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Classification of white matter lesions on magnetic resonance imaging in the elderly

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Abstract

White matter lesions, commonly seen on magnetic resonance images of elderly people, are related to various geriatric disorders including cerebrovascular diseases, cardiovascular diseases, dementia, and psychiatric disorders. Currently, white matter lesions are divided into periventricular white matter lesions and deep white matter lesions. Although the meaning of these terms vary by study and this dichotomization itself is still in debate, a possible dissimilarity in pathogenic mechanisms between periventricular white matter lesions and deep white matter lesions are providing some clues for understanding pathophysiology of many geriatric syndromes associated with white matter lesions.

We have reviewed the distinctions between periventricular white matter lesions and deep white matter lesions in terms of etiology, histopathology, functional correlates, and imaging methodologies. We suggest a new sub-classification of white matter lesions which may have better etiological and functional relevance than the current simple dichotomization. The new categories are juxtaventricular, periventricular, deep white, and juxtacortical. This new classification scheme may contribute to reducing the heterogeneity of white matter lesion findings in future research.

Keywords

White matter lesion; elderly; periventricular; deep white matter; juxtaventricular; juxtacortical

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INTRODUCTION

The areas in cerebral white matter that appear hyperintense on T2-weighted magnetic resonance imaging and hypointense on computed tomography are commonly referred to as white matter lesion (WMLs). WMLs are commonly seen on MR images of elderly people. MRI lesion prevalence in community-dwelling elderly was reported to range from 5.3% to 100%, depending on study design, study population, and assessment method (1–5).

Although WMLs are frequently found in clinically healthy elderly people (6), WMLs were found to influence mental (7,8) and physical function (9,10). Furthermore, WMLs are related to various geriatric disorders: cerebrovascular diseases (11–13), cardiovascular diseases (1,9, 14), dementia (15–17), psychiatric disorders such as major depressive disorder (18–20), bipolar disorder (21), and schizophrenia (22), neurologic disorders such as multiple sclerosis (23) and normal pressure hydrocephalus (24), and inflammatory diseases such as systemic lupus erythematosus (25). Therefore, the presence, form and severity of WMLs may provide additional characterization of aging, pathophysiology of geriatric disorders, and the relation between aging and geriatric disorders.

The forms of WMLs are quite variable: periventricular caps or rims or halos, subcortical multiple punctuate or patchy lesions, partially confluent or confluent lesions (see Figure 1). These various WMLs are often divided into two broad categories: periventricular WMLs (PVWMLs) which are attached to the ventricular system and deep WMLs (DWMLs) which are located apart from the cerebral ventricle in subcortical white matter. Since PVWMLs have been consistently associated with different clinical, histopathological, and etiological correlates from DWMLs, a possible dissimilarity in pathogenic mechanisms between PVWMLs and DWMLs may provide the clues for understanding pathophysiology of many geriatric syndromes associated with white matter lesions.

However, varying terminology and definitions for PVWMLs and DWMLs make it difficult to compare lesion findings across studies, and the PVWML/DWML dichotomization itself is still in debate. Thus, here we reviewed the distinctions between PVWMLs and DWMLs in terms of etiology, histopathology, functional correlates, and imaging methodologies, and have suggested a new sub-classification of WMLs that may help to reduce possible heterogeneities of PVWMLs and DWMLs in future research.

DISTINCTIONS BETWEEN PVWML AND DWML

1. Definitions of PVWML and DWML

Fazekas et al. were first to rate PVWML and DWML separately (16). They defined PVWML as WMLs contiguous with the margins of each lateral ventricle and DWMLs as those separate to it. This ‘continuity [to ventricle] rule’ has been applied in most of the visual rating scales for WMLs (14,16,18,26–28). In those scales, other characteristics of WMLs such as their shape, size, and number were not used in defining PVWML but were used instead in grading the severity of PVWML; shape of WMLs (16,18,27), shape and size of WMLs (26), or size and numbers of WMLs (28).

However, complementary rules were needed for classifying PVWMLs and DWMLs since the irregular PVWMLs tend to coalesce with DWMLs in advanced stages of WMLs. Furthermore, PVWMLs were found to be associated with different histopathologies according to their shapes (16). In some studies, the distance from the ventricular surface was used for classifying PVWMLs and DWMLs. DeCarli et al. defined WMLs within 1 cm from the ventricular as PVWML. (29) Wen and Sachdev applied an empirical distance from the ventricular surface instead of an arbitrary distance such as 1 cm (5). The shape and size of WMLs were additionaly

used for classifying PVWMLs and DWMLs. Irregular PVWMLs were classified as DWMLs in Schmidt et al. (27), and PVWMLs larger than 10 mm were classified as DWMLs in Scheltens et al. (26).

So far, there are no widely accepted rules for defining PVWMLs other than the continuity rule. Using the distance from the ventricular surface or size of the lesion used in defining PVWMLs lacks a physiological or pathological basis. The irregularity of the WML shape, although it has some histopathological basis, is not easily quantifiable. Moreover, the continuity rule is not applicable in the subjects with advanced WMLs since PVWMLs and DWMLs often adjoin each other at this stage. The arbitrary nature, limited feasibility, and inconsistent application of the rules in defining PVWMLs might have increased the heterogeneity of findings related to PVWMLs, and thus confounded the studies on prevalence, risk factors, neurobehavioral outcomes, and histopathologies of WMLs.

2. Functional correlates

The human brain contains multiple networks of interconnected neurons that serve not only motor and sensation but also neurobehavioral functions such as attention, memory, language, visuospatial ability, complex cognition, and emotion (30). Damage to white matter may disrupt higher cortical functions that employ these networks. This disruption may occur even when cortical and subcortical gray matters are intact. Destruction of white matter may be especially critical in late life since white matter volume may decline with age more than gray matter volume (31). In this sense, it is logical that WMLs on MRI may be associated with various neurobehavioral syndromes.

As might be expected, the presence and severity of WML have been consistently related to cognitive function (8,9) and emotion (20,32,33) in the elderly. The disruption of subcortical–cortical connections by WMLs may be detrimental to cortical gray matter integrity and result in cognitive and emotional dysfunctions. Although executive function can be impaired by WMLs regardless to their locations due to substantial convergence of fiber pathways on the frontal lobes (24), neurobehavioral conditions associated with WMLs were not uniform by the location of WMLs. The risk of dementia (15,20) and severity of cognitive impairment in demented patients (34) were preferentially associated with PVWML rather than DWML. In the non-demented elderly, cognitive impairment (especially psychomotor speed) (8,15), rate of cognitive decline (35), and medial temporal lobe atrophy (36) were also preferentially associated with the severity of PVWML rather than that of DWML. In contrast, the risk (20, 32,33) and outcomes (37) of mood disorders were preferentially associated with DWML rather than PVWML. For major depression, there is strong evidence that severity correlates with the WMLs in the frontal lobe, particularly the orbital frontal cortex (38). In addition, among those with depression, the severity of cognitive impairment was also preferentially associated with DWML rather than PVWML (39). These findings indicate that the dichotomization of WML into PVWML and DWML may have a substantial functional relevance. We were unable to find studies on schizophrenia and other non mood-related disorders which endeavored to distinguish deep WMLs from periventricular WMLs. However, this distinction may also be useful in future studies of those conditions.

3. Histopathologic correlates

In addition to the functional correlates, histopathologic correlates of WMLs differ between PVWMLs and DWMLs.

Differences in histopathology between PVWML and DWML are comprehensively discussed in a review by Fazekas et al.(40) PVWMLs were found to be due to one of three main causes: ependymal loss, differing degrees of myelination in adjacent fiber tracts, and cerebral ischemia

with associated demyelination (41). Periventricular caps and smooth halo constituted areas of demyelination associated with subependymal gliosis and discontinuity of the ependymal lining, which are nonischemic in nature. Periventricular caps reflect predominantly a specific anatomic situation characterized by loosely arranged fine-fiber tracts with low myelin and high extracellular fluid content. In these lesions, ependymitis granularis which represents patchy loss of the ependyma with astrocytic gliosis is also frequently observed (42). A smooth periventricular halo has been linked to disruption of the ependymal lining with subependymal gliosis and concomitant loss of myelin. In addition, some PVWMLs, especially the lesions directly periventricular, were found to be related to venous congestion due to non-inflammatory periventricular venous collagenosis (43). In contrast, irregular PVWMLs and DWMLs were associated with microcystic infarcts and patchy rarefaction of myelin which are ischemic in nature (41,44). Punctuate, early confluent and confluent DWML correspond to increasing severity of ischemic tissue damage ranging from mild perivascular alterations to large areas with variable loss of fibers, multiple small cavitations, and marked arteriosclerosis (11). In addition, the underlying histopathology of WMLs may also differ by the characteristics of sample. For example, the punctuate DWMLs smaller than 3mm were found to be predominantly ischemic in depressed subjects but not in normal elderly (45).

WMLs were also found to be associated with cortical atrophy and cortical hypometabolism in both dementia patients and normal elderly (24,46,47). The regional cerebral blood volume (rCBV) was also correlated with the volume of WMLs in the same lobe.(48). Although these observations have not been consistently replicated (49,50), it is reasonable to assume that both the location and the volume of WMLs may influence their effect on regional cortical metabolism and function.(24) It is not clear yet whether the association of WMLs with cortical atrophy and hypometabolism is due to Wallerian degeneration or due to retrograde degeneration and deafferentiation. Considering the histopathologies of WMLs, periventricular caps, rims, and smooth halos may be attributed to Wallerian degeneration whereas irregular PVWMLs and DWMLs may not. (47)

In summary, smooth PVWMLs including caps and halos are more likely to be non-ischemic, whereas DWMLs and irregular PVWMLs ischemic, indicating that the dichotomization of WMLs into PVWMLs and DWMLs may have a considerable histopathologic relevance.

4. Etiologic factors

PVWMLs and DWMLs have been found to be differentially influenced by vascular risk factors. A history of cerebrovascular disease (51), the presence of aortic atherosclerosis during midlife (52), and the presence of carotid atherosclerosis (14) were preferentially associated with PVWML. High serum carotenoid level which had been reported to be protective for carotid atherosclerosis was related to decreased PVWMLs but not to DWMLs (53). The subtype of ischemic strokes has been found to be differentially associated with the type of WML. PVWML was a predictor for the border-zone infarcts especially around the posterior horns, whereas DWML was a predictor for lacunar infarcts (54). High plasma homocysteine level which had been reported to be a risk factor for small vessel disease (SVD) (55) was related to increased DWML but not to PVWML in both normal elderly and AD patients (56,57).

To summarize, PVWMLs and DWMLs may have dissimilar pathogenic mechanisms. PVWML may be more hemodynamically determined whereas DWML may be more attributed to SVD.

Deep periventricular white matter lesions, in area extending between 3 and 13 mm from the ventricular surface, are more likely to be hemodynamically determined (58–60) since this area is supplied by noncollateralizing ventriculofugal vessels arising from subependymal arteries. These branches originate either from the choroidal arteries or from terminal branches of the

rami striate (61). Although these ventriculofugal vessels run toward the penetrating centripetal vessels coming from the pial surface, anastomeses between these two groups of vessels are either scarce or absent (62). Thus, this area is prone to focal or systemic hypoperfusion. Atherosclerosis might be the substrate for the decrease of blood flow, and carotid atherosclerosis which is preferentially associated with PVWML is one of major causes of cerebral hypoperfusion.

In contrast, deep white matter areas such as the centrum semiovale are fed by medullary arteries arising from the cortical branches of middle cerebral arteries, and are more likely sensitive for SVD (63). SVD has different risk factors from large vessel diseases. Hypertension is more common in SVD than large vessel diseases, whereas hypercholesterolemia, smoking, myocardial infarction and peripheral vascular disease are more common in large vessel diseases (64). Hypertension may induce fibrohyalinosis with thickening of the wall and narrowing of the vascular lumen on the small penetrating arteries and arterioles of the white matter. Fibrohyalinosis is a diffuse change in the medullary arteries, a focal or segmental microangiopathy that mainly involves the penetrating arteries in the deep gray matter and cerebral cortex (65). This arteriolosclerosis may alter the blood supply of white matter and lead to either localized ischemic areas of necrosis and cavitation or diffuse rarefaction (66). In contrast to the centrum semiovale which as a single blood supplying source, juxtacortical white matter is irrigated not only by the long penetrating medullary vessels but also by shorter vessels that straddle both the white matter and the adjacent cortex (59,61). Thus the U-fibers, a strip of cerebral white matter (3 to 4mm in width) located immediately beneath the cerebral cortex, are mostly spared from WMLs.

Compared to DWMLs and ischemic PVWMLs, arteriolar vessel wall changes are not a common observation in periventricular caps or halos (11,67). Given the smooth margin of this pencil-thin lining or halolike WMLs, it seems unlikely that ischemia or demyelination would be the cause. It may rather represent the disruption of the ependymal lining and an increase in interstitial water reabsorption (16). The structural alterations in the ependymal cells may result in leakage of CSF into the adjacent brain parenchyma. Age-related changes affecting the penetrating vessels and altering the blood brain barrier (BBB) could hinder the reabsorption of this excessive interstitial fluid (66). This explanation is consistent with the observation that periventricular caps seem to present first, since the area that has to be drained of interstitial water will be greatest for the tips of the ventricles (16). In patients with obstructive hydrocephalus, MRI scans have demonstrated a smooth halo surrounding the ventricles, believed to be indicative of edema from transependymal resorption of CSF.(68)

In summary, irregular PVWMLs are more likely determined by chronic hemodynamic insufficiency, whereas DWMLs are more likely determined by SVD, indicating that PVWML-DWML dichotomization may also have an etiological relevance which is very important when considering potential therapeutic intervention. In addition, smooth PVWMLs may be linked to the increase of interstitial fluid rather than ischemic changes, suggesting that further sub-classification of PVWMLs is needed.

METHODOLOGICAL ISSUES IN QUANTITATING PVWML AND DWML

1. Volumetric and quantitative scoring of WMLs

Until recently, the measurement of WMLs involved qualitative or semi-quantitative visual rating scales. These scales were defined to serve various purposes including overall WML rating, PVWML rating, and differential rating for PVWML and DWML, and thus scores from different rating scales are not directly comparable. This heterogeneity of scales likely contributed to the inconsistent results in previous studies on WMLs (69). In addition, visual

rating scales inevitably have some limitations including nonlinearity of data, lack of sensitivity to small changes, and susceptibility to ceiling effects (9,16,70).

In this sense, quantitative measurements are superior to qualitative or semi-quantitative visual rating scales. Currently, semi-automated quantification methods are often considered as the best alternative to manual contouring or visual rating in large-scale studies because they are more reliable and time-efficient than visual rating scales and can give linear quantitative data (71). However, semi-automated methods are still labor intensive and time consuming and require well-trained analysts. Fully automated quantification methods of WMLs are not yet optimal either since manual correction is needed to improve accuracy (72,73). Although some semi-automated methods include sub-segmentation of PVWML and DWML using distance from the ventricular surface (5,29), sub-segmentation has not yet been included in fully automated methods.

2. Image acquisition

Due to a higher water content and degeneration of macromolecular structures, WMLs have different relaxation rates compared to healthy white matter, and thus are seen as a higher signal on T_2-weighted spin echo sequences (T2), proton density sequencs (PD), and fluid-attenuated inversion-recovery sequences (FLAIR). However the extent of WMLs may not look the same on the different images (74). The FLAIR sequence is especially sensitive to white matter pathology (75,76) because the inversion pulse can be chosen to null the signal from CSF, thus allowing the periventricular region to be easily detected, and reduces the signal from gray matter allowing optimization of lesion contrast with surrounding brain (77). However, there is a risk for overestimating lesions (78,79) and FLAIR may be less sensitive to the lesions in the posterior fossa (79). Although the sensitivity of T2 and PD channels for detecting WMLs was fairly high, the false negative rate was not negligible and was mainly associated with milder pathology (80,81). FLAIR sensitivity and specificity reported for PVWMLs was 95% (87–99%) and 71% (44–90%), and those for DWMLs were 86% (79–93%) and 80% (72–88%). (82).

Therefore, the combination of FLAIR with a redundant source such as T2 will increase the certainty of the lesion delineation and reduce false positives. For example, the signal intensity of lacunar infarcts and Virchow Robin spaces, regions that are generally excluded from WML segmentation, increases on T2 and PD images but decreases in FLAIR. Thus FLAIR and T2 may be complementary sources for a better characterization of WMLs (72).

T1 can be used for further characterization of PVWML. Since frontal PVWMLs showed the lower MTR and higher proportion of the hypointense lesions in T1 than occipital PVWMLs (83), the WMLs on FLAIR, T2, or PD images with the hypointense lesion in the corresponding areas on T1 may have different functional, histopathological, and etiological correlates compared with those without corresponding hypointense lesions in T1.

In addition, magnetization transfer image (MTI) may be useful for characterizing WMLs further (83,84). In MTI, magnetization transfer ratio (MTR) of PVWML was lower than that of DWML (83), which supported the notion that PVWMLs may have different histopathology from DWMLs. Since MTR reflects changes in the macromolecular structure of tissue, MTR may indicate the severity of tissue damage. Hanyu et al.(85) has demonstrated that the MTR of PVWML shows a high positive correlation with global cognition in patients with Binswanger's disease.

Diffusion-weighted imaging (86) has been used to characterize white matter structure and WMLs in depression (87–89). Such methods can measure the apparent diffusion coefficient (ADC) or the fractional anisotropy (FA) of tissue, allowing additional sensitivity to tissue

microstructure. Typically, lesions have elevated values off ADC, reduced values of FA and no differentiation between lesions in normal subjects and controls. However, normal appearing white matter does exhibit FA differences between normal and depressed subjects. Thus diffusion imaging may offer a window into early, more wide-spread white matter alterations of microstructure before the development of specific lesions.

Perfusion weighted imaging can be used to examine the distribution of an MR contrast agent in the vascular space in and around lesions. The method allows assessment of the regional cerebral blood flow and volume. Investigators have found that there is a gradation of flow and blood volume in WMLs that decreases from normal tissue on the periphery to reduced values in the center of a lesion (49).

SUGGESTIONS FOR FUTURE RESEARCH

To improve the value of WMLs as etiological or prognostic markers in research and clinical settings, it is critical to reduce the heterogeneity of WML definition and measurement. To reduce the heterogeneity in measurement of WMLs, it is necessary to eliminate the inconsistencies in detecting and sub-classifying methods for WMLs.

Although the majority of MRI studies of WML have been conducted on 1.5T MR scanners, this will change with the increased availability of high-field MR scanners. With a magnetic field strength of 3.0 T or higher, a variety of exciting improvements in clinical and research applications are expected. In general, high-field MR scan (3T or over) may offer better spatial resolution and higher signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) than a low-field MR scanner (1.5T or below), and thus increase the sensitivity to small WMLs or early WMLs.

No studies report on the influence of static magnetic field strength to sensitivity and specificity for age-related WMLs. This issue has been addressed in MS but findings should be interpreted with caution because of the inherent differences between MS and age-related WMLs such as underlying histopathology. Several studies have addressed this issue by comparing image quality, lesion detection and diagnostic value of higher (3-4T) and lower (1.5T) field MR scanners in multiple sclerosis (MS) patients (90–92). Relative to scanning at 1.5T, the 3T scans showed a 21% increase in the number of detectable contrast enhancing lesions and a 10% increase in total lesion volume measured on proton density weighted images.(90)

Although the MR sequences optimal for detecting WMLs may change as the MRI technology develops, a FLAIR sequence with T2 and/or PD is currently the best combination. In addition to these conventional sequences, magnetization transfer imaging (MTI) which can reflect histological differences (83,84), diffusion-weighted imaging which can distinguish acute periventricular white matter infarction from PVWMLs (37), and diffusion tensor imaging which can show the impact of WMLs on white matter tracts, would be helpful for reducing further the heterogeneity of WMLs detected from conventional MR sequences. Susceptibility-weighted imaging (93) is a method that can enhance the contrast of tissues that concentrate iron. Iron deposition can be involved in normal ageing, dementias, inflammatory processes and microhemorrage and thus this technique may provide additional information about the condition in and near WML. Finally, magnetic resonance spectroscopy (MRS) has been used to evaluate demylinating disorders (principally multiple sclerosis). MRS can detect changes in N-acetyl-aspartate, a marker of intact neurons, as well as choline, creatine, myoinositol and lactate (94). Since many of the measures used to detect lesions (mainly the T2 difference compared to normal tissue) are nonspecific, these latter methods, use in a multiparametric manner may allow, in future research, better understanding and classification of these lesions

Sub-classification of WMLs is recommended but should be based not on arbitrary criteria but on a pathological or functional basis. By sub-classifying WMLs, we aim to make WML findings more relevant etiologically and functionally. In terms of etiology, histopathological and risk factor studies on WMLs have consistently indicated that WMLs should be sub-classified into ischemic WML and non-ischemic WML. (Figure 2)

Ischemic WMLs can be sub-classified into PVWML and DWML since PVWMLs are more likely to be hemodynamically determined whereas DWMLs are more likely to be determined by small vessel disease. Since the periventricular watershed area ranges from 3mm to 13mm from the ventricular surface, we propose defining the WMLs in this area as ischemic PVWMLs regardless of connectivity with the ventricular surface (58–60). WMLs 13mm or further from the ventricular surface should be classified as ischemic DWMLs (see Figure 2).

Non-ischemic WMLs are often located in juxtaventricular areas, usually within 3mm from ventricular surface (58–60) and directly contiguous to the ventricular surface, since they likely result from CSF leakage (16,66,95–97). To differentiate these lesions from the PVWMLs located in the periventricular watershed zones, we suggest classifying them separately as juxtaventricular white matter lesions (JVWML). (Figure 2)

Lastly, DWMLs within 4mm from corticomedullary junction, although their total volume is usually very small, may be further sub-classified as juxtacortical white matter lesion (JCWML) for two reasons. First, JCWMLs may have different vascular etiologies from DWMLs since juxtacortical white matter areas have a dual blood supply. Second, the functional correlates of JCWMLs may differ from those of DWMLs since the majority of juxtacortical white matter consists of U-fibers instead of long white matter tracts. (Figure 2) The definitions of JVWMLs, PVWMLs, DWMLs, and JCWMLs are summarized in Table 1. Although the criteria used in this subclassification may be less precise than desired, it may contribute to reducing the heterogeneity of WML assessment since these rules are supported from better anatomical and pathological bases than the previous ones.

Automated quantification methods of WMLs are rapidly evolving, and should make it easier to apply fine quantitative criteria for the sub-classification WMLs based on the anatomical and pathological factors. Compared to the semiquantitative visual rating scales, these automated quantification methods will be much more accommodating to the minor differences in the sub-classification criteria of WMLs. Therefore, now is the time to develop consensus regarding sub-classification criteria for WMLs that are more etiologically and functionally relevant. Longitudinal studies, particularly those involving middle-aged and older adults, are needed in order to elucidate the etiology of white matter changes.

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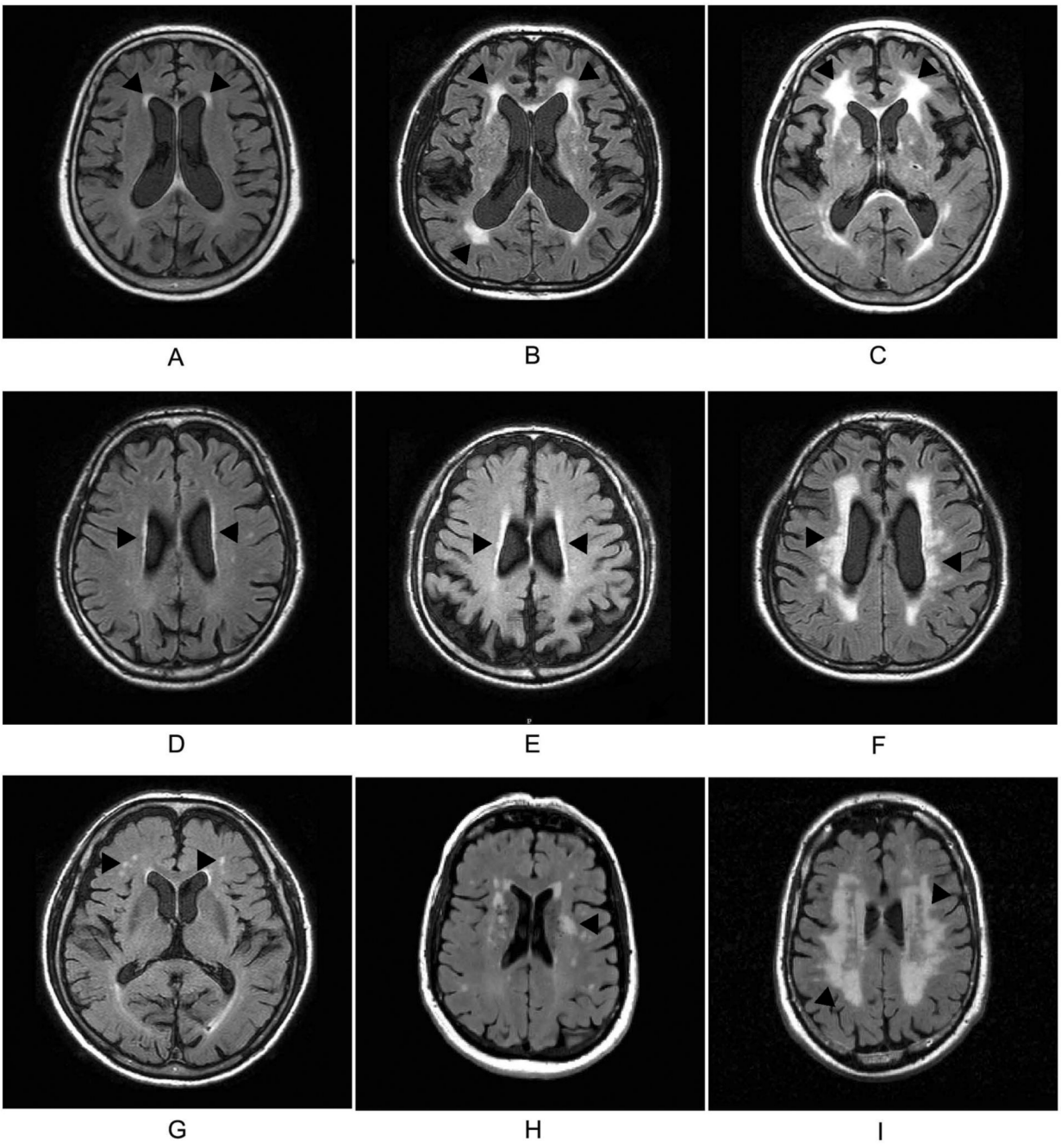

Figure 1.
Forms of white matter lesions (WML); small caps (A), large caps (B), extending caps (C), thin lining (D), smooth halo (E), irregular periventricular WML (F), punctuate deep WML (G), deep WML beginning confluence (H), confluent deep WML (I)

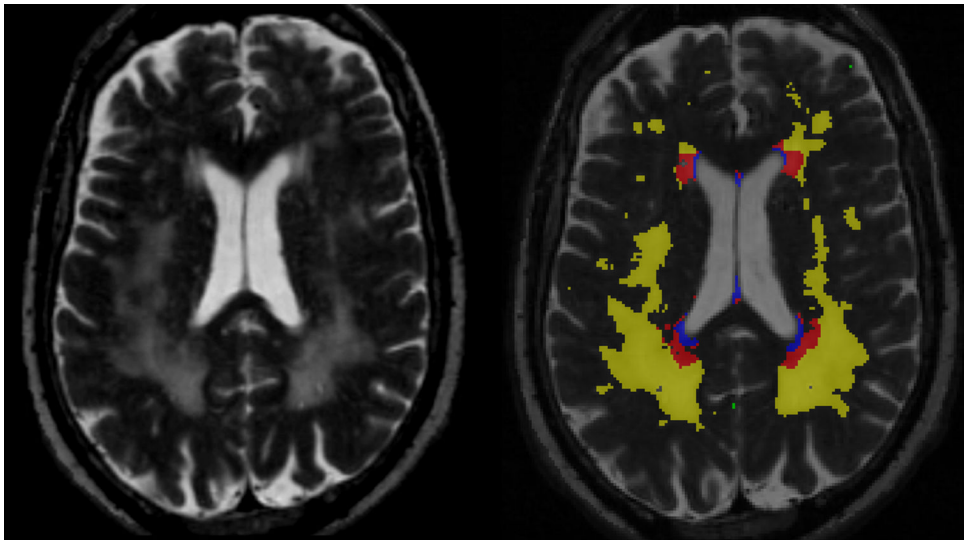

Figure 2.
Sub-classification of white matter lesions (WMLs): juxtaventricular WMLs (blue), periventricular WMLs (red), deep WMLs (yellow), juxtacortical WMLs (green)

Table 1

Proposed Sub-classification of white matter lesions

	Juxtaventricular	Periventricular	Deep	Juxtacortical
Locations	Within 3mm from ventricular surface	Periventricular watershed zone 3–13mm from ventricular surface	Between periventricular white matter and juxtacortical white matter	Within 4mm from corticomedullary junction
Etiologies	CSF leakage	Hypoperfusion	Small vessel disease	Small vessel disease
Pathologies	Non-ischemic	Ischemic	Ischemic	Ischemic
Functions	-	Disruption of long WM tracts	Disruption of long WM tracts	Disruption of U fibers