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Updating data on cognitive impairment in stroke patients

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ABSTRACT

Vascular cognitive impairments are the expression of complex interactions between vascular etiology, risk factors (brain diseases, white matter lesions, etc.) and cellular changes at the brain level. Consequently, vascular cognitive impairment is highly dependent on the location, extent (volume of brain tissue affected) and number of lesions. Memory impairment is not necessarily characteristic of vascular cognitive decline, usually having an evolution with episodic exacerbations and multiple cerebrovascular attacks (cumulative effect), thus producing a gradual deterioration. In recent years, the concept of mild cognitive impairment has emerged as a potential form of predementia, but which can progress to different types of dementia, including Alzheimer's disease or vascular dementia. This review presents recent data related to the etiological and risk factors of cognitive decline after stroke, the associated neuropsychological and behavioral changes, the clinical forms/diagnosis and general principles of vascular dementia therapy. As preliminary conclusions, the Hachinski score is a very useful tool in differentiating vascular dementia from Alzheimer's dementia. A score greater than 7 points (especially when associated with imaging and anamnestic criteria) suggests a vascular etiology of dementia, whereas a score of 4 points or less excludes such an etiology. Although it is not the only factor involved, vascular etiology is still intensively studied because it is the only one that can be prevented and treated.

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Introduction

Cerebral diseases are increasingly common, so the interest shown in the study of cognitive deficits due to vascular diseases is also increasing. In vascular patients, cognitive disorders represent an additional cause of disability, the increase in the number of patients with cognitive disorders being related to the increase in life expectancy as well as vascular and non-vascular pathology [1,2]. Mild or average changes in cognitive functions may go unnoticed during a routine clinical examination, due to compensatory capacities, especially in patients with a higher socio-educational level [2]. Cognitive decline must affect the patient`s daily activities. Neuropsychological tests are difficult to perform in patients with aphasia, so that such patients are excluded from the definition of vascular dementia [3,4]. In vascular dementia the memory deficit is decreased compared to that in Alzheimer disease [1,3]. If the memory deficit occurs early and worsens progressively, without corresponding focal lesions, the diagnosis of vascular dementia is unlikely [4,5]. In general, a temporal association (of approximately three months) is found between stroke and cognitive impairment [6].

Cerebrovascular diseases do not preferentially affect the mesial temporal lobe, as in the case of Alzheimer disease, and therefore the existing evidence to date shows a greater proportion of subcortical dysfunctions compared to memory deficits [3,7]. More recently, the term mixed

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dementia is used, which includes both cerebrovascular disease and Alzheimer dementia [8,9].

Before the 1990s, almost all cerebrovascular diseases leading to dementia were attributed to cortical and subcortical infarcts. The concept of vascular dementia was introduced to describe dementia caused by infarcts of various sizes, including lacunar infarcts and microinfarcts [2,5,10].

Discussions

Etiological and risk factors of cognitive decline after stroke

The most common etiological factors related to cognitive decline after stroke are represented by: damage to the large arteries (arterio-arterial embolism, intra or extracranial arterial occlusion), cardiac embolic events, small vessel disease (lacunar infarcts, ischemic lesions of the white matter), hemodynamic mechanisms, specific arteriopathy, cerebral amyloid angiopathy (CAA), intracerebral and subarachnoid hemorrhages, hematological causes and venous diseases, hereditary conditions (autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy - CADASIL, and autosomal recessive cerebral arteriopathy with subcortical infarcts and leukoencephalopathy - CARASIL) [11,12].

In CADASIL the cognitive impairment occurs in association with diffuse changes in the white matter. Imaging shows hyperintense T2 signals at the level of the periventricular white matter, at the level of the basal ganglia and at the level of the brainstem [11,13]. Blood vessels show concentric thickenings produced by PAS+ deposits of granular material. These deposits which are microscopically observed as consisting of osmophilic granular material are arranged at the level of the basal lamina of the smooth muscle cells [13,14]. This aspect is characteristic of CADASIL. Affected small arteries and arterioles are located in the white matter and leptomeninges [14,15]. For diagnosis, biopsy of skeletal muscle arteries, nerves and skin is also performed [13-15].

Cerebral amyloid angiopathy (CAA) is a common abnormality in the elderly [10]. Existing leptomeningeal deposits have mainly β amyloid properties [16,17]. Rare familial forms are caused by mutations in at least two codons in the β amyloid precursor protein gene [10,16]. Amyloids derived from other proteins have been identified in several hereditary conditions: cystatin c in the Icelandic variant, transthyretin in familial amyloid polyneuropathy [16,17]. The prevalence of the disease increases with age. Sporadic CAA was found in more than 30% of autopsied elderly patients [16,17]. Patients show a different degree of vascular damage. The initial deposits are located in the basal lamina around the smooth muscle cells [16,18]. Later, these cells die and the deposits become thick and circumferential [18]. Congo red staining is required to confirm the amyloid nature of the deposits. Cases of β amyloid angiopathy with additional cystatin C deposits have also been reported [16-18]. Patients with severe CAA have a high risk for hemorrhagic stroke, but CAA was also found in patients with ischemic stroke [16,17]. The most affected are the occipital and parietal lobes [17,18]. CAA can be either a separate entity or associated with Alzheimer disease [5,18]. Cognitive impairment of CAA patients occurs as a result of hemorrhages, cortical microinfarcts or white matter lesions [18].

One of the important risk factors is high blood pressure. Arterial hypertension has as its main effect the acceleration of the atherosclerotic processes [12,19]. The first atherosclerotic changes occur in the carotid artery and the vertebral artery, followed by the arteries of the polygon of Willis. Subsequently, atherosclerotic changes also occur in the smaller cerebral arteries [19,20]. Over time, hypertensive patients show thickening of the media and proliferation of the intima, thus producing a decrease in the vascular lumen and respectively an increase in flow resistance [19,20]. Penetration of plasmatic components at the level of the vascular wall causes hyaline deposits in the media wall [19,21]. Cerebral lipohyalinosis causes continuous alteration of the vascular walls, from progressive thickening and narrowing to post stenotic dilatations, fibrinoid necrosis and thrombosis [16,21]. Due to the fact that there are few collaterals in the white matter, it is very vulnerable to hypoxia [4]. Patients with ischemic lesions in the white matter have leukoaraiosis, meaning diffuse and symmetrical periventricular lesions [20,21].

In the case of Biswanger Disease, the normal appearance of the cortex contrasts with the discoloration of the white matter, corresponding to demyelination [22,23]. Massive demyelination is associated with high astrocytic reactivity and loss of oligodendroglia cells [22,24]. Homogenous or focal demyelination occurs at the level of the oval center, predominantly periventricular, with sparing of the U-shaped fibers, optic radiations, corpus callosum, internal and external capsule and frequently the central portion of the temporal lobe [22,25]. Microscopically, in Biswanger disease the loss of various degrees of myelin can be noted, from the reduction of oligodendroglia to axonal demyelination with relative axonal preservation accompanied by astrocytic gliosis [23-25]. An important hyalinization of the arterioles in the white matter and basal ganglia are also observed while perivascular spaces may be enlarged [26]. White matter areas with increased signal on magnetic resonance images correspond histopathologically to the so-called rarefaction aspect [27,28]. Demyelination - the presence of ″bare″ axons has not been convincing demonstrated, although ″spots″ of myelin loss have been noted, probably secondary to the phenomenon of rarefaction [26,27,29]. The periventricular margins were characterized by

subependymal gliosis and loss of ependyma, the latter leading to extravasation of cerebrospinal fluid and increased water content [27].

Cortical microinfarcts can take any form, but most commonly appear as narrow vertically folded glial scars that extend deep into the cortex in patients with a history of hypertension [27,29]. Areas with a high concentration of these scars present a granular pattern upon external examination of the brain surface [26]. Multiple granular microinfarcts were considered to be the only identifiable substrate for dementia [30]. Another histopathological aspect that should be mentioned is that of pseudolaminar necrosis [30,31]. This involves loss of neurons along the central area of the cerebral cortex in an irregular distribution [27,32]. It can appear either widespread or focal in response to arterial obstruction. The hippocampus is one of the critical areas in which cognitive impairment can develop after ischemic stroke [31,32]. The differential vulnerability of the hippocampus is given by the pattern of neuronal loss and dense gliosis in the CA 1 sector as a consequence of ischemia [10]. In understanding the occurrence of cognitive decline due to vascular causes, an important role is played by the changes at the level of the white matter [10,31]. They appear as deep periventricular hyperintensities. Hyperintensities placed deep in the white matter are present in most patients with vascular dementia and are much more severe than in patients with Alzheimer Disease or dementia with Levy bodies [22]. The distribution of these hyperintensities influences the clinical manifestations of patients with cognitive impairment [10,19]. An important aspect that occurs at the level of blood vessels associated with changes in the white matter is lipohyalinosis [22]. This term actually represents a redefinition of arteriosclerosis. This change occurs more frequently in patients with arterial hypertension. In these patients, hypertension causes smooth cell proliferation, thickening the vascular wall in the absence of other changes [16,19]. Hypertension can alter the endothelium, leading to thickening of the basal lamina and deposition of eosinophilic material [16,22]. There have been studies that attempted to separate arteries from veins in a hyalinized state. Noninflammatory collagenous thickening of the venous wall has been observed to occur in approximately 65% of cases in the periventricular regions in elderly patients [10,16].

Other risk factors for the production of lesions in the white matter excepting hypertension are: advanced age, episodes of hypotension, increased plasma viscosity, the history of lacunar infarcts, diabetes mellitus, vascular diseases and genetic factors (pathogenic mutations/ amyloid precursor protein Notch 3, specific genetic polymorphism/ apolipoprotein E, etc.) [4,12,19]. There are in cognitive impairment after stroke some alterations beyond classical histopathology, which are evident only by immunohistochemical techniques [32,33]. Global ischemia produces accumulation of amyloid β precursor protein in the hippocampus, predominantly in regions surrounding death zones [27,33]. Induction of amyloid β precursor protein in neurons occurs under the auspices of hyperglycemia. Amyloid β is expressed in reactive astrocytes between day 3 and day 60 after stroke [27,32,33]. Amyloid β precursor appears early in the extracellular space [23,26]. Apolipoprotein E expression is also increased [26]. The deposits of this amyloid represent the best argument in favor of the concept of chronic hypoperfusion [19,20].

Mutations in the NOTCH 3 gene are responsible for causing the disease [34]. This gene encodes a transmembrane receptor. Most mutations are in the first two exons; these translate into cysteine increases or decreases, with the production of a number of cysteine residues, thus preventing the formation of disulfide bridges [11,15,33]. Proteolytic NOTCH 3 fragments accumulate in the cell membrane of smooth cell in close proximity, but not in osmophilic granular deposits [34].

Another factor is atrial fibrillation, which can correlate with so-called hemodynamic dementia [19,20]. This usually occurs after an episode of severe hypotension [19,20]. In patients who presented the diagnosis of hemodynamic dementia, they present at necropsy aspects of multi-infarction dementia [35,36]. An infarct with a volume of more than 20 ml (50- 100 cm^3) distinguishes between senile dementia and vascular dementia [36,37]. It is unlikely that there is a certain predictable volume for vascular dementia [38]. Currently, the diagnostic criteria place more emphasis on the number of infarcts than on the volume of the infarct [37,38]. In terms of location, the most frequently involved locations are: thalamus, the territory of the anterior cerebral artery, the left hemisphere and the frontal lobe. Large infarcts generally affect the cerebral cortex [39,40]. Lacunae are visible usually cavitary, with uneven edges, ranging from 0,5 to 15 millimeters in diameter [40,41]. Lacunae will be distinguished from widened perivascular spaces by the characteristic of their borders and by the absence of transverse gliovascular fibers [40,42]. Both lacunae and wide perivascular spaces are preferentially located in the basal ganglia and white matter, predominantly in the frontal lobe [41,42]. They may increase the risk of dementia if are in large numbers or if they are located in critical areas [42]. Lesions in critical areas such as the medial thalamus, head of the caudate nucleus, frontal and cingulate cortex and angular gyrus may be associated with dementia [41-43].

Neuropsychological and behavioral changes

Regarding the neuropsychological and behavioral changes in vascular cognitive decline, they occur either as a result of cerebrovascular injury or as a result of preexisting medical problems [44,45]. Patients with

vascular lesions may also have sudden onset of behavioral changes [46]. For example, parietal lobe infarction can produce a state of agitation and confusion suddenly appearing in patients with normal cognitive status until that moment [44,46]. It is important to be excluded delirium, confusional state or other causes of dementia [47].

It has been observed that depression is a frequent aspect in patients who have suffered a stroke. It appears especially in the first months after stroke [44,48]. The patients with more pronounced cognitive decline showed a longer period of post-stroke depression [48,49]. The occurrence of depression seems to be involved: the location and size of the lesion, psychosocial factors and genetic aspects [45,46]. It was observed that depression had a higher incidence in stroke patients in the left cerebral hemisphere [44,46]. In patients with stroke in the left frontal lobe, it seems that the incidence of depression would be higher compared to localization in other cerebral lobes [46,48,50]. The anxiety is added to most of these patients. Depression after stroke is associated with the presence of silence infarcts, carotid atherosclerosis, hypertension, diabetes and the presence of risk of myocardial infarction [50,51]. There are also cases where depression is underdiagnosed because of the acute symptoms of the cerebrovascular event. It appears that the presence of cortical atrophy correlates with the increased incidence of post stroke depression [52]. It is important to treat depression as early as possible, because untreated depression generally delays recovery [53,54]. Patients with late-onset depression have much more frequent cognitive impairment. The relationship between preexisting depression and stroke could be explained by increased platelet function activity through increased adrenergic activity [51-53]. There were studied and noted that patients with stroke and depression had more pronounced depressive state compared to non-depressed stroke patients [46,51]. In patients with depression and lesions of the left hemisphere, the cognitive impairment was more pronounced than in patients with depression and lesions of the right hemisphere [50,51]. Besides depression, other manifestations that can accompany cognitive decline after stroke are represented by hallucinations, identification disorders, aggression, sleep-wake rhythm disorders and eating disorders [51-54].

Clinical forms of vascular dementia

Vascular subcortical dementia

Vascular subcortical dementia includes Binswanger disease and lacunarism, being caused by damage to small vessels [55,56]. It is characterized by lacunar infarcts, focal and diffuse white matter lesions, and incomplete ischemic lesions [55-57]. In most patients the symptoms start slowly; in addition to the subcortical cognitive syndrome, patients have hemiparesis, dysarthria, gait disturbances, emotional instability, bulbar signs [57,58]. Central motor neuron syndrome may occur in the initial phase [57].

To diagnose Binswanger disease, the patient must present the dementia syndrome, vascular risk factors, eloquent clinical signs and imaging appearance with bilateral and multifocal lesions [56,57]. Episodic memory is severely affected; gait disturbances, dementia, and pseudobulbar status are the main clinical elements that define Binswanger disease [56,58]. Clinical features of these patients also include apathy, depression, and sphincter incontinence. Apraxia, hemiasomatognosia, hemianopsia, or anosognosia rarely occur [56-58].

Vascular cortical dementia or multi-infarct dementia

It is more of a syndrome than a disease, and involves damage to the large cerebral vessels. In addition to medium level memory impairment, it also includes aphasia, agnosia, apraxia, as well as dysexecutive syndrome [59]. Due to multiple cortico-subcortical infarcts, patients have added neurological deficits such as visual field changes, facial paralysis, sensory-motor lateralized changes and gait disorders [59,60]. The existence of episodes of transient ischemia accident and stroke/ the existence of neurological deficits are characteristic of this type of dementia [59-61].

Dementia caused by specific localized infarcts

It is generally caused by small, focal ischemic lesions involving critical sites through their high cortical role. Cortical lesions include the hippocampus, angular gyrus and cingulate gyrus [62]. Bilateral hippocampal infarcts are particularly characterized by amnesia. Subcortical lesions include thalamus, fornix, globus pallidus, or caudate nucleus [62,63]. Bilateral thalamic lesions are characterized by apathy, agnosia, apraxia, aphasia and attention disturbances [62,64].

Dementia from CADASIL

CADASIL begins with migraine as the first symptom in approximately 40% of patients. In most cases, migraine occurs in the third decade of life [65,66]. Smoking and high levels of homocysteine may increase the risk for more strokes and migraine [66,67]. Dementia in CADASIL is of the subcortical type [65,67] and appears as a result of recurrent strokes [14,66]. Depression usually occurs early, with men being more prone to it compared to women [66,67]. Patients may also present with pseudobulbar palsy, epileptic seizures, or cerebellar ataxia [14,65,67].

The diagnosis of the disease is confirmed by the appearance of eosinophilic inclusions in the arterioles at the skin biopsy [14]. These inclusions are visible only in electron microscopy.

Dementia from cerebral amyloid angiopathy (CAA)

There are both familial and sporadic cases of dementia from CAA, so cognitive decline is found in both familial and sporadic cases [17,68]. The earliest age of onset is in the third decade of life [68,69]. First stroke-like episode leads to cerebral microbleeds that may be preceded by diffuse changes in the white matter, an aspect that would

explain the rapid evolution towards cognitive decline [68,70]. The cognitive impairment is accompanied by ataxia, seizures and spasticity [69,70].

Dementia caused by subcortical white matter lesions

These patients show mental slowness, the presence of the masseter reflex, asymmetric left-right motor deficits, and extrapyramidal signs [24,30]. The clinical diagnose of the disease comprise the existence of complicated peripheral vascular disease, changes highlighting in cerebrospinal fluid as signals of blood-brain barrier dysfunction, the existence of a clinical syndrome of subcortical or fronto-cortical type and neuroimaging highlighting the changes in the white matter [24,30].

Paraclinical methods

Electroencephalography (EEG)

EEG aspects in vascular diseases are polymorphic, either normal aspects or with functional changes being described [71]. The lesional anomalies can be focused or diffuse, sometimes masked by paroxysmal grapho-elements [71,72]. In superficial ischemic stroke accompanied by focal edema, EEG shows polymorphic delta activity. In the case of deep lesions, EEG may not be modified, or diffuse theta activity may appear [72,73]. In diffuse vascular lesions, EEG is slightly modified, expressed by slow alpha rhythm, diffuse fast frequencies, diffuse theta or localized in the posterior and bilateral temporal derivations [71,74]. Diffuse increase in slow wave activity occurs in dementia [71,72]. Abnormalities of slow wave appearance occur especially in parietal lobe syndromes. In the case of patients with dementia, EEG shows reduced alpha and beta rhythms as well as an increase in the frequency of slow waves (theta and delta) [75,76]. These rhythms were correlated with the degree of cognitive impairment [71,75]. Quantitative electro-encephalography has been used to compare patients with psychiatric problems with control group [74,76]. This type of electroencephalography requires a set of 15-20 electrodes placed in the classical areas. Data analysis is done using the fast Fourier transform to determine the strength of the EEG signal in each of the four frequency bands (alpha, beta, theta, delta). Quantitative EEG shows a decrease in EEG rhythms correlated with the degree of cognitive deficit assessed using neuropsychological tests [71,74,76]. Theta bands appear to be most appropriate in correlating with cognitive decline [71,76,77]. Significant increase in delta bands is an indicator of advanced stages of dementia [71,77].

Computerized cranial tomography (CT)

It is one of the most widely used investigations in the diagnosis of dementia. First of all, it should be noted the role of CT in differentiating vascular dementia from Alzheimer dementia [78,79]. The most important neuroimaging element that differentiates vascular dementia from Alzheimer dementia is the cerebrovascular lesions highlighted by imaging [80]. The absence of these lesions is one of the criteria for excluding the diagnosis of vascular dementia [79,80]. In Alzheimer dementia, cortical atrophy and internal hydrocephalus are much more important compared to vascular dementia [80,81]. In vascular dementia, parenchymal lesions are prevalent [78,79]. In Alzheimer dementia, predominantly external diffuse cortical cerebral atrophy is evident, with preferential hippocampal topography [81,82]. A predilected cortical atrophy of the temporal lobes is evident in their medio-basal portion [78,79]. When the disease progresses, the diffuse extratemporal cortical atrophy becomes more pronounced [80,81]. It seems currently that the most reliable for diagnosis are volumetric methods [82,83]. The volumetric assessment of the hippocampal atrophy and the amygdala nucleus is especially important [80,82,83]. The aspects described above are particularly characteristic of Alzheimer dementia [82,83]. Multi-infarct dementia occurs in the form of multiple brain lesions with the appearance of bilateral cortical and subcortical hypodensities [80,84]. The tomographic examination also diagnoses strategic infarcts, with localization at the hippocampal level, basal ganglia, caudate or thalamic nucleus [84,85]. Binswanger disease appears on tomographic examination in the form of bilateral and relatively symmetrical hypodensities of the white matter of vascular origin [80,81,86]. Peri and juxta ventricular hypodensities appear in the white matter, with asymmetric boundaries [85,87]. This tomographic aspect gave so called term leukoaraiosis [85,88]. In lacunar dementias, multiple lacunae with size between 2 and 10 millimeters are detected on CT [84,89]. Binswanger disease and lacunar dementia are incorporated into the notion of subcortical vascular dementia [81,86]. By neuroimaging, patients with vascular subcortical show extensive lesions in the white matter and multiple lacunae located deep in the gray matter and white matter [87,90]. These patients have a history of small or repeated TIAs that do not leave significant focal neurological signs [85,90]. Thus, the selection of patients with subcortical vascular dementia must be done primarily by neuroimaging.

Magnetic resonance imaging (MRI)

It represents a method by which images are obtained using radio frequency radiation, which explores the behavior of nuclei with an odd number of electrons inside the body, in a magnetic field. MRI is the most sensitive method of exploration [91,92]. Using MRI, anatomical details are obtained in all three planes, MRI also removing bone and air artifacts. The images obtained during the MRI examination, especially those in T2 are much more sensitive in the discovery of cerebrovascular disease compared to the images obtained by tomography. Hypointensity in T1W1 usually represents tissue

destruction and can be considered as a possible marker for complete infarction [93]. The hyperintense lesions in T2W1 and isointense in T1W1 may correspond only to demyelination [90,91]. FLAIR associated T1W1 has the advantage of differentiating lesions according to their aggressiveness regarding to the potential for cognitive impairment [90,92]. White matter lesions are visible on MRI as an abnormal, diffuse hyperintensity in T2W1, FLAIR and PDW1, without prominent intensity in T1W1 [91,92,94]. Due to the fact that the frequency of their appearance increases progressively with age, they are referred to under the name ARWMC (age related white matter changes) [95].

New magnetic resonance and molecular imaging techniques

Perfusion weighted imaging (PWI) is a magnetic resonance technique that is a good alternative to nuclear medicine in the evaluation of microvascular changes in patients with dementia [96].

Functional magnetic resonance imaging (fMRI) is a powerful technique in assessing brain activity based on changes in blood deoxyhemoglobin concentration [97,98]. In dementia, fMRI shows decreased activity in the mediotemporal lobe of patients [96,98]. Until now, studies using fMRI have been used to screen patients at risk of developing dementia.

Diffusion weighted imaging (DWI) is a technique for observing the microscopic motility of water molecules in tissues [99,100]. Using DWI, recent infarcts responsible for the stepwise decline can be detected in patients with vascular dementia [96,99,100].

Microscopic magnetic resonance requires high scanning fields, strong gradients and larger sequences compared to conventional MRI to create higher resolution images [101].

Single photon emission computed tomography (SPECT)

This method represents an important indicator of cerebral perfusion, useful in the assessment of cerebrovascular disease [102,103]. It is a paraclinical method with very important role in the diagnosis and prognosis of cerebrovascular disease. To study the reserve of vascular hemodynamics, it is necessary to study the human brain in two different conditions, at an interval of 24-48 hours, at rest and during vasodilatation [102-104]. Radioactive isotopes are used, and isotopic images obtained at rest and in vasodilatation can be used to monitor any changes in cerebral perfusion over 24 hours [102,104]. SPECT is also currently used for activation studies in patients with memory disorders [102,103].

Positron emission computed tomography

Positron emission computed tomography (PET) is very useful method in the early detection of cognitive dysfunctions. It can reveal neuronal changes before the appearance of neuronal depopulation, and thus before the appearance of large cognitive deficits [105,106]. It is used to establish functional deficit and diagnostic evaluation of dementia. It offers the possibility of early identification of those with dementia, especially of patients in whom neuropsychological testing is inconclusive and the clinical picture is ambiguous [106,107]. PET studies performed in the normal elderly population have shown the decrease with age in the metabolic parameters of glucose in the frontal lobe [105,107]. These values correlate with the cognitive decline that accompanies normal aging [107]. Both the parameters obtained by SPECT and those obtained by PET can correlate with the severity of cognitive decline, reflecting changes specific to certain forms of dementia. Patients can be classified according to the PET appearance, as a result of measuring the parameters of glucose metabolism [106,107]. Lower values were obtained in the frontal and temporal lobes of these patients [107,108]. Patients with multi-infarct dementia show disseminated focal regions of impaired carbohydrate metabolism [108]. In Binswanger disease, a lower white matter oxygen consumption was observed compared to that in multi-infarct dementia [105,109]. As deficits in cortical blood flow and glucose metabolism are characteristic elements of Alzheimer disease, PET provides important information especially in the case of patients suffering from this disease [106,108]. In multi-infarct dementia, a slight global reduction in glucose metabolism is observed with focal deficits in metabolic activity, disseminated in the cortex and white matter [110].

Principles of treatment in vascular dementia

Medicines were tested that fell into three categories: preventive treatment, treatment to improve cognitive decline, and symptomatic treatment. Understanding the pathophysiological mechanisms that lead to the production of cognitive decline for each individual case is an important step for choosing the correct treatment.

Preventive treatment in vascular dementia

Ideally, the disease should be detected in the presymptomatic stage or in the earliest clinical phase. The control of risk factors as well as the causes of cerebrovascular events is aimed at slowing the progression of the disease, preventing the occurrence of recurrent events [111,112]. As conventional risk factors are involved (hypertension, diabetes, smoking, hyperlipemia), it is very important to control them in the presymptomatic stage [111]. The PROGRESS (perindopril protection against recurrent stroke study) tested the hypothesis that the reduction in blood pressure achieved by the use of the conversion inhibitor (perindopril), could reduce the incidence of dementia among patients with cerebrovascular disease [113]. The definition of dementia in this study was made in two phases. It has an initial screening phase based on the Mini Mental State

Examination (MMSE), and the second phase in which the diagnosis of dementia was made using DSM IV criteria. MMSE is a short-standardized test that evaluates several areas, such as: orientation, short term memory, attention, concentration, long term memory, language reception [114]. The apolipoprotein E polymorphism was also investigated in the study of a possible interaction between the susceptibility of the gene polymorphism and the control effect of arterial hypertension in order to reduce the risk of developing dementia [113]. There is also evidence regarding the relationship between lipids and vascular changes involved in vascular dementia [115]. One of the hypotheses is that lowering lipid levels improves endothelial microvascular function, thus potentially reducing the risk of dementia [116].

Current treatment of vascular dementia

- Antithrombotic therapy

This therapy is very important in both primary and secondary prevention of stroke [117]. It is used in cases of atherosclerosis, whereas anticoagulation is used in cases of hypercoagulable state [117,118].

The studies carried out so far have shown that aspirin used in doses of 325 mg daily had a beneficial effect on the cognitive performance of patients with multi-infarct dementia [119]. The complete mechanism by which antithrombotic drugs can influence cognition remains to be elucidated. One of the hypothesis is that such types of therapeutic agents prevent the worsening of vascular dementia because they reduce the recurrence of stroke [119]. Aspirin has anti-inflammatory effect, an activity through which it can reduce cytokine production [119,120]. The recurrence of stroke can also be reduced using dual antiplatelet therapy. It should be mentioned that the use of this dual therapy increases the risk of hemorrhagic complications [121]. It seems that the use of thrombelastography predicts dual antiplatelet therapy – related hemorrhagic complication [121]. An important role in the occurrence of hemorrhagic complication is also played by the patient's associated pathology (an example would be the association of a stroke in a patient with liver injury). The hepatic injury can lead to coagulopathy and it is followed by encephalopathy [122]. With such a patient profile, the risk of hemorrhage increases in the case of dual antiplatelet therapy administration.

- Ergot alkaloids

Among the medications with the potential to restore the functional deficits of patients with vascular dementia, ergot alkaloids have been the most investigated. The beneficial effect could be explained by their vasodilatory action, by α1 mediated antagonism, and by the effects on the brain parenchyma [123,124]. The latter is modulated by nitric oxide synthesis, through dopaminergic and cholinergic effects. This increases the use of oxygen and the cellular uptake of glucose, which leads to an increase in the resistance of neurons and glial cells to ischemia [124]. The prototype of this drug class is hydergine [125], another representative drug being nicergoline [126]. A study of a heterogeneous group of nondemented subjects with white matter neuroimaging changes lasted 2 years, the conclusion being that treatment with nicergoline produced a significant attenuation of cognition in those subjects [127].

- Xanthine derivatives

Among the action mechanisms of these drugs there are reduction of phosphodiesterase activity, adenosine antagonism, reduction of intracellular calcium influx [128]. These actions can have the effect of decreasing platelet aggregation and fibrinogen levels, thus decreasing blood viscosity [129]. At the parenchymal level, they have a neuroprotective effect, decreasing astrocytic reactivity and increasing mitochondrial function [130]. One study compared the effectiveness of pentoxifylline (400 mg three times a day) with placebo over 9 months, patients diagnosed with multi-infarct dementia being included in this study [131]. Pentoxifylline has shown to increase brain glucose metabolism (measured by PET), selectively improving neuropsychological functions. Thus, cognitive deterioration in patients with vascular dementia was slowed. Denbufylline is another xanthine derivative that has been studied in trials for treatment of cognitive decline. One of the studies was done on patients with vascular dementia or mixed dementia and patients with Alzheimer dementia [132]. The diagnosis of dementia was based on the DSM III criteria and using the Hachinski score. Hachinski score studies the following features: an abrupt onset, progressive cognitive deterioration, fluctuating evolution, nocturnal confusion, relative preservation of personality, the presence of depression, somatic complains, emotional lability, the presence of arterial hypertension, history of stroke, the association of atherosclerosis, the presence of focal neurological symptoms and signs [132]. The MMSE score eligible for inclusion in the study had to be between 10 and 24 points. After 4 weeks of treatments, the patients were divided into two groups: one receiving denbufylline and the other placebo. The study then lasted 16 weeks, the final results of this study showing that the group of patients receiving denbufylline presented a significantly higher MMSE score than the placebo group [132].

It should be noted that in addition to the MMSE, other scales can be used for cognitive assessment. Two frequently used scales are Montreal Cognitive Assessment Scale (MoCA) and Cambridge Cognitive Examination (CAMCOG) [133]. MoCA is a cognitive scale that evaluates cognitive domain as attention, concentration, orientation, as well as visual-spatial abilities [133-135]. CAMCOG assesses attention, memory, language, praxia, orientation and perception [133,136].

- Calcium antagonists

Some preliminary studies looking at the role of nimodipine in the treatment of vascular dementia have

shown promising results. One of the trials treated 31 patients with cognitive decline and white matter imaging changes with 90 mg daily nimodipine and looked at its potential beneficial effect, the results being promising [137]. Another study was done using nicardipine; its effect on the progression of cognitive decline in patients with vascular dementia was studied in a double-blind placebo-controlled trial [138]. A total of 156 patients were included in this study, some of whom received nicardipine 20 mg three times a day and others placebo for a year [138]. Treatment with nicardipine appeared to be more favorable in patients with concomitant antiplatelet therapy [138]. Cyclandelate is another calcium channel blocker; a double-blind multicenter study compared the efficacy of 800 mg twice daily of cyclandelate with placebo in patients with moderate dementia. The results of the study showed a clear superiority in terms of the effectiveness of cyclandelate compared to placebo [139].

- NMDA receptor antagonists

Memantine, an NMDA receptor antagonist has great expectations both in terms of symptomatic and neuroprotective treatment of dementia. One of the most important studies regarding the effectiveness of memantine was conducted by Winblad and Poritis, the results of this trial supporting the hypothesis that treatment with memantine can lead to an improvement in symptoms [140].

- Ginkgo biloba extract

EGb761 is a widely used particular extract of Ginkgo biloba, with the generic indication of ameliorating symptoms associated with cognitive decline in the elderly. The mechanism of action of EGb761 on the central nervous system is only partially known [141]. The main effect seems to derive from its antioxidant properties [142]. There are studies that suggest that Ginkgo treatment is not necessarily effective in treating elderly patients with moderate dementia [141,143].

- Serotonergic receptor antagonists

A double- blind placebo-controlled study evaluated the efficacy of naftidrofuryl over one year of treatment in patients with mixed or vascular dementia. Naftidrofuryl is a serotonin2-receptor antagonist and has demonstrated an inhibitory effect on platelet aggregation [144]. Cranial tomography has helped differentiate vascular dementia from degenerative dementia. Patients were assessed using MMSE and ADAS Cog [145]. These are two useful scales for cognitive assessment. Statistically significant results showed an improvement in both the MMSE score and the ADAS Cog score in patients who received naftidrofuryl [145].

- Cholinesterase inhibitors

The pathogenesis of dementia includes several mechanisms such as cholinergic deficit and multifocal ischemic lesions. It has been observed that the cholinergic index is decreased in patients with vascular dementia [146]. Other studies have found acetylcholine concentration in cerebrospinal fluid significantly lower in patients with vascular dementia compared to control subjects, but significantly higher than in patients with Alzheimer dementia [147]. Also, the concentration of choline in the cerebrospinal fluid of patients with vascular dementia was significantly higher compared to patients with Alzheimer disease [147]. In addition, G4 acetylcholinesterase isozyme activity was significantly higher in patients with vascular dementia compared to control subjects and significantly lower in patients with vascular dementia [148,149]. The efficacy of rivastigmine was investigated in patients with moderate to severe Alzheimer dementia with or without vascular risk factors. The patients were randomized to placebo, low-dose rivastigmine and high-dose rivastigmine [150]. Patients were evaluated using ADAS-Cog, Global Deterioration Scale, and Mini Mental State Examination (MMSE). The results indicated that rivastigmine was associated with an improvement compared to placebo in both cognition and quality of life [150].

Conclusions

Mild or average changes in cognitive functions may not be observed during a routine clinical examination due to compensatory capacities, especially in patients with a higher socio-educational level. Therefore, a good understanding of the neuropsychological evaluation is necessary for the diagnosis of cognitive decline after stroke. Vascular cognitive impairment includes complex interactions between vascular etiology, risk factors and cellular changes at the cerebral level. In the treatment of post stroke cognitive decline, it is very important to know the risk factors and treat them accordingly. A special attention must also be paid to associated manifestations in the psychiatric area, because their correct detection and treatment lead to a good prevention and treatment of cognitive impairment.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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