UPDATE IN RADIOLOGY

Hyperintense punctiform images in the white matter: A diagnostic approach

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PALABRAS CLAVE
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Abstract The presence of hyperintense punctiform images in the white matter in T2-weighted magnetic resonance (MR) sequences is a very common finding and is occasionally a diagnostic challenge for the radiologist.

The present article attempts, using an anatomical approach to the brain circulation, as well as from histopathology correlation studies, to simplify the task of interpreting these images from the description of the three main patterns of hyperintense punctiform images in the white matter: vascular pattern, which corresponds to microvascular lesions; perivascular pattern, which represents inflammatory disease of which the paradigm is multiple sclerosis; and a non-specific pattern, which has to be a microvascular disease.

From the various semiological elements in the MR images, a predominant pattern can be determined in each case and, in this way, helps in the differential diagnosis.

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Imágenes puntiformes hiperintensas en la sustancia blanca: una aproximación diagnóstica

Resumen La presencia de múltiples imágenes puntiformes hiperintensas en la sustancia blanca (IPHSB) en las secuencias de resonancia magnética (RM) ponderadas en T2 es un hallazgo muy frecuente y, en ocasiones, un reto diagnóstico para el radiólogo.

Este artículo pretende, a través de una aproximación a la anatomía de la microcirculación cerebral, así como a estudios de correlación anatomopatológica, simplificar la tarea de interpretación de estas imágenes a partir de la descripción de tres principales patrones de presentación de IPHSB: patrón vascular (PV), que corresponde a lesiones microvasculares, patrón perivascular (PpV), que representa a la enfermedad inflamatoria cuyo paradigma es la esclerosis múltiple (EM), y patrón inespecífico (PI), que suele deberse a enfermedad microvascular.

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Introduction

The interpretation of multiple hyperintense punctate images in the white matter in T2-weighted sequences, which are daily reported at magnetic resonance imaging (MRI) of adult brains, plays a major role in the routine practice of neuroradiologists.

A parallelism can be established between the commonly used term unidentified bright objects (UBO) and the term hyperintense punctate images in the white matter (HPIWM), which is presented in this paper. Accordingly, HPIWM is a semiological entity revealing at least five solitary hyperintense foci of up to 1 cm in diameter on T2-weighted sequences, with or without confluent lesions with an overall diameter >1 cm.

The main goal of this paper is to simplify the radiologist’s task when dealing with cases of HPIWM, so that radiologists can categorize the findings under a predominant pattern and make a more accurate diagnosis. This paper proposes three main HPIWM patterns based on the semiological characteristics: a vascular pattern (VP), which represents microvascular involvement (usually arteriolar); a perivascular pattern (PVp), which represents inflammatory disease (particularly demyelinating disease); and a non-specific pattern (HSP), which usually represents microvascular disease. To make a diagnosis, the predominant semiological pattern should be considered together with the clinical manifestations of patient and the epidemiologic data.

Basic anatomy of brain microcirculation

The brain microcirculation consists of a vascular network with a very complex anatomy that varies across subjects. To understand the HPIWM patterns suggested, the basic aspects of brain microvascular anatomy will be addressed.

Arterial microvascular system

The cortical arteries cross the cerebral cortex and penetrate the white matter perpendicularly to the cortical surface, forming the terminal pial or medullary arterioles up to 4-5 cm long. Along their course, they give off short cortical branches that supply the entire cerebral cortex and the fibres of the juxtaocular white matter (3-4 mm), also called U-fibres. The cortical arteries establish multiple anastomoses, which provide the cerebral cortex with a rich arteriolar network. When running deep into the white matter, pial arteries establish very few capillary anastomoses with the neighbouring pial arterioles, forming relatively independent arteriolar metabolic units.

The deep subependymal arteries, which arise from the choroid arteries, give off penetrating branches to the white matter, although with shorter course than that of the pial arteries.

There is a second terminal system of cortical and subependymal arteries (lenticulostriated and thalamic perforating arteries) that supplies the basal ganglia (BG).

The superficial and deep arteriolar systems (pial penetrating arteries and subependymal arteries) hardly anastomose with each other. For this reason, the parenchyma located on the bordering zone between the superficial and the deep vasculature is less vascularized. In contrast, the U-fibres are more and better vascularized than the rest of the white matter and BG2,3 (Fig. 1A).

Venous microvascular system

The cerebral venules, also known as medullary venules, are divided into two large groups: superficial medullary venules, which are short venous channels draining to the cortical surface from about 1 or 2 cm below the cerebral cortex; and the deep medullary venules, which are longer channels that drain perpendicularly to the ventricular surface towards the subependymal veins. There is a third group including transcerebral venules, less abundant and that connect both systems2,4 (Fig. 1B).

Perivascular space

The arterial system runs parallel to the venous system. The perivascular space surrounds the wall of arteries and arterioles (Virchow–Robin space) and veins and venules (perivenular space) from the subarachnoid space along their intraparenchymatous course. The superficial or cortical arterioles are surrounded by one layer of leptomeninges that separates the vascular surface from the periarterial space. The parenchymatous surface of this space is limited by the pia mater. The perivascular space of the penetrating arterioles of the BG is delimited by the two layers of leptomeninges that surround their endothelium. Apparently there is direct communication of the superficial and deep perivenular space with the subpial space, with no leptomeningeal layers separating them (Fig. 2).5,6

‘‘Normal’’ hyperintense punctate images in the white matter

The presence of a few hyperintense punctate foci in the cerebral white matter at MRI is a very common finding that can be regarded as insignificant in most of the cases. These bright dots, considered as normal, can be a manifestation of dilated perivascular spaces or small glotic or lacunar ischemic foci.
Hyperintense punctiform images in the white matter

Figure 1 Cerebral microcirculation. (A) Arterial microcirculation. 1: cortical arteries; 2: pial arteries; 2.1: short branches; 3: subependymal arteries; 4: subependymal perforating arterioles; 5: lenticulostriated and thalamic perforating arterioles; 6: transcerebral arterioles. (B) Venous microcirculation. 1: cortical veins; 2: superficial medullary venules; 3: subependymal venules; 4: deep medullary venules.

Figure 2 Perivascular space. (A) Periarteriolar space of the pial arterioles surrounded by one leptomeningeal layer that separates it from the subpial space (arrow). Periarteriolar space of lenticulostriated arterioles surrounded by two leptomeningeal layers that separate it from the subpial space (arrowheads in the upper box and asterisks in the lower box); (B) perivenular space that communicates with the subpial space (arrow); (C) photomicrographic detail of the perivascular Virchow–Robin space (arrows) (courtesy of Dr. Susana Boluda).
Perivascular spaces dilated in the corona radiata (A), the semioval centre (B), and the mesencephalic region (C). T1 (shown) and FLAIR sequences demonstrate similar signal to that of the cerebrospinal fluid (D).

At conventional MRI, perivascular spaces appear dilated (dPVS) in 13% of healthy adults and in only 3% of children between 20 months and 16 years of age. In a recent multicentre observational study, cerebral MRI studies using high-resolution 3D sequences of 1818 healthy individuals aged over 65 (dementia-free and with no history of cerebral infarction) were reviewed. dPVS were detected in all patients and dPVS larger than 3 mm were detected in approximately one third of patients. dPVS appear as linear or fusiform foci with similar signal to that of the cerebrospinal fluid in all sequences (Fig. 3). Small perivascular spaces (<2 mm) have been regarded as an anatomic variant, whereas larger (>2 mm) PVS have been associated with ageing, dementia, early inflammatory stages in multiple sclerosis, and inflammatory reaction in traumatic brain injury. A number of recent studies have concluded that dPVS are associated with lacunar ischemic lesions, and thus, this finding can be considered as an indicator of cerebral small vessel disease. As an exception, perivascular spaces may be significantly dilated, typically in the mesencephalothalamic region. They can cause a significant mass effect and hydrocephalus and need to be distinguished from other tumefactive cystic lesions. These giant perivascular spaces are on many occasions incidentally discovered and their presence not always correlates with the clinical manifestations. Some studies have reported a poor association with different degrees of developmental delay, headaches, behaviour anomalies, and nonspecific epilepsy, as well as benign macrocephaly in the paediatric population (Fig. 4).

The appearance of ischemic-like lacunar foci in the periventricular and subcortical white matter is a physiological process because age is a cerebrovascular risk factor itself. Abnormalities of the white matter are almost ubiquitous (95%) in the population over the age of 65 years. There are different visual rating scales for age-related white matter changes (leukoaraiosis) showing a good correlation between them. One of the best known is the Fazekas scale, which was integrated in the ARWMC scale (age-related white matter changes) recommended when lesions of the white matter are not to be quantified by CT or MRI. This is a four-grade rating scale for punctate microvascular lesions in the white matter. Absence of lesions corresponds to grade 0; presence of non-confluent focal lesions corresponds to grade 1; initially confluent lesions correspond to grade 2; diffuse confluent lesions correspond to grade 3 (Fig. 5). Based on this scale, a lesion is considered normal (attributed to ageing) and classified as grade 1, grade 2 is considered abnormal in patients <75 years, and grade 2 is considered abnormal in any age group.

There is a number of studies on pathologic and imaging correlation using magnetization transfer (MT) imaging studies that compare magnetization transfer ratios (MTR). These studies attempt to elucidate the nature of these lesions, and report differences between lesions in the
perivascular white matter and subcortical lesions. Outcomes suggest that ageing induces anomalies in the ependymal membrane, which causes filtration of the cerebrospinal fluid. This filtration leads to gliosis and focal demyelination of the parenchyma. In addition, subependymal penetrating microcirculation degenerates, which means that there is also a certain ischemic component associated, particularly in those cases in which periventricular leukoencephalopathy exhibits irregular borders. Apart from this, subcortical white matter lesions are essentially ischemic in nature due to the senile degeneration of the microcirculation.24-30

``Abnormal’’ hyperintense punctate images in the white matter

When the HPIWM is pathological, it may be indicative of an acquired or inherited disease. Among the acquired diseases of the white matter, microvascular hypoxic/ischemic disease is by far the most common, no matter whether atherothrombotic, embolic or caused by cerebrovascular risk factors (CVRFs). The acquired origin should be considered the first diagnostic option, even in the absence of typical CVRFs, unless there are clinical and analytic evidence suggestive of a different aetiology. Multiple sclerosis (MS) is the second most common disorder, with vasculitis, infection, intoxication, and trauma (among other causes) trailing far behind.31 A large number of patients with a very low vascular risk present with lesions of microvascular appearance for which there is relatively often no alternative or final diagnosis.

With respect to inherited disorders, leukodystrophic diseases are a group of rare diseases. Although they usually occur in the paediatric age, they can present in adult age. They are metabolic diseases that usually affect the white matter in a quite symmetric and extensive (not punctate) manner, and usually damage the brainstem and the cerebellum. An exception is mitochondrial diseases, which cause more asymmetric lesions, and affect primarily the grey matter. In adults, the most common are metachromatic leukodystrophy, globoid cell leukodystrophy, adrenomyeloneuropathy, mitochondrial disorders, vanishing white matter, and cerebrotendinous xanthomatosis.31

Basic pathophysiology

One possible mechanism of damage of the white matter is the primary involvement of an arteriole or cerebral venule, which compromises the blood supply of the parenchyma that depends on them, and induces a

Figure 4  Five-year old child with headache. Visualization of dilated perivascular spaces is an incidental finding with a dubious or unlikely clinical relevance.

Figure 5  ARWMC scale (age-related white matter changes) to assess punctate lesions in the white matter using computed tomography and magnetic resonance.
lesion. White matter microvascular disease encompasses a wide range of conditions: hypoxia-ischemia, granulomatous or nongranulomatous inflammation, infection, disease caused by substance deposit, toxins, metabolic disease, trauma, etc. Another possible pathophysiological mechanism of leukoencephalopathy is cell infiltration or deposition of pathologic substances in the perivascular space that can also manifest radiologically as focal lesions in the white matter. They have a non-infectious inflammatory aetiology (as is the case of MS or other demyelinating diseases, some types of vasculitis, and some granulomatous diseases), an atypical infectious aetiology (Lyme’s disease, cryptococcosis, parenchymatous cysticercosis), a metabolic aetiology (mucopolysaccharidosis) or a traumatic aetiology (diffuse axonal injury). Both pathophysiological mechanisms may co-occur in one same disease.

White matter disease can be approached by taking into account the anatomy of cerebral microcirculation and its interstitium, specifically by determining the most affected elements in the different leukoencephalopathic groups. In this respect, our goal is to get insights into the pathophysiology of the disease underlying the HPIWM by identifying the predominant semiological pattern. Three main patterns can be defined on the basis of several semiological elements:

- A vascular pattern (VP) or microvascular pattern, which is usually caused by an arteriolar lesion, and is the most prevalent (Fig. 6A).
- A perivascular pattern (PvP), which is usually caused by perivascular inflammation, among other less common causes. The paradigm of this pattern is MS, for which an autoimmune perivenular inflammation has been reported that causes demyelinization (Fig. 6B).
- A non-specific pattern (NsP), when neither of the previous patterns can be identified, and which is normally caused by microvascular disease.

**Semiological elements in hyperintense punctate lesions in the white matter**

For the radiologic approach of a case of HPIWM, the semiological elements to be analysed are distribution and location, shape, size, enhancement after contrast administration, presence of haemorrhage or microhaemorrhage, and grey matter involvement. Description of each of these elements may help identify one of the three semiological patterns suggested, thus facilitating an adequate differential diagnosis for each case.

**Distribution and location**

HPIWM may present with a predominantly supratentorial, infratentorial or supra- and infratentorial distribution. As shall be shown below, the presence of lesions with an essentially supratentorial distribution generally suggests small vessel disease as a first option, which favours a VP (Fig. 7). This suggestion is further supported by a predominantly frontoparietal distribution.

Supratentorial distribution concerns four large areas: subcortical area, periventricular area, deep area, and corpus callosum (Fig. 8).

A subcortical lesion can be located either in direct contact with the cerebral cortex (juxtacortical) thus affecting subcortical U-fibres of the white matter, or can be located inside these fibres, which would not be affected. In this latter case, the lesion is classified as _sub-U subcortical_. A sub-U subcortical lesion suggests a VP, whereas a juxtacortical lesion is more suggestive of a PvP, which is typically associated with MS (a PvP is present in one third of MS cases).

A lesion will be regarded as periventricular when it is in contact or virtually in contact (closer than 1 cm) with the ependymal surface. Both microvascular and perivascular lesions can have a periventricular location, the shape of the lesion being the key semiological element.

![Figure 6](http://www.elsevier.es)
Hyperintense punctiform images in the white matter

Figure 7  Distribution. A mainly supratentorial distribution with frontoparietal prevalence is typical of the vascular pattern. The infratentorial involvement with peripheral distribution suggests a perivascular pattern. The infratentorial involvement with central distribution suggests a vascular pattern.

The deep region is located between the subcortical and periventricular regions. The deep region is classified as bordering when located in a border zone between two vascular areas, which is indicative of a VP, or as non-bordering when not clearly located in a border zone, which is indicative of an NsP. The corpus callosum is a specific location as well, as in some other diseases, such as MS—typically in the callosal-septal interface, or in the Susac syndrome—in the Susac syndrome among others.

Infratentorial lesions can have a peripheral location, in contact with the surface of the parenchyma, or a central location, with no involvement of the surface. A central lesion is typically associated with a VP, whereas a peripheral lesion is typically associated with a PvP (Fig. 7).

Figure 8  Location: (1) juxtacortical; (2) sub-U subcortical; (3) non-bordering deep subcortical; (4) bordering subcortical; (5) periventricular, and (6) corpus callosum. A predominantly juxtacortical involvement or involvement of the corpus callosum is not indicative of a vascular pattern (VP); the rest of locations favour a VP or a non-specific pattern, and thus, suggest a microvascular cause. Periventricular lesions may be indicative of a VP or a perivascular pattern depending on the shape of the lesion.
Morphology
There are several lesion types according to their shape: oval or fusiform, punctate or roundish, and amorphous (Fig. 9). Punctate, roundish, and amorphous lesions are non-specific, whereas oval or fusiform lesions usually have a distribution parallel to the cerebral microcirculation, and thus, they normally feature a PvP. Oval or fusiform periventricular lesions in a radial pattern and perpendicular to the longitudinal axis of the lateral ventricles are quite a common feature of MS. They are known as Dawson’s fingers, after the neuropathologist James Dawson, who described finger-like venular and perivenular inflammatory cells in MS patients. Confluence of these lesions makes up a ridge-like configuration, which is also associated with MS. CVRF-induced microvascular periventricular leukoencephalopathy presents with typically more irregular borders.

Size
Localization of an isolated lesion (not several confluent lesions) >10-15 mm in size is suggestive of a PvP (lacunar infarctions are acknowledged to reach 15 mm). Smaller lesions are non-specific, and can be indicative either of a microvascular or a perivascular lesion (Fig. 10).

Enhancement after contrast administration
Although a non-specific finding, the absence of enhancement on leukoencephalopathic foci is suggestive of an inactive stage of the disease. In contrast, the active inflammatory stage of the disease usually involves an increase in permeability or absence of the blood–brain barrier and gadolinium enhancement of the lesion. Punctate, peripheral (in complete or incomplete ring) or central (homogeneous or heterogeneous) contrast enhancement can be observed. Enhancing patterns are generally a non-specific finding, except for peripheral incomplete ring-enhancement, which

Figure 9 Morphology. Ovoid or fusiform lesions suggest a perivascular pattern; the rest are non-specific.

Figure 10 Size. Lesions larger than 10–15 mm (not several confluent lesions) suggest a perivascular pattern (inflammation, infection).
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Figure 11  Enhancement following contrast administration. Absence of enhancement is a non-specific semiological finding. Peripheral incomplete ring-enhancement favours a perivascular pattern caused by multiple sclerosis. Patient with multiple juxtacortical lesions showing typically associated incomplete ring-enhancement.

has been reported as a finding typically associated with MS, and thus, suggestive of a PvP (Fig. 11).

When an image is suspicious of MS, the current diagnostic criteria of the MAGNIMS (magnetic imaging in MS) group do not require gadolinium enhancement as part of the diagnosis for dissemination in space. However, one enhancing lesion among non-enhancing lesions in the same MRI study is enough to determine dissemination in time.

In the follow-up of the disease, many authors opt for contrast administration for the assessment of active inflammation and response to treatment. The number of enhancing lesions may also help predict the prognosis of the disease.

Haemorrhage or microhaemorrhage
At MRI, images of microbleeding are associated with HPIWM in at least 18% of the population over 60 years of age. HPIWM are present in over 95% of the population over 65 years of age. These data provide further evidence of the mixed microvascular disease, which shares a pathophysiological origin with white matter disease and ...

Figure 12  Residual haemorrhage: (A) cortico-subcortical residual haemorrhage suggests amyloid angiopathy; (B) in the basal ganglia, brainstem, and cerebellum suggests AH, and (C) haemorrhage with a history of trauma suggests diffuse axonal injury.
microbleeding.\textsuperscript{18} When a VP with foci of microbleeding is observed in T2*, two pathologic entities are possible: arterial hypertension (AH) and amyloid angiopathy (AA). Involvement of the deep region of the BG and infratentorial involvement suggest hypertensive or arteriosclerotic microangiopathy, whereas a peripheral location in the cerebral cortex or lobes of the bleeding is typically associated with AA\textsuperscript{45} (Fig. 12).

Patients with vasculitis present with foci of cerebral bleeding associated with white matter microvascular-like lesions and cortical ischemic lesions appearing at the onset or secondary to infarct transformation.\textsuperscript{64} Another cause of HPIWM with residual bleeding is the diffuse axonal injury associated with a high-energy traumatic injury. Residual foci of leukoencephalopathy with traces of haemosiderin are detected at the grey matter-white matter border, mainly located in the frontal lobe and typically in the region of basal nuclei and in the splenium of the corpus callosum\textsuperscript{49} (Fig. 12).

Grey matter involvement
Most HPIWM cases are associated with cortical lesions or lesions of the BG region.

Co-presence of lesions in the cerebral cortex and multiple bright foci in the white matter is a non-specific finding. In patients with vasculitis-induced microvascular disease, it is not uncommon to detect peripheral lesions with cortical involvement, which usually represent areas of ischemic infarction.\textsuperscript{46} However, they are not readily visualized in conventional MRI sequences.\textsuperscript{34}

GB involvement typically occurs in patients with hypertensive or arteriosclerotic microangiopathy\textsuperscript{40} (Fig. 13), and is very rare in MS patients.\textsuperscript{34} In patients with acute disseminated encephalomyelitis (ADEM), who may present with lesions indistinguishable from those of MS, the BG region and the spinal cord are usually affected.\textsuperscript{36,46} Diverse forms of vasculitis (systemic lupus erythematosus [SLE], Behcet’s disease, etc.) and neurosarcoïdosis can affect the BG.\textsuperscript{44,47,48} Immunocompromised patients with cryptococcosis typically present with gelatinous cysts in the perivascular space of the lenticulostriate and thalamic perforating arterioles of the BG.\textsuperscript{49}

Differential diagnosis
The general features of each pattern can be defined by considering each of the semiological elements described (Table 1). An adequate differential diagnosis can be made by identifying the predominant pattern and the specific aspects of each case.

Vascular pattern
A vascular pattern in microvascular hypoxic-ischemic disease secondary to CVRFs (especially AH, dyslipidemia, and diabetes) is associated with a great number of lesions that are normally identified in the majority of semiological findings described by this pattern. AH produces traces of haemosiderin, which can be observed in T2*-weighted sequences, particularly in the corpus striatum, thalami, cerebellum, and brainstem (Fig. 14).

![Figure 13 Grey matter involvement (basal ganglia). (A) Lacunar porencephalic foci, which are likely associated with dilated Virchow–Robin spaces in a patient with uncontrolled AH. (B) Gelatinous cysts in the Virchow–Robin spaces of the lenticulostriated vasculature in a 30-year-old patient with AIDS, who firstly presented with cryptococcosis.](image)

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| **Vascular pattern** | - Not juxtacortical  
- Sub-U subcortical  
- Deep bordering  
- Periventricular irregular  
- Supra- > infratentorial  
- Supratentorial frontoparietal  
- Basal ganglia  
- No enhancement (if not acute) or mild enhancement |
| **Perivascular pattern** | - Periventricular ovoid  
- Juxtacortical  
- Fusiform or ovoid  
- Dawson’s fingers  
- Supra- and infratentorial  
- Large lesions |
| **Non-specific pattern** | - Deep non-bordering  
- Amorphous, punctate, round |
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Figure 14  Vascular pattern: cerebrovascular risk factors. Patients with AH showing: (A) foci of leukoencephalopathy confluent in the periventricular white matter; (B) involvement of the basal ganglia and the subcortical white matter but no involvement of the subcortical U-fibres; (C) residual haemorrhage in the basal ganglia, brainstem, and cerebellum.

As already mentioned, microvascular involvement in AA is associated with a VP, typically manifested as cortical foci of peripheral microhaemorrhage or areas of haemorrhage in cerebral lobes\textsuperscript{18,50,51} (Fig. 15).

Studies with migraine patients have reported microvascular-like HPIWM\textsuperscript{52,53} predominantly frontal or located in the semioval centres\textsuperscript{54} (Fig. 16). A recent study with 780 participants confirms this association both in patients with migraine headache and in patients presenting with other headache disorders, especially tension-related headaches. Prevalence for tension-related and migraine headaches was 34\% and 32\%, respectively, and both were much higher than prevalence for HPIWM in the controls (7.4\%).\textsuperscript{35} Migraine with aura has been shown to have a stronger association with clinical or subclinical ischemic infarcts, particularly in the posterior circulation territory (cerebellum, protuberance).\textsuperscript{54} Additionally, and irrespective of the headache type, the presence of cerebral abnormalities does not seem to be associated with cognitive impairment.\textsuperscript{35}

Most blood vessels affected by vasculitis in the central nervous system present with HPIWM typical of a VP, with a certain subcortical prevalence and associated with cortical ischemic lesions and foci of intraparenchymatous bleeding appearing at the onset or secondary to infarct transformation.\textsuperscript{44} Traces of peripheral microhaemorrhage can be found in the BG due to septic vasculitis\textsuperscript{50} and vasculitis caused by vasoactive drugs, such as cocaine and alkaloid derivatives, amphetamine, ephedrine and phenylpropanolamine\textsuperscript{44,50} (Fig. 17).

CADASIL integrates all features typical of VP associated with bilateral temporal involvement of the anterior poles, the external capsules, and the corpus callosum in the callosal-septal interface\textsuperscript{55-57} (Fig. 18).

In short, a leukoencephalopathy can be caused by HPIWM with VP if the patient presents with CVRFs. Otherwise, the

Figure 15  Vascular pattern: amyloid angiopathy. Significant changes of microvascular disease in the fronto-parieto-occipital supratentorial white matter with a vascular pattern (left). Gradient-echo sequences (centre) show punctate foci of hemosiderin in the cortico-subcortical interface, predominantly posterior (arrow), suggesting an underlying amyloid angiopathy. On the right, detail of the mural arteriolar deposits of congophilic \( \beta \)-amyloid matter.
**Figure 16** Vascular pattern: migraine. In patients with migraine (generally with aura), it is common to find frontal punctate lesions in the subcortical white matter with no involvement of subcortical U-fibres (arrows).

**Figure 17** Vascular pattern: vasculitis. 63-Year-old woman free of typical cerebrovascular factors with discrete hyperhomocysteinemia and antiphospholipid antibodies. She presented with punctate lesions in the supratentorial white matter with no involvement of the U-fibres (orange arrow) and some areas of a past cortico-subcortical temporoparietal infarct (red arrow). These findings suggested lupic vasculitis.

differential diagnosis focuses on other causes of microvascular abnormalities, such as AA, headache, toxic-metabolic diseases, some forms of vasculitis and CADASIL, among others.

**Perivascular pattern**

HPIWM with a perivascular pattern is suggestive of MS as the first diagnostic option. The most characteristic semiological findings are: juxtacortical and periventricular ovoid lesions in the form of Dawson’s fingers, typically in contact with the inferior aspect of the corpus callosum (callosal-septal lesions) or adjacent to the anterior aspect of the temporal horn; peripheral infratentorial lesions adjacent to the floor of the fourth ventricle, in the middle cerebellar peduncles and in the brainstem (Fig. 19). If other clinical or analytic indications favour MS, the patient is treated as having MS before the final diagnosis of dissemination in space and time, in consonance

**Figure 18** Vascular pattern: dominant autosomic cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). 50-Year-old patient diagnosed with CADASIL with signs of microvascular disease in the supratentorial white matter and involvement of the anterior temporal poles (arrows).
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Figure 19  Perivascular pattern: multiple sclerosis (MS). (A) juxta-cortical lesions; (B) periventricular lesions in the form of Dawson’s fingers (left and centre). Confluent lesions with a ridge-like configuration in chronic MS and anterior temporal lesion (right); (C) callosal-septal lesions; (D) peripheral infratentorial lesions; and (E) peripheral incomplete ring-enhancement.

with the MAGNIMS criteria. If the clinical setting is not suggestive of MS, the differential diagnosis will include other diseases with a likely autoimmune aetiology, such as atypical MS, ADEM, SLE, Sjögren’s disease, and sarcoidosis, infections such as Lyme’s disease and cryptococcosis, some forms of vasculitis, such as Behçet’s disease, and metabolic diseases, such as mucopolysaccharidosis.

Non-specific pattern
Leukoencephalopathy can be caused by HPIWM with an NsP if the patient presents with CVRFs. Otherwise, the differential diagnosis firstly focuses on causes of atypical microvascular disease, and secondly, on uncommon causes of perivascular disease.

The summary chart in Fig. 20 suggests a diagnostic algorithm to be used in an HPIWM case. This algorithm may help

Figure 20  Diagnostic algorithm of the hyperintense punctate images in the white matter (HPIWM), vascular pattern (VP), perivascular pattern (PvP), and non-specific pattern (NsP). ARWMC: ARWMC scale (age-related white matter changes); CVRFs: cardiovascular risk factors; AH: arterial hypertension; DLP: dyslipidemia; DM: diabetes mellitus; CADASIL: dominant autosomic cerebral arteriopathy with subcortical infarcts and leukoencephalopathy; MS: multiple sclerosis.
make an adequate differential diagnosis once the predominant pattern has been identified.

Conclusions

This study proposes a practical and simple diagnostic tool on the basis of three main semiological patterns of hyperintense punctate images in the white matter: a vascular pattern, a perivascular pattern, and a non-specific pattern. These patterns are established based on the anatomy of cerebral microcirculation. Identifying the predominant semiological pattern enables to narrow down the etiological diagnosis. Most bright dots visualized at MRI of the brain have a vascular aetiology. MS is the most common cause of PVp. An NsP is more likely to be an atypical manifestation of vascular aetiology.

Authorship

1. Responsible for the integrity of the study: SM.
2. Conception of the study: SM, MC and DG.
3. Design of the study: SM.
4. Acquisition of data: SM.
5. Analysis and interpretation of data: SM, MC, DG, JC and SG.
6. Statistical analysis: N/A.
7. Bibliographic search: SM, MC and DG.
8. Drafting of the manuscript: SM, MC and DG.
10. Approval of the final version: SM, MC, DG, JC and SG.

Conflicts of interests

The author declares no conflicts of interests.

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References


