



## **Review on Tauopathies: Clinicopathological Aspect**

**Sonaakshi Kushwaha <sup>a\*</sup> and Anil Wanjari <sup>b<sup>o</sup></sup>**

<sup>a</sup> *Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, India.*

<sup>b</sup> *Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, India.*

### **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2021/v33i60A34521

### **Open Peer Review History:**

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/79963>

**Review Article**

**Received 10 October 2021**  
**Accepted 19 December 2021**  
**Published 20 December 2021**

## **ABSTRACT**

A group of neurodegenerative diseases that differ in their morphology, biochemistry, and clinical presentation are Tauopathies. They are distinguished by aberrant tau protein accumulation in the brain. Currently, there is no conclusive method for preventing or curing tauopathies, but new scientific advancements have transformed this gloomy picture. Evidence from genetic research, experimental animal models, and molecular and cell biology has offered insight into the illnesses' underlying causes. Advances in radiology and biochemistry, notably in PET imaging, may offer critical biomarkers for clinical diagnosis and therapy. Tau, in addition to its role as a microtubule-associated tau protein, is involved in gene regulation, signal transduction, and metabolism. Experimental models allow for the development of novel diagnostic and treatment methods. Tauopathies are a set of disorders that can present with a wide range of clinical signs. It is still difficult to distinguish this disease from other protein-pathologies. In the last year, there has been a lot of interest in cerebrospinal fluid biomarkers and radiotracers. Although the accuracy of diagnosis in non-disease Alzheimer's tauopathies remains debatable, PET tau tracers may be utilised to identify disease process. Although primary tauopathies are uncommon and diverse conditions, their combined incidence, as well as the importance of tau malfunction in Alzheimer's disease and secondary tauopathies, make tauopathy research a top priority since it might assist many people.

<sup>≡</sup> Final MBBS;

<sup>o</sup> Professor;

\*Corresponding author: E-mail: [sonaakshirox@gmail.com](mailto:sonaakshirox@gmail.com);

*Keywords: Alzheimer's disease; secondary; tauopathies; neurodegenerative disorders.*

## 1. INTRODUCTION

The build-up of insoluble protein in neuromuscular system cells distinguishes the majority of neurodegenerative diseases. Because of developments in molecular neuropathology, neurodegenerative disorders may now be classified based on protein accumulation. Micro-tubule linked tau is a protein that plays significant activities in normal neurons but forms insoluble deposits in tauopathies. [1]

Tauopathies are a kind of neurodegenerative illness that is distinguished by the presence of micro-tubule binding protein tau inclusions in neurons and/or glia. Several lines of evidence indicate that tau accumulation plays an important role in the degenerative process in tauopathies [2]. To begin, animal and cell model studies show that badly altered tau may be transported between neighbouring neurons and spread to physically connected brain areas, mirroring human disease.

The accumulation of pathologically unfolded proteins tau is an element shared by a class of neurodegenerative disorders called as tauopathies, the most common being Alzheimer's disease (AD). Tauopathies (DLB) consists of progressive supranuclear palsy (PSP), cortico-basal syndrome (CBS), Down's syndrome (DS), Parkinson's disease (PD), and dementia with Lewy bodies.

Protein wrong folding and aggregation in the brain is a quality shared by a number of neurodegenerative diseases, includes those characterised on aberrant tau build-up. Because of their overlapping clinical manifestations, many tauopathies are challenging to diagnose clinically, especially early in the symptomatic phase. However, the development of tau-specific ligands for use with Positron emission tomography (PET) as allowed researchers to study tau deposition in the initial phases of various neurodegenerative diseases including Alzheimer's disease, Progressive Supranuclear Palsy, Cortico-basal Degeneration, and related conditions such as Down's syndrome, Parkinson's disease, and Dementia with Lewy bodies [3].

Some clinical trials on tau and micro-tubule impairment had been conducted, but none had resulted in disease change. Comprehending tau biology is very important for the progress of

disease-modifying pharmaceutical therapies in primary tauopathies [4].

This review examines the utmost predominant tauopathies and the molecular and pathological characteristics that support the system of classification.

## 2. TAU BIOLOGY

Gene for tau, which may be present on chromosome 17q21, encodes Tau. Tau is a micro-tubule linked protein which aids in microtubule stability and aggregation. Microtubules are necessary for neurotransmission as well as cell structural stability. Tau is found in older brain neurons, namely axons. Tau can also be present in oligodendrocytes and astrocytes, where it functions similarly to neurons. The tau sequence of a protein is separated into four sections: terminal-N domain, being rich in proline, a domain having microtubule, and a terminal-C domain. The terminal-N domain is needed to provide space between microtubules. Cell signalling and protein kinase interactions need the proline-rich domain. The presence of domain having microtubule is required for microtubule binding. The terminal-C domain is essential for controlling polymerization of microtubule. Tau's ability in attaching to microtubules is critical. In reality, binding can cause a modification in tau conformation. Tau is generally expanded and phosphorylation, but in the brain of individual having primary tauopathies, it is hyperphosphorylated and clustered tau with beta pleated like sheet shape. Tau hyperphosphorylation is considered to result in a dearth of tau contact with micro-tubules, resulting in micro-tubule malfunction, decreased axonal transport, and tau fibrillarization [4]. Although tau with three and four repeated binding domains was found in equal amounts in the healthy human brain, a few predominant tauopathies were distinguished via a majority of isoforms with four repetitive binding domains (4R tauopathies), others via higher prevalence of isoforms with 3 successive binding domains (3R tauopathies), and still others via a roughly equivalent mixture of isoforms with three & four replicated associated proteins (3R + 4R tauopathies).

### 2.1 Tau Deposits

Tau is a naturally unfolded phosphoprotein involved in microtubule stabilisation, consisting of

six isoforms categorised in 2 functional varieties depending on frequency of repetitions of the micro-tubule binding domain 3R or 4R. It is usually phosphorylated, but hyperphosphorylation can reduce its attachment to micro-tubules while increasing levels of cytosol; hyperphosphorylated tau assembles into protofibrils after moving from axonal to somatodendritic compartments. On the basis of absence or frequency of twists, these assemblies can be characterised into straight, twisted, or paired helical filaments (PHF); they are found in neurons, astrocytes, and oligodendroglia[3]. Depending on isoform preponderance and post-translational modifications, tau collections may have a variety of morphological polymorphisms. Although, processes producing tau disease are unclear, experimental data shows that abnormal activities of kinase and phosphatase & chronic cerebral hypoperfusion, are involved, contribute to tau hyperphosphorylation; When a protein is hyperphosphorylated, it loses the capacity to attach to microtubules, consequently increasing the discharge of soluble molecules of tau. Translocation of these varieties across cellular structures were demonstrated to happen through both synapse and nonsynaptic mechanisms, resulting in implantation and tau accumulation in recipient cells. The development of tau disease, on the other hand, is considered to follow distinct spatiotemporal patterns [3].

## 2.2 Clinical Features

A notable family of neurodegenerative disorders called as tauopathies were recognised at autopsy by inclusions intracellularly formed by improperly mutated micro-tubule binding protein, tau. Primary tauopathies are important category of Fronto-temporal Lobar Degeneration (FTLD) neuropathology (or FTLD-Tau) and may show clinically through a variety of Frontotemporal Degeneration (FTD) clinical syndromes (or behavioural-variant FTD, bvFTD; primary progressive aphasia, PPA, besides atypical Parkinsonian syndromes resistant to dopamine with prominent progressive supranuclear palsy syndrome(PSPS); cortico-basal syndrome (CBS) [2].

Appearance of numerous neurofibrillary lesions formed by aberrant & hyperphosphorylated micro-tubule linked protein tau is important characteristic neuropathological finding of Alzheimer's disease. Filamentous deposits consisting of tau present in neurons or glial cells

or both, however, are linked with a broad spectrum of neurodegenerative diseases characterised clinically by dementia and/or motor impairments. As a result, all of these disorders are collectively known as tauopathies. This article discusses the structural and bio-chemical features of several important tauopathies, containing Alzheimer's disease, Pick's disease, PSP, cortico-basal degeneration, and Tauopathy Argrophilic-Grain disease (AGD). The other portion would go through latest discoveries transmutations of tau gene in fronto-temporal dementia and parkinsonism associated with 17<sup>th</sup> chromosome, demonstrating that tau impairment may result in degeneration of neurons [5]. Lastly, we shall consider the recent discovery of tau deficient tauopathy in subdivision of individuals with fronto-temporal dementia.

## 3. DISEASES CONSIDERED PRIMARY TAUOPATHIES

Recognizing a profile, or a group of symptoms, indications, has proven to be more useful in predicting an underlying tauopathy than recognising a single sign or symptom. A syndrome is described as a profile or group of indications and presentations. As a result, we have learned to rely on in the absence of a particular biomarker, detecting different symptoms that are highly symptomatic of a tauopathy to best predict an underlying tauopathy [4].

### 3.1 Cortico-basal Syndrome

This syndrome is a disorder linked to an underlying tauopathy, although it's possible that it's the bare minimum to fundamental primary tauopathy. The occurrence of asymmetric clinical features in the cortico-basal syndrome reflects a combo of sub-cortical (basal ganglion) and dysfunction of cortex. Cortical impairment can be seen as foreign limb phenomena (individual loses handling of a limb), which has been linked to sensory motor cortex and associates. Individuals can at times humanize their limb, referring to it as "my little friend". Other common symptom includes existence of apraxia of limb, indicating that the individual could be unable to finish a job that was earlier completed without motor weakness. A patient who has used a screw driver for decades, for example, may forget how to operate it. Some people may experience undesirable actions of different parts of the body (such as opening and shutting lips while doing opposite hand motions), as well as

sensory loss of cortex and agraphesthesia (struggle appreciating a digit or an alphabet that is drawn on the palm of hand).[4] Dystonia and myoclonus (rapid uncontrollable movements) may occur (nonstandard posture). Asymmetry of the limbs and/or akinesia (slower movement speed) must also be present, with no significant or consistent improvement following levodopa delivery. While not always present, frontal and temporal lobe cortical dysfunction might emerge as decision-making impairment, behavioural or behavioural disorders, or aphasia (language disability).

### 3.2 Primary Progressive Speech Apraxia

A slow beginning and sustained development of symptoms characterises primary progressive apraxia of speech. The important signs and symptoms are gradual, forceful speech, sometimes accompanied by trouble in uttering words, subsequently producing distorted speech or replacement of regular speech with distorted speech, or output of speech with prolonged inter-segment intervals between syllables, words, or expressions. It is unusual to notice groping actions of the tongue and mouth, as well as several efforts to make the desired sounds. There are two types of primary progressive speech apraxia at the moment: a phonetic form with articulative faults (Type 1) and prosodic form with slower speech production (Type 2) [4].

### 3.3 Richardson's Syndrome

Richardson's syndrome is the commonest presenting sign of progressive supranuclear palsy, and thus a primary tauopathy. It is characteristic of progressive start and worsening of gait and balance problems, which lead to unexplainable falls. Other symptoms of Richardson's syndrome include delicacy to vivid light, confusion, loud hoarse voice, rigidity of neck, uncommon expression of face having lifted eye brows, and overall movement slowdown. Patients can be seen being indifferent or uninterested in others around them. There is no resting tremor or memory loss, conflicting a diagnosis of Parkinson's or Alzheimer's disease. A brain scan demonstrates executive dysfunction (disorganisation and poor planning) as well as a symmetric akinetic stiff state. There is a loss of postural reflexes, axial stiffness (neck and trunk rigidity), and a loss or slowing of vertical eye movements in response to commands, but the dolls eye manoeuvre preserves comparable eye movements. Treatment with high doses of

carbidopa/levodopa (> 600mg) and related medications is often unsuccessful, with no clinically discernible improvement [4].

### 3.4 Age Related Primary Tauopathy and Alzheimer's Disease: 3/4R Tauopathy

AD is classified as a non-primary or secondary tauopathy because its characterised by both a extracellular plaques and inside cell neurofibrillary tangles consisting of equal parts of 4R and 3R tau. Indeed, in post-mortem investigations of normal people, pre-tangle inclusions in subcortical locations and broad cortical projections, like the locus coeruleus, are observed in a large no. of participants under the age of 30. Furthermore, no in presence of significant a plaque pathology, neurofibrillary tangle pathology can emerge, which is biochemically indistinguishable from Alzheimer's disease and is majorly localised to the medial temporal lobe.[6] This clinical finding was previously called as (TPSD) tangle-predominant senile dementia, but it has now been renamed primary age related tauopathy (PART). Some argue that tau and AB neuropathology coexist like hippocampus tau neurofibrillary pathology in the absenteeism of pathology of cortex is different from AD, while others argue tau neuropathology in PART is a separate entity from AD. A plaque is indistinguishable from the pathophysiological process of Alzheimer's disease. As a result, the distinctions between AD, PART, and normal ageing remain ambiguous.

### 3.5 MAPT Mutation with FTLT-Tau

Tauopathy (FTLD-Tau with MAPT mutation) is caused by around forty pathogenic transmutations in the MAPT tau-gene (chromosome seventeen). MAPT pathogenic mutations are hypothesised to cause illness by limiting tau's normal microtubule-binding ability, increasing tau protein aggregation, or changing exon ten splicing, resulting in 3R/4R tau isoform imbalances . Consequently, particular neuropathological discoveries (such as predominance of tau isoform, inclusion morphology or ultrastructure) differ depending on transmutation, but consisting of inclusions of neuron and glial tau as well as neuro-degeneration all over the central nervous system, having preference for limbic structures along with frontal and temporal neocortex. Individuals having ThS deficiency predominate, and individuals with pathology of tau 4R are ac-K280 reactive. FTLT-Tau with

MAPT transmutations can produce behavioural FTD and/or language impairments (primary progressive aphasia; PPA), as well as extrapyramidal symptoms (Parkinsonism) [6]. In most cases, largely mutations are inherited autosomal dominant, with a great degree of penetrance. The age at which sickness begins varies depending on the individual mutation, but in general, illness begins from 45-65 years of age, with a broad range of period of disease (averaging 10years); nonetheless, instances in the 2<sup>nd</sup> and 3<sup>rd</sup> decades, as well as the 8<sup>th</sup> decade, may occur.

### **3.6 Progressive Supranuclear Palsy : 4R Tauopathy**

PSP is characterised by globose tau inclusions in neurons in the brainstem and subcortical areas, as well as glial "tufted astrocytes," neuronal tangles, and oligodendrocytic "coiled bodies" in the neocortical white matter. Tau illness mostly affects the brainstem, subthalamic nucleus, and dentate nucleus of the cerebellum. Thioflavin-S has weak response to PSP tau pathology. PSPS, an age related atypical Parkinsonian sickness characteristic of substantial axial stiffness and reduced responsiveness to treatment from dopamine, is most prevalent medical presentation. It is highly specific for underlying PSP tauopathy, particularly supranuclear gaze weakness and early postural instability or falls; still it is not susceptible enough to identify each case of PSP neuro-pathology, including those having characteristics of uncommon variety of PPA, cortico-basal syndrome. Furthermore, cognitive and behavioural aspects of PSPS are becoming more recognised, and they can appear at any stage throughout the disease's progression. Even though most of PSP were sporadic, uncommon MAPT mutations may cause neuropathological symptoms that are indistinguishable from sporadic PSP. Further investigation of these and other genetic risk factors will aid in elucidating disease cellular processes [6].

### **3.7 Argyrophilic Grain Disease : 4R Tauopathy**

Tauopathy Argyrophilic-Grain disease(AGD) is a characteristic of spindle-shaped "grains" with 4R-tau predominance in the amygdala and hippocampus . Grains are often ThS+ve and there is reaction with argyrophilic Gallyas silver stain and ac-K280. There are also pre-tangle

inclusion bodies of tau in the cornu-ammonis of the hippocampus, "coiled-bodies" in white area, and "ballooned neurons" in the region of amygdala. The alterations get frequently associated with tau neuro-fibrillary tangles, which are bio-chemically identical to those seen in AD. Grain & tau illnesses were more frequent in neocortex than in the cortex. Because AGD is seen on post-mortem in delayed onset amnesic syndromes and, uncommonly, FTD spectrum illnesses, no one clinical condition can predict AGD; nevertheless, large-scale clinicopathological data are absent [6].

### **3.8 Cortico-basal Degeneration: 4R Tauopathies**

The substantial clinicopathological overlap between Parkinson's disease and cortico-basal degeneration. 4-R tauopathy is illustrated by enormous tau+ve diffuse "astrocytic-plaques" and "ballooned-neurons" in limbic & neocortical grey area. CBD has also been associated to an increase in the number of tau+ve "coiled-bodies" and astrocyte like inclusion bodies of tau in white area. Brainstem and basal ganglia also exhibit significant inclusion loads , and the structure can be difficult to differentiate from Progressive Supranuclear Palsy. Asymmetric and peri-rolandic gross atrophy is common. Although CBD tauopathy is not ThS reactive, it is ac-K280 reactive. We use the expression "Cortico-basal Degeneration" to explain the clinical presentation of asymmetric Parkinsonism, apraxia, disability of executive and parietal lobe that is now called as (CBS) cortico-basal syndrome . The alteration in terminology got prompted by conclusions from extensive post-mortem studies in CBS, which revealed less than half of CBD neuropathology of CBS patients at autopsy; CBS can also be caused by a variety of other causal neuropathology, which includes AD and, occasionally, TDP-43 proteinopathy and PSP. . Because CBS has a low specificity for CBD neuropathology, contemporary clinical research criteria for CBS have been devised, and authentication of these standards are ongoing to better ante mortem diagnosis of tauopathy of CBD. CBS is a significant medical diagnostic problem since patients can report to movement disorder or cognitive specialists with a mix of extrapyramidal and higher cortical processing abnormalities [6]. Unproven ecological risk factors for CBD, and epidemiologic influence on the disorder's frequency is scarce. CBD was linked to PSP genetic risk, especially the haplotype H1 in MAPT.

### 3.9 4R Tauopathy : Globular Glial Tauopathies

There have been several reports suggesting oligodendrocytes are dominated by inclusions of 4R Taus, along with star like punctate astrocytic inclusions of Tau imitating progressive supranuclear palsy-linked tufted astrocytes, according to the literature. The regional distribution of GGIs, as well as the neuronal loss and atrophy that results, varies from substantial, involvement of Fronto-temporal region along with extensive degeneration of white matter to the degeneration of motor cortex and corticospinal tract, individuals demonstrating either types of local sensitivity. This kind of severe oligodendrocytic tauopathy is now known as globular-glial tauopathies (GGT) and patients may come with bvFTD, pyramidal motor impairment, or a mixture of both [7-10].

### 3.10 Pick's Disease : 3R Tauopathy

Tauopathy Pick's disease (PiD) is a characterised by intraneuronal tau-positive "Pick bodies" and glial inclusions have been discovered in the limbic and neocortical areas. The sickness is most commonly seen in the frontotemporal neocortex, although it can also be found in basal ganglion and white area. The ThS reactivity of pick bodies is minimal. PiD pathology of neurons is most commonly linked with the clinical symptoms of bvFTD, although it can also be linked with different types of PPA and CBS. Because of the limited specificity of the bvFTD in diagnosis of PiD tauopathy, the name "Pick's Disease" is being exclusively used to refer to the neuropathological diagnosis of 3R tauopathy having "Pick body" inclusions above, which is equivalent to aforementioned bvFTD clinical diagnostic CBD nomenclature changes. Indeed, numerous tauopathies (e.g., PSP, CBD, AGD) may be identified at autopsy in bvFTD patients, with TDP-43 proteinopathy being the most common. Furthermore, only a small percentage of bvFTD patients develop neuropathology AD at autopsy. As a result, further work is needed to develop the bvFTD social compartment problem in order to better discover PiD and other tauopathies. Autopsies of various types of PPA reveal different rates of causal tauopathies; naPPA is typically caused by tauopathies (e.g., CBD, PSP), whereas semantic type of PPA (svPPA) is predominantly caused by TDP-43 proteinopathies, albeit those connections were not definite. Extrapyrimal symptoms in bvFTD/PPA, such as PSPS or CBS, may

indicate an underlying tauopathy. Thus, in In FTD clinical syndromes, there is a convoluted connection between clinical phenotype and underlying neuropathology [11-13].

## 4. CONCLUSIONS

With mounting evidence that tau aggregation, misfolding, and propagation play major roles in tauopathies disease development, many current therapeutic research efforts are aimed at decreasing pathogenic tau transmission within the CNS. Unable to identify tauopathies before death is a significant limitation for the use of such drugs, as autopsy is the gold standard for diagnosis. For understanding the linkages between ageing, AD, and PART, the novel tauopathies-specific biomarkers will be highly useful.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Williams DR. Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. *Intern Med J.* 2006 Oct;36(10):652–60.
2. Delenclos M, Jones DR, McLean PJ, Uitti RJ. Biomarkers in Parkinson's disease: Advances and strategies. *Parkinsonism Relat Disord.* 2016 Jan;22(Suppl 1):S106–10.
3. Leuzy A, Chiotis K, Lemoine L, Gillberg P-G, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies-still a challenge. *Mol Psychiatry.* 2019 Aug;24(8):1112–34.
4. Josephs KA. Current Understanding of Neurodegenerative Diseases Associated With the Protein Tau. *Mayo Clin Proc.* 2017 Aug;92(8):1291–303.
5. Tolnay M, Probst A. The neuropathological spectrum of neurodegenerative

- tauopathies. IUBMB Life. 2003 Jun;55(6):299–305.
6. Irwin DJ. Tauopathies as Clinicopathological Entities. *Parkinsonism Relat Disord.* 2016 Jan;22(01):S29–33.
  7. Sukhdeve N, Singh S. Assess the effectiveness of planned teaching on knowledge regarding early warning signs and management of Alzheimer's disease among care givers of elderly client.
  8. Jiwode U, Chakole S, Bhatt N. Alzheimer's Disease: History, Stages, Diagnosis and Its Future. *Journal of Pharmaceutical Research International.* 2021;33(39A):41–5.
  9. Acharya S, Shukla S, Andhale A, Annadatha A, Gupte Y. Neuroleptic Malignant Syndrome (NMS) after Treatment with Metoclopramide--A Rare Case Report. *Journal of Evolution of Medical and Dental Sciences.* 2020 Oct 12;9(41):3065-7. Available: <https://doi.org/10.14260/jemds/2020/671>.
  10. Andhale A, Acharya S, Shukla S. Primary systemic amyloidosis with peripheral and autonomic neuropathy presenting as recurrent presyncope: A case report. *Medical Science.* 2020; 24(104): 1818-21.
  11. Behere PB, Behere AP, Chowdhury D. Rise in cases of alcohol withdrawal following lockdown in dry district of Wardha. *Journal of neurosciences in rural practice.* 2020 Jul;11(03):478-80. Available: <https://doi.org/10.1055/s-0040-1712554>.
  12. Kovacs GG. Tauopathies. *Handbook of clinical neurology.* 2018 Jan 1;145:355-68.
  13. Novak P, Zilka N, Zilkova M, Kovacech B, Skrabana R, Ondrus M, Fialova L, Kontsekova E, Otto M, Novak M. AADvac1, an active immunotherapy for Alzheimer's disease and non Alzheimer Tauopathies: an overview of preclinical and clinical development. *The journal of prevention of Alzheimer's disease.* 2019 Jan;6(1):63-9.

© 2021 Kushwaha and Wanjari; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*

*The peer review history for this paper can be accessed here:*  
<https://www.sdiarticle5.com/review-history/79963>