Tau Diagnostics and Clinical Studies

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Abstract: This short editorial provides our point of view of the first EURO TAU meeting focusing on tau diagnostics and clinical studies. We cover postmortem analyses toward the identification of new biomarkers, tau imaging as a diagnostic biomarker, cerebrospinal fluid (CSF) sampling with emphasis on tau fragments, blood tests and genetic evaluations for sporadic cases, treatment aspects, drug development and points for future developments toward disease modification of devastating tauopathies.

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Introduction

Recently, Tong Guo, Wendy Noble, and Diane P. Hanger published a comprehensive review about the roles of tau protein in health and disease (Guo et al. 2017). In combination with previous reviews, including the Alzheimer's Association Research Roundtable Fall 2015—Tau: From research to clinical development (Holtzman et al. 2016) and the excellent first EURO TAU meeting, Lille, France, April 2017 (http://lucbuee.fr/crbst_10.html), we are now ideally positioned to discuss advances and future projections for tau diagnostics and clinical trials. This short review presents our own perspectives, trying to portray an objective view (Gozes 2002; Matsuoka et al. 2007; Vulih-Shultzman et al. 2007; Matsuoka et al. 2008; Shiryayev et al. 2009; Gozes 2010a, 2010b; Knake et al. 2010; Shiryayev et al. 2010; Stamelou et al. 2010; Gozes 2011; Höglinger et al. 2011; Idan-Feldman et al. 2012; Jouroukhin et al. 2012; Jouroukhin et al. 2013; Boxer et al. 2014; Gozes et al. 2014; Höglinger et al. 2014; Magen et al. 2014; Schirer et al. 2014; Tolosa et al. 2014; Kouri et al. 2015; Sun et al. 2015; Levin et al. 2016; Stamelou and Höglinger 2016; Boxer et al. 2017; Gozes 2017; Hansson et al. 2017; Höglinger et al. 2017; Höglund et al. 2017; Respondek et al. 2017).

Key Terms of Reference/Definitions

The article discusses key terms regarding postmortem analyses, tau imaging as a diagnostic biomarker ($[^{18}\text{F}]\text{AV1451}$ and of $[^{18}\text{F}]\text{THK5351}$); cerebrospinal fluid (CSF) sampling with emphasis on tau fragments (N-terminal fragments, NTF and C-terminal fragments, CTF); blood tests; genetic evaluations for sporadic cases; treatment options and drug development (NAP=davunetide=CP201, O-GlcNAcase inhibitors, tau vaccine AADvac1) toward future clinical trials.

Round Table Discussion and Questions Related to Tau Diagnostics and Clinical Studies

Postmortem Analyses, Toward Biomarkers

From the meeting perspective, recent advances at the diagnostic postmortem level were discussed. Irina Alafuzoff discussed incidence and distribution of tau pathology as well as amyloid plaques, TDP43 and α -synuclein pathologies, in various ages and clinical conditions. One of her major findings suggests that altered proteins are common in the brains of cognitively unimpaired aged subjects. This finding should be further considered while developing diagnostic biomarkers, particularly for identifying subjects at early stages of neurodegenerative diseases (Elobeid et al. 2016). Johannes Attems continued with the role of tau in the multi-morbid old brain, showing co-existence of pathologies and potential additive effects in the human brain - cross-seeding and molecular interactions between disease-associated aggregates/proteins, exemplifying interactions of pathological proteins in neurodegenerative diseases (Attems 2017). These postmortem analyses can be carried further in an automated mode for quantifying pathology in multiple brain regions to allow the identification of novel clinico-pathological phenotypes for the improvement of stratification of clinical cohorts according to underlying pathologies (Walker et al. 2017). Alberto Rabano discussed tau immunoreactive nuclear indentations in the entorhinal cortex of early Alzheimer's disease (AD) pathology. Specifically, Rabano's recent results suggest that tau immunoreactive nuclear indentations can become a possible indicator of increased total tau and/or increased 4R/3R-tau ratio in the affected neurons (Fernandez-Nogales et al. 2017). One of the coauthors of this article (Gunter Hoglinger) discussed the distinct postmortem pathology of the primary tauopathies corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Hoglinger et al. 2017) showing astrocytic plaques and tafts, respectively (Stamellou et al. 2010; Levin et al. 2016).

Tau Imaging as a Diagnostic Biomarker

This topic was not extensively discussed but should be mentioned in the context of diagnosis. Indeed, recent studies are now showing hierarchical organization of tau and amyloid deposits in the cerebral cortex of the elderly brain. These deposits generally display well-defined hierarchical cortical relationships as well as overlaps between the principal clusters of both pathologic alterations in the heteromodal association regions, representing systematic, large-scale mechanisms of early AD pathology (Sepulcre et al. 2017). [^{18}F]AV1451, used to label tau tangles in frontotemporal dementia, with the V337M MAPT mutation, showed a significant correlation between the degree of regional MRI brain atrophy and the

extent of binding in the proband (Spina et al. 2017). It should be noted that [^{18}F]AV1451 interacts also with neuromelanin in the midbrain, and may therefore be a measure of the pigmented dopaminergic neuronal count in the substantia nigra (Hansen et al. 2016). Furthermore, a difference was noted for [^{18}F]AV1451 imaging results in AD and PSP and a cautionary note was added regarding potential off-target labeling (Passamonti et al. 2017). Imaging with [^{18}F]THK5317 (tau deposition) and [^{18}F]FDG (glucose metabolism) highlighted the heterogeneous propagation of tau pathology among patients with symptomatic AD, in contrast to the homogeneous changes seen in glucose metabolism, which better tracked clinical progression (Chiotis et al. 2017). However, high levels of [^{18}F]THK5317 retention in brain regions thought to contain negligible concentrations of tau paired helical filaments raise questions about the interpretation of the positron emission tomography (PET) signals, particularly given interactions between quinolone derivatives, as with [^{18}F]THK5317 and monoamine oxidase B (MAO-B). Thus, the interpretation of [^{18}F]THK5317 PET images, with respect to tau, is confounded by the high MAO-B availability across the entire brain (Ng et al. 2017), paving the path to future studies.

Recommendation improved tau imaging markers are required to standardize the methodology and apply it to clinical use, with new generation tracers such as Merck's MK-6240 (Walji et al. 2016) or Piramal's PI-2620 (presented at the AD/PD meeting, 2017, http://www.acimmune.com/content/images/ADPD%202017%20_PI2620_Seibyl_final.pdf).

Cerebrospinal Fluid (CSF) Sampling with Emphasis on Tau Fragments, Blood Tests and Genetic Evaluations for Sporadic Cases:

Tau measured in CSF is an established biomarker for AD; increased CSF concentrations of total tau (T-tau) are thought to reflect neurodegeneration whereas highly phosphorylated tau (P-tau) is believed to reflect tangle pathology. Importantly, despite the observation that primary tauopathies present severe neurodegeneration and tau pathology, CSF T-tau and P-tau show no clear change (Masters et al. 2015). This may be due to the fact that current tau immunoassays are based on antibodies binding to the mid region of tau and may miss pathogenic tau due to truncation or masking during oligomer/aggregate formation. Recent studies suggest that CSF tau consists of several protein fragments (Meredith et al. 2013, Barthelemy et al. 2016), and metabolic processing of tau into N-, mid and C-terminal fragments may also be key for secretion, aggregation and spreading pathology of tau, and may differ between the tauopathies (see below). Furthermore, the potential of tau oligomers or cis-tau variants (Kondo et al. 2015) as specific biomarkers for tauopathies has not been

explored. Levels of tau oligomers have been shown to rise in both the CSF (Sengupta et al. 2017) and plasma (Kolarova et al. 2017) of patients with AD compared to healthy controls.

Recent data suggest that tau is actively secreted into the extracellular space and total tau along with tau fragments have been identified in the interstitial fluid (ISF) (Yanamandra et al. 2017). This suggests that some tau fragments may be actively secreted presenting a potential to give additive biomarker information. In this respect, proteolysis of tau is mediated by a range of different proteases, some of which break down the tertiary paper clip like structure of tau (Wang and Mandelkow 2015) resulting in exacerbated tau aggregation (Sokolow et al. 2015). The resulting proteolytic fragments have different characteristics dependent on the site of cleavage within tau and also depending on the inclusion of the microtubule-binding domain (Yin and Kuret 2006), (Wray et al. 2008, Matsumoto et al. 2015). One CTF, termed tau35 (Arai et al. 2004; Wray et al. 2008), that is specific to CBD and PSP, induced cognitive deficits when expressed at low levels in the Tau35 mouse, which could be reversed with sodium-4-phenylbutyrate treatment (Bondulich et al. 2016). Notably, sodium 4-phenylbutyrate is a well-known histone deacetylase inhibitor and chromatin modification through histone acetylation is a molecular pathway involved in the regulation of transcription underlying memory storage. Another transgenic mouse expressing tau₁₅₁₋₃₉₁ developed hyperphosphorylated and aggregated tau species, deficits in locomotor activity, and had a reduced lifespan (Zimova et al. 2016). Recently, a study characterizing tau CTFs in 12 cortical samples from both control and late Braak stage AD, led to the identification of 21 novel tau fragments (Derisbourg et al. 2015).

Proteolytic fragments of tau have been found in the CSF and plasma (Henriksen et al. 2013; Henriksen et al. 2015; Inekci et al. 2015) of patients with different tauopathies, presenting these fragments as potential novel biomarkers for disease progression. Recent data have shown that fragments of tau are able to cross the blood-brain barrier with different rates, depending on the precise amino acid sequence (Banks et al. 2016). The CSF tau profile is composed entirely of tau fragments rather than full-length protein, with different fragmentation patterns dependent on disease state and progression (Johnson et al. 1997; Meredith et al. 2013). CSF tau CTF and NTF levels are decreased in PSP, while increases were observed in AD (Wagshal et al. 2015). There is much interest in the use of CSF fragments of tau as a biomarker, with data being presented by Kina Höglund showing that the asparagine endopeptidase mediated-NTF, tau₁₋₃₆₈ (Zhang et al. 2014) could potentially act as an AD specific biomarker.

Tau protein can also be measured in blood, but the potential for identification of AD or neurodegeneration is lower for blood tau than for CSF tau (Mattsson et al. 2016). This lack of correlation between blood and CSF might be due to the “wrong” pool or the fragment of tau that is being analyzed.

An intriguing finding is that exosomes, which are secreted in body fluids such as CSF and serum, contain tau protein (Winston et al. 2016). Exosomes are believed to be a way for cells to communicate, and thus, may present a potential mechanism for cell-to-cell propagation of tau aggregates. Some studies indicate that tau from isolated brain-specific exosomes in blood may have value as a biomarker for brain disorders such as AD (Winston et al. 2016).

From the point of view of the authors of this article, Kina Höglund expands the cerebrospinal fluid endopeptidome (Hansson et al. 2017; Hoglund et al. 2017), while Illana Gozes studies potential blood biomarkers using genome-wide transcriptomic profiling and bioinformatics data mining (Hadar et al. 2016). A proteomic approach identified the tau-interacting activity-dependent neuroprotective protein (ADNP) (Oz et al. 2012; Schirer et al. 2014; Ivashko-Pachima et al. 2017), as the only protein down-regulated in serum samples from early AD patients (Yang et al. 2012). These studies were corroborated showing that blood borne expression of ADNP is correlated with premorbid intelligence, AD pathology, and clinical stage. Age adjustment showed significant associations between: 1) higher premorbid intelligence and greater serum ADNP, and 2) greater cortical amyloid and lower ADNP mRNA. Furthermore, increased ADNP mRNA levels were observed in patients ranging from mild cognitive impairment (MCI) to AD dementia, suggesting additional, tau-related blood markers (Malishkevich et al. 2016).

Thibaud Lebouvier discussed clinical aspects aiming to identify genetic markers and gene signatures associated with CSF biomarker levels of t-tau, p-tau181, and with the two ratios t-tau/A β 1-42 and p-tau181/A β 1-42 in the context of progression from MCI to AD, and to identify a panel of genetic markers that can predict CSF biomarker p-tau181/A β 1-42 ratio with consideration of APOE4 stratification. The group analyzed genome-wide the AD Neuroimaging Initiative (ADNI) dataset. They identified a panel of five SNPs, rs6766238, rs1143960, rs1249963, rs11975968, and rs4836493, that are predictive for p-tau181/A β 1-42 ratio (high/low) with a sensitivity of 66% and a specificity of 70% (AUC 0.74). These results suggest that a panel of SNPs is a potential prognostic biomarker in ApoE4-negative MCI patients (Sun et al. 2015). Furthermore, from a genetic point of view, Gunter Hoglinger showed that the tau encoding gene MAPT, is the major risk gene for PSP (Hoglinger et al. 2011) and CBD (Kouri et al. 2015).

Recommendation large cohorts and longitudinal studies are needed to verify potential tau fragments or other proteins/peptides as specific biomarkers in CSF and perhaps in other body fluids, e.g. blood.

Treatment Options

Treatment options for the primary tauopathy, PSP, were discussed by Gunter Hoglinger, including levodopa, amantadine, amitriptyline, zolpidem, CoQ10 and Botulinum toxin A, all extensively reviewed in the published literature (Stamelou and Hoglinger 2016).

Drug Development

Table 1 shows ongoing clinical trials directed at tau. Meanwhile, there were a few failures and some hope.

The most recent failure was with Leuco-methylthioninium bis (hydromethanesulfonate; LMTM), a stable reduced form of the methylthioninium moiety, acting as a selective inhibitor of tau protein aggregation both in vitro and in transgenic mouse models, which was tested in patients with mild to moderate AD (Gauthier et al. 2016). It is possible that drug administration was too late in the disease process, and unable to reverse previously accumulated cell damage. An additional

previous failure was with the GSK-3 inhibitor tideglusib (Dominguez et al. 2012), for example, in AD (del Ser et al. 2013) and PSP (Tolosa et al. 2014). Interestingly, while there were no physical or behavioral benefits for tideglusib, it did reduce progression of brain atrophy (Hoglinger et al. 2014).

In contrast to PSP (Boxer et al. 2014), intranasal NAP (davunetide, AL-108) showed efficacy in other indications, namely MCI, significantly increasing cognitive scores (Gozes et al. 2009; Morimoto et al. 2013) and in cognitive impairment associated with schizophrenia, significantly protecting functional activity and brain matter (Javitt et al. 2012; Jarskog et al. 2013). NAP (now called CP201) is poised for further clinical trials in the ADNP syndrome (Gozes et al. 2015, 2017a, b), within the autism spectrum disorders (<http://www.coroniss.com/Pipeline/575/CP201-for-ADNP-syndrome>). In this respect, ADNP through its NAP (octapeptide snippet, NAPVSIPQ) binds to microtubule end binding proteins, which in turn bind to tau and dramatically

Table 1: The Tau Therapeutic Pipeline

Drug	Company	Mode of action	Reference	Disease	Phase	ClinicalTrials.gov identifier
1P1-287	Academic	Microtubule stabilizer	Brunden et al., Bioorg Med Chem. 2014;22:5040-9.	AD, CBD, PSP	1	NCT01966666 NCT02133846
1Rx0237	TauRx Therapeutics	Tau aggregation inhibitor	Hochgrafe et al., Acta Neuropathol Commun. 2015;3:25	AD, bvFTD	3	NCT01689233 NCT01689246 NCT01626378 NCT02245568
Young Plasma	Academic	Rejuvenation	Villeda et al., Nat Med. 2014;20:659-63.	PSP	1	NCT02460731
Salsalate	Academic	Inhibiting tau acetylation	Min et al., Nat Med. 2015;21:1154-62	PSP	1	NCT02422485
CCT020312	Academic	PERK Activator	Bruch et al., EMBO Mol Med. 2017;9:371-384.	PSP	Preclinical	n.a.
ABBV-8E12 (C2N-8E12)	AbbVie (from C2N Diagnostics)	Anti-tau monoclonal antibody	Yanamandra et al., Neuron. 2013;80:402-14.	PSP	2	NCT02985879
BLIB092 (BMS-986168)	Biogen (from Bristol Myers Squibb)	Anti-tau monoclonal antibody	Bright et al., Neurobiol Aging. 2015;36:693-709.	PSP	2	NCT03068468
ACI-35	Janssen (from AC Immune)	Tau active vaccination	n.a.	AD	1	n.a.
AADvac1	Axon Neuroscience	Tau active vaccination	Novac et al., Lancet Neurol. 2017;16:123-134.	AD, FTD	1/2	NCT02579252 NCT03174886
A SN120290	Asceneuron	0-GlcNAcase inhibitor	Yuzwa et al., Nat Chem Biol. 2008;4:483-90	PSP	1	n.a.
MK-8719	Merck (from Alectos)	0-GlcNAcase inhibitor	n.a.	n.a.	1	n.a.
AZP2006	Alzprotect	n.a.	i.a.	n.a.	1	n.a.

Abbreviations: N.A. = not available

Source: www.ncbi.nlm.nih.gov/pubmed; Clinicaltrials.gov; www.alzforum.org; last database access: 02.10.2017

enhance tau interaction with the microtubules (Ivashko-Pachima et al. 2017), protecting against tauopathy associated with ADNP deficiency (Vulih-Shultzman et al. 2007) and enhancing synaptic plasticity (Oz et al. 2014). These results were presented by Illana Gozes at the Eurotau meeting.

Lastly, Dirk Beher presented a future clinical trial in PSP with O-GlcNAcase inhibitors with supporting evidence from preclinical trials [e.g. (Yuzwa et al. 2014; Hastings et al. 2017)] and Michal Novak discussed the safety and immunogenicity of the tau vaccine AADvac1, toward future clinical trials (Novak et al. 2017).

Recommendation results from clinical trials currently underway will help to inform and focus the development of new tau-targeting therapies.

Discussion and Future Directions

The discussion focused on three major issues, improving early diagnosis, choosing the right cohort with relevant clinical endpoints and designing/developing drugs.

In terms of early diagnostics to provide for better treatment modalities, Johannes Attems discussed the possibility of addressing the olfactory pathology toward better, simpler early diagnosis (Attems et al. 2015).

Kina Höglund raised the issue that basic biochemical studies in brain tissue focusing on endogenous fragments/peptides of tau is one way forward to identify novel tau biomarkers. For clinical validation, it is important to have access to already established biomarkers such as CSF A β 42, total tau, p-tau (181) as well as tau and A β PET imaging and MRI.

It was further suggested to take advantage of the established biomarkers to exclude, for example, patients with amyloid pathology, either based on amyloid PET or CSF A β 42. Further studies to examine the profile of neurofilament light chain in blood in various tauopathies may also enable a screening tool where exclusion or inclusion criteria can be applied.

Illana Gozes raised the possibility of developing more/better blood biomarkers (Hadar et al. 2016; Malishkevich et al. 2016) and emphasized sex differences, both in diagnostics as well as in clinical trial design and statistical analysis of the outcomes (Malishkevich et al. 2015).

With Dirk Beher (who led the discussion) starting a clinical trial in PSP [as well as the trials outlined in Table 1 (Boxer et al. 2017)], the issue of possible success was raised, and early mild cognitive impairment as a promising indication was suggested, targeting disease before extensive pathology has accumulated (Morimoto et al. 2013) (Illana Gozes).

In terms of drug design and development, the idea of multi-target drugs or drug mixtures was discussed for future pivotal meeting/trials.

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Compliance with Ethical Standards

Competing Interests IG is the Chief Scientific Officer of Coronis Neurosciences (www.coronisns.com).

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