalopathy	27
Cortical atrophy	6
Subcortical cystic leukoencephalopathy	5
Ventriculomegaly	2
Cerebellar lesions	3
Post stroke encephalomalacia	1
Leukoaraiosis	1

Table 2: *NRM images on small cerebral vessel disease.*

The following comorbidities or risks factors were found: high blood pressure, arteriosclerosis, cardiac disease, diabetes, stroke, hypothyroidism and epilepsy.

Discussion

Leys., *et al*. [19] earlier emphasized the relationship of magnetic resonance image and the vascular dementia. Magnetic resonance imaging (MRI) techniques are of major interest to detect the vascular origin of dementia: the lack of focal lesions or leukoencephalopathy excludes the vascular origin of dementia Occlusions of large extra-cerebral arteries usually lead to cortical or large subcortical infarcts or both. Dementia may be due to multiple infarcts or to a single infarct located in a strategic area. Lacunar infarcts are due to the occlusion of a thickening arterial wall due to lipohyalinosis, usually in a patient with arterial hypertension. Lacunes are located in a territory supplied

by the deep perforators. According to these Authors, fifteen patients exhibited microangiopathy and leukoencephalopathy indicating the vascular source of dementia of small vessel disease.

We have found six cases of Alzheimer disease related with migraine, high blood pressure and vascular dementia. According to Hentschel., *et al*. [20-22], Alzheimer's dementia (AD) and vascular dementia (VD) are the two major forms of dementia in the elderly. They have been separated categorically on the basis of pathophysiological findings and clinical operationalized criteria. A controversial discussion exists about the coincidence or interaction of genetically determined risk factors of AD (Alzheimer disease) and/or vascular dementia (VD). Further interactions between AD and VD exist with regard to perivascular mediators and those factors which impair cerebral blood flow. Based on these and other recent neuropathological and therapeutic findings the Authors proposed the hypothesis that the two specific etiopathologies of AD and VD interact to precipitate clinical dementia in the individual and that the individual phenomenology of these dementias is modified by vascular risk factors. Microangiopathic lesions of the brain tissue correlate with the clinical diagnosis of vascular subcortical dementia.

The prevalence, morphology, and pathogenesis of vascular dementia (VaD), recently termed vascular cognitive impairment (VCI), and of mixed dementia (Alzheimer disease associated with vascular encephalopathy) are a matter of discussion and clinical diagnostic criteria for these disorders [15]. According to Jellinger (2004), further studies are needed to validate diagnostic criteria for VaD/VCI and to clarify the impact of vascular lesions on cognitive impairment as a basis for more precise clinical diagnosis, early prevention and management.

Alzheimer pathology and small vessel disease may interact synergistically. The lesion pattern of "pure" VaD, related to arteriosclerosis and microangiopathies, differs from that in mixed-type dementia (AD with vascular encephalopathy), more often showing large infarcts, which suggests different pathogenesis of both types of lesions [16].

In our study we have found 27 cases related with microangiopathy and leukoencephalopathy (81%). Microangiopathic lesions of the brain tissue has been correlated with the clinical diagnosis of vascular subcortical dementia [20-22]. According to Targosz-Gajniak., *et al*. [18], the age of patient is a significant factor correlating with the location of white matter lesions (WML) in patients with VCI and AD. The amount and size of white matter lesions (WML) in the periventricular and subcortical regions of the brain correlates with the severity of dementia. These Authors did not related their findings with blood hypertension. However, a great number of previous studies demonstrates a strong association of frequency and severity of WML with increasing age and presence of cerebrovascular risk factors such arterial hypertension.

According to Bartolini., *et al*. [23], cortical hypoperfusion may be related to cerebral atrophy or may reflect deafferentation secondary to severe leukoencephalopathy and may possibly contribute to severe motor and cognitive impairment.

In the present study we have found neurobehavioral disorder in seventeen cases whereas depression was found in six cases. Some earlier studies revealed an association with neuropsychiatric deficits including gait disorders, urinary incontinence, affective lability and reduced attention and information processing speed [24].

In the present study we described leukoaraiosis in one patient. Unspecific changes of the white matter signal are often called leukoaraiosis. They differ from the normal white matter signal. These changes are found with increasing frequency in persons older than 60 years and also patients with dementia and cerebrovascular diseases Bischoff and von Einsiedel (1997) earlier postulated that neuroradiological and clinical criteria differentiate between leukoaraiosis and diseases of the white matter, especially enlarged Virchow-Robin spaces, lacunar infarction, subcortical arteriosclerotic angiopathy (Binswanger's disease), leukoencephalopathy of different origin, and demyelinating diseases [25].

The terms Binswanger's disease and arteriosclerotic subcortical encephalopathy are often applied to elderly patients with dementia and a diffuse hypodensity of the white matter on CT scan (or increased signal on MRI). Recently, similar white matter abnormalities have been reported in non-hypertensive patients with Alzheimer's disease and in elderly healthy people, casting doubt upon Binswanger's disease as an entity. These findings also suggest that the descriptive term leukoaraiosis meaning rarefied white matter is more appropriate than the term leukoencephalopathy. Nevertheless, within the group of patients with an ischemic stroke, several data suggest that leukoaraiosis is not a fortuitous finding and does not simply reflect ageing. Actually, these patients have a particular clinical profile, with intellectual deterioration, chronic hypertension, usually patent carotid arteries, and a deep location of the presenting infarct. Moreover, hypertension seems to be still more strongly associated with leukoaraiosis than with a deep location of the infarct (lacunar infarction) [26].

Arteriosclerotic narrowing of cerebral arteries was once viewed as the key to mental decline. As Alzheimer's disease gained recognition and the concept of multi-infarct dementia achieved acceptance, vascular dementia came to be regarded as uncommon. The changing nature of cerebral vascular disease, the aging of the population and the widespread use of brain imaging techniques have brought new prominence to vascular dementia, chiefly in the form of an epidemic of "Binswanger's disease". Growing evidence suggests that not only grey matter lesions but also white matter lesions contribute to dementia, that vascular factors commonly coexist and interact with Alzheimer changes and that Alzheimer's disease has a vascular and potentially treatable component. Vascular dementia needs to be redefined, reappraised and reinvestigated [27]. Vascular dementia is the most common cause of dementia in the elderly after Alzheimer's disease. Many forms of vascular dementia have been described: multi-infarct dementia, lacunar dementia, Binswanger's subcortical encephalopathy, cerebral amyloid angiopathy, white matter lesions associated with dementias, single infarct dementia, dementia linked to hypoperfusion and haemorrhagic dementia. The difficulty of diagnosing vascular dementia must not be underestimated and an international consensus is needed for epidemiological studies. The NINCDS-AIREN group has recently published diagnostic criteria. The State of California Alzheimer's Disease Diagnostic and Treatment Centers also proposed some which differ from the NINCDS-AIREN criteria in considering only ischemic vascular dementia and not other mechanisms such as hemorrhagic or hypoxic lesions. Most studies stress hypertension as the most powerful risk factor for all forms of vascular dementia [28,29]. Our study also supports this point of view.

More recently, small areas of signal loss on T(2)-weighted images called microbleeds (MBs), have been reported. Cerebral MBs are focal deposits of hemosiderin that indicate prior microhemorrhages around small vessels, related to either ruptured atherosclerotic microvessels or amyloid angiopathy. Consequently, using brain MRI for the detection of microangiopathy may prove useful to improve our understanding of the impact of the vascular burden in AD pathology. The relationship between microangiopathy and the clinical course of AD or the conversion of mild cognitive impairment to AD remains questionable in terms of cognitive or affective symptoms, particularly if we consider MBs [11].

White matter locations that were likely to contain hyperintensities tended to be hypoperfused in ADs compared with healthy aging. This finding is suggestive of AD-specific pathology that reduces the perfusion at anatomic locations susceptible to the formation of through either the neurodegenerative process or AD-related vasculopathy or both [30].

Some Authors have postulated the hypothesis of mitochondrial vasculopathy. Mitochondrial vasculopathy manifests as either microangiopathy or macroangiopathy. Clinical manifestations of mitochondrial microangiopathy include leukoencephalopathy, migraine-like headache, stroke-like episodes, or peripheral retinopathy. Mitochondrial macroangiopathy manifests as atherosclerosis, ectasia of arteries, aneurysm formation, dissection, or spontaneous rupture of arteries [31-33].

In our study high blood pressure and cardiovascular disease are closely related with the neurobehavioral and mental diseases. Therefore, the term vascular dementia might be appropriated applied. In addition, the diabetes type two in elderly and the associated metabolic syndrome should be considered as risk factors.

According to Duerin., *et al*. [34] significant clusters for cognitive performance were detected for both lacunar lesions and white matter hyperintensities. Strategic locations included the anterior parts of the thalamus, the genu and anterior limb of the internal capsule, the anterior corona radiata and the genu of the corpus callosum.

We found six cases of migraine with leukoencephalopathy related with Alzheimer and Parkinson diseases. Patients with migraine are at an increased risk for white matter lesions, typically multiple, small, punctate hyperintensities in the deep or periventricular white matter. The underlying pathogenesis of white matter lesions in migraineurs is unknown, and the lesions are usually nonspecific and of unclear clinical significance. Occasionally, white matter lesions may represent a secondary cause for headaches such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [35].

Genetic leukoencephalopathies with exclusive adulthood presentation, most of which have an autosomal dominant inheritance. The most common forms are related to vascular pathology, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), COL4A1 [36].

We found two cases of epilepsy with visual hallucinations, mutism, wandering, low blood pressure, disorders of memory, frontotemporal cortical atrophy, ventriculomegaly, constipation and family background of mental diseases and epilepsy, associated to microangiopathy and leukoencephalopathy. Verhagen., *et al*. [37] described a case of 11-year-old girl with intractable type II epilepsia partialis continua and severe progressive central and cortical atrophy, mainly of the right hemisphere. Brain biopsy revealed microangiopathy of the cortex-penetrating arteries, patchy necrosis of the cortex, and small loose infiltrates of lymphocytic cells. Biochemical analysis showed normal pyruvate metabolism and citric acid cycle in gray and white matter. Patients with epilepsy are at a higher risk for microangiopathy presented as retinopathy and nephropathy. Long-term antiepileptic drug (AED) therapy, particularly with enzyme-inducing AEDs, high triglyceride levels, and inflammatory processes play an important role in the development of microangiopathy in patients with epilepsy [38].

We have found a relationship between Parkinson disease and microangiopathy and leukoencephalopathy in eight patients. Ebersbach., *et al*. [39] also report similar a relationship between idiopathic Parkinson disease and microangiopathy. This study was conducted on a population composed of 20 patients with Parkinson disease (PD) whose neuroimaging exams revealed vascular alterations in the white matter. Apparently, there are not further reports suggesting this relationship since we have not found similar additional studies dealing with Parkinson disease and vascular diseases. It is interesting in further studies to establish a precise differentiation between Parkinson disease and vascular parkinsonism.

Parkinsonism due to cerebrovascular disease (vascular parkinsonism, VP) is a distinct clinicopathological entity [40]. Studies of presynaptic striatal dopamine transporters (using single photon emission computed tomography) showed a significant reduction in striatal uptake ratios in Parkinson disease (PD) but not in VP [41]. VP develops as a result of ischaemic cerebrovascular disease, so aetiologically it is classified as secondary parkinsonism. It has been variably referred to in the literature as arteriosclerotic parkinsonism, vascular pseudo-parkinsonism, and lower body parkinsonism [41]. In VP the DAT-scan proved normal dopamine content of the striatum in contrast with Parkinson's disease (PD) [42].

It was interesting to observe a twenty eight years old patient with microangiopathy and leukoencephalopathy indicating that small vessel disease can also be observed in young adult patients.

In six patients we found cortical atrophy apparently due to blood hypoperfusion inducing severe motor and cognitive impairment [23].

Two elderly patients, one with trigeminal neuralgia and another with ophthalmoplegia also exhibited microangiopathy and leukoencephalopathy suggesting a close relationship with cranial nerve pathology.

Conclusion

Most patients with nuclear resonance images of microangiopathy and leukoencephalopathy showed cervicalgia, language disturbances, sleep disorder, loss of short and long term memory (implicit and explicit memory), aggression, crisis of hyperexcitability, sleep, appetite and recognition disorders, headache, sinusal arrhythmia, tonic-clonic convulsive syndrome with aura, visual and auditive hallucinations, temporo-spatial disorientation, impaired balance and coordination, muscle weakness, gait disorders as onward and slow march, persecution delusions, loss of sphincter control, mood disorders, tachylalia, mutism, wandering, constipation and spasticity of lower limbs and constipation. We found the following neuropathological changes: leukoaraiosis in one case, microangiopathy and leukoencephalopathy arteriosclerotic in 27 cases. Some patients exhibit subcortical white matter hyperintensive focus, ventriculomegaly, areas de encephalomalacia related with previous strokes, cortical atrophy, and cortical calcifications, granulomatous in nature. We observed the following interactions leading to vascular dementia: Alzheimer disease and migraine (Alzheimer mixed dementia), migraine and Parkinson disease, stroke and high blood pressure, stroke and migraine, and epilepsy and high blood pressure. Some patients exhibit subcortical white matter hyperintensive focus and ventriculomegaly.

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