Should We Search for Early Brain Disease Biomarkers in Urine

Abstract

Neurons are exquisite sensitive to alterations. The brain has a high metabolic rate; thus, it requires rapid mobilization of nutrients and clearance of metabolites to maintain constant homeostasis in the environment around the neurons and glia. We discuss the normal ranges of metabolic products in the cerebrospinal fluid (CSF), blood and urine and the direction of nutrient supplement from blood to CSF. Furthermore, we summarize the clearance pathway of the metabolic products from CSF to urine. Body fluids, which take nutrients from others, discard metabolites to others and have a narrower normal range of metabolic products, have a higher homeostasis status. We suggest the cerebrospinal fluid has higher homeostatic priority than blood. Unlike CS For blood, which is kept stable by homeostatic mechanisms in which early changes associated with disease were removed, urine is an ideal source of changes that can reflect conditions of the brain, especially chronic conditions.

Keywords: Homeostatic ranking; Cerebrospinal fluid; Interstitial fluid; Cerebral wastes; Biomarkers; Homeostasis; Blood; Urine

Abbreviations: CSF: Cerebrospinal fluid; CNS: Central nervous system; BBB: Blood brain barrier

The Importance of Homeostatic Ranking of CSF, Blood and Urine

Biomarkers can be used to measure changes associated with physiological or path physiological processes. Thus, the most fundamental feature of a biomarker is the ‘change’ between healthy and disease states (Figure 1). We believe that urine is more optimal for early biomarker detection because it accumulates many changes [1]. The cerebrospinal fluid (CSF), which is associated with the central nervous system (CNS), will rapidly discard the changes to remain stable. Blood, which circulates throughout the body to interact with organs, also has a relatively dynamic steady state. In the early stage of disease, it is difficult to detect early biomarkers under the condition of a compensatory steady state. During the dyshomeostasis stage, in which the stacking velocity of metabolite products is greater than the clearance speed, the detectable changes are probably not early biomarkers [2]. By contrast, urine accumulates changes in the blood and may tolerate and even magnify changes without causing harm to the body [3-5]. When the CSF and blood are in homeostasis in the early stage, urine, which collects bodily waste, reflects the early changes that are occurring inside of the body [6-8].

The evaluation principle of homeostatic priority

The body fluid which has a narrower normal range has a higher homeostasis status; the body fluid which takes nutrients from others has higher homeostasis ranking; the body fluid which discards metabolite products to others has higher homeostasis ranking. Thus, we suggest that the brain has a higher homeostatic priority than blood (Figure 2).
The CNS is the most critical and sensitive system in the human body. To maintain brain homeostasis, the blood supplies nutrients to the brain, and the blood brain barrier (BBB) restricts potentially harmful molecules that are present in blood [9,10]. The BBB, which is formed by endothelial tight junctions, pericytes, perivascular astrocytes, and basement membrane in the vasculature [11] regulates ion balance in the brain and facilitates the transportation of nutrients to the brain [11]. Proper neuronal function necessitates a highly regulated extracellular homeostasis in which the concentrations of ions and pH must be maintained within very narrow ranges.

Glucose, which provides the energy to support all activities in the body, is modulated according to the body’s metabolism. The normal range of glucose in the CSF is narrower than in the blood [12,13] while serum glucose fluctuates throughout the day. When the blood glucose concentration is low, such as when food intake is limited or in disease, the glucose level in the cerebrospinal fluid does not rapidly change. Furthermore, the reabsorption function of the kidneys ensures that sugars are not readily excreted through the urine [14]. When blood sugar increase, [for instance, during intravenous glucose injection], the glucose concentration changes fast, while the CSF glucose changes more slowly [15]. Glucose is usually regarded as the primary energy source for body tissues. Lactate, which is provided by glial cells to neurons [16], may be another energy source for neurons in the brain [17]. Lactate is important for the brain metabolism in the early stages of development in prenatal and early postnatal subjects. In these stages, lactate is abundant in the CSF, and its levels fluctuate more in the CSF than in blood [17,18]. The CSF has a higher priority based on its metabolic requirements, and despite wide fluctuations between meals or the occasional consumption of meals, blood glucose levels tend to remain within a narrow range. However, the glucose levels in urine are dynamic to maintain the homeostasis of the whole body.

Acid-base balance is a premise for internal homeostasis, especially for the brain, in which neurons and glia are exquisitely sensitive to changes. The normal acid-base range in the CSF is narrower than in blood [19,20]. With chronic acid-base disturbances, the pH fluctuation in the CSF is also narrower than in blood [20]. The CSF pH is stable. In past studies, a transient increase in pCO₂ in the artery did not alter CSF pCO₂ [21,22] after an intravenous infusion of hydrochloric acid over approximately 24h followed with isotonic sodium bicarbonate, the pH in the CSF was not significantly different [23]. Urine that contains various changes from kidney which transfer the acid into urine and reabsorb HCO₃⁻ consumed in blood has a broad range of pH [24]. The range of 4.8–7.4 has suggest that there are a lot of changes in urine and the CNS is in a stable environment all the time, even in acid-base disturbance [25,26].

In ion tests of the CSF and blood (Table1), most ions ranges of the CSF are narrower than of blood [12,27,28] except for chloride, which is narrower in blood than the CSF [29]. The osmolality and the sodium ions ranges of the CSF and blood are approximately similar [29] while the sodium and potassium levels in urine tend to fluctuate widely over the course of a day [29]. With renal injury, electrolyte disturbances can occur. Because of kidney dysfunction, both metabolic wastes and ions, such as serum urea nitrogen, creatinine and potassium, will accumulate and cause harm to the body. The cumulative levels of harmful electrolytes in cerebrospinal fluid are lower than in blood.

Supply of nutrition from blood to brain

It is well known that the blood, which provides nutrients to the whole body, also provides adequate nutrients to the brain to ensure optimal function of the CNS [30]. Adequate supply of glycogen has important implications for the functioning of the brain, especially the cooperation between astrocytes and neurons [31]. As for glucose consumption, the central nervous system has absolute priority. Many nutritional solutes in blood can enter the central nervous system. Small molecules, such as amino acids, hormones, water, and fat-soluble molecules, (e.g., oxygen), can easily cross the BBB. Specific glucose transporters (GLUTs) can transport special nutrients, such as glucose, across the BBB [32]. In addition to the primary energy source, lactate, can also be transported into the brain [31]. Some substances, such as organic anions that can’t easily cross the BBB, are mainly carried by transporters. For the transportation of large amino acids and polypeptides, OATPs and LAT1 play important roles [33] and PEPT2 in choroid plexus tissue quickly transports di peptides into the brain [34]. Members of the OAT family transport a wide range of drugs, such as aspirin, ibuprofen, various antibiotics, and pesticides [33].

It is well-accepted that blood provides nutrients to the brain; thus we focus minimal attention to cerebral nutrition directions in this review. Because the BBB restricts the removal of cerebral products, we focus on the discharge direction of metabolic products.
Table 1: The normal range of CSF and blood.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Unit</th>
<th>Cerebrospinal Fluid</th>
<th>Fluctuating Value</th>
<th>Ref.</th>
<th>Blood</th>
<th>Fluctuating value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>mmol/L</td>
<td>2.8~4.4</td>
<td>1.6</td>
<td>[12]</td>
<td>3.5~5.5</td>
<td>2</td>
<td>Fasting [13]</td>
</tr>
<tr>
<td>Lactate level</td>
<td>mmol/L</td>
<td>1.1~2.4</td>
<td>1.3</td>
<td>[12]</td>
<td>0.5~1.6</td>
<td>1.1</td>
<td>Arterial [18]</td>
</tr>
<tr>
<td>pH</td>
<td>no unit</td>
<td>7.28~7.32</td>
<td>0.04</td>
<td>[12]</td>
<td>7.35~7.45</td>
<td>0.1</td>
<td>[15]</td>
</tr>
<tr>
<td>Metabolic acid-base imbalance</td>
<td>no unit</td>
<td>7.315~7.337</td>
<td>0.022</td>
<td>[19]</td>
<td>7.350~7.523</td>
<td>0.173</td>
<td>[19]</td>
</tr>
<tr>
<td>Respiratory acid-base imbalance</td>
<td>no unit</td>
<td>7.314~7.336</td>
<td>0.022</td>
<td>[19]</td>
<td>7.382~7.485</td>
<td>0.103</td>
<td>[19]</td>
</tr>
<tr>
<td>PC02</td>
<td>mmHg</td>
<td>44~50</td>
<td>6</td>
<td>[19]</td>
<td>35~45</td>
<td>10</td>
<td>Arterial [28]</td>
</tr>
<tr>
<td>PO2</td>
<td>mmHg</td>
<td>40~44</td>
<td>4</td>
<td>[12]</td>
<td>75~100</td>
<td>25</td>
<td>Arterial [28]</td>
</tr>
<tr>
<td>Osmolality</td>
<td>mmol/L</td>
<td>280~300</td>
<td>20</td>
<td>[12]</td>
<td>280~296</td>
<td>16</td>
<td>[114]</td>
</tr>
<tr>
<td>Potassium (K)</td>
<td>mmol/L</td>
<td>2.6~3.0</td>
<td>0.4</td>
<td>[12]</td>
<td>3.5~5.0</td>
<td>1.5</td>
<td>[115]</td>
</tr>
<tr>
<td>Sodium (Na)</td>
<td>mmol/L</td>
<td>135~150</td>
<td>15</td>
<td>[12]</td>
<td>135~147</td>
<td>12</td>
<td>[115]</td>
</tr>
<tr>
<td>Chloride (Cl)</td>
<td>mmol/L</td>
<td>1.15~1.30</td>
<td>15</td>
<td>[12]</td>
<td>100~110</td>
<td>10</td>
<td>[116]</td>
</tr>
<tr>
<td>Calcium (Ca)</td>
<td>mmol/L</td>
<td>1.0~1.4</td>
<td>0.4</td>
<td>[12]</td>
<td>2.1~2.8</td>
<td>0.7</td>
<td>[116]</td>
</tr>
<tr>
<td>Magnesium (Mg)</td>
<td>mmol/L</td>
<td>1.2~1.5</td>
<td>0.3</td>
<td>[12]</td>
<td>1.5~2.0</td>
<td>0.5</td>
<td>[114]</td>
</tr>
<tr>
<td>Urea</td>
<td>mmol/L</td>
<td>3.0~6.5</td>
<td>3.5</td>
<td>[12]</td>
<td>3.0~7.0</td>
<td>4</td>
<td>[117]</td>
</tr>
</tbody>
</table>

Removal of cerebral wastes from brain to blood

Extracellular homeostasis requires the ability to rapidly clear metabolic products from the brain [34]. In addition to transporting biologically active substances to the CNS [35], cerebral fluids, which are indispensable for brain homeostasis, remove metabolites from the parenchyma through several pathways (Figure 3).

Wastes from the parenchyma to CSF

Neurons are surrounded by interstitial fluid (ISF), which carries metabolite wastes from cells to maintain constant homeostasis of the CNS [36]. Small compounds can readily pass into the CSF; however, it is impossible for larger molecules located deep within the brain parenchyma to easily move into the CSF [36]. Some studies have suggested that perivascular spaces may remove larger wastes from the parenchyma into the CSF [37]. Physical connections between the CSF and perivascular spaces around the brain vasculature [38,39] and between ISF and perivascular spaces suggest that extracellular markers that are injected into the parenchyma will be cleared from the brain [40,41]. Thus, the changes happened in brain will be removed from brain parenchyma in a certain form.

It was thought that substances slowly diffuse into the CSF [43], However, albumin requires more than 100 hours to diffuse through 1 cm of brain tissue [42] which conflicts with the two-photon imagines that show that the CSF is exchanged rapidly with the ISF in the brain [43]. In one study solutes; varying in size from 4,000 to 69,000 Dalton; were injected directly into the brain and left the brain at similar rates, suggesting that convective loss was a major pathway of solute removal from the brain rather than diffusion [44,45].

Metabolic products, including small changes and larger wastes, are removed from the parenchyma and move into the CSF [46-48]. The perivascular spaces existing between the walls of veins and astrocyte end feet are known as the lymphatic system [49,50]. Interestingly mice lacking the water channel aquaporin-4 in astrocytes [51,52] exhibit a reduction in interstitial solute clearance [53] suggesting that the efflux is supported by the water...
channel aquaporin-4 [54]. Partial ligation of the brachiocephalic artery prevents rapid paravascular reflux of tracers, suggesting that artery pulsation improves the clearance of potentially harmful products, including amyloid β [55,56]. During the movement of cerebral fluids, other physiological factors potentially influence the clearance of cerebral products, such as sleep [57,58] body posture [59].

The importance of understanding the mechanisms of brain waste efflux from the parenchyma is highlighted in neurodegenerative diseases, characterized by the pathological accumulation of misfolded proteins in the interstitial space, including β-amyloid (Aβ) [60,61] and tau [62] Aβ is thought to be a pathogenic peptide in Alzheimer’s disease. Endogenous substances, such as Aβ and tau, are cleared in the perivascular spaces to maintain homeostasis of the brain [53,63].

**Wastes from the CSF to blood**

The BBB provides constant protection for the CNS, while restricting the removal of metabolic products that will harm neural tissue [64]. The CSF can transport products from the brain into the bloodstream via capillaries or the lymphatic system, which play a major role in maintaining the electrolytic and acid-base balance of the CNS (Table 2).

The CSF, formed mainly in the ventricles of the brain, flows through the cerebral ventricles into the subarachnoid spaces; then the CSF moves into the bloodstream by arachnoids villi and the cerebral changes are moved to the blood [65]. This classical route is efficient for the excretion of water and small compounds into the bloodstream, while larger compounds are unlikely to be transferred to blood through this route [66].

It is generally accepted that the CNS, which required rapid clearance of ISF and solutes, does not contain lymphatic vessels. However, vessels expressing lymphatic endothelial cell markers in the dura suggest that there may be lymphatic structure here [67,69]. Larger molecules, such as basic bumin can be measured continuously in cerebral perivascular spaces, dura lymphatic system and lymph nodes when injected into the brain [70,75] suggesting that lymphatic structures allow macromolecules to flow from the brain to the blood [76,79]. Aplasia of dura lymphatic vessels will reduce macromolecules clearance [80]. These findings suggest that non-cardiovascular structures play an integral role in transporting wastes from the brain, including larger molecules [81]. The functional lymphatic system also provides a way for the outflow of immune cells, which mainly accounts for the slower immune reactions in the brain [82]. The transportation of APCs by the dura mater lymphatic system may play a central role in experimental autoimmune encephalomyelitis (EAE), in which T cells specific to CNS antigens traffic to the brain and result in paralysis [83]. To our regret, the process of immune cell activations in deep cervical lymph nodes after injury remains poorly understood [84].

In addition to the above pathways of CSF drainage, olfactory bulbs are another efflux pathway of the CSF [85-89]. Tracers are located not only in the subarachnoid compartment, but also within the olfactory sub mucosa. Furthermore, the tracers are situated within an extensive network of lymphatic vessels in the nasal sub mucosa, which suggests that the way through the cribriform plate may take the CSF from the brain to the lymphatic system, which is associated with the sub mucosa of the olfactory and respiratory epithelium [90,92]. The cribriform plate plays a major role in the efflux of immune cells, such as CD47, dendritic cells (DCs) and monocytes, from the brain to the peripheral lymphatic system [93,94].

The CSF absorption takes places not only through arachnoid granulations in the subarachnoid space or lymphatic system, but also through capillaries inside the brain ventricles in other words, the CSF disappears and is reabsorbed everywhere in the cerebral system [95,96]. There is no need for directed CSF circulation from the choroid plexus (CP) to the arachnoid villi; instead, CSF production and absorption occurs at the level of the capillaries and is not limited to the location of the capillaries [97,98].

The high sensitivity of neural cells to toxic substances demands that the brain remove products quickly and efficiently, which is the premise for the homeostasis of the brain [53]. Small molecules, hydrophobic compounds, and larger compounds can be excluded from the brain [36,99] though the cerebral changes may be modified, degraded or have other transformations, it is reasonable for us to suggest that cerebral changes can move from the brain to the blood.

**Clearance of wastes from blood to urine**

In most issues and organs, metabolic products in the interstitial fluid are excreted into the local lymphatic system and eventually into the blood, preventing the accumulation of potentially toxic compounds that will harm the body [66]. The blood transports metabolites, including cerebral metabolic products and peripheral metabolic wastes, to certain organs that will excrete them from the body, such as the lungs [100] skins [101] and kidneys [102]. The kidneys, which act as filters, are main excretory organs and play an important role in removing metabolic products from the blood into the urine [103]. The kidneys maintain electrolyte and acid-base balance when the body is not performing properly. The kidney can excrete small wastes, such as urate, urea, and toxins [104] and also some proteins into urine [105] while restricting substances that are necessary for maintaining normal homeostasis. Thus, the majority of products are discharged into the urine. Cerebral changes, including wastes or other metabolic information, will be excluded from the brain to the blood in a certain form. Some changes will be excluded from the blood to urine, which collects early metabolic information associated with the whole body [6,8].

**Urine is an ideal place to search for early biomarkers of chronic brain diseases**

The CSF has a greater homeostatic priority than blood, and changes in the CSF may happen later than in blood. Changes in urine occur more rapidly than in blood; thus, urine may be a more optimal environment for detection of earlier biomarkers of brain disease [106,107] which may have important clinical significance. Cerebral wastes are excreted from the brain to blood and eventually to urine, which suggests that we should be able to detect early biomarkers of brain diseases in urine. Previous reviews have summarized several brain diseases, especially chronic diseases such as neuropsychiatric disorders [108] neurodegenerative diseases [109] and neuroendocrine neoplasm [93,110] that are difficult for early diagnosis. These diseases are mainly diagnosed based on a subjective symptom assessment. Thus far, no objective and effective measurement procedures are available [111].
Table 2: Crucial experiments proving larger molecules can be excluded from brain.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Subject</th>
<th>Injection site</th>
<th>Substance</th>
<th>Molecular Weight</th>
<th>Region</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada K et al. [62]</td>
<td>mouse</td>
<td>left hippocampus</td>
<td>Aβ solution</td>
<td>4kDa</td>
<td>lymphatic pathways</td>
<td>[62]</td>
</tr>
<tr>
<td>Carare RO et al. [76]</td>
<td>mouse</td>
<td>striatum</td>
<td>ovalbumin (OVA) / fluorescent dextran</td>
<td>49/3-10kDa</td>
<td>lymphatic pathways</td>
<td>[76]</td>
</tr>
<tr>
<td>Kress BT et al. [66]</td>
<td>mouse</td>
<td>cisterna magna</td>
<td>Texas Red conjugated dextran</td>
<td>3kDa</td>
<td>lymphatic pathways</td>
<td>[61]</td>
</tr>
<tr>
<td>Schwalbe et al. [73]</td>
<td>dog, rabbit</td>
<td>CSF</td>
<td>Berlin blue</td>
<td>859</td>
<td>lymph nodes</td>
<td>[73]</td>
</tr>
<tr>
<td>Goldmann [85]</td>
<td>dog, rabbit</td>
<td>CSF</td>
<td>Trypan blue</td>
<td>960</td>
<td>lymph nodes olfactory nerves</td>
<td>[85]</td>
</tr>
<tr>
<td>Mortensen</td>
<td>dog</td>
<td>cisterna magna</td>
<td>Thorotrast</td>
<td>1626</td>
<td>lymph nodes</td>
<td>[74]</td>
</tr>
<tr>
<td>Yoffey et al. [86]</td>
<td>rabbit, monkey</td>
<td>lateral wall and septum of the nose</td>
<td>Higgin' India ink</td>
<td>--</td>
<td>lymph nodes olfactory nerves</td>
<td>[86]</td>
</tr>
<tr>
<td>Cser et al. [72]</td>
<td>rat</td>
<td>caudate nucleus</td>
<td>polyethylene glycols/dextran</td>
<td>70/4kDa</td>
<td>lymph nodes</td>
<td>[72]</td>
</tr>
<tr>
<td>Cser et al. [44]</td>
<td>rat</td>
<td>caudate nucleus</td>
<td>serum albumin/</td>
<td>69/4kDa</td>
<td>lymph nodes</td>
<td>[78]</td>
</tr>
<tr>
<td>McComb et al. [70]</td>
<td>rabbit</td>
<td>ventricles/cisterna magna</td>
<td>RISA with dextran</td>
<td>&gt;45kDa</td>
<td>olfactory nerve</td>
<td>[87]</td>
</tr>
<tr>
<td>Cser et al. [79]</td>
<td>rabbit</td>
<td>caudate nucleus</td>
<td>radiolabelled albumin</td>
<td>&gt;45kDa</td>
<td>deep cervical lymph</td>
<td>[79]</td>
</tr>
<tr>
<td>Brinker et al. [88]</td>
<td>cat dog</td>
<td>CSF</td>
<td>dextran</td>
<td>70kDa</td>
<td>olfactory nerves Nasallymphatics</td>
<td>[88]</td>
</tr>
<tr>
<td>Boulton et al. [75]</td>
<td>rat</td>
<td>lateral ventricle</td>
<td>human serum albumin</td>
<td>&gt;45kDa</td>
<td>lymph nodes</td>
<td>[75]</td>
</tr>
<tr>
<td>Zakharov et al. [89]</td>
<td>neonatal</td>
<td>cranial sub-arachnoid</td>
<td>Yellow Microfil</td>
<td>--</td>
<td>olfactory Nerves</td>
<td>[89]</td>
</tr>
<tr>
<td>Liu H et al. [90]</td>
<td>rabbit</td>
<td>cisterna magna</td>
<td>Microfil</td>
<td>--</td>
<td>around the olfactory nerves and within lymphatic vessels</td>
<td>[90]</td>
</tr>
<tr>
<td>Kaminski et al. [37]</td>
<td>mouse</td>
<td>left entorhinal cortex</td>
<td>Monocytes</td>
<td>--</td>
<td>lymph nodes</td>
<td>[37]</td>
</tr>
<tr>
<td>Laman JD et al. [83]</td>
<td>animals / humans</td>
<td>subarachnoid space</td>
<td>antigen presenting cells</td>
<td>--</td>
<td>lymph nodes</td>
<td>[83]</td>
</tr>
<tr>
<td>Mathieu E et al. [81]</td>
<td>mouse</td>
<td>cisterna magna</td>
<td>Quantum dot 655</td>
<td>--</td>
<td>lymph nodes</td>
<td>[81]</td>
</tr>
<tr>
<td>Stern JN et al. [84]</td>
<td>鼠</td>
<td>cisterna magna</td>
<td>the meninges, parenchyma</td>
<td>--</td>
<td>lymph nodes</td>
<td>[84]</td>
</tr>
<tr>
<td>Mohammad et al. [94]</td>
<td>mouse</td>
<td>lateral ventricle</td>
<td>CFSE-labeled immune cells</td>
<td>--</td>
<td>lymph nodes olfactory nerves</td>
<td>[94]</td>
</tr>
<tr>
<td>Plog BA et al. [77]</td>
<td>mouse</td>
<td>cerebral cortex</td>
<td>AlexaFluor-555-ovalbumin / 3H-dextran / 14C-inulin</td>
<td>45/40/6kDa</td>
<td>lymph nodes</td>
<td>[77]</td>
</tr>
<tr>
<td>Louveau A et al. [66]</td>
<td>mouse</td>
<td>cisterna magna</td>
<td>Evans blue</td>
<td>--</td>
<td>lymph nodes</td>
<td>[67]</td>
</tr>
<tr>
<td>Daniel R Lu</td>
<td>multiple sclerosis</td>
<td>central nervous system</td>
<td>B cells</td>
<td>--</td>
<td>peripheral lymph nodes</td>
<td>[118]</td>
</tr>
<tr>
<td>Aspelund A [68]</td>
<td>mouse</td>
<td>brain parenchyma</td>
<td>ethylene glycol / Alexa Fluor 488-conjugated OVA</td>
<td>20/45kDa</td>
<td>cervical lymph nodes</td>
<td>[68]</td>
</tr>
</tbody>
</table>
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However, we can search for some early biomarkers that are associated with these brain diseases in urine, which can enhance assessments and predict treatment response. Urine analyses of control and disease samples in this review provide valuable clues for the diagnosis of these diseases [112] clinically applicable urine biomarkers of brain diseases may exist and should be explored in future diagnoses for complex brain diseases.

Concluding Remarks

The CSF has a homeostatic priority than blood, the urine which doesn’t have steady state is an ideal place to search for early biomarkers for the complex chronic brain diseases, especially the early changes that cannot be captured in CSF or blood which is in homeostasis.

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