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PERSPECTIVE

Extracorporeal apheresis therapy for Alzheimer disease—targeting lipids, stress, and inflammation

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Abstract

Current therapeutic approaches to Alzheimer disease (AD) remain disappointing and, hence, there is an urgent need for effective treatments. Here, we provide a perspective review on the emerging role of "metabolic inflammation" and stress as a key factor in the pathogenesis of AD and propose a novel rationale for correction of metabolic inflammation, increase resilience and potentially slow-down or halt the progression of the neurodegenerative process. Based on recent evidence and observations of an early pilot trial, we posit a potential use of extracorporeal apheresis in the prevention and treatment of AD. Apolipoprotein E, lipoprotein(a), oxidized LDL (low density lipoprotein)'s and large LDL particles, as well as other proinflammatory lipids and stress hormones such as cortisol, have been recognized as key factors in amyloid plaque formation and aggravation of AD. Extracorporeal lipoprotein apheresis systems employ well-established, powerful methods to provide an acute, reliable 60–80% reduction in the circulating concentration of these lipid classes and reduce acute cortisol levels. Following a double-membrane extracorporeal apheresis in patients with AD, there was a significant reduction of proinflammatory lipids, circulating cytokines, immune complexes, proinflammatory metals and toxic chaperones in patients with AD. On the basis of the above, we suggest designing clinical trials to assess the promising potential of such "cerebropheresis" treatment in patients with AD and, possibly, other neurodegenerative diseases.

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Introduction

More than a quarter of a century of intense research efforts into Alzheimer disease, and after investing a huge amount of resources, we have not succeeded in providing patients with an effective treatment for this devastating disease. Regrettably, there are still no therapies that can either reliably delay the onset or ameliorate, slow down or halt the clinical progression of AD.

Although there has been significant progress in understanding the pathophysiologic mechanisms of AD, the assumption that a mere pharmacological blockade of secretases or a simple immune-assisted clearance of amyloid depositions would solve the problem remains wishful thinking. Recently, our understanding of how to tackle this problem includes targeting metabolic and inflammatory pathways, outside the proteolytic processing of amyloid precursor protein [1]. This is supported by the fact that metabolic inflammation has been associated with an increased incidence of mild cognitive impairment and progression to dementia [2]. Conversely, it has been proposed that keeping the inflammasome at bay promotes healthy cerebral aging [3].

Alzheimer disease and metabolic disorders

Early-stage Alzheimer disease is associated with simultaneous systemic and central nervous system dysregulation of insulin-linked metabolic pathways including insulin resistance and dyslipidemia [4]. As central insulin resistance is involved in the pathophysiology of AD, it is of interest that visfatin an insulin-mimetic, antiapoptotic and neuroprotective peptide, was significantly lower in AD patients than controls [5]. We have previously shown beneficial effects of novel antagonists of growth hormone-releasing hormone (GH-RH) in different models of Alzheimer disease [6, 7]. Interestingly, GH-RH antagonists decreased secretion of apolipoproteins through a glucagon peptide 1 (GLP1) dependent mechanism [8]. Based on these recent findings, there are plans to evaluate the effect of novel antidiabetic agents, such as the GLP-1 analog liraglutide in Alzheimer disease [9]. Indeed, ample preclinical evidence in animal models of AD suggested that GLP-1 exerts a neuroprotective effect by reducing amyloid oligomers and by correcting the metabolic dysregulation and inducing neuronal regeneration of the brain [10].

More importantly, it seems that metabolic syndrome, including insulin resistance, dyslipoproteinemia, and smoldering inflammation results in increased permeability of the blood–brain–barrier. This leads to a more unrestricted entry of potential toxins, immune cells, and pathogens to the brain, thus, initiating the process of "neuroinflammation" which is one of the hallmarks of neurodegenerative diseases [11]. In this process of metabolic dysregulation and neuroinflammation, lipids seem to play a key role. Relatedly, in a mouse model of disease, inhibiting the inflammasome also improved the clearance of amyloid beta from the brain [12].

Lipids and Alzheimer disease

Lipid metabolism and the pathogenesis of AD are closely linked. Apolipoprotein A-1 deficiency is associated with excessive cholesterol accumulation and increased cortical amyloid exposition whereas apoliprotein A-I decreases Aß aggregation and toxicity [13]. On the other hand, apolipoprotein E (apo E), a circulating glycoprotein of 299 amino acids associated with triglyceride-rich lipoproteins, is a strong and well-established risk factor for the development of AD [14].

In the central nervous system, Apo-E binds amyloid ß and tau-proteins and these aggregates contribute to the complex processes that result in neurodegeneration. Cerebral beta-amyloidosis, a condition in which amyloid-ß (Aß) proteins are deposited in the cerebral cortex, has been associated with higher levels of LDL-cholesterol and lower levels of HDL-cholesterol [15]. Although statins reducing lipid levels have been shown to have immunomodulating properties and anti-inflammatory potential [16, 17], a recent systematic review could not confirm a clear efficacy of statins for the treatment of AD [18].

In particular, large LDL particles were significantly correlated with enhanced cerebral amyloidosis and lower hippocampal volumes [15]. A competition between Apo-E enriched larger LDL particles and brain-derived Aß for hepatic Aß clearance and degradation might be suggested as a disease mechanism, granted that Aß is cleared by the LDL receptor family, such as lipoprotein—like receptor-1 (LRP-1) [15].

Interestingly, data from a recently conducted multicohort study of amyloid-related cerebrospinal fluid biomarkers for AD were analyzed. In this largest ever DSF-based multi-analyte platform by rules-based medicine study, there was a consistent association of lipoprotein(a) and immunoglobulin A (IgA) with Aß 1-42 [19].

Lipoprotein(a), a well-established cardiovascular risk factor that to date can only be treated with lipoprotein apheresis [20], has been significantly associated, in a non-linear correlation, with an increased risk for AD. Interestingly, this robust correlation was independent of apolipoprotein E genotypes [21].

In addition, LDL particles, oxidized LDL, Lp(a), apolipoprotein E, and other lipids known to induce metabolic inflammation, were recently identified as risk factors for AD.

Thus, among men, the highest tertile of most ceramides and sphingomyelins were associated with an increased risk of AD in the Baltimore Longitudinal Study of Aging [22]. Likewise, there was an altered phospholipid and sphingolipid metabolism in patients with familial forms of AD, such as individuals carrying presenilin-1 mutations responsible for autosomal dominant AD. There were striking correlations between these lipids with both cerebrospinal fluid amyloid and tau [23].

Interestingly, lipidomic analysis of senile plaques the hallmark lesion of Alzheimer disease, revealed an impressive enrichment of these plaques with saturated ceramides [24].

Moreover, not only there was an evidence for the potential role of ceramides in AD pathogenesis, but also there was a clear stage-specific association between plasma ceramide levels and neuropsychiatric symptoms in patients with AD [25].

In fact, there is a major, consistent role of many lipids in the pathogenesis, progression and severity of AD. A comprehensive epidemiologic analysis, with a symmetrical flow field fractionation and nano-flow ultrahigh performance liquid chromatography-tandem mass spectrometry, revealed [25] significantly altered, high abundance lipids in AD [26] and untargeted lipidomic analysis revealed lipid signatures that predicted AD progression and brain atrophy [27]. These included various lipid classes, such as triacylglycerols, ceramides, phosphatidylethanolamine, and diacylglycerol, which demonstrated a strong correlation with the degree of brain atrophy [26, 27]. Conversely, the relevance of the lipidome for healthy aging, and the susceptibility to numerous diseases has been reported after screening almost 400 individuals [28].

Unfortunately, to date, there is no specific medication that would be able to target in a comprehensive manner the different lipids.

However, we do have a well-established therapeutic approach, which allows an effective and sustainable reduction of all the lipid classes that were recently identified as key factors in the pathogenesis of AD.

This is the application of therapeutic apheresis systems that have been used in thousands of patients with severe lipid disorders.

High cortisol and AD

Activation of the adrenal stress system leading to elevated peripheral and central cortisol levels in elderly patients have been associated with an increased risk for dementia and AD [29–32]. It has been known for many years that higher cortisol levels are correlated with poorer cognitive performance [29]. Interestingly, cortisol may affect cognitive function even at levels that are still in the normal range via both glucocorticoid and mineralocorticoid receptors. This suggests that relatively minor changes in cortisol levels can trigger meaningful effects on memory performance. More recently it has become clear that high cortisol exerts multiple neurotoxic effects on various brain structures including the hippocampus on memory performance [33]. An activated hypothalamic–pituitary–adrenal (HPA) axis with elevated glucocorticoid levels promotes oxidative stress and amyloid ß peptide toxicity, thus directly contributing to AD pathology [33]. High cortisol concentrations have been shown to trigger and accelerate disease progression and cognitive decline. In addition to increased systemic cortisol levels it has also been reported that AD patients exhibit significantly elevated cortisol concentrations in the cerebral spinal fluid (CSF) [34]. Higher baseline CSF cortisol levels were also associated with faster clinical deterioration and cognitive impairment in patients with AD [34]. In animal models, corticosterone is also a strong negative regulator of adult hippocampal neurogenesis [35]. Adult neurogenesis, on the other hand, is impaired in AD and might result in very early hippocampal symptoms in the course of the disease [36].

Moreover, further underlying mechanisms of high cortisol aggravating AD may encompass the interaction with other stress-related peptides and metabolic inflammation. Thus, we and others have previously shown that inflammatory cytokines can activate the HPA axis [37, 38]. Inflammatory cytokines, lipids, and growth factors that can stimulate the adrenal steroid production are significantly elevated in patients with AD. On the other hand, increased cortisol levels will then promote and perpetuate the disease process both maintaining and exacerbating the metabolic syndrome and the increase of lipids that are implicated in the progression of AD. This will form a vicious cycle of lipids, stress hormones, and inflammation explaining the rapid and continuous decline in many patients with AD. Furthermore, we have recently demonstrated a specific adrenal progenitor cell type in the HPA axis responding to mental, metabolic, and inflammatory stress [39, 40]. These "stress-inducible stem cells" may shape the systemic progeny and responsiveness to chronic and damaging external and internal stimuli in early life. This may help to explain why patients exposed to various forms of chronic stressors in early life also have an increased risk to develop dementia in later life.

Therapeutic apheresis and lipid concentrations

Lipoprotein apheresis is currently the most efficient method for reducing cholesterol, triglyceride, and lipoprotein(a)

plasma levels. It is, therefore, the golden standard treatment of choice for patients with severe forms of familial hypercholesterolemia. Based on our own extensive experience, and that of other centers around the world, lipoprotein apheresis prevents myocardial infarction and stroke in patients with high risk for cardiovascular disease.

For the treatment of patients with elevated levels of lipoprotein(a), which is major independent risk factor for cardiovascular disease, lipoprotein apheresis remains the only efficient therapeutic modality to this date. Recent data from the German Lipoprotein Apheresis Registry confirmed early results of the Pro(a) Life study, which reported a reduction of major coronary (83%) and noncoronary events (63%) [41, 42].

In these patients, therapeutic apheresis does not only reduce atherosclerosis [43], but also decreases different inflammatory and coagulation parameters [41, 44]. Thus, lipoprotein apheresis acutely reduces Lp(a), proatherosclerotic LDL receptor LOX-1 adhesion molecule VCAM-1 [45], and plasma apo E by more than 60% [46] and large LDL-particles [47] more efficiently than any other lipid lowering modality including PCSK9 inhibitors [48].

Furthermore, lipoprotein apheresis decreases circulating oxidative stress parameters, including oxidized LDL, anti-oxidized LDL antibodies, and advanced oxidation protein products [49, 50], all of which have been implicated in neuroinflammation and the pathogenesis of AD.

Finally, we have demonstrated by lipidomic profiling that lipoprotein apheresis reduces by at least 50% other inflammatory lipids identified to induce AD, including ceramides and sphingomyelins [51].

Therefore, plasma apheresis might be suited to provide resistance and resilience and might prevent the development and progression of AD.

If the assumption that has been substantiated by considerable evidence from both experimental models and patients holds true that pro-atherogenic and inflammatory lipids play a key role in neuroinflammation and cerebral amyloidosis in AD, therapeutic apheresis, i.e., cerebropheresis, could become a treatment of choice. It will have to be established of course, to which extent there is also a beneficial lipidome associated with healthy cognitive aging so that, ultimately, a balance would have to be obtained. In the case of patients with manifest AD, the removal of detrimental factors will outweigh putative side-effects, but this could be different in prodromal or later stages.

Apheresis and stress hormone levels

Although there is ample evidence suggesting a role for elevated cortisol levels in progression and aggravation of AD there has been so far little efforts to explore the potential of cortisol lowering agents as a therapeutic approach for AD. This may be largely related to the fear of a life-threatening Addisonian crisis that will occur with an effective blockade of cortisol synthesis or action. There is recent evidence derived from animal models of AD that the glucocorticoid receptor antagonist mifepristone can effectively decrease both Aß and tau load in the brain as well as ameliorate cognitive impairment [52, 53]. Currently a phase II trial of an 11ß-HSD1 inhibitor (UE2343) able to inhibit synthesis of active cortisol is being conducted as a potential treatment for AD [54, 55]. We have analyzed cortisol levels in 39 patients with dyslipidemia before and after extracorporal apheresis. Independent of the apheresis technologies we observed a highly significant 40% reduction of cortisol after apheresis [55]. This however did not involve a clinically relevant adrenal insufficiency. Therefore, extracorporal apheresis may be ideally suited to lower spikes of elevated cortisol levels in patients with AD allowing for metabolic regeneration of the brain.

Is there a potential for extracorporeal apheresis in patients with AD?

Employing an extracorporeal double-membrane filtration (INUSpheresis) system we have shown a consistent and sustainable decrease of all lipid species by 60–80% [44].

This included all the lipid classes that have been implicated in the pathogenesis of AD, as mentioned above.

Furthermore, in a pilot study in eight patients with early AD we observed a significant clinical improvement after three therapeutic apheresis applications based on assessment of the dementia scores. In addition to a reduction in lipids the extracorporeal double-membrane filtration system induced a significant decrease of inflammatory molecules, such as cytokines and chemokines in this group of patients with AD.

Cytokines and chemokines, including the inflammasome, play an important role in neurologic diseases, such as AD [56]. Inflammatory lipids and reactive oxygen species are instrumental in triggering this process. On the other hand, chemokines and their receptors have been shown to affect amyloid-β (Aβ)-tau-related pathologies in mouse models of Alzheimer disease by driving microglial movement and monocyte/macrophage recruitment into the brain and promoting microglia- and monocyte-associated neuroinflammation. These immunocytes, in turn, promote Aß phagocytosis and degradation and tau phosphorylation [57]. Recent results indicate that alterations in serum and brain inflammatory chemokines, such as RANTES are evident as early signs of Alzheimer disease pathology [58].

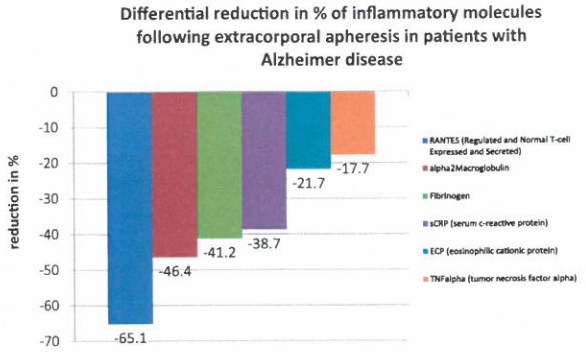

Fig. 1 Differential reduction of inflammatory molecules following extracorporal apheresis under Cerebropheresis® in patients with AD

In our pilot study, extracorporeal double-membrane filtration reduced RANTES (C–C Motif Chemokine ligand 5, CCL5) levels by more than 60% (see Fig. 1). This and other chemokines play key roles in monocyte/macrophage recruitment and function, as well as microglia cell function, promoting both atherosclerosis and neuro-inflammation. Microglia act as brain tissue macrophages and in AD, amyloid deposition provokes activation of microglia and secretion of proinflammatory chemokines and cytokines creating a vicious cycle in the disease process [59].

Chemokin-binding proteins and lipid-lowering drugs reduce both the level of RANTES and the process of neuronal metabolic inflammation [60, 61].

Therefore, RANTES is both a pro-atherogenic chemokine, as well as a crucial part of the inflammatory reaction involved in immune cell recruitment and function and plaque formation in AD patients [62].

These data suggest that a reduction in the secretion of this chemokine and, possibly, other proinflammatory mediators, will provide a beneficial effect in AD patients. These findings are in line with the observed reduction of other proinflammatory molecules involved in the pathogenesis of AD, including fibrinogen, CRP, ECP, and TNF-alpha. (Fig. 1) Finally, there was a 50% reduction of circulating alpha-2 macroglobulin in patients with AD.

Alpha-2 macroglobulin was recently identified as a chaperone protein that can regulate both leukocyte migration and cytokine secretion [63]. Plasma alpha-2 macroglobulin concentrations were significantly associated with cerebrospinal fluid markers of neuronal disease in AD patients [63]. Thus, higher alpha-2 macroglobulin levels predicted a higher risk for progression and aggravation of AD. As a result, alpha-2 macroglobulin was proposed as a promising therapeutic target in AD [4]. Beyond the powerful reduction of both inflammatory lipids and proteins that have been implicated in the pathogenesis of AD the extracorporeal apheresis system removed other factors that may play a role in the disease process.

These included a significant reduction in immune complexes, including immunoglobulin Alpha-2 macroglobulin (Fig. 1), and several intestinal and environmental toxins that were significantly elevated in our AD patients (not shown). Aluminum is the most abundant neurotoxic metal on earth and has been shown to accumulate in AD-susceptible neuronal foci [64]. In our INUSpheresis center preforming apheresis for more than 1000 patients exposed to environmental toxins, we achieved a reduction of blood aluminum levels by 60%. We also demonstrated a decrease in toxic metals including mercury and lead, both of which have been shown to induce amyloid deposits in AD [65].

Moreover, aluminum and organophosphorus pesticides, which have been linked to dementia and neurodegenerative disease [66, 67], were efficiently eliminated with the extracorporeal double filtration system used in our pilot trial.

Conclusion

Recent initiatives to develop an effective therapy for AD involving biophysical and extracorporeal apheresis technologies may be highly promising. This includes novel combination therapies with plasma exchange and haemopheresis using albumin and intravenous immunoglobulins, and focusing on reducing the beta-amyloid peptide (Aß) burden in the brain by sequestering plasma Aß, which in the circulation is primarily bound to albumin [68].

It also involves novel approaches, such as hemodialysis, potentially allowing the rapid removal of amyloid ß protein, using hollow-fiber dialysis. Such extracorporeal systems may act as peripheral Aß sinks preventing accumulation of this peptide in the brain [69].

We note, however, that the latter approaches target the accumulation of Aß which is a rather late event in the disease process. Here we propose the use of an extracorporeal double-membrane filtration system based on the well-established lipoprotein apheresis technology combined with filters for environmental toxins. Such a form of "cerebropheresis" would allow a comprehensive therapeutic approach eliminating most of the major disease-causing molecules that trigger cerebral inflammation and amyloidosis. This will include a combined removal and lowering of lipids, high cortisol levels and inflammatory proteins that have been identified in triggering and aggravating the disease process of AD. Similar to current lipid apheresis protocols such a therapy would most likely involve a long-term treatment providing a constant reduction of inflammatory lipids, proteins, and steroids.

We suggest a randomized trial analyzing the change from baseline to 12 months in z scores for clinical and cognitive measures, including Alzheimer Disease

Assessment Scale-Cognitive Subscale and Executive domain scores of the Neuropsychological Test Battery, Clinical Dementia Rating Sum of Boxes, and Alzheimer Disease Cooperative Study-Activities of Daily Living. We would also assess other secondary outcomes, such as change in magnetic resonance imaging-assessed volume, diffusion tensor imaging parameters, reduction in microglial activation in a subgroup of participants, reduction in tau aggregation and cerebral amyloid levels assessed by PET, and changes in composite scores using support machine vector analysis in the treatment group compared with the placebo group. We believe that "cerebropheresis" has a realistic potential to provide an effective prevention and treatment for patients with AD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing financial interests in relation to the work. KVB, RB work for the INUS clinic and SRB is a consultant.

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