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REVIEW ON SUPERNUCLEAR PALSY DISORDER

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ABSTRACT

In recent years, anunusual syndrome of supranuclear palsy disorder, milddementia was described. The substrates of the new clinicopathologic entity of Progressive Supranuclear Palsy (PSP), also known as Steele-Richardson-Olszewski syndrome. Tau-immunoreactive tufted astrocytes are the pathognomonic histological feature. PSP-tau is comprised predominantly of 4-repeat tau. High frequency of concomitant pathologies such as Alzheimer disease and argyrophilic grains in PSP may partly contribute to the clinical heterogeneity. It produces an akinetic-rigid form of parkinsonism characterized by early falls and abnormalities of extraocular movements. We also discuss useful imaging tools and review various management strategies. Clumps of tau are also characteristic of other neurodegenerative disorders, such as Alzheimer's disease. Rarely, progressive supranuclear palsy occurs within a family. Mean age of onset is approximately 63 years, and mean survival from symptom onset is 9 years. Women are less affected of PSP as compare to Men. It frequently much more found in men. Progressive Supranuclear Palsy (PSP) is an akinetic- rigid form of Parkinson Syndrome. We reviewed medical records of 16 patients with PSP identified. Neuroimaging in patients with PSP by computed tomography (CT) and MRI have shown atrophy and signal increase in the midbrain. The only proven risk factor for supranuclear palsy is age. Conventional structural brain MRI can helpon the differentiationbetween PSP and PD, and other atypical parkinsonian subtypes. A genetic variation in or near the tau gene on chromosome 17 appears to be associated with an increased risk of developing PSP. The Risk factor are only proven by age for PSP.

KEYWORDS: Supranuclear Palsy Disorder, Alzheimer disease, Parkinson Syndrome, MRI, Age, Risk factor, SPECT imaging.

INTRODUCTION

In 1964, an unusual syndrome of supranuclear gaze palsy, progressive axial rigidity, pseudobulbar palsy and mild dementia was described.[1] In this seminal paper, extensive subcortical neurofibrillary degeneration predominantly found in the globus pallidus, subthalamic nucleus, substantia nigra and cerebellar dentate nucleus were characterized as the pathological substrates of the new clinicopathologic entity of Progressive Supranuclear Palsy (PSP), also known as Steele-Richardson-Olszewski syndrome. Steele predicted that 'clinical variants of the syndrome are likely to occur as the disease affects different nuclei at different times and to different degrees'. Since then, increasing recognition of phenotypic heterogeneity has been linked to the regional severity of abnormal tau accumulation and neuronal loss, although all PSP regardless of clinical variants share similar neuropathologic features and fulfill the neuropathologic criteria for PSP.[4] In most cases, the evaluation of histological findings cannot lead to deduction of the clinical phenotype due to significant overlap in regional pathologies. Tau-immunoreactive tufted astrocytes are the pathognomonic histological feature, commonly observed in the precentral gyrus, striatum, superior colliculus, thalamus, subthalamic nucleus and red nucleus. Globose neurofibrillary tangles (NFTs) in the brain stem nuclei, flame shaped NFTs, coiled bodies, neuronal loss and gliosis are other accompanying findings. PSP-tau is comprised predominantly of 4-repeat tau. High frequency of concomitant pathologies such as Alzheimer disease and argyrophilic grains in PSP may partly contribute to the clinical heterogeneity.[6] Progressive supranuclear palsy (PSP) is a degenerative condition of unknown an etiologythat produces an akinetic-rigid form of parkinsonism characterized by early falls and abnormalities of extraocular movements. Mean age of onset is approximately 63 years, and mean survival from symptom onset is 9 years. Men are much more frequently affected than women.

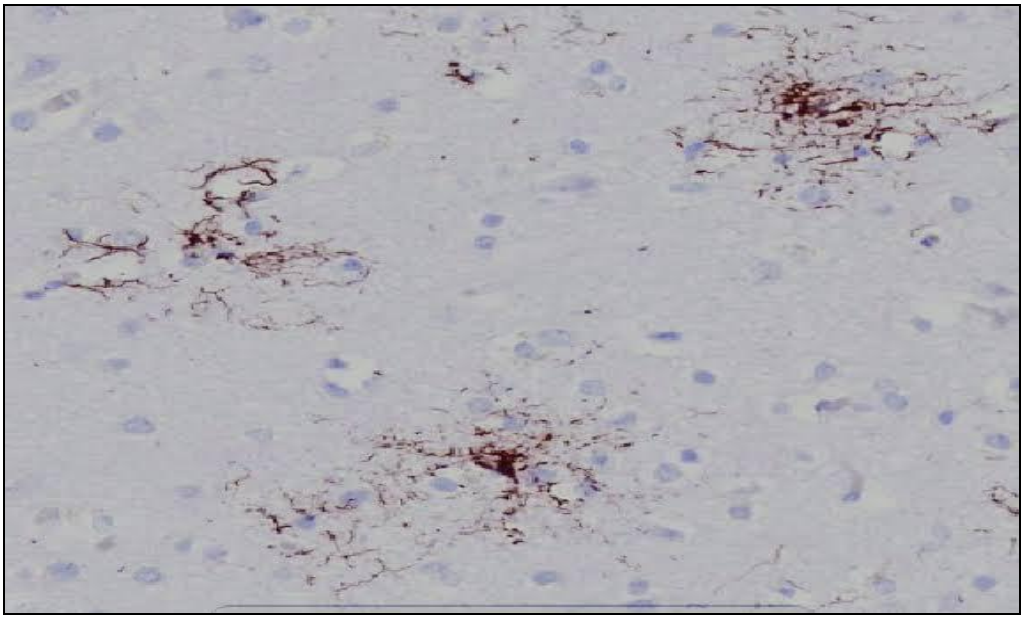


Fig 1: Tau immunohistochemistry using anti-tau (AT8) antibody tufted astrocytes in the frontal cortex of a case with pathologically confirmed PSP.

Progressive Supranuclear Palsy (PSP) is a Parkinson-plus syndrome associated with a variety of different clinical presentations. We describe the clinical and pathological features of the 7 major phenotypes of PSP in addition to new information about the genetic causes of PSP. We also discuss useful imaging tools and review various management strategies. The classic form of PSP (PSP-Richardson syndrome) is more likely to be associated with postural instability, vertical gaze palsy, akinesia and cognitive changes, compared to the milder variants of PSP.

HISTORY

The prevalenceof PSP is 5.8–6.5 per 100,000.[3] Patients with the classic PSPRichardson syndrome (PSP-RS) usually develop their firstsymptoms intheir mid-60s and the condition graduallyprogresses from symptom onset to death over an average of 7 years. Clinical subtypes of PSP-parkinsonism (PSP-P) and PSP-pure akinesia with gait freezing (PSP-PAGF) have a more benign course with a survival periodof a decade or more11 and both subtypes have an overall tau burden less than those in PSP-RS and the distribution of abnormal tau is relatively restricted to the brain stem. The phenotypes of PSP-P and PSP-PAGF are sometimes referred as the ‘brain stem’ variants of PSP, as opposed to the ‘cortical’ variants which present with predominant cortical features including PSP-corticobasal syndrome (PSP-CBS), PSP-behavioural variant of front temporal dementia and PSP-progressive non-fluent aphasia (PSP-PNFA).[13] A study of disease progression in 110 pathologically confirmed PSP showed that intervals from disease onset to the development of

frequent falls was 3.9 (± 2.5) years, cognitive impairment 4.2 (± 2.9) years, unintelligible speech 6 (± 2.5) years, residential care 6.1 (± 3.0) years, urinary catheter 6.3 (± 3.1) years, wheelchair dependence 6.4 (± 2.7) years and severe dysphagia 6.4 (± 2.4) years.14 A PSP rating scale with 28 items in six categories provides useful quantitative assessment in clinical practice and research trials.[14] Mean progression rate is + 11.3 points per year with the scores ranging from 0–100. The cause of PSP is unknown. Advanced age is the only established risk factor. It was characterized pathologically by neuronal degeneration of the basal ganglia, brainstem and cerebellum. They named it "Progressive Supranuclear Palsy" (PSP).

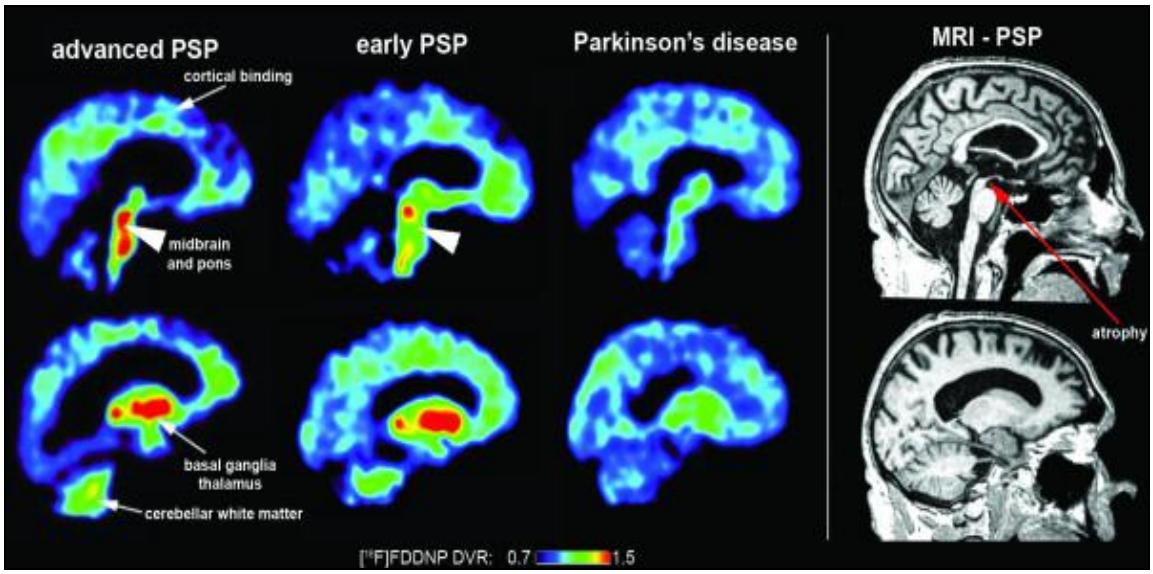


Fig 2: Progressive Supranuclear Palsy.

SIGNS AND SYMPTOMS

People with progressive supranuclear palsy (PSP) develop a range of difficulties with balance, movement, vision, speech and swallowing.

- **Early symptoms**

 Muscle stiffness, particularly in the neck.

 Sudden loss of balance when walking that usually results in repeated falls, often Backward.

 Change in personality, such as irritability, apathy (lack of interest) and moodswings.

 Changes in behavior, such as recklessness and poor judgement.

 Some people have early symptoms that are very similar to those of Parkinson's disease, such as tremors (involuntary shaking of particular parts of the body) and slow movement.

- **Mid-stage symptoms**

Controlling the eye muscles will become more difficult, increasing the risk of falls and making everyday tasks, such as reading and eating, more problematic.

 Reduced blinking reflex, which can cause the eyes to dry out and become irritated.

 Involuntary closing of the eyes (blepharospasm), which can last from several seconds to hours.

 Slowness of thought and some memory problems.

 Neck or back pain, joint pain and headaches.

- **Advanced stages**

As PSP progresses to an advanced stage, people with the condition normally begin to experience increasing difficulties controlling the muscles of their mouth, throat and tongue. There may also be some problems with thinking, concentration andmemory (dementia), although these are generally mild, and the person will normally retain an awareness of themselves.

- **End stage**

This stage is to detect but may indicated by reduced level of consciousness, inability to eat or drink.

 Severe impairments and disabilities.

 Rapid and marketed deterioration in conditions.

CAUSES

While progressive supranuclear palsy (PSP) is usually sporadic, some cases run in families. In most cases, the genetic cause is unknown, but some are due to mutations or "variations" in the MAPT gene. The MAPT gene gives the body instructions to make a protein called tau. This protein isfound in nerve cells (neurons) in the brain and in other parts of the nervous system. It plays a part in putting together and stabilizing components of the structure of cells, helping cells to keep their shape, and aiding in cell division and the transport of materials. It appears thatgene mutations or variations that affects the function of the tau protein cause PSP or cause an increased risk for a person to develop PSP. The cause of progressive supranuclear palsy isn't known. The signs and symptoms of the disorder result from deterioration of cells in areas of your brain, especially those that help you control body movements (midbrain) and thinking (frontal lobe). Researchers have found that the deteriorating brain cells of people

with progressivesupranuclear palsy have abnormal amounts of a protein called tau. Clumpsof tau are alsocharacteristic of other neurodegenerative disorders, such as Alzheimer's disease.

PATHOPHYSIOLOGY

Progressive supranuclear palsy (PSP) is a degenerative condition of unknown a etiology that produces an akinetic-rigid form of parkinsonism characterized by early falls and abnormalities of extraocular movements. Mean age of onset is approximately 63 years, and mean survival from symptom onset is 9 years. Men are much more frequently affected than women. The classic clinical finding is supranuclear ophthalmoplegia, which may not present until late in the illness, if at all. The clinical diagnosis of PSP can be difficult to make, as the sites of pathology are heterogeneous. Structural and functional neuroimaging studies, although not specific for PSP, may be of some assistance in making the diagnosis. The definitive diagnosis of PSP requires the presence of both clinical and neuropathological evidence. Multiple anatomical sites are affected in PSP. The most consistently involved are the subthalamic nucleus, globus pallidus interna and externa, pontine nuclei, periaqueductal grey matter and the substantia nigra. The location of the pathology accounts for the clinical features.

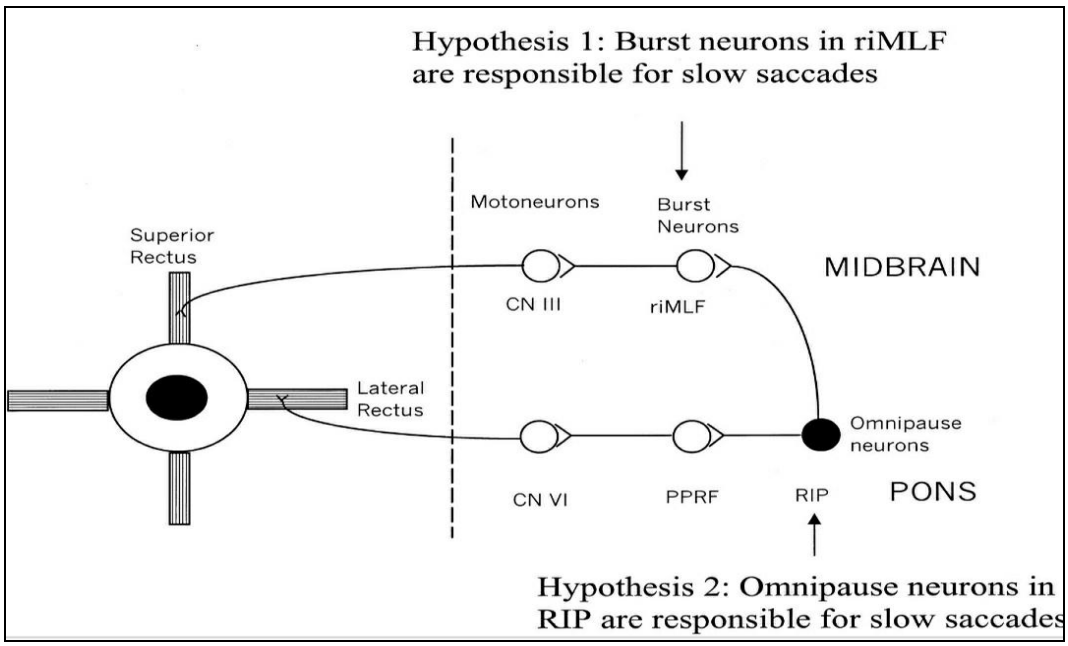


Fig 3: Pathophysiology of slow vertical saccades in Progressive Supranuclear Palsy.

- **Epidemiology**

Considering that it is not always possible to make the clinical diagnosis during a patient's lifetime, studies of the incidence and prevalence of PSP are most likely to underestimate the

rates. In a Rochester, Minnesota, US, population-based study by Bower etal. an average annual incidence rate of 5.3 new patients per 100 000 person-yearswas observed for individuals aged 50 to 99 years. The incidence Increaseddramatically with age and was consistentlyhigher in males. The prevalence of PSP has been reported as being between 1.39 and 4 patients per 100 000.[5]

- **Pathology**

The pathology in patients with PSP is widespread; figure 1 shows the sites of involvement. The area's most consistently involved include globus pallidus, substantia nigra, subthalamic nucleus, locus coeruleus, periaqueductal grey matter, midbrain tectum and pontine nuclei. There is frequent involvement of the caudate, putamen and cerebral cortex. Occasionally, the Purkinje cells of the cerebellum are affected. Enlargement of the aqueduct of Sylvius, because of atrophy of the periaqueductal grey matter and superior colliculi, is variably present. In patients with long-standing disease, even the third and fourth ventricles may be dilated.[5]

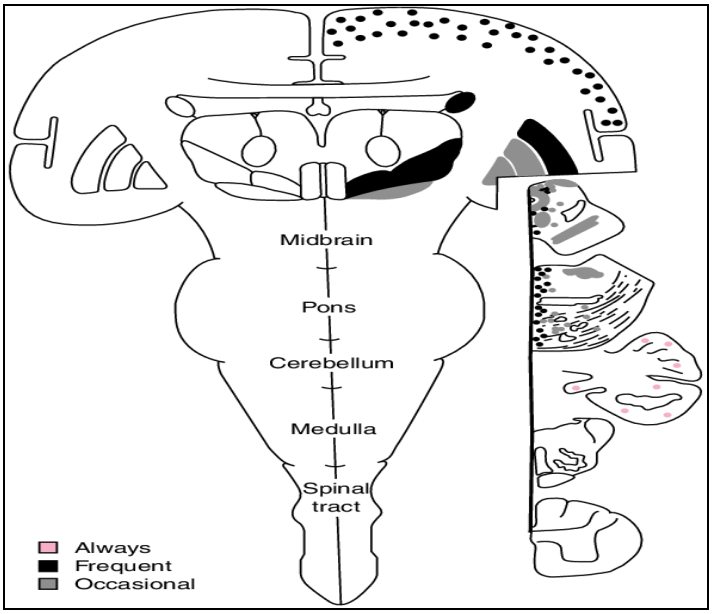


Fig 4: Anatomical sites of pathology in progressive supranuclear palsy.

- **Aetiology**

The cause of PSP remains unknown. It is a sporadic degenerative disease without known associated epidemiological factors. There are rare reports of familial disease.[10] Mitochondrial dysfunction has been implicated in the pathogenesis of PSP. Swerdlow et al. reported reduced complex I activity in PSP cyprid lines, and elevated antioxidant enzyme

activities. Excitatory amino acids may also play a role, as elevated brain glutamate levels were found in several regions in pathologically verified PSP. Lipoperoxidation was found to be selectively involved in the formation of NFTs in PSP, but not in Alzheimer's disease. The splicing in or out of exon 10 in the tau gene determines whether it will be a three- or four-repeat tau. Only the four repeat tau is observed in PSP. They noted a complete disequilibrium between polymorphisms which coversapproximately 100kb of DNA.

CLINICAL FEATURES

PSP is an akinetic-rigid form of Parkinson syndrome. The onset of disease is insidious and in most patients it is symmetrical. The midline structures are involved primarily, and individual limb testing may not show significant abnormality early in the course. Gait difficulty and falls are the most common initial manifestations reported. Other mode of onset includes non-specific dizziness, generalized motor slowing, personality change and dystonia; occasionally, the onset may be resting tremor.[16] Cognitive and behavioural difficulties attributable to frontal lobe dysfunction include impaired executive function that requires shifting between mental tasks, and spontaneous motor behaviour, such as palilalia, motor perseveration, compulsive spitting, etc. Memory tends to be relatively preserved in these patients, but some cognitive impairment is evident in most patients during illness. We reviewed medical records of 16 patients with PSP identified at autopsy at our center. There was evidence of cognitive decline in 62.5% during life. Behaviour change was Rfgty7890 the first manifestation in one patient and dementia with parkinsonism was the initial presentation in another. Unilateral apraxia has been reported but was more commonly seen in patients with CBGD. The variation in clinical features is attributable to the predominant site of pathology. Although extraocular movement abnormalities are characteristic of patients with PSP, only a minority present with gaze palsy. Symptomatic eye movement abnormalitiesdo not begin until nearly 4 years (median) after disease onset.

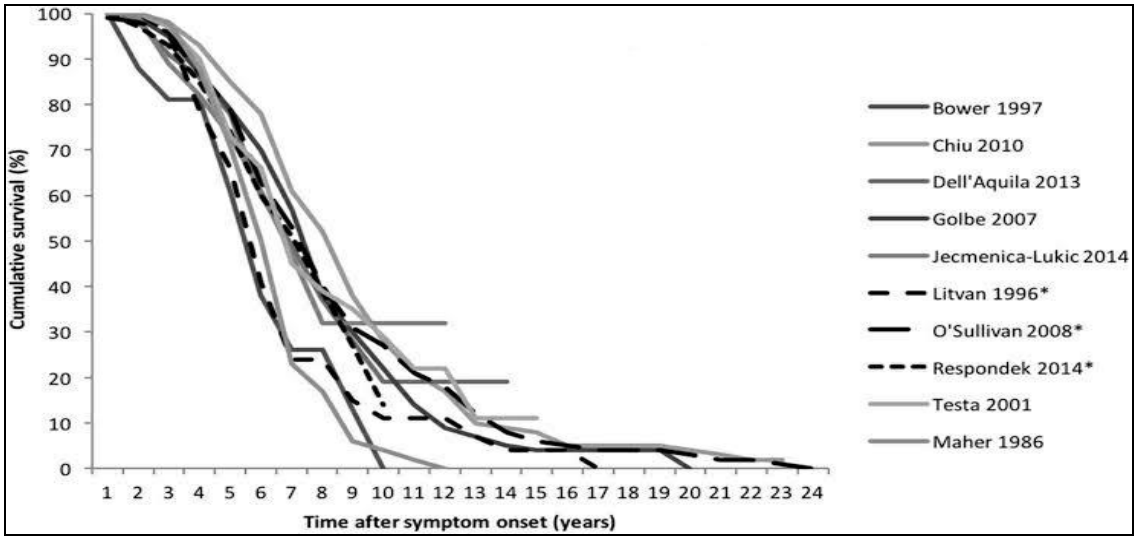
INVESTIGATION

Neuroimaging in patients with PSP by computed tomography (CT) and MRI have shownatrophy and signal increase in the midbrain, degeneration of thered nucleus, atrophy of the quadrigeminal plate and enlargement of the aqueduct (and third ventricle, as well as atrophyof the pons, cerebellum and signal increase in the inferior olives. With progression of disease, frontal and temporal lobeatrophy may develop. Schrage etal17. reported that more than 70% of PSP and more than 80% of cerebellar predominant MS Acould bedifferentiated

onthe basis of routine MRI. The findings significant in differentiating PSP from MSA were: midbrain diameter less than 17mm, signal increase in the midbrain and dilatation of the third ventricle, frontal and temporal lobe atrophy, atrophy of the red nucleus and signal increase in the globus pallidus (only on 0.5Tscans).[5] Neuroimaging is helpful in excluding other diseases that can mimic PSP, such as multi-infarct state, hydrocephalus or midbraintumor's.

- **Risk Factor**

The only proven risk factor for supranuclear palsy is age. Thecondition typically affects people around the age of 60 and is virtually unknown in people under the age of 40.



Graph 1: Survival of PSP patients.

DIAGNOSIS

- **Clinical criteria for the diagnosis of PSP**

There are many proposed clinical criteria for PSP and most of them have asimilarcharacteristic: high specificity and low sensitivity. Although theclassic PSP syndrome presents with clear clinical signs in later stages, the clinical variants recently described areless distinctive, and many patients with PSP are initially thought to have PD, multiple system atrophy, Levy body disease and other sporadic primary tauopathies. Maybe this fact explainsthe high specificityand low sensibility of clinical criteria for PSP.[2] NINDS/SPSP clinical diagnostic criterion (Table) was compiled to reliably identify patients for clinical research who had underlying PSP-tau pathology. This specific criteria state that early falls due to postural instability andsupranuclear gaze palsy or slowed vertical saccades are themost

helpful definingclinical features. In spite of this, the absence of falls and gaze palsies in many patients do not exclude the diagnosis of PSP. In accord to some studies, the application of current available operational criteria, including those proposed by the NINDS/SPSP, fails to improve the accuracy of final diagnosis by neurologists. Although supranuclear gaze palsy, prominent early postural instability with falls, and frontal behavioral or cognitive deficits are the cardinal features of PSP, all may occur in other neurodegenerative disorders, potentially leading to some false-positive diagnoses. Early differentiation between PSP and other neurodegenerative movement disorder syndromes or dementias can be important for a number of reasons, including foreseeing differences in the natural course, choosing appropriate pharmacologic approaches, and avoiding inclusion of misdiagnosed patients in treatment trials.

Table 1: NINDS-SPSP clinical for the diagnosis of PSP.

PSP	Mandatory inclusion criteria	Mandatory exclusion criteria	Supportive criteria
Possible	Gradually progressive disorder Onset at age 40 or later Either vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria	Recent history of encephalitis Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy Hallucinations or delusions unrelated to dopaminergic therapy Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to NINCDS-ADRA criteria) Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances)	Symmetric akinesia or rigidity, proximal more than distal Abnormal neck posture, especially retrocollis Poor or absent response of parkinsonism to levodopa therapy Early dysphagia and dysarthria Early onset cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs
Probable	Gradually progressive disorder Onset at age 40 or later Vertical (upward or downward gaze) supranuclear palsy and prominent postural instability with falls in the first year of disease onset No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria	Severe, asymmetric parkinsonian signs (i.e., bradykinesia) Neuroradiologic evidence of relevant structural abnormally (i.e. basal ganglia or brainstem infarcts, lobar atrophy) Whipple's disease, confirmed by polymerase chain reaction, if indicated	
Definite	Clinically probable or possible PSP and histopathology evidence of typical PSP		

PSP: Progressive Supra Nuclear Palsy; NINDS-SPSP: National Institute of Neurological Disorders and Stroke Society for Progressive Supra Nuclear Palsy; NINCDS-ADRA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

- **Biomarkers for thediagnosis of PSP**

One of the key issues in the management of neurodegenerative disorders is the requirement for reliable biomarkers to increase diagnostic accuracy. In the last few years, several biologic markers have been tested, but no specific biologic tool for early PSP detection is available.

All the proposed biomarkers showed an individually considerable overlap between PSP and other neurodegenerative disorders. Several studies aimed at evaluating tau levels in cerebral spinal fluid (CSF) in PSP compared with patients affected by either other tau-related disorders orother neurodegenerativeextrapyramidal syndromes, such as synucleinopathies. In CSF, extended (55 kDa) and truncated (33 kDa) tau forms have beenpreviously recognized, and the tau 33 kDa/55 kDa ratio has been found significantly reduced in PSP in comparison with other neurodegenerative disorder.

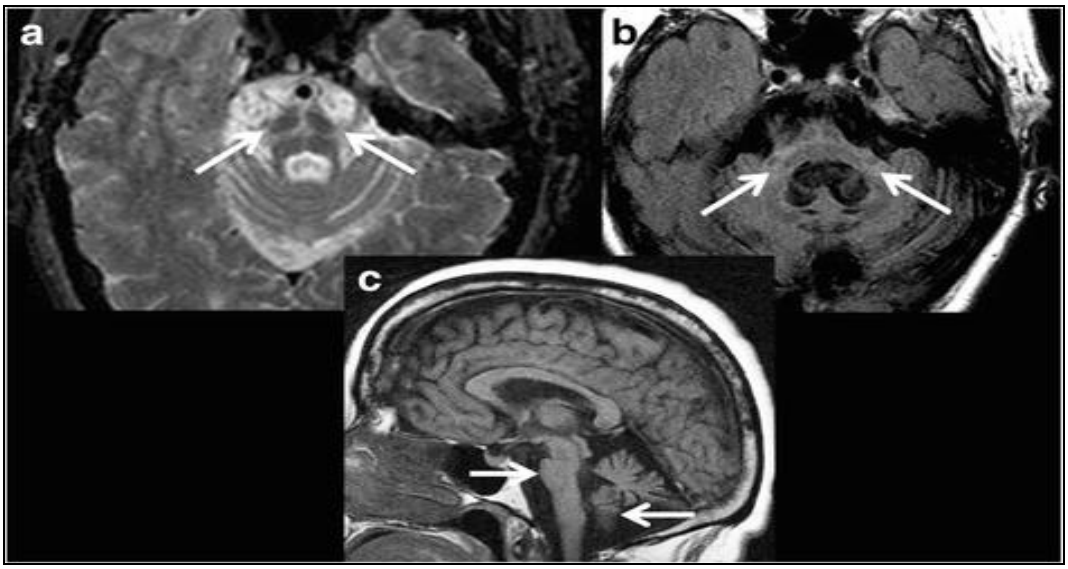


Fig 5: Biomarkers imaging in PSP.

- **Brain imaging**

As aforementioned, the diagnosis of PSP relies mainly on clinical data, and misdiagnosis can be frequent, especially in the early disease stages.[17] According to a recent study it is estimated that at least 1 in every 20 patients taking medication for PD is misdiagnosed 19, and these data may be even worse taking into account PSP, which is much less frequent than PD, and under diagnosed. Nevertheless, conventional structural and functional brain imaging may help not only in the differential diagnosis of PSP between PD and other atypical forms of parkinsonism [multiple system atrophy (MSA)], but also aid to understand the neurobiological basis of this neurodegenerative disorder.

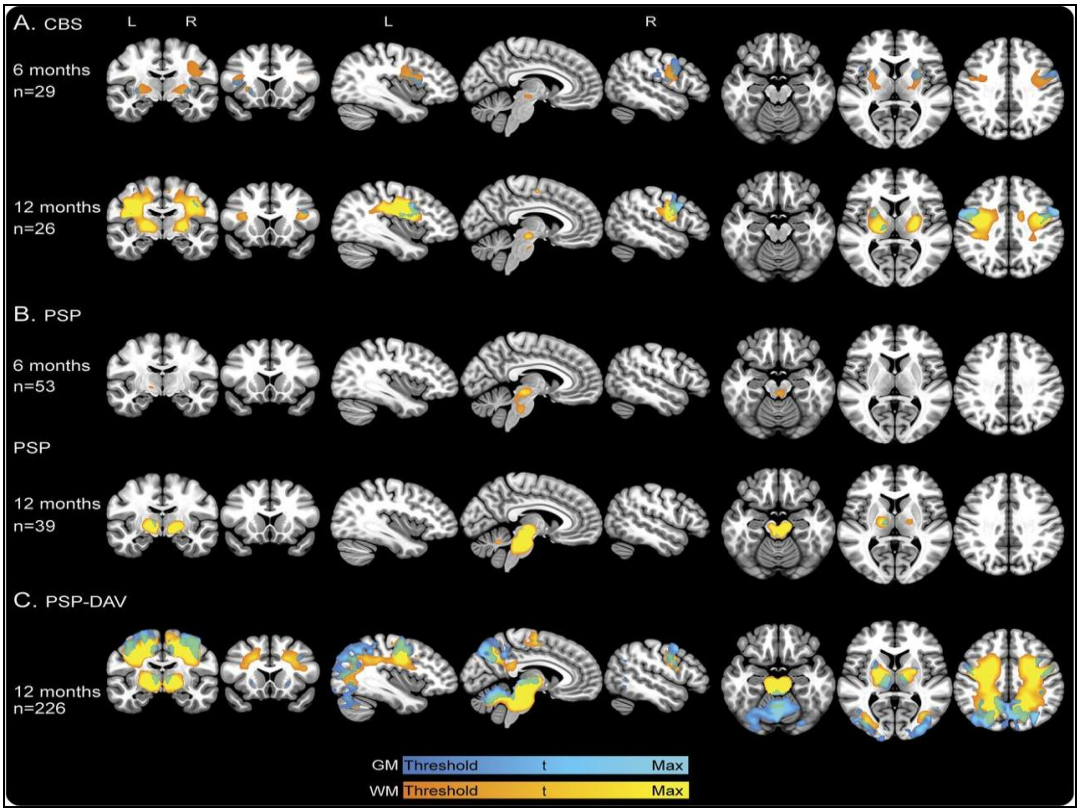


Fig 6: Brain atrophy in PSP.

- **Conventional structural brain MRI**

Conventional structural brain MRI can help on the differentiation between PSP and PD, and other atypical parkinsonian subtypes. Using an automated computer differential classification in parkinsonian syndromes via pattern analysis on MRI, Duchesne and coworkers obtained 91% accuracy (agreement with long-term clinical follow-up), 88% specificity, and 93% sensitivity in the diagnosis of PSP [8]. In the paper by Cosottini andcoworkers, assessing midbrain atropthrough morphometric measurements in patients with clinically diagnosed PSP they found that the midbrain area had the highest diagnostic accuracy in distinguishing between PSP and other conditions, with a sensitivity of 100% and specificity of 90.5% .The following brain MRI regions should be carefully analyzed in the evaluation of patients with suspected PSP, and further details on the measurement procedures can be found elsewhere: [1] Presence or not of enlargement of the third ventricle; [2] Anteroposterior diameter of the midbrain; [3] Quadrigeminal plate thickness; [4] Interpeduncular angles; [5] Brainstem volumetry; [6] Volumetry of the caudate nucleus and putamen; [7] Presence or not of hypersignal in the periaqueductal region. We make available illustrative brain MRI images of a patient with PSP.

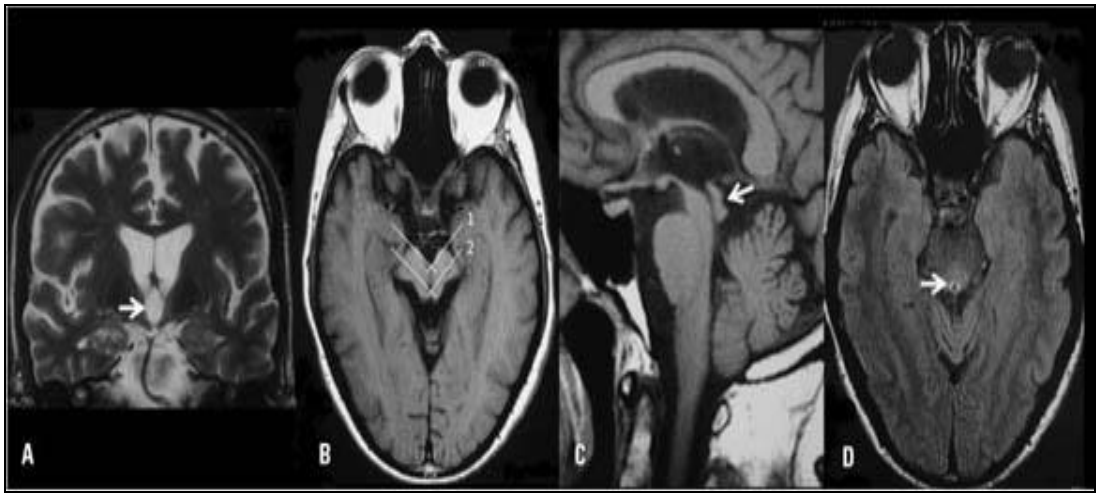


Fig 7: Brain MRI illustrative images of patient with progressive supranuclear palsy.

- **Regional cerebral blood flow (rCBF)**

SPECT imaging techniques using the technetium-based radioligand ECD showed hypoperfusion of the anterior cingulate and medial frontal cortex in PSP patients as compared to controls and PD. In PSP patients the rCBF impairment extended to the pre-supplementary motor area and prefrontal cortex, areas involved in executive function and motor networks. Compared with PSP patients, PD patients showed a mild rCBF decrease in associative visual areas which could be related to the known impairment of visuospatial function.

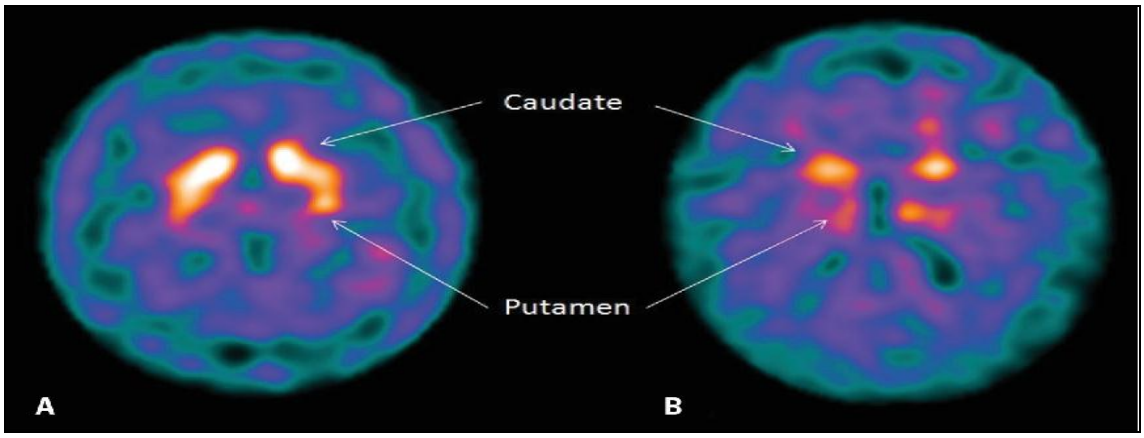


Fig 8: An illustrative brain SPECT imaging (axial plane) using a dopamine transporter ligand.

TREATMENT

Most specialist centers give trialsof levodopaand amantadine but unfortunately their symptomatic benefits are limited. Zolpidem, a GABA agonist, may improve motor function, dysarthria and ocular abnormalities according to anecdotal evidence fromcase reports.

Selective serotonin re-uptake inhibitors are effective at treating depression, obsessive-compulsive behavior and emotional lability but mayworsen apathy. Memantine may provide symptomatic benefit in patientswith PNFA.[12] A multidisciplinary team approach with input of swallowing and language therapist, dietician, physiotherapist, psychologist, palliative care team, occupational therapist and social worker (allocation of local health care service) is extremely important to ensure the needs of the patients are met. Disease-modifying therapeutic trials inthe past years have improved our insights in the natural course of thisdevastating disorder.

- **Symptomatic treatment**

Although parkinsonism is a characteristic feature in PSP, it is often distinct from that typically seen in PD, not only in clinical picture, but also in levodopa (LD) responsiveness. This is explained by the pathology distribution of PSP, involving subthalamic nucleus, pallidum, substantia nigra, striatum, and other regions in brainstem.[3]

- **Botulinum toxin**

According to our previous published experience the overall frequency of dystonia in Brazilian patients with atypical parkinsonian syndromes is of 50% 46. Therefore, botulinum toxin may be helpful in PSP for treating dystonia, such as retro Collis, and apraxia of eyelid opening, reducing disability provoked by these symptoms.[15]. This must be used with cautions to avoid worsening of dysphagia.

- **Disease modifying therapies**

The Neuroprotection and Natural HistoryinParkinson PlusSyndromes (NNIPPS) study randomized PSPand MSA patients forreceiving riluzole, evaluating survival as primary outcome. This drugdid not have a significant effect on survival neither in the rate of function-al deterioration. Development of future therapies will come from a greater understanding of PSP and other tauopathies pathophysiology. Glycogen synthase kinase 3 (GSK-3) may play a role in tau diseases because it can phosphorylate tau in *vivo*, and inhibitionof this enzyme in transgenic mice and in drosophila leads tofunctional improvement. Lithium seems to be a GSK-3 inhibitor in mice with increased activity of this enzyme, preventing neuropathologic changes.

- **Surgical treatment**

As deep brain stimulation (DBS) surgery for PD requires response to LD most patients with PSP do notfulfill this criterion. A published case that was initially diagnosed as PD responsiveto LD, but later developed atypical signs compatible with PSP-P, presented benefit with subthalamic nucleus DBS in ameliorating parkinsonism. Because of the widespread pathology, abnormalities of the pre- and post-synapticnigrostriatal dopaminergic pathway and the cholinergic, GABAergic, serotonergic and adrenergic systems and pathways have all been identified. Compared with patients with Parkinson's disease, drug therapy is much less effective and has only a short duration of effect. Levodopa was the first medication reported to benefit patients with PSP and has been tried by several groups. Most investigators have reported no patient improvement, whereas some have reported improvement, including some improvement in extra ocular motility, but a response in eye movement is very rare.

Drugs use in treatment

- **Levodopa (Dopamine precursor)**

Levodopa has a specific salutary effect in PD. It is inactive by itself, but it is immediate precursor of the transmitter.

Mode of Action: Aretrospective study of cases from the Queen Square Brain Bank (with a diagnosis of CBS or pathologically proven CBD) showed that 56% of patientstaking levodopa experienced mild-to-moderate improvement in their symptoms. Of these, 17%developed dystonia and choreiform movements (level IV).[7] Striatal dopamine levels in symptomatic Parkinson's disease are decreased by 60 to 80%, striatal dopaminergic neurotransmission may be enhanced by exogenous supplementation of dopamine through administration of dopamine's precursor, levodopa. A retrospective study of patients with histologically proven CBD found no significant or sustained improvement from levodopa (level IV). Similarly, a retrospective study of 14 patients with CBD concluded that no patient had a dramatic response to levodopa. In a retrospective study of 147 patients with a clinical diagnosis of CBD. In a case series of ten patients with PSP, two experienced moderatetransient improvementin symptoms.

Pharmacokinetics

Absorption: Levodopa is rapidly absorbed from the proximal small intestine by the large neutral amino acid (LNAA) transport carrier system.

Distribution: Levodopa administered alone is widely distributed in body tissues with a volume of distribution about 65% the total body volume. However, distribution into the CNS is minimal, accounting for less than 1% of the dose.

Protein binding: High.

Metabolism: 95% of an administered oral dose of levodopa is pre-systemically decarboxylated to dopamine by the L-aromatic amino acid decarboxylase (AAAD) enzyme in the stomach, lumen of the intestine, kidney, and liver. Levodopa also may be methoxylated by the hepatic catechol-O-methyltransferase (COMT) enzyme system to 3-O-methyldopa (3-OMD), which cannot be converted to central dopamine.

Elimination: Metabolites of dopamine are rapidly excreted in the urine; 80% of a radioactively labelled dose is recovered within 24 hours.

Pharmacological action: CNS: levodopa hardlyproduces any effect in normal individually or in patients with other neurological disease.

CVS: The peripherally formed DA can cause tachycardia by acting on β adrenergic receptor. Instead, postural hypotension is quite common.[9]

CTZ: Dopaminergic receptors are present in this area and DA acts nan excitatory transmitter. Tolerance develops gradually to this action.

Clinical uses: Levodopa is used in the treatment of Parkinson Disease. This medication may be prescribed for other uses.

Side effects: Nausea, vomiting, constipation, dystonia, choreiform movements, palpitations, postural hypotension, on/off episodes, psychosis, depression, and urinary retention.

Contraindications: Levodopa is contraindicated for and in patients with known hypersensitivity to the drug. Levodopa should be administered cautiously to patients with severe cardiovascular or pulmonary disease, asthma, renal, hepatic or endocrine disease.

Drug interactions: Hypertensive crisis with type A MAOIs. Enhancement of antihypertensive medication effect.

Standard dose: Initially, levodopa 50 mg 3–4× daily, with a dopa decarboxylase inhibitor such as benderizine (as co-beneldopa) or carbidopa (co-care dopa) titrated slowly according to response, up to 800 mg daily in divided doses.

Table 2: Levodopa Response in PSP.

	No Levodopa	Levodopa†
Total POA	18.2 ± 5.8	19.3 ± 5.5
Functional reach, cm (in)	21.3 ± 8.4 (8.4 ± 3.3)	24.1 ± 5.3 (9.5 ± 2.1)
Central sway	0.21 ± 0.17	0.23 ± 0.15
Total maximum stability, %	53.4 ± 11.2	54.4 ± 10.6
Limits of stability, s	55.0 ± 5.7	53.2 ± 7.7
Limits of stability, path sway	2339 ± 535	2305 ± 622
Short-latency responses, No./Total No. (%)	14/40 (35)	12/40 (30)

**PSP indicates progressive supranuclear palsy; POA, performance-oriented assessment. Unless otherwise indicated, data are given as mean ± SD. Differences between groups were not significant.*
†Given as a combination of carbidopa (25 mg) and levodopa (250 mg)

Diazepam (Hypnotics and Anxiolytics)

It is the prototype of benzodiazepines which acts in the brain on specific receptors.

Mode of Action: In a study of 147 patients with a clinical diagnosis of CBD, 23% reported improvement in myoclonusand 9% improvement in dystonia following treatment with benzodiazepines; side effects of somnolence were reported in 26% (level IV).[9] Diazepam is a benzodiazepine tranquillizer with anticonvulsant, sedative, muscle relaxant and amnesic properties. Benzodiazepines, such as diazepam, bind to receptors in various regions of the brain and spinal cord. This binding increases the inhibitory effects of gamma-aminobutyric acid (GABA). GABAs functions include CNS involvement in sleep induction.

Pharmacokinetic

Absorption: After oral administration, it is considered that diazepam is rapidly and completely absorbed from the gastrointestinal tract as >90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 – 1.5 hours with a range of 0.25 to 2.5 hours. This results in an average decrease in Cmax of 20% in addition to a 27% decrease in AUC (range 15% to 50%) when administered with food.

Distribution: In young healthy males, the volume of distribution at steady state is 0.8 to 1.0 L/kg.

Metabolism: Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are further largely eliminated by way of conjugation to glucuronic acid via glucuronidation.

Elimination: Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates.

Pharmacological action

CNS: The overall action of BZDis qualitatively similar, but there are prominent difference in selectively for different facets of action, and in their time- course of action.[9]

Antianxiety: Some BDZ_sexert relatively selective antianxiety action which probably not dependent on their sedative property.

Muscle relaxant: BDZs produce centrally mediated skeletal muscle relaxation without impairing voluntary activity.

Other action: Diazepam decrease nocturnal gastric secretions and prevent stress ulcers.

Clinical uses: It acts in the brain on specific receptors enhancing GABAergic transmission. Muscle tone is reduced by supraspinal rather than spinal action; muscle relaxant; sedative activity ratio is low.

Side effects: Fatigue and lethargy are common, also confusion, poor concentration, drowsiness, dizziness, hypotonia, malcoordination, headache, irritability, and memory loss.

Contraindication: Hypersensitivity to Benzodiazapem, Myasthenia gravis. Respiratory depression, sleep apnea, neuromuscular disorders, and myasthenia.

Drug interactions: Opioids, antidepressants, antipsychotics, and antifungals.

Standard dose: Two to 15 mg daily in divided doses; can be increased to 60 mg daily (in divided dose) in spastic conditions.

Trazodone (Atypical antidepressants)

It is the atypical antidepressant; less efficiently blocks 5-HT uptake.

Mode of Action: Significant improvement in depression was seen following treatment with trazodone in 20 patients with PD (level III). A randomized, double-blind, placebo-controlled cross over trial of 26 patients with FTD demonstrated a significant decrease in the NPI and improvements in behavior following treatment with trazodone (level II). These beneficial effects were sustained in an open-label extension of this study (level III). In another open-label study of 14 patients with FTD, trazodone was shown to have a dose-dependent effect on behavioral symptoms, but it did not improve cognition (level III).

Pharmacokinetics

Absorption: Rapidly and almost completely absorbed following oral administration. Food may decrease the rate and extent of absorption.[7]

Distribution: The apperean volume of distribution and total body clearance for trazodone were estimated to 0.84 +/- 0.16 l/kg and 5.3 +/- 0.9 l/hr, respectively.

Metabolism: Undergoes extensive hepatic metabolism via hydroxylation, N-dealkylation, N-oxidation and splitting of the pyridine ring. Cytochrome P450 (CYP) 3A4 catalyzes the formation of the major active metabolite, m-chlorophenyl piperazine (m-CPP).

Elimination: The mean blood elimination half-life of trazodone is biphasic: the first phase's half-life is 3 to 6 hours, and the following+ phase's half-life is 5 to 9 hours. Metabolites are conjugated to gluconic acid or glutathione and around 70 to 75% of C-labelled trazodone was found to be excreted in the urine within 72 hours.

Pharmacological Action

CNS: Effects differ in normal individuals and in the depressed patients.

ANS: Most TCA_s are potent anticholinergics cause dry mouth, blurring of vision, constipation and urinary hesitancy as side effect.

CVS: Effect on cardiovascular function are prominent, occur at therapeutics concentration and may be dangerous in over dose.

Clinical uses: Trazodone has the following clinical uses.

- Unipolar depression, with or without anxiety
- Anxiety disorder
- Insomnia.

Side effects: Hypertension, myalgia, arthralgia, hypersalivation, dry mouth, gastrointestinalupset, weight change; blurred vision, palpitations, dyspnea, QT prolongation.

Contraindications: MAOIs should not be taken 2 weeks before or after treatment with this medication. Pimozidecontraindicated. Contraindicated in acute porphyria, manic phase of bipolar disorder, in the immediate recovery period following MI, and in arrhythmias.

Main drug interactions: Risk of serotonin syndrome with concomitant use of St. John's Wort, MAOIs, other SSRIs, and SNRIs. May affect plasma concentration of antiepileptics. Risk of arrhythmias when administered with drugs that prolong QT interval.

Standard dose: Initially, 150 mg (100 mg in elderly) daily in divided doses (after food) or as a single dose at bedtime. Increased up to 300 mg daily.

Atropine (Anticholinergics)

The action of atropine can be largely predicted from knowledge of parasympathetic response.

Mode of Action: In the NICE full clinical guidance on the management of PD, sublingual 1 % atropine ophthalmic solution twice daily was suggested as an option for themanagement of hypersalivation. Atropine binds to and inhibit muscarinic acetylcholine receptors, producing a wide range of anticholinergic effects.

Pharmacokinetics

Absorption: Atropine is rapidly and well absorbed after intramuscular administration. Atropine disappears rapidly from the blood and is distributed throughout the various body tissues and fluids.

Distribution: Atropine has a volume of distribution of 1 - 6 L/kg. Protein binding is moderate, with approximately 50% of the drug bound in plasma. Its plasma clearance is 8ml/min/kg.

Protein binding: The protein binding of atropine is 14 to 22% in plasma.

Metabolism: Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver. From 13 to 50% is excreted unchanged in the urine.

Elimination: Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver; from 13 to 50% is excreted unchanged in the urine.

Pharmacological action: CNS: It is CNS stimulant and can acts as sedative.

Secretion: Atropine blocks the watery salivarysecretion giving rise to dryness of mouth, nose, pharynx and bronchi.

Uterus: Atropine have no significant effect on the tone and motility of the uterine smooth muscle.

Urinary tract: Atropine produce reduction in normal as well as drug induced ureteral peristalsis.

Clinical uses: Atropine is specific antidote for antichE.

Side effects: Constipation, dry mouth, bradycardia, urinary urgency and retention, visual disturbance, and photophobia.

Contraindications: Myasthenia gravis, urinary retention, gastrointestinal obstruction.

Drug Interaction: Atropine delays gastric emptying.

Standard dose: One percent atropine ophthalmic solution administered sublingually, one drop twice daily

CONCLUSION

PSP is a degenerativedisease of unknown a etiology that produces a clinical picture of akinetic rigid parkinsonism. Although the age of onset is similar to that of Parkinson's

disease, the prognosis for patients with PSP is much worse than for patients with Parkinson's disease treated with currently available drugs. The mean survival in PSP is approximately 9 years from symptom onset. A genetic variation in or near the tau gene on chromosome 17 appears to be associated with an increased risk of developing PSP. Recently, an emerging knowledge in PSP physiopathology, diagnosis and treatment has become available to physicians, but despite all these information PSP still remain an under diagnosed disorder. Therefore, we should always be careful in the evaluation of patients with parkinsonian disorders and keep in mind the most important "red flags" that may point out to PSP or other atypical forms of parkinsonism. These main "red flags" that we should take into consideration in clinical practice are: supranuclear gaze palsy, early falls, and unresponsiveness to LD. Conventional structural MRI is very helpful, improving diagnosis accuracy, and some areas especially of the cerebellum-brain stem region should be thoroughly assessed. Caution, however, should be considered in patients with recent disease onset since these characteristic brain MRI alterations may not be evident.

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