

DEPRESSION IN CADASIL PATIENTS

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Abstract – Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary neurological disease accompanied by recurrent ischemic events, characterized by the presence of psychiatric disorders. The aim of this study was to examine the occurrence of depression and its severity among patients with CADASIL. Sixteen patients with diffuse white matter changes on MRI and clinical signs suggesting CADASIL were included in the study. Definitive diagnosis of CADASIL was obtained by electron microscopic analysis of skin biopsies. Testing of the patients' affective status was primarily devoted to detecting depression. Electron microscopic examinations of all skin biopsies revealed numerous granular osmiophilic material (GOM) deposits embedded into the basal lamina around altered or degenerated vascular smooth muscle cells (VSMCs). Clinical symptoms of depression were present in a great number of examined CADASIL patients. The frequency of depression was higher than previously reported. Psychiatric disturbances might also represent the onset of CADASIL, especially in young patients, and should be evaluated by differential diagnosis.

Key words: CADASIL; depression; electron microscopy; skin biopsy

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary neurological disease accompanied by recurrent ischemic events (Tournier-Lasserre, 1993). It is rare nonamyloid and nonatherosclerotic disease of small and medium brain arteries. Pathological changes are not exclusively localized in the brain, but they can also be found in the small blood vessels of almost all organs (Andre, 2010).

CADASIL is caused by a defective Notch3 gene that is located in chromosome 19p13.1. Over 170 mutations have been described so far, and they induce progressive degeneration of vascular smooth muscle cells (VSMC), thickening and fibrosis of the vascular wall as well as an accumulation of granular osmiophilic material (GOM) in the basal lamina of VSMCs (Dichgans, 2002). These vascular changes cause ischemic brain events that subsequently lead to cognitive decline and often dementia (Kalimo et al., 2002). The presence of GOM is a pathognomonic

hallmark in CADASIL. Considering that GOM deposits have also been detected within dermis blood vessels, a skin biopsy is the most commonly used diagnostic tool (Rouchoux et al., 1995). CADASIL is characterized by four common manifestations: 1) ischemic strokes, 2) migraine with aura, 3) psychiatric symptoms and 4) cognitive decline leading to subcortical vascular dementia. However, the disease is not associated with common risk factors such as hypertension and increased cholesterol levels, as is the case among other ischemic strokes (Bousser and Tournier-Lasserre, 2001). Due to its slow and unpredictable progression, it is very hard to access therapeutic effects and regrettably, only symptomatic therapy is available for now (Chabriat et al., 2000). Although neurological symptoms are the most frequent feature of CADASIL, this disease is also characterized by the presence of psychiatric disorders that are not enough described in previous literature (Lačković et al., 2008, Lačković, 2010, Valenti et al., 2011). Meta-analysis that included all studies based on psychiatric disorders in CADASIL patients in the period from 1997 to 2007 showed that the studies poorly and rarely focused on psychiatric events and psychopathological aspects of CADASIL (Valenti et al., 2008). Taylor and Doody (2008) reported that psychiatric manifestations have been detected in 30-40% of patients positively diagnosed with CADASIL. Psychiatric disorders most often appear in the progressive phase of the disease, and are rarely its first manifestations. In a French study that included 45 patients, 4.4% of patients had psychiatric manifestations as initial symptoms (Chabriat et al., 1995). However, a German study that included 102 CADASIL patients found this rate to be just above 1% (1.2%) (Dichgans et al., 1998). Mood disorders are the most common psychiatric manifestation of CADASIL and they are present in one-fifth of these patients (Chabriat and Bousser, 2007). Episodes of major depression have been described in about 10% of the 80 CADASIL patients in the study of Peters et al. (2005). Furthermore, it has recently been shown that apathy is common in CADASIL. It can be associated with cognitive decline, global functional disability and severe neuropsychiatric symptoms during the course of the disease, and can occur as

a phenomenon separate from depression (Reyes et al., 2009).

The aim of this study was to assess the occurrence of depression and its severity among patients positively diagnosed with CADASIL using electron microscopy of skin biopsies.

MATERIALS AND METHODS

Subjects

This prospective study included 16 patients hospitalized at the Neurology Clinics at the Clinical Center of Serbia and Military Medical Academy in Belgrade, Serbia, from 2001 to 2011. The inclusion criteria were diffuse white matter changes on MRI and clinical signs suggesting CADASIL. Definitive diagnosis of CADASIL was obtained with electron microscopic analysis of skin biopsies. Psychiatric evaluation was accessed at Clinic of Psychiatry (Clinical Center of Serbia) by a trained psychiatrist. Each patient underwent a medical examination and an interview in order to screen for the presence of risk factors for cerebrovascular disease, such as hypertension, lipid status, cardiac diseases with and without rhythm disorders, coagulation status, smoking and family anamnesis. In order to exclude antiphospholipid syndrome, the level of circulating anticoagulants (lupus anticoagulant and anticardiolipin antibodies) was assessed for each patient. Table 1 describes demographic characteristics, risk factors and family anamnesis of the CADASIL patients.

Ultrastructural analysis

Samples of skin biopsy from the deltoid region were fixed in 3% glutaraldehyde and post-fixed in 1% osmium tetroxide overnight at +4°C for 1 h, respectively. Both glutaraldehyde and osmium tetroxide were dissolved in cacodylate buffer (0.1 mol/l, pH=7.4). After dehydration in linear ascending gradient of ethanol concentration, tissue samples were embedded in 4.8 ml of Epon (Epoxy Embedding Medium), 1.7 ml of DDSA (dodecenyl succinic anhydride) and 0.2 ml BDMA (N-benzyltrimethylamine). Semi-thin

sections of skin were stained with a mixture of 1% toluidine blue and 1% azure A in 1% aqueous solutions of borax and observed under light microscopy in order to select the most representative small artery or arterioles in the deep dermal tissue. Stained sections were observed under a light microscope and photomicrographs were taken using an Olympus BX41 microscope. All the slides were photo documented by an Olympus C-5060 ADU wide zoom camera and the Olympus DP-soft Image Analyzer program. Ultra-thin sections were mounted on copper grids, stained with uranyl acetate and lead citrate and examined with transmission electron microscope (Fei Morgagni 268D, Eindhoven, The Netherlands). The transmission electron microscope was equipped with a MegaViewIII Soft Imaging System digital camera (Olympus Soft Imaging Solutions GmbH, Münster, Germany).

Assessment of depression

The testing of the patients' affective status was primarily devoted to detecting depression. One of the 16 patients with CADASIL was not enrolled in the study due to a lack of compliance during testing. The Hamilton Rating Scale for Depression (HRSD) was used to assess the severity of present depressive symptoms (Hamilton 1960, Hamilton, 1967). This scale consists of 21 items evaluating mood, inhibition, feelings of guilt, suicidal thoughts, psychomotor agitation, anxiety, self-criticism, disorders of appetite and sleep. HRSD takes into account the somatic manifestation of depression, which makes it suitable for patients who lack insight into their depressiveness. This scale is not designed especially for dementia patients with depression so that errors are possible. Dementia patients often have somatic complaints not due to depression, and on the other hand, they can have problems in answering some cognitive questions from the scale (Pavlović, 2002, Pavlović et al., 2003).

Data analysis

Statistical analysis of the collected data included descriptive and inferential methods. The database was analyzed using the Software Package for Social Sci-

ences for Windows v. 14.0 (SPSS Inc. Chicago, IL). The normality of distribution was tested by Kolmogorov-Smirnov test. Difference significance was examined using the Student's t-test, Fischer's accurate probability test and Mann-Whitney U-test. Differences were considered significant at $p < 0.05$.

Ethics

The study was approved by the Local Ethical Committee and carried out in accordance with the codex of good scientific practice of the Faculty of Medicine, University Belgrade.

RESULTS

Subject data

The subjects' gender distribution, family anamnesis, existence of vascular risk factors, clinical signs and manifestations are shown at Table 1. The mean age of the patients was 48.81 ± 9.55 years.

Ultrastructural analysis

Diagnosis of CADASIL was confirmed using electron microscopic analysis of skin biopsies of each patient. Semi-thin sections of skin displayed dermal small blood vessels with thickened, sometimes disintegrated, vascular walls and narrowed or occasionally obliterated lumen (Fig. 1). Electron microscopic examination of all skin biopsies revealed numerous GOM deposits of different texture embedded into thickened basal lamina around altered or degenerated VSMCs (Fig. 2). Occasionally granular deposits were found free between altered VSMCs. These deposits were observed most frequently in the shallow or deep indentations of VSMC plasma membrane embedded in the thickened basal lamina (Fig. 3). The number of GOM deposits varied between patients as well as their size, shape, electron density and granular composition.

Assessment of depression

Using the 21-item HRSD, depression was detected

Table 1. Gender distribution, family anamnesis, vascular risk factors, clinical signs and manifestations of CADASIL patients.

Parameter	N	%	
Gender			
Male	8	50.0	
Female	8	50.0	
Family anamnesis			
Positive	10	62.5	
Negative			4 25.0
Not acquired	2	12.5	
Vascular risk factors			
Hypertension	5	31.2	
Smoking	5	31.2	
Increased cholesterol	4	25.0	
Clinical signs and manifestations			
Headache	11	68.8	
Hemiparesis	11	68.8	
Stroke	11	68.8	
Epileptic seizures	-	-	
TIA	-	-	
N – number of patients		% – percent	

Table 2. The distribution of depression rates.

Depression	Without	Mild	Moderate	Severe
N, %	4 (26.7%)	-	11 (73.3%)	-
N,% – number of patients and percent of total				

in 11/15 (73.3%) patients with CADASIL. All 11 patients showed moderate rate of depression, with a mean score of 16.93 ± 6.55 . Table 2 gives the distribution of depression rates.

DISCUSSION

Skin biopsies of the CADASIL patients showed significant alterations in the structural organization of small blood vessels' vascular walls. VSMCs were more or less degenerated and GOM was observed in all cases, which implies the correct diagnosis of CADASIL, since GOM is a specific histopathological hallmark of this disease. Ultrastructural analysis remains the golden standard for CADASIL diagnosis (Lackovic et al., 2012). According to many previous researches, it can be assumed that morphological factors could play an important role in CADASIL patho-

genesis (Miao et al., 2004, Miao et al., 2006, Kalimo et al., 2008, Tikka et al., 2009). On the other hand, a relatively small number of studies determined that brain perfusion is reduced and insufficient to satisfy regular needs. Oxygen extraction level is increased in asymptomatic and demented patients with CADASIL (Chabriat et al., 1995). Cerebral flow and blood volume as well as cerebral utilization of glucose are significantly decreased (Chabriat et al., 2000, Bruening et al., 2001, Pfefferkorn et al., 2001). Cerebral vasoreactivity is damaged, which is in accordance with our results of degenerated VSMCs in small cerebral arteries and arterioles. Beside damaged VSMCs, there is a dissociation of myoendothelial junctions, including changes in gap junctions and alterations of focal adhesions (Lackovic et al. 2008). All this points to the high fragility of small cerebral blood vessels, which is confirmed by the increased frequency of cerebral

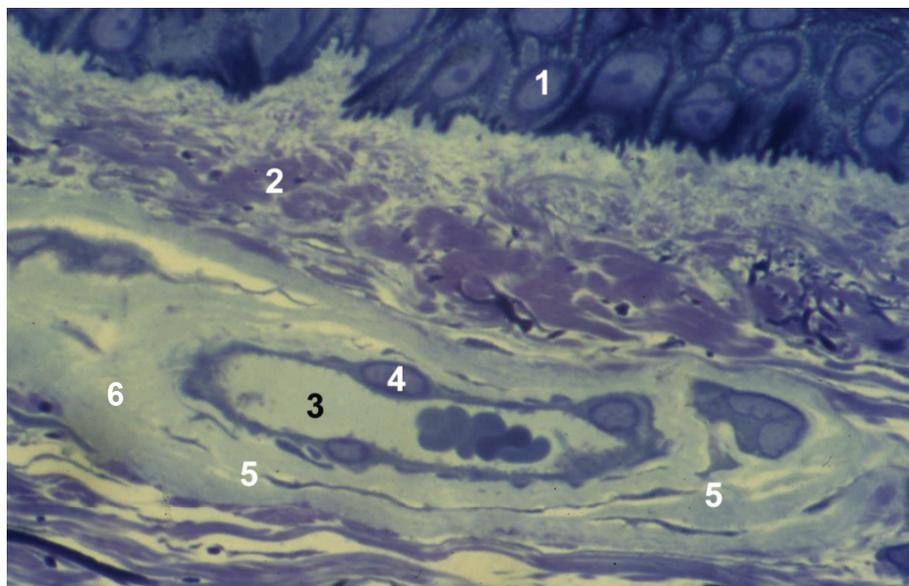


Fig. 1. Dermal arteriole (semi-thin sections, toluidine blue, X320). Epidermis (1), dermis (2), slightly narrowed blood vessel lumen (3), endothelium (4), fragmented vascular smooth muscle cells (5) and significantly thickened vascular wall (6).

microhemorrhages observed in autopsies and MRI analyses (Dichgans, 2002). Since all our patients had prominent subcortical vascular changes and altered, degenerated and narrowed small blood vessels, including prominent fibrosis, the previous statements lead to the consideration of mood disorders in CADASIL as part of the concept of vascular depression (Alexopoulos et al., 1997). Most of our patients were clinically depressed (73.3%) and the HRSD rate of depression was moderate in all of them. Depression is a leading cause of disability, diminished or lost productivity, increased use of health care resources, and is can also be associated with a decreased quality of life and increased mortality across all age groups (Stojanović-Špehar et al., 2010).

A large number of studies investigated a possible relation between vascular disorder and depression, leading to the formulation of the hypothesis that connects etiology and clinical presentation. Such hypotheses are “vascular depression” and “post-stroke depression”. Alexopoulos et al., (1997) presumed that the depression that appears in the late phase of disease is characterized by specific symptoms such as cognitive dysfunction, psychomotor retardation, lack of insight and depressive ideation. According to

this research, the disruption of prefrontal pathways caused by ischemic lesions of white matter has a key role in the pathogenesis of depression. Based on the biological substrate in the etiology of post-stroke depression, two hypotheses have been proposed. One considers the role of biogenic amines as important in generating psychiatric disorders and the other the role of cytokines. According to the biogenic amine theory, ischemic brain lesions can interrupt ascendant axons that come from the brain stem and contain biogenic amines. This leads to a decrease in the overall production of serotonin and noradrenalin in non-damaged areas of the axonal trunk. The consequential dysfunction of strategic limbic structures in the frontal and temporal cortices, as well as the basal ganglia, is able to induce clinical symptoms of depression (Robinson and Bloom, 1977). The theory about the role of cytokines in psychiatric disorders is based on the results of an experiment that showed that an increase of proinflammatory cytokines (IL-1 β and TNF- α) after cerebral stroke can induce depression-like behavior in experimental mice similar to the vegetative symptoms of depression in men. Several studies demonstrated high levels of IL-1 β and TNF- α among patients with major depressive disorder and dysthymia (Maes et al., 1993, Levine

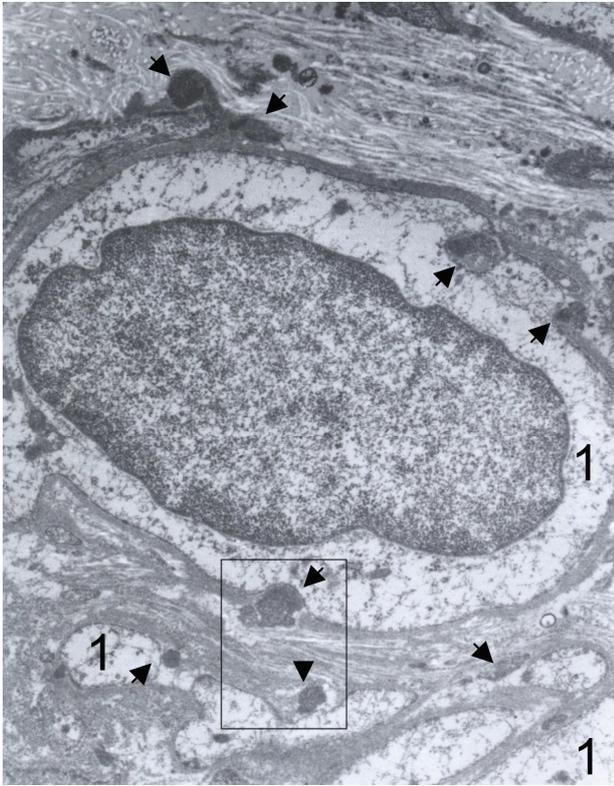


Fig. 2. Electron micrograph (X 5.000) of dermis arteriole with the appearance of numerous GOM deposits (arrowheads) around altered vascular smooth muscle cells (1).

et al., 1999). Two studies have also found that IL-18 was overexpressed in the serum of depressed patients (Merendino et al., 2002, Kokai et al., 2002). Although the hypothesis that proinflammatory cytokines may mediate post-stroke depression is proposed, it will be difficult to prove that any of the proposed cytokines are central to the mechanism of post-stroke depression (Spalleta, 2006).

Modern research has considered the correlation of MRI findings and neuropathological changes, especially white matter hyperintensity, in order to examine the importance of cerebral pathological changes in the pathogenesis of depression. Thomas et al., (2002) demonstrated that all changes in depressive patients comprise ischemic damages, supporting the “vascular depression” hypothesis, which states that vascular diseases are a predisposing factor for the appearance and maintenance of depression.

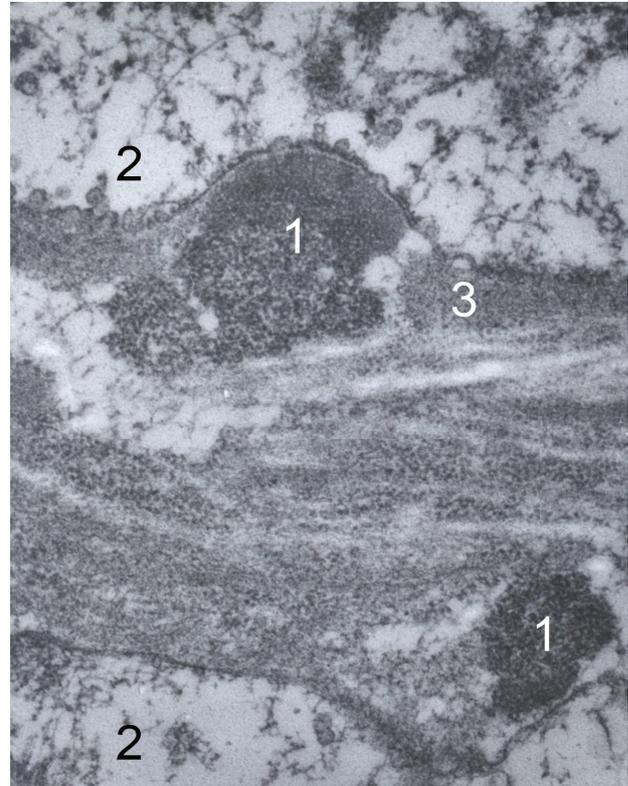


Fig. 3. Same arteriole wall part at higher magnification (X 25.000), which is highlighted with a rectangle in Fig. 2. GOMs are visualized as dark deposits (1) around altered vascular smooth muscle cells (2). Note that GOMs are embedded in the basal lamina (3) and located in the invaginations of vascular smooth muscle cells.

They also showed that all changes are ischemic, appearing as hyperintensive regions on MRI, and that they are located in the prefrontal lobe in depressive patients. Spot lesions were more frequent than usual and they were considered as predictors of depression.

Studies to date suggest that the CADASIL phenotype is variable not only between families but also within them (Opherk et al., 2006, Adib-Samii et al., 2010). This could explain the rarest CADASIL cases where psychiatric symptoms including depression represented the onset of disease (Valenti et al., 2008, Taylor et al., 2008). Early psychiatric manifestations are of the utmost importance in differential diagnosis of CADASIL since they can remain misdiagnosed for a long period of time (Haritunians et al., 2005).

CONCLUSIONS

This study revealed that depression is frequent in CADASIL patients. The frequency of depression was higher than previously reported. It is important to determine which psychiatric disorders develop during CADASIL progression, in order to assign adequate therapy and to improve patients' quality of life. We suggest that if psychiatric symptoms such as depression appear in relatively older patients and/or patients who don't respond adequately to applied psychopharmacotherapy, MRI should be performed. If MRI analysis uncovers leukoencephalopathy in the absence of cardiovascular risk factors and positive family anamnesis of stroke and/or dementia, CADASIL can be suspected. Subsequently, a skin biopsy should be performed so that the correct diagnosis can be made. In addition, special attention should be paid to the appearance of early psychiatric symptoms in cases of positive family history, since a long time before the correct diagnosis is made, mood disturbances, including depression, may represent the first manifestation of CADASIL.

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