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Panel 1: Glossary of terms

Chronic inflammation: *A protracted low-grade maladaptive inflammatory state, characterised by a vicious cycle of inflammation and tissue damage, that may arise due to a failure to effectively clear an initial noxious stimulus in a timely manner, loss of self-tolerance (autoimmune disease), or recurrent episodes of acute inflammation. Chronic inflammation can occur on both sides of the blood-brain barrier (BBB) in the form of neuroinflammation and chronic systemic inflammation.*

Neuroinflammation: *inflammation within the central nervous system, largely orchestrated by the actions of activated resident microglia and astrocytes but also contributed to by endothelial cells and infiltrating peripheral immune cells. Over time, neuroinflammation can result in tissue destruction and is associated with an array of neurodegenerative diseases.*

Systemic inflammation: *inflammation outside of the central nervous system (CNS) which can modulate neuroinflammation.*

Inflammaging: *a state of chronic low-grade systemic inflammation, characterised by the expression of proinflammatory genes, that is associated with advancing age. Maladaptive inflammaging is influenced by an individual's underlying genotype and its interaction with environmental stressors throughout life. Ultimately a pathological irreversible proinflammatory threshold is reached and the development of age-related conditions typically ensue.*

Blood-brain barrier (BBB): capillary *endothelial cells connected by tight junctions, pericytes and the enveloping end-feet of astrocytes collectively form a selectively permeable membrane between the circulatory system and the brain that tightly controls the passage of immune cells, drugs and pathogens. The integrity of this barrier can be disrupted by inflammation.*

Tau*: encoded by the microtubule-associated protein tau (MAPT) gene, tau is a protein that plays a role in the axonal structural integrity through the stabilisation of microtubules. Mutations in the MAPT gene, as well as idiopathic factors, can result in the misfolding and mislocalisation of tau to the somatodendritic compartment where it accumulates, resulting in neurodegenerative pathology. The MAPT gene can be spliced in a manner which results in the expression of tau isoforms that contain either three or four repeats of the microtubule binding repeat domain.*

Tauopathies: neurodegenerative conditions characterised by the accumulation of tau to form intracellular inclusions. This heterogenous group of conditions can be classified as primary (resulting from mutations in the MAPT gene) or secondary (downstream of an alternate instigator of neuropathology e.g. the accumulation of beta-amyloid).

Tauopathies can also be classified on the basis of the tau isoform(s) that predominate in the intracellular inclusions: 3-repeat (3R) tauopathies, 4-repeat (4R) tauopathies, or 3R/4R tauopathies.

Neurofibrillary tangles (NFTs): *abnormal aggregates of hyperphosphorylated filaments of tau that reside within cells. Paired helical filaments are the predominant form of aggregated tau seen in neurofibrillary tangles in Alzheimer's disease.*

Mild traumatic brain injury (mTBI): *injury to the brain of traumatic origin causing structural and/or physiological disruption that includes subconcussion and concussion and is associated with a Glasgow Coma Scale (GCS) score of 13-15. It can often manifest clinically with amnesia, headache and behavioural changes.*

Chronic effects of inflammation on tauopathies

Summary

Tauopathies are a heterogenous group of neurodegenerative disorders characterised by the aggregation of the microtubule-associated protein tau into filamentous inclusions within neurons as well as glia. Alzheimer's disease is the single most prevalent tauopathy. Despite years of intense research efforts, clinicians remain deprived of disease-modifying interventions for these conditions. The detrimental role that chronic inflammation plays in the pathogenesis of Alzheimer's disease is increasingly recognised yet largely ascribed to the accumulation of beta-amyloid, leaving the impact of chronic inflammation on tau pathology and neurofibrillary tangle-related pathways greatly overlooked. Tau pathology can independently arise secondary to a range of triggers each associated with inflammatory processes including infection, repetitive mild traumatic brain injury, seizure activity, and autoimmune disease. A greater understanding of the chronic

effects of inflammation on the development and/or progression of tauopathies may forge a path for the establishment of effective immunomodulatory disease-modifying interventions for clinical use.

Introduction

Tauopathies are clinically, topographically and pathologically heterogeneous. They can be primary, for example, related to mutations in the MAPT gene (primary tauopathies) (1) or secondary, related to a defined cause, for example the accumulation of beta-amyloid (Aβ) (secondary tauopathies) (2). Alzheimer's disease (AD) is the most prevalent secondary tauopathy but tau neurofibrillary tangle (NFT) pathology can also be caused by seizure activity (3), traumatic brain injury (4), infection (5), and autoimmune disease (6). Often NFT pathology occurs as part of a mixed neuropathological process.

Normally, inflammation is resolved in a timely manner that benefits the host, however a vicious cycle of deregulated inflammatory responses and excessive or long-lasting tissue damage can lead to the development of chronic inflammatory diseases. This process has been implicated in the aetiopathogenesis of late-onset AD (7). Chronic inflammation has principally been studied in relation to pathways leading to Aβ accumulation, whilst its impact on tau pathology and NFT-related pathways is less studied.

There are no well-established disease-modifying interventions for AD and other tauopathies and an understanding of the important role of chronic inflammation across these conditions may generate a fresh approach to therapeutics. In this

Personal View, we initially recap the immune landscape of the central nervous system (CNS) and highlight the genetic evidence for the contribution of inflammation to tauopathy. Next, we profile a range of tauopathies, each associated with inflammatory risk factors, which we divide into two main neuroanatomical subsets: (1) neocortical and medial temporal lobe tauopathies and (2) basal ganglia and brainstem tauopathies. We present these tauopathies in approximate order of neuroanatomical origin working down from the neocortex to the brainstem. We consider neuropathological and clinical hallmarks, as well as the respective links between underlying aetiology and tau deposition. Ultimately, we outline the convergence of these diverse potential triggers of neuropathology onto a common pathway of chronic inflammation as evidenced by basic and clinical research findings.

An overview of relevant neuroimmunology

Innate immunity within the CNS is mediated through the responses of resident microglia and astrocytes (8). Microglia represent a complex heterogeneous population of cells. Their state is highly context-dependent and is swayed by factors such as age, sex, genotype, location within the CNS, CNS pathology, and the activity of the peripheral immune system (9). As such, with the exception of acknowledging redundant dichotomic nomenclature to describe microglial states, a superseding classification system lacks consensus (9).

Inflammaging (see glossary) alters the function of both adaptive and innate components of the peripheral immune system, the chronic maladaptive proinflammatory state that culminates is believed to contribute to a range of age-

related conditions (10). It is feasible these processes are upholding in the central immune system. Regardless, despite the blood-brain barrier (BBB), the peripheral and central immune systems are not insular. Crosstalk between the two systems is well defined in homeostasis and neurological disease (11) and includes the response of microglia to peripheral cytokine production plus lymphocyte and macrophage migration into the CNS, the latter of which can assume microglial morphology (9).

A key neuroinflammatory output of certain reactive microglia states is the release of the proinflammatory cytokines IL-18 and IL-1β, mediated by the canonical NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome. Two signals are required for the NLRP3 inflammasome to become functional: priming and activation. Priming of the NLRP3 inflammasome is principally achieved via MyD88-dependent signalling downstream of activated toll-like receptors (TLRs). This ultimately leads to the nuclear translocation of NF-κB which activates the transcription of NLRP3 as well as the inactive precursors of IL-1β and IL-18. Caspase-1-mediated proteolytic cleavage gives rise to IL-1β that is capable of triggering the phosphorylation of tau in neighbouring neurons, an event which enhances its seeding capacity (12) (figure 1). Furthermore, caspase-1 also cleaves gasdermin D (GSDMD), a key step in pyroptosis: a form of cell death that has been shown to be active in tauopathies such as AD (13). TLR activation from the endosomal compartment by lipopolysaccharide (LPS) or nucleic acid instead triggers TRIF-dependent signalling that is linked to the induction of type I interferons (IFNs) (figure 1).

Another facet of innate immunity relevant to neuroinflammation and tauopathy is the expression of type I interferons resulting from activation of the cyclic GMP-AMP

synthase (cGAS)-stimulator of interferon genes (cGAS-STING) pathway (figure 1). Other outputs of this pathway include upregulation of proinflammatory cytokines via NF-κB and the induction of autophagy (14). Double-stranded DNA (dsDNA) of endogenous or exogenous origin is the archetypal trigger, although emerging evidence suggests tau may also activate this pathway (15) (figure 1).

Following a robust immunological response to an initial trigger, inflammation should settle as a resolution phase is reached in which normal tissue homeostasis is regained. However, when tissue damage is incurred during the process of inflammation it can lead to a self-perpetuating deleterious cycle of inflammation and tissue damage; the hallmark of chronic inflammatory diseases. A mixture of genetics, autoimmunity and endothelial or epithelial barrier disruption is posited to underlie this pathological transition (16).

The genetic basis for chronic inflammation in the aetiopathogenesis of tauopathies stems from large-scale AD genome-wide association studies (GWAS) that highlight *TREM2*, *CD33*, *ABCA7*, *CLU*, *CR1*, *EPHA1*, and *HLA* as risk loci (17–20). Chronic TREM2 activation in mice inoculated with AD brain-derived tau results in increased tau pathology without alteration of the Aβ plaque burden (21). Recently, *APOE* isoforms have gained traction as being implicated in immunological processes (22–25) and genes associated with TNFα signalling have surfaced as AD risk factors (20).

Neocortical and medial temporal lobe tauopathies

Chronic traumatic encephalopathy

Chronic traumatic encephalopathy (CTE) is a pathologically defined condition associated with repetitive mild traumatic brain injury (mTBI). In its earliest stages, CTE affects focal regions of the frontal, temporal, and parietal neocortex which over time extends to subcortical nuclei of the medial temporal lobe and brainstem (26). Characteristically, neurofibrillary tangles (NFTs) and neuropil threads consisting of aggregated, hyperphosphorylated tau are identified at the depths of the cerebral sulci in close approximation to vasculature and associated with neuroinflammation (26) (figure 2). Although neuronal intracellular tau inclusions are composed of both 3R and 4R tau, and Aβ plaques have been reported to co-exist with tauopathy, CTE differs from AD on both a cell type and an ultrastructural basis (26,27).

So, what connects these neuropathological and clinical changes to repetitive mTBI? In mouse models, rapid acceleration-deceleration forces, acting on vulnerable axons and blood vessels, elicit the dissociation of tau from its native position on microtubules leading to hyperphosphorylation and aggregation (28). Others favour a vascular route to tauopathy citing cerebrovascular dysfunction in the form of blood brain barrier (BBB) disruption, haemorrhages and ischaemic changes as the driving force behind Aβ deposition and the hyperphosphorylation and aggregation of tau into NFTs (29). These initial changes are then compounded by reduced clearance of pathological proteins seen in states of hypoxia (29). This notion of cerebrovascular dysfunction leading to the development of tau pathology aligns more closely with the perivascular accumulation of tau NFTs at the sulcal depths.

A unifying hypothesis is that repetitive, frequent mTBI can elicit axonal injury, neuroinflammation and neuronal death, with the subsequent formation of damage-

associated molecular patterns perpetuating this cycle and ultimately leading to the development of tauopathy. This process may be augmented by hypoxic changes and BBB disruption, the latter allowing for greater crosstalk between the central and peripheral immune systems. Cherry et al., (30) found that neuroinflammation correlated with both AT8 immunostaining for tau NFTs and greater lengths of exposure to repetitive head injury in a brain bank cohort of 66 former American football athletes with confirmed CTE. Utilising binary logistic regression, this study elucidated a link between neuroinflammation and the development of dementia, which appeared to be mediated through tau pathology (30). Moreover, neuroinflammatory astrocytic transcriptomic signatures have been found to be upregulated in CTE white matter samples (31). A genetic predisposition bestowing chronic host inflammatory responses may favour the development of tauopathy in the context of brain injury as a significant association was found between the *APOE* ε4 haplotype and tau burden in neocortical regions from the post-mortem tissue of individuals with a history of repetitive mTBI (32) which was supported by data from rodents (33). Overall, both chronic neuroinflammation and tau deposition is associated with repetitive mTBI.

Nodding syndrome

Nodding syndrome is a geographically restricted neurological condition, predominantly affecting the paediatric populations of South Sudan and Northern Uganda (34). Endemic to these regions is the parasite, *Onchocerca volvulus,* which causes ‘river blindness’. An association between the two is evidenced by the reduced incidence in recent years in areas where ivermectin treatment has been provided for this parasitic infection, along with interventions to control the blackfly

vector of *O. volvulus* (34). Nodding syndrome typically develops between the ages of 5-15, manifesting as a form of epilepsy. Its name makes reference to the atonic seizures that arise in clusters and lead to head-drop (34). This is accompanied by progressive cognitive impairment (34,35). MRI data shows varied patterns of marked atrophy in the parietal, occipital and cerebellar regions of the brain in affected individuals (36).

An initial case series published by Pollanen et al., (37) defined Nodding syndrome as a tauopathy with neuronal NFTs composed of both 3R and 4R tau isoforms along with neuropil threads and pretangles (figure 2). In a follow-up study (38), the authors list three hallmarks of Nodding syndrome: cerebellar atrophy, white matter degeneration and tauopathy (38). Cases studied harboured multifocal tau pathology in the superficial layers of the neocortex as well as more concentrated pathology in the locus coeruleus (LC) and a lack of glial tau pathology.

Despite its links, *O. volvulus* has not been detected in the brains of individuals with Nodding syndrome (34). It has been proposed that initial parasitic infection instigates a secondary autoimmune reaction that perpetuates disease following host clearance of the pathogen. This para-infectious phenomenon has previously been described for viral infections including the development of an anti-NMDA receptor encephalitis in patients as a sequela of herpes simplex encephalitis (39). Autoantibodies against the actin filament nucleation factor leiomodin-1 are detectable in the CSF and sera of patients with Nodding syndrome (40). However, leiomodin-1 gene expression in the CNS is fairly non-specific and it includes the hippocampus which is devoid of tau

pathology in Nodding syndrome. Further efforts to isolate autoantibodies are likely necessary.

A case series by Hotterbeekx et al., (41) argues that inflammation drives the clinical manifestations of Nodding syndrome rather than tau-associated neurodegeneration given that microgliosis was invariably present across all cases of Nodding syndrome and onchocerciasis-associated epilepsy, with tau pathology seen in 80% and 50% of these cohorts, respectively. A separate case-control study found evidence of complement activation and elevated CRP levels in the CSF of long-standing cases of Nodding syndrome highlighting the importance of innate immune responses in this condition (42). Neuroinflammation may hold bimodal significance across the evolution of Nodding syndrome where it firstly drives epileptogenesis following parasitic infection then establishes chronicity in this epileptic state, and over time this chronic inflammation results in tau pathology. This is supported by both clinical and basic research findings that show seizures share a bidirectional connection with neuroinflammation (43). While plasma exchange and intravenous immunoglobulin therapy has shown no short-term clinical benefits in a small cohort of Nodding syndrome patients (44), there remains evidence to support longer-term targeting of chronic inflammation to limit tau-mediated effects in Nodding syndrome.

Subacute sclerosing panencephalitis

SSPE is a progressive neurodegenerative disorder that presents on average around 9.5 years after measles infection (5) with an incidence of 4-11 cases of SSPE per 100,000 cases of measles (5). It presents with initial changes in behaviour and

intellectual performance followed by alterations in motor function; most commonly generalised myoclonus.

Pathologically, early findings in SSPE include widespread inflammation and demyelination which correlate with subcortical and periventricular white matter changes seen on MRI (5). In the advanced stages, hyperphosphorylated tau accumulates in the form of NFTs (figure 2) and atrophy ensues. The most profoundly affected cortical region is the parieto-occipital cortex. Tangles are also found in the superficial layers of the limbic cortex and to a lesser extent the midbrain and brainstem (45).

Viral isolates from the brains of affected SSPE cases have revealed mutations that impact the fusion glycoprotein (F protein). As neurons do not typically express receptors for the measles virus, the consequence of these mutations in primary neuron cultures are enhanced membrane fusion and thus neuroinvasiveness (46). Recent basic research found that the SARS-CoV-2 S1 spike glycoprotein could facilitate the spread of tau via extracellular vesicles in vitro (47). In a similar manner, it is plausible that the neuroinvasive measles virus may expedite tau propagation rather than promote a chronic inflammatory environment that leads to de novo tau pathology.

In contrast, although still poorly understood in genetic terms (48), viral persistence may set in motion chronic inflammatory changes that ultimately result in tau pathology. A post-mortem study found that although antiviral treatment for diagnosed cases of SSPE did suppress measles viral titers, this did not prevent the

development of tauopathy in long disease durations which instead was considered to be a sequela of widespread inflammation as inferred by the non-overlapping distributions of phosphorylated tau and measles virus (45). Mouse models of tauopathy have shown that NF-κB activation drives tau seeding following their inoculation with exogenous tau (49). Interestingly, a case-control study found a genetic polymorphism in the *NOD1* gene to be protective against SSPE. This is further attributed to a reduced capacity for the nod-like receptor encoded by this gene to activate NF-κB signalling upon recognition of pathogen-associated molecular patterns (50). It is possible that in SSPE, long-term diffuse activation of NF-κB, and thus chronic inflammation, may underlie the development and spread of tauopathy in genetically-vulnerable individuals.

Alzheimer's disease

AD is characterised by the accumulation of extracellular plaques consisting of Aβ peptides and intracellular neuronal inclusions composed of hyperphosphorylated tau in the form of paired helical filaments (PHFs) and straight filaments (SFs) (51). Pathological tau filaments accumulate in the soma as NFTs, and around neuritic plaques (NPs) within dystrophic neurites (figure 2).

Clinically, early AD presents with a progressive impairment in episodic and topographical memory (52). Over time, other cognitive domains become affected resulting in visuospatial impairment, executive dysfunction, language disturbance, as well as changes in behaviour and mood (52). Although the exact aetiology of AD lacks detailed understanding, tauopathy is strongly associated with age. AD also has been linked to several modifiable risk factors including length of education, head

injury, air pollution, cardiovascular disease, diabetes, social and physical inertia (53). Midlife obesity has been posited as the most important modifiable risk factor (54) and it will prove interesting as to whether this relates to epigenetic reprogramming of innate immune cells as recently observed in mice with a history of obesity that became primed to elicit neuroinflammatory retinal changes (55).

AD dementia and vascular pathology frequently coexist (56), the latter characterised by cerebral hypoperfusion that is associated with neuroinflammation as discovered in murine studies (57). BBB disruption is a necessary but not sufficient event in AD pathophysiology, with endothelial dysfunction more profound in AD-relevant areas of the medial temporal lobe (MTL) and hippocampus in *APOE* ε4 carriers (58). This may make the CNS more amenable to modulation by the peripheral immune system thereby perpetuating inflammation.

The notion that infection, both bacterial and viral, is associated with the development of AD has recently gained attention. The Gram-negative anaerobe, P. gingivalis, synonymous with periodontal disease, has a number of intriguing associations with AD. Gingipains, trypsin-like cysteine proteases produced by this bacterium, have been detected in AD brains and correlate with tau load (59). Not only does P. gingivalis elicit a reactive increase in Aβ42 production in the murine brain which holds antimicrobial implications, in vitro gingipains were found to be capable of cleaving tau into pathological fragments associated with self-nucleation (59). Infections outside of the CNS that elicit chronic systemic inflammation such as chronic periodontitis, may result in long-term cross-talk between the adaptive and innate arms of the immune system, on both sides of a more permeable BBB (11).

Commensal bacteria of the gut too have been implicated in tau pathology, where transgenic mice prone to accumulating tau raised in sterile conditions developed significantly less tau-associated neurodegeneration with advancing age. This effect was reversed upon faecal transplantation from sex-matched mice raised in non-sterile conditions (60). The effects of microbiota manipulation on tau-associated neurodegeneration were both APOE isoform and sex-dependent and correlated with the peripheral cytokine response to bacterium-derived short chain fatty acids (60).

The most widely studied pathogen in relation to AD is HSV-1. HSV-1 has a range of clinical manifestations from the very rare, namely acute HSV-1 encephalitis (HSE), to the very common, specifically herpes labialis (cold sores). HSV-1 infection can also set in motion immunological phenomena that result in a loss of self-tolerance as exemplified by the development of an anti-NMDA receptor encephalitis following acute HSE (39). On a neuroanatomical level, after initial infection with HSV-1, the virus establishes latency in the trigeminal ganglion. It is from here that HSV-1 can reactivate, travelling anterograde to reach the nerve termini followed by the oral mucosa. The trigeminal ganglion is connected to the LC via reciprocal connections shared by the spinal trigeminal nucleus and LC. In 1982, Ball made reference to the limbic predilection of HSV-1 and suggested that retrograde reactivations are implicated in the pathogenesis of AD (61). Interestingly, the LC is one of the early regions vulnerable to accumulating tau, an event which may be related to localised inflammation incited upon viral reactivations to this region of the brainstem over time. Noradrenergic neurons of the LC may exert anti-inflammatory actions themselves in projection regions, especially the orbitofrontal cortex and MTL. Therefore, degeneration of these neurons could hold neuroinflammatory implications in AD.

HSV-1 is uniquely able to enter cells via heparin-sulfate proteoglycans (HSPGs). In particular, 3-O sulfated heparin-sulfate serves as a key receptor for neuroinvasive HSV-1 (62). Polymorphisms in genes encoding 3-O sulfotransferases could predispose individuals to central viral reactivations resulting in an increased risk of AD (20,63). Cellular uptake of tau has been shown to be significantly augmented by both the 6-OS (64,65) and 3-OS (66) moieties. Taken together, a marked increase in 3-O sulfated HSPGs may be conducive not only to propagation of pathological tau but also to the neuroinvasion of HSV-1, the latter, more overlooked, association would highlight a role for HSV-1 and inflammation in the aetiology of AD and requires further investigation.

The relationship between HSV-1 and tau might be best interpreted in the context of the neuropathological complications of chronic inflammation in genetically predisposed individuals. Epidemiological studies stratified by *APOE* genotype illustrated an association between HSV-1 infection and dementia (67). Although more data is needed, akin to data collected in MS patients in relation to EBV infection (68), these findings point to a genetic-environmental interplay with neuropathological changes following HSV-1 infection. In vitro, HSV-1 has been shown to induce the formation of hyperphosphorylated tau, amyloid plaques and elicit neuroinflammation in 3D silk porous scaffolds seeded by human-induced neural stem cells (69).

Clinical findings are also supportive of a role for systemic inflammation in AD. A large prospective cohort study found that raised markers of systemic inflammation in midlife are associated with a sharper decline in cognitive testing over a 20-year

period (70). Patients treated with anti-TNFα biologics for rheumatoid arthritis or psoriasis have a reduced likelihood of developing dementia according to a retrospective case-control study (71). Evidence also suggests cognitive decline is accelerated following systemic inflammatory events including delirium (11,72). Additionally, PET imaging studies targeting the 18 kDa translocator protein (TSPO) have illustrated that the temporal pattern of changes in microglia in the presence of Aβ is predictive of tau-spread and cognitive decline (73). The precise nature of these changes require further investigation given the emerging uncertainties of TSPO expression in humans being a by-product of microglial activation or increased density (74) [preprint].

In summary, a persistent neuroinflammatory state with crosstalk between central and peripheral immune compartments in susceptible individuals can result in tau-associated neurodegeneration and cognitive decline in AD.

Temporal lobe epilepsy with cognitive decline

Temporal lobe epilepsy (TLE) is a common form of focal epilepsy. In a study on surgically excised tissue, Tai et al., (75) identified NFTs, neuropil threads and pretangles of a 3R/4R isoform composition, with one subset of the cohort displaying neuropathology reminiscent of CTE and another exhibiting early AD-like tauopathy. Common to both were the unique neuropathological changes of mossy fibre axons of dentate granule cells (75) that could represent an epileptic tauopathy signature. A transcriptomic study of TLE brain tissue identified over-expression of MAPT associated with memory dysfunction (76). One hypothesis linking TLE to tauopathy is that focal seizures may accelerate tau spread as basic research has found that

hyperexcitability can augment the propagation of tau across functionally connected neurons (77,78).

As already explored in the context of Nodding syndrome, seizure activity and neuroinflammation are interlinked. Unique patterns of progressive cortical thinning in TLE and other epilepsy syndromes have been described through the ENIGMA consortium on MRI (79,80). Neuroimaging and gene expression data, supported by post-mortem analysis, showed elevated fractions of reactive microglia in regions of reduced cortical thickness (81). The same study also provided evidence of how depletion of microglia in a mouse model of acquired epilepsy limited cortical thinning highlighting the role of the innate immune system in epilepsy-related atrophy (81). Mouse models of TLE have also found that seizures result in the hyperphosphorylation of tau which is associated with the activation of astrocytes and microglia (3). Moreover, rodents subjected to status epilepticus exhibited glial activation accompanied by the long-term upregulation of inflammatory mediators. Treatment with anakinra, an IL-1R antagonist, reduced the frequency of seizures (82). Case studies mirror these findings as children with febrile infection-related epilepsy syndrome (FIRES), a condition associated with intractable seizures and medial temporal lobe atrophy, experienced a significant reduction in relapse rate when treated with anakinra (83). Finally, the expression of NLRP3 was upregulated in sclerosed hippocampi from patients with medial TLE (84) which was shown to be of significance to tauopathy in mice (12). Thus, treatment of neuroinflammation in certain epileptic disorders may not only ease the burden of seizures but reduce the likelihood of tauopathy as a complication of chronic disease.

Basal ganglia and brainstem tauopathies

Postencephalitic parkinsonism

Post-mortem analyses of postencephalitic parkinsonism (PEP) brains show severe depigmentation and atrophy of the substantia nigra and the LC with gliosis apparent in the basal ganglia and brainstem. Widespread, abnormally phosphorylated tau accumulation is the pathological signature of PEP and although it can also involve the neocortex, it is most concentrated within regions of the basal ganglia, brainstem, nucleus basalis, and the amygdaloid complex of the MTL. Subcortical neuropil threads and globose NFTs were shown to consist of SFs and PHFs immunopositive for both 3R and 4R isoforms of tau (figure 2) and also for TDP-43 (85,86).

Despite its links to the influenza epidemic of 1918, to date, no influenza virus RNA has been detected in the brains of patients with PEP (87). This does not however rule out involvement of the H1N1 influenza A virus as initial transient infections might instigate longer-term autoimmune-mediated pathology.

Accounting for hypersomnolence as a leading feature of EL, curiously, a molecular mimicry phenomenon is observed between the influenza nucleoprotein A and the human hypocretin receptor. This receptor's associated signalling pathway is implicated in the pathogenesis of narcolepsy (88). The incidence of narcolepsy increased following the 2009 H1N1 influenza A pandemic and was associated with the Pandemrix vaccine targeting this virus (88). Sera from Pandemrix-vaccinated individuals that went on to develop narcolepsy contained antibodies that cross-reacted with this viral nucleoprotein and the narcolepsy-associated hypocretin receptor in vitro (88). Another study involving 20 individuals with presentations

consistent with EL and PEP following streptococcal pharyngitis identified autoantibodies against basal ganglia antigens in 19 out of the 20 participants (89). Together, these studies highlight a possible role for autoimmunity in basal ganglia pathology in the post-infectious setting.

Further work will be needed to clarify the conjunction of autoimmunity and tauopathy in EL and PEP and to determine the role of chronic inflammation in connecting these two phenomena in this disease context.

Anti-IgLON5 disease

Anti-IgLON5 disease presents clinically as a progressive sleep disorder, with bulbar impairment, cognitive impairment, and gait instability (90). It is characterised by the presence of autoantibodies that target a neural cell adhesion molecule. An early diagnosis of anti-IgLON5 disease and prompt initiation of immunotherapy correlates with improved prognostic outcomes (91). There may be a role for B cell depleting therapies given the presence of IgG4 antibodies which respond best to these treatments (92).

Neuropathological examination of anti-IgLON5 post-mortem tissue revealed gliosis and neuronal aggregates of hyperphosphorylated tau in the tegmentum of the brainstem, hypothalamus, entorhinal cortex and hippocampus (6,93). These aggregates accumulated as NFTs, neuropil threads and pretangle tau composed of both 3R and 4R isoforms (6) (figure 2). Consistent glial fibrillary tau pathology or concomitant amyloid or TDP-43 pathology was not seen (6). Although there is

sparse evidence for inflammatory changes when examining post-mortem parenchymal tissue (6), CSF inflammatory changes are frequently reported (94).

A genetic predisposition has been reported in anti-IgLON5 disease with respect to both the HLA and MAPT loci. Specifically, HLA-DRB1*10:01 and DQB1*05:01 are more frequent in anti-IgLON5 disease than in the general population (95) and homozygosity for the H1 haplotype of MAPT, associated with greater risk of tauopathy, is roughly 57% more prevalent in diagnosed cases of anti-IgLON5 disease than controls (96).

The link between anti-IgLON5 autoantibodies and the formation of tau tangles is unclear but basic research conducted by Landa and colleagues (97) has yielded a testable hypothesis. Rat hippocampal neurons treated with patient-derived IgG anti-IgLON5 antibodies resulted in cytoskeletal alterations which could precipitate tau's detachment from microtubules. Although tau hyperphosphorylation was not documented in this study (97) it has been described following the treatment of human neural stem cells with IgG anti-IgLON5 antibodies which recapitulated these neuronal morphological alterations and thus implied neuroinflammation in this condition initiates tauopathy (98).

More research into understanding the aetiopathogenesis of anti-IgLON5 disease is needed, particularly regarding the inflammatory mechanisms associated with autoimmune reaction to IgLON5, the causative IgG subclass (91), and the wider association with tauopathy. In doing so, this rare condition may serve as a good initial basis for investigation of the broader implications of autoantibodies in

tauopathies with inflammatory associations. Overall, inflammatory processes associated with the generation of autoantibodies against neural cell adhesion molecules appear particularly potent in achieving tau-associated neurodegeneration.

Conclusions and future directions

In this Personal View, we have discussed a range of tauopathies each with their own associated risk factors including infection, autoimmunity, hypoxia, mTBI, and seizure activity (figure 3). We propose chronic inflammation, encompassing neuroinflammation and chronic systemic inflammation, to be a unifying theme. Whilst risk factors capable of inciting an inflammatory response are not sufficient alone to cause disease, an interplay between such risk factors and a genetically-predisposed immune system may tilt the balance in favour of disease.

Although beyond the scope of this Personal View, inflammation is also implicated in the development and progression of PD and Lewy Body Dementia (LBD) (99,100). Despite its exact immunomodulatory roles remaining ill-defined, it is of interest how *APOE* ε4 is also one of the major genetic loci that increases the risk of LBD (101). Inflammation would appear to be ubiquitous amongst neurodegenerative disorders pathologically characterised by the accumulation and spread of proteinaceous deposits. This Personal View highlights the merited inclusion of tauopathies in this category with numerous examples of how chronic inflammation may not only drive disease progression but also influence their development. Although **direct** links between inflammatory risk factors and tau pathology are not evident in all examples provided in this Personal View, the co-existence of chronic inflammation and tauopathy across multiple contexts suggest causality and necessitates follow-up

studies to delineate this. Similarly, a lot of the data highlighted in this Personal View is based on the anti-phospho-tau epitope, AT8. Whilst the presence of this epitope and thus phospho-tau accumulation does not lead to NFTs or full-blown disease, they represent necessary precursors. More studies will be required to assess the full extent of tau pathogenicity in this context.

An important question that needs to be addressed is how risk factors for chronic inflammation that seem to converge on a shared pathophysiological pathway can result in such a plethora of tauopathies. It is likely that a mixture of at least three factors determine the clinical entity: (1) genetic vulnerability of the patient, (2) tau-specific effects of the primary insult(s), and (3) the neuroanatomical affliction of the primary insult(s). The incidence for each of the respective tauopathies presumably increases with advancing age as a result of inflammaging and the chronicity of neuroinflammatory processes reaching a required threshold to set in motion a vicious cycle of neuroinflammation, tau aggregation, and tissue damage (figure 4).

Clinically, awareness of the risk factors associated with chronic neuroinflammation and tauopathy could allow for risk stratification for patients that may warrant longer-term follow-up following infection with certain neuroinvasive pathogens – a category which may extend to SARS-CoV-2 (102). Alternatively, a change in the neurological picture of patients with longer-term conditions associated with chronic inflammation may prompt consideration of further investigations for an underlying emerging tauopathy.

Future research should investigate the underlying inflammatory pathways associated with tau pathology and their relative contribution to the development and/or clinical progression across different tauopathies, which may vary. Regarding disease progression, chemical kinetic modelling of tau aggregation and spread in AD has inferred that from Braak stage III, tauopathy progression correlates more strongly with localised amplification rather than further spread of tau (103). Work that investigates whether this local replication of tau correlates with inflammation could prove informative. Moreover, the contribution of both the peripheral and central immune systems may differ depending on the stage of disease and remains an unaddressed high priority question. In order to probe these matters longitudinal studies will be imperative. Such studies should identify asymptomatic individuals genetically predisposed to common tauopathies like AD and measure the activity of the central and peripheral immune systems at regular intervals over time in health and disease. The development of non-TSPO PET ligands reflective of NLRP3 inflammasome activity may augment this type of research.

Barring retrospective studies, current data on anti-inflammatory treatment and tauopathy risk is relatively sparse (table 1). With a greater understanding of the role of chronic inflammation in tauopathies; whether this is more relevant to disease risk, progression, or both, and which facets of the immune system drive these pathological changes, a knowledge basis can be built which will aid the design of clinical trials that target inflammation in tauopathies. Ultimately, this may permit therapeutic approaches tailored to the disease stage with clinicians able to make evidence-based decisions on whether to pursue anti-tau or anti-inflammatory treatments for tauopathies.

Search strategy and selection criteria

References for this Personal View were identified by searches of PubMed and Google Scholar from Jan 1, 2018, to Jan 19, 2023, with no language restrictions. The keyword search items: “inflamm*” AND “tau”, “tauopath*” AND “neuroinflammation”, “tauopath*” AND “infection”, “inflammation” AND “chronic traumatic encephalopathy”, “inflammation” AND “nodding syndrome”, “inflammation” AND “SSPE”, “inflammation” AND “Alzheimer’s”, “Alzheimer’s” AND “HSV”, “inflammation” AND “anti-IgLON5”, “chronic traumatic encephalopathy”, “nodding syndrome”, “subacute sclerosing panencephalitis”, “epilepsy” AND “tau”, “post-encephalitic parkinsonism”, “ALS PDC Guam”, and “anti-iglon5” were used. Subject heading searching was also used in PubMed with a search for “inflammation” (MeSH) AND “tauopathies” (MeSH), “inflammation” (MeSH) AND “chronic traumatic encephalopathy” (MeSH), “inflammation” (MeSH) AND “Alzheimer’s disease” (MeSH), “inflammation” (MeSH) AND “temporal lobe epilepsy” (MeSH), and “inflammation” (MeSH) AND “IgLON5” (MeSH). Following these searches, references were prioritised on the basis of their title, abstract, and where appropriate the content of their full-text; specifically, we considered their originality and relevance to the context of this Personal View prior to excluding the unselected references. Additional references were extracted from the reference lists of select articles and our own files. Included are also landmark publications prior to 2018 that were deemed important for inclusion in this Personal View to provide context and benefit the understanding of the readership. The final reference list was generated on the basis of relevance to the scope of this Personal View.

Contributors

KD and CLG conceptualised the manuscript with contributions from all other authors. CLG conducted the literature research, with contributions from MT, and wrote the draft manuscript. Figure 1 was prepared by CLG. Figure 2 was prepared by CLG and contributed to by MT and ZJ. Figure 3 was created by SP. Figure 3 was created by CLG and SP. Table 1 was prepared by CLG. KD, MZ, HM, EJ, ZJ, AL, MT and JH critically reviewed, revised and contributed to the writing of the manuscript. All authors approved the final version of the manuscript including its overall content and organisation. All authors approved the final version of the table and figures.

Declaration of interests

MZ received an honorarium for a lecture to UCB Pharma in December 2019 and has received support for attending a European Academy of Neurology Encephalitis workshop meeting in April 2022. MZ receives salary support for research time from the UCL/UCLH NIHR BRC. HM is funded by grants from Parkinson's UK, the Michael J Fox Foundation, the PSP association, CBD solutions and the Drake Foundation. Unrelated to the current work HM receives consulting fees from Roche and Amylyx. HM has received personal lecture fees from Kyowa-Kirin, the BMJ, and the Movement Disorders Society. HM is a co-applicant on a patent application related to C9ORF72 – method for diagnosing a neurodegenerative disease (PCT/GB2012/052140). HM is on the advisory board for CurePSP Association, the Association of British Neurologists Movement Disorders Special Interest Group, and the Association of British Neurologists Neurogenetics Advisory Group, all of which are unrelated to this work. EJ has received research funding from the UK Medical Research Council, PSP Association and CurePSP. JH and KD receive support and grants from the UK DRI (MRC, AS, ARUK). JH also is a recipient of a grant from the Dolby foundation. JH and KD are consults for and hold stock options for Ceracuity Inc, a startup which has no drugs on the market. JH has received payment for lectures and consults for Eli Lilly, Eisai and Merck. KD is a recipient of grants from the NIH and Cure Alzheimer's fund. KD has received royalties or licenses from University South Florida, the Research foundation for mental hygiene and Rainwater charitable fund. KD has received payment from academic institutions for keynote/plenary talks. KD has patents relating to a PS/APP and hTau mouse models.

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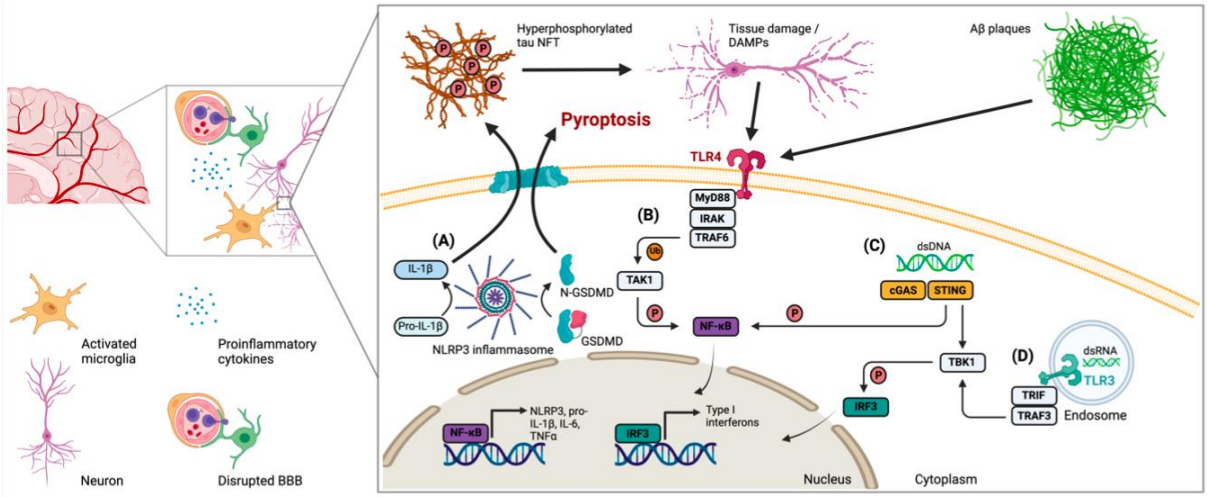

Figure 1: Neuroimmunology implicated in tau pathology

(A) Activation of the NLRP3 inflammasome is marked by the assembly of NLRP3, apoptosis-associated speck-like protein (ASC) and caspase-1, the latter of which is subsequently cleaved rendering it capable of carrying out its own protease function. Caspase-1 cleaves pro-IL-1β into IL-1β. IL-1β is capable of triggering the phosphorylation of tau in neighbouring neurons, an event which enhances its seeding capacity (12). Caspase-1 also frees the N-terminus of Gasdermin D (N-GSDMD) which can form pores in the plasma membrane that results in not only the release of cytokines but also pyroptosis, a form of cell death associated with inflammation. Non-canonical inflammasome activation can also result in pyroptosis via caspase-4 in neurons (13). (B) TLR4 is characteristically activated upon recognition of bacterial LPS, however TLR4 homodimers are also capable of recognising DAMPs and Aβ peptides. MyD88-dependent signalling downstream of activated TLR4 receptors ultimately leads to the nuclear translocation of NF-κB and the induction of proinflammatory cytokines as well as priming the NLRP3 inflammasome. (C) The presence of dsDNA in the cytosol is sensed and actioned by the cGAS-STING pathway that stimulates both NF-κB signalling and the induction of type I interferons via IRF3, the latter of which is also achieved via (D) TRIF-dependent signalling from endosomal compartments, typically as a result of TLR3 recognition of dsRNA. Created with BioRender.com.

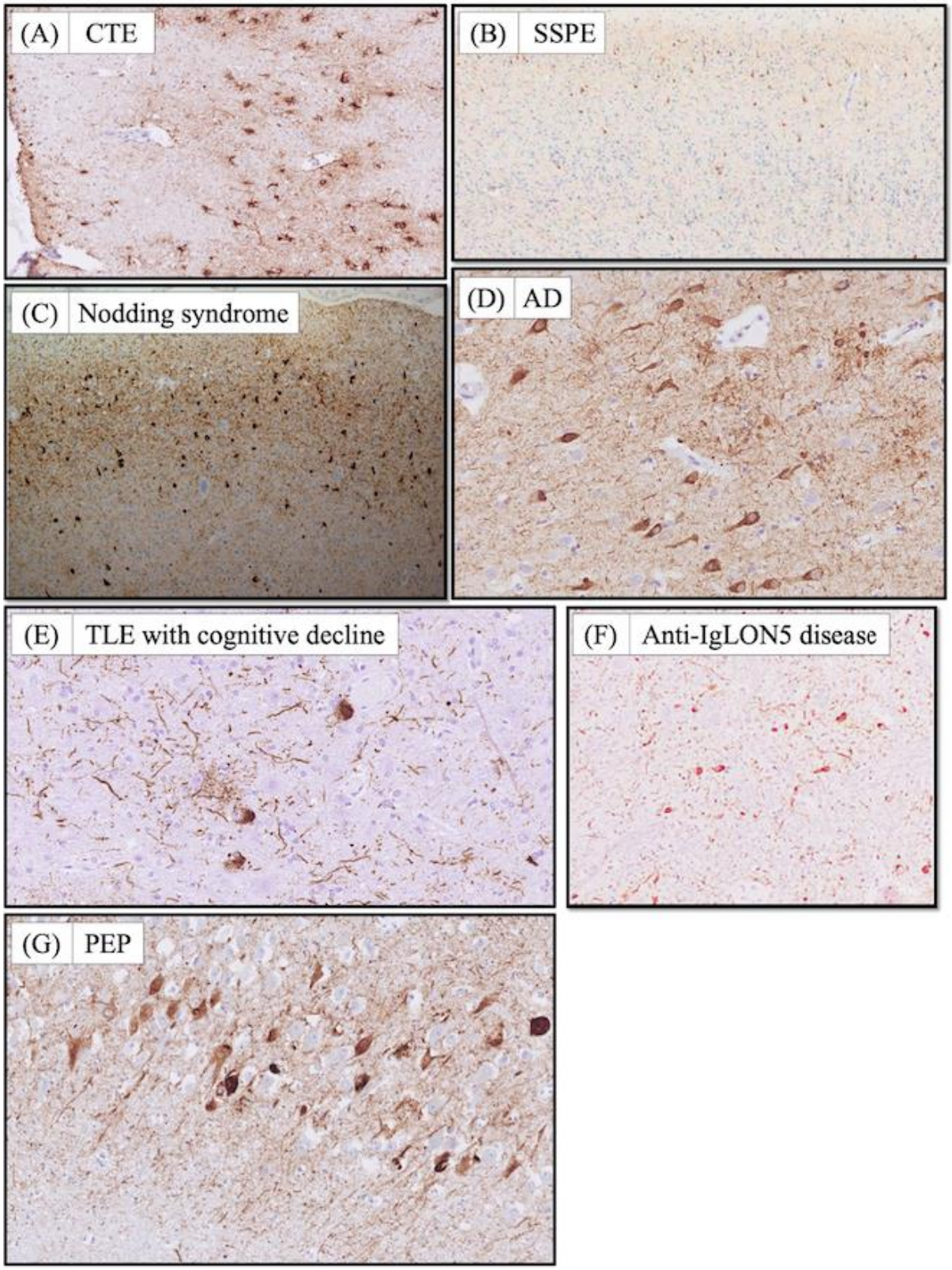

Figure 2: **select images of AT8 immunohistochemistry across a range of tauopathies each associated with chronic inflammation**. (A) AT8 immunopositive staining for tau NFTs at the depths of a cerebral sulcus in the frontal cortex in a case of CTE (scale bar: 250 μm) (unpublished data). (B) NFTs immunolabelled with AT8 widely present throughout the

cortex in SSPE, particularly apparent within the superficial layers closer towards the top of the image (scale bars: 500 μm and 50 μm) reproduced with permission from (45). License granted from RightsLink. © 2022 The Authors. Brain Pathology Published by John Wiley & Sons Ltd on behalf of International Society of Neuropathology. This image was adapted with permission to replace the original scale bar with that of a different font and labelled (top left). (C) AT8-positive staining for NFTs in the cerebral cortex of a confirmed case of Nodding syndrome (scale bar: 200 μm) reproduced with permission from (37). License granted from RightsLink; http://creativecommons.org/licenses/by/4.0. This image was adapted to replace the original scale bar with that of a different font and labelled (top left). (D) AT8 positive immunolabelling for tau NFTs in the hippocampus of AD post-mortem tissue (scale bar: 250 μm) (unpublished data). (E) AT8 immunopositive tau in dysmorphic neurons in focal epilepsy in a case with type IIB cortical dysplasia (scale bar: 100 μm) (unpublished data). (F) AT8-immunoreactive neuropil threads and NFTs in the nucleus ambiguus in anti-IgLON5 disease (93), reproduced with permission from Elsevier. (G) A case of PEP that revealed AT8 immunopositivity within the hippocampus, here shown is CA2 (scale bar: 250 μm) (unpublished data).

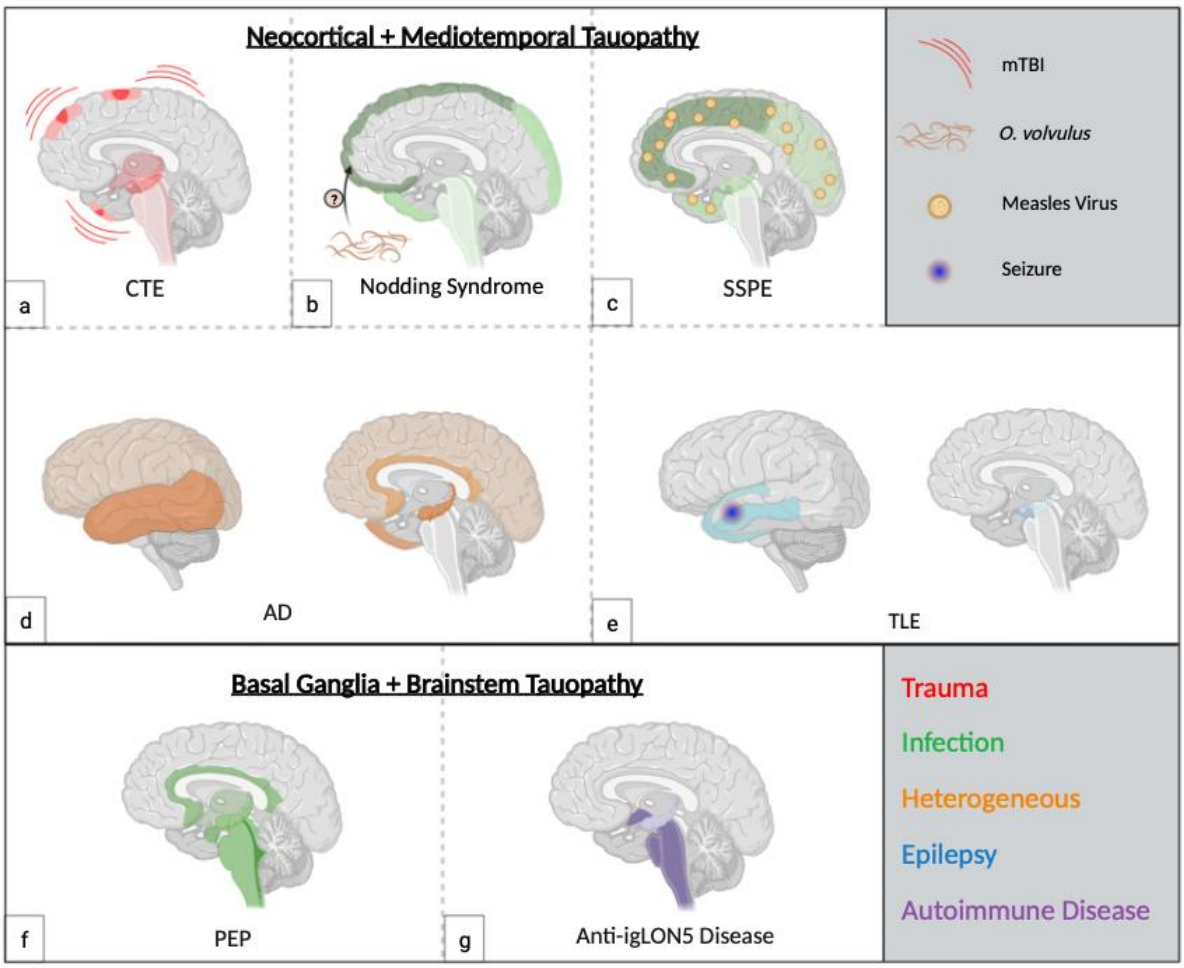

Figure 3: Anatomical representation of regions affected by pathological tau in different tauopathies and defined or possible causes for each disease. (A) CTE – associated with mTBI, tau pathology primarily affects superficial layers of the neocortex in early disease (B)

Nodding Syndrome – associated with parasitic infection. Tau pathology is seen in the superficial layers of the neocortex at the gyral crests are affected by tau pathology first, followed by the rest of the cortex and later brainstem involvement; (C) SSPE – a long-term sequlae of infection by the neuroinvasive measles virus, tau pathology is primarily found in the deep layers (II – V) of the frontal cortex, followed by other cortical regions and later hippocampal and brainstem involvement; (D) Alzheimer's Disease (AD) – a likely multifactorial aetiology – early stages of tau pathology are described in the transentorhinal region, perirhinal cortex and hippocampus with temporal involvement which later spreads to all other cortical regions; (E) temporal lobe epilepsy (TLE) – seizure activity has been linked to tau deposition, which has been described in the temporal lobe with a distinct pattern of subpial tau pathology, hippocampal tau pathology has been described, but in some cases it is not seen, which may be a result of neuronal loss following seizure activity; (F) Post-encephalitic parkinsonism (PEP) – associated with H1N1 viral infection, tau pathology is mainly concentrated within the basal ganglia, the brainstem, the nucleus basalis, and the amygdaloid complex; (G) Anti-IgLON5 disease – associated with autoantibodies, tau pathology is described in the brainstem, hypothalamus and the entorhinal cortex. Created with BioRender.com.

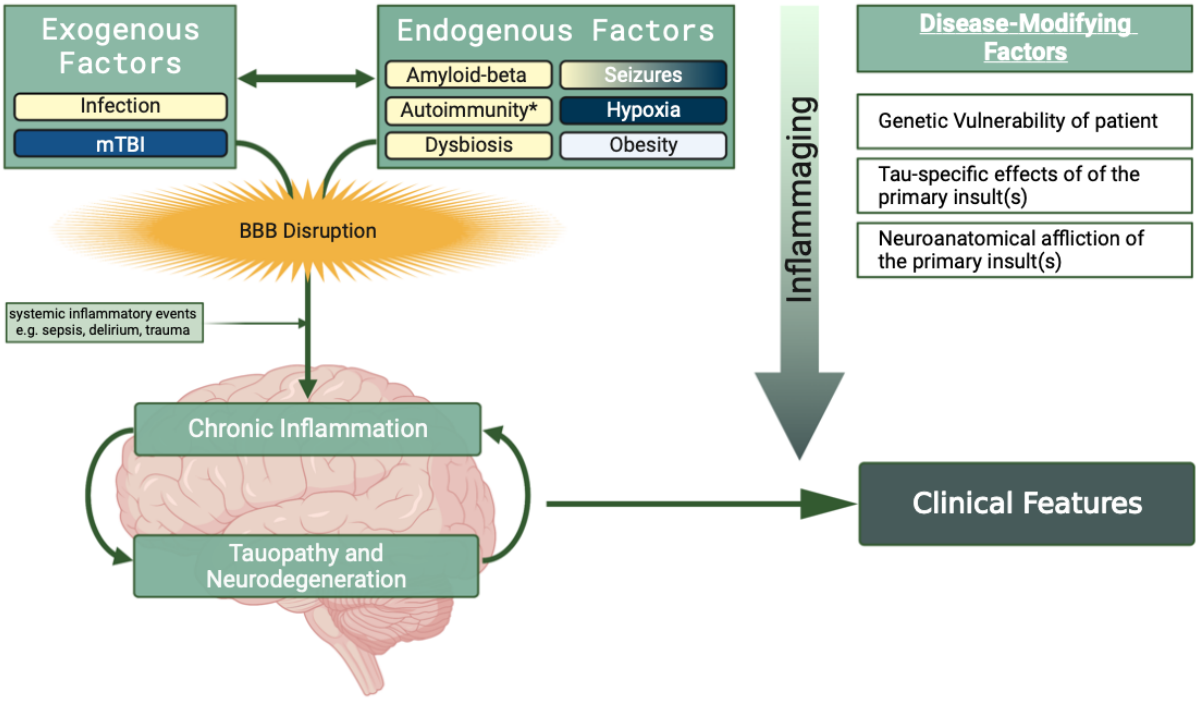

Figure 4: Chronic inflammation, a common pathway leading to tauopathy

Multiple risk factors are associated with both chronic inflammation; be that neuroinflammation and/or chronic systemic inflammation, and tau deposition. These risk factors can be exogenous or endogenous and are often interconnected (corresponding colours highlight risk factors that may be interconnected). BBB disruption is a necessary but not sufficient event in tauopathy aetiopathogenesis and may permit systemic inflammatory events (e.g. sepsis, delirium or trauma) to exacerbate neuroinflammation due to infiltration of

peripheral immune cells and pro-inflammatory cytokines, which will in turn modulate the activity of microglia and astrocytes. Although the triggers for tauopathy appear to converge onto a common pathway, these conditions vary in their neuroanatomical affliction and resulting clinical manifestations. It is likely that a mixture of at least three factors determine the clinical entity: (1) genetic vulnerability of the patient, (2) tau-specific effects of the primary insult(s), and (3) the neuroanatomical affliction of the primary insult(s). Overall, the incidence for each of the respective tauopathies presumably increases with advancing age as a result of inflammaging. *Autoantibodies can also give rise to specific neurological features. Created with BioRender.com.