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CEREBROSPINAL FLUID BIOMARKERS

Clearance of interstitial fluid (ISF) and CSF (CLIC) group—part of Vascular Professional Interest Area (PIA)

Cerebrovascular disease and the failure of elimination of Amyloid- β from the brain and retina with age and Alzheimer's disease—Opportunities for Therapy

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Abstract

Two of the key functions of arteries in the brain are (1) the well-recognized supply of blood via the vascular lumen and (2) the emerging role for the arterial walls as routes for the elimination of interstitial fluid (ISF) and soluble metabolites, such as amyloid beta ($A\beta$), from the brain and retina. As the brain and retina possess no conventional lymphatic vessels, fluid drainage toward peripheral lymph nodes is mediated via transport along basement membranes in the walls of capillaries and arteries that form the intramural peri-arterial drainage (IPAD) system. IPAD tends to fail as arteries age but the mechanisms underlying the failure are unclear. In some people this is reflected in the accumulation of $A\beta$ plaques in the brain in Alzheimer's disease (AD) and deposition of $A\beta$ within artery walls as cerebral amyloid angiopathy (CAA). Knowledge of the dynamics of IPAD and why it fails with age is essential for establishing diagnostic tests for the early stages of the disease and for devising therapies that promote the clearance of $A\beta$ in the prevention and treatment of AD and CAA. This editorial is intended to introduce the rationale that has led to the establishment of the Clearance of Interstitial Fluid (ISF) and CSF (CLIC) group, within the Vascular Professional Interest Area of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment.

KEYWORDS

cerebrospinal fluid, clearance, interstitial fluid, IPAD, ISTAART

1 | FOCUS OF CLIC

Why is there a need for the CLIC Group within ISTAART's Vascular PIA? For 20 years, the focus of treatments to relieve the burden of amyloid in the Alzheimer's disease (AD) brain has been on immunotherapy, but this

has not been a complete success. Although amyloid beta ($A\beta$) deposits are removed from the cerebral cortex, there is a significant increase in cerebral amyloid angiopathy (CAA) after $A\beta$ immunotherapy; this indicates that $A\beta$ removed from the cortex is deposited in artery walls due to blockage of the intramural peri-arterial drainage (IPAD) system.^{1,2}

Shifting the focus from the brain tissue to IPAD may allow us to free a bottleneck and to increase the effectiveness of immunotherapy. A similar strategy for improving IPAD will help to prevent the initial age-related accumulation of A β in the brain, thus preventing the development of AD.

What are the structure and aims of the group? This is an interdisciplinary assembly of scientists, clinicians, and drug developers who have already contributed significantly to the mechanisms of central nervous system (CNS) fluid balance and exchange, pathology of cerebrovascular disease, pathogenesis of A β accumulation in AD and cerebral amyloid angiopathy (CAA), development of AD therapeutics, and delivery of therapeutics to the brain via intrathecal dosing into the cerebrospinal fluid (CSF). The role of each member of CLIC will become apparent in the brief account below of the anatomy, physiology, and pathology of IPAD and CSF related to AD.

2 | MISSION OF THE CLIC GROUP

In the short term, members of the group will establish contacts and familiarize themselves with the spectrum of research in IPAD and related fields. Virtual meetings hosting seminars for greater mutual understanding of respective research focuses are envisioned.

In the longer term, members of CLIC will form multidisciplinary groups to gain a greater understanding of the dynamics of IPAD and CSF circulation in AD and CAA. Each group will establish funding streams to facilitate collaborative multidisciplinary research.

The overarching objectives of the CLIC are to:

1. Understand the changes with age in the peripheral physiology that underly impaired IPAD.
2. Understand the cellular and molecular mechanisms underlying IPAD physiology in the brain.
3. Establish novel diagnostic tests for AD, CAA, and vasomotion based on our knowledge of IPAD and the fluid dynamics of CSF.
4. Establish novel therapies that facilitate IPAD for the elimination of A β from the aging brain to prevent or reduce established AD (and CAA?) pathology.

3 | BACKGROUND TO IPAD AND ITS FAILURE WITH AGE, AD, AND CAA

A β and other soluble peptides such as cystatin C are present in the interstitial fluid (ISF) of the brain. A β is normally cleared from the brain by several mechanisms: it is eliminated across the vascular endothelium via a lipoprotein receptor LRP-1,³ or taken up by microglia, astrocytes, and perivascular macrophages.⁴⁻⁶ Another major pathway for the elimination of A β is via ISF drainage. As there are no conventional lymphatic vessels in the brain, ISF is eliminated along the walls of cerebral blood vessels. Several anatomical routes have been proposed for elimination of ISF, including alongside venules (glymphatic system)

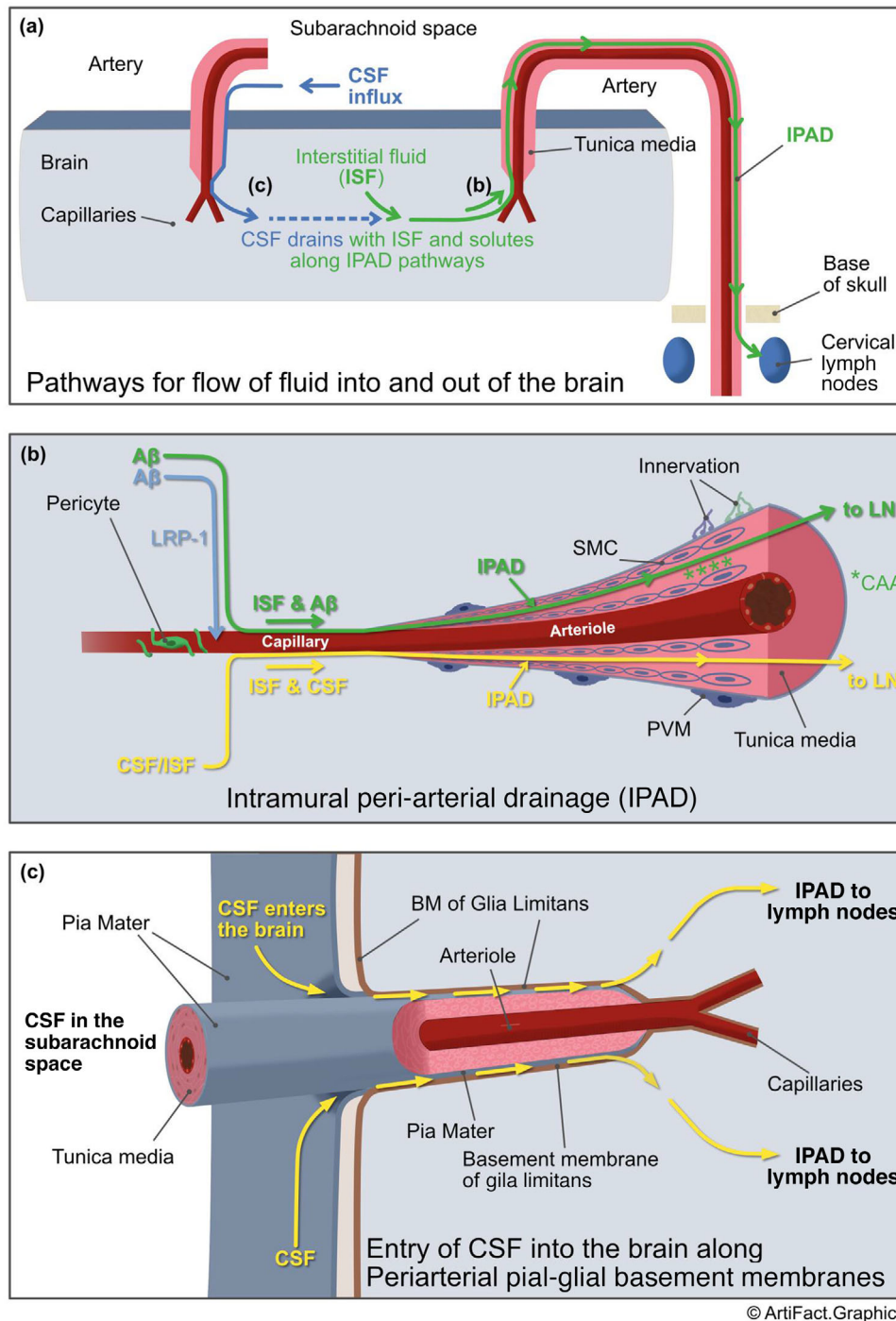
and along basement membranes in the walls of capillaries and arteries (IPAD pathways;^{7,8} Figure 1A,B). Although the exact roles of the observed drainage pathways have not been fully elucidated, the IPAD pathway corresponds more closely to neuropathological observations of vascular A β deposits in CAA, which are mainly found in the walls of capillaries and arteries. IPAD becomes less effective with age, in the presence of the apolipoprotein E (APOE)4 genotype, and with apparent transient overloading after immunotherapy for A β ⁷ and CAA-related inflammation (CAA-ri),^{8,9} all leading to increased CAA.¹⁰⁻¹⁴ IPAD is not a passive process and the motive force for IPAD is derived from vascular pulsations. Recently it has been suggested that the spontaneous low-frequency contraction and relaxation of vascular smooth muscle cells (ie, vasomotion), and possibly pericytes, may be important drivers for IPAD.¹⁵⁻¹⁷ The diversity of the vascular mural cells and their relative vulnerability during aging is likely to impact the efficiency of IPAD from different regions of the brain.^{18,19} Components of the extracellular matrix within the IPAD pathways, in particular perlecan, appear to impede the clearance of A β .²⁰ Finally, the complex interactions between APOE and A β , although not fully understood, likely influence clearance of ISF and A β as well.^{21,22}

4 | AMYLOID ANGIOPATHY IN RETINAL ARTERIES

Deposits of A β have recently been identified in the tunica media of retinal arteries in post-mortem retinae of patients with AD.^{23,24} Accumulation of A β in the retina has been closely linked to an early loss of retinal vascular smooth muscle cells (vSMC) and pericytes expressing platelet-derived growth factor receptor (PDGFR) β .²⁵ Furthermore, the extent of loss of vascular PDGFR β predicted retinal amyloid angiopathy scores.²⁵ Levels of amyloid angiopathy in the retinal vessels may prove to be a readily accessible and potentially valuable index of severity of CAA in the brain.

5 | MODELS OF CAA OR SMALL VESSEL DISEASE

While CAA due to accumulation of A β in the IPAD pathway is a common feature of cerebral small vessel disease, CAA is also seen in rarer disorders involving IPAD such as Familial British dementia due to mutations in the *BRI* gene and Icelandic CAA due to mutations in the gene encoding the cystatin protein.^{26,27} It is important to identify appropriate models to study therapeutic targets for CAA or other small vessel diseases. Different transgenic mouse models such as APP/PS1, TgSwDI, or Tg2576 are used to test individual hypotheses related to CAA, albeit with limitations.²⁸ Rodent models for the study of vascular dysfunction include hyperhomocysteinemia and hypoperfusion due to occlusion of a carotid artery.²⁹⁻³² In addition, non-human primate models are known to develop extensive CAA thus offering potential preclinical avenues for investigation, especially in the context of white matter lesions.^{33,34} Intramural accumulation of cystatin amyloid aggregates in Icelandic CAA are also observed in skin vessels, suggesting that in vitro



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FIGURE 1 A, Intramural peri-arterial drainage (IPAD) pathways for the lymphatic drainage of interstitial fluid (ISF) and soluble amyloid beta ($A\beta$) from the brain. Right side of diagram: ISF and $A\beta$ (green line and arrows) pass from the extracellular spaces of the brain to drain along the walls of capillaries and arteries ultimately to the cervical lymph nodes adjacent to arteries under the base of the skull. Details of the IPAD pathway are shown in (B). Left side shows how cerebrospinal fluid (CSF) enters the brain along the outer aspects of penetrating arteries and passes into the ISF of the brain parenchyma (details in [C]) and then flows out of the brain along IPAD pathways (green line and arrows). B) Details of the IPAD pathway, cerebral amyloid angiopathy (CAA) and LRP-1-related absorption for $A\beta$. Soluble $A\beta$ (light blue arrow), produced by cells in the brain, is absorbed into the blood involving LRP-1 as one of the pathways for elimination of $A\beta$. Another major pathway is by IPAD (green line and arrows). $A\beta$ in the ISF enters the basement membranes of endothelial cells in the walls of capillaries. Contractile pericytes surround capillaries and may supply the motive force for IPAD in capillaries. $A\beta$ then rapidly passes into basement membranes (100 to 150 nm thick) surrounding smooth muscle cells (SMCs) in the tunica media of cerebral arteries. Changes occur in the walls of arteries as they age and IPAD is impaired resulting in the deposition of fibrillar $A\beta$ in the IPAD pathways as CAA (green asterisks). As more $A\beta$ is deposited and the severity of CAA increases, the wall of the artery is disrupted, SMCs are replaced by $A\beta$ and IPAD is further impaired. The yellow line passing along the IPAD pathway shows how CSF that has entered the ISF of the brain also drains from the brain along IPAD pathways in artery walls. SMCs in the tunica media of arteries supply the

models of this disorder could provide convenient platforms to study mechanistic properties of affected vessels.³⁵

6 | DEVELOPING NOVEL THERAPEUTIC STRATEGIES

New therapeutic avenues for CAA (and AD) that act via IPAD include interventions modulating vasomotion, the postulated motive force of IPAD. This could potentially be accomplished by enhancing low-frequency oscillations of the vascular smooth muscle cells through neurovascular coupling or during sleep,³⁶ or by noradrenergic innervation of cortical vSMCs.³⁷ Other potential therapeutic targets are intracellular mitochondrial systems,³⁸ chaperone molecules such as clusterin,^{39,40} or combination therapies.⁴¹ Pharmaceutical approaches may include vasoactive drugs that promote IPAD, resulting in maintenance of vascular integrity and reduction of A β deposits.⁴²

Other proposed mechanisms for vascular dysfunction in the brain include mitochondrial dysfunction, metabolic failure, autoimmunity, initiation of mechanisms of cell death and inflammation (with involvement of the neurovascular unit, including endothelial cells, vSMCs, pericytes, as well as glial cells). Each of these processes may contribute to impaired clearance of fluids, including soluble A β and hyperphosphorylated tau from the brain.^{43,44} Multiple studies are currently evaluating strategies to ameliorate these pathways.

7 | CEREBROSPINAL FLUID

CSF is produced by the choroid plexus and while some CSF may pass into venous blood via arachnoid villi and granulations in humans, CSF also drains along lymphatics located in the dural meninges and in cranial and spinal nerve sheaths en route to regional head, neck, and perispinal lymph nodes.⁴⁵⁻⁴⁷ The route along channels that are adjacent to olfactory nerves entering the nasal mucosa is emerging as an important pathway for the diagnosis of AD.⁴⁸

The relative contribution of these drainage pathways to overall clearance of CSF and solutes as well as a specific point of anatomical confluence between vascular wall and lymphatic routes remains to be further elucidated. Measures of overall clearance of molecules via the CSF to the periphery or along each of these specific routes could emerge as important biomarkers for diagnosing failure of clearance of fluid from the CNS in diseases such as AD.⁴⁸⁻⁵¹

8 | INTERCONNECTIONS BETWEEN CSF AND ISF IN THE BRAIN

In vivo imaging data from human studies show that molecules within the CSF are in direct communication with the ISF.^{52,53} In vivo imaging studies showed that tracers administered into CSF enter the brain along the periarterial pial-glial basement membranes between pia mater coating the arteries and the glia limitans of the cerebral cortex.^{54,55} These boundaries give rise to a periarterial compartment filled with extracellular matrix around arteries (observed as "perivascular spaces" on in vivo imaging⁵⁶), facilitating the transport of CSF into the brain.⁸ After tracers have entered the parenchyma from the CSF they mix with ISF,⁵⁵ prior to leaving the brain by IPAD⁵⁵ (Figure 1a-c). As suggested by the glymphatic system, an alternative clearance route for ISF may be alongside the walls of venules. Further experimental studies are needed to fully elucidate the relative contribution of venules and arteries to the clearance of ISF from the parenchyma. There is an increased incidence of AD pathology, including CAA, in patients with idiopathic normal pressure hydrocephalus (iNPH), most likely as a result of disturbances in the dynamics of CSF-ISF.⁵⁷ Patients with iNPH could therefore be a valuable model for the study of interactions CSF-ISF.

As CSF enters the brain along basement membranes surrounding the walls of cortical arteries, this represents an important pathway for drug delivery, including novel antisense oligonucleotides.⁴⁹ Drugs injected into the CSF may also have unique access to influence the dynamics of ISF clearance along IPAD pathways.

There are meningeal lymphatics in the dural lining of the skull, but their role in clearing ISF is unclear.⁵⁸ Tracers injected into the CSF drain into parasagittal lymphatics in the dura and reach cervical lymph nodes.⁵³

9 | CAA-RI AND ARIA: CLINICAL-RADIOLOGICAL ABNORMALITIES POTENTIALLY RELATED TO THE FAILURE OF DRAINAGE OF FLUID FROM THE BRAIN

It is widely accepted that amyloid-related imaging abnormalities (ARIA) represent a major unwanted effect of A β immunotherapy for AD. The features of both ARIA-E, in which there is evidence of vasogenic edema and inflammation, and ARIA-H, in which there is evidence of hemosiderin deposits, microhemorrhages, and cortical superficial siderosis suggest the disruption of the normal interactions among

motive force for IPAD and have both adrenergic and cholinergic innervations. C, Entry of CSF into the brain along periarterial pial-glial basement membranes. As arteries enter the surface of the cerebral cortex they are coated by a layer of pia mater that is firmly associated with the basement membranes of the glia limitans on the surface of the brain. There are no perivascular spaces around cortical arterioles so tracers injected into the CSF enter the brain along the periarterial pial-glial basement membranes and mix with the ISF in the brain parenchyma. CSF tracers are then eliminated from the brain along IPAD pathways. This route could be used to deliver drugs to increase the efficiency of elimination of A β along aging IPAD pathways. PVM, perivascular macrophage; SAS, subarachnoid space

ISF, CSF, and walls of blood vessels.^{7,59} Both ARIA-E and ARIA-H phenomena have been demonstrated spontaneously in CAA-ri, a rare autoimmune encephalopathy mediated by autoantibody targeting cerebrovascular A β .⁸

Like immunotherapy-induced ARIA, it is hypothesized that increased anti-A β auto antibodies in the CSF promote the clearance of A β plaques from the CNS as evidenced by the increased amount of soluble A β 40 and A β 42 and reduced A β -PET uptake. According to the "ARIA Paradox" pathogenic model⁹ the initiating factors and immune-mediated mechanisms of CAA-ri and ARIA are thought to be a complicated mixture of genetic, vascular, and immunological risk factors closely related to the A β burden and the dose- and time-related effects of anti-A β antibodies.⁵⁹ It is thus likely that the severity of CAA and the CAA-related impairment of neurovascular coupling functions, including the complex interplay among microglia, astrocytes, endothelial, and vSMC are the game-changers in determining vascular dysfunction and impairment of clearance of A β and hyperphosphorylated tau from the brain.^{60,61}

To this end, anti-A β autoantibodies and CAA-ri could offer a unique possibility to explore the relationships between pathways of A β clearance and enable development of innovative therapies, representing a human spontaneous model of A β immunotherapy.

10 | CONCLUSION

Our interdisciplinary group aims to further the understanding of how ISF and CSF are involved in the pathology of AD and related dementias and how ISF and CSF may be harnessed for diagnostic tests and for disease-modifying therapies.

CONFLICTS OF INTEREST

Multiple authors are members of the ISTAART Vascular Cognitive Disorders PIA. The authors declare no conflicts of interest.

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