Alzheimer’s disease (AD), described for the first time in 1906 by Alois Alzheimer, is a neurodegenerative disease and the most frequent cause of dementia worldwide. The major neuropathological hallmarks of the disease are loss of neurons and synapses, and senile plaques (extracellular aggregates primarily composed of β-amyloid; Aβ) and neurofibrillary tangles (aggregates of hyperphosphorylated forms of the microtubule-associated tau protein) throughout cortical and limbic regions of the brain.1 Definite diagnosis still requires pathology according to these criteria; however, in recent years substantial progress has been made in the area of early clinical biomarker development. The use of cerebrospinal fluid (CSF) as a testing platform seems to be very promising because the CSF protein composition reflects the pathological processes of the brain and because it is easily accessible by lumbar puncture. Some proteins have been reported to meet criteria for a biomarker, such as Aβ, total tau, and hyperphosphorylated tau (p-tau).2–4 Another series reported transthyretin (TTR) as a potential biomarker in AD. Whereas the aforementioned biomarkers have been studied extensively and were suggested to be included into clinical AD criteria, less information is available on TTR. This article focuses on the potential of transthyretin as an additional biomarker in the neurochemical differential diagnosis of AD.

**Abstract**

Alzheimer’s disease (AD) is the most common cause of dementia. Aβ1-42, Aβ1-40, total tau, and hyperphosphorylated tau have been reported to be suitable biomarkers in the diagnosis of AD. Additionally, transthyretin has been suggested as a biomarker since it has been shown to inhibit Aβ aggregation and the formation of senile plaques. Aggregates of Aβ1-42 are an important hallmark of the pathogenesis of AD. Patients with AD show significantly lower levels of transthyretin in the cerebrospinal fluid (CSF) compared with aging controls or patients with other kinds of dementia. Furthermore, some data indicate that transthyretin levels reflect disease severity in AD. In conclusion, recent work demonstrates the potential of transthyretin as an additional biomarker in the neurochemical differential diagnosis of AD.

**Keywords**

Dementia, Alzheimer’s disease (AD), cerebrospinal fluid (CSF), transthyretin (TTR), biomarker, disease severity, transthyretic, prognosis

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**Serum TTR** is also involved in the transport of plasma retinol-binding protein complex to vitamin A.5 TTR is synthesized in the liver and the choroid plexus of the brain,6–8 and TTR messenger RNA (mRNA) has also been found in kidney cells.9 In the CSF it is composed of two fractions: one originating in the blood (about 10%) and one from the choroid plexus.10 Studies on the plexus fraction are limited, but they are extremely important and urgently needed, since both morphological and functional changes in the choroid plexus are known to occur in AD. The ratio of the concentration of TTR in CSF to the concentration in serum is 200 times in excess compared with albumin.11 The concentration of TTR in serum is a sensitive indicator for malnutrition and illness owing to a reduction in its production rate in combination with its very rapid rate of disappearance from the circulation: about 50% per day.12

**Transthyretin and Alzheimer’s Disease**

**Cerebrospinal Fluid Studies**

In healthy elderly people, TTR levels increase with age.5 However, there was no correlation found between CSF production and CSF total protein concentration.12 By contrast, AD patients display significantly lower concentrations despite some overlap between AD patients and aging controls. A potential explanation for this phenomenon is that AD is associated with the flattening of choroid plexus epithelial cells and with an increase in the diameter of the basal lamina.13 As both structures are involved in the production and filtration of CSF, it is likely that there is an association between morphological changes in the choroid plexus and a reduced TTR secretion rate.13

Transthyretin—Synthesis

TTR is a 55kDa plasma homotetrameric protein that was first discovered in 1942. In the CSF, it is the main iodothyronine-binding protein, transferring T4 from the blood into the brain across the blood–choroid plexus barrier.1–2
Pathology/Effect on Aβ Aggregation

Aggregates of the amyloidogenic (Aβ1–42) peptide play a major role in the pathogenesis of AD, although the precise mechanism is unclear. TTR plays an important role in keeping intra-cerebral proteins such as amyloid fibrils in a soluble form and some in vitro experiments have demonstrated that TTR inhibits Aβ aggregation and the formation of senile plaques. Synthetic unlabeled Aβ was incubated with CSF, TTR, or albumin and analyzed later using Western blot techniques with anti-TTR and anti-Ac antibodies. TTR–Aβ complexes with an apparent molecular mass of 30kDa were observed under non-reducing conditions, which points toward high-affinity binding between those molecules. Transmission electron microscope (TEM) and light scattering analysis showed that TTR inhibited Aβ aggregation, and tryptophan (Trp) fluorescence quenching experiments also showed that full-length Aβ, but not non-aggregating Aβ fragments (Aβ1–12) and Aβ1–28 quench TTR’s Trp fluorescence. In human CSF under physiological conditions, TTR forms soluble complexes by binding to Aβ protein. An important inhibition of Aβ aggregation is found at a molar ratio of 1:300, which suggests that TTR in CSF could be the major Aβ binding protein and protects against Aβ deposition. As CSF concentrations of Aβ have been reported to increase with age, the concomitant increase in TTR concentrations with age could be an important feature maintaining Aβ in soluble complexes. In AD, this physiological sequestration could be imperfect owing to inadequate concentrations of TTR or potentially some TTR modifications, the latter being possibly related to epithelial atrophy in the choroid plexus in patients with late-onset AD.

In Vivo and In Vitro Experiments

In 2008, Buxbaum et al. obtained in vitro evidence of direct protein–protein interaction between TTR and Aβ aggregates. These findings suggest that TTR is protective because of its capacity to bind toxic or pre-toxic Aβ aggregates in both the intracellular and extracellular environment in a chaperone-like manner.
Neurodegenerative Diseases

Alzheimer’s Disease

Transhyretin as a Biomarker for Alzheimer’s Disease

Most of the literature described reduced levels of TTR in patients with AD. TTR levels in the CSF of patients with AD are shown to be reduced in comparison with patients without dementia.15,22,23 Other studies have reported decreased TTR concentrations in the CSF of patients with depression and normal pressure hydrocephalus (NPH).24,25 Although hampered by an artificial study design, similar results were achieved for post mortem CSF in AD.26 In other neurodegenerative diseases, normal concentrations of TTR are detected.21 Table 1 summarizes the data available on TTR from CSF studies. TTR levels are significantly reduced in the CSF of patients with AD and NPH compared with controls and other dementia, and TTR CSF values in AD did not differ significantly from those in NPH patients (see Figure 1).26 TTR levels did not correlate with, Aβ1-42, or Aβ1-42 CSF.21

Several attempts have been made to identify parameters that might reflect disease severity in AD. Studies on this subject are limited and contradictory results have been obtained so far. Both positive and negative associations have been reported. Increased levels of p-tau and tau were reported to reflect disease severity in AD in a study that analyzed the abundance of symptoms in AD and low levels of Aβ1-42. The investigators found a higher risk of early death in AD in those with low Aβ1-42, and the follow-up patients who died had significantly lower levels of Aβ1-42 and significantly higher concentrations of tau.27 By contrast, Haense et al.28 found no associations between tau and p-tau with dementia severity in AD. In another study that analyzed tau, Aβ1-42, and TTR in the same population, clear differences between biomarkers were elucidated. Whereas no association of dementia severity with tau and Aβ1-42 levels were detected, this was clearly observed for TTR: patients with severe AD showed a significantly lower TTR concentration (P=0.05) compared with mild cognitive impairment or mild dementia. At a cut-off of 15mg/l both stages could be discriminated, with a sensitivity of 91% and a specificity of 75% (Youden=0.66). Such an effect was not seen in patients with NPH (see Figure 2).29 In summary, TTR levels have been demonstrated to be selectively decreased in AD compared with other dementia. In addition, some data indicate that levels reflect disease severity in AD, which makes this protein an interesting biomarker for AD diagnosis. Studies on early AD stages are lacking so far, and more must follow.