Neurovascular-glymphatic dysfunction and white matter lesions

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Abstract Cerebral white matter lesions (WML) represent a spectrum of age-related structural changes that are identified as areas of white matter high signal intensity on brain magnetic resonance imaging (MRI). Preservation of white matter requires proper functioning of both the cerebrovascular and glymphatic systems. The cerebrovascular safeguards adequate cerebral blood flow to supply oxygen, energy, and nutrients through a dynamic process of cerebral autoregulation and neurovascular coupling to keep up with global and regional demands of the brain. The glymphatic system maintains white matter integrity by preserving flow of interstitial fluid, exchanging metabolic waste and eventually its clearance into the venous circulation. Here, we argue that these two systems should not be considered separate entities but as one single physiologically integrated unit to preserve brain health. Due to the process of aging, damage to the neurovascular-glymphatic system accumulates over the life course. It is an insidious process that ultimately leads to the disruption of cerebral autoregulation, to the neurovascular uncoupling, and to the accumulation of metabolic waste products. As cerebral white matter is particularly vulnerable to hypoxic, inflammatory, and metabolic insults, WML are the first

recognized pathologies of neurovascular-glymphatic dysfunction. A better understanding of the underlying pathophysiology will provide starting points for developing effective strategies to prevent a wide range of clinical disorders among which there are gait disturbances, functional dependence, cognitive impairment, and dementia.

Keywords White matter · Neurovascular unit · Glymphatic system · Aging · Small vessel disease

Cerebral white matter lesions: normal aging or pathology?

With the widespread use of brain magnetic resonance imaging (MRI), more and more older adults are found to have cerebral white matter lesions (WML) [1]. WML are marked as areas of white matter high signal intensity using T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI which are due to an increased water content [2]. What we see on a regular MRI scan as WML are just the tip of an iceberg. More detailed brain MRI techniques such as diffusion tensor imaging (DTI) can demonstrate extensive microstructural alterations in these affected areas of white matter reflecting a whole spectrum of pathological changes [3, 4]. These pathologies do not represent a “new” disease as new diseases are rarely really new. Most new diseases have gone undiagnosed because they have escaped our recognition, such as WML until MRI arrived.

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Prevalence of WML varies widely depending on the clinical setting and age of populations under study. WML can be found in as many as 90% of older adults with various forms of severity [5]. At the beginning, these changes in white matter were not yet recognized as signs and symptoms of disease and were thus ascribed to “normal” aging. Now we know that WML are closely related to gait disturbances, urinary incontinence, risk of cerebrovascular events, worse clinical outcomes after an acute medical condition, and cognitive impairment [6]. We and others have shown that the amount of WML builds up over time and an accelerated accumulation of WML is linked with poor prognosis [7]. WML are prototypical aging phenomena, the reflection of damage and not normal [8]. This accumulation of damage to proteins and cells leads to cerebrovascular dysfunction and culminates in brain dysfunction, disability, and an increased susceptibility to death. Therefore, the distinction between aging, pathologies, WML, and neurologic disease later in life seems in large part arbitrary [9].

The definition of a pathology is subject to current opinions and scientific understanding, and usually it is an act of intellectual creativity when the age-related changes are recognized as signs and symptoms of disease. Several studies have sought to characterize the neuropathological correlates of WML. Arteriosclerosis, morphologically dysfunctional small arteries, and stiffness of these vessels are abundantly found in the affected regions [3]. These pathologies are commonly seen in conjunction with (ischemic) degeneration of myelinated axons and neuronal damage. WML represent the process of damage accumulation of an aging brain in the absence and/or failure of repair mechanisms. This accumulation of damage in white matter is an insidious process that ultimately leads to disruption of motor and sensory signal processing and, depending on individual brain vulnerability and reserve capacity, results in cognitive decline and dementia.

In this article, we discuss that an accumulated damage over the life course in two major physiologic processes in the brain, the neurovascular unit and glymphatic system, leads to the cerebrovascular dysregulations and metabolic waste products build up which directly harm the cerebral white matter. Here, we emphasize that these two systems play a complementary role in maintaining white matter homeostasis and need to be viewed as intertwined mechanisms for studying the etiologic factors underlying WML development and progression.

Neurovascular unit and brain health

The brain is an intensely vascularized organ with an unparalleled metabolic demand. Its biological structure and functional capacity are closely tied with the integrity of its vascular bed and circulation [10]. Maintaining an adequate and efficient cerebral blood flow requires intact cardiac function, a patent vasculature over the whole heart-brain axis, and a well-regulated cerebrovascular circulation [11, 12]. Moreover, the regulation of cerebrovascular flow is dependent on the harmonized interactions between endothelium, smooth muscle cells, neurons, astrocytes, and pericytes which all together form a highly functional band named “neurovascular unit” (see Fig. 1) [15].

The neurovascular unit reflects the interface between the body and brain. Red blood cells carry oxygen, immune cells confer protection to pathogens, platelets provide coagulation homeostasis and a myriad of nutrients, and chemical and biochemical molecules meet and interact with the brain at this site [10, 16]. After the concept of the neurovascular unit was developed, a growing body of evidence has been produced suggesting that a proper function of this unit is closely linked with brain health [13]. The neurovascular unit is an active player in two key cerebrovascular physiologic phenomena: cerebral autoregulation and neurovascular coupling. Cerebral autoregulation ensures that the brain receives adequate and constant cerebral blood flow despite fluctuations in systemic perfusion pressure, whereas neurovascular coupling ensures that regional cerebral blood flow is adequately matched with metabolic activity [17, 18]. In brief, a flawless neurovascular unit preserves optimal flow through the macro- and micro-circulation to keep up with the necessary global and regional demands of the brain.

A well-functioning cerebrovascular system is also a prerequisite of white matter integrity. It is well-established that systemic risk factors such as hypertension, diabetes, and smoking accelerate aging of the cerebrovascular system and are strongly associated with the occurrence of white matter lesions already beginning in young adulthood [19, 20]. At old age, the paucity of collateral blood vessels and insufficient blood flow reserve renders white matter extremely sensitive to hypoxic-ischemic derangements [21]. This is evident, for instance, in patients with border zone infarcts in the setting of impaired systemic perfusion pressure

Fig. 1 Illustration of the Neurovascular Unit interacting with the glymphatic system and white matter. **a** Cerebrospinal fluid (CSF) flows from the subarachnoid space to the para-arterial space driven by CSF production and pulsatile arterial activity. **b** Movement of

CSF from the perivascular space to brain parenchyma with the help of AQP-4 receptors on astrocytes. **c** Movement of the interstitial fluid (ISF) along the white matter tracks collecting waste products towards the perivenular and venous circulation [13, 14]

or upstream blood vessel stenosis/occlusion where it is mainly the subcortical white matter that is affected [22]. Oligodendrocytes are not a part of neurovascular unit; however, one of the key pathways linking the neurovascular dysfunction to WML is secondary insult to the oligodendrocytes due to ischemic, hypoxic-metabolic, and inflammatory derangements. Hypoxic-ischemic insults are particularly detrimental for oligodendrocytes, i.e., the myelin-sheath forming cells of the central nervous system (CNS) [23]. It is these oligodendrocytes that play an active role in the maintenance and repair of white matter. Damage to oligodendrocytes can incite a cascade of pathological processes that ultimately lead to neuronal apoptosis and axonal loss [24]. Of note, oligodendrocytes interact closely with various cell components in the neurovascular unit with which it constantly exchanges biological signals [25]. As an example, communications between oligodendrocytes, pericytes, and microglial cells are essential for angiogenesis, inflammatory response, repair, and remyelination of neural conduits [26].

A glymphatic system to clear the waste

The extraordinary metabolic activity of the brain requires a sophisticated system to clear metabolic waste products [27]. The lymphatic system serves as the main clearance path for most bodily organs, and as a general rule, the greater the metabolic activity, the greater is the lymphatic network in that organ [28]. For a long time, the brain seemed to lack such a clearance system as a conventional lymphatic architecture is missing. Instead, a unique structure called the “glymphatic system” has been identified and serves as the major mean to clear the brain from waste products [29]. The glymphatic system is a network of perivascular spaces in the brain that contributes to the flow of interstitial fluid exchanging waste products and ultimately the clearance of these interstitial solutes into the venous circulation (see Fig. 1). Cerebrospinal fluid (CSF) in the subarachnoid space influxes to the brain through periarial spaces, passes into the interstitial tissue via perivascular astrocytes, and drives the fluid and its solutes towards the perivenular space. The interstitial solutes are ultimately cleared into the sinus-associated cisternal compartments along

which white matter tracks end in the deep parenchymal veins. The term glymphatic refers to the dependency of the system on the perivascular astroglial end-feet being lined up with aquaporin-4 water channels and their critical roles in response to brain tissue swelling [30].

Our understanding about the driving force behind the movement of fluids and solutes within the interstitium is evolving. Diffusion and bulk flow are likely to play major roles in movement of interstitial fluid, and it has been suggested that diffusion contributes to transport of smaller molecules over shorter distances, whereas bulk flow drives larger molecules, particularly along white matter tracks over longer distances [31]. Accumulating evidence suggests that various metabolic end-products and major pathological proteins in the brain are cleared via this pathway [14]. For instance, it has been shown that injection of fluorescently-tagged amyloid beta ($A\beta$) and tau are transported through the glymphatic system and drain along subcortical white matter tracts and large-caliber draining veins [32, 33]. This transport system is an active area of research, and future studies need to shed further light on the close links between (mal)function of the glymphatic system, the accumulation of pathological proteins, and brain health. Here, it should be noticed that white matter tracks are active conduits for functioning of the glymphatic system but are also maintained by the glymphatic system. This constellation implies that WML are both cause and consequence of glymphatic dysfunction. Intriguingly, WML often co-localize with another feature of cerebral small vessel disease, i.e., enlarged perivascular spaces [34]. This co-location may suggest that enlarged perivascular spaces, as WML, are not be innocent age-related bystanders but signs and symptoms of structural damage and functional impairment. Enlarged perivascular spaces are associated with abnormal collagenosis in the downstream venular system [35], and fluid stasis in the perivascular space is now interpreted as a sign of glymphatic dysfunction [36]. In addition, experimental studies have shown that dysfunction in certain components of the glymphatic system such as AQP4 water channels can have direct deleterious effects on oligodendrocytes. As an example, Marigner and colleagues, using cell culture models, showed that the neuromyelitis optica immunoglobulin G/aquaporin-4 antibody impairs astrocytic function and secondarily leads to demyelination independent of complement activation [37]. In another experimental study, Vasas and colleagues studied the histological consequences of

prolonged hydrostatic pressure injury by inducing a pathologically elevated intracranial pressure as a manifestation of glymphatic dysfunction. The intervention resulted in a prominent degree of reactive astrogliosis, a hallmark pathological feature of WML, and leads to glial scarring of perivascular, ependymal, and subependymal spaces in a neonatal feline model [38]. It has been shown that AQP4 proteins are not only involved in fluid balance regulation but also send key signals for astroglial cell migration, which occurs during glial scar formation [39].

Neurovascular-glymphatic dysfunction and white matter lesions

From the above, it becomes clear that the neurovascular unit and glymphatic system are closely related to provide the white matter with oxygen, energy, water, and nutrients; to preserve electrolyte balance; and to clean up (toxic) waste products from metabolic, maintenance, and repair activities. The cerebrovascular and glymphatic systems are complementary systems although they have distinct functional roles in nutrient supply and waste product removal. The neurovascular unit and glymphatic system closely interact at multiple levels. At a systemic level, the flow of CSF along the perivascular space is mainly driven by CSF production force and arterial pulsations [40]. Regulation of rhythmic arterial pulsation is determined by cardiac function and heart-brain axis vascular continuity. Hence, irregular cardiac function and loss of cerebrovascular vessel elasticity and compliance can both contribute to an impairment of CSF flow [41, 42]. Physiologic experiments have revealed how CSF flow along the perivascular space is synced with cardiac cycles and pulsatile wall motion of arterioles, both providing a drive force for CSF movement via the glymphatic system [43]. At the microvascular level, mediated by the structural interconnections of neurons and vessels, neural activities, regional blood flow, and clearance of metabolic byproducts are tightly matched, which again highlights the importance of proper glymphatic functioning for the neurovascular integrity and vice versa. In an experimental study, Venkat and colleagues studied white matter changes and glymphatic dysfunction in relation to multiple microinfarctions in retired breeder rats. The investigators showed that rats subjected to multiple microinfarctions developed significant degrees

of white matter injuries manifested by decreased myelin thickness, oligodendrocyte progenitor cell numbers, axon density, as well as dilation of perivascular spaces and water channel dysfunction indicated by lower aquaporin-4 (AQP-4) expression around blood vessels. This study was based on an animal model of vascular dementia with no prior vascular pathologies. While the induction of vascular injury was an initiating event in this experiment, it is plausible that simultaneous dilation of the perivascular spaces and water channel dysfunction perpetuated axonal and oligodendrocyte injuries [44]. The regulation of brain homeostasis through sleep-awake cycles is a clear example how deep the structural and functional characteristics of the neurovascular unit and the glymphatic system are interwoven. The sleep-awake cycle has a major influence on the regulation of the cardiac cycle and vascular tone through activity of the autonomic nervous system [45]. Similarly, activity of the glymphatic system changes significantly during sleep-awake cycles. Experimental studies have demonstrated that the interstitial space expands considerably during sleep and this cooccurs with an increase of interstitial fluid flow and clearance of misfolded proteins [46, 47].

The neurovascular unit and glymphatic system form a structural and functional continuum for maintenance of the neuronal homeostasis, and both systems need to be taken into account to arrive at a comprehensive view on the pathophysiology of WML. Hypoperfusion at a systemic and/or local level induces oxidative stress and inflammation and is a major drive for the occurrence and progression of WML [48, 49]. Myelinated axons are particularly sensitive to ischemic and inflammatory insults as they lack a well-developed collateral vascular support system, whereas oligodendrocytes are especially vulnerable to waste metabolic product accumulation as compared to other brain cells [50, 51]. The vulnerability of white matter to those insults increases with advancing age as compensatory mechanisms progressively fail due to accumulating damage of brain structures and loss of neurovascular-glymphatic function [52, 53]. Long-lasting exposures to vascular risk factors such as hypertension and diabetes thus accelerate brain aging and are among the most common risk factors for WML. Observations in older adults have shown that an impaired periodicity of cerebral blood flow during sleep is associated with WML [54]. Consistently, several observational studies have shown that less and lower quality of

sleep is associated with both cerebrovascular dysregulation and WML [55, 56].

Implications for brain health and structural integrity

With a rapid rise in the number of old and very old individuals, the concept of healthy brain aging has received an increasing attention, and attempts have been made to determine the predictors such phenotype [57]. Age-related disorders such as dementia and stroke impose a great burden on patients, families, and healthcare systems [58]. The term “brain aging” denotes a constellation of morphological and neurophysiological alterations in the brain that ultimately leads to impairments in motor, cognitive, and social skills. Diminished neuronal activity and connectivity are among the key features in an aging brain [59]. This underscores the integral role of white matter health in maintenance of the brain function. WML are among the most common consequences of cerebral small vessel disease and are closely linked with the process of aging [60]. The occurrence of WML upon MRI examination of older adults should not be normalized in the diagnostic report as “this pattern is expected given the age of the patient.” First, it does not help when physicians convey the message that everything is “normal” when older adults themselves experience symptoms of a failing brain. The presence of WML indicates that their brain is vulnerable, identifies those at an increased risk of stroke, and is a harbinger of accelerated cognitive decline and dementia. Second, age-related presence of WML should guide scientists to unravel the complex root causes of these brain pathologies with an emphasis on the interrelation between a failure of neurovascular and glymphatic system of the brain. Third, a better understanding of this pathophysiology will provide starting points for developing effective strategies for prevention and therapy. Finally, as late-onset dementias have a long prodromal phase, there is an increasing need to define intermediate pathophysiological derangements before the brain damage becomes too extensive and irreversible. These will prove the necessary criteria when guiding preventive and therapeutic strategies to prevent cognitive disability.

In this article, we put forward a biological framework which explains how two key physiological systems act in concert to preserve the cerebral white matter integrity and dampen the adverse effects of ischemic, hypoxic,

toxic, and metabolic derangements. WML are strongly related with adverse health outcomes, and understanding the pathophysiology of these pathologies is of paramount importance for early recognition of high-risk individuals and development of preventive and therapeutic interventions. Maintenance of white matter structural and functional integrity requires a collective action of the neurovascular unit and glymphatic system in order to provide adequate energy and regulate intracellular and extracellular electrolytes and nutrient homeostasis and waste metabolic removal. This highlights the importance of developing strategies that take into account both systems as compared to the current fragmented pathophysiological models.

Declarations

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