ISSN 0362-1197, Human Physiology, 2022, Vol. 48, No. 8, pp. 938–945. © Pleiades Publishing, Inc., 2022.
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MRI in the Assessment of Cerebral Small Vessel Disease

E. V. Gnedovskaya[a], *, L. A. Dobrynina[a], M. V. Krotenkova[a], and A. N. Sergeeva[a]

[a] *Research Center of Neurology, Moscow, Russia*

**e-mail: lavrentevan@mail.ru*

Received January 15, 2018; revised February 6, 2018; accepted February 25, 2018

Abstract—Cerebral small vessel disease (cSVD) is the leading cause of vascular cognitive impairments and dementia, cerebral hemorrhages and lacunar strokes, as well as the most common form of asymptomatic vascular brain lesion. Major forms of cSVD are age- and arterial hypertension (AH)-associated arteriolosclerosis and cerebral amyloid angiopathy. The etiologies and the underlying mechanisms of disease development and progression remain unclear for a substantial group of cSVD types. Significant difficulties in the study of this pathology are explained by technical limitations in assessing smallest vessels in vivo. A modified correlation between MRI equivalents and their morphological manifestations in cSVD to use them subsequently as a surrogate marker of lesions in small vessels has allowed clinicians to establish disease progression regularities and the association of the latter with clinical symptoms. This review presents the results of studies showing the clinical significance and role of the leading MRI features in the assessment of disease progression, including white matter hyperintensity (WMH, formerly known as leukoaraiosis), lacunes, enlarged perivascular spaces, and microbleeds. The recognition of MRI features as diagnostic criteria for cSVD was specified by international experts in the Standards for Reporting Vascular Changes on Neuroimaging (the STRIVE criteria). Despite the enormous importance of this standardization for the improvement of concepts about the significance of different factors in the development and understanding of heterogeneity of cSVD forms, this categorization cannot provide for the prediction of the disease course in a particular patient and assess the treatment efficacy in short- and medium-term prospects. One of the approaches to solution was based on the use of diffusion methodologies for assessing a microstructural lesion in the visually unaltered brain matter. The obtained consistent association of the expressiveness of microstructural alterations with clinical impairments substantiates the expediency of multimodal MRI studies aimed to evaluate the pathophysiological mechanisms of disease progression, beginning from the subclinical brain lesion stage.

Keywords: cerebral small vessel disease, white matter hyperintensity, lacunar infarcts, microbleeds, perivascular spaces

DOI: 10.1134/S0362119722080023

INTRODUCTION

Scientific publications in the English language apply the terminology "cerebral small vessel disease" (cSVD) exclusively to describe clinical (including cognitive impairment and dementia), neuroimaging, and morphological manifestations caused by the lesion of perforating cerebral arterioles, capillaries, and venules, which lead to impairments in the brain white matter and nuclei [1]. In Russia, this pathology is considered within a broader context of dyscirculatory encephalopathy. cSVD is currently among the priority problems for the health care systems of developed countries, judging by its participation in invalidation and mortality [1–3]. CSVD has been recognized as the leading cause responsible for vascular cognitive impairments and dementia [4, 5], intracerebral hemorrhages [6], a fifth of ischemic strokes [7], and the most common asymptomatic vascular brain lesions [5, 8], as well as a risk factor for Alzheimer's disease [9]. The most frequently occurring cSVD forms are age- and arterial hypertension (AH)-induced arteriolosclerosis and cerebral amyloid angiopathy [1, 5, 8]. However, researchers admit that both the etiology and the underlying development mechanisms in a significant number of cSVDs remain not well understood so far [3, 5], and that it is impossible to predict the reversibility of brain impairment even in cases with fully controlled hypertensive microangiopathy [10]. The main complexity in cSVD studies is explained by technical limitations of small vessel imaging in vivo. Essential breakthroughs in the understanding of the pathology became possible owing to the modified correlation between the neuroimaging equivalents and morphological manifestations of cSVD and their use as surrogate markers of small vasculature impairment and disease progression. The accumulation of evidence confirming associations between neuroimaging features and clinical manifestations and invalidation of patients served as a foundation for systematizing the ideas and applying the MRI criteria clinically significant in cSVD as diagnostic, using STandards for

ReportIng Vascular Changes on nEuroimaging (STRIVE) [11]. The criteria include recently occurring small subcortical infarcts, lacunes, white matter hyperintensities (WMHs) (formerly, leukoaraiosis), enlarged perivascular spaces, and microbleeds, etc. [11]. This review presents data on the MRI features on which numerous confirmations of their association with disease progression have been obtained, including their neuroimaging characteristics and the clinical significance of the feature expansion, as well as the confirmed risk factors for their development.

White matter hyperintensities (WMHs, or formerly leukoaraiosis) are MP signal zones of increased intensity on T2- and proton density-weighted fluid-attenuated inversion recovery (FLAIR) images [11, 12]. The WMH focal shapes are rather variable, including periventricular caps or strips, multiple pinpoint-sized or larger foci, partially or fully confluent, commonly, bilateral and symmetrical [13].

The expansion and expressiveness of WMHs are assessed in the periventricular, deep, and subcortical white matter. To assess the expressiveness of white matter lesions, clinicians use different visual scales and volumetric methods. Among the most popular is the Fazekas scale with three lesion stages, namely, Fazekas I, II, and III, respectively [14]. Other visual assessment tools include the Rotterdam Scan Study (RSS) [15], the Scheltens [16], Wahlund [17], and Longstreth [18] scales, and the Prins scale for rating WMH changes in dynamics [19].

Comparisons between WMHs on postmortem MRIs and the histological changes in the brain confirmed the association between their expressiveness and the expansion of changes [20]. The myelin paleness is associated with periventricular WMHs, loosened fibers, venular tortuosity, and, more frequently, with the absence of arteriolosclerosis and the loss of the ependyma integrity with gliosis of different expressivity degrees. Deep WMH was characterized in individual foci by the absence of ischemic changes, loss of myelin, atrophy of neuropil surrounding arterioles with hyalinosis and perivenous alterations; in early confluent foci, by perivascular myelin thinning, mild or moderate fiber losses, and different severities of gliosis; and in confluent foci, by uneven sites of incomplete parenchymal necrosis with transition to true infarctions [20].

Clinical significance. WMHs have long been considered as a neuroimaging phenomenon associated with normal aging of the brain. Both population-based cohort and clinical studies have later shown that WMH intensity expansion over time depends not only on aging. The established WMH expansion rate varies from 0.1 to 2.2 mL/year, differing by more than 20 times between groups [21–24].

Numerous prospective MRI-based studies have proven the significance of WMHs in the development of clinical manifestations associated with cerebral small vessel lesions. It has been shown that the presence of WMHs is accompanied in elderly people by an increased risk of dementia and stroke [25], progression of cognitive impairments in patients with both neurodegenerative and vascular diseases [26, 27], invalidation [28] and depression [29]. We should note that the absolute majority of studies included the senior age group, whereas data on the middle-aged group (45–60 years) were more limited. For example, the Northern Manhattan (NOMAS) [30] and American Religious Identification Survey (ARIS) [31] population-based cohort studies have shown an increased risk of stroke in a group of middle-aged persons with asymptomatic lacunar foci and WMHs, and these results coincided with the data obtained in the senior patient category. At the same time, the ABC study based on a cohort of 320 people aged below 60 years has shown no significant associations, in contrast to the older group, between WMHs and impairments in cognitive performance [32].

The literature contains solid reports confirming the influence of genetic factors on the WMH progression. There were descriptions of monogenic forms of the disease, and a high level of leukoaraiosis hereditability was shown in twin-based studies [33], whereas the genome-wide association studies (GWASs) allowed researchers to identify the locus associated with an increased risk of WMH development [34–36]. Some studies have recently shown that epigenetic deregulation, including DNA methylation alteration and deregulation of microRNA expression, is also significant for WMH formation and progression [37].

A large number of studies have confirmed the association of WMH expressiveness with the duration, profile, and manageability of AH as the leading cardiovascular risk factor [25, 28, 38, 39]. WMH progression was more clearly expressed in patients with untreated uncontrolled AH, compared to the treated patients with the same diagnosis [10]. We have previously shown the association between the WMH expressiveness and the severity of AH in asymptomatic first-ever diagnosed patients during the indiscriminate screening of an open population of working-age persons [41].

Other factors influencing WMH progression include diabetes mellitus, smoking at the time of assessment, and background WMH expressivity [19, 38, 42]. The Austrian Stroke Prevention Study has established that the volumetric growth rate was 1.3 mL/year in persons with confluent WMH foci, whereas changes practically did not grow in patients with pinpoint-sized foci [43]. Similar data were obtained in the Redboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC) study, for example, the probability of WMH progression was higher, if WMH was recorded as moderate and severe during the background assessment, whereas no progression of foci has been identi-

fied over a 9-year observational period in patients with mild WMH [44]. Differences in WMH progression regularities may most probably depend on the degree of their background expressivity. The expansion of focal and early confluent WMH was found to progress from the frontal to parietal brain regions and from the subcortical to deep white matter [40], whereas confluent WMH progression was associated with the transformation of the visually unaltered WMH penumbra into visual WMH [41, 45].

The studies have identified the association between risk factor significance and age. According to a large multifocal study comprising 2699 patients with stroke, an increased cholesterol level was an important risk factor for WMH appearance in old age patients with AH, whereas age in itself was an important risk factor in elderly patients without AH [46]. Similar data were obtained by the Rotterdam study, for example, a more expressed WMH progression was recorded in the group of more elderly persons irrespective of AH [15].

Lacunes (lacunar strokes) of vascular etiology are rounded or ovoid fluid-filled cavities with diameters from 3 to 15 mm, corresponding to an earlier occurred acute small deep cerebral infarct or a microbleed into the basin of one perforating artery. The signal of lacunar strokes is analogous to the cerebrospinal fluid under T2 and T1 modalities, i.e., hyper- and hypointensive, respectively; under the FLAIR modality, lacunes have a hypointensive MP signal (analogous to the cerebrospinal fluid) with a hyperintensive ring in the periphery [11].

The lacunar frequency rate reaches 9.5% per year, significantly differing between clinical and population-based studies [47]. For example, the annual frequency of lacunar detection in the large population-based Age, Gene/Environment Susceptibility Study (AGES-Reykjavik) constituted 0.8%, and the corresponding figures in the Rotterdam Scan Study and the Cardiovascular Health Study were represented by 3.5 and 2.9%, respectively. At the same time, according to the clinical Leukoaraiosis and Disability (LADIS) and Scan studies, the frequency of lacunar detection was equal to 5.8 and 9.5% per year and was most probably associated with both the expressiveness of clinical symptoms and the age of patients under observation.

The predictors of lacunar detection in dynamics include WMH expressiveness, the presence of lacunes during the baseline assessment, a stroke in anamnesis, atrial fibrillations, carotid artery atherosclerosis, and the presence of vascular risk factors, such as arterial hypertension and hypercholesterolemia [48, 49]. The newly detected lacunes are predominantly localized in the cerebral regions closely located to existing WMHs or those partially overlaying the latter [50].

The lacunar syndromes with their characteristic neurological symptoms develop when lacunes are located in the projection of conductors significant for clinical symptoms. Among lacunar syndromes, the absolute majority of cases are represented by pure motor, pure sensitive, and ataxic hemiparesis. The development of lacunes beyond the projection of significant conductors is commonly unaccompanied by clinical symptoms in patients with early cSVD. However, as the LADIS 2001–2011 [51], NOMAS [52], Rotterdam Scan [53], and Cardiovascular Health [48] Studies have shown, the risk of strokes, dementia, gait disorders, and developing pseudobulbar and pelvic impairments increases with the number of silent lacunes growing (NOMAS [52], Rotterdam Scan Study [53], Cardiovascular Health [48], and LADIS [51]).

Microinfarcts are ischemic foci with sizes of 50–400 μm to 3 mm, which were localized in the cortical grey and subcortical matter. Their number may reach hundreds and thousands per elderly person [18, 54]. They may be diagnosed under microscopy [55] and on a high-resolution 7T-MRI, corresponding to lacunes in their characteristics. The visualization of strokes on an MRI is limited to the sizes of 1–3 mm, and, therefore, MRI detection constitutes 0.5% of strokes detected microscopically [56, 57]. The current technical complexities in in vivo imaging of microinfarcts limit the use of this symptom as a clinical marker of cSVD progression. At the same time, their presence confirmed by the microscopy data is recognized as a reliable neuropathological symptom of vascular dementia [58].

Cerebral microbleeds correspond, in a majority of cases, to small areas of hemosiderin accumulation in macrophages. Microbleeds are identified as hypointensive rounded foci with sizes from 2 to 5 mm, and, rarely, up to 10-mm foci on "gradient echo" MP-sequences sensitive to paramagnetics (hemosiderin), including T2-GRE, SWI sequences, and those undetected under standard MRI modalities [11, 59]. They are located at the boundary of the cortex and the subcortical white matter, in the cortex, the deep white matter of the hemispheres, in the stem, and the cerebellum. The diagnoses of cerebral amyloid angiopathy [60] in case of their lobar location and sporadic nonamyloid, cSVD in case of their deep location [61] should be considered possible.

Population-based and clinical studies annually detect 2.9–3.5 and 2.2–31.2% of cerebral microbleeds, respectively [62–64]. The studies underlined the association of their growth with age. According to the population-based RSS data, the annual detection rate for microbleeds was 7.6% in 60–69-year olds, 15.6% in persons aged 70–79 years, and 18.6% in patients over 80 years [62]. Their highest detection rate (up to 41.8 per year) was recorded in patients with intracerebral hematomas and cerebral amyloid angiopathy.

The population-based Rotterdam study [65] showed the association of deep microbleeds with vascular risk factors, such as AH and smoking, whereas

lobar microbleeds were shown to be associated with the risk of developing cerebral amyloid angiopathy, the apolipoprotein E epsilon 4 (APOE ε4) genotype [66]. Among other factors in favor of microbleed expansion are their number during the baseline assessment, the presence of lacunes, WMH expressiveness, and the identified APOE genotype.

Perivascular spaces (Virchow–Robin Spaces) are liquor-filled expansions surrounding vessels. Perivascular spaces may be linear in shape, if the scanning sections are parallel to the course of vessels and circular or ovoid if the sections are perpendicular to the course of vessels. The perivascular spaces in norm frequently become expanded in normal aging. The Virchow–Robin Spaces contain cerebrospinal liquor, and therefore, their signal is of increased intensity on T2-weighted imaging (WI) and FLAIR and decreased in the T1 sequence. They differ from lacunes in the absence of hyperintensive signal in their periphery in the FLAIR sequence and, generally, in smaller sizes. Perivascular spaces are usually localized in the semioval center, subcortical formations, and the hippocampus. This state is called état criblé in the cases when the expansion of these spaces is expressed [11, 13].

The differences detected between healthy subjects and patients with cSVD in the significance of enlarged perivascular spaces were as follows: no cognitive dysfunctions were present in this case in healthy subjects [69], whereas the presence of cognitive impairments was associated with age and cognitive losses in patients with cSVD [70, 71]. The interest in the role of perivascular spaces in cSVD was mainly caused in the last years by the correlation of significance of the recently discovered glymphatic system in the development of cognitive impairments belonging to this system. Their expansion is considered as one possible sign of stasis in the interstitial fluid with brain drainage dysfunction [72].

Diffusion-Weighted MRI Methodologies

The absence of a direct association between WMH expressiveness and cognitive impairments [67] in a significant portion of cSVD cases, which may be explained by heterogeneity of pathological processes underlying this phenomenon [20], motivated the search for sensitive indicators of the microstructural brain impairments. The diffusion-weighted (DW-MRI) methodologies with assessing different characteristics of free (extracellular) water diffusion in the brain matter and, correspondingly, the maintenance of its microstructural integrity, allow researchers to approach to the explanation of individually specific clinical manifestations of the disease and, possibly, predict its course under dynamic observation. The main indicator of a DW-MRI is the measured apparent diffusion coefficient (ADC, or mean diffusivity). The diffusion-tensor MRI, a modification of this method, offers estimated indicators, such as fractional anisotropy, axial and radial diffusion, to give one a possibility to determine not only the value, but also directionality (anisotropy) in the diffusion of water molecules. The lower significance of fractional anisotropy and, correspondingly, a high mean diffusion coefficient reflect a great loss to the microstructure. The axial and radial diffusion are used as the markers of neuronal impairments, which, according to experimental data, are associated, respectively, with the involvement of axon and myelin [73, 74]. The results of some accomplished studies dedicated to the correction of association between microstructural alterations in the brain of patients with cSVD and clinical manifestations of the disease have recently been published. An increase in ADC was diagnosed in the externally unaltered matter as a result of memory losses, disorders in controlling brain functions and the speed of psychic processes, but irrespective of vascular risk factors and the volume of a white matter lesion [67]. The association has also been found between an increase in ADC in the hippocampus, thalamus, cingulate gyrus, and hook-like bundle and subclinical depression, alarmism, and memory difficulties in patients with the first-ever diagnosed asymptotic AH and cSVD-specific MRI alterations [41]. It has also been found that fractional anisotropy and medium diffusion are associated in cSVD with AH severity, as well as fractional anisotropy and radial diffusion are associated with cognitive and gait disorders [75, 76]. The predictive ability of diffusion-weighted methodologies has also been shown in relation to the appearance of WMH under dynamic observation in the visually unaltered white matter with decreased fractional anisotropy and increased diffusion [77].

CONCLUSIONS

Thus, the current numerous evidences of association between the leading MRI features of cSVD and its clinical manifestations allow us to recognize the expediency of diagnosing this pathology only with its neuroimaging confirmation. Diagnosing cSVD by MRI must become for clinicians a foundation for correcting the form of the disease, its possible risk factors, and prediction. It should be recognized that the established regularities in the progression of the main MRI features at the group level are not reproduced at the individual level, generally demonstrating non-correspondence between the expressiveness of WMHs and cognitive impairments. In addition, the disease progression rates obviously depend on different cSVD forms, but this issue is not debated in the literature. These contradictions were partially resolved with the start of using the diffusion-weighted methodologies for assessing the structural brain lesions. However, this approach is currently limited to the confirmation of association between microstructural and clinical impairments. Taking into account the fact of a high social significance of the disease and population aging

potentially increasing the percentage of cSVD patients, it is very important to conduct prospective studies, starting from the stage of subclinical brain lesions, using the MRI sequences aimed to assess different components of the pathological process. Considering that the therapeutic successes in the management of arterial hypertension, as the leading cSVD risk factor, have not led to a reduction in the healthcare burden generated by this pathology, it is necessary to consider different potential risk factors and their association with the disease progression.

FUNDING

The study was not supported by any particular organization.

Conflict of interests. The authors declare the absence of a conflict of interest.

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Translated by N. Tarasyuk