Chapter 4

Tau Protein as a Biological Fluid Biomarker in Neurodegenerative Dementias

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Abstract

Tau is a microtubule-associated protein, whose main function is the modulation of the stability of axonal microtubules. In physiological conditions tau is abundant in neurons while its expression in glial populations is low and restricted to astrocytes and oligodendrocytes. The aggregation of tau in neurofibrillary or gliofibrillary tangles is the main hallmark of tauopathies, a complex group of human neurodegenerative conditions where tau hyper-phosphorylation causes its increased insolubility and aggregation leading to tangle formation and microtubule destabilization. Tau can be detected in biological fluids in physiological and pathological conditions. In several neurodegenerative dementias, either associated or not to a primary tauopathy, tau levels are altered in a disease-specific pattern, which can be used as a biomarker for disease diagnosis and prognosis. The study of tau levels in biological fluids has been mainly performed in the cerebrospinal fluid (CSF), although the recent development of ultrasensitive techniques allows the robust quantification of tau in blood-based biofluids such as serum and plasma. The presence of elevated total-tau in the CSF is assumed to reflect the degree of axonal damage in the brain tissue. Consequently, highest total-tau CSF levels are found in sporadic Creutzfeldt-Jakob disease, which is characterized by massive neuronal damage and a rapid progressive course. Elevated total-tau is also detected in Alzheimer's disease and dementia with Lewy bodies, while in other dementia conditions such as vascular dementia, frontotemporal dementia and corticobasal degeneration are unchanged, inconclusive or not determined. Additionally, total-tau rises temporarily due to cerebral infarction. In contrast, elevated phospho-tau levels seem to be restricted to Alzheimer's disease pathology, most likely mirroring the presence of the hyper-phosphorylated form in the brain tissue, although phospho-tau levels are mainly unaffected in tauopathies. Additionally, isoforms and different structural and truncated tau forms have also been reported to be altered in neurodegenerative dementias. In this complex scenario the diagnostic accuracy of diverse tau forms as disease-specific biomarkers needs to be established. In this chapter, we summarize the current knowledge on the alterations of diverse tau forms

in biological fluids of neurodegenerative dementias and its relevance in the differential diagnostic context. Additionally, we explore how tau alterations in the brain tissue may explain the etiology of its regulated levels in CSF and blood.

Keywords: total tau, phospho-tau, neurodegenerative diseases, cerebrospinal fluid, serum, plasma

1. Introduction

Tau is a microtubule-associated protein produced through alternative splicing of the MAPT (microtubule-associated protein tau) gene. Tau is highly abundant in the axons of nerve cells [1] where it plays a role in the stabilization and dynamics of the microtubules. To a lesser extent tau is also localized in the synaptic compartments [2] where it is suggested to modulate postsynaptic receptor activity by interaction with a broad range of synaptic proteins [3]. Besides its neuronal localization, tau is also expressed in oligodendrocytes, where it stabilizes microtubules during process outgrowth and myelination [4–6] and in astrocytes at trace levels [4], where it does not appear to be a major cytoskeletal protein. Although tau is mainly an intracellular protein, it can also be actively secreted by neurons to the brain interstitial fluid. The mechanisms of tau secretion under physiological conditions are not well understood, but it can be induced by neuronal hyperexcitability [7] and its release through ectosomal and exosomal vesicles [8, 9] or alternative secretory pathways [10] has been proposed. Additionally, under certain pathological conditions associated to neuronal degeneration tau can be released from the neurons to the brain interstitial fluid, usually correlating with the degree of neuro-axonal damage.

Tau released into the interstitial fluid may drain into the cerebrospinal fluid (CSF) within the subarachnoid space as well as into blood. Therefore, alterations of tau levels in biological fluids may mirror the pathological state of the brain in those conditions associated to neuronal degeneration. Additionally, since tau is hyper-phosphorylated in patients suffering from primary tauopathies and Alzheimer's disease (AD), a tauopathy associated with beta-amyloid deposition, increased phospho-tau (p-tau) levels in biological fluids may reflect the undergoing tau pathology in the brain tissue.

Consequently, the quantification of tau levels in biological fluids is extensively studied as a diagnostic and prognostic biomarker in a broad range of neurological conditions either associated or not to a concomitant tauopathy. Additionally, the analysis of different tau forms is also explored in the evaluation of the efficacy of disease-modifying therapies and to better understand the underlying molecular mechanisms associated to neuronal degeneration and tau pathology.

2. Tau pathology and neuro-axonal damage

Tauopathies are a complex and heterogeneous group of neurodegenerative diseases characterized by the presence of hyper-phosphorylated and aggregated tau forms in neuronal and

glial cells [11, 12]. The spectrum of tauopathies encloses more than 20 sporadic and familial diseases, in which their neuropathological phenotypes can be classified according to the involvement of different cell types (neurons of glial cells), affected brain regions, and the type of tau form/s associated to the pathological protein deposits [12]. In contrast to primary tauopathies where the common pathological hallmark is the presence of disease-related tau forms, AD is a neurodegenerative disease where tau pathology is accompanied by the accumulation of abnormally folded amyloid beta peptides in the tissue in form of extracellular amyloid plaques [13].

Keeping this in mind, the understanding of correlation between different tau forms present in the biological fluids regarding and the pathological changes occurring in the brain tissue is challenging. On one hand, there are neurodegenerative mechanisms not associated to tauopathies (or tauopathies associated to beta-amyloid deposition such as in AD), but leading to acute or chronic neuronal damage drive to a release of tau forms in their non-pathological (basal) state: i.e. basal phosphorylation levels and absence of truncated forms. On the other hand, in the presence of a tauopathy, tau release due to neuro-axonal damage could be accompanied by the release of its pathological forms (hyper-phosphorylated and truncated forms). In this regard, the tau biomarker field has been closely associated to the study of AD pathology since, among the group of tauopathies, AD cases are showing the most robust and clinically relevant alterations on tau levels in biological fluids. However, the precise cellular and molecular mechanisms leading to tau alterations in biological fluids remain elusive. Indeed, the current knowledge about the pathophysiological mechanisms of these diseases does not completely explain the disease-specific changes observed in biological fluids.

3. Cerebrospinal fluid tau

Enzyme-linked immunosorbent assays (ELISA) has been used extensively for the analysis of tau concentrations in the CSF. The most established immunoassays are developed for the quantification of total-tau (t-tau), which detects non-phosphorylated and phosphorylated tau forms, and phospho-tau (p-tau), which detects tau being phosphorylated at specific epitopes. Among them, the quantification of phospho-threonine-181 (p-tau-181) is broadly extended for research and clinical diagnosis purposes, especially in the context of AD-related pathology. Additionally, several studies have also shown the usefulness of assays detecting phospho-serine-199 (p-tau-199) and phospho-threonine-231 (p-tau-231) [14]. Finally, the recent development of a non-phospho-tau assay detecting non-phosphorylated tau at positions Thr-175, Thr-181 or Thr-231 [15], extended the range of available tools for the dissection of the contribution of each specific tau form in the pathology of the spectrum of neurological conditions with altered tau concentrations in the CSF.

3.1. Total tau

The presence of increased total-tau (t-tau) levels in the CSF is reported in several neurodegenerative diseases such as sporadic Creutzfeldt-Jakob disease (sCJD), AD and dementia with Lewy bodies (DLB) [16–18].

The highest t-tau levels are recurrently detected in sCJD, the most common form of human prion disease where deposition of prion protein, gliosis and massive neuronal damage accompanied with spongiform degeneration are common neuropathological hallmarks in the brain tissue [19]. The first report on the presence of high t-tau in the CSF of sCJD cases was in 1997 in a relatively small cohort of cases [20]. Further, several studies validated these observations in large populations [21–24]. A cut-off point of 1300 pg/mL t-tau was established for the discrimination of sCJD from non-CJD cases [21] and although t-tau is not included in the World Health Organization diagnostic criteria for sCJD, its quantification is used in several worldwide diagnostic centers as a supportive tool in the differential diagnosis of prion diseases.

In sCJD, patient's molecular subtype is composed of two different kinds of information: (1) codon 129 genotype in the *PRNP* gene (MM, MV, or VV) and (2) prion protein (PrP) type (1 or 2) and it is a prognostic marker for disease progression and patient survival [19]. The different progression rates for each molecular subtype are associated to their differential neuropathological hallmarks, which in turn reflect the degree of neuronal degeneration. Accordingly, a significant association between CSF t-tau levels and sCJD molecular subtype was reported [25, 26]. Additionally, CSF t-tau levels are inversely associated with disease duration, suggesting a role for CSF t-tau as a prognostic marker for sCJD [27]. While t-tau protein tends to increase in sensitivity from onset to the advanced stage, these changes are only statistically significant in patients with methionine-valine (MV) heterozygosis at codon 129 in the *PRNP* gene [28].

Besides sporadic forms, prion disease can also present a genetic (or hereditary) etiology [29]. Hereditary prion diseases are a heterogeneous group of conditions classified as familial or genetic CJD prion diseases (gCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS-S) and fatal familial insomnia (FFI), all of them associated to mutations in the prion protein gene and with an autosomal inheritance pattern. The most common gCJD types in the European population are those associated to mutations at codon 200 (E200K) and codon 210 (V210I). From a clinical and neuropathological point of view gCJD E200K and gCJD V210I resemble sCJD [30, 31]. Indeed, gCJD cases are often misclassified as sCJD in the absence of family history and genetic testing. In agreement with this, CSF t-tau levels in gCJD patients show levels comparable to those in sCJD [22, 32]. Instead, in GSS-S (associated to several mutations such as P102L, P105L, A117V, F198S) and FFI (associated to D178N mutation accompanied by a cis-129 M), CSF t-tau is usually below the sCJD cut-off point, [22, 32]. These differences are explained by the differential clinico-pathological hallmarks observed in these cases. First, GSS-S and FFI patients usually present a slower disease progression and prolonged disease duration compared to sCJD and gCJD cases [30]. Secondly, the brain regions affected are not overlapping those affected in sCJD. Indeed, FFI cases present a pathology which is usually restricted to the thalamic and olivary nucleus with spongiform changes in the cerebral cortex only in patients with long disease duration [30, 33, 34]. In contrast, neuropathological findings in GSS-S cases are heterogeneous depending on mutation type, but in general a widespread accumulation of PrP positive plaques in the cerebral and cerebellar cortices and the basal ganglia is observed [35, 36]. Although t-tau quantification lacks of clinical significance in the differential diagnosis of FFI and GSS-S, it is worth to mention that their mean CSF t-tau levels are increased compared to controls [22] indicating that, at some extent, t-tau may also reflect brain damage occurring in both conditions.

In AD, CSF t-tau is considered as one of the three core biomarkers together with p-tau and amyloid beta-42. The first studies reporting elevated t-tau concentrations in AD patients compared to controls date from 1995 [37–40]. Since them these results have been replicated in many studies [41, 42] with a predictive value around 90%.

Since t-tau is considered a marker of neurodegeneration, its levels are proposed to be changed latter during the progression of the disease and correlating with clinical symptom severity. This is in contrast to amyloid beta peptides which become abnormal before alterations in neurodegenerative biomarkers and cognitive symptoms are detected [43]. Importantly, as CSF t-tau reflects the intensity of acute neuronal damage and chronic neuronal degeneration elevated t-tau levels in MCI patients has been demonstrated to predict the progression to dementia [44], especially in short-term prognosis [45]. These observations are in agreement with a meta-analysis study that strongly supports the use of CSF t-tau in the identification of MCI-diagnosed subjects at higher risk of evolving to AD [46]. However, higher predictive values are reached when combined with p-tau, amyloid beta-42 and/or imaging biomarkers [45, 47]. Indeed data from longitudinal studies indicate that the combination of CSF t-tau, p-tau and amyloid beta-42 at baseline reach high prognostic values (95% sensitivity and 83% specificity) in the detection of early AD cases with MCI [48].

Besides the well documented elevated t-tau levels in sCJD, AD and DLB, several studies found slightly elevated t-tau levels in the spectrum of frontotemporal dementia (FTD)-related disorders [17] as well as in vascular dementia (VaD) [49, 50], although the reproducibility of these alterations are under discussion [17, 51]. Although meta-analysis studies support the presence of elevated t-tau levels in frontotemporal lobar-degeneration (FTLD) and VaD, these alterations are not as high as those detected in AD and CJD [52]. Importantly, alterations on t-tau levels in VaD and FTLD are dependent on the heterogenic presentation of these conditions. For instance, elevated t-tau is observed in VaD patients without progressive leukoaraiosis, while VaD patients with progressive leukoaraiosis have normal t-tau values [49]. Additionally, studies in VaD cases may have selection bias as co-occurrence of vascular and AD-related pathology is well-known [53]. In regard to FTLD cases, the two major subtypes, FTLD-TDP (FTLD with TAR DNA-binding protein 43 inclusions) and FTLD-tau (FTLD with tau inclusions) did not seem to differ on t-tau levels [54], although it has been recently shown that t-tau harbors a better discrimination rate than TDP-43 proteins in the differentiation of both FTLD subtypes [55]. Overall, in FTLD cases, despite the presence of slightly to moderate increased tau levels compared to controls in several studies, these differences, when observed, do not harbor clinical significance [56]. However, a potential prognostic role of t-tau levels in FTD has been suggested as non-inherited FTD patients with high t-tau levels (≥400 pg/mL), who had shorter survival than those with low levels. Instead, p-tau concentrations were not associated with disease prognosis [57].

In Parkinson's disease dementia (PDD) t-tau levels are also elevated compared controls or to Parkinson's disease patients with normal cognition, but lower than those detected in DLB [58, 59]. Whether elevated levels of t-tau in PDD are related to an underlying tau pathology participating in the development of dementia, similar to AD, or just reflecting increased neuroaxonal damage compared to PD cases is still a matter of debate.

In corticobasal degeneration (CBD), initial reports suggested the presence of elevated t-tau levels [60, 61], but decreased or non-altered levels were later reported in other studies [62, 63]. Similarly, patients with progressive supranuclear palsy (PSP) showed total-tau levels comparable to those detected in controls [61, 63].

Increased CSF t-tau levels in normal pressure hydrocephalus (NPH) patients compared to controls have also been reported [64]. Interestingly, t-tau levels correlated with the severity of dementia, urinary incontinence, and gait disturbance. However, further studies have not been able to replicate the presence of elevated t-tau in NPH patients [65, 66].

In Huntington's disease (HD), a recent study reported elevated levels of CSF t-tau in gene expansion carriers compared with their control subjects. Additionally, t-tau concentrations were associated with phenotypic variability, thus a role for t-tau as a biomarker of disease progression was proposed [67]. However, a diagnostic role for t-tau in HD is excluded as no differences between HD patients compared with pre-manifest gene expansion carriers have been reported [68].

As a marker of neuronal damage, elevated t-tau levels have been reported in acute stroke [69] and head trauma [70]. CSF t-tau levels in acute brain injury present a transitory peak. For instance in traumatic brain injury (TBI), t-tau levels increased shortly after contusion, peaking in the second week post-trauma, slowly decreasing after this period and reaching basal values at 43 days [70]. Instead, in Olympic boxers subjected to repetitive trauma t-tau levels increased after boxing and remained elevated after a rest period of at least 14 days [71]. In acute stroke, t-tau levels are associated to disease severity and long-term outcome [72]. The sizes and localization of the lesion generally affects the profile of CSF t-tau levels after stroke which vary to a great extent, generally reaching maximum levels after 3 weeks to 1 month and returning to normal levels after 3–5 months [69, 73]. Other neurological conditions with transiently elevated t-tau levels include acute Wernicke's disease [74, 75], after chemotherapy treatment for hematologic malignancies [76], and patients with temporary neurologic dysfunction after aortic surgery [77]. Altogether, these studies support the idea of CSF t-tau reflects the degree of brain injury and harbors a prognostic value in transient acute neuronal damage syndromes.

An important confounding factor in the biomarker field is the age of subjects in the study. In this regard, the discriminative power of CSF t-tau is higher in young old (<70 years) than in old (≥70 years) control and AD cases, indicating that CSF t-tau loses its discriminative power along the aging process [78]. Therefore, the age effect should be considered when establishing the diagnostic parameters of t-tau quantification as CSF biomarker. Increased t-tau levels during aging in healthy individuals have been validated in several independent cohorts [79], which in turn were associated to ApoE genotype [80, 81]. Consequently, age-dependent t-tau cut-off values in neurologically and psychiatrically healthy individuals have been established [82].

3.2. P-tau

While t-tau reflects axonal degeneration, p-tau levels reflect the phosphorylation state of tau in the brain tissue. This idea is supported by the absence of alterations in p-tau in neurological diseases presenting neuronal damage but no p-tau pathology in the brain tissue, such as in acute stroke [69].

Contrary to t-tau, elevated CSF p-tau levels seem to be more restricted to AD cases [83]. This is an interesting recurrent observation as aberrant tau phosphorylation also occurs in the brain tissue of tauopathies such as FTD with Parkinsonism linked to chromosome 17 (FTDP-17), Pick disease (PiD), CBD and PSP leading to aggregation into neurofibrillary tangles (NFT) and axonal transport dysfunction [84–86].

Neurofibrillary changes are composed of hyper-phosphorylated tau forms that correlate with disease duration and severity [87]. Indeed, the severity of cognitive impairment correlates better with the burden of neocortical neurofibrillary tangles than with amyloid pathology [87–89]. While meta-analysis studies indicate that CSF p-tau levels are a moderate prognostic marker in AD [90], longitudinal studies show that p-tau-181 levels correlated with the progression of cognitive decline [91]. Additionally, a low p-tau-181/tau ratio has also been reported as a strong predictor of cognitive decline [92]. In contrast, p-tau-231 levels correlate with the rate of hippocampal atrophy in AD cases, which are independent of disease duration and severity [93] as well as with a reduction hippocampal volume detected by magnetic resonance imaging (MRI) [94]. Since rates of hippocampal atrophy are suggested to reflect reduction of neuronal density, these observations suggest that p-tau231 is directly associated to extensive neuronal damage but not to disease stage. Additionally, p-tau-199 levels have been shown to be useful in the discrimination of AD patients from non-AD-related dementia and non-demented patients in a large-scale multicenter study [95].

A comparative study on p-tau231, p-tau181 and p-tau199 performance showed that the three p-tau forms were significantly elevated in patients with AD compared with FTD, DLB, VaD and control cases [96]. This study also indicated that p-tau231 and p-tau181 assays performed similarly in the discrimination of AD from non-demented controls, whereas the p-tau199 assay showed a weaker discriminatory value. However, the combinations of the three measurements did not add discriminative power compared to single measurements. Although alternative p-tau epitopes have been studied in the context of AD pathogenesis, it is generally considered that p-tau181, 199 and 231 are those more characteristic to AD. Indeed, most studies have focused on p-tau231 and p-tau181 [14], which in turn, are the most standardized assays for p-tau quantification.

For p-tau-181, a cut-off of >60 pg/mL is generally used to define pathological levels due to AD pathogenesis [97].

While other p-tau species have also been measured such as p-tau199, p-tau199 + 202, as well as p-tau396 + 404, importantly, p-tau levels in AD are increased not only compared to controls, but also compared to other tauopathies and neurodegenerative diseases [98]. Measurement of them becomes a useful marker in the differentiation of AD from its most relevant differential diagnoses. Phosphorylation at Thr-231 is helpful in the discrimination of AD from FTD, and its levels are correlated with disease progression, whereas p-tau-181 (the most established p-tau assay [99]) improves the differentiation between AD and DLB [96, 100, 101]. Additionally, p-tau, when used in combination with amyloid beta-42 (p-tau/amyloid beta-42 ratio), shows the best diagnostic performance in the discrimination of AD from FTLD [102]. This meta-analysis study also reports that p-tau alone would be more useful for high Mini-Mental-State-Examination (MMSE scores), while p-tau/amyloid beta-42 would be preferable for low MMSE scores and younger patients.

Several explanations have been postulated for the specific preserve of high CSF p-tau concentrations in AD. First, it could be that primary tauopathies may present different phosphorylation profiles than those observed in AD. While the complete differential phosphorylation signatures in the spectrum of tauopathies is still not completely defined, in AD, tau is hyper-phosphorylated at multiple sites (>30 sites). However, presence of tau hyper-phosphorylation at several epitopes such as 181, 199, 231,396 and 404 is a common hallmark in tauopathies [103].

A decrease on CSF t-tau in non-AD tauopathies could compensate the absence of elevated p-tau levels. However, t-tau levels are altered neither in the brain, nor in the brain tissue of non-AD tauopathies. Another aspect to be considered is the differential susceptibilities to clearance between tau forms. While tau turnover is delayed for insoluble forms, it is accelerated for soluble and phosphorylated tau [104]. Therefore, it is tempting to speculate that the combination of some or all these factors may have an influence in the differential CSF t-tau and p-tau profiles observed between tauopathies and AD.

CSF p-tau levels (p-tau-181) have also been reported to be moderately increased in CJD [17, 105]. Although p-tau values in sCJD are only from marginal to slightly elevated, most likely reflecting basal phosphorylation of tau molecules released into the CSF as a consequence of neuronal damage, these alterations are subtype-dependent. In fact, sCJD subtypes VV2 and MV2K showed the highest p-tau levels positively correlating with the amount of tiny tau deposits in brain areas showing spongiform change [24]. In agreement with these observations higher p-tau levels were detected in PRNP codon 129 VV cases compared to MM and MV cases where prion type was unknown [27].

Compared to controls, slightly increased p-tau concentrations have been reported in DLB [17], an observation supported by meta-analysis studies [52]. However, a large amount of studies report normal p-tau concentrations [106–109]. While several studies detected similar concentrations between DLB, PD, and PDD groups [22, 110], other reports suggest that among the group of α-synuclein aggregation disorders, DLB patients show the highest levels of p-tau [59].

Although it is broadly accepted that p-tau levels in FTLD are lower than those reported in AD and similar to controls [111], it has been recently shown that CSF p-tau levels are positively correlated with postmortem tau pathology (cerebral tau burden) [112]. Another interesting finding of this study was the observation that CSF p-tau levels in FTLD-TDP were lower than those detected in FTLD-tau.

In contrast to t-tau, p-tau levels are not elevated in acute brain injury or in TBI [69, 71, 73]. These results support the idea that CSF t-tau and p-tau reflect different pathogenic processes occurring in the brain tissue. While t-tau would be associated to the degree of neuro-axonal damage, p-tau would mirror the presence of hyper-phosphorylated tau forms, and therefore, the presence of neurofibrillary tangles.

Interestingly, a straightforward association has been suggested between ischemic events, tau hyper-phosphorylation and the formation of NFT. In this regard, hyper-phosphorylated and truncated tau-forms, resembling those detected in AD, accumulate after a transient cerebral ischemia [113, 114]. In humans NFT pathology is detected in TBI, but presenting remarkable differences in terms of temporal and regional affection: in TBI, NFT are concentrated in the

superficial layers in the neocortex, whereas in AD they predominate in the deep layers [115, 116]. Additionally, in mouse model of repeated TBI, elevated p-tau without NFT formation was observed in aged mice overexpressing human tau [117]. Finally, the absence of altered p-tau levels in the CSF of acute brain damage could also be explained by the presence of different isoforms of aggregated tau. Indeed, this might also explain the unaltered CSF p-tau levels in tauopathies showing NFL pathology such as PSP [118].

3.3. P-tau/t-tau - (t-tau/p-tau) ratio

As described above, the partial overlap on t-tau levels observed in sCJD and AD cases decreases the specificity of tau quantification in the differential diagnostic context of both diseases. An interesting addition to the biomarker field was the observation that p-tau/t-tau ratio greatly improved the discrimination of sCJD cases, not only from AD, but also from other tauopathies showing increased t-tau levels. This finding was initially reported by Riemenschneider and colleagues in a small cohort of sCJD cases (n = 20) [119] and further validated by many independent studies in large sample populations [16, 120, 121]. Diagnostic parameters and cut-off values were calculated in a cohort of more than 1000 sCJD cases [22]. For the discrimination of sCJD from neurological controls and AD the area under the curves were from 0.996 and 0.990 respectively, indicating that p-tau/t-tau ratio is able to almost fully discriminate sCJD from non-CJD cases.

Finally, p-tau/t-tau ratio has been proved in independent studies to discriminate the two main forms of FTLD; FTLD with TAR DNA-binding protein 43 (TDP-43) inclusions (FTLD-TDP) and FTLD with tau inclusions (FTLD-tau), with reduced p-tau/t-tau ratio detected in cases with FTLD-TDP pathology [122, 123]. This goes in line with the recent observation that patients with primary progressive aphasia with a non-AD profile (presumably FTLD) were stratified in two clusters according to p-tau/t-tau ratio, possibly corresponding to FTDP-tau and FTDP-TDP pathologies [124].

3.4. Non-p-tau

Recently, an assay able to reliably measure CSF concentrations of non-phosphorylated tau (non-p-tau) has been developed. The assay specifically measures non-p-tau at epitopes 175, 181 or 231 [15]. The non-p-tau CSF levels in AD cases (at MCI or dementia stages) were increased compared to controls. Additionally, the authors did not find differences on non-p-tau levels between patients in the MCI and the dementia stages of AD, in agreement with the presence of increased t-tau concentrations in MCI [43, 46, 125].

One of the major handicaps in the use of t-tau and p-tau concentrations in the differential diagnosis of neurodegenerative dementias is the partial overlap on both biomarkers among several conditions [17, 22, 83]. Thus, it could be hypothesized that the comparative study of non-p-tau in diseases with brain injury (elevated t-tau), but differential tau pathology could improve the discrimination achieved by both t-tau and p-tau. In this regard, a recent study investigated if non-p-tau quantification could improve the current diagnostic performance of the AD-associated CSF biomarker panel (amyloid beta-42, t-tau and p-tau-181)

in differential diagnosis of four neurodegenerative dementias (AD, FTLD, DLB, CJD) [107]. While the authors concluded that non-p-tau quantification had no added diagnostic value as a CSF biomarker for the differential diagnosis of neurodegenerative dementia, it improved the discrimination of sCJD cases. Unfortunately, as t-tau levels were above the quantification limit in 17 out of 19 CJD cases analyzed in this study, no significant conclusions could be drawn on the differential diagnostic accuracy of both tests.

In summary, preliminary observations indicate that the non-p-tau assay may be an interesting additional tool for the study of the dissociation between neuronal damage and tau pathology in the brain and biological fluids of neurodegenerative disorders.

3.5. Tau truncated forms

A growing body of literature is pointing to tau fragments, produced by cleavage events, as major players in the onset and the progression of the pathology [126–129]. In AD brains, after an initial misfolding at early stages of the disease which involves the physical contact of the N-terminal region with the microtubule binding repeats, tau is cleaved first at residue D421 followed by cleavage at residue E391, while N-terminal cleavage appears in later stages of the disease [126, 130]. The differential enzymatic cleavages during the pathological process is mostly dependent on Caspases activation, which lead to the generation of several tau fragments, each displaying its own profile of neurotoxicity [131]. Additionally, Calpain proteases have been shown to produce a triplet of tau fragments spanning from 35 kDa to 15 kDa. Similarly to full length tau [132, 133], several reports have shown that tau fragments can be secreted and uptaken from cells and brain slices and mediate toxicity [134–136].

These and other findings led researchers to investigate the presence of tau fragments in CSF and other biological fluids as potential biomarkers for the differential diagnosis of tauopathies and associated diseases. In CSF, at least 10 fragments were characterized in AD by mass spectrometry [137]. The presence of the 20 kDa caspase-6 cleavage product of tau in the CSF of AD has been reported to be associated with brain pathology and was found to be increased with the severity of the disease and the overall measure of global cognition [138]. Other reports found a 26–28 kDa fragment in both AD and strokes patients [139]. Tau bands ranging from 20 to 40 kDa were found in AD and control CSF [140, 141], which corresponded to N-terminal and mid-domain fragments, while no C-terminal fragments were found. Therefore, biomarker-based diagnosis would strongly depend on the subset of tau species analyzed.

Tau fragments have been proposed as biomarkers not only for the discrimination of AD from controls, but also for the differential diagnosis within related neurodegenerative diseases. For instance, a divergent pattern of expression of different N-terminal tau fragments was found between AD and PSP, even though such kind of studies are limited by the frequently overlapping clinical diagnosis [142]. Nonetheless, the ratio between a 33 kDa and a 55 kDa fragment in CSF was proposed as a more specific and reliable biomarker for the diagnosis of PSP [63]. Moreover, in CSF derived from TBI patients, a 30–50 kDa tau fragment was found to correlate with the extent of axonal damage [143]. Lastly, in CSF derived from either lumbar or cervical puncture from amyotrophic lateral sclerosis (ALS) patients the neurotoxic 17 kDa fragment produced by calpain cleavage was found to be elevated compared to controls [144].

While no C-terminal tau fragment was detected in CSF, a combination of ELISA and mass spectrometry analysis [145] revealed the presence of a C-terminal tau fragments in serum derived from AD patients. The levels of this fragment inversely correlated with the Mattis Dementia Rating Scale, suggesting that the increase of the fragment in the serum might parallel the cognitive decline.

3.6. Tau-seeding-based assays

The development and implementation of seeding-based methodologies for disease diagnostic purposes is an emerging topic with demonstrated clinical applicability in the field of prion diseases due to the real-time quaking-induced conversion assay (RT-QuIC). This assay exploits the self-propagating replication capacity of the abnormally folded and pathogenic PrP (seed), which induce the misfolding of naive PrP molecules (template) into a similar pathogenic structure. This reaction can be amplified to detectable levels and quantified in real-time. Importantly, the use of CSF from prion disease cases as a seeding material in the RT-QuIC assay allows the discrimination of CJD from non-CJD cases with high diagnostic accuracy and almost full specificity [146, 147].

Although the precise mechanism of neurofibrillary tangle formation in the brain tissue is not fully understood, the observation of tau spreading implicates the presence of a prion-like pathogenesis, where abnormal tau forms may induce the misfolding of non-pathological forms in a regional-dependent manner. Therefore, the principles of the RT-QuIC assay could be applied to the amplification of tau pathological forms in biological tissues. Although, successful cell- and tissue-based tau seeding assays have been recently developed the presence of tau seeding activity in the CSF of a tau-related pathology has been only reported once. Saijo et al. developed a tau RT-QuIC based on the use of a 3-repeat tau fragment as a substrate, a tau isoform that preferentially accumulates in Pick bodies. The authors detected positive tau RT-QUIC signal in the CSF from Pick disease (PiD) cases, suggesting that this assay may be helpful in discriminating PiD and non-PiD cases [148].

4. Tau in blood-based biofluids

Although lumbar puncture is a routine technique in the diagnosis of neurological syndromes, it entails important side effects for the patient being headache and cranial nerves dysfunction the most frequent ones [149, 150]. Therefore, many efforts are focused to identify biomarkers in other body fluids. Among them, blood analysis has arisen as a promising and cost-effective tool to identify biomarker molecules out of the CSF. Besides avoiding side-effects associated to lumbar puncture, blood extraction is suitable to be practiced in ambulatory centers or in home visits for first disease screening. However, the blood-CSF barrier imposes a decrease in the concentration of brain-specific molecules in the blood compared to that found in the CSF, which creates the need to develop ultra-sensitive quantification methods [151]. Several works have investigated the use of amyloid-beta peptides levels in plasma as a biomarker candidate for AD, but little research is done for other proteins [152, 153].

Owing to the lack of high-sensitive techniques and the low amount of tau in blood compared to CSF, the initial measurement of tau in human plasma was technically complicated impeding the detection of this molecule in 80% of samples [154]. However, novel quantification methods were later developed to overcome this limitation. They include immunoassays based on carboxylated microsphere beads [155], digital array technology [156], immunomagnetic reduction assay [157, 158] and ultra-sensitive commercial ELISA kits [159]. This way, in the recent years, plasma tau has arisen as a promising biomarker in neurodegenerative conditions. Importantly, it does not show significant correlation with demographic parameters such as age, sex or educational level [160].

Although a study showed reduced plasma t-tau levels in AD patients compared to normal cognitive individuals [159], the current consensus data point toward the opposite direction. Indeed, in the blood-based diagnostics of AD, t-tau is the only significant biomarker in the discrimination of the disease, displaying an AD/control mean ratio between 1.5 and 4.5 [42, 161]. The use of an assay based on antibodies coupled to magnetic nanoparticles rendered very high values (>90%) of specificity and sensitivity when comparing healthy controls versus AD+MCI cases [157]. This method was subsequently validated in a study enrolling two independent cohorts, where those high levels of specificity and sensitivity were almost reached (>89%) in the combination of cohorts when comparing healthy with AD cases [162]. With these data, the authors concluded that the best performance of plasma t-tau in the AD diagnostics was in combination with plasma Amyloid beta-42 levels, in a similar manner than combination biomarkers increase the diagnostic accuracy of single measurement markers in the CSF [18].

In the differential diagnostic context, plasma t-tau also appeared elevated in AD compared to MCI. However, the overlap between groups hinders the clinical utility of plasma t-tau as a routine biomarker [163]. Plasma t-tau was not found increased in MCI cases that later developed AD compared to controls, neither in cases with pre-MCI stage of subjective cognitive decline (SCD) [164]. These findings suggest that plasma t-tau is a late marker of neuronal damage and cannot be used as a prognostic tool of the likelihood to develop AD-related dementia sensitivity of the methodologies is improved.

Plasma t-tau does not seem to be a good reporter of the tau pathology in AD brain, as no strong correlation between plasma and CSF t-tau could be soundly demonstrated so far in AD [163]. However, plasma and CSF t-tau appeared correlated in a very recent study performed in a cohort with various neurological syndromes [161]. On the other side, mild association of high plasma t-tau with AD-specific pathology cannot be discarded. Within the MCI group, those cases positive for amyloid beta-42 had elevated t-tau compared with those amyloid beta-42 negatives [163]. In addition, high plasma t-tau levels in AD patients are associated to rapid disease progression in late clinical stages, including cognitive impairment and brain dysfunction [163]. The detailed relationship between plasma t-tau and the pathological state of the brain during the course of the disease is not yet clear. The t-tau concentration in plasma has been associated to abnormal cortical thickness and memory performance in a cohort of MCI patients [165]. However, in another cohort of MCI and AD cases, plasma t-tau appeared unrelated to cortical thickness in AD-specific regions [166]. In the same study though, the authors did report a significant association of high plasma t-tau levels and reduced gray matter density.

Specific measurement of p-tau in plasma still represents a technical challenge. One of the first attempts to measure p-tau-231 in human plasma was based on a complex immunoassay using multi-arrayed fiber optics coupled to rolling circle amplification (a-EIMAF) [167]. Although the authors only measured 5 sCJD plasma samples and 5 controls, t-tau was increased in all the disease cases. By contrast, no differences between p-tau-231 levels were detected. Interestingly, a similar pattern of t-tau and p-tau-231 was found in the brain tissue. It should be noted that the authors used arbitrary units for p-tau-231 quantification due to technical impediment [167]. Very recently, fine quantification of plasma p-tau-181 has been possible using a novel immunoassay based on digital array technology that has been modified to detect this phosphorylated form. In an exploratory case–control study that included 3 small cohorts (<50 cases per cohort), AD, Down syndrome (DS), neurological controls and healthy controls were analyzed [168]. In general, p-tau-181 was specifically increased in AD and DS patients compared to controls. Correlation between age and p-tau-181 was found in the DS group, supporting the link between this protein and the presence of amyloid pathology. A striking correlation was also found between p-tau-181 levels in plasma and in CSF, in contrast to the weak or no correlation between CSF and plasma t-tau [160]. Therefore, it is possible that phosphorylated tau, in contrast to t-tau in blood, is only originated in the brain.

Besides plasma, the levels of t-tau and p-tau-181 have been recently evaluated in the serum of AD cases by real time Surface Plasmon Resonance. Both concentrations were increased in AD compared to controls, with a better performance of tau than p-tau-181. Tau was also significantly elevated in AD compared to MCI. Tau and p-tau-181 in serum appeared strongly correlated, which could mean un-specificity in the CSF-blood filtration of tau species [169]. Similar to plasma, serum tau levels also presented a negative correlation with scores of cognitive assessment (HMSE and MoCA).

Blood tau levels have also been investigated in rapid progressive dementias. One of the pioneering works reported an increase of t-tau levels in serum in CJD patients compared of those is serum of AD and other non-CJD rapid progressive dementias. In spite of the small number of cases analyzed (<15 per group), it provided a valid proof-of-concept toward measuring t-tau in blood to differentially diagnose CJD [170]. A very recent study has validated these data using a larger and autopsy confirmed cohort. The levels of plasma tau in sporadic CJD appeared more than 2-fold elevated compared to neurological controls and to AD. Genetic CJD cases also presented increased plasma tau compared to AD. Comparison among different subtypes of sCJD also revealed differences in plasma tau, which was higher in MM/MV1 and MM1 + 2 subtypes. On the opposite, the subtype MV2 (kuru plaque) presented the lowest levels of plasma tau among the disease group [161]. These results indicate that plasma t-tau may be also reflecting the subtype-specific hallmarks of sCJD pathology.

5. Tau in the evaluation of disease-modifying therapies

Several strategies have been considered in order to prevent tau deposition. Compounds inhibiting tau aggregation [171], stimulating immune system against misfolded and

phosphorylated tau, as well as inhibiting of kinases responsible for tau hyper-phosphorylation, especially glycogen synthase kinase-3, have been proposed [172–174]. Therefore, tau and p-tau quantification in biological fluids is emerging as a potential tool in the evaluation of disease-modifying therapies. On one hand, alterations in p-tau levels would be informative of the phosphorylation and aggregation state of tau in the brain tissue. On the other hand, therapeutic approaches preventing neuronal damage would also alter the levels of t-tau protein in the CSF.

Interestingly, decreased CSF p-tau levels have been reported in patients treated with bapineuzumab, an antibody capable of binding to soluble and fibrillary forms of amyloid beta despite clinical trials do not lead to clinical benefit for intravenous bapineuzumab treatment [175].

However, as this research field is in its early phases, longitudinal studies are required to definitely demonstrate the relationship between temporal alterations in tau levels and clinical outcome. Additionally, as the effect of disease-modifying therapies on CSF biomarkers may be influenced by the mechanism of action of the therapeutic compound, alternative biomarkers should be used in order to assess the complete panel of hallmarks associated to the neurodegenerative process.

6. Conclusion

CSF t-tau and p-tau concentrations display good sensitivity and specificity in the discrimination of AD patients from non-demented control cases and a high diagnostic accuracy in the discrimination of sCJD cases. Both biomarkers become useful in the identification of patients at risk of progression to AD. The partial overlap between t-tau and p-tau levels among several neurodegenerative dementias indicates that more specific biomarkers are required in order to improve the accuracy in the differential diagnostic context. Alternative tau-based approaches have been recently developed and form the basis of the second-generation tau assays. On one side, the use of composite biomarkers, the development of non-p-tau assays and tau seeding methodologies, and the detection of tau truncated forms and alternative phosphorylation sites are promising alternatives that need further research to maximize their potential as diagnostic and prognostic tools. On the other side, the quantification of tau in blood-based fluids is gaining experimental momentum due to the advantages of using blood instead of CSF and to the implementation of high-sensitivity tests that can detect scarce tau amounts in plasma and serum. Several contradictory findings in the field might be related to the use of differential methodologies, which in some of the cases are not yet fully implemented and validated in large and independent cohorts.

Finally, the clinical diagnostic utility of tau measurements is complemented by the role of this protein as a reporter of the degree of neuro-axonal damage in the brain and the pathological hyper-phosphorylation tau state, which is specifically present in tauopathies. Since we are in the dawning of second-generation tau assays, future studies are necessary to validate them in larger and independent cohorts of patients in order to prove their clinical utility while they

	Total tau	*Phospho-tau*	*Non-phospho-tau*
Cerebrospinal fluid			
Alzheimer's disease	++	++	+
Parkinson's disease	=	=	NA
Parkinson's disease dementia	+	=	NA
Dementia with Lewy bodies	+	=	=
Creutzleft-Jakob disease	+++	+	+++
Frontotemporal dementia	+	=	=
Vascular dementia	+	=	NA
Amyotrophic lateral sclerosis	+	=	NA
Normal pressure hydrocephalus	+	=	NA
Plasma			
Alzheimer's disease	+	++	NA
Creutzfeldt-Jakob disease	+++	=	NA
Serum			
Alzheimer's disease	+	++	NA
Creutzfeldt-Jakob disease	+++	NA	NA

=	Unchanged
+	Slightly increased
++	Increased
+++	Highly increased
NA	Not analysed

Table 1. Tau levels in the biological fluids of major neurodegenerative diseases and associated disorders compared to control cases.

might provide important clues toward understanding the molecular events taking place in neurodegenerative processes.

A summary of the findings on tau-related biomarkers in the CSF and blood of neurodegenerative dementias is shown in **Table 1**.

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