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PROJECT REPORT

Name : **Dr.Syam.K**

Program : **DM Neurology**

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Cognitive Functions in Multiple System Atrophy, Progressive Supranuclear Palsy and Parkinson's Disease

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CERTIFICATE

I, Dr. Syam.K hereby declare that I have actually carried out the project under report.

Place: Thiruvananthapuram

Date: 28-10-2005

Signature

DR. SYAM.K

Forwarded. He has carried out the project under report.

Signature

PROF (DR). K. RADHAKRISHNAN

HEAD OF THE DEPARTMENT

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INTRODUCTION

INTRODUCTION

Parkinson's disease (PD) is characterized by rigidity, bradykinesia, rest tremor, impaired postural reflexes, asymmetric onset and a good and sustained clinical response to levodopa. Approximately 80-85% of parkinsonism patients seen in Movement Disorder clinics have PD while the rest belong to the categories of atypical parkinsonism and secondary parkinsonism (115). Patients with parkinsonism and additional neurological features, which are atypical for PD, are classified as having Parkinsonism Plus Syndromes or Atypical Parkinsonism. Even when they present as pure parkinsonism without the atypical signs, there are clinical differences in the pattern of extra pyramidal signs, the distribution of extrapyramidal signs and the response to dopaminergic treatment, which help to differentiate them from PD. However, diagnostic distinctions between these entities can be difficult as the atypical signs may appear late in the course of the disease and may be mistaken for PD in the early stages. Diagnostic criteria have evolved and these help to differentiate PD from atypical parkinsonian syndromes during life [3,67,122]. Differentiation of these entities is of great significance as the natural history, therapeutic options and outcome are more favorable for PD than atypical parkinsonism.

Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA) are the two relatively common forms of atypical parkinsonism encountered in Movement Disorder clinics. Diagnosis of these conditions, as in the case of PD, is purely clinical, and based on a group of

symptoms and signs. Neuroimaging and other ancillary investigations may be supportive. Few studies have compared the pattern of cognitive dysfunction in these 2 diseases vs. PD [170,178,179,180].

Basal Ganglia and Cognition

The basal ganglia have been implicated in cognitive processes and behavioral regulation. Cognitive changes have long been observed in patients with degenerative diseases that involve primarily the basal ganglia such Huntington's disease. In general, the cognitive disturbances found in movement disorders belong to the category of 'subcortical dementias' consisting of a frontal lobe-like syndrome, without genuine amnesia or impairment of instrumental functions (aphasia, apraxia or agnosia). This is explained by the fact that neuronal pathways connecting the basal ganglia to the cortex project not only to regions involved in the control of movements (motor, premotor and supplementary motor areas) but also to cortical areas involved in cognitive functions (prefrontal cortex).

The severity and pattern of cognitive dysfunction seen in different parkinsonian syndromes vary. The use of appropriate neuropsychological tests to detect these deficits may also contribute to the diagnosis of these conditions [182]. PD and MSA are reported to have a similar subcortical pattern of cognitive impairment [135,136,138-146,164,171,172,173]. Usually this does not amount to dementia. Dementia is rare in MSA, and is an exclusion criterion for this disease [3,5]. However, dementia can occur in around 30-40% of patients with PD [150,151,152]. It has been found that severity of motor dysfunction, rather than the disease duration or age of

onset of disease, correlates with dementia in pathologically proven PD [138,185]. In PSP, the striatofrontal dysfunction is so severe that it leads to dramatic planning, monitoring and recall deficits, evolving towards dementia. The salient features of dementia in PSP patients include significant memory retrieval defects [169] and a predominantly 'frontal lobe type' of dysfunction including disturbances in attention, set shifting, abstract thinking and insight [51,161,165-169]. Very few studies have compared the cognitive dysfunction in PD, PSP and MSA. In the studies done prior to the emergence of the current diagnostic criteria [3], patients with hereditary spinocerebellar degenerations often 'contaminated' the 'MSA group'. [164] Others [170, 178, 179] consisted of patients with MSA-P only. It is also not known whether cognitive impairment is more common when there is a greater clinical diagnostic certainty of MSA.

REVIEW OF LITERATURE

The Atypical Parkinsonism Syndromes – Multiple System Atrophy and Progressive Supranuclear Palsy

Multiple System Atrophy

The term multiple system atrophy (MSA) denotes an adult-onset sporadic progressive neurodegenerative disorder of unknown etiology that is clinically characterized by the variable combination of autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal signs. Recent epidemiological surveys have established a prevalence rate of 4.4 per 100,000 and an incidence rate of 3 per 100,000 per year [1,2]. Two major motor presentations can be distinguished clinically. Parkinsonian features predominate in 80% of patients (MSA-P subtype), and cerebellar ataxia is the major motor feature in 20% of patients (MSA-C subtype) [3].

The disease affects both men and women, usually starting in the sixth decade of life and progressing relentlessly until death after an average of 9 years [4]. Table 1 lists the frequencies of clinical features in 203 pathologically verified MSA cases [5]. Bradykinesia, rigidity, and postural and rest tremor as well as dysequilibrium and gait unsteadiness characterize parkinsonism associated with MSA. Up to 90% of patients with MSA-P, treated long term with L-dopa, fail to respond. The cerebellar disorder comprises gait ataxia, limb kinetic ataxia, scanning dysarthria as well as cerebellar oculomotor disturbances. Autonomic failure in MSA manifests predominantly as symptomatic orthostatic hypotension frequently associated with absent reflex tachycardia upon standing.

Table 1: Frequency of Individual Clinical Features in 203 Cases of MSA.

Feature	Frequency
Autonomic Symptoms	
Urinary incontinence	55%
Postural faintness (Including syncope)	51%
Impotence	47%
Recurrent syncope	18%
Urinary retention	18%
Fecal incontinence	12%
Parkinsonism	
Akinesia	83%
Tremor	67%
Rigidity	63%
Dyskinesias	27%
Cerebellar Signs	
Gait ataxia	49%
Limb ataxia	47%
Intention tremor	24%
Nystagmus	23%
Pyramidal Signs	
Hyperreflexia	46%
Extensor plantar response	41%
Spasticity	10%
Other Features	
Cognitive disturbances	2.5%
Strider	13%
Dystonia	12%

Erectile disturbances represent the most common and often the earliest feature of male MSA patients. In addition, patients may note increased constipation and hypohidrosis or anhidrosis. Urological features are common and include urinary urgency, frequency, nocturia, and urge incontinence.

The clinical diagnosis of MSA rests largely on history and physical examination. Additional investigations are particularly helpful in excluding differential diagnoses; however, they may also support a presumptive clinical diagnosis.

CLINICAL DIAGNOSTIC CRITERIA Clinical diagnosis may be fraught with difficulties, particularly in early stages of the disease. In a recent clinicopathological study, MSA was correctly diagnosed in only 25% of patients at the first neurological visit. Even at the last neurological follow-up, the disorder was misdiagnosed in half of the patients. A correct diagnosis in the other half was established on average 4 years after disease onset.

In 1989 Quinn [6] first proposed diagnostic criteria for MSA, and these were subsequently modified in 1994 [7]. The Quinn criteria distinguish parkinsonian and cerebellar presentations as well as three levels of diagnostic certainty (possible, probable, definite). So far, sensitivity and specificity of the Quinn criteria have never been prospectively determined. A retrospective validation based on postmortem verification of MSA cases demonstrated sub optimal diagnostic accuracy [8].

In April 1998, an international consensus conference was convened to develop optimized criteria for a clinical diagnosis of MSA [3]. The MSA conference recommended three diagnostic categories of increasing certainty: possible, probable, and definite (Table 2). A definite diagnosis requires a typical neuropathological lesion pattern as well as deposition of glial cytoplasmic inclusions (GCIs). The diagnosis of possible and probable MSA is based on the presence of clinical features listed in Table 3. In addition, exclusion criteria have to be considered (Table 4)

Table 2: Diagnostic Categories of MSA

I. Possible MSA
One criterion plus two features from separate other domains. When the criterion is parkinsonism, a poor levodopa response qualifies as one feature (Hence only one additional feature is required)
II. Probable MSA
Criterion for autonomic failure / urinary dysfunction plus poorly levodopa responsive parkinsonism or cerebellar dysfunction.
III. Definite MSA
Pathologically confirmed by the presence of a high density of glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways

Table 3: Clinical Domains, Features and Criteria Used in the Diagnosis of MSA

I. Autonomic and Urinary Dysfunction

A. Autonomic and urinary features.

1.Orthostatic hypotension by 20 mm of Hg systolic or 10 mm of Hg diastolic.

2.Urinary incontinence or incomplete bladder emptying.

B. Criterion for autonomic failure or urinary dysfunction in MSA

Orthostatic falls in blood pressure by 30 mm of Hg systolic or 15 mm of Hg diastolic or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men) or both.

II. Parkinsonism

A. Parkinsonian features

1.Bradykinesia

2.Rigidity.

3.Postural instability.

4.Tremor.

B. Criterion for parkinsonism in MSA

Bradykinesia plus at least one of items 2 to 4.

III.Cerebellar dysfunction

A. Cerebellar features

1.Gait ataxia. 2.Ataxic dysarthria 3.Limb ataxia. 4.Sustained Gaze evoked nystagmus.

B. Criterion for cerebellar dysfunction in MSA

Gait ataxia plus at least one of items 2 to 4.

IV.Corticospinal tract dysfunction.

A. Corticospinal tract feature: Extensor plantar response with hyperreflexia.

No 'criterion, in corticospinal tract dysfunction.

Table 4: Exclusion Criteria for the Diagnosis of MSA

I. History
Symptomatic onset under 30 years of age.
Family history of similar disorder.
Systemic disease or other identifiable causes for the features.
Hallucinations unrelated to the medications.
II. Physical examination
DSM Criteria for dementia.
Prominent slowing of vertical saccades or vertical supranuclear gaze palsy.
Evidence of focal cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction.
III. Laboratory investigations
Metabolic, molecular genetic and imaging evidence of an alternative cause of features listed in table 3.

DIFFERENTIAL DIAGNOSIS In clinical practice, parkinsonian features associated with MSA need to be distinguished from PD as well as other atypical parkinsonian disorders like Progressive Supranuclear Palsy, Diffuse Lewy Body Disease, and Corticobasal Degeneration.. Recognition of typical disease manifestations will facilitate a correct clinical diagnosis in many instances. In contrast to patients with atypical parkinsonian disorders, including MSA-P, PD patients usually exhibit a beneficial response to chronic L-dopa therapy that may be complicated by motor fluctuations and dyskinesias [9]. Although both patients with PD and those with MSA-P may

develop orthostatic and urogenital disturbances, these manifest early in MSA-P and late in PD [10]. Early unexplained falls combined with vertical gaze palsy represent cardinal features of PSP [11]. Patients with CBD typically develop an asymmetrical extrapyramidal syndrome comprising bradykinesia, rigidity, dystonic posturing, and superimposed myoclonus. In addition, there is prominent cortical dysfunction, predominantly ideomotor apraxia [12, 13].

Progressive cognitive decline associated with marked fluctuation of attention and vigilance, as well as visual hallucinations, characterizes the dementia syndrome of patients with DLB. A substantial proportion of DLB patients develop additional parkinsonian features.

The differential diagnosis of MSA-C includes other adult-onset cerebellar ataxias. Principally, molecular genetic testing for spinocerebellar ataxia type 1 (SCA1) and type 2 (SCA2) should exclude the hereditary ataxias associated with olivopontocerebellar atrophy (OPCA)-like pathology. The early presence of autonomic and urogenital dysfunction represents a helpful red flag indicating MSA-C rather than sporadic OPCA (5, 14).

ADDITIONAL INVESTIGATIONS Noninvasive cardiovascular function tests such as the Valsalva maneuver, or heart rate variability should be performed to define the pattern and severity of autonomic dysfunction in MSA [15]. However, these tests may be less helpful for differential diagnosis. Nonspecific changes in the electroencephalogram are also not helpful for diagnostic purposes [16]. In patients with urogenital complaints, external anal sphincter electromyography frequently shows prolonged and

polyphasic muscle potentials consistent with denervation and reinnervation of voluntary sphincter muscles [17]. However, similar changes may also occur in advanced PD or PSP.

Cranial computed tomography may demonstrate infratentorial atrophy in MSA patients; however, the diagnostic sensitivity is unsatisfactory. In up to 90% of MSA patients magnetic resonance imaging (MRI) reveals typical changes in the striatum, brain stem, and cerebellum. In T2-weighted images there is frequently a hyperintense band like signal adjacent to the posterior lateral putamen. Such increased signal intensity may correspond to activated microglia[18] and is frequently associated with putaminal atrophy and/or hypointensity. The hyperintense periputaminal signal and other MRI changes have been confirmed as useful diagnostic markers with a sensitivity of 93% and specificity of 88% [19]. Hyperintense T2 signal changes are also frequently present in the pons (``hot cross bun" sign [19]). Atrophy-related changes of basal ganglia, brain stem, and cerebellum have been quantified [20] in patients with parkinsonian disorders using MR volumetry (MRV). The results suggest that, as a group, patients with MSA-P can be distinguished from those with PD using MRV. Whether MRV improves diagnostic accuracy in individual patients with possible MSA remains to be demonstrated. MR spectroscopy (MRS) of the lentiform nucleus has been performed in a number of MSA patients and revealed reduced N-acetylaspartate as a metabolic correlate of neuronal cell loss.[21]

Functional imaging with single photon emission computed tomography (SPECT) may be helpful in patients with questionable IBZM

SPECT consistently shows reduced striatal dopamine D2 receptor binding in MSA patients. Schwarz and colleagues [22] were able to show that a reduction in striatal IBZM binding predicts unresponsiveness to L-dopa in all patients with untreated de novo parkinsonism. Most of these patients developed either MSA-P or PSP [22] In contrast, SPECT investigations using dopamine transporter ligands such as beta-CIT appear to be unhelpful in the diagnosis for patients with possible MSA [23] Positron emission tomography (PET) can contribute to the early diagnosis of MSA; however, it is still not widely available.

NEUROPATHOLOGY Neuropathologically, MSA is characterized by selective neuronal loss and gliosis predominantly affecting the substantia nigra and striatum (striatonigral degeneration, SND) as well as olivopontocerebellar (OPCA) pathways and the intermediolateral cell column of the spinal cord. [24,25,26] Glial inclusion formation is a prominent feature of MSA pathology and has therefore been added to the diagnostic criteria of definite MSA according to a consensus conference on MSA. [3]

Although inclusions have been described in five cellular sites (i.e., in oligodendroglial and neuronal cytoplasm and nuclei as well as in axons), [27] GCIs appear to represent the subcellular hallmark lesion of MSA. [28] Their distribution selectively involves basal ganglia, supplementary and primary motor cortex, the reticular formation, basis pontis, the middle cerebellar peduncles, and the cerebellar white matter. [28,29] The origin of GCIs remains mysterious. GCIs are argyrophilic and

half-moon, oval, or conical in shape. [28,30] They consist of filaments 20 to 30 nm in diameter and contain the classical cytoskeletal antigens ubiquitin and tau. [28, 31] The tau profile of MSA was shown to be different from the tau pattern in Alzheimer's disease, PSP, and CBD, more closely resembling normal adult tau. [28,32,33] Furthermore, alpha-synuclein, a presynaptic protein that is affected by point mutations in some families with autosomal dominant PD [34] and is present in Lewy bodies, [35] has also been observed in both neuronal and glial cytoplasmic inclusions [36,37,38] in MSA brains. This has led to the assumption that MSA belongs to the synucleinopathies, such as PD and DLB. Alpha-synuclein is a 140-amino-acid protein that is abundantly expressed in the brain, typically enriched at presynaptic terminals [39,40] and might be implicated in the process of lifelong learning and memory function. [39] The exact function of alpha-synuclein in the central nervous system and its subcellular distribution remain unknown. However, there is experimental evidence from mutant mice suggesting that alpha-synuclein is a presynaptic, activity-dependent, negative regulator of dopamine transmission. [41] It is established that the expression of this protein is exclusively found in the soluble fraction of the neuronal cytoplasm, whereas in MSA brains alpha-synuclein forms insoluble aggregates. Whether the aggregation of alpha-synuclein is induced by some other factor(s) or is the primary trigger of MSA pathology is unknown. Abnormalities in the alpha-synuclein gene have also been evaluated in MSA because A53T and A30P mutations have been reported in some families with autosomal dominant PD. [42,43] However, a detailed

nucleotide sequence analysis of the alpha-synuclein gene in 11 confirmed cases of MSA has suggested that mutations are not likely to contribute to the pathogenesis of MSA. [44] Other questions that remain to be elucidated are to what extent alpha-synuclein is normally expressed by oligodendrocytes and whether the formation of GCIs precedes or follows neuronal degeneration.

THERAPY The available therapeutic strategies in MSA are summarized in Table 5. Although the parkinsonian syndrome of most MSA patients fails to respond to L-dopa, 30% of the patients experience a definite, albeit transient, L-dopa response. Indeed, only 5% of patients still respond to L-dopa after 5-6 years of therapy. [4] Dyskinesias emerge in half of the treated patients and they are often dystonic, predominantly affecting orofacial muscles. The response to dopamine agonists such as lisuride, bromocriptine, or pergolide is even more disappointing. In a controlled trial of amantadine in a small number of patients with atypical parkinsonian syndromes, including MSA-P, there was no significant antiparkinsonian effect. [45] Stereotaxic procedures such as pallidotomy and subthalamic stimulation fail to improve the parkinsonian motor disturbance of MSA-P patients. [46] Alternative therapeutic strategies such as neuroprotection and neurotransplantation are currently being explored experimentally. [47] Amphetamine- and apomorphine-induced rotation asymmetries in a double-lesion rat model of MSA-P appear to be partly reversible by mesencephalic-striatal cografts. [47,48] Further experimental studies are required to

optimize the neurotransplantation procedure in the double-lesion rat model [49,50].

Table 5: Symptomatic Treatment of Multiple System Atrophy.

Parkinsonian Symptoms
First choice: Dopamimetics (L-dopa, dopamine agonists)
Second choice: Amantadine.
Orthostatic Hypotension
Increased salt intake
Head up tilt
Elastic stockings
Fludrocortisone, Ephedrine, Octreotide, Pyridostigmine
Detrusor Hyperreflexia (Urgency, Incontinence)
Oxybutynin
Intermittant self catheterization
Myoclonus
Clonazepam
Dystonia (Including antecollis)
Botulinum toxin
Depression
Amitryptilline, Serotonin reuptake inhibitors
Dysphagia and Dysarthria
Semisolid diet, Nasogastric feeding, Feeding gastrostomy, Speech therapy
Sialorrhea
Anticholinergics
Gait Disorders
Physical therapy
Use of walking aids
Wheel chair.

Progressive Supranuclear Palsy.

In 1964, Steele, Richardson, and Olszewski described PSP as a clinicopathological entity, although a few single clinical or pathologic descriptions had been previously reported [51,52] PSP is the most common parkinsonian disorder after PD, even if still underdiagnosed. Previous studies [53] showed that only half of PSP patients receive the correct diagnosis at the first clinical visit, 3 1/2 years after symptom onset. A study estimating the incidence of PSP in Olmsted County, Minnesota [54] found an average annual incidence rate (new cases per 100,000 person-years) of 5.3 for ages 50 to 99 years. The incidence of PSP increased with age (from 1.7 at 50 to 59 years to 14.7 at 80 to 99 years) and was consistently higher in men. Moreover, these figures are still underestimates if one considers that the same authors did not include autopsy-confirmed PSP cases evaluated during the same period that were misdiagnosed as other disorders [55] In addition, a large population-based prevalence study using currently accepted diagnostic criteria conducted in the London area to measure the frequency of PSP found even higher prevalence rates (6.4 per 100,000). [56] Again, in this study most of the PSP cases identified had not been diagnosed as PSP until the study. All these studies show that PSP has a higher prevalence and incidence than previously estimated.

The prognosis and survival of patients with PSP are different from those of patients with PD. Whereas PSP patients have a median survival time from symptom onset of 5 to 6 years, patients with PD, if appropriately treated, have a median survival time similar to that of the

general population. Thus an early and accurate diagnosis is very important for prognosis, management, and patients' participation in research.

CLINICAL FEATURES Typically, PSP patients present with early postural instability, supranuclear vertical gaze palsy, parkinsonism (bradykinesia and axial more than limb rigidity) not benefiting from levodopa therapy, pseudobulbar palsy, and subcortical dementia. Subsequent to the onset of postural instability, dysarthria and bradykinesia are the most common problems.

In the National Institute of Neurological Diseases and Stroke (NINDS) study, at the first visit to a specialized neurology center, which generally occurred 3 to 3.5 years after disease onset, [57] 96% of 24 PSP patients had gait disorder and postural instability (83% history of falls), 88% bilateral bradykinesia, 79% vertical supranuclear palsy (downward gaze abnormalities in 67%), 75% dysarthria, 63% a predominant akinetic-rigid disease course, 63% axial rigidity, 50% personality changes (comprising mostly apathy and depression), 46% frontal lobe-type symptomatology, 21% neck dystonia, and 16% dysphagia. In the series of Colosimo et al, [58] which evaluated symptoms within 3 years of onset, in 94% of the 16 PSP patients, symptoms progressed rapidly, and in 81% of the patients, onset was symmetric. Staring, nonblinking facies and sitting ``en bloc" are also characteristic of PSP patients. [59]

An absent, poor, or waning response to levodopa is a characteristic feature defining the atypical parkinsonian disorders. Similarly,

although not always, patients with these disorders may exhibit axial more than limb muscle involvement, although this feature is more evident in PSP.

Several features should make us suspect that a patient may suffer from PSP. Early instability and falls, particularly during the first year of symptom onset, should suggest the diagnosis of PSP. However, early instability and falls may also rarely develop in patients with corticobasal degeneration (CBD) when asymmetric symptoms develop in the lower extremities. [60] Instability and falls may also develop early in multiple system atrophy (MSA), although these symptoms are usually present when patients already exhibit autonomic disturbances. Marked slowing of vertical saccades (rapid eye movement between two stimuli not letting the eyeball movement be seen) usually precedes the development of vertical supranuclear gaze palsy and should readily point toward the diagnosis of PSP. The saccades in CBD may have increased latency but normal speed and are similarly affected in the vertical and horizontal planes, whereas in MSA the saccades have normal speed and latency. Patients with PSP may present prominent early or severe speech and swallowing difficulties and may exhibit oversized mouthfuls or overstuffing the mouth when eating, but these features may also be present in CBD. Florid frontal lobe symptomatology (apathy, impaired abstract thought, decreased verbal fluency, ``imitation" behavior, or frontal release signs) usually manifests at early stages in PSP, whereas it is typically less evident or manifests later in the other parkinsonian disorders. On the other hand, pyramidal signs, usually bilateral, are a feature that is seen later in PSP. Disproportionate

retrocollis, although thought to be characteristic in PSP, is usually a relatively late and infrequent sign in PSP.

In general, symptoms progress steadily for an average of 5-6 years, although some patients with neuropathologically confirmed PSP survive up to 16 years from onset. Neuropathologically confirmed PSP cases without ophthalmoplegia or presenting only with dementia or akinesia have been reported infrequently. [61,62,63,64] PSP patients rarely present with asymmetric parkinsonism, unilateral dystonia, or apraxia. [65,66] These are the features that, when present, should make one doubt the diagnosis of PSP (see Table 6)

Table 6: Red Flags Against the Diagnosis of PSP.

Onset earlier than age 40, Duration of more than 20 years
Aphasia, Cortical dementia, Cortical sensory or visual deficits
Hallucinations or delusions not due to medications
Fluctuating states of cognition and arousal
Severe postural faintness
Unilateral contractures
Maintained levodopa response and levodopa induced dyskinesias.

DIAGNOSTIC CRITERIA To improve accuracy in classifying PSP patients (increase sensitivity and decrease number of false-positive cases), the NINDS and the Society for PSP, Inc. (SPSP) sponsored an international workshop on the clinical diagnosis of this disorder in May 1995. The criteria

adopted by NINDS-SPSP, based on criteria proposed using the NINDS series of neuropathologically confirmed cases, proposed the inclusion and exclusion criteria for the clinical diagnosis of probable and possible PSP listed in Table 7. [67] In the NINDS series, the probable NINDS-SPSP criteria were highly specific (100%) but could identify only 50% of PSP cases. Such specific criteria are ideal for genetic studies, clinical drug trials, or analytic epidemiologic studies. The possible NINDS-SPSP criteria, which achieved 83% sensitivity and 93% specificity in the NINDS series, are useful for clinical care or for descriptive epidemiological studies. More recently, Lopez et al [68] confirmed the high specificity and positive predictive value of both possible and probable NINDS-SPSP criteria using an independent study sample and different clinical investigators. It would then be appropriate to rename as clinically definite the probable NINDS-SPSP criteria and as clinically probable the possible NINDS-SPSP criteria (Table 7) In addition, these investigators showed that this set of criteria is highly reliable.

Table 7: NINDS-SPSP Criteria for PSP

Definite PSP

Clinically probable or possible PSP and histologically typical PSP

Probable PSP (Clinically definite PSP)

Step 1: *Mandatory inclusion criteria*

Gradually progressive disorder

Onset at age 40 or later

Vertical supranuclear ophthalmoparaesis and prominent postural instability

With falls in the first year of symptom onset.

Possible PSP (Clinically probable PSP)

Step 1: *Mandatory inclusion criteria*

Gradually progressive disorder

Onset at age 40 or later

And either: (a) vertical supranuclear ophthalmoparaesis *or* (b) slowing of

Vertical saccades and prominent postural instability with falls within 1 year

of symptom onset.

For both probable and possible PSP

Step 2: *Mandatory exclusion criteria*

History compatible with encephalitis lethargica

Alien hand syndrome, cortical sensory deficits, focal frontal or temporal

Atrophy. Hallucinations or delusions unrelated to dopaminergic therapy.

Cortical dementia of Alzheimer's type, Prominent cerebellar symptomatology

or unexplained and early dysautonomia. Severe asymmetry of parkinsonian

signs

Neuroradiological evidence of relevant structural abnormality.

Whipples disease, confirmed by PCR, if indicated.

Neuropathologic Features Neuropathologically, PSP is characterized by abundant neurofibrillary tangles and/or neuropil threads in particular areas of the basal ganglia and brain stem; neuronal loss and gliosis are variable. Neurofibrillary tangles, neuronal loss, and gliosis in PSP particularly affect the striatum, pallidum, subthalamic nucleus, substantia nigra, oculomotor complex, periaqueductal gray, superior colliculi, basis pontis, dentate nucleus, and prefrontal cortex [51,69] Table 8 lists the inclusionary and exclusionary features included in the adopted NINDS neuropathologic criteria. [69,70] Pathological tau in PSP is composed of aggregated four-repeat isoforms that accumulate as abnormal filamentous lesions in cells and glia in subcortical and cortical areas. [71,72,73]

Table 8: NINDS Neuropathologic Criteria for Typical PSP.

Inclusion Criteria	**Exclusion criteria**
A high density of neurofibrillary tangles and neuropil threads in at least three of the following areas: pallidum, subthalamic nucleus, substantia nigra, or pons; and a low to high density of neurofibrillary tangles or neuropil threads in at least three of the following areas: striatum, oculomotor complex, medulla or dentate nucleus and clinical history compatible with PSP.	Large or numerous infarcts; marked diffuse or focal atrophy; Lewy bodies; changes diagnostic of Alzheimer's disease; oligodendroglial argyrophilic inclusions; Pick bodies; Diffuse spongiosis; Prion-P positive amyloid plaques.

Neurochemical studies indicate that the degenerative process in PSP involves dopaminergic neurons that innervate the striatum and form the nigrostriatal dopamine system as well as cholinergic and GABAergic efferent neurons in the striatum and other basal ganglionic and brain stem nuclei, thereby explaining the lack or transient nature of the levodopa response.

Laboratory Testing Eye movement recordings, evoked potentials, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, or positron emission tomography (PET) scans may be helpful to support the diagnosis or exclude other disorders.

Electrooculographic recording may help distinguish PSP from other parkinsonian disorders at an early stage. [74] There is slight or no saccade impairment in patients with idiopathic PD and pure striatonigral degeneration (i.e., those with no cerebellar signs). [74] PSP patients have decreased horizontal saccade amplitude and velocity but normal latency, whereas opposite results were obtained for CBD patients. [74] The antisaccade task (looking in the direction opposite to a visual stimulus), which correlates well with frontal lobe dysfunction, is reported to be bilaterally markedly impaired in parkinsonian patients with PSP, [74] although it may also be impaired in patients with Alzheimer's disease.

PSP patients have both slowed movement and slowed information processing. Their cognitive slowness can be evaluated with

complex reaction time tasks or with cognitive evoked potentials. [75,76,77] Event-related brain potentials recorded while PSP patients perform an Oddball task show a normal N1 component but dramatically increased latencies and decreased amplitudes of the P2 and P300 components. The remarkably delayed latencies found in PSP have not been reported in any other type of dementia. [78]

Computed tomography (CT), as well as MRI, may at some stage in the disease show definite atrophy of the midbrain and of the region around the third ventricle in more than half of PSP patients. [79,80] Thinning of the quadrigeminal plate, particularly in its superior part, seen in sagittal MRI sections, has been shown to support a diagnosis of PSP. [79] Minimal signal abnormalities in the periaqueductal region could also be seen in proton density MRI. Although CT and MRI of the brain are generally of little help in establishing the diagnosis of PSP, they can aid in ruling out other diagnoses (e.g., CBD when asymmetric atrophy may be present in the parietal area or MSA when there may be atrophy of the pons, middle cerebellar peduncles, and cerebellum or altered signal intensity in the putamen; they may also be used to rule out multi-infarct states, hydrocephalus, or tumors).

Magnetic resonance spectroscopy imaging detects different patterns of cortical and subcortical involvement in PSP, CBD, and PD [81] PSP patients, compared with controls, have reduced NAA/Cre in the brain stem, centrum semiovale, and frontal and precentral cortex and reduced

NAA/Cho in the lentiform nucleus. On the other hand, CBD patients, compared with control subjects, have reduced NAA/Cre in the centrum semiovale and reduced NAA/Cho in the lentiform nucleus and parietal cortex. Although significant group differences can be found using this technique, magnetic resonance spectroscopy is not helpful in differentiating between individual patients.

Fluorine 18 fluorodeoxyglucose PET scans and ^{123}Iodoamphetamine (IMP) single photon emission computed tomography (SPECT) blood flow studies [82,83,84] have shown marked reduction in frontal and striatal metabolism in PSP. Frontal hypometabolism in PSP is secondary to deafferentation and cortical pathology. [85] However, this finding is not specific to PSP. [86,87] PET measures of striatal dopamine D2 receptor density using ^{76}Br-bromospiperone or ^{11}C-raclopride are also significantly reduced in most PSP patients, [88,89] but again, these findings are not specific to PSP [90] Hypometabolism of glucose in the frontal cortex and decreased ^{18}F-fluorodopa uptake in the presynaptic nigrostriatal dopaminergic system (with similar reduction in both putamen and caudate) have also been shown by PET in PSP patients. [82,91]

THERAPEUTIC MANAGEMENT: Symptomatic Therapy Current treatments for PSP are ineffective because of the widespread involvement of dopaminergic and nondopaminergic neurotransmitter systems (GABAergic striatal interneurons, cholinoceptive striatal interneurons, cholinergic brain stem and opioid striatal neurons). [92] Neurotransmitter replacement

therapeutic approaches have thus far failed. There are no published well-designed randomized, controlled clinical trials using levodopa therapy, but single case studies and our clinical experience show no significant improvement with levodopa[93] Similar findings are observed in double-blind placebo-controlled studies with dopamine agonists (e.g., bromocriptine, pergolide) [94] It is likely that newer dopaminergic agonists such as ropinirole or pramipexole will show poor beneficial effects.[95] Although dopaminergic replacement therapies are usually only transiently and/or mildly effective, they should be tried when patients have parkinsonism[94,96] because lack of sustained and/or marked benefit from levodopa therapy effectively rules out PD and may also support the diagnosis of PSP (or other atypical parkinsonism). Future studies should evaluate the effects of selective D1 agonists because D1 receptors are relatively preserved in PSP.

In addition, two randomized, double-blind controlled trials with cholinergic agents (physostigmine and RS-86) showed mild or no efficacy. [97] On the other hand, as PSP patients' mental status and gait may worsen with anticholinergic drugs, these drugs should generally be avoided unless needed to treat particular symptoms. [98] Idazoxan, a noradrenergic agent reported to result in some minor improvement in the patient's motor performance, also has marked side effects. [99]

Palliative therapeutic approaches used in practice are listed in Table 9.

Table 9: Palliative Treatments

Feature	**Palliative Approach**
Gait instability	Weighted walkers; ?amitryptyline, physiotherapy.
Dysphagia	Change in food consistancy, Percutaneous endoscopic gastrostomy
Dysarthria	Speech therapy, communication aids
Decreased rate of eye blink	Artificial tears to avoid exposure keratitis
Blepharospasm, levator inhibition, other dystonias	Botulinum toxin
Depression	Antidepressants; support therapy.
Emotional incontinence	Antidepressants.
Drooling	Anticholinergics (Use cautiously)
Patient and family support	Social services; various support groups for PSP. Eg: Society for PSP (SPSP) in US. PSP(Europe) Association.

A small number of PSP patients have been subjected to pallidotomy without significant benefit. At present, there is no evidence that pallidotomy or any other surgical procedure helps PSP patients.

Possible Biologic Therapies: Although the etiopathogenesis of PSP is unknown, this disorder is associated with the inheritance of a specific

haplotype in the tau gene. [100,101] Some of the clinical and pathologic features in PSP resemble those found in some forms of familial frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) with defined mutations, including neuronal and glial tau inclusions consisting predominantly of four-repeat tau. [102] These observations emphasize the fundamental importance of tau protein in the neurodegeneration in PSP. However, despite the fact that a genomic defect in tau is implicated in the etiology of PSP, this abnormality does not explain the presence of the H1 haplotype in a considerable percentage of unaffected normal controls.[101]

Several laboratories have shown that lipid peroxidation may play a role in the neurodegeneration occurring in PSP[103-109] Albers et al[106] measured tissue malondialdehyde (MDA) levels in the subthalamic nucleus and cerebellum from brain tissue of 11 patients with PSP and 11 age-matched control cases using sensitive high-performance liquid chromatographic techniques and found a significant MDA increase in the subthalamic nucleus, but not in the cerebellum, of the PSP patients. These findings suggest that lipid peroxidation may explain regionally specific neurodegeneration in PSP. Significant increases (+36%) were also found in tissue MDA levels in the superior frontal cortex of 14 PSP patients as compared with controls, and significant decreases (-39%) were also found in the alpha-ketoglutarate dehydrogenase complex/glutamate dehydrogenase ratio. [104] Increased oxidation has also been found in the substantia nigra of PSP patients. [110] Further, Odetti et al [103] showed

that lipoperoxidation is selectively involved in PSP, and they hypothesized that intraneuronal accumulation of toxic aldehydes may hamper tau degradation, leading to abnormal aggregation. It is probable that irrespective of the primary cause of PSP, the onset of oxidative stress is a common mechanism by which neuronal death occurs and one that contributes to disease progression. Thus, it is conceivable that therapeutic strategies aimed at limiting free radical production and oxidative stress and/or damage may slow the advance of PSP.

Given the progress that has been made in understanding the significance of tau in the development of FTDP-17, it would seem likely that drugs that prevent the expression or accumulation of four-repeat tau may represent a potential therapy in this disease. Use of agents that prevent the aggregation of tau such as oligonucleotides or peptide nucleic acids that inhibit the splicing of tau E10 or the translation of E10+ messenger RNA, and thus the generation of four-repeat tau isoforms, may turn out to be a promising therapeutic approach.

Exploration of biologic therapies requires additional pathogenetic studies, but clearly these offer the most promise for future drug design. If studies confirm that free radicals are increased [103-110] the use of free radical scavengers that cross the blood-brain barrier (BBB) should be explored. Similarly, anti-inflammatory agents should be considered if the involvement of reactive glia is confirmed.

Because neurotrophic factors promote growth, survival, and differentiation of cholinergic, dopaminergic, and GABAergic neurons in cell

cultures and animal models and because these are the principal neuronal types affected in PSP, a therapeutic trial might be proposed with trophic factors or small molecules having nerve growth-like activity. Potentially useful proteins, such as growth factors, cannot be administered systemically because they have peripheral and central side effects and do not cross the BBB. Administration of proteins into the lateral ventricle by acute and/or chronic infusions may provide a means of delivery, but there is no compelling evidence that such an approach is effective in the human brain. [111] High levels of growth factors in the cerebrospinal fluid can lead to side effects associated with circulating growth factors. In addition, the ventricular lining is rich in receptors that can trap growth factors, thereby preventing diffusion into the brain parenchyma. Direct intraparenchymal injection of proteins into the brain, either by convection-enhanced delivery (CED) or by bolus injection, can achieve high drug concentrations in specific sites. [112] CED (infusions that are performed while maintaining a pressure gradient over time) distributes molecules to large areas of brain tissue (up to several square centimeters). [112] Alternatively, delivery by bolus injection relies on diffusion alone and results in high concentrations of drugs in tissue surrounding the needle tract with otherwise limited distribution.

Administration of therapeutic genes only to the disease-affected regions of the brain may be more beneficial than current treatment strategies, [111] which are largely based on the systemic administration of small molecules or proteins. Using CED to administer viral vectors into the brain in PSP may improve the spread of vector particles in the brain and

result in more uniform transgene expression. This should enable the chronic delivery of therapeutic growth factors that might slow down or halt the degeneration process in PSP.

Because current neurotransmitter replacement therapies in PSP are ineffective, coordinated efforts [113] to delineate the research needed in this area to find the cause and cure for this devastating disease have been initiated. It is hoped that as a result of these research efforts, biologic therapies will be developed that will prevent the abnormal aggregation of tau and prolong neuronal survival in this disorder and will in turn slow or stop the progression of PSP.

The Diagnosis of Parkinson's Disease

Parkinson's disease (PD) is characterized by rigidity, bradykinesia, rest tremor, impaired postural reflexes, asymmetric onset and a good to excellent response to levodopa. Pathological features include degeneration of pigmented neurons in substantia nigra along with the presence of Lewi bodies. [114]. Approximately 80-85% of parkinsonism patients seen in movement disorder clinics are found to have typical features of PD. [115] The diagnosis of IPD is purely clinical. The sensitivity and specificity of various clinical signs (and combinations of signs) for the diagnosis of PD vary widely for pathologically confirmed cases. [116]. Various diagnostic criteria have been proposed for the clinical diagnosis of PD [117,118,119,120,121]. But the most widely accepted one is probably the U.K Brain Bank Criteria. (Table 10,11,12). [122]

15-20% of patients with Parknosonism seen in Movement Disorder Clinics belong to the category of neurodegenerative diseases other than IPD (115). A great emphasis is being placed on the identification of clinical clues in these patients, who have a clinical diagnosis of Parkinsonism with additional or atypical clinical features. These patients are classified as having Parkinsonism Plus Syndromes or atypical parkinsonism. Several differences exist between IPD and parkinsonism plus syndromes in the pattern of extra pyramidal features, pattern of onset of illness, and therapeutic responses (Table 13)

PSP, MSA and Diffuse Lewi Body Disease (DLBD) are the common types of atypical parkinsonism syndromes. Diagnosis of these conditions, as in the case of PD, is purely clinical, based on a group of symptoms and signs, as discussed in detail earlier. Other investigations like neuroimaging [80,123-129] and sphincter electromyography [130,131] may be supportive. But a final (definite) diagnosis is based on autopsy study [121,132, 133, 134]

Table **10**: The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for the diagnosis of Parkinson's disease: Inclusion criteria

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
And at least one of the following:
Muscular rigidity
4-6Hz rest tremor
Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Table **11**: The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for the diagnosis of Parkinson's disease: Exclusion criteria

History of repeated strokes with stepwise progression of parkinsonian features.
History of repeated head injury
History of definite encephalitis
Oculogyric crisis
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features even after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language and praxis.
Babinski sign
Presence of cerebral tumor or communicating hydrocephalus on CT scan
Negative response to large doses of levodopa (if malabsorption excluded)
MPTP exposure

Table **12**: The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for the diagnosis of Parkinson's disease: Supportive criteria

(Three or more required for diagnosis of definite PD)
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting side of onset most
Excellent response (70-100%) to levodopa
Severe levodopa induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

Table 13: clinical features differentiating atypical parkinsonism & IPD

	IPD	**Atypical parkinsonism**
1. Patten of onset	Asymmetrical	Usually symmetrical
2.Ridigity	Peripheral more	Axial more
3. Rest Tremor	Present	Absent or atypical
4. Associated features (Early dementia, vertical gaze	Absent	Usually present (depending upon the type) abnormality, pyramidal dysfunction, cerebellar signs, autonomic dysfunction, myoclonus, cortical sensory loss)
5. Response to L-dopa	Excellent	Poor
6. Progress	Slow	Usually Rapid

Cognition in PD, PSP and MSA

The basal ganglia have been implicated in cognitive processes and behavioral regulation on the basis of two main arguments. [135]

1. Experimental studies in primates have shown that limited lesions of the striatum induce deficits in rule acquisition, behavioral control, working memory performance and selected attention
2. Cognitive changes have long been observed in patients with degenerative diseases that involve primarily the basal ganglia, such as Parkinson's disease, Huntington's disease and PSP.

From the clinical picture of these neuro-degenerative disorders, the main changes postulated to result from basal ganglia dysfunction are slowing of information processing, frontal-lobe like symptomatology, impaired memory retrieval, and personality changes like inertia and depressed mood [135]. These symptoms have been brought together under the term "subcortical dementia". But, often, these patients have only a mild degree of cognitive dysfunction, not severe enough to be called dementia. The clinical criteria commonly accepted to define dementia do not fit well with these patients, whose global intellectual deficiency is rarely severe, and whose loss of autonomy can be attributed largely to associated movement disorders [135]. Focal and isolated lesions within the basal ganglia structures have also been found to cause different types of cognitive dysfunction. The characteristics include 1) behavioral abnormalities with inertia, blunted affect and stereotyped and compulsive activities 2) normal

intellectual efficiency 3) preserved linguistic and spatial abilities 4)'frontal lobe' dysfunction 5) memory retrieval deficit 6) procedural learning disorders. [135] This syndrome shares several features with the consequences of frontal lobe lesions.

The cognitive impairments associated with PD span the full spectrum from mild executive and memory failure to florid dementia with confused thinking, severe memory dysfunction and profound behavioral changes. Some degree of cognitive dysfunction can be documented in almost all PD patients who undergo formal neuropsychological assessment. [136] The mild, but ubiquitous cognitive impairment in PD likely results from disturbances in multiple neurochemical and anatomical systems. Findings that cognitive dysfunction in PD correlates most with axial motor symptoms that do not respond to L Dopa administration suggest that cognitive impairment in PD may be due primarily to the pathology in non-dopaminergic systems. [137]

A disturbance in processes believed to be mediated by the dorsolateral regions of the frontal lobes, which have integral connections with the caudate, is thought to be fundamental to the cognitive deficits in PD. [138, 139, 140, 141] Many of these deficits cause executive dysfunction involving initiation, selection, planning, programming and monitoring of sensory inputs and goal directed behaviors, especially in non-routine situations. These higher order cognitive processes include the ability to maintain or shift cognitive or behavioral task, reason abstractly, form new concepts and use feedback to monitor and alter behavior. Working memory

deficits, involving disruption in the capacity to temporarily maintain and manipulate information required for complex cognitive tasks, also are related to dorsolateral frontal lobe dysfunction. Impairments in executive control and working memory are invoked to explain deficits exhibited by patients with PD on various behavioral tasks, such as conceptual classification, and set shifting when card sorting, fluency and flexibility in generating novel responses on word-list generation tasks, planning and executing multicomponent, ordered, goal directed activities and construction of complex visuospatial patterns. [142,143,144]

Executive dysfunction is also related to impaired memory for the temporal order of newly presented information, disturbed organization and strategic processing during memory encoding and retrieval, and deficits comprehending syntactically complex sentences. [140,145,146]

Another core feature of cognitive impairment in PD is "bradyphrenia". [147] Bradyphrenia, or slowed mental processing, is the mental corollary of bradykinesia or slowed motor functioning. It is characterized by slowed mental processing, an impairment of sustained mental effort and concentration, along with diminished interest and initiative. This type of slowed information processing is most disruptive in activities that have a high-cognitive load with many simultaneous mental operations, and it is postulated to underlie some of the working and long-term memory deficits in PD. [138]

Impaired visuospatial processing is a common deficit in PD, which can be associated with parkinsonian oculomotor dysmotility, impaired

visual contrast sensitivity, and the loss of executive functions that are typical features of disturbed cognition in PD. Visuospatial disturbances also are observed, however, on tasks that do not involve complex motor or mental operations. Difficulties have been documented, for example, in perceptual discrimination of visuospatial stimuli, body-spatial and extrapersonal localization, and visuospatial attention that cannot be explained by the typical sensory or motor problems of PD. [138,148]

Although explicit declarative memory, or the ability to learn and consciously recollect newly presented information, is relatively preserved in PD, recent studies have documented impairments in selective aspects of implicit memory. Implicit memory refers to performances that reveal the influence of prior learning but without awareness or explicit recollection by the subject. Implicit, or nondeclarative, memory dissociates behaviorally from explicit memory recall and recognition and appears to be mediated by different neural systems. [138] Patients with PD show relatively intact implicit memory for recently presented verbal stimuli, demonstrated by the fact that their recognition or completion of slightly degraded verbal stimuli is better for recently presented items than novel stimuli. These patients are impaired, however, on procedural tasks involving the implicit learning of new rule-based responses (Tower of Hanoi) or complex motor skills, such as pursuit rotor. [138,149]

In contrast with the previously noted disturbances, many other cognitive processes are remarkably well-preserved in non-demented patients with PD. Simple attention, as demonstrated in tasks such as

forward digit span and simple reaction time, is relatively normal in patients with PD. Non-demented and even most demented patients with PD show relatively spared language knowledge in terms of vocabulary and word meanings (semantic memory). [138] Nondemented patients with PD also perform relatively well on tests assessing memory for remote events. Moreover, patients with PD are able to encode new information for long-term memory, as inferred from their normal performance on tests that assess memory for recently learned information using recognition rather than free-recall paradigms. [138]

Dementia is defined as an impairment in three or more cognitive domains (e.g., language, long-term memory, visuospatial processing, attention, working memory, executive control, and praxis), which is of sufficient severity to interfere with work, social activities, or interpersonal relationships. [138] It is now well accepted that dementia is common in association with PD and that it is distinct form the milder cognitive impairment seen in almost all patients with PD. The recent estimates of dementia in PD are between 30% and 40%. [150,151,152]

Several clinical features are associated often with the development of dementia in patients with PD. Patients on the young side of the age spectrum when symptoms first appear, and in whom gait and balance are relatively intact, are less likely to become demented, at lease in the short term. [138] In contrast, patients whose illness begins at an older age (after age 60 years), and who have postural instability and gait difficulty

as the dominant motor manifestations, are at increased risk to become demented as the disease advances. [147]

Longer disease duration also is associated with increased incidence of dementia in patients with PD. Longitudinal studies found that dementia accrues at the rate of 40 to 70 cases per 1000 years of observation, representing a relative risk of almost four times that of age-matched peers without PD. [153,154,155] The duration of the illness may be less important as a risk factor for dementia than the age the motor symptoms began. [138] Dementia is rare in patients with PD under age 60 years, despite the fact that patients who develop the motor symptoms in their 30s or 40s will have had the illness for more than 20 years by the time they reach their 7th decade. It has been suggested that an interaction between the pathology of PD and the normal aging process might contribute to the development of dementia in older patients. Others, however, note that the absolute risk of dementia for PD patients is constant over time and that the apparent rise in incidence with age is caused by an increase in the overall base rate of dementia that is naturally associated with advancing age. [138]

Several studies found that the occurrence of dementia is directly associated with the severity of motor symptoms in patients with PD. [156,157] Additionally it was reported that dopaminergic therapy is less efficacious in patients with PD who develop dementia. Because cognitive impairment correlates most strongly with those motor symptoms that respond least well to dopaminergic therapy (postural and gait disturbance),

it is not surprising that severe cognitive dysfunction is more prevalent in this subset of patients with PD. [137,138]

Dementia in PD is associated with a higher occurrence of psychiatric symptoms, such as major depression. It is unclear whether the relationship between dementia and these neuropsychiatric symptoms in casual, coincidental, or the result of a common third factor. [138]

Recent evidence suggests that dementia is not a simple extension of the mild cognitive impairment seen in most patients with PD. Longitudinal studies show that patients with PD who subsequently become demented tend to exhibit a specific neuropsychiatric pattern early in the course of the disease, and this pattern is different from the one seen in non-demented patients with PD and in patients with early Alzheimer's disease. [153,156,158,159] Disproportionate impairment on measures of executive function early in the course of PD predicts later development of more global and severe cognitive disturbance. Such findings suggest that dementia in PD is a qualitatively distinct disorder and likely reflects involvement of a variety of neurodegenerative and biochemical factors, in addition to the classical depletion of the striatal and mesolimbic dopamine pathways. [160]

The term "subcortical dementia" is used to characterize the constellation of cognitive and behavioral impairments in demented patients with predominant pathology in subcortical areas, including PD, Huntington's disease, progressive supranuclear palsy, and multiple sclerosis. [161] The symptoms of subcortical dementia differ from those seen in the "cortical" types of dementia, such as Alzheimer's disease and Pick's disease. [138]

The clinical features of the subcortical dementia syndrome include pronounced bradyphrenia or cognitive slowing, impaired executive and working memory functions necessary for abstraction, concept formation and complex problem solving, visuospatial processing deficits, and impaired memory retrieval. Subcortical dementia syndromes involve deficits in the motoric aspects of speech production (i.e., reduced rate, loudness, prosody, and articulatory precision) and distortions in the mechanics of writing (i.e., micrographia). [162] Mood disorders, especially depression, occur more often with subcortical than cortical dementia. Although subcortical dementia usually is not associated with prominent language dysfunction, some demented patients with PD do exhibit semantic impairment and agnosias. Presentation of dementia in PD is heterogeneous. Characteristics of subcortical dementia are found in most patients with PD and dementia, but there is no single pathognomonic neuropsychologic profile.

The clinical heterogeneity of parkinsonian dementia probably reflects the essential variability of the underlying pathologic substrate. Several competing etiologic hypotheses have evolved from two decades of autopsy studies, most focusing on Alzheimer's disease (AD). [138] But only in the last 10 years has the development of sensitive immunostaining shown that intraneuronal cortical Lewy bodies (CLB) are the most common pathologic finding in the brains of patients with PD, especially when dementia is an added feature. [162] Before immunostaining, at least half of all autopsied patients with dementia were thought to have no obvious cause for the dementia except for nigral degeneration. For example, dementia in

PD was linked to neuronal loss in the medial substantia nigra, which projects to the caudate nucleus and frontal association areas and is unlike the lateral substania nigra, an essential component of a frontal-striatal cognitive feedback loop. [163]

The concept of dementia associated with the widespread distribution of CLB was first postulated by Okazaki et al and later expanded by Kosaka et al as examples of a disorder that became known as diffuse Lewy body disease (DLBD). The clinical hallmark of DLBD was a contemporaneous combination of progressive dementia and secondary, usually less severe, parkinsonism. [138] Histopathologic examination in these cases showed amorphous eosinophilic (hematoxylin and eosin) intracytoplasmic cortical inclusions that were called CLB, although they lacked the discrete and easily identified eosinophilic center and halo of the classic Lewy bodies (LBs) found in the substantia nigra.

Reports on the pathologic basis of dementia associated with PD began to appear in the early 1980's with the predominant finding at autopsy of AD pathology as the presumed cause of the dementia. In about one half of the demented PD patients the severity of co-existent neuritic plaque and neurofibrillary tangle pathology is sufficient to justify an independent diagnosis of AD. More recently developed techniques for immunostaining of ubiquitin, an intraneuronal protein and constituent of CLB, have enabled pathologists to identify CLB with much greater precision than was ever possible with Hematoxylin and Eosin. [138] The recent discovery that the protein alpha synuclein is mutated in rare autosomal dominant PD and that

immunostaining identifies this protein in all LB in the nigra and cortex further sharpened the precision of immunostaining as an investigative and diagnostic tool. [138] Because of these developments, CLB have become an almost universal finding in PD, and have replaced AD as the signature pathology of dementia in the setting of PD. Although the density of CLB has been reported to correlate with the severity of dementia, these inclusions have also been found abundantly in some patients who were not clinically demented. The concurrent presence of Alzheimer plaques and tangles in many patients has led to the application of the term Lewy body variant of AD to this frequently occurring mixture. [138] The frequent coexistence of Alzheimer and Lewy body pathologies raises the still unanswered questions of whether a common etiology produces both pathologies or whether, because they are both common, they occur coincidentally but without a pathogenetic linkage. Even among cases where the total plaque and tangle pathology fails to exceed the diagnostic threshold for AD, it is likely that the presence of even modest Alzheimer pathology represents an additional risk factor for dementia.

Dementia in PD has also been associated with degeneration of the nucleus basalis of Meynert, a deep, subcortical assembly of cholinergic neurons, from which axons project to association cortex and hippocampus, among other regions. Nucleus basalis lesions are thought to contribute to a deficiency of cortical acetylcholine, which in turn plays a role in producing an evolving dementia in PD. In some studies, the severity of dementia, but not other clinical manifestations of PD, correlates with reduced levels of

brain choline acetyltransferase, the synthesizing enzyme for acetylcholine and the stable pathologic marker for loss of neurons in the nucleus basalis. Cell loss in the nucleus basalis of patients with PD and dementia is seen even in the absence of plaques and tangles. Because the studies of the nucleus basalis in PD were published before the advent of immunostaining, it is likely that CLB were present but not identified in these brains.

Finally, the pontine locus ceruleus, a site of neuronal pathology in PD, provides noradrenergic projections to the cerebellum, hypothalamus, striatum, septum, hippocampus, and neocortex. Some investigators speculated that the loss of neurons in the locus ceruleus might be responsible for the high frequency of dementia and depression on patients with PD. [138]

In summary, the most rational working hypothesis is that the dementia of PD and selected other parkinsonian disorders is caused by the uncontrolled proliferation of poorly understood intraneuronal cortical pathology, of which the α-syn CLB is currently the most sensitive and specific marker. The additional contribution of AD pathology, reduced acetylcholine, and other biochemical deficiencies is probably important, for the clinical heterogeneity of the dementia of PD.

The presence of cognitive and behavioral abnormalities in PSP was recognized by the original authors and has been studied in detail by subsequent investigators. The nine patients described by Steele et al developed personality changes and mild mental deterioration early in their clinical course. [51] The majority developed mild to moderate cognitive

impairment, whereas two went on to develop severe dementia. The prominent features were irritability, indifference, lability of mood, and impairment of memory retrieval, calculation, abstract thinking, insight, attention and comprehension. [165] Later on, Albert et al reintroduced the concept of subcortical dementia in PSP and described it as involving deficits in activation and timing, and characterized by bradyphrenia (slowness of thought process), personality change (apathy or depression), forgetfulness rather than true memory impairment, and impaired manipulation of acquired knowledge (calculating and abstracting). [161] Aphasia, agnosia and apraxia- prominent in cortical dementias- were absent. [164]

Most of the subsequent studies support the concept that a profile of subcortical dementia characterizes the cognitive deficits in PSP. The negative studies (Kimura et al and Fisk et al)[164] finding no cognitive impairment in PSP did not include tests considered particularly sensitive to frontal system impairment.

Maher et al and Dubois et al found a frontal lobe type of cognitive profile in PSP. [166,167] The latter used verbal fluency tasks, a revised version of the Wisconsin Card Sorting Test, a graphic series and observation for imitation and utilization behavior. Pillon et al compared the severity of cognitive impairments in patients with PSP, Huntington's Disease (HD), PD and Alzheimer's disease (AD). Dementia was more common and more severe for PSP patients than patients with PD. The PSP group had significantly lower scores in all frontal lobe tests; compared to PD. PSP patients also had more difficulty in tests of attention. [168]

Litvan et al sought to clarify the extent and nature of memory impairment in PSP (12 patients and 12 age matched controls) and found that there was significant impairment of several aspects of memory including abnormally rapid forgetting, increased sensitivity to interference and difficulty in using strategic, long term memory search mechanisms. Recognition memory was less impaired than recall. [169]

Robbins et al compared the performance of patients with PSP, PD and multiple system atrophy (MSA) on tasks sensitive to frontal lobe function including an attentional set shifting test, a planning test (the Tower of London), and a test of spatial working memory. Although all the groups were impaired on these tasks, the patients with PSP demonstrated more severe disturbance on the attentional set-shifting test. [170]

Dementia is an exclusion criterion for the diagnosis of multiple system atrophy [3] and a significant degree of cognitive decline was seen only in 2% of patients in a large series of 203 patients [5]. But cognitive impairments (not necessarily amounting to dementia) have recently been reported in patients with MSA. [164] Sullivan et al in 1991 reported a single case of probable MSA with emphasis on Neuropsychological aspects. The patient, a 55 year old woman, was found to have selective impairments on only a few tasks in the absence of global dementia / mood disturbances. The patient performed well on the Wisconsin Card Sorting Test and also on tasks of visual search, design fluency, verbal and non verbal recognition and recall, language function and visuospatial function. On the contrary, she committed significant errors on the picture completion and picture

arrangement subtests of the WAIS-R, impaired motor sequencing for manual gestures and impaired memory span for serial arm movements. Letter fluency, but not semantic fluency, was significantly impaired; the patient also did poorly on a distracter test of short-term memory. [171]

Robbins et al compared the performance of 16 patients with MSA and 16 normal control subjects on a variety of psychometric tests with emphasis on three measures believed to be specific for frontal lobe dysfunction – computerized adaptation of an attentional set-shifting paradigm, the Tower of London planning task and a test of spatial working memory. Patients with MSA showed significant deficits on all three of these tests with a qualitative and quantitative pattern of performance more similar to frontal lobe lesions than to that of patients with PD. There was no evidence of any significant intellectual deterioration, perceptual difficulty, naming difficulty, or any significant learning or memory abnormality. There was no correlation between extent of cognitive impairment and disease duration / severity of motor deficits. [172]

Testa et al, [173] by administering a battery of neuropsychological tests emphasizing visuospatial capabilities and memory, found that patients with MSA and PD showed similar cognitive function, performing poorly compared to controls.

According to the current concept, MSA consists of two sub groups – MSA-P [The 'Parkinsonian' type – formerly called Striatonigral Degeneration (SND)] and MSA-C [The cerebellar type- formerly called sporadic 'Olivo Ponto Cerebellar Atrophy' (OPCA]. [3,50,174,175,176,177]

Around 4/5th of all cases are of the MSA-P type. [3,50] Almost all of these studies have included only patients with SND, and for the same reason, didn't probably represent the MSA group per se. [164]. Positive family history is an exclusion criterion for MSA. [3,176] Majority of the studies on the cognitive functions of the cerebellar type had patients with positive family in the patient cohort, which means that the groups were not homogenous MSA-C, but 'contaminated' by hereditary spinocerebellar degenerations. [164]

There have been some studies comparing the cognitive functions of the three parkinsonian syndromes. Pillon et al compared the neuropsychological pattern of 14 consecutive patients of MSA with PD and PSP. The MSA group consisted of patients with SND alone. Compared with controls, the performance of patients with SND was impaired on category and phonemic fluency, frontal behaviors, trail making test A and B, and free recall of the Grober and Buschke test, but normal on the revised WAIS verbal scale, Raven 47 colored progressive matrices, Wechsler memory scale, California verbal learning test, Wisconsin card sorting test, and the Stroop interference condition. The performance of patients with SND was also compared with that of 14 patients with Parkinson's disease and 14 patients with progressive supranuclear palsy (PSP) matched for age at onset, duration of disease, severity of intellectual deterioration, and depression. The results showed that the dysexecutive syndrome of SND is similar to that of Parkinson's disease and less severe than in PSP. [178]

Robbins et al using three computerised cognitive tests previously shown to be sensitive to frontal lobe dysfunction compared groups of patients with PD, MSA and PSP matched for overall clinical disability. On a test of planning based on the Tower of London task, all three groups were impaired, but in different ways. The groups PSP and PD were slower in the measure of initial thinking time, whereas the group with multiple system atrophy was only slower in a measure of thinking time subsequent to the first move, resembling patients with frontal lobe damage. On a test of spatial working memory, each group showed deficits relative to their matched control groups, but the three groups differed in their strategy for dealing with this task. On a test of attentional set shifting, each group was again impaired, mainly at the extradimensional shifting stage, but the group with PSP exhibited the greatest deficit. The results are compared with previous findings in patients with Alzheimer's disease or frontal lobe damage. It is concluded that these basal ganglia disorders share a distinctive pattern of cognitive deficits on tests of frontal lobe dysfunction, but there are differences in the exact nature of the impairments, in comparison not only with frontal lobe damage but also with one another. [170]

Soliveri et al did a neuropsychological follow up in patients with PD, MSA-P, and PSP. Twenty-three patients with SND and 21 with PSP referred consecutively, and 18 patients with PD matched for severity of parkinsonism were compared on a comprehensive battery of cognitive tests and motor invalidity scales. A mean of 21 months later (range 18-24 months)

the patients were called for retesting. Only 12 patients with PD (66.6%), 14 with SND (60.8%), and 11 with PSP (52.4%) were retested; those who dropped out refused, had died, or were too disabled. The patients with PSP performed worse than patients with PD or SND in the short tale, verbal fluency, visual search, and Benton tests at first evaluation. Overall cognitive performance was similar in the PD and SND groups except that the SND group did significantly worse on the verbal fluency test. Between group comparison of changes in scores from first to second evaluation showed that patients with PSP deteriorated significantly in the Nelson test compared with patients with PD or SND, and those patients with PSP or SND declined significantly on the visual search test compared with patients with PD. There was no difference between the groups for motor decline. Two patients with PSP were demented (DSM IV criteria) at first evaluation and six at second evaluation; no patients with PD or SND were demented at either evaluation. The greater decline of patients with PSP in attention, set shifting, and categorization abilities is probably related to the conspicuous frontal deafferentation associated with direct premotor and prefrontal involvement, and to dysfunction of the midbrain ascending activating system, known to occur in PSP. [179]

Bak [180] et al examined the ability of a brief and simple cognitive screening test – the Addenbrooke's cognitive examination (ACE)[181] - to detect cognitive deficits in atypical parkinsonian syndromes. ACE, the mini-mental state examination (MMSE), and the dementia rating scale (DRS) were applied to 26 patients with MSA, 39 with PSP, and 25 with

corticobasal degeneration (CBD). The results were then compared with those obtained in 30 healthy age matched volunteers and 30 patients with Alzheimer's disease. In all four diseases the rate of detection of cognitive impairment on ACE was higher than on MMSE and comparable with DRS. The severity of cognitive impairment was most pronounced in the CBD group, which showed a similar degree of impairment to the Alzheimer group. In contrast, MSA patients were the least cognitively impaired. The PSP group took an intermediate position.

Thus, summarizing, PD and MSA have a similar subcortical pattern of cognitive impairment, not amounting to dementia. Dementia may occur in around 30% of patients with PD; however, it is rare in MSA, and is an exclusion criterion for this disease. In PSP, the striatofrontal dysfunction is so severe that it leads to dramatic planning, monitoring and recall deficits, evolving towards dementia. [182]

AIM OF THE STUDY

To evaluate and compare the profiles of cognitive dysfunction in Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP) and Parkinson's Disease (PD).

MATERIALS AND METHODS

MATERIALS AND METHODS

Study Design: A prospective study that compared the cognitive function test results of 25 consecutive cases each of MSA and PSP with that of 25 cases of PD.

Patients and Methods: The study was conducted at the Comprehensive Care Center for Movement Disorders, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology during the period June 2003 to May 2005. Twenty-five consecutive cases each of MSA and PSP that satisfied diagnostic criteria for these conditions were selected from the Movement Disorders Clinic. MSA was diagnosed using the Consensus Diagnostic Criteria and PSP was diagnosed using the NINDS-SPSP (National Institute of Neurological Diseases and Stroke – Society for Progressive Supranuclear Palsy) criteria. The inclusion and exclusion criteria were those specified for the respective diseases (Tables 2, 3, 4, 7, 10, 11, 12) [3,67,122]. The diagnosis was verified by the Movement Disorder Specialist in all the cases. Presence of any significant neurological / psychiatric co-morbidity likely to confound the results (history of strokes / depression / active psychosis), and advanced disease causing significant physical debility (making co-operation with the examiner performing the neuropsychological tests difficult) were additional exclusion criteria. All the patients, along with the caretakers, underwent a detailed interview and a detailed history was taken in all cases. A thorough and systematic

neurological examination was done for all patients, including application of the UPDRS (Unified Parkinson's Disease Rating Scale motor subset; mUPDRS). The patient groups were comparable with respect to age as well as UPDRS motor scores (mUPDRS). The MSA patients were subcategorized into two groups – MSA-P (The 'Parkinsonian' Type- where parkinsonism was the predominant manifestation; equivalent to the previous 'striato-nigral degeneration') and MSA-C or the 'Cerebellar' type, with cerebellar dysfunction as the predominant manifestation (previously called sporadic olivopontocerebellar atrophy').

Neuropsychological Tests: All the patients were examined using a battery of Neuropsychological Tests, selected by the Cognitive Neurologist. This consisted of Folstein's Mini Mental Status Examination (MMSE), Addenbrooke's Cognitive Examination (ACE), tests for fluency, the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT), consisting of 2 parts, TMT-A and TMT-B. The tests were performed under the close supervision of a Neuropsychologist, experienced in the assessment of cognitive dysfunction using this test battery

MMSE: The purpose of this test is to screen for mental impairment, to document intellectual changes that occur with time, and to assess the effects of potential therapeutic agents on cognitive functioning. It is brief, easily administered and easily scored. The test consists of a variety of items that assess the orientation to time and place, attention / concentration, language, constructional ability, and immediate and delayed recall. Widely

used by neurologists, the items were formalized by Folstein, Folstein and Mc Hugh [183]. The MMSE score is the total number of correct answers. Failure to respond should be scored as errors. The maximum score is 30 points.

ACE: The Addenbrooke's Cognitive Examination was developed with the aim of offering clinicians a brief and simple cognitive screening battery incorporating the MMSE, but extending it to cover a wider range of cognitive domains including language and frontal executive functions [181]. It consists of 6 subtests assessing orientation, attention, verbal fluency, memory, language and visuospatial function. It is more sensitive and reliable than MMSE for the early detection of dementia in Alzheimer's disease and Frontotemporal dementia. The maximum score for all the six subtests taken together is 100 points.

Tests for Fluency: The tests for fluency were the standard ones incorporated in ACE itself. Fluency was tested under two headings – literal fluency and category fluency. To test for literal fluency, the patient was asked to tell as many words (common nouns) as possible in 1 minute, beginning with the letter 'p' (The consonant 'Pa' in Malayalam). The ability to tell the names of as many animals as possible in one minute, tested category fluency.

The Wisconsin Card Sorting Test: A modification (Hazel E Nelson, 1976) of the Wisconsin Card Sorting Test, consisting of 4 unique stimulus cards

and 48 response cards was used [184]. The purpose of the test is to assess the ability to form abstract concepts, to shift and maintain set and utilize feedback. The test is considered a measure of executive function in that it requires strategic planning, organized searching, the ability to use environmental feedback to shift cognitive sets, goal oriented behavior, and the ability to modulate impulsive responding.

The Trail Making Test: This is a test for attention, sequencing, mental flexibility, visual search and motor function. It requires the connection, by making pencil lines between encircled numbers randomly arranged in a page, in proper order (Part A) and encircled numbers and letters in alternating order (Part B). The time taken to complete, and the number of errors are noted.

Neuropsychological Data of Idiopathic PD Patients: Previously collected data, from the Parkinson's disease patients under follow up in the Comprehensive Care Center for Movement Disorders, SCTIMST, was used for comparison. The PD patients were matched, with respect to age and physical debility (as judged by the UPDRS subset 3), with the atypical parkinsonism patients.

Statistical analysis: The statistical analysis was made using the T test for independent samples.

RESULTS

RESULTS

Demographic Characteristics:

Age and Sex: The mean age was 61.4 years (Range: 48 years to 73 years) for patients with MSA, 62.4 years (Range: 50 years to 72 years) for patients with PSP and 58.6 years for patients with PD (Range: 50 years to 76 years) The male to female ratio was 15:10 for MSA group, 16:9 for the PSP group and 15:10 for the PD group. (See Table 14)

Table 14: Demographic Characteristics of the Three Patient Groups

		Mean age, in years (Range)	**M: F**
MSA (n=25)	Possible (n=13)	61.5 (51-73)	10:3
	Probable (n=12)	61.3(52-71)	5:7
	Total	61.4 (48-73)	15:10
PSP (n=25)	Possible (n=6)	63.3 (50-72)	2:4
	Probable (n=19)	62.2 (52-72)	14:5
	Total (n=25)	62.4 (50-72)	16:9
PD (n=25) (All cases 'definite' PD)		58.6 (50-76)	15:10

Characteristics of the 'Atypical Parkinsonism' Group:

MSA: Out of the 25 patients, 11 were being treated as and referred as PD by the referring doctor. Four patients were referred with a diagnosis of 'Parkinsonism' and three with 'ataxia'. The diagnosis at the time of referral was 'myelopathy', 'polyneuropathy', 'movement disorder' and 'cerebellar degeneration' for one patient each. The referring doctor diagnosed MSA in only three cases.

The average duration of symptoms was 3.3 years for the MSA group (Range: 1 year to 8 years). MSA was of the parkinsonian type (MSA-P) in 80% (n=20) of the patients; the rest had MSA-C (Cerebellar type). Symptoms of autonomic nervous system dysfunction (postural giddiness, bladder dysfunction, erectile dysfunction) were the commonest, at least one of them being present in all the patients. All but one patient had symptoms of parkinsonism, but rest tremor was less common (present only in 11 of the 25 patients). Significant postural instability with falls was present in 10 patients. Only patients (all) with MSA-C had symptoms of cerebellar dysfunction. Dysarthria was a symptom in 11 patients and dysphagia in three at the time of presentation to us. Out of the 20 patients with MSA-P and five with MSA-C, 17 and two respectively were exposed to L-Dopa in sufficient doses without any sustained benefit; three had L-Dopa induced dyskinesias.

Though symptoms of ANS dysfunction were present in all patients, they were the first to come in only 10 patients. Rest (n=15) of the patients had symptoms of parkinsonism as the initial manifestation. None

had cerebellar dysfunction as the sole first symptom, though one patient with MSA-C had ataxia, along with bladder symptoms as the initial manifestation.

Examination showed significant postural hypotension in 22 of the 25 patients (88%). It was sufficient enough to be classified as 'criterion' (as per the Consensus Diagnostic Criteria) in 10 patients, and as 'feature' in the rest [3]. None of the patients had any eye movement abnormalities. Axial cerebellar signs (ataxia) were seen in all patients with MSA-C, and in addition, three patients with MSA-P who had no symptoms pertaining to cerebellar involvement. But appendicular cerebellar signs were present only in the MSA-C group (all the five patients). Two patients with MSA-C had cerebellar type of nystagmus, and four had cerebellar dysarthria. These findings were not seen in any of the patients of the MSA-P group. Pyramidal signs were seen in 10 patients, all of whom had exaggerated deep tendon reflexes. Bilateral extensor plantar response was seen in three of them.

Symptoms of cognitive dysfunction were less common among patients with MSA; symptoms of frontal subcortical dysfunction were a problem only for 5 patients; 6 had memory disturbances.

MRI scans of the brain were available for 11 patients, and the findings were: cerebellar atrophy in 10 patients, brainstem atrophy in 8, putaminal signal changes in 5 and mild cortical atrophy in 3 patients. Of the five patients with putaminal signal changes, three had a hyperintense posterolateral putaminal rim, while the rest had only putaminal hypointensity. Sphincter EMG studies were available for six patients. Of

them, 4 (one with MSA-C and three with MSA-P) had denervation changes, while the other two were normal (both being MSA-C patients)

The Consensus Diagnostic Criteria for MSA was applied, and 12 of the patients (48%) were classified as 'Probable MSA', and the rest as 'Possible MSA'. None of the patients died during the study and therefore there was no autopsy-proven case of 'Definite MSA'.

PSP: The referring doctor had made a diagnosis of PD in 13 of the 25 patients. Five patients were referred as 'Parkinsonism'. The diagnosis at the time of referral was 'hemiplegia', 'stroke', 'neurologic problem' and 'ataxia' for one patient each. The referring doctor diagnosed PSP in three of the patients.

The average duration of symptoms was 3.3 years (Range: 1 year to 7 years). Symptoms of parkinsonism (bradykinesia, stiffness of limbs, tremor, postural instability) were the commonest, at least one of them being present in all the patients. But rest tremor was less common (Present only in 8 of the 25 patients). All the patients had history of significant postural instability with falls. Symptoms of autonomic nervous system dysfunction, in the form of urinary symptoms and / or erectile dysfunction were present in 19 patients. No patient had symptoms suggestive of cerebellar dysfunction. 18 patients had dysarthria and 11 had dysphagia at the time of presentation to us. All the patients except one were exposed to L-Dopa in high doses without any sustained benefit. No patient developed L-Dopa induced dyskinesias.

All the patients had parkinsonism as the first and predominant symptom.

Significant postural hypotension was not present in any patient. Eye movements were abnormal in all patients. 80%(n=20) had supranuclear ophthalmoparaesis, with down gaze affected in all; the rest had slowing of vertical with or without slowing of horizontal saccades. Axial / appendicular cerebellar signs or nystagmus were not seen in any of the patients. Pyramidal signs were seen in 19 patients, all of who had exaggerated deep tendon reflexes. Bilateral extensor plantar response was seen in 7 of them.

MRI scans of the brain were available for 14 patients, and the findings were: midbrain atrophy in 12 patients, additional periaqueductal signal changes in 8 patients, and mild diffuse cortical atrophy in eight. None had cerebellar atrophy or putaminal signal changes. Two had normal MRI scans

The NINDS-SPSP criteria were applied, and 19 of the patients (76%) satisfied the criteria for 'probable PSP'. The rest were 'possible PSP'. No case came to autopsy during the study. Symptoms of cognitive dysfunction were totally denied by four of the patients and their caregivers. The rest (21 patients; 84%) had cognitive symptoms at the time of presentation. Caregivers of 20 patients gave history suggestive of frontal sub cortical dysfunction, (apathy, inertia, and reduced social interactions) while 11 complained of memory problems. Any patient or caregiver did not report symptoms of language, visuospatial orientation or praxis disturbances.

Characteristics of the PD patients

Prospectively collected data of PD patients, done earlier, was used for comparison with the atypical parkinsonism Group. Table 14 gives the demographic characteristics of the PD cases. The age and UPDRS motor scores of the PD patients were comparable to those of MSA and PSP cases. All the PD cases belonged to the category of 'definite' Parkinson's disease, as per the diagnostic criteria used. Cognitive symptoms were present in 16 (64%) of the 25 patients. 14 patients had symptoms suggestive of an executive dysfunction; five of them complained of memory disturbance in addition. Memory disturbance was the only cognitive symptom in two patients. No patient had symptoms suggestive of language dysfunction/ apraxias/ visuospatial disorientation.

Tests for Global Cognitive Functions

MMSE Scores: The mean Mini Mental Status Examination score was 28.3 for MSA (SD 1.7), 22.5 for PSP (SD: 2.6) and 27.2 for PD (SD: 1.8) patients. MSA group performed better than PSP ($p<0.001$) and PD. PD patients performed significantly better than PSP in MMSE.($p <0.001$)

Table 15: MMSE Scores of the Three Patient Groups

Diagnosis	MMSE (Range)	MMSE (Mean)	MMSE (SD)
MSA	24 - 30	28.3	1.7
PSP	17 - 27	22.5	2.6
PD	23 -30	27.2	1.8

ACE: The MSA group performed significantly better than PSP ($p<0.001$) and PD ($p= 0.003$) in Addenbrooke's Cognitive Examination. The mean ACE Score was 83.9 (SD: 7.0) for the MSA group, 77.0 (SD: 8.3) for the PD group and 66.5 (SD: 8.6) for the PSP group. The PD group performed significantly better ($p <0.001$) than PSP.

Table 16: ACE scores of the three groups of patients

Diagnosis	ACE (Range)	ACE (Mean)	ACE (SD)
MSA	70 - 96	83.9	7.0
PSP	54 - 81	66.5	8.6
PD	66 - 93	77.0	8.3

Tests for Frontal Lobe Function

Tests for Fluency: For MSA group, the mean score for literal fluency task was 9.5 (SD: 3.3). The scores for PSP and PD groups were 4.9 (SD: 1.4) and 8.8 (SD: 4.7). There was no statistically significant difference between the MSA and PD groups ($p = 0.538$) while both fared significantly better than the PSP group ($p<0.001$). The mean scores for the Category Fluency Task were 11.1 (SD: 3.1), 7.2 (SD: 2.7) and 11.9 (SD: 3.6), for the MSA, PSP, and PD groups. Again, there was no statistically significant difference between MSA and PD ($p=0.39$), while the performance was significantly better than PSP ($p<0.001$).

Table 17: Results of the tests of fluency

Diagnosis	Literal Fluency: Mean (SD)	Category Fluency Mean (SD)
MSA	9.5 (3.3).	11.1 (3.1)
PSP	4.9 (1.4)	7.2 (2.7)
PD	8.8 (4.7)	11.9 (3.6)

Wisconsin Card Sorting Test: WCST scores were available for all patients with MSA, 23 patients with PSP (2 patients refused to perform the test/ didn't complete) and 21 patients with PD. The mean of the total errors made

in WCST was 7.6 (SD: 3.7) for the MSA group, 15.1 (SD: 5.7) for the PSP group, and 5.3 (SD: 2.8) for the PD group. The mean perseverative errors made were 3.6 (SD: 2.4), 6.0 (SD: 2.3) and 1.8 (SD: 1.8) respectively, for the three groups. The mean non-perseverative errors were 4.6 (SD: 2.8), 9.0 (SD: 4.6) and 3.5 (SD: 1.6) respectively. The mean number of categories passed was 4.6 (SD: 1.4) for the MSA group, 2.2 (SD: 1.8) for the PSP group and 4.7 (SD: 1.37) for the PD group. MSA and PSP patients did significantly lesser number of errors ($p<0.001$) and passed more number of categories ($p <0.001$), compared to PSP patients.

Table 18: The Wisconsin Card Sorting Test

Diagnosis	Errors Mean (SD)	Perseverations Mean (SD)	Categories passed Mean (SD)
MSA (n=25)	7.6(3.7)	3.6(2.4)	4.6(1.4)
PSP (n=23)	15.1(5.7)	6.0(2.3)	2.2(1.8)
PD (n=21)	5.3(2.8)	1.8(1.8)	4.7(1.3)

Comparison of the MSA and PD groups yielded interesting findings. The PD group fared better compared to MSA in all the four (total errors, perseverative errors, non-perseverative errors and the number of categories passed) parameters (unlike their performance in the tests of

global cognitive functions - MMSE and ACE). But the difference was not statistically significant for the number of categories passed (p=0.843) and the non-perseverative errors (p=0.108). The difference was statistically significant for the total (p=0.028) and perseverative (p=0.009) errors.

Trail Making Test: Twenty-three patients with MSA and 15 patients with PSP completed Trail Making Test- Part A. The test scores were available for 23 patients with PD. The mean time taken to complete TMT-Part A was 295.6 seconds (SD: 90.4) for the MSA group, 370.6 seconds (SD: 72.9) for the PSP group and 206.2 seconds (SD: 124.0) for the PD group. The mean number of errors made was 2.3 (SD: 2.6), 6.4 (SD: 3.9) and 0.7 (SD: 1.6), respectively for the three groups.

Trail Making Test- Part B was completed only by 19 patients with MSA, and six patients with PSP (The rest either refused to do or gave up the test half way through). The test scores were available for 22 patients with PD. The mean time taken was 425.7 seconds (SD: 113.7) for the MSA group, 398.3 seconds (SD: 176.2) for the PSP group and 335.0 seconds (SD: 125.0) for the PD group. The mean number of errors made was 7.7 (SD: 3.6), 11.1 (SD: 3.4) and 13.1 (SD: 9.1) respectively.

Table 19: Trail making test- results.

Diagnosis	TM-A Time (Seconds)	TM-A Errors	TM-B Time (Seconds)	TM-B Errors
MSA	295.6 (90.4)	2.3(2.6)	425.7 (113.7)	7.7(3.6)
PSP	370.6 (72.9)	6.4 (3.9)	398.3 (176.2)	11.1(3.4)
PD	206.2 (124.0)	0.7 (1.6)	335.0 (125.0)	13.1(9.1)

Comparison between MSA and PSP (TMT- Part A) showed that the performance of MSA group was better with regard to the time taken to complete the test ($p=0.011$) as well as the number of errors ($p<0.001$). PD patients also performed better compared to PSP in both the parameters ($p<0.001$). Comparison of the results of TMT-Part B, between PSP and the other two groups was not made as only a small number (six) of the patients with PSP could complete the test. Comparing the MSA group and the PD group, it was found that the performance of PD patients was significantly better with respect to the time taken to perform the test (p-0.008) as well as the number of errors ($p=0.022$) [Trail Making Test- Part A]. For Trail Making Test- Part B, the MSA group took significantly more time to complete the

task, compared to PD (p=0.020), but the number of errors made was lesser (p=0.021).

Comparison between MSA-P and MSA-C: Comparison between the neuropsychological test result profiles of MSA-P and MSA-C was not attempted, as the number of MSA-C cases was too small (Only five)

Comparison between "Possible" and "Probable" Cases: Comparison of the results between 'Possible' PSP and 'Probable' PSP was not attempted because of the small sample size of the 'Possible' PSP group. Comparison of 'Possible' MSA with 'Probable' MSA showed that there was no statistically significant difference between the two groups, with regard to the MMSE and ACE scores. But the 'Possible' MSA group did significantly better in the tasks of literal fluency (p=0.001) and category fluency (p=0.017). The performance of the possible MSA group on WCST was also clearly better, committing a significantly lesser number of perseverative errors (p=0.006) and passing a significantly more number of categories (p=0.002). There was a trend towards statistical significance with regard to the total number of errors also (p=0.061). Similarly, for the Trail Making Test- Part A, the time taken by the possible MSA

Group to finish the task was significantly lesser compared to the probable MSA group (p=0.009). The possible MSA group performed lesser

number of errors compared to the probable group, but this didn't reach statistical significance. For Trail Making Test- Part B, the time taken to perform the test as well as number of errors made was lesser for the possible MSA group. But the difference did not reach statistical significance.

Table 20: Cognitive functions – 'possible' Vs 'probable' MSA.

	Possible MSA Mean (SD)	**Probable MSA Mean (SD)**
MMSE	28.46 (1.8)	28.25 (1.7)
ACE	85.92 (6.9)	81.75 (6.7)
Literal Fluency	11.54 (2.8)	7.42 (2.5)
Category Fluency	12.54 (2.6)	9.58 (3.1)
WCST - perseverative errors	2.38 (1.8)	5.00 (2.3)
WCST- non-perseverative errors	3.92 (2.1)	5.50 (3.3)
WCST- total errors	6.31 (3.7)	9.08 (3.2)
WCST- categories passed	5.46 (0.7)	3.83 (1.4)
TMT-A time (seconds)	250.83 (74.5)	344.55 (82.7)
TMT-A errors	1.83 (2.2)	2.82 (2.9)
TMT-B time (seconds)	407.27 (121.4)	451.25 (104.3)
TMT-B errors	6.82 (3.8)	9.00 (3.2)

DISCUSSION

DISCUSSION

Our study evaluated the profile of cognitive dysfunction in patients with the atypical parkinsonian syndromes – MSA and PSP, and compared it with cases of PD matched for severity of parkinsonism. We also examined whether cognitive dysfunction was more common in MSA when the diagnostic certainty increased, by comparing the cognitive functions of possible and probable cases of MSA.

The three groups of patients were matched for age of and severity of parkinsonism. The age distribution was also comparable to the mean age of patients examined in the previous studies comparing the cognitive functions of PSP, MSA and PD. [170,179] The average disease duration was 3.3 years for both the atypical parkinsonism groups, which was comparable to the series by Soliveri et al; [179] but slightly lesser than the patients studied by Robbins et al. [170]. Our PD cases matched for disease severity had a longer mean duration of disease. Previous studies in PD patients have shown that the duration of the illness may be less important as a risk factor for dementia than the severity of parkinsonim [138,185]. Previous studies in MSA patients also found no correlation between extent of cognitive impairment and disease duration.

MSA-P patients constituted 80% of our MSA cases; the rest were having MSA-C. This ratio is comparable to previous reports. [3,50]. Thirteen of our patients had probable MSA and the rest (12) possible MSA.

Out of the 25 patients with PSP, 19 belonged to 'Probable' PSP group, and the rest (six), possible PSP. All our PD cases belonged to the definite category.

The neuropsychological test results showed interesting findings, which are concordant with previous reports. The performance of PSP patients was uniformly poor in the tests of global cognitive functions as well as in tests sensitive to frontal lobe function. This is similar to previous studies [170, 178, 179, 180]. The PD group performed poorer than the MSA group in tests of global cognitive function and is concordant with the observation that severe cognitive impairment is rare in MSA and is therefore considered an exclusion feature for the disease [3]. A significant degree of cognitive dysfunction was found only in around 2% of a large series of 203 patients with MSA [5]. On the contrary, PD is associated with a significant degree of cognitive dysfunction in around 30-40% of cases [150, 151, 152].

When more specific tests sensitive to frontal lobe function were applied, it was found that MSA patients performed poorly, compared to PD in our study. Cognitive impairments (not necessarily amounting to dementia) have recently been reported in patients with MSA. [164]. Comparison of cognitive functions between PD and MSA, using tests sensitive to frontal lobe function by Robbins et al [170,172] yielded results similar to ours. But Pillion et al [178] found that the dysexecutive syndrome of MSA and PD are similar in severity.

Our study has examined a better-classified group of patients with MSA, a large proportion of probable cases of PSP and definite cases of PD.

In the studies done prior to the emergence of the current diagnostic criteria [3], patients with hereditary spinocerebellar degenerations often 'contaminated' the 'MSA group'. [164] Other reports [170, 178, 179] consisted of only patients with MSA-P. Our study population consists of patients satisfying the latest diagnostic criteria, thus eliminating hereditary spinocerebellar degenerations and other 'mimickers' of MSA. Unlike previous studies, both the sub-categories of MSA were included in our study population.

We also made a novel attempt to see whether the executive dysfunction of MSA worsens with increasing degrees of diagnostic certainty. We found that the global cognitive functions as assessed by the MMSE and ACE scores didn't differ significantly between the possible and probable MSA groups. But tests sensitive to frontal lobe functions yielded significant differences between the two groups, with the 'probable' MSA group performing poorly. The results again show that MSA is associated with frontal executive dysfunction, which increases with higher degrees of diagnostic certainty. A similar analysis was not attempted in the PSP group because of the small number of 'possible' PSP cases.

CONCLUSIONS

CONCLUSIONS

1. The akinetic rigid syndromes- Multiple System Atrophy, Progressive Supranuclear Palsy and Parkinson's disease, matched for age and disease severity, are associated with variable severity of cognitive dysfunction.
2. Global and frontal lobe dysfunction is more in PSP patients compared to MSA and PD patients.
3. Tests for frontal lobe dysfunction may reveal impairment in MSA patients, which are undetected by tests of global cognitive dysfunction such as MMSE or ACE composite scores.
4. MSA patients perform poorly compared to PD patients in tests sensitive to frontal lobe function.
5. The cognitive dysfunction in MSA detected by the tests of frontal function increases as the degree of diagnostic certainty increases.

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Out of Pocket Health Expenditure involved in treatment of Carcinoma Cervix –Hospital based Study at Coimbatore District, Tamil Nadu, India.

Interview Schedule

Unique ID

Hospital (A) (B) (C)

A/B/C	Pt.ID	Inf.ID

I. Survey Information **Date of Interview**

D	D	M	M	Y	Y

Sl.No.	Questions	Response	Code
1.	Patient ID at the Hospital		A 1
2.	Informant If response is 2,3 then mention Relationship	Patient……..1 Primary Care Giver…..2 Both……..3 Relationship……	A 2

II. Demographic Information of Patient

3.	What is patient's age? (in completed years)	……yrs	B 1
4.	Address and Phone Number		B 2
5.	Usually how much time it takes for you to reach this hospital from your house?		B 3
6.	What is patient's current Marital status?	Married……..1 Unmarried……2 Divorcee……3 Widow……..…4 Separated……..5 Refused……..99 Others……..7	B 4

Interview Schedule

		Specify……..	
7.	What is patient's highest level of education?	No formal education .1 Primary school completed……..2 Middle/High School completed……..3 Above High School..4 Graduate and above……4 Refused……...99	B 5
8.	Which of the following best describes patient's employment status?	Government ……...1 Self employed…….....2 Non paid……3 Homemaker……4 Retired……5 Unorganized labor…..6 Others……7 Specify…….. Refused……99	B 6
9.	Who is sponsoring patient's treatment if patient is unemployed?	……..	B 7
10.	What was patient's household expenditure during the last month?	……	B 8
11.	How many members are there in the Household?		B 9
12.	What is patient's religion?	Hindu……1 Muslim.....2 Christian ……...3 Others……4 Specify……..	B 10

Interview Schedule

		Refused……..……99	
13.	To which of the following social groups does the patient belong?	Scheduled tribe…….1 Scheduled caste…….2 Other backward class.3 Others ……..4 Specify……... Refused……..……99	B 11

III. Medical History:

	Past Medical History		
14.	When was the patient diagnosed with Carcinoma Cervix (month, year)?	……,……..	C 1
15.	What were the symptoms observed by the patient that made her consult the doctor?	Bleeding per Vagina....1 Painful Sexual Intercourse……2 Abnormal Vaginal Discharge……..3 Don't know……..4 Others ……..5 Specify ……..	C 2
16.	Before coming to this hospital did the patient avail consultation from any other hospitals?	Yes……..1 No……2 Refused……..……99	C 3
17.	Before coming to this hospital did patient avail treatment from any other hospitals?	Yes……..1 No……2 Refused……..……99	C 4

Out of Pocket Health Expenditure involved in treatment of Carcinoma Cervix –Hospital based Study at Coimbatore District, Tamil Nadu, India.

Interview Schedule

18.	Before coming to this hospital how much did you spend totally?	`.....	C 5
19.	Did the patient opt for any complementary/alternative therapy? If yes answer next question	Yes.....1 No.....2 Refused.....99	C 6
20.	What were the Complementary/Alternative Therapies patient opted for?	Ayurveda.....1 Homeopathy.....2 Naturopathy.....3 Acupuncture.....4 Diet and vitamin cancer cures.....5 Energy therapies.....6 Herbal remedies.....7 Spiritual therapies.....8 Others .....9 Specify.....	C 7
21.	How much did the patient spend on the complementary alternative therapies per visit? No. of Times i. Ayurveda X ii. Homeopathy X iii. Naturopathy X iv. Acupuncture X v. Diet and vitamin cancer cures X vi. Energy therapies X vii. Herbal remedies X Spiritual therapies X	Per One Time Total `..... ..... `..... ..... `..... ..... `..... ..... `..... ..... `..... ..... `..... ..... `..... ..... `.....	C 8

Interview Schedule

22.	Of the following what were the screening tests that the patient has underwent?	Visual Examination.....1 PAP Smear.....2 Don't know.....3 Others.....4 Specify.....	C 9
23.	How much did the patient spend on the following screening tests within the past one year? No. of times a. Visual Inspection X b. PAP Smear X c. Others X (Specify).....	Per Test Total `..... ..... `..... ..... `.....	C 10

IV. Diagnostic Information

24.	At what stage of Carcinoma Cervix were you diagnosed? If Don't know then, check the Medical records of the patient	Stage 0.....1 Stage I.....2 Stage II .....3 Stage III.....4 Stage IV.....5 Don't know.....99	D 1
25.	What were the diagnostic tests that patient underwent in the past one year?	Biopsy.....1 CT Scan.....2 MRI.....3 X-ray.....4 Blood tests.....5 Ultrasound.....6	D 2

Interview Schedule

		ECG.....7 Others.....8 Specify.....	
26.	How much did the patient pay for per test from the below mentioned diagnostic tests? No. of Times i. Biopsy X ii. CT Scan X iii. MRI X iv. X-ray X v. Blood tests X vi. Ultrasound X vii. ECG X viii. Others X (Specify).....	Per Test Total `..... ..... `..... ..... `..... ..... `..... ..... `..... ..... `..... ..... `..... ..... `.....	D 3

V. Treatment Information

27.	Did the patient pay for the registration fees? If paid then answer next question	Free.....1 Paid.....2	E 1
28.	How much did the patient pay for the Registration?	`.....	E 2
29.	Did the patient pay for the consultation charges of the treating doctor? If paid then answer next question	Free.....1 Paid.....2	E 3
30.	How much did the patient pay for the Consultation/per visit?	`.....	E 4
31.	Did the patient receive any special consultations? If yes then answer next question	Yes.....1 No.....2	E 5
32.	How much did the patient pay for any Special Consultation/per visit?	`.....	E 6

Interview Schedule

33.	Among the following what were the treatment procedures that patient has underwent? i. Radiotherapy ii. Chemotherapy iii. Surgical procedures iv. Others Specify.....	Yes/No Yes/No Yes/No Yes/No	E 8
34.	How much did the patient pay for the following treatments? No. of times i. Radiotherapy X ii. Chemotherapy X iii. Surgical procedures X iv. Others X (Specify).....	Per One Time Total `..... ..... `..... ..... `..... ..... `.....	E 9
35.	What was the course duration of the following treatments? i. Radiotherapy ii. Chemotherapy	No. of Days	E 10
36.	Did the patient use any of the following?	Blood Transfusion.....1 Oxygen Cylinder.....2 Dialysis.....3 Ambulance services...4	E 11
37.	How much did the patient pay for the below mentioned services? No. of Times i. Blood Transfusion X ii. Oxygen Cylinder X	Per One Time Total `..... ..... `.....	E 12

Interview Schedule

	iii. Dialysis X iv. Ambulance services X	`..... ..... `.....	
38.	Where did the patient buy the medicines from?	From Hospital.....1 Outside Hospital.....2 Others.....3 Specify.....	E 13
39.	How much did the patient pay for medicines till now?	`.....	E 14
40.	Was the patient admitted in the hospital? If yes, mention the number of times.....	Yes.....1 No.....2	E 15
41.	For how many days was the patient admitted in the hospital?	.....	E 16
42.	How much did the patient pay for the bed charges during the stay at hospital?	`.....	E 17
43.	How much did the patient pay for the following per visit? No. of Times i. Food X ii. Travel X iii. Lodging X	Per One Time Total `..... ..... `..... ..... `.....	E 18
44.	How much did the patient spend for the treatment that was not reported elsewhere?	`.....	E 19
45.	On the whole how much the patient did spend for	`.....	E 20

	treatment of Carcinoma Cervix?		

VI. Funding Sources

Interview Schedule

46.	Was the patient covered under any of the following financial schemes?	Government Health Insurance.....1 Reimbursements.....2 Employer Provided Private Health Insurance.....3 Self/Household Provide Private Insurance.....4 Social Insurance.....5 Others.....6 Specify.....	F 1
47.	How much money did you receive from any source on account of your treatment till now?	`	F 2
48.	For this treatment how much money do you expect to receive?	`	F 3
49.	From the following what were the ways adopted for meeting your treatment cost?	Savings.....1 Sale Of Assets.....2 Unsecured Loans.....3 Mortgage Of Assets...4 Mortgage Of Land....5 Assistance from organizations.....6 Assistance from Friends/Relatives.....7 Others.....8 Specify.....	F 4

Please check the completeness of all the entries before leaving the place. Thank the participant for their valuable time and cooperation and end the interview.

Signature of the interviewer