Seizure: European Journal of Epilepsy 128 (2025) 24–28

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Review

Fluid biomarkers unveil signatures of pathological aging

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ARTICLE INFO

Keywords:
Pathological and physiological aging
Fluid biomarkers
Blood biomarkers
Inflammaging
Neural autoantibodies
Late-onset epilepsy

ABSTRACT

Aging is a multifaceted and highly varied process in the brain. Identifying aging biomarkers is one means of distinguishing pathological from physiological aging. The aim of this narrative review is to focus on two new developments in the field of fluid biomarkers and draw attention to this excellent tool for the early detection of potential brain pathologies that delay, alter, or enable physiological aging to become pathological. Pathological aging can lower the threshold for the development of specific diseases such as late-onset epilepsy. Fluid biomarkers can reveal pathological levels at an early stage and thus indicate disease processes in the brain that begin before symptoms develop; they thus differ from physiological aging.

1. Aging biomarkers

Aging is caused by various processes in the brain and takes place in different regions of the brain. Recent concepts include inflammaging [1, 2], which focus on inflammatory pathways activated to varying degrees as we age. Neurodegeneration also occurs in physiological aging, but differs considerably from pathological aging in its extent. Healthy aging is sometimes difficult to differentiate from pathological aging in conditions revealing symptoms of cognitive decline. One reason for this may be that symptoms can be subjective and sometimes fail to appear during neuropsychological testing procedures, for example. Thorough diagnosis is therefore necessary to determine whether cognitive decline's initial, subjective symptoms can already be attributed to a brain pathology. Although the number of imaging techniques to visualize individual pathologies in aging individuals keeps growing, they are often specific, such as amyloid positron emission tomography for pathological amyloid beta deposits in the brain in Alzheimer's disease (AD) or single photon emission computed tomography involving ioflupane I123 injections to visualize dopamine transporter density for detecting alpha-synucleinopathies, which only yields indications of certain pathological processes. In contrast, the examination of blood or cerebrospinal fluid as fluid biomarkers allows the simultaneous investigation of different brain pathologies. Fluid biomarkers can therefore be regarded as an indispensable tool for the simultaneous visualization of different biological processes in the brain. Blood tests are less specifically suited for visualizing brain processes, but blood biomarkers have been gaining new importance and appreciation in conjunction with certain diseases of old age such as AD [3–9]. The aim of this review is to briefly describe the most recent developments in fluid and particular blood biomarkers in conjunction with two exemplary pathologies of the brain occurring in old age, such as AD pathology, but also inflammatory pathologies in autoantibody-associated diseases in old age. We provide an insight into their current scientific significance and describe in this narrative review how such pathologies as signatures of neurodegeneration and autoimmunity can be detected in aging processes. This focused review is narrative only, and not a systemic review. In brief, we conducted a PubMed search applying the following terms: fluid biomarkers, blood, CSF, neurodegeneration, inflammaging, autoantibodies, pathological aging, AD, autoimmune encephalitis, late onset epilepsy in combination or alone. Articles were chosen for this review at the authors subjective discretion.

2. Fluid biomarkers as signatures of neurodegeneration

AD is a prime example of pathological aging. Although its diagnostic criteria now biologically rely on biomarkers, there is also a clinical entity [10]. The prominent clinical phenotype of AD is hippocampus dependent memory impairment, which certainly overlaps with mnestic syndromes as seizure disorders such as temporal lobe epilepsy or limbic encephalitis. There are also other rare phenotypes of AD such as posterior cortical atrophy as well as the logopenic variant of primary progressive aphasia [10]. There have been suggestions to consider AD as a

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https://doi.org/10.1016/j.seizure.2024.05.019
Received 26 March 2024; Received in revised form 29 May 2024; Accepted 30 May 2024
Available online 31 May 2024

biological-clinical entity [10]. CSF biomarkers of amyloid beta pathology and tau pathology can serve to differentiate AD from other neurodegenerative diseases [11]. Novel biomarkers have also emerged in the pipeline for diagnosing AD, such as phosphorylated tau protein 217 (p-tau217) and phosphorylated tau protein 205 (p-tau205) [12] for AD's early (ptau217) and later stages (ptau205). A recent interesting study impressively substantiated well-known facts about AD's pathogenesis [13]. In their study the authors examined 648 patients who developed AD, and compared them to 648 matched controls who were cognitively unimpaired over 20 years by investigating fluid biomarkers [amyloid-beta (Aβ) 42, the ratio of Aβ42 to amyloid-beta 40 (Aβ40), phosphorylated tau 181 (p-tau181), total tau, neurofilament light chain (NfL)]. They found that pathological levels of Aβ42 were detectable already 18 years, the Aβ42/40 ratio 14 years, p-tau181 11 years, total tau protein (t-tau) 10 years and NfL 9 years before their AD diagnosis [13]. In fact, the initial pathological biomarker levels did not change over the disease course [13]. This study underlies the significance of such fluid biomarkers for capturing the neurodegenerative process at between 18 and 9 years prior to diagnosis. The discovery of blood biomarkers for AD could enable decisive advances in our understanding of ageing within just a few years. Such biomarker anomalies before the onset of sporadic AD symptoms were confirmed in another study: the Aβ ratio 42/40 in CSF and plasma and p-tau217 in CSF changed 15–19 years before symptom onset [14]. Pathological changes in plasma levels of 1) p-tau217, glial fibrillary acidic protein (GFAP) and Nfl in plasma, as well as 2) a synaptosomal-associated protein of 25 kDa (SNAP25), neurogranin and myeloid cell expressed receptor 2 (TREM2) in the CSF were detected 12–14 years before the onset of cognitive-impairment symptoms [14]. Within a 10-year period before symptom diagnosis, p-tau205 and YKL-40 biomarkers in the CSF were already revealing pathological abnormalities [14]. What this evidence indicates is that AD's neurodegenerative trajectory is already existent up to 20 years prior to the onset of symptoms. The diagnosis of ageing is gaining whole new meaning, especially in the case of preliminary stages of dementia including mild cognitive impairment, but it is even generating novel ethical challenges. The measurement of the epitopes of beta-amyloid peptides and phosphorylated tau protein in blood probes will soon be part of routine neurochemical dementia diagnostics due to its high diagnostic accuracy, minimal invasiveness and relative insensitivity. There is evidence that p-tau217 is already elevated in preclinical and prodromal AD [15,16] - before phospho-tau181 becomes elevated in blood and the CSF - and that it can predict cognitive decline [17]. However, we still need more standardization of blood-based multi-parameters in dementia diagnostics. Here, automated and already validated assays for biofluid marker based dementia diagnostics in the CSF are the most promising. Furthermore, in real-life diagnostic scenarios, a single blood biomarker such as p-tau217 or Aβ1–42/1–40 cannot meet these intricate differential diagnostic requirements—in particular at preclinical stages such as subjective cognitive decline due to AD. Therefore there is an urgent requirement for research to identify the most valid and reliable multi-parameter signature utilizing different fluid biomarkers—preferentially using automated platforms for staging pathological aging. Overall, it is now clear that AD's pathological processes start early and therefore differ from physiological aging and characterize pathological aging. However, it is also important to note that neuronal cell damage in the form of elevated tau protein but also amyloidopathy can also occur in acquired, non-lesional late-onset epilepsy [18]. A review [18] reported that overall, there is strong evidence that late-onset epilepsy of unknown origin (LOEU) could be an indicator of AD. Epidemiological studies have also shown a significant association between LOEU and AD [18]. This may in turn mean that people with LOEU carry an increased risk of developing manifest AD shortly after the onset of epilepsy. The investigation of fluid biomarkers is of particular interest in the presence of AD's epileptic variant. A relevant correlation was detected in such patients between the CSF Aβ-42 and Aβ-40 blood levels with interictal epileptiform discharges and delta slowing on EEGs [19]. Other clinical entities should be differentiated as well, such as transient epileptic amnesia, which is also a potential feature of epileptic variant prodromal AD as late onset epilepsy [20]. For this form of pathological aging, it is important to assess neurodegeneration markers, especially amyloid beta peptides (Table 1, Fig. 1). However, the determination of biomarkers is not only potentially relevant in the context of a possible preclinical AD: recently published study results indicate that amyloid beta and tau protein markers in histological preparations from epilepsy surgery were even elevated in patients with medial temporal lobe epilepsy attributable to limbic encephalitis [21]. It is therefore clear that neurodegeneration markers can also develop in connection with pathological aging characterized by LOEU or as a result of chronic autoimmune inflammation.

3. Fluid biomarkers as a tool for establishing signatures of autoimmunity

Inflammatory and immune processes in the brain are other very important factors that change with age. Immune ageing is also regarded as an aging process that includes pathological alterations within the immune system. Various processes are found in the immune system during the process of aging like degeneration of the thymus, spleen and lymph nodes, as well as a reduction in the frequency of naïve B cells and the capacity to produce antibodies [28] or alterations in macrophages [29]. There is also evidence of an altered B-cell subpopulation in old age, which has an influence on Toll-like receptor 7 and Toll-like receptor 9 signaling in conjunction with Th1 cytokines [30]. It is assumed that this B-cell subpopulation contributes to the reduced B-cell production in old age and a weaker immune response [30]. Such changes can trigger an altered immune defense and thus also affect autoimmunity processes in old age. However, age-associated B-cells are very effective at producing autoantibodies. However, a certain predisposition is required for immune aging involving alterations in T-cell aging leading to a chronic inflammatory state also referred to as inflammaging, leading to autoimmune inflammation [31]. T-cell-dependent aging is already considered a risk factor for the development of autoimmunity [32]. There is additional evidence that epigenetic mechanisms also contribute to immunosenescence and the development of autoimmunity in old age (for a review see Ray and Yung, [33]). In contrast to this impaired ability of the immune system to eliminate antigens, proinflammatory responses occur simultaneously, such as the upregulation of specific proinflammatory cytokines (i.e., interleukin-6, C-reactive protein, tumor

Table 1
Neuronal cell damage markers and neural autoantibodies in pathological aging with late onset epilepsy.

Parameter	Biofluid	Results	Reference
Neuronal cell damage marker			
Aβ42/40	Plasma ↓	Decrease from midlife to late life was associated with development of epilepsy	[22]
Aβ42	CSF ↓ (37.5 %)	17.5 % of patients with late onset epilepsy converted to Alzheimer's dementia vs. none among healthy controls	[23]
Ptau181	CSF ↑	Worse cognitive performance in patients with late onset epilepsy and elevated ptau181	[24]
T-tau	CSF ↑	Alzheimer's dementia with seizures and behavioral symptoms	[25]
Neural autoantibodies			
KCNA2 abs	CSF and/or serum	Cognitive impairment and seizures	[26]
LGI1 abs	CSF and/or serum	Cognitive impairment 100 % and seizures 97 %	[27]

Abbreviations: Aβ42, amyloid beta 42; Aβ42/40, amyloid beta 42/40; CSF, cerebrospinal fluid; KCNA2, potassium voltage-gated channel subfamily A member 2; LGI1, leucin rich glioma inactivated protein 1; Ptau181, phosphorylated tau protein 181; T-tau, total tau protein.

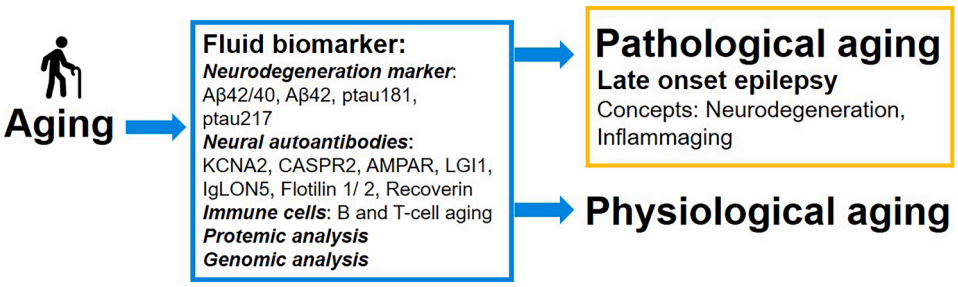

Fig. 1. Fluid biomarkers track pathological ageing.
Fluid biomarkers are crucial to distinguishing pathological from physiological aging. Pathological aging might lead to late-onset epilepsy.

necrosis factor alpha, interleukin-1 and interleukin-8 [28]. However, the body's capability to produce autoantibodies against its own antigens is not affected. There are many new autoantibodies to intracellular and membrane surface antigens not yet reported to coincide with cognitive impairment [34]. Neural autoantibodies associated with cognitive disorders in old age have been identified, such as flotillin 1/ 2, recoverin or potassium voltage-gated channel subfamily A member 2 (KCNA2), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR), IgLON5, Leucin Rich Glioma Inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) [26,35–38]. Nevertheless, their significance is poorly understood, and large cohort studies are still needed. It is important to better understand normal aging's phenomenology in order to recognize subtle changes and investigate these via blood biomarkers and neural autoantibodies. KCNA2 autoantibodies were identified recently and found to be significantly associated with the cognitive impairment phenotype of pathologic aging. There is evidence that KCNA2 antibodies bind in memory structures such as the hippocampus [26] potentially leading to memory disturbances and/ or seizures. At the same time, brain biopsy evidence showed that immune cell invasion occurs in patients presenting KCNA2 antibodies [26]. In addition, there are other neural autoantibodies such as LGI1, which lead to cognitive impairment in old age, but also to seizures [27]. In addition, a case series has shown that LGI1 patients often continue to have video-polysomnographic abnormalities even after initial immunotherapy in the first year, which would benefit from renewed immunotherapy [39]. This circumstance emphasizes the importance of targeted diagnostics of pathological processes in old age. Ultimately, as the pathogenicity of neural autoantibodies associated with cognitive impairment has not been conclusively clarified, the question arises as to whether such autoantibodies are also increasingly detectable in healthy people - as suggested by a larger study involving over 7000 patients and 49 tested antibodies [40] and thus also potentially co-existing with healthy ageing. However, there is ample evidence indicating that specific autoantibodies play a potentially pathogenic role, such as KCNA2 autoantibodies. The study [26] reported detecting immune cells in the tissue and KCNA2 antibodies bound to the hippocampus and cerebellum of animal slices. There is thus indirect evidence of these antibodies' pathogenicity. Other transfer models from humans to animals have shown that other antibodies against glutamatergic receptors can cause synaptic transmission and thus cognitive disorders [41]. Autoantibodies occurring in old age could therefore be pathogenic. Further research is required to assess the significance of neural autoantibodies specifically in conjunction with pathological aging, but also their occurrence and significance in healthy aging.

4. Novel proteomic and genomic approaches for investigating pathological aging

The analysis of fluid biomarkers is important when assessing neurodegenerative and autoimmune processes in pathological aging. Fluid biomarkers have been analyzed by taking hypothesis-driven approaches. However, it is important to consider unbiased genomic and proteomic interactions to acquire deeper understanding of neurodegenerative processes and immune-inflammatory processes in pathological aging. Plasma and brain tissue, and a genomic atlas of different protein levels were generated in a recent CSF analysis [42]. Important proteins associated with AD were identified applying the randomized mendelization method [42]. Such tissue examinations are therefore very valuable to correlate results from genome-wide association studies (GWAS) studies with functionally relevant genes. They also play an important role in immune-inflammatory autoantibody-associated diseases, i.e., neurological syndromes with glutamic acid decarboxylase 65 (GAD65) positivity via genome-wide testing, and a human leukocyte antigen system analysis in a large cohort of 1214 participants (including 167 patients with neurological syndrome and GAD65 autoantibodies) [43]. The GWAS findings were validated on a CSF proteome and a total of 16 relevant gene loci in a neurological syndrome with GAD65 autoantibodies identified [43]. Another proteomic CSF examination revealed a dysregulated complement system in patients with autoimmune encephalitis compared to controls, as well as additional deficits in immune regulation and the nerve-cell function [44], making it clear that proteomic and genomic analyses of brain tissue, but also of fluid biomaterial, should accompany the biomarker analyses mentioned above.

5. Immune cell signatures in pathological aging

To confirm the relationship between clinical features and relevant immune cell profiles in the CSF and blood, a multidimensional examination of immune cells in blood and CSF could prove to be groundbreaking, as has been shown prototypically for neurological diseases in the study by Gross et al. [45]. In their study, the features were selected by reducing the dimensionality in combination with machine learning methods [45]. The disease parameters in our study mainly involved immune cells. Such an approach may help to generate subtypes of CNS-driven autoimmunity in pathological aging. By using multidimensional flow cytometry in the CSF together with investigations of immune subset cell populations, it is possible to distinguish psychotic diseases from inflammatory diseases [46]. Such an approach could also help when assessing the pathological aging process to distinguish physiological aging from pathological aging involving organically caused diseases.

6. Synopsis and perspective

By examining fluid biomarkers, we may eventually be able to help clarify the brain's transition from healthy to diseased. Neurodegenerative processes as pathological aging of the brain can also cause increased epileptic discharges, as recently demonstrated in Lewy body dementia patients [47]. In a larger study of 1251 patients, it was exhibited that more cortical thinning as well as white matter structural abnormalities were existent on MRI in patients with late-onset epilepsy prior to the onset of seizures [48]. There is thus evidence that pathological aging in form of neurodegenerative processes can favor the occurrence of late-onset epilepsy. The 20–50 % of all epilepsies occurring in old age

without a clear etiology are attributable to LOEU [49], whereas the rest of late onset epilepsy tends to be lesional. A recent study of 54 people with non-lesional LOEU found that the main seizure type was characterized by bilateral tonic-clonic seizure (30 %), by motor seizures revealing focal-onset impaired awareness (22 %) and focal onset impaired awareness nonmotor seizures (22 %) semiology [50]. Aβ42 levels were found to be lower in patients with LOEU and MCI than in LOEU patients without MCI [51]. Overall, it is therefore conceptually useful to assess neurodegenerative markers in patients with LOEU when making a differential diagnosis of pathological aging. Another study confirmed the detection of decreased Aβ42 in CSF as well as increased levels of tau protein and relevant cognitive impairment in patients with LOEU [24]. Such examples underlie the current discussion that amyloid beta peptides are part of a continuum from epilepsy to cognitive decline [52]. Fluid biomarkers represent an excellent opportunity to detect processes of pathological ageing some 10–20 years before the onset of clinical symptoms. However, such early diagnosis also raises new ethical issues that warrant discussion. The potential value of unmasking pathological ageing processes has risen considerably. However, this often fails to clarify whether a pathological process is already present, because this is about more than just detecting a pathology, namely, how we define a disease such as epilepsy and AD and harmonize this with the commitment to treating certain symptoms.

Acknowledgments

JW is supported by an Ilídio Pinho professorship, iBiMED (UIDB/04501/2020) at the University of Aveiro, Portugal. We thank Carole Cürten for editing and proofreading the English language in this manuscript.

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