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BRAIN LYMPHATIC DRAINAGE SYSTEM IN FETUS AND NEWBORN: BIRTH OF A NEW ERA OF EXPLORATION

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ABSTRACT

A peculiar brain lymphatic drainage system has been recently fully recognized in animals and humans. It comprises different draining pathways, including the lymphatic system, the perivascular drainage pathway, and the cerebrospinal fluid (CSF) drainage routes. Although scant data are available about its function during the neonatal period, it may play a role in neonatal brain diseases. In this review, we focus on the actual knowledge of brain lymphatic drainage system, and we hypothesize potential implications of its impairment and dysfunction in major neonatal neurological diseases.

Keywords: neonates, brain injury, glymphatic system, brain lymphatic drainage system, fetal development, cerebrospinal fluid drainage, schematic

Lymphatic drainage is fundamental to maintain tissue homeostasis. The interstitial fluid (ISF) slowly flows through the extravascular compartment of most organs, providing cells with nutrients and signaling molecules, including cytokines and hormones, and collecting proteins, solutes, and waste substances deriving from cell metabolism (1). These substances, forming the lymph, are eventually drained into the lymphatic vessels to reach nearby lymph nodes. The lymphatic system begins to develop during early fetal life and, although few data are available about its function during the early stages of human development, it has been observed that fetal lymph flow is greater than in the adult (2). Although a conventional network of lymphatic vessels is absent in the brain parenchyma, a peculiar cerebral lymphatic drainage system has been recently fully recognized (3). The main components of the brain lymphatic network include the glymphatic system, the perivascular drainage pathway, and the CSF drainage routes. In adults, dysfunctions of the brain lymphatic system have been related to several neurological diseases, including neurovascular (4), neurodegenerative (5) (6), and neuroinflammatory brain disorders (7). In addition, some studies suggest a contribution of lymphatic drainage pathway impairment in the pathogenesis of traumatic brain injury and tumors (8,9).

Despite accumulating evidence of its role in several adult diseases (10), to date scarce literature has focused on the anatomy and physiology of the fetal and neonatal brain lymphatic system.

Newborn infants, both term and preterm, are at risk of brain damage, which involves different brain structures depending on gestational age and perinatal risk factors (11). Although neonatal brain injuries have been widely studied, their pathogenesis and the factors affecting their evolution haven't been completely understood. In particular, the contribution of the brain lymphatic system in neonatal brain disease is unknown at the present time.

The present review focuses on the actual knowledge of the brain lymphatic drainage system, and we speculate on potential implications of its impairment and dysfunction in major neonatal neurological diseases.

Brain Lymphatic Drainage System

The brain lymphatic drainage system integrates the brain ISF exchange and CSF circulation and represents the drainage route of ISF from brain parenchyma to deep cervical lymph nodes. It is composed of different pathways which are closely connected and provide a regulation of the composition and volume of cerebral fluids. Structures associated with cerebral fluid turnover include the CSF circulation and drainage routes, the glymphatic system, and the intramural periarterial drainage of brain ISF (12). As a lymphatic equivalent in the brain, the cerebral lymphatic drainage system may have several functions: the clearance of solutes and metabolites from the brain interstitium, the maintenance of water and ion homeostasis as well as the regulation of intracranial pressure, the transportation of signaling molecules among neurons and glia, and the support of neuroimmune interactions (10). A representation of the brain lymphatic drainage system is presented in *Fig. 1*.

Glymphatic System

The glymphatic system was first described by Iliff and Nedergaard in 2013 as a brain wide network of paravascular spaces through which the clearance of solutes and wastes takes place (13,14). CSF enters the brain from the subarachnoid space flowing along the para arterial spaces surrounding the penetrating arteries, facilitated by a combination of arterial pulsatility, respiration, and pressure gradient. Then, it moves within the brain parenchyma through aquaporin-4 (AQP-4) water channels expressed by astrocytic endfeet and plays a crucial role in regulating water permeability in the central nervous system (15). CSF exchanges with ISF which flows towards the perivenous spaces and drains in the subarachnoid compartment.

The glymphatic system is currently supposed to be an essential route of distribution of electrolytes and macromolecules including glucose (16) and lipids (17) and the major clearance pathway of ISF solutes and wastes from the brain's parenchyma (13).

Recent animal studies demonstrated that the glymphatic system is fully active during sleep, while its function is suppressed during wakefulness. Using an in vivo 2-photon imaging of glymphatic system Xie and colleagues showed that the CSF influx decreased by 90% in the awake state compared to anesthetized or naturally sleeping mice (18). An enhanced function of this system during sleep may prevent the accumulation of neurotoxic waste products. Sleeping is the main brain activity during late foetal and early neonatal period, and its impact on neurosensory and cortex development has been demonstrated (19,20). We speculate that one of the reasons of prolonged sleep in neonates could be the necessity of preventing the accumulation of several toxic substances produced by the high rate metabolism of the neonatal brain.

Intramural Peri-Arterial Drainage Pathway

The intramural peri-arterial drainage of brain ISF was observed in mice, both in adult and young individuals (21,22). It consists of a drainage route of the brain parenchyma located within the basement membranes of capillaries and arteries within the smooth muscle cells of the tunica media and it flows in the

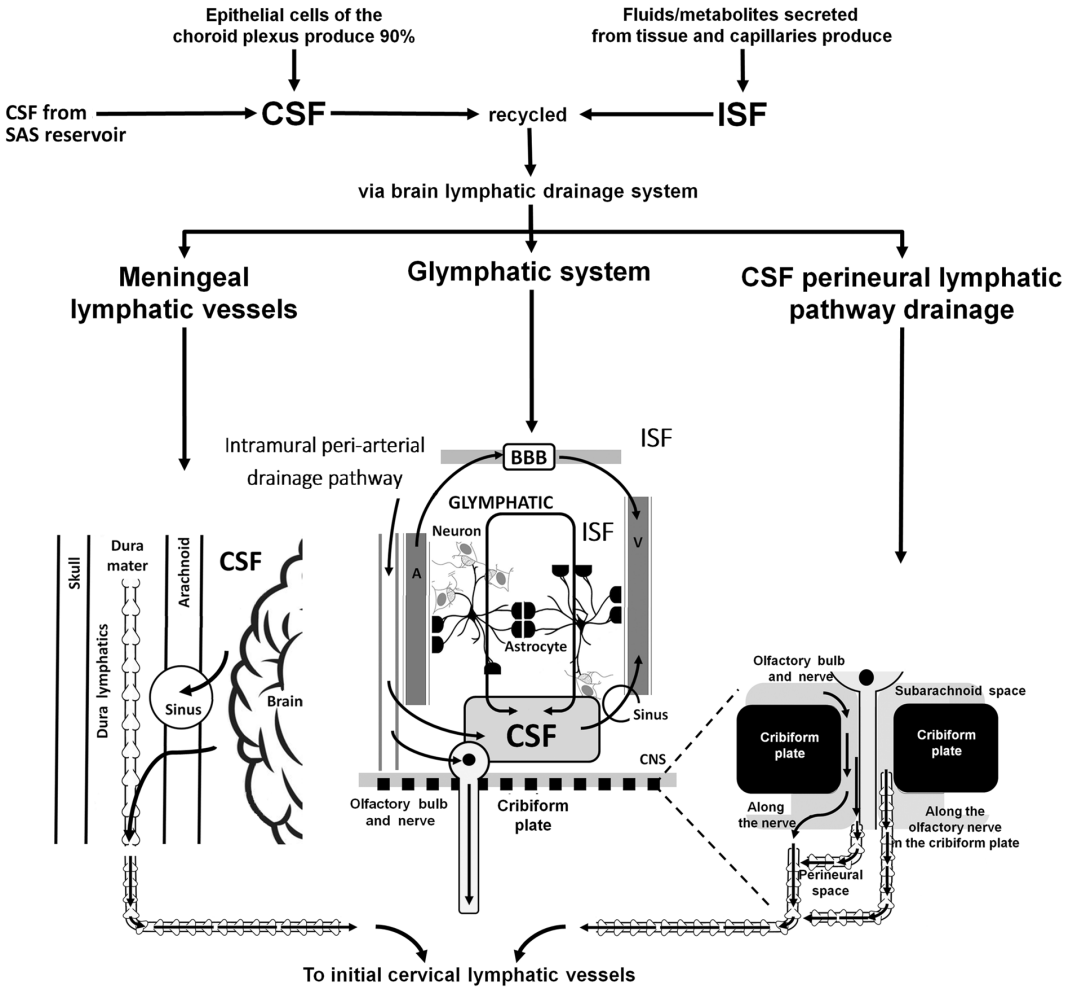

Fig. 1. Brain lymphatic drainage system. The connection between CSF circulation and brain ISF occurs through the peculiar lymphatic drainage system of the brain. The meningeal lymphatic vessels are distributed along dural sinuses and meningeal arteries and drains CSF from SAS into cervical lymph nodes; the glymphatic system represents a CSF/ISF exchange network and comprises a CSF influx from para-arterial spaces, a CSF/ISF exchange system within the brain parenchyma, and CSF-ISF efflux through para-venous spaces toward CSF circulation and venous blood; the intramural peri-arterial drainage pathways is responsible for brain ISF drainage towards CSF circulation; the olfactory lymphatic pathway drains CSF and ISF through the cribriform plate along perineural spaces toward cervical lymph nodes. Abbreviations: interstitial fluid (ISF), cerebrospinal fluid (CSF), subarachnoid spaces (SAS), central nervous system (CNS), blood brain barrier (BBB).

opposite direction of the arterial blood flow. The bulk flow drainage of ISF and brain solutes occurs along the intramural spaces of the brain arterial network and reaches the cervical lymphatics of the exterior skull base via the leptomeningeal arteries (23). A small percentage (10 to 15%) of solutes drained by this route seems to flow back into CSF through meningeal stomata on the pia mater (23,24).

CSF Circulation and Drainage Routes

CSF is a fluid circulating through the subarachnoid space which of protects the brain from external physical forces and provides metabolic, nutritional, immunologic, and scavenging functions (25). CSF is primarily secreted by the four choroid plexuses (CPs) which develop in early stages of human development and form, together with arachnoid and arachnoid villi, the blood cerebrospinal fluid barrier (26). CPs are present in the two lateral, third and fourth ventricles and consist of fenestrated blood vessels, with a single layer of intimately opposed choroid epithelial cells, joined by tight junctions (27). Passing from the ventricular system into the subarachnoid spaces through the Luschka and Magendie foramina, CSF partly drains into venous sinuses via arachnoid villi and granulations that are distributed along the superior sagittal sinus (28). First identified by Pacchioni in the 18th century (29), the microscopic arachnoid villi and the macroscopic arachnoid granulations represent herniations of the cranial arachnoid membrane and project into the venous sinuses of the dura mater on the convexity of the brain. Absorption is facilitated by the hydrostatic pressure gradient between the CSF compartment and the venous system (30). Active phagocytosis, pressure dependent pinocytosis, vacuoles, transcellular channels, gaps between cells of the endothelium surrounding the venous sinus, and passive transport via extracellular cisterns are all possible mechanisms which are believed to be involved in CSF transport (31). Arachnoid granulations are poorly formed and non functional in utero; they are present as villi in the late third trimester, as granulations around birth, and become fully functional later (32). As the global CSF transport parameters seems to be similar in foetus and adult (33), one or more alternative reabsorption mechanisms are supposed to be predominant in the first stages of brain development, while arachnoid projections may play a limited role (34).

It has been demonstrated that CSF is also absorbed in the paraneural sheaths of cranial and spinal nerves to reach the nasal and dural lymphatic vessels and eventually the cervical lymph nodes (25,35). The major pathway of lymphatic CSF drainage is represented by the perineural sheath along the olfactory nerve (33). CSF passes through the cribriform plate along perineural spaces of the ethmoid bone near the olfactory nerves to a lymphatic network in the nasal mucosa, and finally reaches the retropharyngeal lymph nodes (36,37). In addition, tracers injected into the CSF system have been shown to reach the lymphatic system along many cranial nerves including the trigeminal, acoustic (38), hypoglossal and vagus nerves (39).

Recently, discovery of meningeal lymphatic vessels associated with venous sinuses and meningeal arteries has opened a new hypothesis on CSF and ISF drainage pathways (40). Although their precise localization and function has not been completely clarified, meningeal lymphatic vessels absorb CSF from subaracnoid spaces (SAS) and ISF from perivenous spaces and drain to deep cervical lymph nodes (41).

Lymphatics manage roughly 50% of the total CSF absorption and their activity increases in the presence of an augmented intraventricular pressure (42).

Previous observations supported the hypothesis that lymphangiogenesis plays an important role in nuchal edema, since increased nuchal translucency may be related to a developmental delay of the lymphatic system (43). It is possible to speculate that in the presence of increased nuchal translucency, delayed or disturbed development of the fetal

lymphatics of the cervical region may trigger a reduction in the drainage of CSF via the perineural space through the cribriform plate.

In addition, it has been observed that increased intracranial pressure can force cerebrospinal fluid across the ependymal barrier and into the extracellular space of adjacent periventricular white matter, acting as an additional pathway for CSF flow under abnormal conditions (44).

Possible Implications in Neonatal Brain Diseases

Considering its importance in brain fluid homeostasis, the brain lymphatic drainage system may play a role in the pathogenesis of neurological injuries in both term and preterm infants. Its involvement can be hypothesized according to several observations.

Acute hypoxic-ischemic brain injury occurring at birth is a major cause of death and disability in term infants. The cellular and molecular basis of hypoxic-ischemic encephalopathy comprises various mechanisms, including neurovascular unit and blood brain barrier integrity, neuroinflammation, adaptive intracellular mechanism, and brain repair capacity (45). Extracellular accumulation of excitatory amino acids and over-activation of their receptors are important factors in early injury progression (46), and eliminations of these toxic substances may be secondary to the glymphatic system functioning status. Astrocytes, a key component of both blood brain barrier and glymphatic system which contribute to neuronal function and homeostasis, are an important source of inflammatory mediators following cerebral ischemia (47).

Interestingly, a recent MRI study has shown that meningeal lymphatic flow runs countercurrent to venous flow in the superior sagittal sinus of the human brain (48). This finding suggests that a large proportion of CNS lymphatic flow is directed to the cribiform plate, a feature that needs to be considered in development of models of fluid flow in health and disease.

Furthermore, cerebral edema is the most prominent histological sign during hypoxia ischemia, and it is one of the main factors affecting its prognosis. In animal studies, an increased AQP-4 expression in cerebral edema caused by several pathways of brain injury has been observed (49). In mice, hypoxic-ischemic injury was associated with an increased permeability of brain blood barrier through the up regulation of AQP-4 and, consequently, to the development of cerebral edema (50).

The brain lymphatic drainage system may also be involved in the pre-term white matter injury. Many factors occurring both during pregnancy and in the perinatal period may cause an impaired maturation of oligodendrocytes, which are responsible for central nervous system axons myelinization, leading to white matter damage in the developing brain. Reactive astrogliosis is one of the restorative mechanisms following neuronal injury in the preterm brain, and its occurrence may alter the glymphatic system structure and function (51,52). In addition, the removal of waste metabolites produced by oxidative stress and neuroinflammation, which represent the major mechanisms of disturbance of white matter development (53-55), is of paramount importance to limit brain damage and subsequent neurological impairment in this fragile population.

CONCLUSIONS

More than a half-century ago, seminal experimental and clinical observations by Földi et al regarding the anatomy and function of the meningeal lymphatics and the effect of experimental ligation of the cervical lymphatics draining the brain and a related clinical syndrome of “lymphogenic encephalopathy” established a fundamental basis for the recent enlightening studies (56-61). Over the last few years, the brain lymphatic drainage system has gained great interest, and many studies have focused on delineating its anatomy and function. Scant data, however, are available about its role in the neonatal brain. Acute

brain injury likely impairs glymphatic function, thus enhancing brain damage due to the accumulation of both normal metabolic waste as well as injury induced debris. Although its presence and activity in newborn infants, especially pre-term infants, has not been clarified yet, a deeper comprehension of its components and functions in fetal and neonatal brain may reveal new insights into the pathogenesis of neonatal brain disorders and provide novel targets for therapeutic intervention.

CONFLICT OF INTEREST DISCLOSURE

All authors declare no competing financial interests exist.

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