

**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL
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**“CLINICAL PROFILE OF LOWER BODY PARKINSONISM IN A
TERTIARY CARE HOSPITAL IN SOUTHERN INDIA- A
RETROSPECTIVE OBSERVATIONAL STUDY”**

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By

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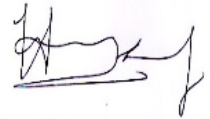
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DECLARATION BY THE STUDENT

I, **Dr. Hema Krishna P**, hereby certify that I had personally carried out the work depicted in the thesis titled, “**Clinical profile of lower body parkinsonism in a tertiary care hospital in Southern India- A retrospective observational study**”. No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.



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This is to certify that **Dr. Hema Krishna P**, Department of Neurology of this institute has fulfilled the requirements prescribed for the Post doctoral fellow in Movement disorders of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum. The thesis entitled, '**Clinical profile of lower body parkinsonism in a tertiary care hospital in Southern India- A retrospective observational study**' was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date. Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

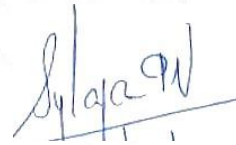


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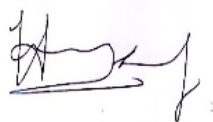
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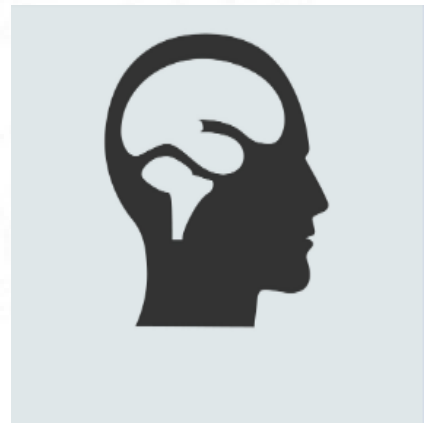
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Chapter 1

Introduction



INTRODUCTION

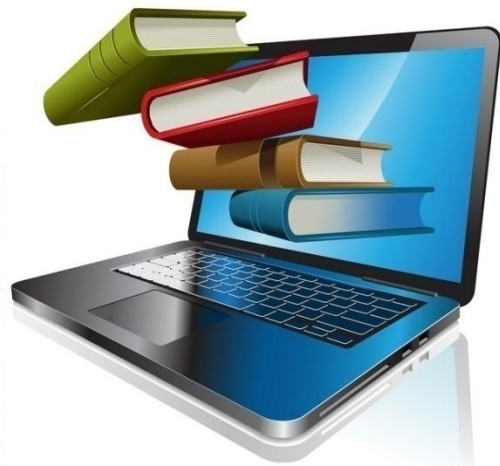
Lower body parkinsonism is a commonly encountered yet vaguely defined clinical syndrome in neurological practice. It is characterized by predominant and disproportionate gait difficulty out of proportion to upper limb involvement. A standardized definition for lower body parkinsonism is yet to be formulated. Vizcarra et al. defined lower-body parkinsonism as a syndrome of reduced gait mobility, with shortened stride length, diminished step height, increased step width, with or without freezing of gait episodes, with poor response to external cues and L-dopa (1). The etiological profile of Lower body Parkinsonism is heterogenous ranging from vascular to degenerative and non-degenerative causes. The most common causes include Vascular Parkinsonism (VP), Normal pressure hydrocephalus (NPH) and Progressive Supranuclear Palsy (PSP) (2). Other less common causes include Frontal lobe tumors and other lesions involving frontal lobe, subdural hematoma, functional gait disorder, hypoxic injury of the basal ganglia, carbon monoxide and manganese intoxication (3).

The diagnosis of NPH is considered in patients presenting with gait disturbance, urinary incontinence, and cognitive impairment with evidence of communicating hydrocephalus (Evans index >0.3), out of proportion to cerebral atrophy with normal intracranial pressure (<20 mmHg) (4). It usually has a good clinical response to external lumbar drainage (ELD) followed by ventriculo-peritoneal shunt placement. In patients with vascular risk factors and typical imaging findings, gait difficulty as an initial symptom with freezing episodes but absent festination, absence of tremor, poor response to dopaminergic therapy, rapid progression of symptoms point towards diagnosis of vascular parkinsonism (5). Vascular parkinsonism responds poorly to dopaminergic medications and responds variably to external lumbar drainage. Differentiation between NPH and vascular parkinsonism can be at times challenging since vascular risk factors can coexist in patients of NPH (6). Lack of persistent response to ventriculo-peritoneal shunt should raise the suspicion of diagnosis other than NPH (2). Presence of supranuclear gaze palsy or early bulbar involvement can point towards a degenerative cause of lower body parkinsonism like progressive supranuclear palsy. However, the clinical distinction may not be always possible in selected cases at initial evaluation and follow-up of patients may provide insights into possible etiology.

The current study aims to describe the clinical profile of patients presenting with lower body parkinsonism to the Neurology department of a tertiary care center in Southern India. Despite being a very common clinical presentation, very limited literature is available on lower body parkinsonism. To the best of our knowledge, no long term studies are available on clinical profile of patients presenting with lower body parkinsonism. Similarly, no definite validated clinical criteria have been formulated for diagnosing various etiologies causing lower body parkinsonism till date. Hence, long term follow-up may be needed to identify the exact etiology. Thus we undertake this study. The study, apart from describing various clinical features of patients presenting with lower body parkinsonism, will also provide information on basic demographic parameters, etiologies, radiological findings, treatment response and clinical phenotypic evolution in the study participants.

Chapter 2

Review of Literature



REVIEW OF LITERATURE

Lower body parkinsonism is a clinical syndrome with varied etiologies and is frequently encountered in clinical practice. Though clinicians are frequently faced with this syndrome, very limited data is available on clinical profile of syndrome of lower body parkinsonism. The term was initially used to describe individuals with predominant and disproportionate gait difficulty, often associated with chronic hypertension and subcortical vascular disease. A multitude of terms are often used interchangeably to describe this syndrome, which include gait apraxia, frontal ataxia, *marche a petits pas*, lower-half parkinsonism (7).

Frontal ataxia as a distinct entity was first noticed by Bruns in 1892 in a patient with frontal lobe mass, who had difficulty mainly while standing and walking, with short, shuffling steps and tendency to retropulsion without any signs of cerebellar ataxia. It was thought to be due to interruption of frontopontocerebellar fibres (8). But, similar gait was also noted in patients with vascular disease of the frontal lobes, suggesting compression of subcortical structures may not be the only mechanism resulting in this syndrome. Gerstmann and Schilder (1926) reported two patients with similar gait and frontal lobe release signs like perseveration, incontinence, and awkward limb movements (9). The disproportionate difficulty in walking in comparison to spontaneous leg movements lead to proposal of the concept of apraxia of gait, which was referred to as “apraxia de la marche” by Van Bogaert and Martin. They suggested the term “frontal disequilibrium” for this phenomenon (10).

In 1958, Denny-Brown, coined the term “magnetic apraxia” or “magnetic foot response” for trunk and leg apraxia resulting from frontal lobe lesions, causing ones foot to get stuck to the floor causing gait initiation and stepping difficulty (11). Meyer and Barron described the pattern of frontal gait as a wide based, short, shuffling steps, interrupted by freezing, with retropulsion and tendency for the feet to stick to the ground. Frontal release signs, rigidity, hypokinesia and *gegenhalten* may be associated. Frontal gait disorders constitute almost as much as 30% of gait problems in the elderly (Sudarsky and Ronthal, 1983; Nutt et al., 1993) (12).

Adams et al. had described the gait associated with hydrocephalus as an ataxia and apraxic gait (13). Cognitive and urinary disturbances, rigidity, frontal lobe release signs are amongst the

associated features. In 1966, Messert and Baker, described the evolution of the “periventricular white matter syndrome” of hydrocephalus and stratified it into four stages as below (14).

- First stage: Hydrocephalic paraplegia- due to involvement of leg fibres of corticospinal tracts close to dilated lateral ventricles
- Second stage: Frontal ataxia- due to involvement of frontal pontocerebellar fibres
- Third stage: Apraxia of gait- Further slowing of movement and involvement of trunk
- Fourth stage: Total apraxia or akinetic mutism

Prompt consideration for shunting would result in resolution of the syndrome in the reverse order with residual spastic ataxia. In patients with cerebellar tumors, Williams et al. had noticed improvement of gait after shunting even without excision of the tumor suggesting that stretching of the frontal sub cortical fibres due to hydrocephalus is responsible primarily for the gait disorder, than the tumor itself.

Similar descriptions were made by Critchley, who first postulated vascular mechanisms as a cause of parkinsonism and used the term ‘arteriosclerotic parkinsonism’ for patients with predominant gait involvement (15). Critchley, however did not provide a pathological correlate supporting the vascular etiology. He described five subgroups of arteriosclerotic parkinsonism: type 1 with rigidity, fixed facies, and short-stepping gait; type 2, with presence of pseudobulbar features in addition to type 1; type 3, with dementia and incontinence in addition to type 1; type 4, a mixed pyramidalpallidal syndrome; and type 5, with cerebellar and pallidal features. An upright posture of upper body and exaggerated arm swing was noted in some of these patients. The concept of arteriosclerosis and vascular nature was questioned until the emergence of CT and MRI imaging techniques. In 1987, Thompson and Marsden described 12 patients with gait difficulty, parkinsonian findings, with background hypertension, and CT evidence of fronto-parietal white matter changes (16). These patients had predominant lower body symptoms and freezing with relative sparing of the upper limbs and face. Festination was not noted among these patients, but varying combinations of UMN signs, cognitive and urinary symptoms were noted. They termed these cases as having “lower half parkinsonism.” As, etiology of all white matter lesions may not be always vascular and as white matter changes may be found in a variety of

conditions, including among normal individuals, the term “Leuko-araiosis,” was proposed by Hachinski in 1987 without implying on specific cause (17).

The term lower body parkinsonism was first used in 1989 by Drs FitzGerald and Jankovic's and an operational definition was formulated which was later used synonymously with vascular Parkinsonism (18). They had identified this clinical syndrome in patients otherwise diagnosed as Parkinson's disease, but with disproportionate gait involvement, often as initial symptom, lack of upper limb involvement and tremor, poor response to dopaminergic therapy, relatively rapid progression and an association with hypertension at a much higher frequency. Their patients had significant start hesitation, freezing, lack of festination, and improvement with various sensory cues. These cases were thought to be different from PD and of vascular origin. They subsequently proposed a criteria for lower body parkinsonism in 1989 as individuals presenting with impaired parkinsonian like gait; mild or absent tremor, rigidity, or clumsiness in the arms; and absence of dementia, spasticity, and lateralizing findings. It was postulated that this syndrome is more than a nigral disease and results from involvement of corticostriatal and thalamocortical fibers coursing around the ventricle as a result of end arteriolar ischemic changes (18).

In 2002, Della Sala et al. proposed the term “gait apraxia” to describe frontal gait disequilibrium, impaired postural reflexes, gait ignition failure with start hesitation in a patient with bilateral SMA infarctions (19). Upon review of literature, medial frontal lobe lesions (which were bilateral in 53%) were reported to be the commonest lesions causing gait apraxia. Gait apraxia is often used synonymously with LBP. It was defined by Meyer and Barron as “the loss of ability to properly use the lower limbs in the act of walking which cannot be accounted for on the basis of demonstrable sensory impairment or motor weakness.” The supplementary motor area of the frontal lobe, which receives the major basal ganglia output tracts is involved in programming the motor tasks. Thus, it is also postulated that chronic subcortical ischemia, due to vascular disease results in disconnection between basal ganglia and supplementary motor area and causes gait apraxia. In 2007, Elble proposed that HLGD or frontal gait apraxia arises from dysfunction of cortical basal ganglia loop and described four characteristic features (20).

- 1st: Variable gait performance which is dependent on the environment, mood and other factors.
- 2nd: Presence of start and turn hesitation and FOG
- 3rd: Bizarre postural synergies
- 4th: Absent or inappropriate rescue reactions

With recognition of expanding etiological profile of patients presenting with lower body parkinsonism, the definition of lower body parkinsonism underwent further refinements. In 2015, Vizcarra et al. proposed a definition of lower-body parkinsonism as a syndrome of reduced gait mobility, with shortened stride length, diminished step height, increased step width, with or without freezing of gait episodes, with poor response to external cues and L-dopa (1). Most common causes of LBP encountered in clinical practice are Vascular parkinsonism, NPH, PSP, amongst others. Other less common causes include Frontal lobe tumors and other lesions involving frontal lobe, subdural hematoma, functional gait disorder, hypoxic injury of the basal ganglia, carbon monoxide and manganese intoxication (3). HLGD were broadly categorized as predominant locomotor type presenting as start and turn hesitation and FOG and as predominantly disequilibrium type, as seen in PSP (21). Most of the patients eventually develop a mixture of both types. During the initial phases, patients with HLGD, show behavioural adaptations in the form of acquiring a cautious gait with a widened base, slowing of gait, shortened steps and enbloc turns. The term primary progressive FOG is often used in patients presenting with predominant locomotor problems without any identifiable cause. Amongst important causes of disequilibrium type of HLGD, PSP and frontal lobe lesions are of note. The table below mentions important reported causes of lower body parkinsonism in neurological practice.

CAUSES OF LOWER BODY PARKINSONISM	
1.	Vascular Parkinsonism • Binswanger's Disease (subcortical arteriosclerotic encephalopathy) • CADASIL • Multiple Lacunar Infarcts • Acute Onset Stroke (Midbrain) • COL4A1 Related Disorders • Dilation of Vascular Spaces
2.	Normal Pressure Hydrocephalus
3.	Progressive Supranuclear Palsy
4.	Secondary Hydrocephalus • Meningitis • Head Trauma, Others
5.	Frontal Lobe Lesions • Tumours • Ischemia (ACA Infarcts) • Demyelination • Abscess, Others
6.	Others • Hereditary Diffuse Leukoencephalopathy With Axonal Spheroids(CSF 1R) • Striatonigroluysian Degeneration • Alzheimer's Disease

Table 1: Most common reported causes of syndrome of lower body Parkinsonism (1, 2)

EPIDEMIOLOGY

Lower body parkinsonism results from a variety of etiologies and till date very limited literature is available regarding patient profile and epidemiology of different diseases resulting in lower body parkinsonism as a whole. In a community based clinic study, done amongst people more than 70 years, 16% had features of neurologic gait, of which 13 % were qualified as frontal gait disorder. Parkinsonian gait accounted for 9% of the neurological gaits (22).

PATHOPHYSIOLOGY

The pathophysiological mechanisms causing in lower body parkinsonism essentially result from interruption of connections between the cortex and the brainstem. Various anatomical regions involved in the balance and locomotor circuits are primarily affected in LBP. Abnormalities in the frontal and prefrontal regions, basal ganglia, the mesencephalic locomotor region (pedunculopontine and cuneiform nuclei), and the cerebellar locomotor region in varying combinations form the basis for LBP depending upon the underlying etiology (23). DTI findings in vascular parkinsonism has suggested abnormalities in subcortical tracts of frontal lobe, anterior limb of internal capsule, genu of corpus callosum and also in PPN and cerebral peduncles. In PD with FOG, evidence of decreased connectivity between medial frontal lobe and PPN was noted, while in NPH abnormalities in anterior white matter and genu of corpus callosum were noted.

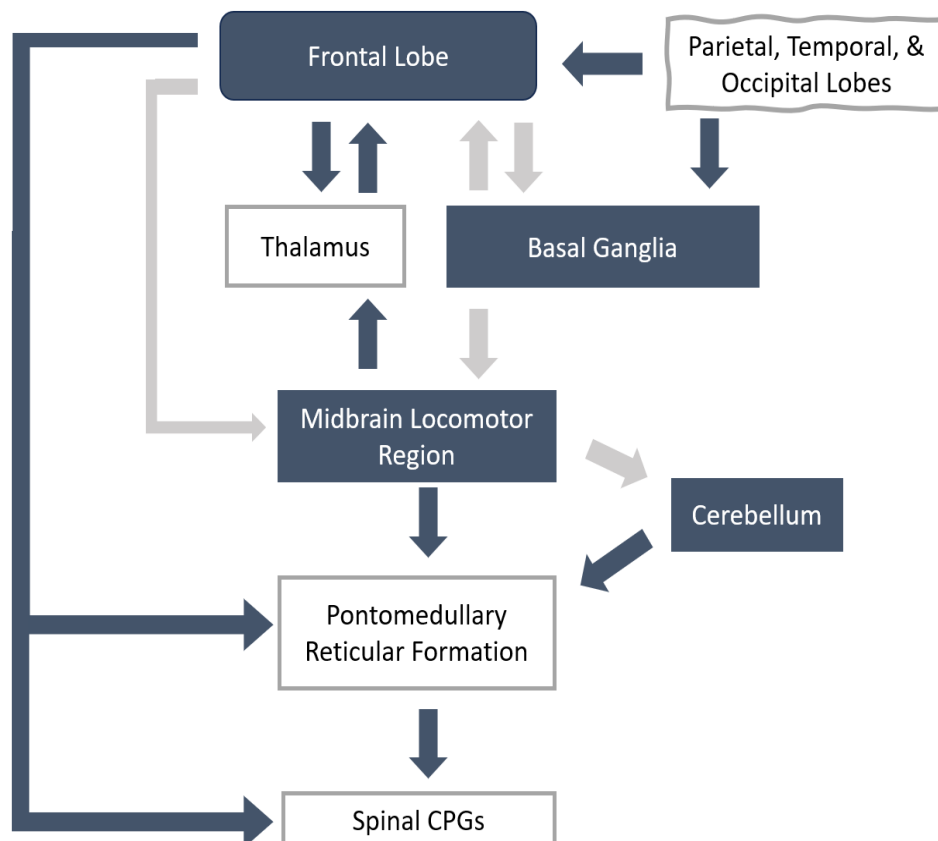


Fig. 1. Illustration of balance and locomotor networks. The highlighted structures are postulated to be involved in gait apraxia or higher level gait disorders (23)

VASCULAR PARKINSONISM

Vascular parkinsonism is one of the most important and common causes of secondary parkinsonism. However, it is a poorly defined syndrome and its features often overlap with other diagnoses. Its age of onset is higher than that of PD, most commonly in eighth decade and it is more common in males. VP has been reported to constitute 2.5-5% of total cases of parkinsonism in various population based studies (24). VP is often an under diagnosed entity and its epidemiological data had shown variable results. In a clinicoradiological study of patients with gait difficulty and parkinsonism, almost 33% of patients who had history of stroke developed parkinsonian signs 1 year after their stroke onset (25).

The exact pathogenesis of VP yet to be understood clearly. The essential proposed mechanism in patients with diffuse subcortical white matter lesions is disconnection between the basal ganglia and the higher cortical centres. There is damage to the net thalamocortical drive, decreasing the influence of basal ganglia on supplementary motor cortex and other higher centres. These white matter changes are thought to be due to chronic or recurrent partial ischemia. In patients with strategic infarcts, disruption of the putamino-pallido-thalamic loop is proposed. Literature regarding location of strategic infarcts resulting in parkinsonism is variable. Theoretically, substantia nigra (SNr), striatum or the ventroanterior/ ventrolateral (VA/VL) nuclei of the thalamus have been proposed. Reports of striatal, lenticular, thalamic, mesencephalic and frontal lobe infarcts causing parkinsonism are not uncommon (24). However, asymptomatic basal ganglia infarcts and white matter hyperintensities are also common. In a study by Lee et. al., amongst asymptomatic individuals between 20 to 78 years old, silent infarcts were noted on MRI in 5.84%, most commonly in basal ganglia followed by periventricular white matter (26). Hence, establishing the causal relationship is often difficult. The major pathological changes in VP includes includes gliosis, perivascular pallor, hyaline thickening of arteriolar walls, and enlargement of perivascular spaces. However, these changes are not specific to VP. The white matter changes are usually accompanied by severe loss of oligodendrocytes. Microscopic examination of the lesions is often useful to identify the underlying process like CADASIL, infection, vasculitis etc. Rarely, SNr neuronal loss may be seen in VP, especially in patients with large basal ganglia infarcts, but to a lesser degree in comparison with PD patients.

The diagnosis of VP is often considered in elderly patients with vascular risk factors like past ischemic strokes, hypertension, diabetes, coronary artery disease, hypercholesterolaemia, smoking and a family history of ischaemic heart disease. An association of antiphospholipid antibody and anticardiolipin antibody and VP had also been noted (22). Patients with VP is more likely to have a shorter duration of illness and rapid progression in comparison with PD. VP had been classified as an acute onset presentation following a vascular event, noted in around 25% of the patients and an insidious onset presentation. It is often very difficult to distinguish between these two patterns. Most common presentation of VP encompasses an insidious onset and progressive illness with predominant gait involvement. A stepwise worsening of symptoms in a less common phenotype. A minority of patients may present with unilateral symptoms initially and later become bilateral, possibly because diffuse white matter lesions become superimposed on the lacunar state. Hemiparkinsonism secondary to well defined stroke is very rare and often recovers spontaneously (27).

CLINICAL SYNDROMES OF VASCULAR PARKINSONISM

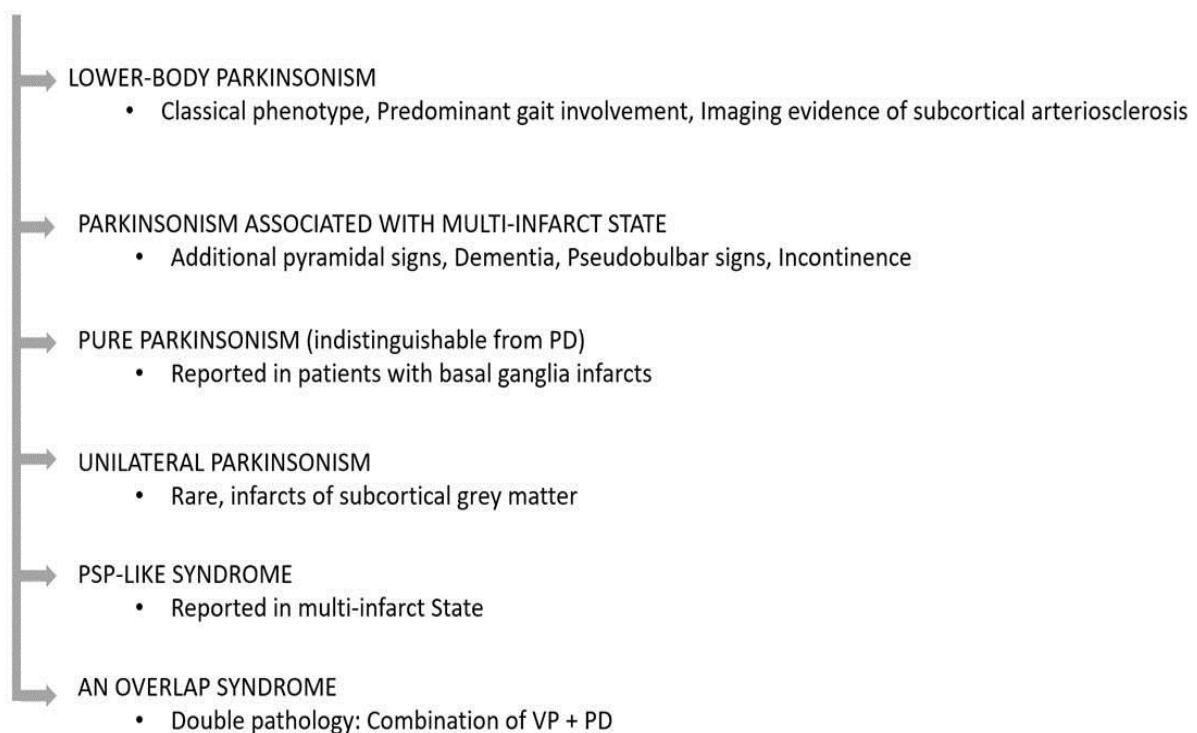


Fig. 2. Clinical syndromes of Vascular parkinsonism (22)

VP most commonly presents with lower body parkinsonism, with bilaterally symmetrical involvement, affecting the lower limbs more than the upper limbs and absence of rest tremor. Gait abnormalities are characteristic and patients have an upright posture with a wide base, start hesitation, steps are short and shuffled, with reduced or an exaggerated arm swing and marked retropulsion. Freezing may be seen, but festination is uncommon unlike in PD (24). Gait in VP frequently has a component of ataxia with variable step length. In advanced cases, magnetic foot response and truncal ataxia develop. Patients with VP are often considered to have a poor response to levodopa. Increased tone noted usually may be due to a combination of rigidity and spasticity. Bradykinesia of varying degree has been reported in patients with VP. Facies in VP is masked but not expressionless. Additional findings of cognitive impairment, pseudobulbar palsy, pyramidal signs, incontinence, 'gegenhalten' and speech disturbance may be present. Cognitive disturbance is usually a dysexecutive syndrome with predominant involvement of attention, planning and judgement, with relative preservation of cortical functions (22).

A diagnosis of VP is thought of in patients with vascular risk factors, presenting with predominant gait difficulties and imaging evidence of vascular disease. However, mere presence of vascular lesions does not establish the diagnosis of VP, as these lesions can be noted also in asymptomatic individuals and not every patient with vascular lesions develops parkinsonism. MRI is often the preferred imaging modality used in VP. Zijlmans et. al. proposed the first clinical criteria for vascular parkinsonism in 2004. However, this criteria had not been validated in a large number of patients.

Similarly, Winikates' proposed criteria for diagnosis of vascular parkinsonism by putting emphasis on risk factors, pathology and angiography findings. Despite these attempts, an universally accepted consensus criteria for diagnosis of VP is yet to be formulated. Apart from MRI, DAT- SPECT had been reported to be helpful in differentiating VP from PD and other atypical parkinsonian syndromes. DAT-SPECT is classically normal in VP, with the exception of patients with focal infarcts in basal ganglia.

Zijlmans' Diagnostic Criteria for Vascular Parkinsonism:

The components of this criterion for the diagnosis of "probable" VP are:

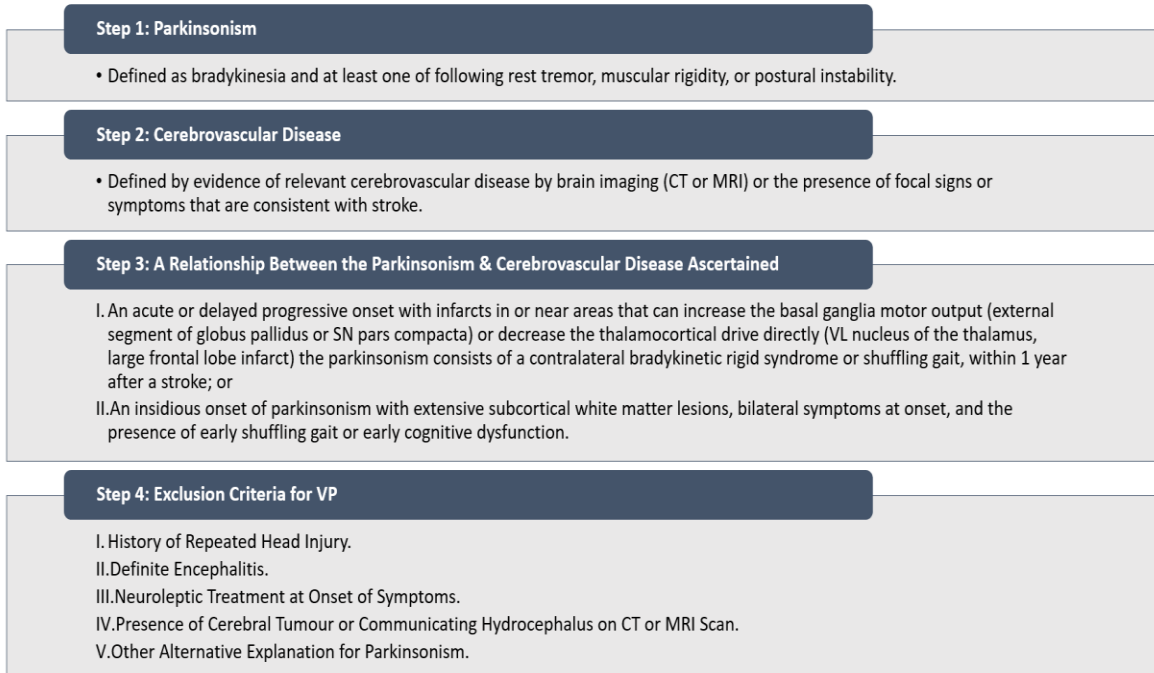


Fig. 3. Zijlman's diagnostic criteria for vascular parkinsonism (5)

Winikates' Vascular Parkinsonism Criteria:

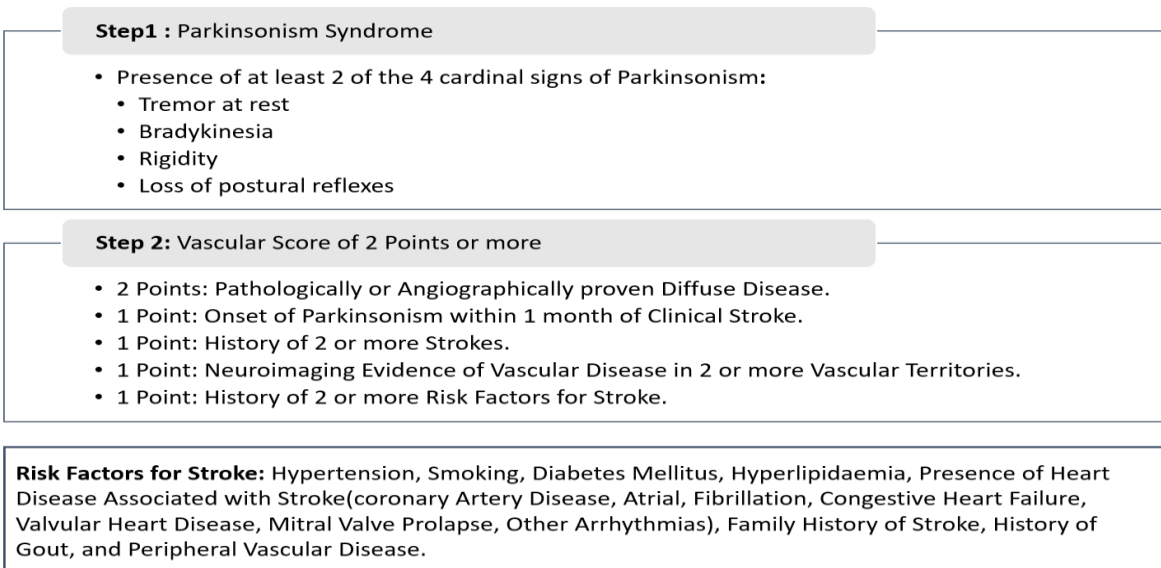


Fig. 4. Winikates diagnostic criteria for vascular parkinsonism (28)

Traditionally, VP is considered to be refractory to dopaminergic treatment. However, about 20-40% of the patients with VP have reported improvement with levodopa. Hence, it is reasonable to give a trial of levodopa in all patients of VP, with doses upto 1000mg/day for at least 3 months. Among responders, the duration of sustained response varied from 1 to 2 years. Within VP, patients with lesions near nigrostriatal pathway have better levodopa response than those with a white matter disease (24). The possible explanation for levodopa response in VP patients may be the presence of a remaining pool of striatal dopaminergic nerve terminals in a dysfunctional nigrostriatal pathway that can convert exogenous levodopa to dopamine. There are reports of improvement of gait in VP with therapeutic CSF drainage. In a study by Ondo et al. 37.5% of VP patients had significant improvement in gait after removal of 35-40 ml of CSF. The proposed mechanism of improvement was reduction in the intracranial pressure, thereby improving the perfusion pressure of the brain (29). Management of vascular risk factors and secondary stroke prevention strategies are amongst the important interventions targeted at halting the disease progression.

NORMAL PRESSURE HYDROCEPHALUS

The syndrome of NPH was first recognized by Hakim et al. who proposed the clinical triad of NPH composed of gait difficulty, cognitive impairment and urinary incontinence (30). Its core feature described was presence of ventriculomegaly. In 1975, Shenkin et al. reported cases of symptomatic hydrocephalus with normal ICP, without any obvious identifiable cause, and proposed the term, *idiopathic* NPH (iNPH) (31). Hydrocephalus secondary to cerebral atrophy is labelled as exvacuo secondary hydrocephalus and is seen in myriad of neurodegenerative conditions like AD, FTD, CBD and others (32). Other secondary causes of hydrocephalus, such as SAH, meningitis, intracerebral hemorrhage, brain tumor or head trauma have been reported and are often classified as secondary NPH. However, the term secondary NPH is debatable and is rarely used in clinical practice (33).

iNPH is mainly seen in adults over 60 years of age and affects both sexes equally. The prevalence of NPH in a Norwegian study was reported to be around 21.9 cases per 1 lakh population and the incidence was around 5.5/100,000. A more common occurrence of NPH in general population was suggested by a Swedish study by Jaraj et al., where the prevalence of

probable iNPH was reported to be 0.2% amongst individuals within the age group 70-79 years and 5.9% in those aged 80 years and older (34).

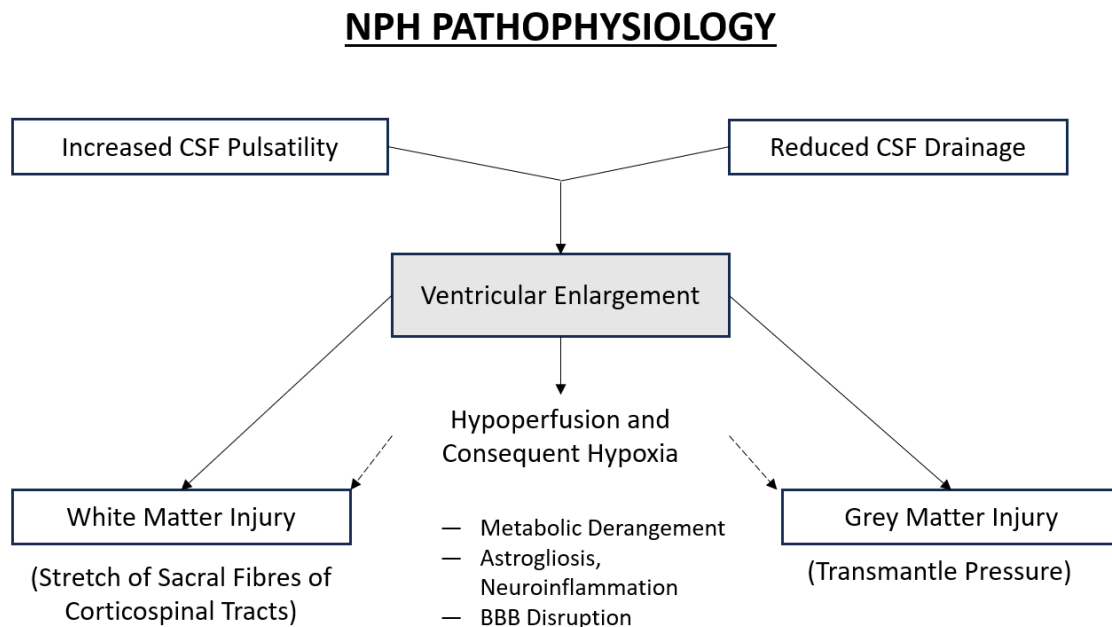


Fig. 5. Suggested pathophysiology of iNPH (35)

The exact pathophysiological mechanisms causing NPH are still not clear. However, alterations in CSF dynamics resulting in ventriculomegaly and subsequent cerebral hypoperfusion and involvement of subcortical white matter fibres appears to be the core mechanism causing injury. No standardized criteria are accepted worldwide for diagnosis of NPH. Some suggest only one feature among the classical triad may be enough to make the diagnosis of possible iNPH, whereas the Japanese guidelines mandate atleast two features to be present for making the diagnosis of possible iNPH (34).

Gait difficulties are often the earliest features of NPH and it the symptom that is most responsive to shunting. Gait is characteristically slow, with a wide base, small steps, and often described as magnetic or apraxic gait. The patient uses multiple steps to turn, described as piecemeal turning. Upper body involvement is usually mild and retropulsion may be seen sometimes. FOG has been reported in around 30% of the NPH cases and postural instability and falls are also a common

feature (34). There is usually no mask like facies reported in NPH. Cognitive symptoms manifest as a frontal dysexecutive syndrome. The presence of anomia or other cortical features should alert the clinician to look for comorbid neurodegenerative pathology. Urinary symptoms also are one of the core manifestations of NPH ranging from urgency of urine to incontinence. The response of cognitive and bladder symptoms to shunting is variable especially when it is delayed.

Japanese diagnostic criteria for Idiopathic Normal pressure hydrocephalus (36)

Possible iNPH (meets all 5 of the following)

- Age $\geq$ 60 years
- > 1 symptom of the clinical triad (cognitive impairment, urinary incontinence, gait disturbance).
- Ventricular dilation (Evans index > 0.3)
- Symptoms not explainable by other neurological or non-neurological disease
- Preceding diseases possibly causing ventricular dilation are not obvious, including subarachnoid hemorrhage, meningitis, head injury, congenital hydrocephalus, and aqueductal stenosis

Probable iNPH

- Meets criteria for possible iNPH
- CSF pressure < 200 mm H₂O and normal CSF content
- One of the following three investigational features:
 - Neuroimaging of narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH) in the presence of a gait disturbance
 - Improvement of symptoms after CSF tap test
 - Improvement of symptoms after CSF drainage test.

Definite iNPH

- Improvement of symptoms after the shunt procedure

The hallmark imaging feature is ventricular enlargement out of proportion to the cerebral atrophy. Other supportive features for diagnosis of NPH include, presence of aqueductal flow void and disproportionately enlarged subarachnoid space hydrocephalus (DESH) , which is defined as the presence of a “tight” convexity with an enlarged sylvian fissure and associated hydrocephalus (36). The idiopathic normal pressure hydrocephalus (iNPH) Radscale was

developed as a screening tool to differentiate NPH from its mimickers. A score of more than 8 in the presence of clinical symptoms makes the diagnosis of NPH very likely, whereas an alternate diagnosis should be considered if the score is less than 4 (37).

Apart from the radiological tests, confirmatory invasive tests are routinely included in the evaluation of patients suspected to be having NPH before considering for shunting. This can be done either by a high volume lumbar puncture or external CSF drainage at a rate of 10 cc per hour over 1–3 days. The most common method implemented in clinical practice is large volume lumbar puncture test or tap test. No standardized protocols are available for the tap test and the protocols are highly variable. The Román NPH Protocol (Houston Methodist Hospital protocol) advocates removal of 50 ml CSF in supine posture and comparing gait and neuropsychology performance before and 3 hours after the CSF tap (38). Whereas, according to Kuopio idiopathic normal pressure hydrocephalus protocol, 20–40 ml of CSF is to be removed and gait is to be assessed after 1 hour. Patient needs to lie supine for 1 hour post CSF tap. Gait is assessed by making patient walk for 10 metres to and fro (total 20 metres) and gait speed, step number and length are calculated. A positive test was defined as at least 20% improvement in gait speed (39). An improvement in neuropsychology performance of 10% has been variably defined as positive test (34). In 2018, Souza et al. suggested removal of 30 ml CSF on two consecutive days, with a 24-hour interval between the lumbar punctures and gait speed was assessed before LP and 3 hours after second LP (40). Similarly, Damasceno et al. proposed repeated or continuous 3 day external lumbar drainage (minimum of 150 ml CSF drained daily) to increase tap test sensitivity to 50-100%, while maintaining a high positive predictive value (80-100%), compared to the one time tap test with a low sensitivity of 26-61% (41). Despite multiple such protocols, a standardized protocol is yet to be formulated.

The mainstay of treatment in NPH is the implantation of a ventriculoperitoneal (VP) shunt. Ventriculo-atrial shunts are rarely done now owing to their complications. Lumboperitoneal shunts are also done in NPH patients routinely, especially when VPS is not a feasible option. Endoscopic third ventriculostomy (ETV) is a useful option in patients with locally confined, infratentorial, extraventricular obstruction to CSF flow and not in NPH cases. Diuretics, carbonic anhydrase inhibitors and serial CSF taps are not used as routine therapeutic options in NPH, except in patients in whom shunting is not a feasible option. Among patients undergoing VP

shunt, reports suggest maximum benefit in gait in as much as 70% to 90% of patients, especially when done early in the course of the disease. Cognition and bladder symptoms improve variably. The duration of clinical benefit lasted from 1 to 7 years upon follow up (34). The current guidelines support use of adjustable shunts, which enables fine tuning of ventricular drainage. Recent advancements, include development of gravity controlled valves (G valves), where the opening pressure is mainly controlled by gravity. In the SWASONA study, G valves have shown to lower the risk of over drainage by 90% without affecting the therapeutic efficacy in walking patients (42).

PROGRESSIVE SUPRANUCLEAR PALSY

The syndrome of PSP was first described by Drs Steele, Richardson, and Olszewski, because of which, its most common subtype was named after them (43). It is most common form of atypical parkinsonian syndromes. It is differentiated from PD by the presence of significant axial involvement, freezing, early loss of postural reflexes and falls and decreased insight. A characteristic feature of PSP is inability to perform volitional saccades and progressive supranuclear ophthalmoparesis (limitation of downgaze is most sensitive). Other eye movement abnormalities include upgaze restriction, slowed saccades, optokinetic nystagmus, macro square wave jerks, saccadic intrusions, apraxia of eyelid opening, amongst others. Complete gaze palsy and frozen eyes with lack of blinking had been described as classic ‘‘Mona Lisa’’stare or stone face. Patients usually have a characteristic astonished facial expression due to dystonia of facial muscles (44). Additional features include spastic or hypernasal dysarthria, progressive dysphagia and bulbar weakness. Other features include a frontal subcortical dementia, frontal lobe release signs, disinhibition and emotional incontinence.

The NINDS-SPSP criteria, is the most widely used criteria for ante mortem diagnosis of the classic PSP phenotype and it has an excellent specificity (95-100% for probable and 80-93% for possible PSP). However, its sensitivity for overall PSP diagnosis at first visit is low (14-83%). The criteria for possible or probable PSP included a progressive disorder with onset after the 40 years of age with postural instability, significant falls, slowing of vertical saccades, or vertical gaze palsy and exclusion of other causes. A diagnosis of Definite PSP required pathologic evidence (45). With better understanding of PSP and literature from autopsy findings, as many as

ten subtypes of PSP have been identified based on predominant phenotype and a criteria for their diagnosis was proposed in 2017 (MDS-PSP criteria) (46). The common variants of PSP include, PSP-RS (Richardson syndrome), PSP-P (parkinsonism), PSP- PGF (progressive gait freezing), PSP-CBS (corticobasal syndrome), PSP-F (frontal variant) etc.

The hallmark of PSP is abnormal deposition of tau, especially involving basal ganglia, dentate, pontine, and oculomotor nuclei with relative sparing of the cortex. There is associated gliosis and marked midbrain atrophy, loss of pigmented cells in the SNr, and atrophy of STN, superior and middle cerebellar peduncles, dentate nucleus and the frontal cortex. Preferential involvement of motor cortex (and frontal sub cortex), pons and cerebellum is noted in the PSP-PAGF variant in comparison to extensive involvement of midbrain, basal ganglia and dentate nucleus noted in the classical variant which explains early and predominant lower body involvement in the PAGF variant (47). PSP as a cause of lower body parkinsonism has been increasingly recognized in recent years. In 2015, Vizcarra et al. had reported 2 patients presenting with predominant lower body parkinsonism, who were initially suspected to have Richardson syndrome, which was later pathologically proven. PSP, especially the PGF variant is amongst one of the important causes of lower body parkinsonism (1).

Diagnosis of PSP is mainly clinical and there is no single blood, CSF or imaging marker for PSP. However, atrophy of midbrain and superior cerebellar peduncles, help in differentiating PSP from other parkinsonian disorders. Midbrain atrophy may result in characteristic hummingbird or penguin body appearance in the sagittal plane. A midbrain by pons ratio may be helpful in confirming midbrain atrophy in PSP. It is usually calculated in midsagittal plane, by 2 methods. An area ratio, using free hand method is more preferred and values <0.2 to 0.22 are suggestive of PSP (48). When a cut off of <0.16 was used, the ratio had 100% sensitivity and specificity for PSP (49). Another method is calculating short axis diameter ratio and values <0.52 are indicative of PSP (50). A more comprehensive tool, MRPI had been developed which can be used to identify PSP patients early in the disease course. It is calculated by multiplying the ratio of pons by midbrain area with average width of MCP by SCP and a value of > 13.55 is suggestive of PSP (with a sensitivity and specificity of $>95\%$ in differentiating PSP from PD) (51). The updated version of MRPI, MRPI 2.0 also includes third ventricular width and maximum width of frontal horns, but was not found to be superior to conventional MRPI measurements in

differentiating PSP from other atypical parkinsonian syndromes (52). Also, it may be noteworthy to mention that it may be less reliable especially when applied in patients presenting with lower body parkinsonism as some of the patients may have associated hydrocephalus. PET and SPECT images have shown hypometabolism of bilateral frontal cortex, caudate, thalamus, cingulate gyri, and midbrain in PSP patients.

No specific disease modifying treatment is available for PSP and its management is primarily symptomatic. It requires multidisciplinary team approach with physical, occupational therapy, speech and swallow therapy. Gait therapy, assisted and wheel chair ambulation should be encouraged in patients with significant postural instability and falls. Option of Ryle's tube and PEG feeding should be given in advanced cases with dysphagia and recurrent aspirations. A levodopa trial upto 1200 mg/d for a minimum of 1 month needs to be given to assess responsiveness, especially in PSP-P subtype. Dopamine agonists provide only minimal improvements, Amantadine had been reported to be helpful in gait and dysphagia (47). However, studies supporting this are limited. Other supportive therapies include, Botulinum toxin for painful dystonia, Cholinesterase inhibitors for cognitive symptoms and SSRI and other mood stabilizers for depression and mood related symptoms.

Chapter 3

Aims & Objectives



AIMS AND OBJECTIVES

Lower body parkinsonism is a clinical syndrome with varied etiologies and is frequently encountered in clinical practice. However, only limited number of studies have looked into its clinical profile and literature is lacking. Therefore, we would like to conduct this study with the following aims and objectives.

- Aim:
 - To study clinical profile and evolution of lower body parkinsonism in a tertiary care hospital in Southern India.
- Objectives:
 - To determine clinico-radiological profile of lower body parkinsonism among the study participants at presentation.
 - To assess the clinical phenotypic evolution in these patients.

Chapter 4

Materials & Methods



MATERIALS AND METHODS

Study design: Retrospective, single center, Observational study

Study setting: In-patient and Out-patient blocks of Neurology Department of Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram

Study Population: All patients attending the In-patient and Out-patient blocks of Neurology Department of SCTIMST between January 1, 2006 to December 31, 2021 with predominant lower body Parkinsonism fulfilling the following inclusion and exclusion criteria (1).

Inclusion criteria:

Patients presenting with

- Reduced gait mobility with slowness,
- Shortened stride length,
- Diminished step height,
- Increased step width (wide base),
- With or without Freezing of gait episodes,
- Poor objective response to external cues and L-dopa.

Exclusion criteria:

Patients presenting with

- Primary gait abnormality unrelated to lower body parkinsonism.

Sample size: This study is hypothesis-free and exploratory in nature and will be using the data from available patients. All consecutive patients who fulfilled the criteria in the study period were included. A total of 202 patients were included in the study.

Study period: June 2023 to December 2023 (Duration: 7 months)

Ethical approval: The study commenced after the approval from the Institutional Ethics Committee of SCTIMST. Consent waiver was obtained. (SCT/IEC/2056/MAY/2023). Consent waiver was obtained as the study was retrospective in nature.

Data collection: The data collection and analysis is planned in around 7 months. Study will start in June 2023, and will be completed by December 2023. We screened the case records of patients using the diagnostic keywords of “Lower body parkinsonism”, “Gait apraxia”, “Magnetic gait”, “Normal pressure hydrocephalus”, “Progressive supranuclear palsy”, “Vascular parkinsonism”. Data of patients satisfying inclusion and exclusion criteria was collected retrospectively from the case files in the electronic database (EMR) in a predesigned structured data collection proforma. Their basic demographic profile, risk factors, clinical (history and examination) and radiological findings were collected. Details of treatment given, response to treatment, appearance of additional neurological signs and evolution of new clinical phenotypes were collected from follow-up records and entered in a structured proforma.

Radiological evaluation details: Details of MRI or CT, wherever available were collected, with details of components of iNPH radscale, midbrain by pons ratio, MRPI, small and large vessel ischemic changes as applicable.

Statistical Analysis:

The collected data was entered in Microsoft excel spreadsheet and double checked for errors. The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means $\pm$ SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Shapiro-Wilk test. The cases in which the data was not normal, we used non parametric tests. The following statistical tests were applied for the results:

1. The comparison of the variables which were quantitative and not normally distributed in nature were analyzed using Kruskal Wallis test (for more than two groups) and variables which were quantitative and normally distributed in nature were analyzed using Independent t test (for two groups) and ANOVA (for more than two groups). For all normally distributed data, a Post Hoc test (Bonferroni correction) was applied after ANOVA. For all not normally distributed data a Post Hoc analysis by Dunn's multiple pair wise comparison test was carried out.

2. The comparison of the variables which were qualitative in nature were analyzed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. Bhapkar test was used for comparison of qualitative variables between initial and final evaluation.

All statistical analyses were performed using SPSS 25.0 software (IBM Corp, Armonk, New York). For statistical significance, p value of less than 0.05 was considered statistically significant.

Chapter 5

Results



RESULTS

Table 2.0:- Distribution of age at onset (years)

Age at onset(years)	Frequency	Percentage
<=40 years	5	2.48%
41 to 50 years	8	3.96%
51 to 60 years	22	10.89%
61 to 70 years	84	41.58%
71 to 80 years	74	36.63%
>80 years	9	4.46%
Mean $\pm$ SD	67.4 $\pm$ 10.4	
Median(25th-75th percentile)	69(63-74)	
Range	11-88	

Majority 84 (41.6%) of the study participants belonged to the age group of 61-70 years, followed by 74 (36.6%) to 71-80 years, 22 (10.9%) to 51-60 years, 9 (4.5%) to >80 years, 8 (4.0%) to 41-50 years and only 5 (2.5%) to <40 years age group. Mean value of age at onset of the study subjects was 67.4 ± 10.4 years with median (25th-75th percentile) of 69 (63-74) years.

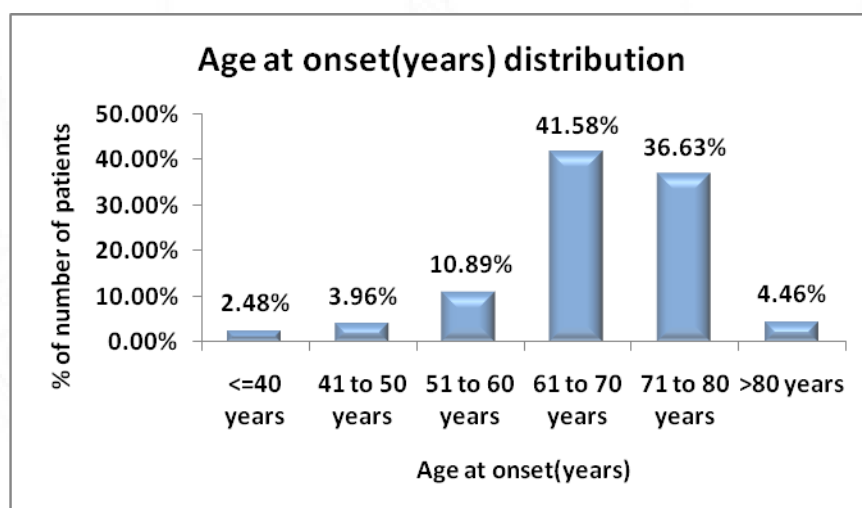


Figure 6.0:- Distribution of Age at onset (years)

Table 2.1:- Distribution of gender among study participants

Gender	Frequency	Percentage
Female	48	23.76%
Male	154	76.24%
Total	202	100.00%

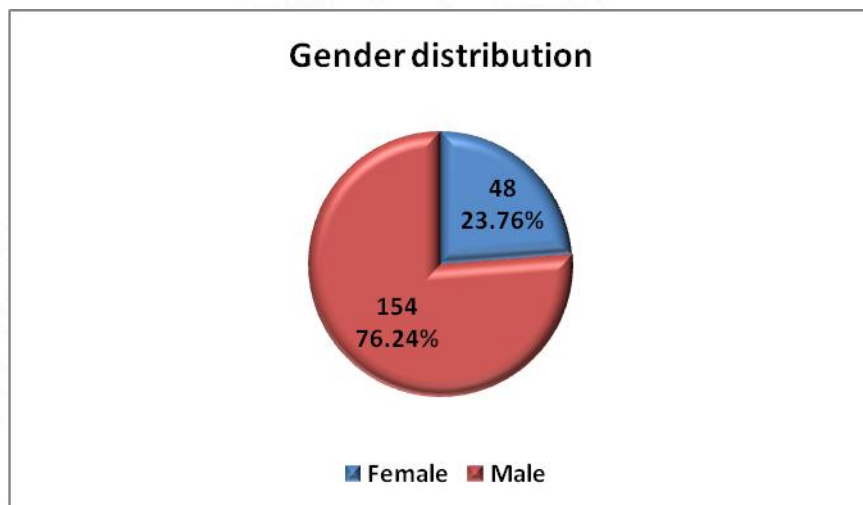


Figure 6.1:- Distribution of gender among study participants

Males were 154 (76.2%) and females were 48 (23.8%).

Table 2.2:- Distribution of initial symptom at onset

Initial symptom at onset	Frequency	Percentage
Gait difficulty	135	66.83%
Postural instability/Falls	5	2.48%
Slowness of activities	16	7.92%
Stiffness	2	0.99%
Rest tremor	1	0.50%
Action tremor	5	2.48%
Cognitive dysfunction	23	11.39%
Urinary symptoms	4	1.98%
Behavioural symptoms	9	4.46%
Headache	2	0.99%
Total	202	100.00%

Majority, 135 (66.8%) of the patients had gait difficulty as the initial symptom at onset. The next common initial symptom at onset was cognitive decline in 23 (11.4%) cases, followed by slowness of activities in 16 (7.92%), behavioral symptoms in 9(4.46%), postural instability/Falls and action tremor in 5(2.48%) each and urinary symptoms in 4(1.98%) study participants.

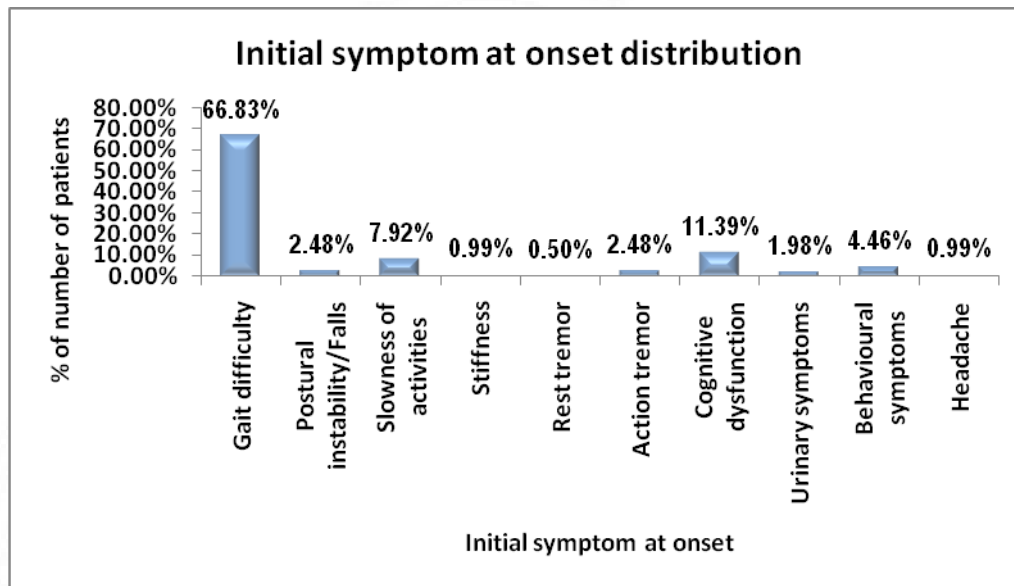


Figure 6.2:- Distribution of initial symptom at onset

Table 2.3:- Duration of symptoms (months) distribution

Duration of symptoms(months)	Frequency	Percentage
<6 months	22	10.89%
6 to 12 months	59	29.21%
13 to 24 months	53	26.24%
25 to 36 months	31	15.35%
37 to 48 months	12	5.94%
49 to 60 months	10	4.95%
>60 months	15	7.43%
Mean $\pm$ SD	25.1 $\pm$ 20.61	
Median(25th-75th percentile)	21(12-36)	
Range	0-96	

Majority, 59 (29.2%) of the study participants had symptoms for a duration of 6-12 months, followed by 53 (26.2%) for 13-24 months, 31 (15.3%) for 25-36 months, 22 (10.8%) for <6 months, 15 (7.4%) for >60 months, 12 (5.9%) for 37-48 months and 10 (5%) for 49-60 months. Mean value of duration of symptoms (months) of study subjects was 25.1 ± 20.61 with median (25th-75th percentile) of 21(12-36).

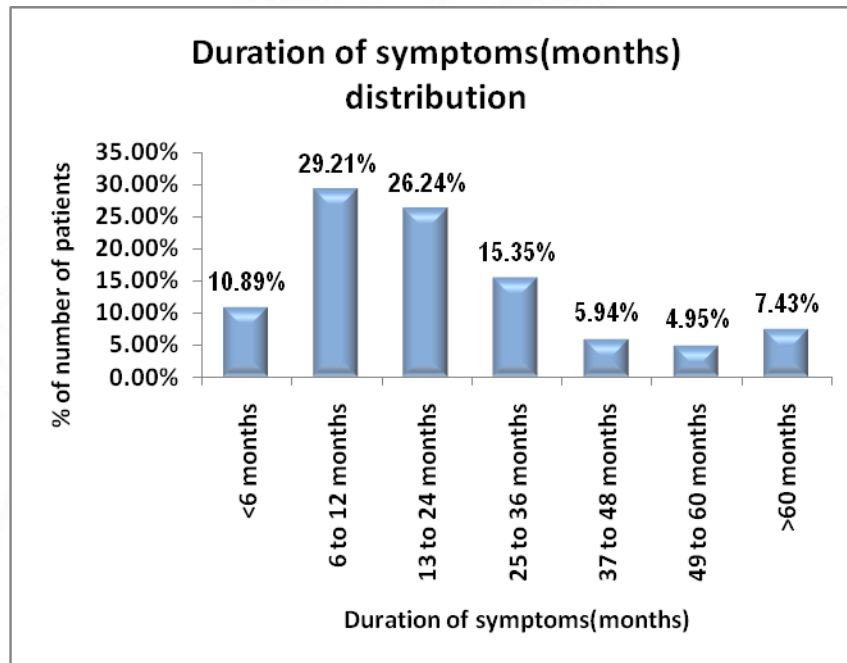


Figure 6.3:- Duration of symptoms (months) distribution

Table 2.4:- Abrupt onset/step wise progression of symptoms distribution

Abrupt onset/step wise progression of symptoms	Frequency	Percentage
Absent	190	94.06%
Present	12	5.94%
Total	202	100.00%

Abrupt onset/step wise progression of symptoms was present in 12 (5.9%) of the study participants while it was absent in 190 (94.1%).

Table 2.5:- Limb involved at symptom onset distribution

Limb involved at symptom onset	Frequency	Percentage
Upper limb	12	5.94%
Lower limb	184	91.09%
Upper and lower limb	6	2.97%
Total	202	100.00%

Lower limb was most commonly involved among 184 (91.1%) of the study participants followed by upper limb among 12 (5.9%), while both the limbs were involved simultaneously among 6 (3%) of the study participants.

Table 2.6:- Distribution of other symptoms at presentation

Other symptoms at presentation	Frequency	Percentage
Gait difficulty	200	99.01%
Freezing of gait	105	51.98%
Postural instability/Falls	114	56.44%
Slowness of activities	117	57.92%
Stiffness of limbs	42	20.79%
Rest tremor	12	5.94%
Action tremor	33	16.34%
Dysarthria	54	26.73%
Dysphagia/Choking	20	9.90%
Limb ataxia	6	2.97%
Orthostatic symptoms	1	0.50%
Presence of cognitive symptoms	134	66.34%
Behavioural symptoms	64	31.68%
Urinary symptoms		
Absent	54	26.73%
Urgency	136	67.33%
Urinary incontinence	12	5.94%
Miscellaneous symptoms		
Headache	5	2.47%
RBD	1	0.50%
Erectile dysfunction	1	0.50%
Emotional lability	2	0.99%
Orthostatic tremor	1	0.50%

Myoclonus	1	0.50%
Fasciculations	1	0.50%
Residual HP weakness	5	2.48%
New weakness	3	1.49%
Visual hallucinations	2	0.99%
Visual blurring	1	0.50%
Anxiety	1	0.50%
Fluctuating, variability of symptoms	1	0.50%
Weight loss	1	0.50%
Multiple somatic complaints	1	0.50%
Diplopia,vomiting	1	0.50%
Fluctuating cognition	1	0.50%
Vertigo	1	0.50%
Stereotypy	2	0.99%
Seizure	3	1.49%
Numbness of face, hearing loss	2	0.99%
Left hemibody chorea+ cervical dystonia following HP	1	0.50%
Upper limb dystonia	2	0.99%
Perioral dyskinesia	1	0.50%
Nil	163	80.69%

Gait difficulty was the most common symptom, present in 99% (200) of the patients, followed by urinary symptoms in 148 (73.3%) and cognitive symptoms in 134 (66.3%) cases. Among urinary symptoms, urgency was present in 136 (67.33%), while incontinence was present in 12 (5.94%) cases. Other common symptoms include slowness of activities and falls. Among miscellaneous symptoms, headache was seen in 5 (2.47%) patients. Other combination of symptoms noted among patients include, 1 (0.5%) had Fasciculation with new onset weakness, 1 (0.5%) had headache, new onset weakness and weight loss, 1 (0.5%) had visual hallucinations with fluctuating cognition, 1 (0.5%) had ED with emotional lability and 1 (0.5%) had Upper limb dystonia with perioral dyskinesias.

Table 2.7:- Symmetry of symptoms at onset

Symmetry of symptoms at onset	Frequency	Percentage
Asymmetric	34	16.83%
Symmetric	168	83.17%
Total	202	100.00%

The symptoms were symmetric in 168 (83.1%) study participants and asymmetric in 34 (16.8%) study participants.

Table 2.8:- Distribution of cognitive symptoms

Cognitive symptoms	Frequency	Percentage
Absent	61	30.20%
Attention deficit only	58	28.71%
Memory (amnesic) only	3	1.49%
Multidomain	80	39.60%
Total	202	100.00%

Multidomain cognitive symptoms were noted among 80 (39.6%) study participants followed by attention deficit alone in 58 (28.7%) and memory deficit alone in 3 (1.5%), while cognitive symptoms were absent in 61 (30.2%) study participants.

Table 2.81:- Cognitive status distribution

Cognitive status	Frequency	Percentage
Normal	61	30.20%
Single domain MCI	59	29.21%
Multidomain MCI	50	24.75%
Dementia	32	15.84%
Total	202	100.00%

Among patients with cognitive symptoms, most common pattern noted was single domain MCI in 59 (29.2%) subjects, followed by multi-domain MCI in 50 (24.75%) subjects, while dementia was noted only in 32 (15.84%) subjects.

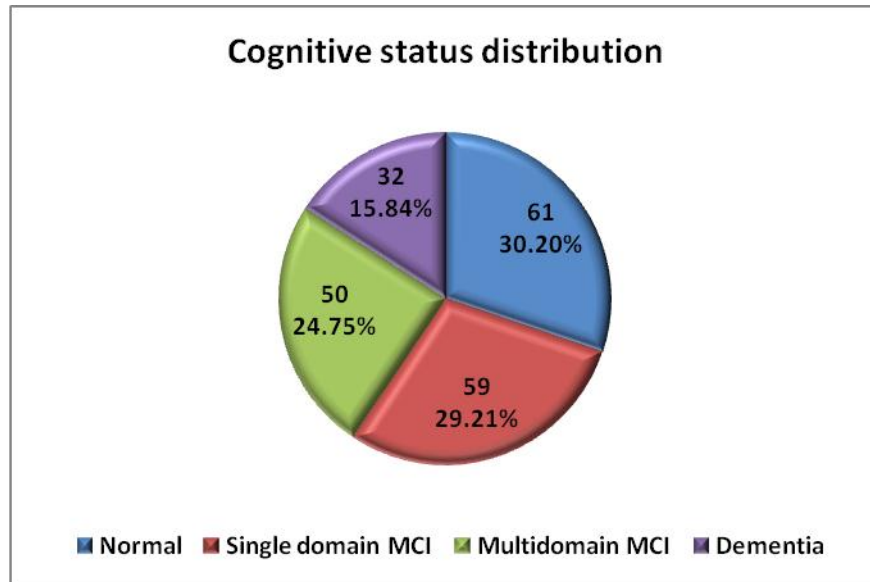


Figure 6.4:- Cognitive status distribution

Table 2.9:- Distribution of most disabling symptom at presentation

Most disabling symptom at presentation	Frequency	Percentage
Gait difficulty	84	41.58%
Freezing of gait	44	21.78%
Postural instability/Falls	52	25.74%
Cognition	15	7.43%
Urinary incontinence	3	1.49%
Behavioural symptoms	1	0.50%
Headache	2	0.99%
Dysphagia	1	0.50%
Total	202	100.00%

The most disabling symptom was gait difficulty, seen in 84 (41.5%) study participants followed by falls/postural instability in 52 (25.7%), FOG in 44 (21.8%), cognitive symptoms in 15 (7.4%) and others in remainder.

Table 3.0:- Distribution of vascular risk factors

Risk factors	Frequency	Percentage
Diabetes mellitus	121	59.90%
Hypertension	128	63.37%
Coronary artery disease	42	20.79%
Dyslipidemia	60	29.70%
Obstructive sleep apnea	4	1.98%
Smoking	36	17.82%
Alcoholism	13	6.44%

The most common vascular risk factor in the past was HTN, seen in 128 (63.4%) study participants, followed by diabetes in 121 (59.9%), dyslipidemia in 60 (29.7%). Coronary artery disease was present in 42(20.79%) cases, 36(17.82%) cases had history of smoking, 13 (6.44%) cases had history of alcoholism and 4(1.98%) cases had obstructive sleep apnea.

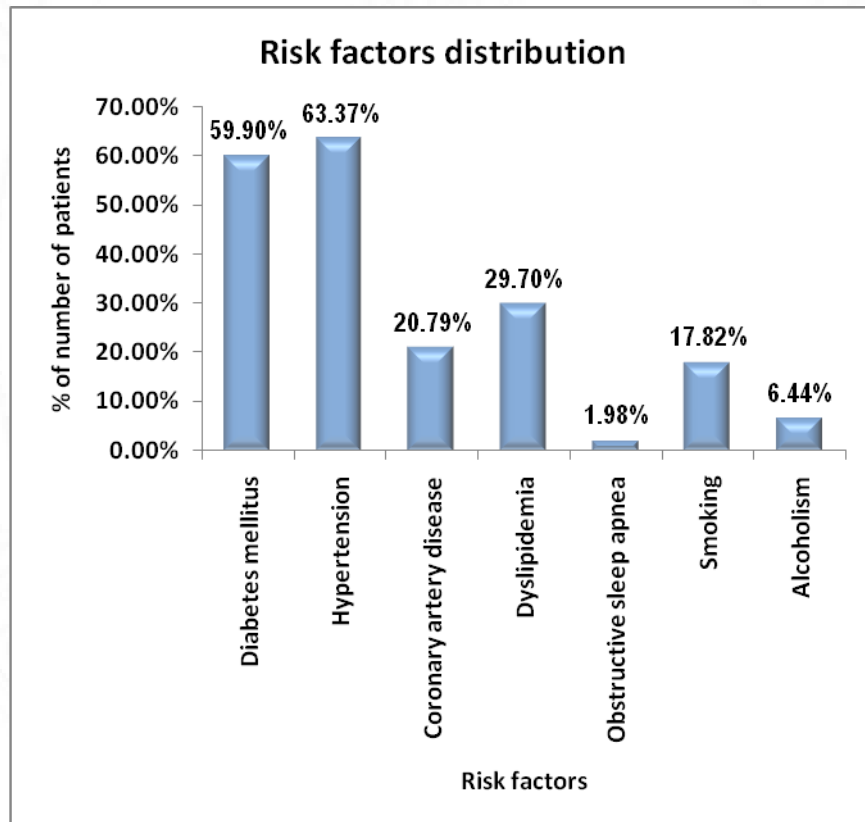


Figure 6.5: Risk factors distribution

Table 3.1:- History of documented stroke in the past

History of documented stroke in the past	Frequency	Percentage
Absent	169	83.66%
Ischemic stroke	29	14.36%
Intracerebral hemorrhage	2	0.99%
Subdural hemorrhage	1	0.50%
Subarachnoid hemorrhage	1	0.50%

A history of documented ischemic stroke in the past was present in 29 (14.3%), while ICH was present in 2 (1%) and SAH, SDH were present in 1 (0.5%) each. Single stroke event was seen in 23 (11.4%) study participants, 2 events in 8 (4%), 3 events in 1 (0.5%) and 4 events in 1 (0.5%), i.e ≥ 2 events were seen in 10 cases. The mean of no of events of stroke was 0.23 ± 0.59

A temporal relation of stroke to parkinsonism onset (onset of parkinsonism within 1 year of stroke) was present in 9(4.46%) patients.

Table 3.2:- Distribution of other co-morbidities.

Other co-morbidities	Frequency	Percentage
Nil	135	66.83%
Mood disorders /BPAD	8	3.96%
Depression	6	2.97%
SDH	1	0.50%
SAH	2	0.99%
Oligodendroglioma	2	0.99%
HIE with static encephalopathy	1	0.50%
RCC	1	0.50%
Papillary thyroid carcinoma	1	0.50%
TB CNS/Abdomen/Disseminated	4	1.98%
Intestinal obstruction	1	0.50%
Chronic spinal arachnoiditis	1	0.50%
ILD	1	0.50%
Pituitary adenoma	1	0.50%
Epilepsy	7	3.47%
Hypothyroidism	12	5.94%
Carcinoma tonsil	1	0.50%
CKD	6	2.97%

CLD	1	0.50%
BPH	8	3.96%
RHD	1	0.50%
COPD	1	0.50%
Recent COVID	1	0.50%
Meniere's disease	2	0.99%

Among other associated co-morbidities, most common was hypothyroidism, followed by BPAD and BPH. Other common co-morbidities were epilepsy, CKD. 6 patients had associated malignancy in the brain or anywhere in the body history and 4 patients had history of Tuberculosis.

Table 3.3:- Distribution of family history of Parkinsonism

Family history of Parkinsonism	Frequency	Percentage
Absent	194	96.04%
Present	7	3.47%
Present(Family history of cognitive decline with ataxia and spasticity)	1	0.50%
Total	202	100.00%

A family history of parkinsonism was present in 7 (3.5%) study participants and a family history suggestive of leukodystrophy was present in 1 patient.

Table 3.4:- Treatment history among the study participants

Treatment history	Frequency	Percentage
Levodopa		
Not given	166	82.18%
Given	36	17.82%
Levodopa equivalent daily dose		
200	13	6.44%
250	1	0.50%
300	16	7.92%
400	5	2.48%
600	1	0.50%
Dopa agonist		
Not given	199	98.51%
Given	3	1.49%
Other treatments		
Nil	181	89.6%
Typical antipsychotics	8	3.96%
Levosulpiride	1	0.50%
Radiotherapy	3	1.49%
Chemo-nimotuzumab	1	0.50%
ATT	2	0.99%
AED	1	0.50%
VP shunt	2	0.99%
Excision of glioma	1	0.50%
SDH evacuation	1	0.50%
Excision of pituitary adenoma	1	0.50%

Among subjects, only 36 (17.8%) received levodopa in the past. Dopa agonists were given only in 3 (1.5%) subjects. Other significant drugs in the treatment history include typical antipsychotics given in 8 (4%) subjects, history of radiotherapy in 3 (1.5%) subjects and chemotherapy and levosulpiride in 1 (0.5%) subject each.

A history of tap test was present in 7 subjects out whom, 3 (1.5%) were reported positive, 3 (1.5%) were reported borderline and 1 was reported negative.

Table 3.5:- Distribution of general examination findings among the study participants

General examination	Frequency	Percentage
Normal	129	63.86%
Hypomimia/ mask facies	19	9.41%
Staring look / PSP facies	13	6.44%
Pseudobulbar effect	6	2.97%
Frontal release signs (GT, PM)	32	15.84%
Signs of atherosclerosis	2	0.99%
Asterexis	1	0.50%
Cachexia	1	0.50%

General examination of 129(63.86%) cases was normal, 32(15.84%) cases had frontal lobe release signs (GT, PM), 19(9.41%) cases had hypomimia/ mask like facies, 13(6.44%) cases had staring look / PSP facies, 6(2.97%) cases had pseudobulbar effect and emotional incontinence, 2(0.99%) cases had signs of atherosclerosis and 1(0.50%) each showed asterexis and cachexia.

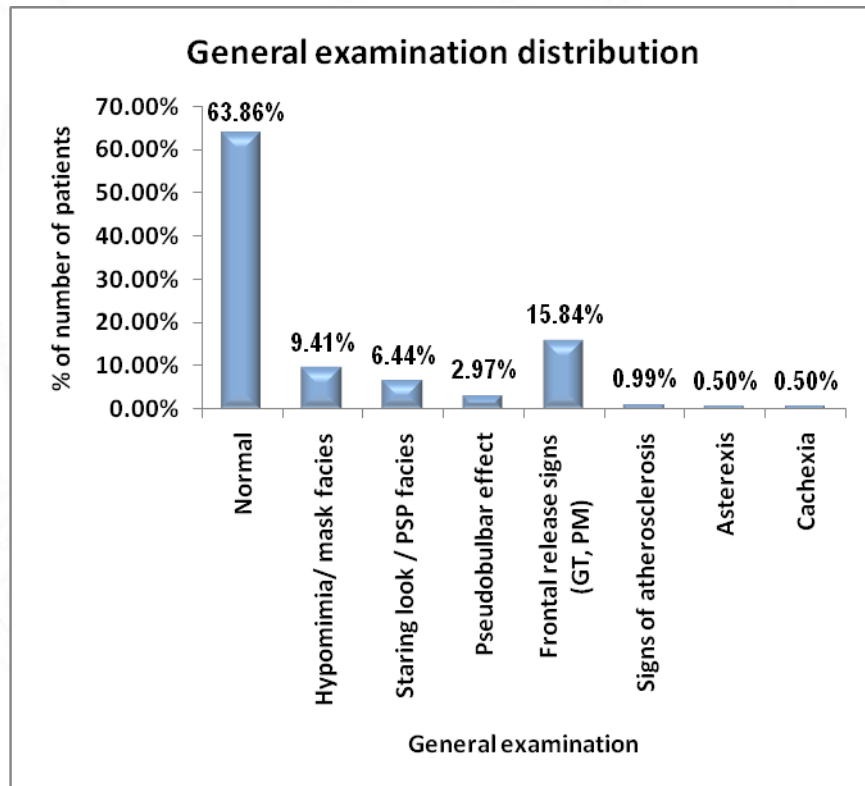


Figure 6.6:- Distribution of general examination findings among the study participants

Table 3.6:- Distribution of MMSE scores among the study participants

MMSE scores	Frequency	Percentage
Poor patient co-operation	3	1.49%
5 to 10	5	2.48%
11 to 15	13	6.44%
16 to 20	24	11.88%
21 to 25	59	29.21%
26 to 30	98	48.51%
Mean $\pm$ SD	23.85 $\pm$ 5.3	
Median(25th-75th percentile)	25(21-28)	
Range	5-30	

MMSE scores of 98(48.51%) cases were between 26 to 30, 59(29.21%) cases were between 21 to 25, 24(11.88%) cases in the range of 16 to 20, 13(6.44%) cases was between 11 to 15, 5(2.48%) cases was between 5 to 10 and in 3(1.49%) cases, MMSE could not be done due to poor patient co-operation. Mean value of MMSE scores of study subjects was 23.85 ± 5.3 with median (25th-75th percentile) of 25(21-28).

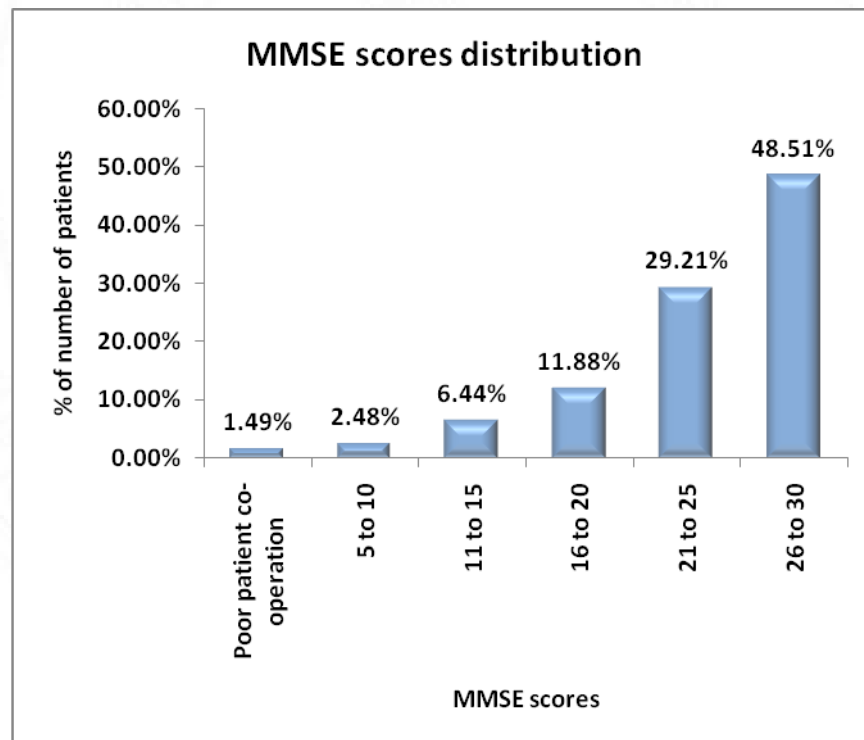


Figure 6.7:- Distribution of MMSE scores among the study participants

Table 3.7:- Distribution of Eye movements findings among the study participants

Eye movements	Frequency	Percentage
Normal eye movements	125	61.88%
Vertical gaze restriction (Up+down)	2	0.99%
Vertical gaze restriction (Up)	10	4.95%
Vertical gaze restriction (Down)	1	0.50%
Saccadic slowing (Vertical)/ Round the house sign	34	16.83%
Saccadic slowing (Vertical, horizontal)	12	5.94%
Frequent macro square wave jerks/Apraxia of eyelid opening	4	1.98%
Hypometric saccades	12	5.94%
Oculomotor apraxia	1	0.50%
Gaze evoked nystagmus	1	0.50%

The eye movements were normal in 125(61.88%) subjects. The most common eye movement abnormality was Vertical saccadic slowing / Round the house sign seen in 34(16.83%) cases. 12(5.94%) cases had both vertical and horizontal saccadic slowing, 12(5.94%) cases had hypometric saccades. 10(4.95%) subjects showed vertical gaze restriction (Upgaze). Eye movement abnormalities in 4(1.98%) cases were frequent macro square wave jerks/Apraxia of eyelid opening, in other 2(0.99%) cases were vertical gaze restriction (Up+down gaze) and in 1(0.50%) case was vertical gaze restriction (Downgaze). Oculomotor apraxia and gaze evoked nystagmus were present in 1 case each. Convincing eye signs suggestive of PSP were present in total of 63 (31.1%) subjects.

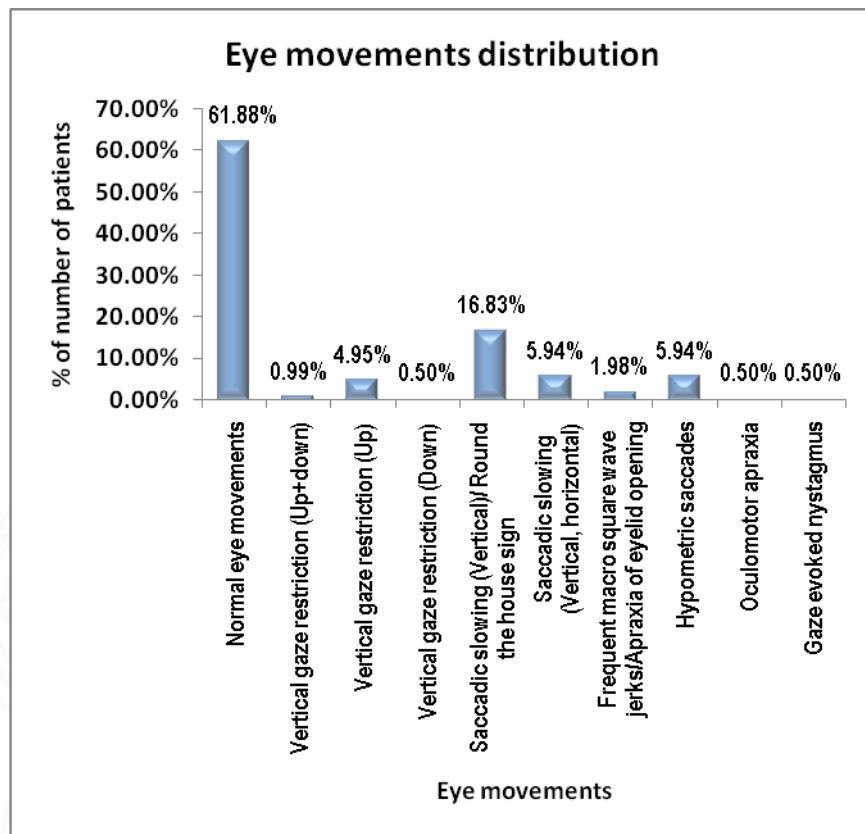


Figure 6.8:- Distribution of Eye movements' findings among the study participants

Among study population, spastic dysarthria was absent in 174(86.14%) cases and present in 28 (13.86%) cases. Palatal movements of 197(97.52%) cases was normal, 3(1.49%) cases had an exaggerated gag response and 2(0.99%) cases had absent gag or reduced palatal movements. 193(95.54%) cases did not have any other cranial nerve involvement. 5(2.48%) subjects had evidence of UMN 7 nerve palsy, 2(0.99%) cases had SNHL and 1(0.50%) case had bitemporal hemianopia and optic disc pallor (bilateral) each.

Table 3.8:- Distribution of Extra pyramidal system examination findings

Extrapyramidal system examination	Frequency	Percentage
Axial rigidity		
Absent	140	69.31%
Axial=APP rigidity	37	18.32%
Axial>APP rigidity	25	12.38%
Limb rigidity		
Absent	22	10.89%
Lower limb only	48	23.76%
Lower limb>Upper limb	68	33.66%
Lower limb+Upper limb	64	31.68%
Extrapyramidal examination		
Bradykinesia	127	62.87%
Rest tremor	12	5.94%
Action tremor	56	27.72%
Parkinsonism	125	61.88%

Majority of study participants 140(69.31%) did not have axial rigidity. Axial more than appendicular rigidity was present in only 25(12.38%) cases, while axial and appendicular rigidity of equal degree was present in 37(18.32%) cases.

Lower limb more than upper limb rigidity 68(33.66%) was the most common pattern of limb rigidity noted among the study participants. Equal degree of lower limb and Upper limb rigidity was noted in 64 (31.68%) cases, while lower limb alone was noted in 48(23.76%). Limb rigidity was absent in 22(10.89%) cases.

Bradykinesia was present in 127(62.87%) study participants, and parkinsonism was noted in 125(61.88%) study participants. Action tremor was present in 27.72% (56) of the study participants, while rest tremor was present only in 12(5.94%) subjects.

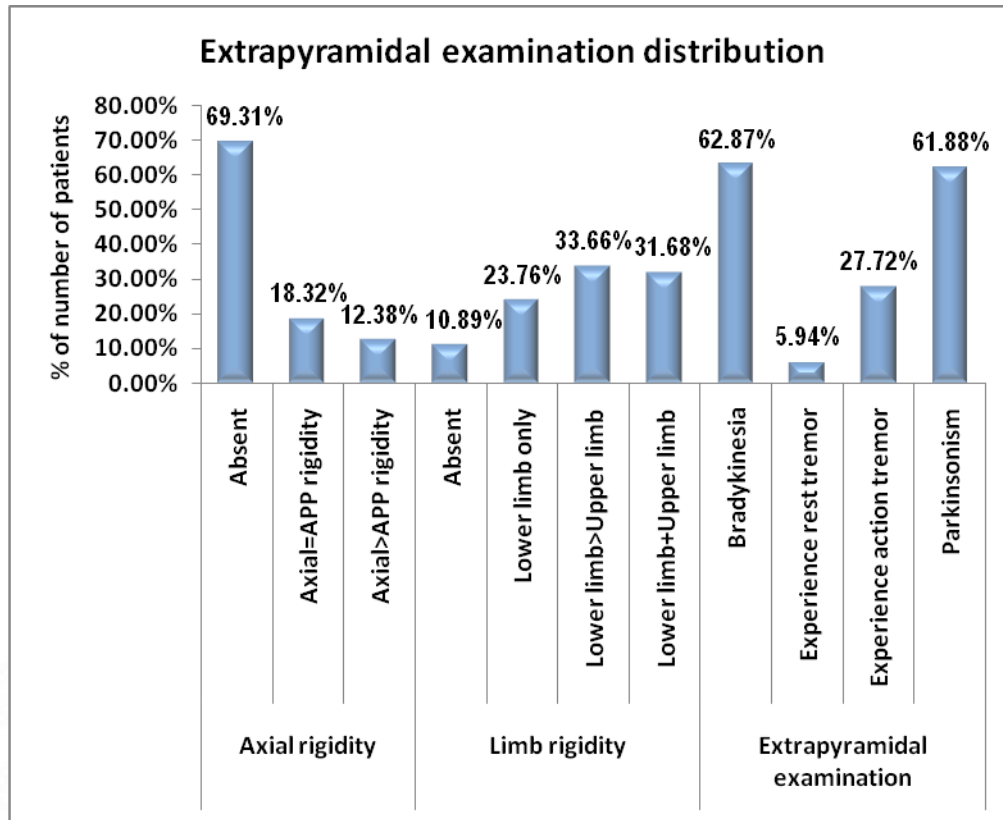


Figure 6.9:- Distribution of Extra pyramidal system examination findings

Table 3.81:- Upper limb examination findings at initial evaluation

Upper limb findings at initial evaluation	Frequency	Percentage
Rest tremor {Upper limb sings}		
Absent	191	94.55%
Present	11	5.45%
Parkinsonism {Upper limb sings}		
Absent	87	43.07%
Present	115	56.93%

Among subjects, an upper limb rest tremor was present in only 5.45% (11), while upper limb parkinsonism was present in 115(56.93%) cases.

Table 3.82:- Distribution of Parkinsonism

Distribution of Parkinsonism	Frequency	Percentage
U/L or hemibody	4	2.86%
Asymmetric	51	36.43%
Symmetric	85	60.71%
Total	140	100.00%

The most common pattern of parkinsonism among the study participants was symmetric in 85(60.71%) cases, followed by asymmetric in 51(36.43%) cases. A hemibody or a strictly unilateral presentation was seen in only 4(2.86%).

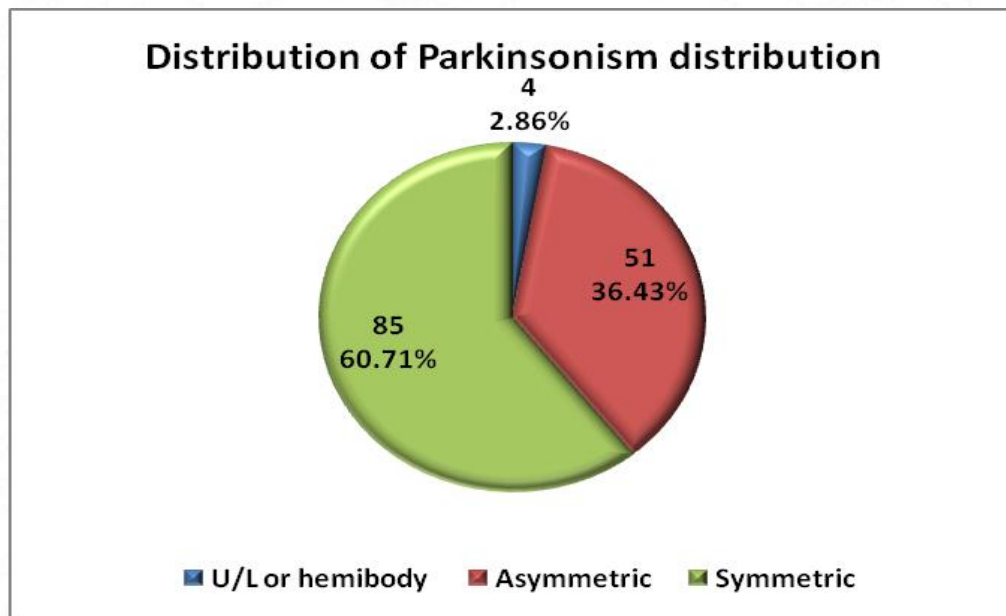


Figure 7.0:- Distribution of Parkinsonism

Table 3.9:- Distribution of gait examination findings

Gait examination findings	Frequency	Percentage
Postural instability		
Absent	55	27.23%
Grade 1	83	41.09%
Grade 2	49	24.26%
Grade 3	12	5.94%
Grade 4	3	1.49%
Gait initiation difficulty / failure	149	73.76%
Gait apraxia	202	100.00%
Freezing of gait finding	117	57.92%
Gait variability/distractibility	2	0.99%

The most common gait finding in the subjects was gait apraxia, noted in all patients, followed by gait initiation failure in 149 (73.76%) cases, postural instability in 147 (72.7%) cases, FOG in 117(57.92%) cases. Gait variability and distractibility was noted in 2 (0.99%) cases.

Postural instability was present in a total of 147 (72.7%) subjects, of which grade 1 was most commonly noted in 83(41.09%) cases, followed by grade 2 in 49(24.26%) cases, grade 3 in 12(5.94%) cases and grade 4 in 3(1.49%) cases. Postural instability was absent in 55 (27.23%) cases.

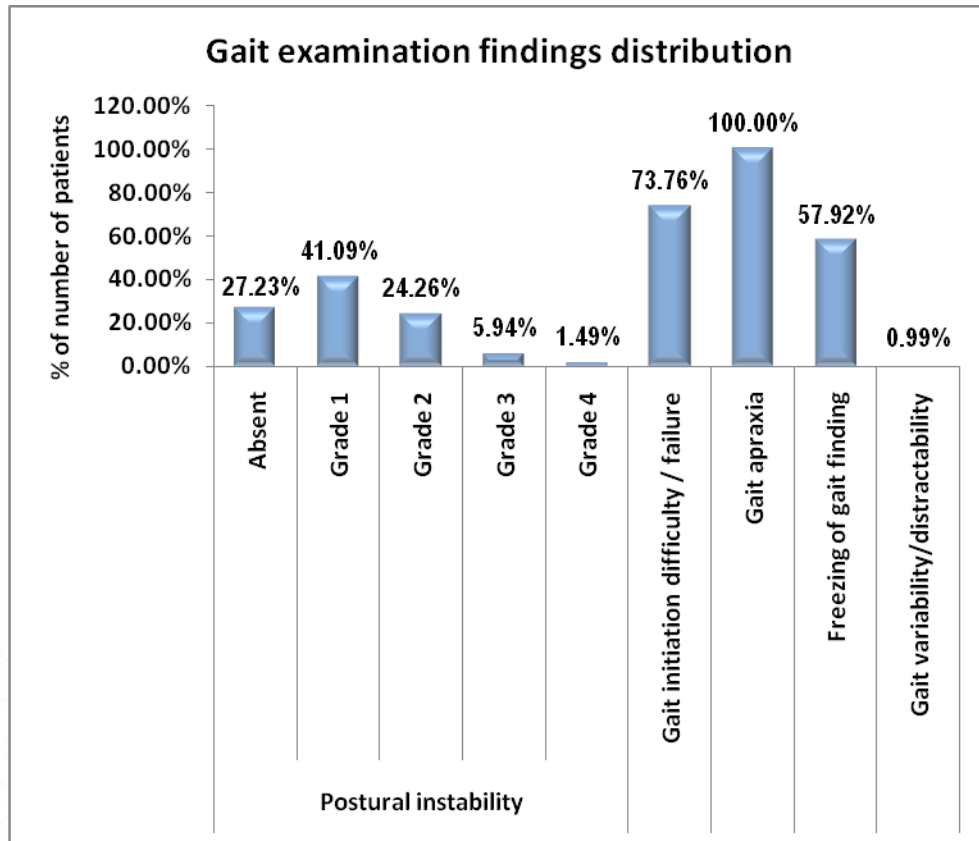


Figure 7.1:- Distribution of gait examination findings

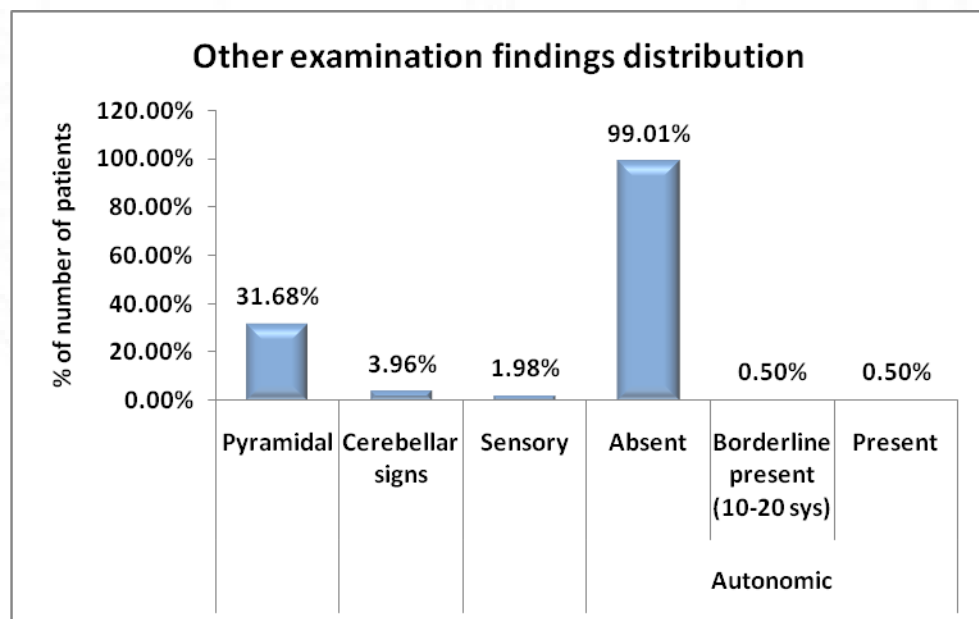


Figure 7.2:- Distribution of other examination findings

Among study subjects, pyramidal signs were present in 64(31.68%), cerebellar signs were present in 8 (3.96%) cases and sensory signs were present in 4(1.98%) subjects. Autonomic dysfunction in the form of orthostatic hypotension was present in 1 subject, while only borderline drop in BP (10-20mm Hg drop in systolic BP) was noted in 1 subject. In rest 200(99.01%) cases, autonomic dysfunction was absent.

Table 4.0:- Miscellaneous examination findings distribution

Other findings	Frequency	Percentage
Nil	173	85.64%
Multifocal myoclonus	9	4.46%
Dystonia	9	4.46%
Limb Apraxia	1	0.50%
Cortical sensory loss	3	1.49%
Fasciculations	3	1.50%
Orthostatic tremor	1	0.50%
Residual hemiparesis	2	0.99%
Pelvic mass	1	0.50%
New onset weakness	1	0.50%
Striatal toe	3	1.49%
Chorea, stereotypy	1	0.50%
Hemichorea, cervical and orofacial dystonia	1	0.50%
Astasia abasia	1	0.50%

Among miscellaneous examination findings, multifocal myoclonus and dystonia were the commonest and noted in 9 (4.5%) cases. Fasciculations and cortical sensory loss were noted in 3 subjects each. A pelvic mass was noted in 1 subject. 1 study participant had acute onset hemichorea on one side with orofacial, cervical dystonia following vascular event and gradually progressive parkinsonism with significant gait difficulty, postural instability and FOG.

CT/MRI availability

Out of 202 subjects, detailed neuro-imaging films were available for review and analysis in 163 (80.69%) subjects, out of which only CT (limited analysis feasible) was done in 12 patients. Only report was available (done from elsewhere) in 33 (16.34%) cases, hence complete data could not be collected in such cases. No imaging was done in 6 subjects (2.97%).

Table 4.1:- Distribution of GCA score among study participants

GCA score	Frequency	Percentage
Absent	4	1.98%
Grade 1	126	62.38%
Grade 2	44	21.78%
Grade 3	1	0.50%
Report only	21	10.40%
Not done	6	2.97%
Total	202	100.00%

Around 126 (62.38%) subjects had grade 1 atrophy, which was the most common GCA grade, followed by 44(21.78%) cases with grade 2 and 1 case with grade 3 atrophy. Atrophy was absent in 4 subjects. Among patients with report only, a mention of diffuse cerebral atrophy was made.

Table 4.2:- Hydrocephalus distribution

Hydrocephalus	Frequency	Percentage
Absent	75	37.13%
Present	102	50.50%
Report only (without mention of hydrocephalus)	19	9.41%
Imaging not done	6	2.97%
Total	202	100.00%

Among subjects with available imaging, hydrocephalus was present in 102 (50.50%) cases, of which 97 (95.1%) cases were a communicating hydrocephalus. The hydrocephalus was disproportionate to the atrophy in 74 (72.55%) of the patients. Hydrocephalus was absent in 75(37.13%) cases and imaging was not done in 6 (2.9%) cases. An obstructive cause of hydrocephalus was noted in 5 (4.9%) cases.

Out of these 102 patients, detailed images or PACS was available for 88 patients, while only mention of hydrocephalus was there in the report in 14 patients. (Total number of patients with only report are 33, out of which hydrocephalus was mentioned in report in 14. 1such patient had obstructive hydrocephalus due to aqueductal stenosis).

Total number of patients with detailed imaging or PACS available were 162, out of which, hydrocephalus was present in 88 (54.32%) cases.

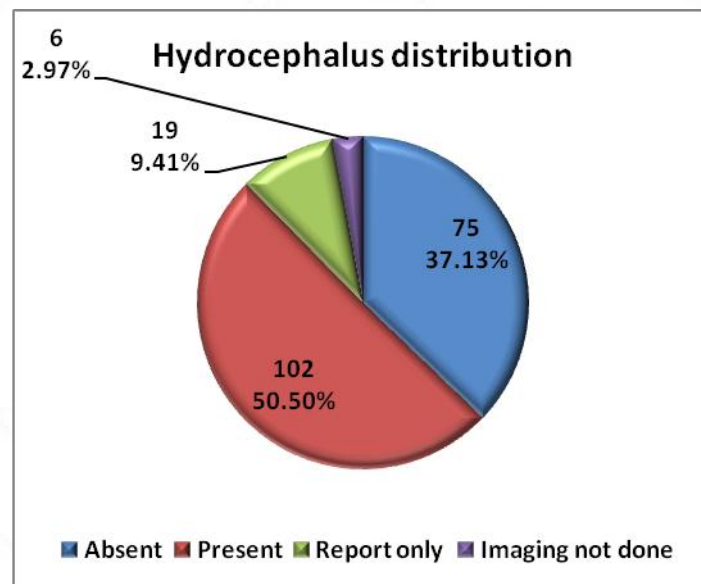


Figure 7.3:- Hydrocephalus distribution

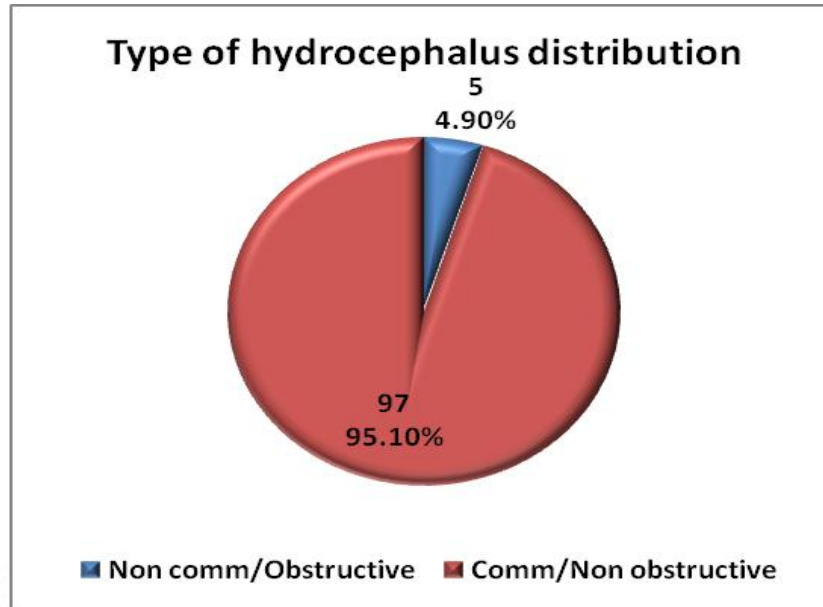


Figure 7.31:- Distribution of type of hydrocephalus

Table 4.21:- Evans index score (n=176) distribution among subjects.

Evans index score (n=176)	Frequency	Percentage
≤ 0.25	65	36.93%
0.25 to 0.3	11	6.25%
> 0.3	100	56.82%
Total	176	100.00%

Out of 176 subjects presenting with LBP, Evans index score was 2 i.e $EI > 0.3$ in 100 (56.82%) subjects, it was 0, i.e ≤ 0.25 in 65 (36.93%) subjects and EI score was 1 between 0.25 to 0.3 in 11(6.25%) subjects.

Table 4.22:- Components of iNPH radscale - findings among patients with hydrocephalus with films/PACS available (n=88)

Parameters of patients who have hydrocephalus among those with films/PACS(n=88)	Frequency	Percentage
Narrow sulci		
Normal	50	56.82%
Parafalcine	36	40.91%
Vertex	2	2.27%
Sylvian enlargement		
Normal	4	4.55%
Enlarged	84	95.45%
Focal enlarged sulci		
Absent	26	29.55%
Present	62	70.45%
Temporal horn		
<4mm	2	2.27%
4 to 6mm	58	65.91%
>6mm	28	31.82%
Callosal angle		
>90	36	40.91%
>60 to 90	43	48.86%
<=60	9	10.23%
Peri-ventricular changes		
Absent	4	4.55%
Frontal horn caps	48	54.55%
Confluent areas	36	40.91%

Amongst the components of iNPH rad scale, the most common finding present in patients with hydrocephalus is sylvian enlargement present in 84 (95.45%) cases, followed by focal enlarged sulci in 62 (70.45%) cases, grade 1 temporal horn enlargement in 58(65.91%) cases, grade 1 periventricular changes- frontal horn caps in 48(54.55%) cases and an acute callosal angle between 60 to 90 degrees in 43(48.86%) cases.

Table 4.23:- Distribution of total iNPH radscale in hydrocephalus patients with films/PACS (n=88)

Total iNPH Rad scale in hydrocephalus patients with films/PACS(n=88)	Frequency	Percentage
Total iNPH Rad scale in hydrocephalus patients with films/PACS		
4	4	4.55%
5	12	13.64%
6	10	11.36%
7	13	14.77%
8	25	28.41%
9	15	17.05%
10	6	6.82%
11	2	2.27%
12	1	1.14%
Mean ± SD	7.45 ± 1.77	
Median(25th-75th percentile)	8(6-9)	
Range	4-12	
Total iNPH Rad scale distribution in hydrocephalus patients with films/PACS		
<=8	64	72.73%
>8	24	27.27%

The most common Total iNPH Rad scale score among patients with hydrocephalus in our study was 8.0 in 25(28.41%) cases, followed by 9.0 in 15(17.05%) and 7.0 in 13(14.77%). Mean value of total iNPH Rad scale in our study was 7.45 ± 1.77 with median (25th-75th percentile) of 8(6-9). The iNPH Rad scale was ≤ 8 in 64 (72.73%) cases and > 8 in 24(27.27%) cases.

Among other supporting features of NPH, DESH was present in 14(13.73%) cases and aqueductal flow void was present in 12(11.76%) cases.

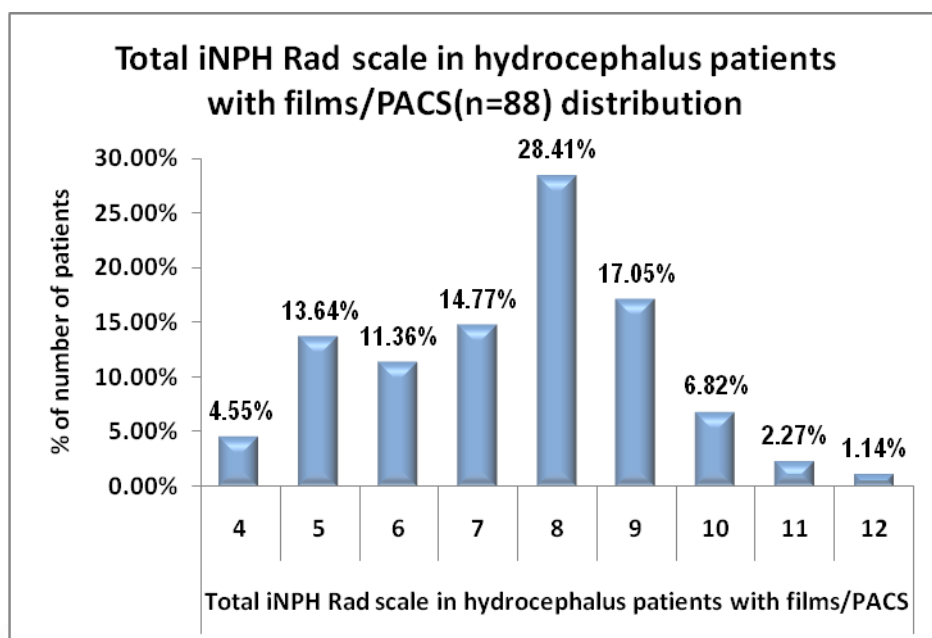


Figure 7.32:- Distribution of total iNPH radscale in hydrocephalus patients with films/PACS (n=88)

Table 4.3:- Distribution of brainstem imaging findings

Brainstem	Frequency	Percentage
Midbrain Atrophy (Visually) (n=167)		
Absent	111	66.47%
Mild (tectal atrophy)	46	27.54%
Moderate	10	5.99%
Severe	0	0%
Midbrain to pons ratio(n=144)		
<0.2	28	19.44%
0.2 to 0.22	27	18.75%
>=0.23	89	61.81%
Mean $\pm$ SD	0.24 $\pm$ 0.04	
Median(25th-75th percentile)	0.24(0.21-0.26)	
Range	0.13-0.38	
MRPI(n=144)		
<=13.55	118	81.94%
>13.55	26	18.06%
Mean $\pm$ SD	12.09 $\pm$ 2.46	
Median(25th-75th percentile)	12(10.575-12.95)	
Range	6.4-23	

Among study subjects, mild Midbrain Atrophy (Visually) was present in 46 (27.54%) cases and moderate midbrain atrophy was present in 10(5.99%) cases.

The Midbrain to pons ratio (n=144) of 89 (61.81%) cases was normal i.e ≥ 0.23 , of 28(19.44%) cases was <0.2 and of 27(18.75%) cases was borderline in the range of 0.2 to 0.22. Mean value of midbrain to pons ratio (n=144) of study subjects was 0.24 ± 0.04 with median (25th-75th percentile) of 0.24(0.21-0.26). In patients with outside MRI scans and those with CT scans, Midbrain by pons ratio and MRPI could not be calculated.

MRPI (n=144) of 118 (81.94%) cases was normal, ≤ 13.55 and of 26(18.06%) cases was >13.55 . Mean value of MRPI (n=144) of study subjects was 12.09 ± 2.46 with a median (25th-75th percentile) of 12(10.575-12.95).

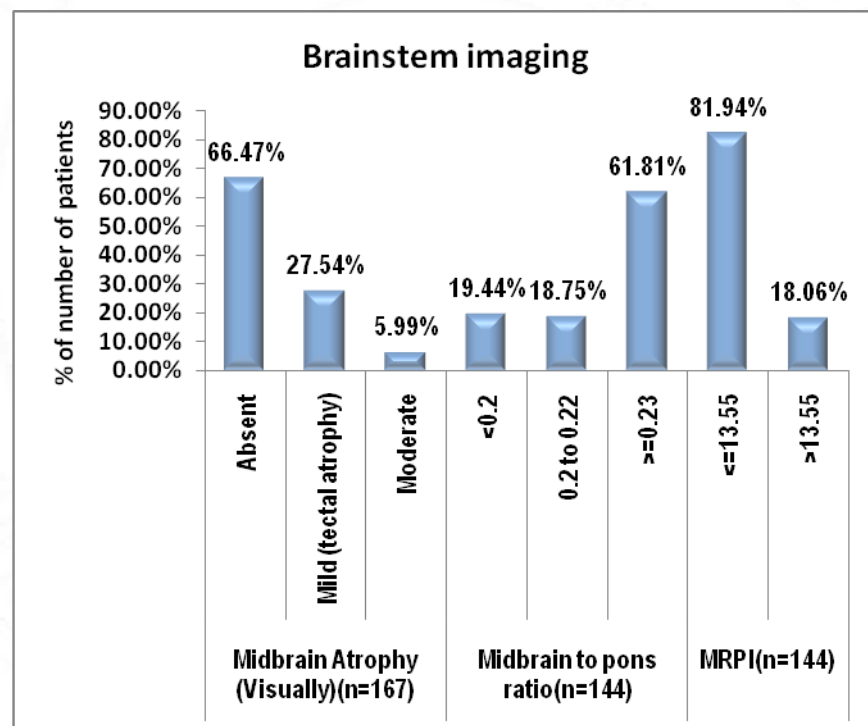


Figure 7.4:- Distribution of brainstem imaging findings

Table 4.4:- Distribution of evidence of small vessel ischemic changes

Evidence of small vessel ischemic changes	Frequency	Percentage
Fazekas grade (PV)(n=185)		
Absent	12	6.49%
1	95	51.35%
2	65	35.14%
3	13	7.03%
Fazekas grade (DWM)(n=185)		
Absent	23	12.43%
1	82	44.32%
2	46	24.86%
3	34	18.38%
Evidence of small vessel ischemic changes		
Lacunar infarcts (n=175)	56	32.00%
Microbleeds (n=173)	16	9.25%

Among study subjects, evidence of periventricular fazekas changes were present in 173 (93.5%) cases, of which grade 1 was the commonest finding followed by grade 2 and 3. Among study subjects, evidence of deep white matter fazekas changes were present in 162 (87.5%) cases, of which grade 1 was the commonest finding followed by grade 2 and 3. Lacunar infarcts were present in 56 (32%) cases and microbleeds were present in 16 (9.25%) cases.

Table 4.41:- Distribution of evidence of large vessel ischemia/ past stroke changes

Evidence of large vessel ischemia/ past stroke changes	Frequency	Percentage
Absent	146	83.91%
Present	28	16.09%
Total	174	100.00%

Evidence of large vessel ischemic changes were present in 28(16.09%) of the study participants.

Figure 7.5:- Distribution of evidence of small vessel ischemic changes

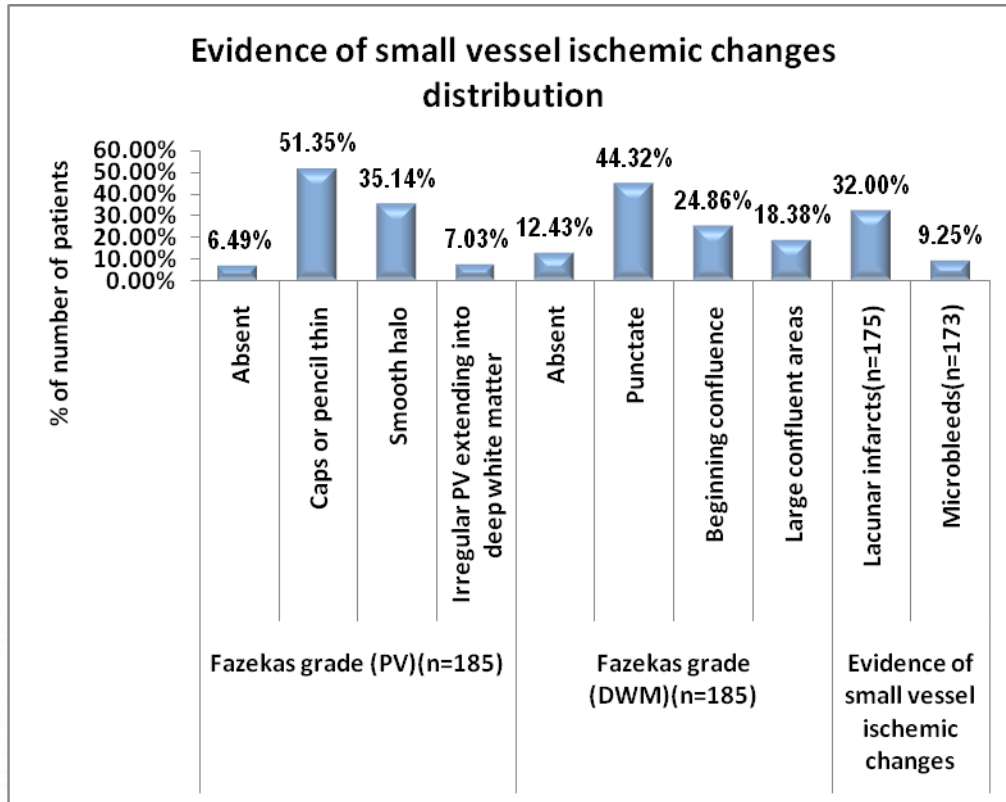


Table 4.42:- Distribution of strategic infarcts or other lesions in the striatal dopaminergic system

Strategic infarct or lesion in striatal dopaminergic system	Frequency	Percentage
Infarct(n=173)	16	9.25%
Bleed(n=172)	1	0.58%
Other lesions in striatal dopaminergic system(n=172)	0	0.00%

A strategic infarct in striatal dopaminergic system was noted in 16 (9.25%) cases, among the subjects, while a bleed in the the striatal dopaminergic system was seen in 1 (0.58%) patient.

Table 4.5:- Distribution of other imaging findings

Other imaging findings	Frequency	Percentage
Nil	132	74.58%
Aqueduct shows narrowing with funnelling distally, normal size of 4th ventricle	1	0.56%
Asymmetric parietal atrophy	2	1.13%
Frontotemporal atrophy	5	2.82%
Prominent foramen of luschka, prominent flow voids in 3, 4th ventricles- Extraventricular obstructive hydrocephalus	1	0.56%
Bilateral temporal atrophy	7	3.95%
T1 Hyper b/l Gpi, Midbrain, post pons. Blooming in SWI. Mineralisation of b/l SNr, red nucleus	1	0.56%
Frontal predominant atrophy	3	1.69%
Bilateral symmetric T2 hyperintensity in GpI	1	0.56%
Aqueductal stenosis with obstructive hydrocephalus	2	1.13%
Mineralisation of Gpi, SNr, red nuclues. MRS- increased Choline, Myoinositol, lactate	1	0.56%
Large cystic lesion in vermis with supratentorial extension, obstructive hydrocephalus	1	0.56%
Cortical ribbon, T2 hyper in caudate, put, pulvinar	1	0.56%
SAH (Left)	1	0.56%
SDH(Right FPT)	1	0.56%
Left Vestibular Schwannoma	1	0.56%
MRS-No lactate/ choline peak	1	0.56%
Residual pituitary adenoma	1	0.56%
DSA-No evidence of vasculitis	1	0.56%
Pituitary Macroadenoma	1	0.56%
Multiple cortical, PV micro, macrobleeds with cortical superficial siderosis	1	0.56%
Resection cavity Rt frontal with exvacuo dilation of Rt lat vent. T2 HI in PV and Centrum semiovale region- anterior predominant (Post RT changes). No tumour recurrence	1	0.56%
Cerebellar atrophy, no abnormal mineralisation	1	0.56%
Right Parietal lobar chronic hemorrhagic infarct	1	0.56%
Gpi Hemorrhagic infarct right	1	0.56%
Multiple microhemorrhages in WM, Cortex,	1	0.56%

brainstem		
Right Cerebellar mass lesion, CT Chest- Adenoma carcinoma lung	1	0.56%
Parietal> frontal atrophy	1	0.56%
Multifocal CE T2 HI with restricted diffusion, R>L, posterior dominant	1	0.56%
Left CP angle lesion- meningioma with obstructive hydrocephalus	1	0.56%
Right superior parietal enhancing lesion ? TB/Neoplastic	1	0.56%
Increased mineralisation of bilateral deep gray matter	1	0.56%

Among other imaging findings, 7 cases had bitemporal atrophy, 5 cases had frontotemporal atrophy, 3 had frontal predominant atrophy, 2 had asymmetric parietal atrophy. 1 subject had features of CJD, 1 had extraventricular obstructive hydrocephalus, 1 had post radiotherapy subcortical white matter changes, 5 subjects had evidence of tumours of varied nature and etiology.

Figure 7.6:- Distribution of CSF tap test results

Among 202 subjects, CSF tap test was considered in 85 subjects, out of whom it was deferred in 2 cases in view of minimal deficits, 2 subjects did not give consent. In the remaining 81 subjects, a positive tap test result was obtained among 33(16.34%) cases, in 29(14.36%) cases, it was negative and in 19 (9.41%) cases, it was borderline.

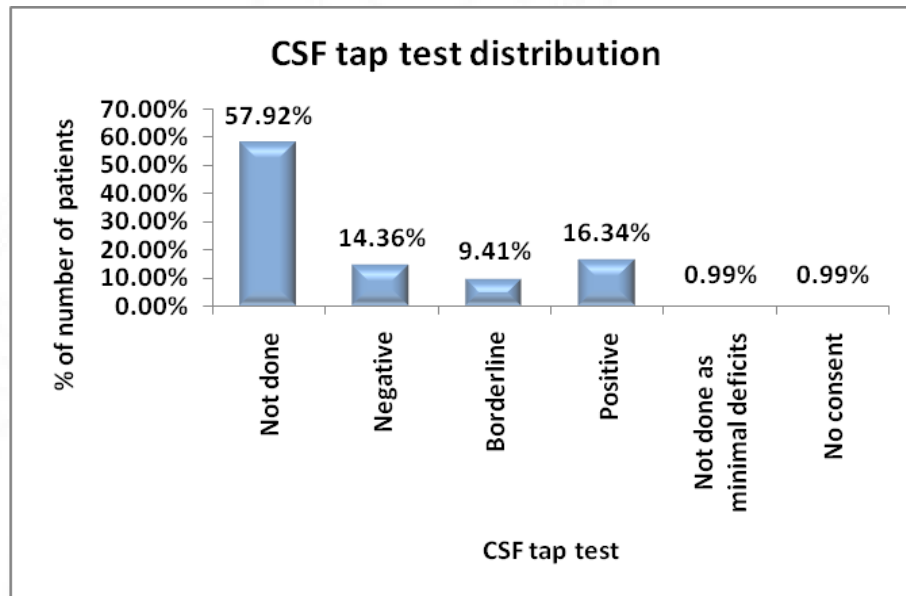


Table 4.6:- Improvement in MMSE (CD) with CSF drainage distribution

Improvement in MMSE (CD) with CSF drainage	Frequency	Percentage
Absent	25	54.35%
Present	21	45.65%
Total	46	100.00%

Among subjects who underwent tap test and had cognitive symptoms, improvement in MMSE with tap test was noted in 21 (45.6%) cases.

Table 4.7:- Distribution of other investigations results

Other investigations	Frequency	Percentage
Nil findings in other investigations	180	89.11%
EMG: Diffuse AHC inv +	1	0.50%
CSF autoimm, paraneoplastic panel negative	10	4.95%
Wilson -ve, ferritin level normal	2	0.99%
Clinical exome-PLA2G6+	1	0.50%
EEG Triphasic waves	1	0.50%
CSF- protein -384, cell-80 L, anti cysticercal Ab +ve, TB PCR -ve	1	0.50%
EEG (IED+ Abnormal)	1	0.50%
Giant SSEP	2	0.99%
CSF TB PCR +ve	1	0.50%
PSG: Central + OSA	1	0.50%
NCV-Demyelinating S+M polyradiculoneuro, Nr, Mus Biop-awaited, Aryl Supl- awaited	1	0.50%
USG: Pelvic mass	1	0.50%
EEG-Diffuse slowing, Wilson, HD- Neg	1	0.50%
DSA, Meningeal biopsy neg	1	0.50%
Anti Ro: strongly +, Anti Hu: borderline +ANA 3+, IGLON -ve	1	0.50%
EEG-FIRDA, CSF Protein- elevated, CSF Autoimm, paraneo-Neg, AMA +	1	0.50%
EEG-Dys: Normal lactate, pyruvate, Plasma amino acids- Negative	1	0.50%

Among miscellaneous investigations, Giant SSEP were noted in 2 cases, EMG evidence of diffuse AHC involvement was noted in 1 case, Anti Ro was strongly positive in 1 case, AMA positive in 1 case, CSF TB PCR was positive in 1 patient and CSF Anti cysticercal antibody was positive in 1 patient, among other investigations.

Table 4.80:- Distribution of diagnosis at initial evaluation

Diagnosis at initial evaluation	Frequency	Percentage
NPH	41	20.30%
PSP	30	14.85%
VP	13	6.44%
VP with VCI	34	16.83%
CAA +VP with VCI	1	0.50%
PIGD-PD	6	2.97%
CBS	2	0.99%
MSA	3	1.49%
FTD	4	1.98%
Mixed (NPH+VP)	4	1.98%
Mixed (NPH+PD)	1	0.50%
Mixed (NPH+PSP)	5	2.48%
Mixed (NPH+AD)	5	2.48%
Mixed (VP with VCI +PSP)	1	0.50%
Mixed (VP with VCI +AD)	4	1.98%
PSP+ALS complex	3	1.49%
Mixed (VP with VCI +NPH)	6	2.97%
Mixed (DLBD + VP with VCI)	2	0.99%
Mixed (MSA-P+NPH)	1	0.50%
DLBD	1	0.50%
Mixed (PSP +Vascular hemichorea with dystonia)	1	0.50%
Immune mediated Parkinsonism with dementia	5	2.48%
AD	1	0.50%
Functional movement disorder/Phobic gait	2	0.99%
Sphenoid wing meningioma with mass effect on frontal lobe	1	0.50%
Bipyramidal syndrome with GF-PLS	1	0.50%
Acquired hepatocerebral degeneration with cirrhosis	1	0.50%
Pallidopyramidal PLA2G6	1	0.50%
Adult onset Leukodystrophy	4	1.98%
Obstructive hydrocephalus due to mass	3	1.49%
Drug induced Parkinsonism	2	0.99%
Adeno ca lung with brain mets	1	0.50%
Parkinsonism d/t CJD	1	0.50%

Post radiotherapy subcortical WM disease	2	0.99%
Aqueductal stenosis with obstructive hydrocephalus	3	1.49%
Post traumatic communicating hydrocephalus	1	0.50%
Extraventricular obstructive hydrocephalus	1	0.50%
Parkinsonism d/t CNS vasculitis	1	0.50%
Diffuse high grade glioma ass Parkinsonism	1	0.50%
Communicating hydrocephalus d/t CNS TB	1	0.50%
Parkinsonism d/t NCC arachnoiditis ass. communicating hydrocephalus	1	0.50%

The most common diagnosis at initial evaluation in the current study was Vascular parkinsonism (includes VP, VP with VCI and VP with CAA), which was noted in total 48 (23.8%) cases, followed by NPH 41(20.30%) cases, then by PSP 30 (14.85%) cases and PIGD variant of PD noted in 6 (2.97%) subjects. This was followed by mixed pathologies, among which NPH+VP (including VCI) was the commonest seen in 10 subjects, followed by NPH+PSP and NPH+AD noted in 5 subjects each. Immune mediated causes were noted in 5 subjects.

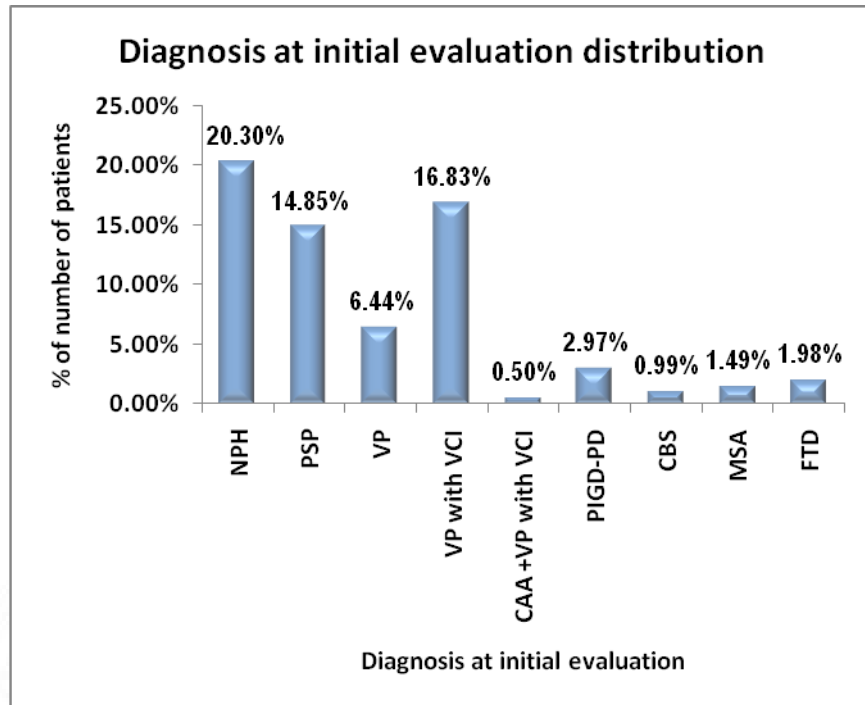


Figure 7.7:- Distribution of diagnosis at initial evaluation

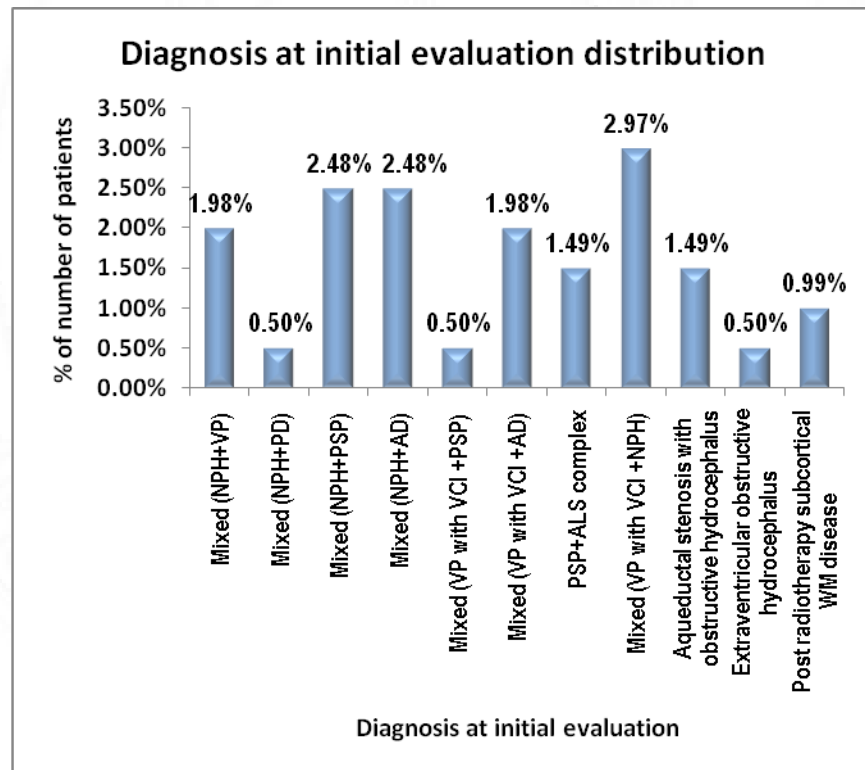


Figure 7.71:- Distribution of diagnosis at initial evaluation

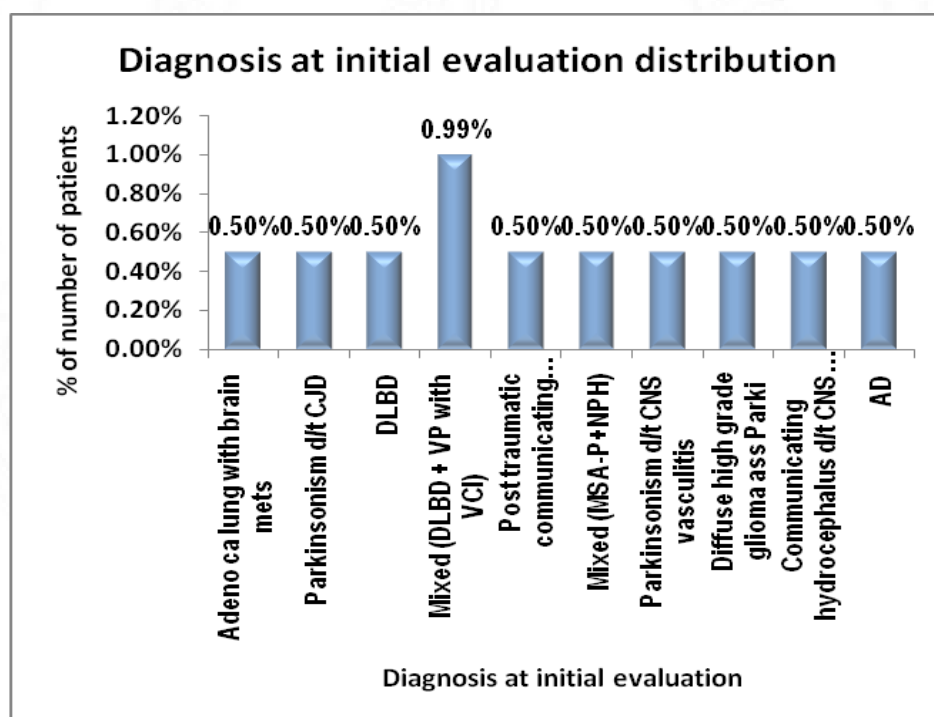
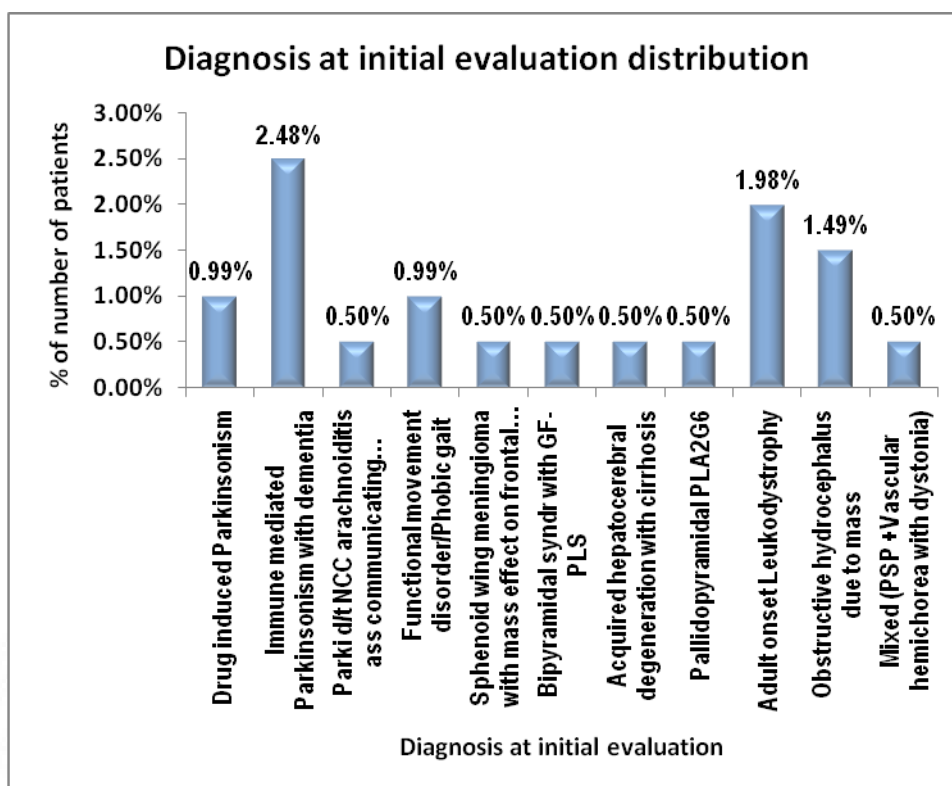


Table 4.81:- Distribution of subtype of PSP and diagnostic certainty (n=41) at initial evaluation

Subtype of PSP and certainty (n=41) at initial evaluation	Frequency	Percentage
Subtype of PSP at initial evaluation		
RS	22	53.66%
PAGF	14	34.15%
CBS	2	4.88%
Frontal	1	2.44%
PI	2	4.88%
Certainty at initial evaluation		
Definite	0	0.0%
Probable	22	53.66%
Possible	19	46.30%

Among patients diagnosed as PSP at initial evaluation, the most common subtype was RS noted in 22(53.66%) cases, followed by PAGF in 14(34.15%), CBS and PI in 2(4.88%) each and Frontal variant in 1(2.44%) patient.

The most common level of diagnostic certainty in the PSP subjects was probable noted in 22(53.66%) cases, followed by possible in 19(46.30%) cases.

Table 4.82:- Distribution of certainty of NPH diagnosed (n=64) at initial evaluation

Certainty of NPH (n=64) at initial evaluation	Frequency	Percentage
Probable	35	54.69%
Possible	29	45.31%
Total	64	100.00%

Among subjects diagnosed with NPH at initial evaluation, probable NPH was noted in 35(54.69%) cases and in 29(45.31%) cases, a diagnosis of possible NPH was made.

Table 4.9:- Distribution of initial MRS among study participants

Initial MRS	Frequency	Percentage
2	16	7.92%
3	130	64.36%
4	56	27.72%
Total	202	100.00%

Majority of subjects had moderate disability at initial diagnosis with an initial MRS score of 3 in 130 (64.36%) cases, followed by a score of 4 in 56 (27.72%) cases and 2 in 16 (7.92%) cases.

Table 5.0:- Distribution of initial treatment given among study participants

Treatment given	Frequency	Percentage
L-Dopa		
Not given	56	27.72%
Given	146	72.28%
VPS		
Not done	166	82.18%
Done	24	11.88%
No consent	11	5.45%
Planned	1	0.50%
Other treatment given		
Nil	141	69.80%
Diuretics	17	8.42%
Supportive (baclofen)	9	4.46%
Riluzole	1	0.50%
ATT	1	0.50%
Clonazepam	1	0.50%
Excision of lesion	3	1.49%
Endoscopic 3rd ventriculostomy	1	0.50%
Endoscopic 3rd ventriculostomy+Aqueductoplasty	2	0.99%
Endoscopic 3rd ventriculostomy+Septostomy	1	0.50%
Thecoperitoneal shunt	1	0.50%
ChE inh	10	4.95%
Stop L Dopa	1	0.50%
Antipsych	1	0.50%
Botox	1	0.50%
Hepatic enceph Rx	1	0.50%

Safinamide	1	0.50%
Withdraw offending drug, replace with better group	2	0.99%
Immune rx (IVMP f/b oral steroid/MTx)	6	2.97%
Immune rx (IVMP f/b cyclophosphamide)	1	0.50%
Albendazole+Praziquantel+Steroid	1	0.50%

Among the subjects, Levodopa was the most common treatment given, and it was given in 146(72.28%) subjects. VPS shunt was the next common treatment administered in study population and was done in 24(11.88%) cases. 11(5.45%) cases were advised VPS, but was deferred as subjects did not consent for the surgery.

Among other treatments given, the most common treatment given was oral diuretics followed by cholinesterase inhibitors, baclofen, immune therapy and supportive treatment.

Figure 5.1:- Response of gait to initial treatment

Response of gait to levodopa was excellent in only 7 (4.79%) cases, while it was moderate in 64(43.84%) cases, very minimal in 62(42.47%) cases and absent in 13(8.90%).

Response of gait to VPS was excellent in 13(54.17%) cases, moderate in 9(37.50%) cases and very minimal in 2(8.33%) cases.

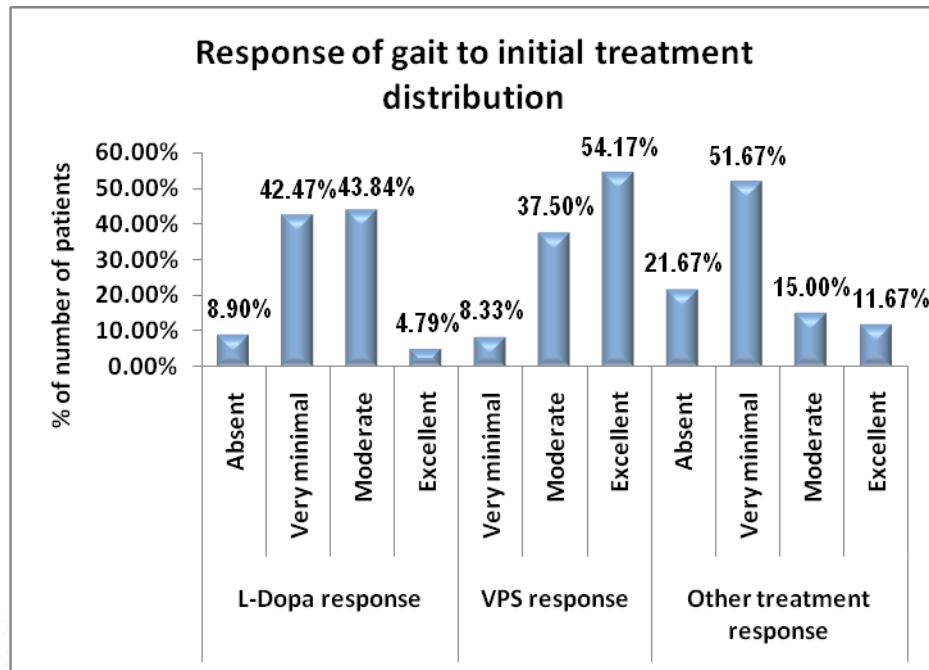


Figure 7.8:-Descriptive statistics of duration of follow up (months)

Out of 202 patients, 25 (12.38%) were lost to follow up after initial diagnosis. Mean duration of follow up period among remaining study participants (in months) was 13.76 ± 17.07 with a median (25th-75th percentile) of 7 (4-17) and range (0-96).

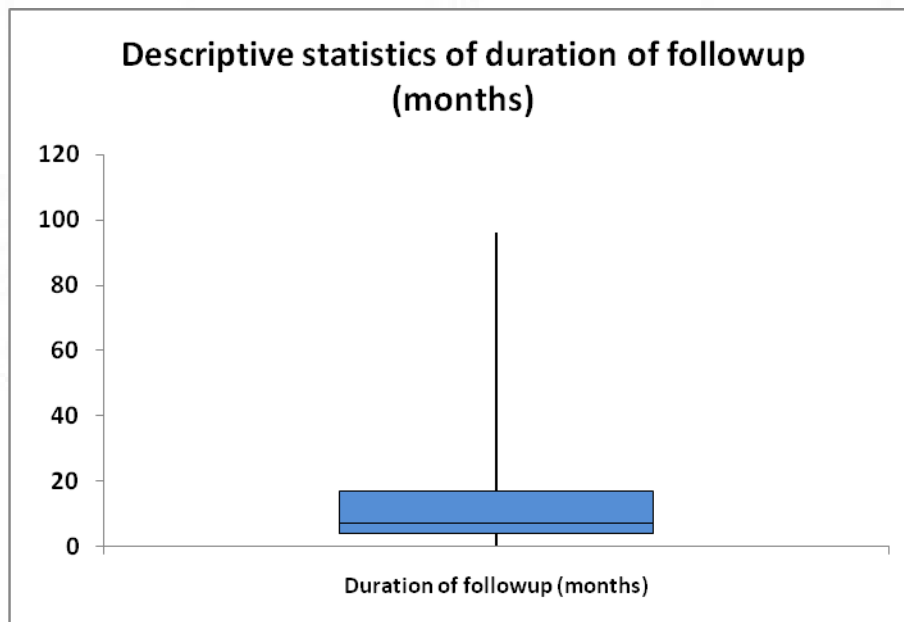


Table 5.12:- Sustained benefit or stable course with treatment (n=177)

Sustained benefit or stable course with treatment(n=177)	Frequency	Percentage
Absent	50	28.25%
Present but waning	79	44.63%
Present	47	26.55%
No specific treatment given	1	0.56%
Total	177	100.00%

Among majority of subjects who were on regular follow up, though initial benefit with treatment was there, the effect was gradually waning and this was noted in 79(44.63%) subjects. In 50 (28.25%) cases, there was no sustained benefit with treatment, while in 47(26.55%) cases, a persistent benefit with treatment was present.

Table 5.2:- Distribution of additional findings at last visit (n=177)

Additional findings at last visit(n=177)	Frequency	Percentage
Clinical findings		
Nil	107	60.45%
VGR	22	12.43%
SS	9	5.08%
Dysphagia/choking	2	1.13%
New/ worsening Parki (Br/R/Tr)	2	1.13%
Worsening of GD	24	13.56%
Worsening of CD	16	9.04%
Wor/new onset of PI	8	4.52%
New CD	2	1.13%
New stroke (malignant MCA infarct)	2	1.13%
Limb apraxia	1	0.56%
Disappearance of Parkinsonism	1	0.56%
Atrophy of 1st websp, retrocollis, pyramidal+	1	0.56%
Tap test +	1	0.56%
Orthostatic tremor	1	0.56%

Fall, coma, atrial flutter	1	0.56%
Improvement in dyskinesias	1	0.56%
Orthostatic hypotension	1	0.56%
Imaging findings		
Nil	145	81.92%
Fz 3, Midbrain Atrophy (MRPI- 14.	1	0.56%
Worsening of frontotemporal atrophy	1	0.56%
Midbrain atrophy	2	1.13%
Worsening of Fz 1 to 3 and INPH scale to 10	1	0.56%
New SDH	3	1.69%
No worsening of Hydrocephalus/NPH features	2	1.13%
No worsening of Fazekas changes	1	0.56%
New infarct/ICH	3	1.69%
B/L Medial temporal atrophy	4	2.26%
Worsening of Fz, but no change in ventricular size	8	4.52%
Fz 2 ischemic changes, Chronic lacunar infarcts, No NPH features	1	0.56%
No f/o NPH	1	0.56%
B/L Cerebellar Atrophy, Mild Pons Atrophy	1	0.56%
Worsening of Ventriculomegaly, but no increase in Fz	2	1.13%
Clinical exome-VUS msT01 (mito myo+ataxia), PLEKHG2(Leuko, microceph, dyst)	1	0.56%
HPE-Pilocytic astrocytoma grade 1	1	0.56%

Among study participants, no additional clinical signs were noted in 107 (60.45%) cases. The most common additional signs noted were worsening of GD in 24 (13.56% cases), followed by new eye signs among which VGR was commonest noted in 22(12.43%) cases, followed by

worsening of CD in 16 (9.04%) cases and saccadic slowing in 9 (5.08%) cases. New onset stroke was noted in 2(1.13%) cases, 1 patient developed atrial flutter and was dead and in 1 patient tap test done at follow up was positive.

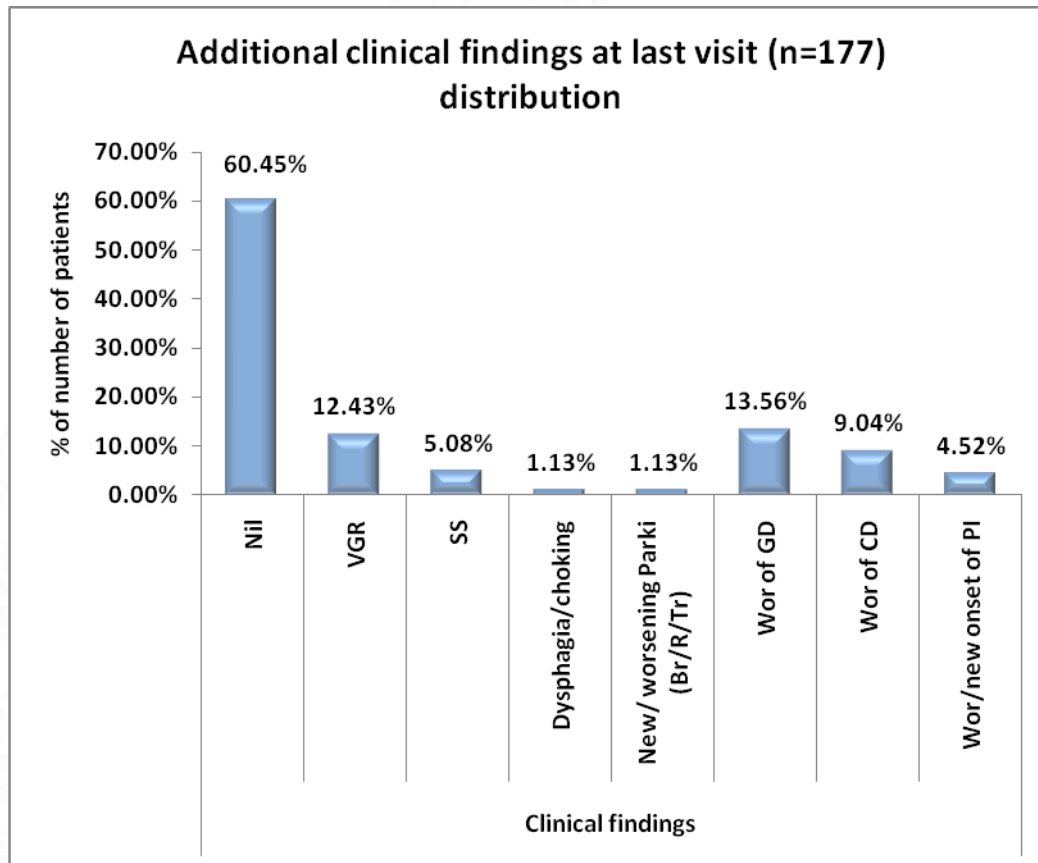


Figure 7.9:- Distribution of additional clinical findings at last visit (n=177)

Imaging findings were either not available or no additional findings were noted in 145(81.92%) subjects at last visit. Among subjects with additional imaging findings, 8(4.52%) cases had worsening of Fazekas ischemic changes, but no change in ventricular size, 4(2.26%) cases had evidence of bilateral medial temporal atrophy, in 3(1.69%) cases, there was evidence of new vascular event, 2(1.13%) cases showed evidence of midbrain atrophy, 1 case showed worsening of fazekas changes and iNPH score to 10. Worsening of MRPI to 14 was noted in 1 subject.

Table 5.3:- Distribution of diagnosis at last evaluation (n=177)

Diagnosis at last evaluation(n=177)	Frequency	Percentage
NPH	25	14.12%
PSP	35	19.77%
VP	10	5.65%
VP with VCI	28	15.82%
CAA +VP with VCI	2	1.13%
PIGD-PD	4	2.26%
CBS	1	0.56%
MSA	3	1.69%
FTD	3	1.69%
Mixed (NPH+VP)	5	2.82%
Mixed (NPH+PD)	1	0.56%
Mixed (NPH+PSP)	5	2.82%
Mixed (NPH+AD)	3	1.69%
Mixed (VP with VCI +PSP)	6	3.39%
Mixed (VP with VCI +AD)	10	5.65%
PSP+ALS complex	3	1.69%
Mixed (VP with VCI +NPH)	4	2.26%
Aqueductal stenosis with obstructive hydrocephalus	3	1.69%
Post radiotherapy subcortical WM disease	1	0.56%
Immune mediated Parkinsonism with dementia	1	0.56%
Parkinsonism d/t NCC arachnoiditis associated communicating hydrocephalus	1	0.56%
Functional movement disorder/ phobic gait	3	1.69%
Sphenoid wing meningioma with mass effect on frontal lobe	1	0.56%
Acquired hepatocerebral degeneration with cirrhosis	1	0.56%
Pallidopyramidal PLA2G6	1	0.56%
Adult onset Leukodystrophy	1	0.56%
Obstructive hydrocephalus due to mass	2	1.13%
Mixed (PSP +Vascular hemichorea with dystonia)	1	0.56%
Parkinsonism d/t CJD	1	0.56%
Mixed (DLBD + VP with VCI)	2	1.13%

Post traumatic communicating hydrocephalus	1	0.56%
VPS malfunction	1	0.56%
Mixed(PSP-ALS complex+VP)	1	0.56%
Mixed (NPH+FTD)	1	0.56%
Mixed (Post RT SC WM D+PSP)	1	0.56%
AD-Frontal variant	1	0.56%
Mixed (PIGD-PD+VP)	1	0.56%
SDH	3	1.69%
Mixed (PSP+AD)	1	0.56%
Mixed (Imm mediated Parki anti Ro +VP)	1	0.56%
Mixed (Imm mediated Parki anti AMA +PSP)	1	0.56%
Mitochondrial Leukoencephalopathy	1	0.56%

The most common diagnosis at last evaluation in the current study was Vascular parkinsonism (includes VP, VP with VCI and VP with CAA), which was noted in total 40 (22.6%) cases, followed by PSP in 35 (19.77%) cases, NPH in 25(14.12%) cases. This was followed by mixed pathologies, among which VP (with VCI) + AD accounted for 10 (5.65%) cases, followed by NPH+VP (including VCI) seen in 9 (5.1%) subjects, VP + PSP in 6(3.39%), followed by NPH+PSP in 5 (2.82%) cases. PIGD variant of PD was noted in 4 (2.26%) subjects. Amongst others, 3(1.69%) cases were MSA and FTD each, 3(1.69%) cases were mixed (NPH+AD) and PSP+ALS complex each. Aqueductal stenosis with obstructive hydrocephalus was noted in 3(1.69%) cases and 3(1.69%) cases were of functional movement disorder/ phobic gait.

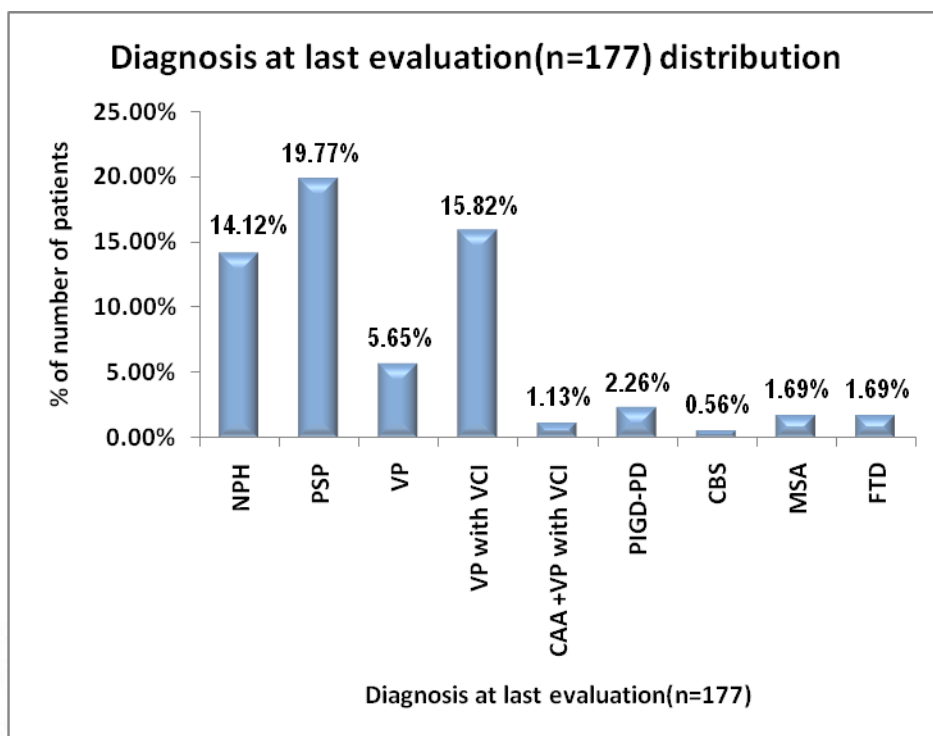


Figure 8.0:- Distribution of diagnosis at last evaluation (n=177)

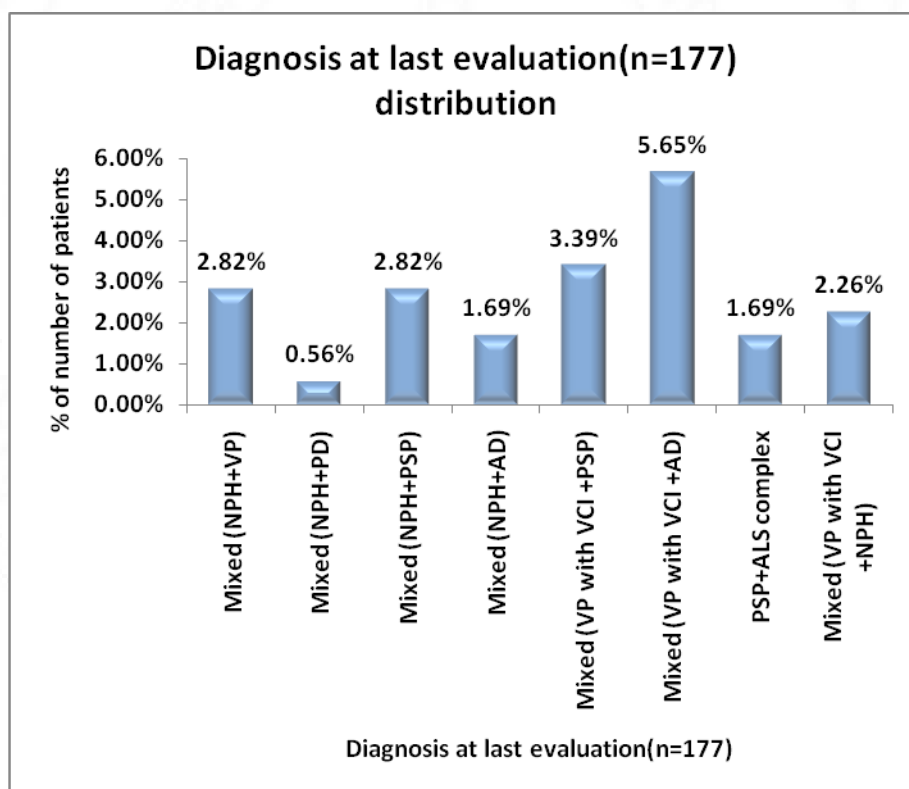


Figure 8.1:- Distribution of diagnosis at last evaluation (n=177)

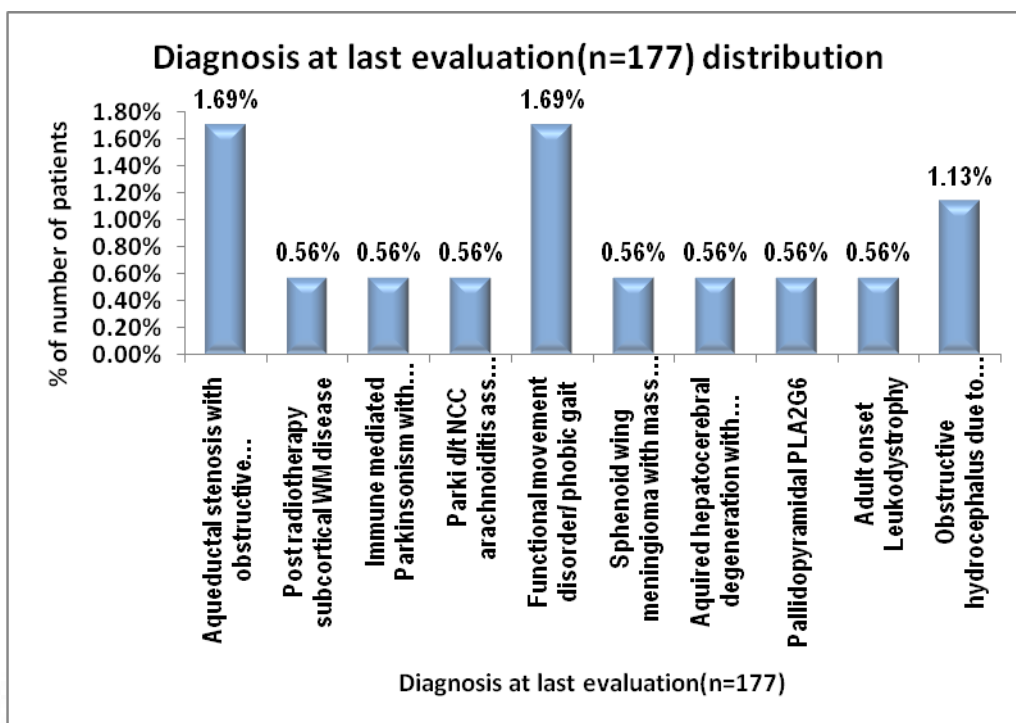


Figure 8.11:- Distribution of diagnosis at last evaluation (n=177)

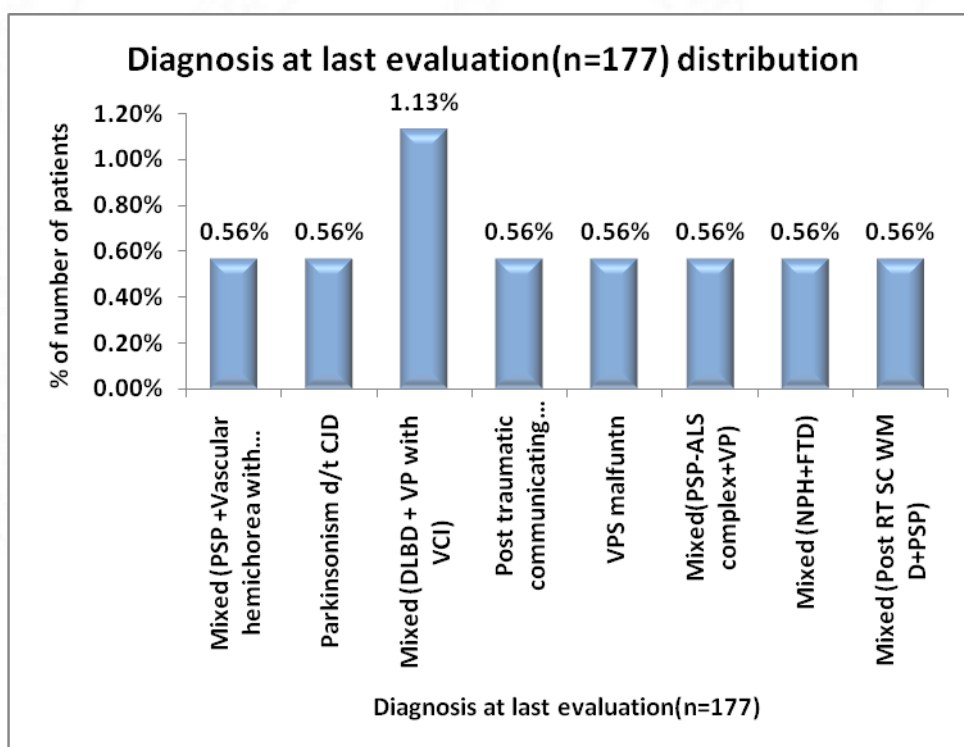


Figure 8.12:- Distribution of diagnosis at last evaluation (n=177)

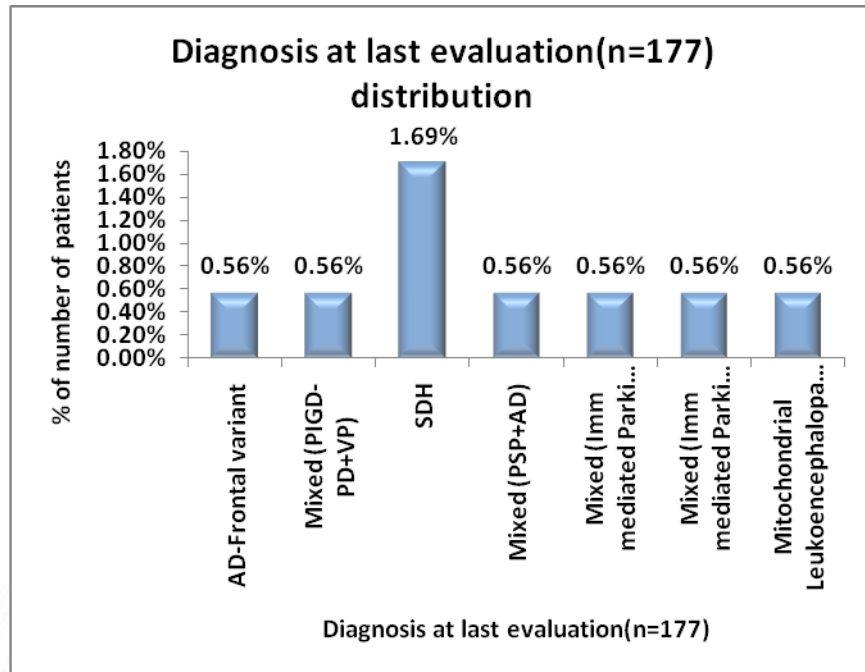


Figure 8.13:- Distribution of diagnosis at last evaluation (n=177)

Table 5.31:- Distribution of subtype of PSP and diagnostic certainty (n=54) at last evaluation

Subtype of PSP and diagnostic certainty(n=54) at last evaluation	Frequency	Percentage
Subtype of PSP at last evaluation		
RS	36	66.67%
PAGF	14	25.93%
CBS	3	5.56%
PI	1	1.85%
Diagnostic Certainty at last evaluation		
Probable	36	66.67%
Possible	18	33.33%

Among patients diagnosed as PSP at last evaluation, the most common subtype was RS noted in 36 (66.67%) cases, followed by PAGF in 14(25.93%), CBS in 3 (5.56%) and PI in 1 (1.85%) case.

The most common level of diagnostic certainty in the PSP subjects was probable noted in 36 (66.67%) cases, followed by possible in 18 (33.33%) cases.

Table 5.32:- Distribution of certainty of NPH diagnosis at last evaluation (n=46)

Certainty of NPH wherever applicable(n=46) at last evaluation	Frequency	Percentage
Definite	16	34.78%
Probable	18	39.13%
Possible	12	26.09%
Total	46	100.00%

Among subjects diagnosed with NPH at last evaluation, the most common diagnostic probability subtype was probable NPH in 18 (39.13%). Definite NPH was diagnosed in 16 (34.78%) cases and possible NPH in 12 (26.09%) cases.

Table 5.4:- Distribution of additional or new treatment considered at last visit (n=177)

Additional or new treatment considered at last visit(n=177)	Frequency	Percentage
Absent	154	87.01%
L-DOPA	10	5.65%
VPS	2	1.13%
VPS program, pressure reset	1	0.56%
External lumbar drain	1	0.56%
Mitochondrial cocktail	1	0.56%
DBS (planned)	1	0.56%
SDH evacuation	2	1.13%
ChE inh	4	2.26%
Anticerebral edema measures	1	0.56%
SDH evacuation not done as brain dead	1	0.56%

In majority of subjects 154 (87.01%), no new treatment was considered at last visit. In subjects, in whom new treatment was added, levodopa was the most common treatment given in 10 (5.65%) cases. VPS was done in 2 (1.13%) cases, Cholinesterase inhibitors were added in 4 (2.26%) cases. External lumbar drain was done in 1 patient, VPS pressure was reset for its malfunction in 1 patient and in 1 patient with PIGD-PD, DBS was planned.

Table 5.5:- Distribution of functional status at last visit (Final MRS) (n=177)

Functional status at last visit (Final MRS)(n=177)	Frequency	Percentage
1	9	5.08%
2	26	14.69%
3	70	39.55%
4	63	35.59%
5	7	3.95%
6	2	1.13%
Total	177	100.00%

At last evaluation, majority of subjects had moderate disability with an MRS score of 3 in 70(39.55%) cases, followed by a score of 4 in 63(35.59%) cases, 2 in 26(14.69%) cases, 1 in 9(5.08%) cases and 5 in 7(3.95%) cases. A MRS of 6 (dead) was noted in 1 subject secondary to cardiac arrhythmia followed by a fall and SDH.

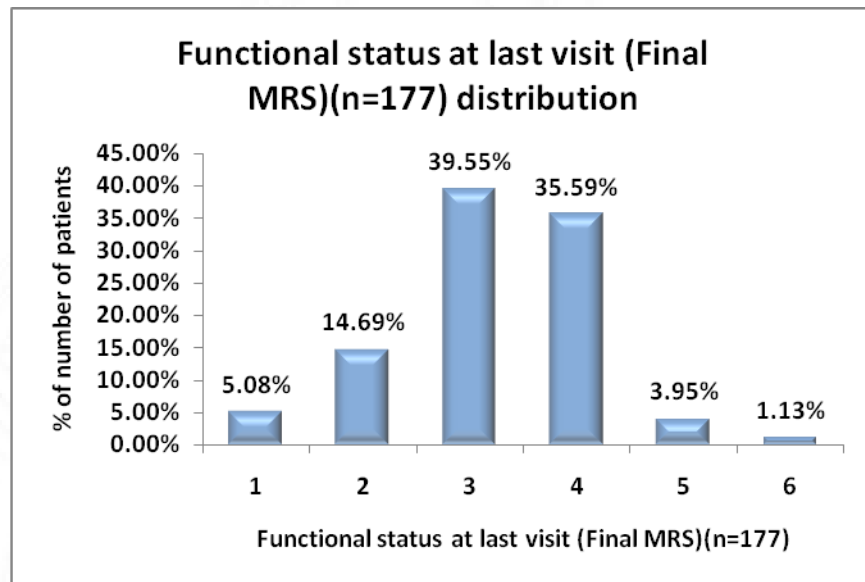


Figure 8.2:- Distribution of functional status at last visit (Final MRS) (n=177)

Table 6:-Comparison of diagnosis between initial and final evaluation

Diagnosis at last evaluation	Diagnosis at initial evaluation												Total	P value
	NPH(n=34)	PSP(n=29)	VP(n=45)	PIGD-PD(n=6)	CBS(n=2)	MSA(n=2)	FTD(n=3)	Parkinsonism d/t CJD(n=1)	DLBD(n=1)	AD(n=1)	Mixed(n=27)	Others(n=26)		
NPH	23 (67.65%)	1 (3.45%)	0 (0%)	1 (16.67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	25 (14.12%)	0.007 [¶]
PSP	1 (2.94%)	27 (93.10%)	0 (0%)	1 (16.67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	3 (11.11%)	2 (7.69%)	35 (19.77%)	
VP	1 (2.94%)	0 (0%)	35 (77.78%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (11.11%)	1 (3.85%)	40 (22.60%)	
PIGD-PD	0 (0%)	0 (0%)	0 (0%)	3 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (2.26%)	
CBS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.56%)	
MSA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.85%)	3 (1.69%)	
FTD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.69%)	
Parkinsonism d/t CJD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.56%)	
AD-frontal variant	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.85%)	1 (0.56%)	
Mixed	9 (26.4%)	1 (3.45%)	9 (20%)	1 (16.67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	21 (77.78%)	3 (11.54%)	45 (25.42%)	
Others	0 (0%)	0 (0%)	1 (2.22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	18 (69.23%)	19 (10.73%)	
Total	34 (100%)	29 (100%)	45 (100%)	6 (100%)	2 (100%)	2 (100%)	3 (100%)	1 (100%)	1 (100%)	1 (100%)	27 (100%)	26 (100%)	177 (100%)	

[¶]Bhapkar test

Proportion of subjects with NPH at last diagnosis was significantly higher among patients with NPH (67.5%). Proportion of subjects with PSP at last diagnosis was significantly higher among patients with PSP (93.1%). Proportion of subjects with VP at last diagnosis was significantly higher among patients with VP (77.7%). Proportion of subjects with PIGD-PD at last diagnosis was significantly higher among patients with PIGD-PD (50%). (p value <0.0001).

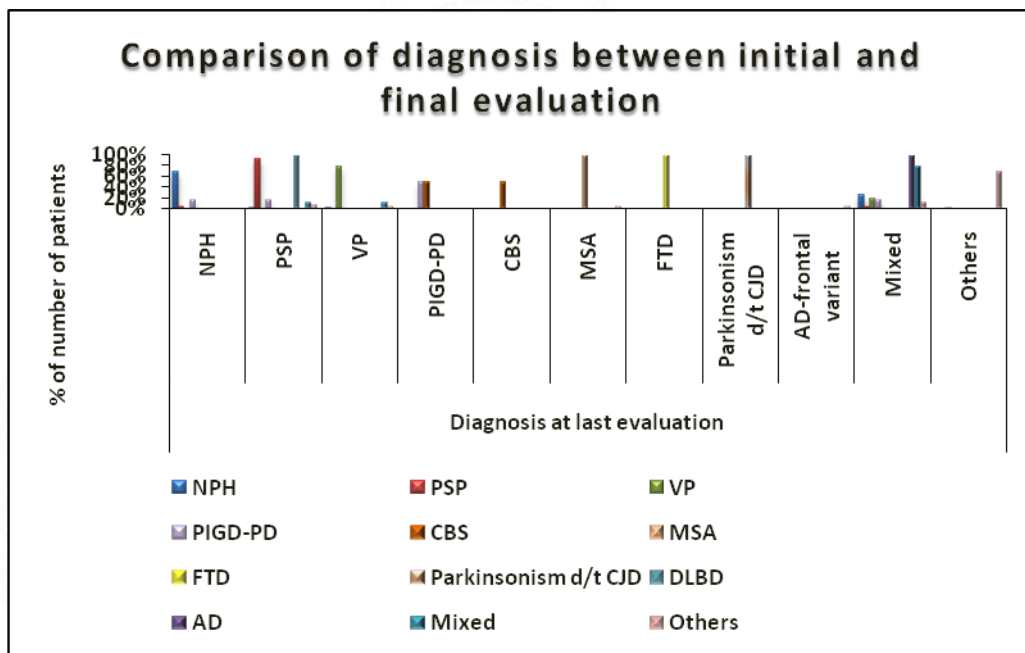


Figure 9:-Comparison of diagnosis between initial and final evaluation

Table 6.1:-Comparison of subtype of PSP between initial and final evaluation

16 subjects, who had no diagnosis of PSP at initial evaluation, were diagnosed as PSP at final visit, out of which RS subtype was diagnosed in 9, PAGF in 4, CBS in 2 and PI in 1 subject and this was significantly higher.

Proportion of subjects with RS at last diagnosis was significantly higher among patients with RS (100%). Proportion of subjects with PAGF at last diagnosis was significantly higher among patients with PAGF (69.2%). Proportion of subjects with CBS at last diagnosis was significantly higher among patients with CBS (50%).

Subtype of PSP at last evaluation	Subtype of PSP at initial evaluation						Total	P value
	No PSP(n=16)	RS(n=21)	PAGF(n=13)	CBS(n=2)	Frontal(n=1)	PI(n=2)		
No PSP	0 (0%)	0 (0%)	1 (7.69%)	0 (0%)	0 (0%)	0 (0%)	1 (1.82%)	<.0001 [¶]
RS	9 (56.25%)	21 (100%)	3 (23.08%)	1 (50%)	1 (100%)	1 (50%)	36 (65.45%)	
PAGF	4 (25%)	0 (0%)	9 (69.23%)	0 (0%)	0 (0%)	1 (50%)	14 (25.45%)	
CBS	2 (12.50%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	3 (5.45%)	
PI	1 (6.25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.82%)	
Total	16 (100%)	21 (100%)	13 (100%)	2 (100%)	1 (100%)	2 (100%)	55 (100%)	

[¶]Bhapkar test

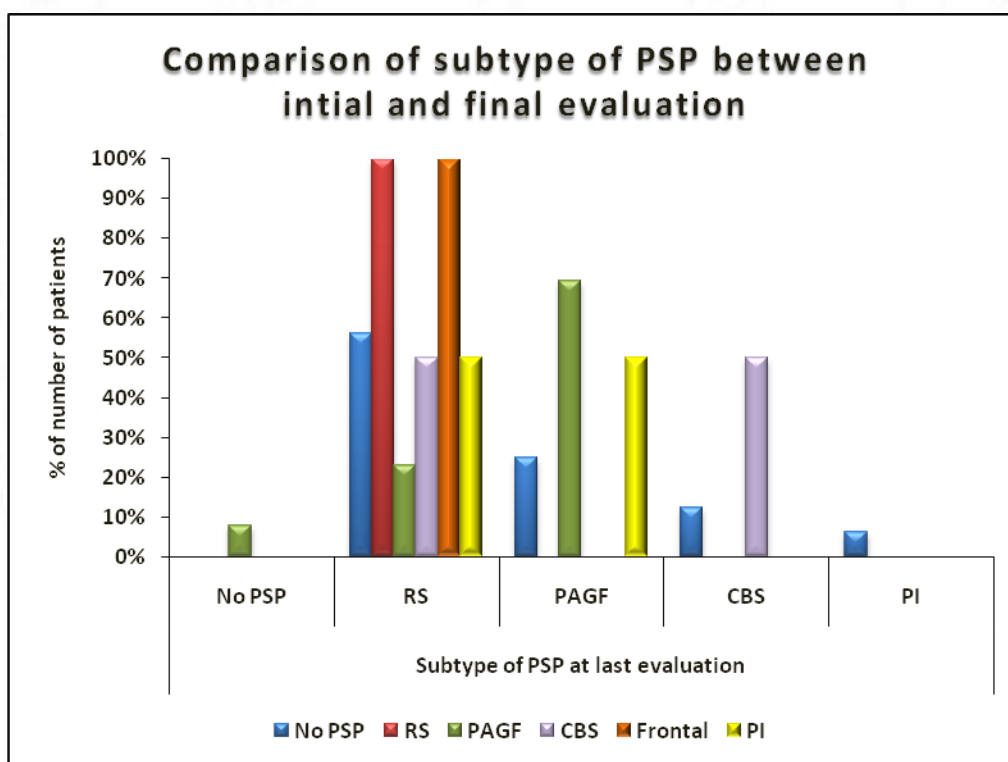


Figure 9.1:-Comparison of subtype of PSP between initial and final evaluation

Comparison of certainty of PSP between initial and final evaluation

Among patients with no PSP at initial evaluation, a diagnosis of probable PSP was made in 6 (37.5%) and possible PSP in 10 (62.5%) subjects at last evaluation and this was statistically significant.

Proportion of subjects with probable PSP at last diagnosis was significantly higher among patients with probable PSP (100%). Proportion of subjects with possible PSP at last diagnosis was significantly higher among patients with possible PSP (47%).

Table 6.2:-Comparison of MRS between initial and final evaluation

Functional status at last visit (Final MRS)	MRS at initial evaluation			Total	P value
	2(n=14)	3(n=117)	4(n=46)		
1	2 (14.29%)	6 (5.13%)	1 (2.17%)	9 (5.08%)	<.0001 [¶]
2	2 (14.29%)	13 (11.11%)	11 (23.91%)	26 (14.69%)	
3	7 (50%)	57 (48.72%)	6 (13.04%)	70 (39.55%)	
4	3 (21.43%)	39 (33.33%)	21 (45.65%)	63 (35.59%)	
5	0 (0%)	1 (0.85%)	6 (13.04%)	7 (3.95%)	
6	0 (0%)	1 (0.85%)	1 (2.17%)	2 (1.13%)	
Total	14 (100%)	117 (100%)	46 (100%)	177 (100%)	

[¶]Bhapkar test

Proportion of patients with functional status at last visit (Final MRS):- 1.00, 3.00, 6.00 was significantly higher in 2 and 3 as compared to 4. (1.00:- 14.29%, 5.13% vs 2.17% respectively, 3.00:- 50%, 48.72% vs 13.04% respectively, 6.00:- 0%, 0.85% vs 2.17% respectively). Proportion of patients with functional status at last visit (Final MRS):- 2.00, 4.00, 5.00 was significantly higher in 4 as compared to 2 and 3. (2.00:- 23.91% vs 14.29%, 11.11% respectively, 4.00:- 45.65% vs 21.43%, 33.33% respectively, 5.00:- 13.04% vs 0%, 0.85% respectively). (p value <0.0001).

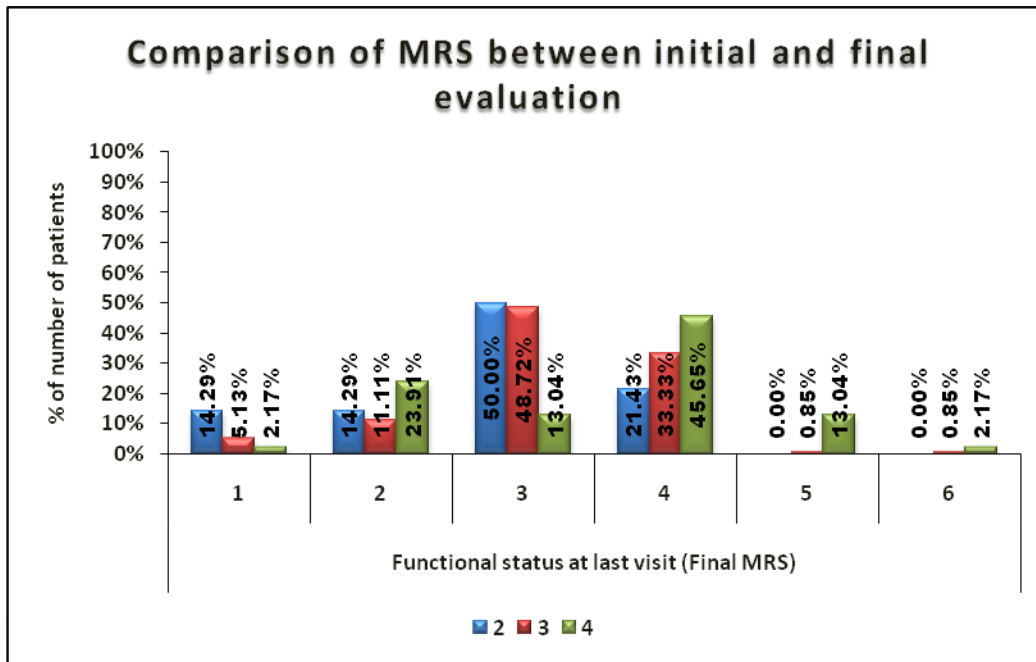


Figure 9.2:-Comparison of MRS between initial and final evaluation

ASSOCIATIONS BETWEEN NPH, PSP AND VP

Table 7:-Association of age at onset (years) with NPH, PSP and VP

Age at onset(years)	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
41 to 50 years	2 (4.88%)	0 (0%)	0 (0%)	0.174* NPH vs PSP:0.051* NPH vs VP:0.434* PSP vs VP:0.339*
51 to 60 years	2 (4.88%)	6 (20%)	5 (10.42%)	
61 to 70 years	16 (39.02%)	16 (53.33%)	23 (47.92%)	
71 to 80 years	17 (41.46%)	8 (26.67%)	17 (35.42%)	
>80 years	4 (9.76%)	0 (0%)	3 (6.25%)	0.051 [‡] NPH vs PSP:0.058 NPH vs VP:1 PSP vs VP:0.152
Mean $\pm$ SD	70.29 $\pm$ 7.66	66.1 $\pm$ 7.17	69.48 $\pm$ 7.2	
Median(25th-75th percentile)	71(67-74)	67(61-71.5)	69.5(64.75-75)	
Range	49-86	51-78	55-86	

* Fisher's exact test, [‡] ANOVA

The mean age of onset was comparable between NPH, PSP and VP.

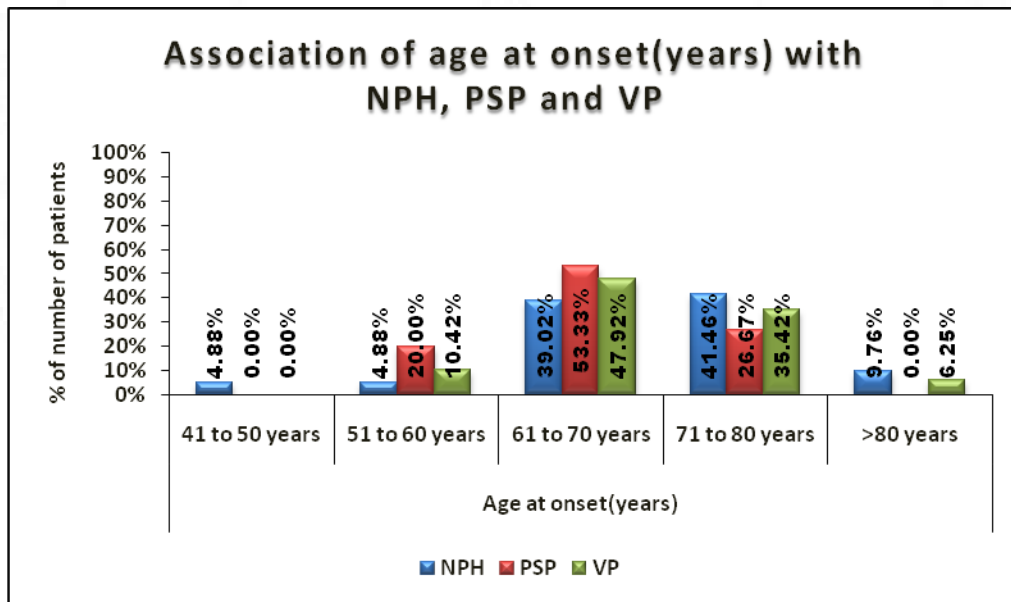


Figure 9.3:-Association of age at onset (years) with NPH, PSP and VP

Table 7.1:-Association of other symptoms at presentation with NPH, PSP and VP

Other symptoms at presentation	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
Gait difficulty	41 (100%)	29 (96.67%)	48 (100%)	0.252 [*] NPH vs PSP:0.423 [*] NPH vs VP:NA PSP vs VP:0.385 [*]
Freezing of gait	16 (39.02%)	24 (80%)	22 (45.83%)	0.002 [†] NPH vs PSP:0.0006 [†] NPH vs VP:0.517 [†] PSP vs VP:0.003 [†]
Postural instability/Falls	17 (41.46%)	28 (93.33%)	25 (52.08%)	<.0001 [†] NPH vs PSP:<.0001 [*] NPH vs VP:0.317 [†] PSP vs VP:0.0001 [*]
Action tremor	5 (12.20%)	11 (36.67%)	5 (10.42%)	0.007 [†] NPH vs PSP:0.015 [†] NPH vs VP:0.791 [†] PSP vs VP:0.005 [†]
Dysphagia/Choking	1 (2.44%)	6 (20%)	4 (8.33%)	0.045 [*] NPH vs PSP:0.037 [*] NPH vs VP:0.369 [*] PSP vs VP:0.171 [*]
Urinary symptoms				
Absent	2 (4.88%)	15 (50%)	13 (27.08%)	<.0001 [*] NPH vs PSP:<.0001 [*] NPH vs VP:0.003 [*] PSP vs VP:0.055 [*]
Urgency	34 (82.93%)	14 (46.67%)	34 (70.83%)	
Urinary incontinence	5 (12.20%)	1 (3.33%)	1 (2.08%)	

^{*} Fisher's exact test, [†] Chi square test

Proportion of patients with FOG and postural instability were significantly higher in PSP in comparison with VP, NPH; while urgency of urine was significantly higher in NPH in comparison with VP and PSP (p<0.001). FOG and postural instability were comparable among VP and NPH. Dysphagia was comparable among the groups.

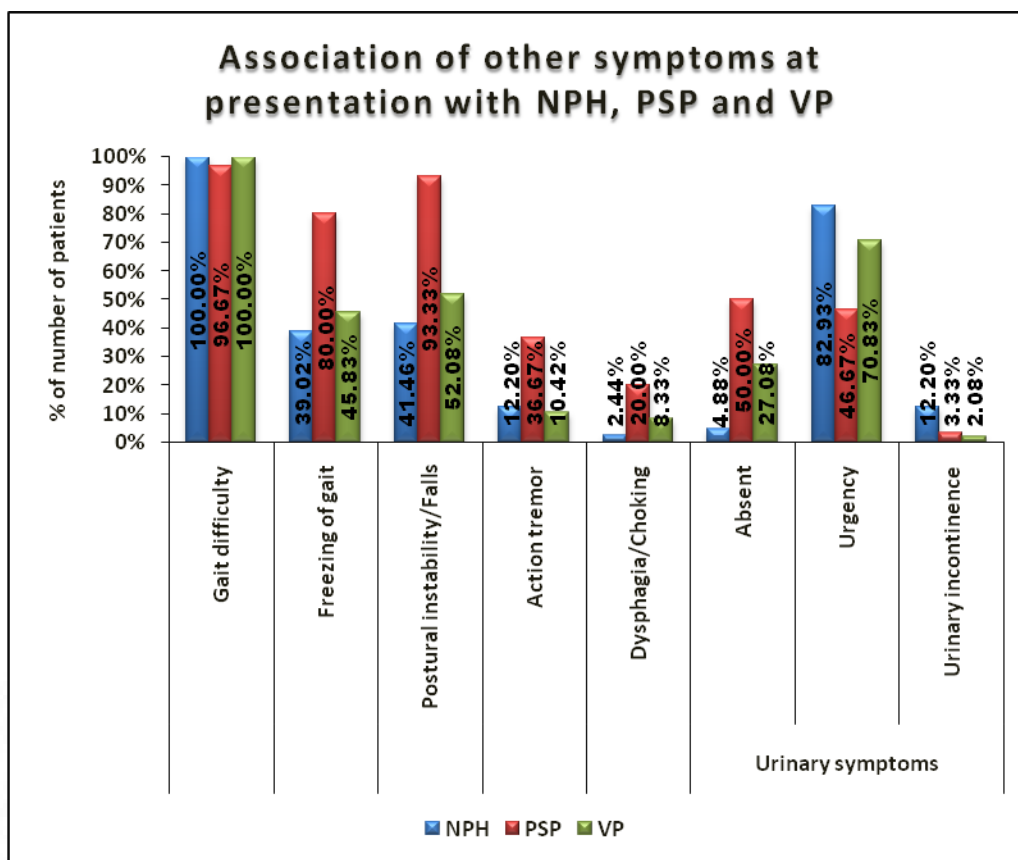


Figure 9.4:-Association of other symptoms at presentation with NPH, PSP and VP

Table 7.2:-Association of cognitive symptoms with NPH, PSP and VP

Cognitive symptoms	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
Absent	11 (26.83%)	13 (43.33%)	13 (27.08%)	0.132* NPH vs PSP:0.232* NPH vs VP:0.226* PSP vs VP:0.102*
Attention deficit only	18 (43.90%)	11 (36.67%)	13 (27.08%)	
Memory (amnesic) only	0 (0%)	1 (3.33%)	2 (4.17%)	
Multidomain	12 (29.27%)	5 (16.67%)	20 (41.67%)	
Total	41 (100%)	30 (100%)	48 (100%)	

* Fisher's exact test

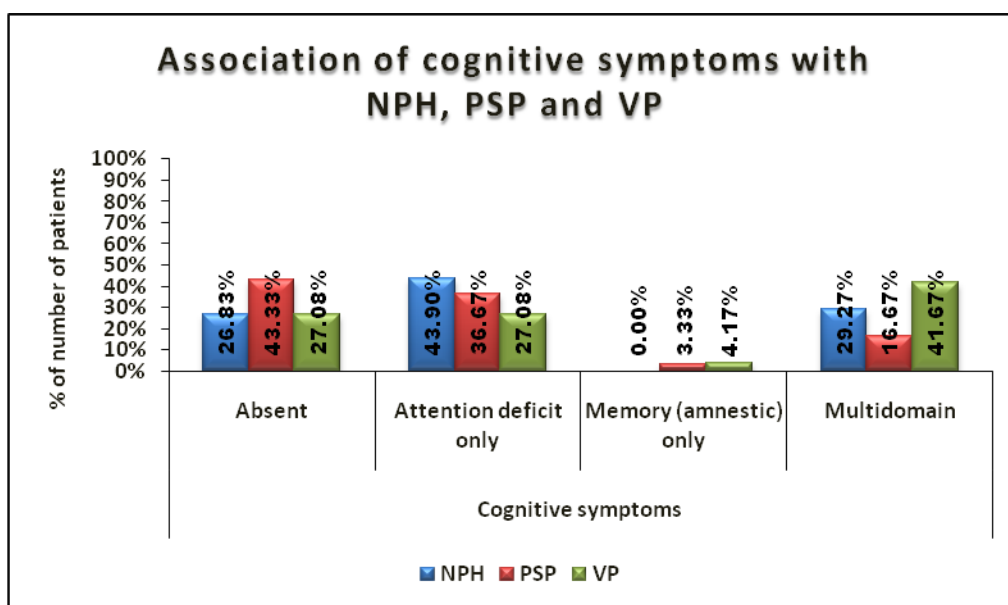


Figure 9.5:-Association of cognitive symptoms with NPH, PSP and VP

Distribution of cognitive symptoms were comparable among the three groups and no statistically significant difference was noted.

Table 7.3:-Association of risk factors with NPH, PSP and VP

Risk factors	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
Diabetes mellitus	27 (65.85%)	13 (43.33%)	33 (68.75%)	0.062 [†] NPH vs PSP:0.059 [†] NPH vs VP:0.771 [†] PSP vs VP:0.056 [†]
Hypertension	28 (68.29%)	15 (50%)	42 (87.50%)	0.001 [†] NPH vs PSP:0.119 [†] NPH vs VP:0.028 [†] PSP vs VP:0.0003 [†]
Coronary artery disease	13 (31.71%)	7 (23.33%)	14 (29.17%)	0.737 [†] NPH vs PSP:0.438 [†] NPH vs VP:0.795 [†] PSP vs VP:0.572 [†]
Dyslipidemia	9 (21.95%)	10 (33.33%)	25 (52.08%)	0.012 [†] NPH vs PSP:0.285 [†] NPH vs VP:0.004 [†] PSP vs VP:0.105 [†]
Obstructive sleep apnea	0 (0%)	1 (3.33%)	0 (0%)	0.252 [*] NPH vs PSP:0.423 [*] NPH vs VP:NA PSP vs VP:0.385 [*]

Smoking	5 (12.20%)	3 (10%)	20 (41.67%)	0.0006 [†] NPH vs PSP:1* NPH vs VP:0.002 [†] PSP vs VP:0.004*
Alcoholism	2 (4.88%)	2 (6.67%)	4 (8.33%)	0.898* NPH vs PSP:1* NPH vs VP:0.683* PSP vs VP:1*

* Fisher's exact test, [†] Chi square test

Among the risk factors, hypertension and smoking were found in significantly higher frequency among VP subjects and the difference was statistically significant. Other risk factors were comparable among the study participants. There was no statistically significant difference with respect to hypertension between PSP and NPH. Dyslipidemia was significantly higher in VP in comparison with NPH.

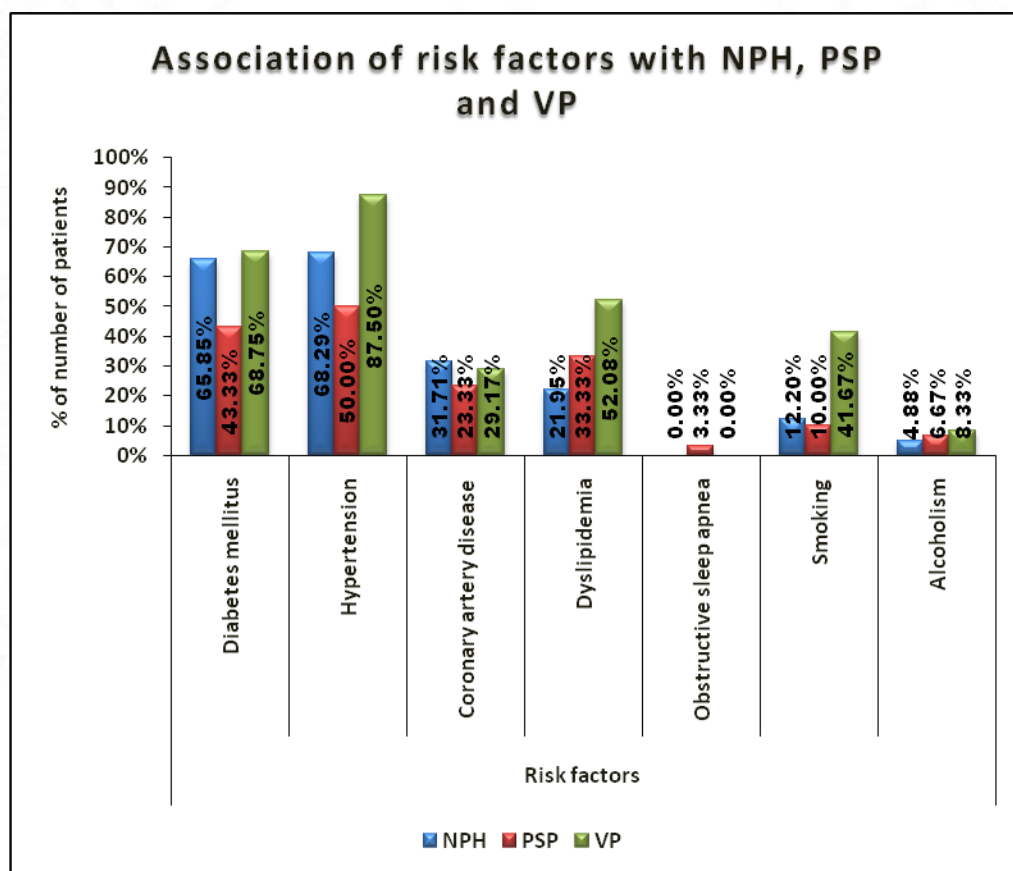


Figure 9.6:-Association of risk factors with NPH, PSP and VP

Table 7.4:-Association of eye movements with NPH, PSP and VP

Eye movements	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
Normal eye movements	35 (85.37%)	5 (16.67%)	33 (68.75%)	<.0001 [†] NPH vs PSP:<.0001 [†] NPH vs VP:0.066 [†] PSP vs VP:<.0001 [†]
Vertical gaze restriction (Up+down)	0 (0%)	1 (3.33%)	0 (0%)	0.252 [*] NPH vs PSP:0.423 [*] NPH vs VP:NA PSP vs VP:0.385 [*]
Vertical gaze restriction (Up)	1 (2.44%)	4 (13.33%)	1 (2.08%)	0.096 [*] NPH vs PSP:0.155 [*] NPH vs VP:1 [*] PSP vs VP:0.069 [*]
Vertical gaze restriction (Down)	0 (0%)	1 (3.33%)	0 (0%)	0.252 [*] NPH vs PSP:0.423 [*] NPH vs VP:NA PSP vs VP:0.385 [*]
Saccadic slowing (Vertical)/ Round the house sign	4 (9.76%)	15 (50%)	6 (12.50%)	<.0001 [†] NPH vs PSP:0.0003 [*] NPH vs VP:0.748 [*] PSP vs VP:0.0003 [†]
Saccadic slowing (Vertical, horizontal)	0 (0%)	4 (13.33%)	3 (6.25%)	0.052 [*] NPH vs PSP:0.058 [*] NPH vs VP:0.246 [*] PSP vs VP:0.419 [*]
Frequent macro square wave jerks/Apraxia of eyelid opening	0 (0%)	1 (3.33%)	1 (2.08%)	0.72 [*] NPH vs PSP:0.423 [*] NPH vs VP:1 [*] PSP vs VP:1 [*]
Hypometric saccades	1 (2.44%)	0 (0%)	4 (8.33%)	0.256 [*] NPH vs PSP:1 [*] NPH vs VP:0.369 [*] PSP vs VP:0.156 [*]
Oculomotor apraxia	0 (0%)	0 (0%)	0 (0%)	NA
Gaze evoked nystagmus	0 (0%)	0 (0%)	0 (0%)	NA

* Fisher's exact test, [†] Chi square test

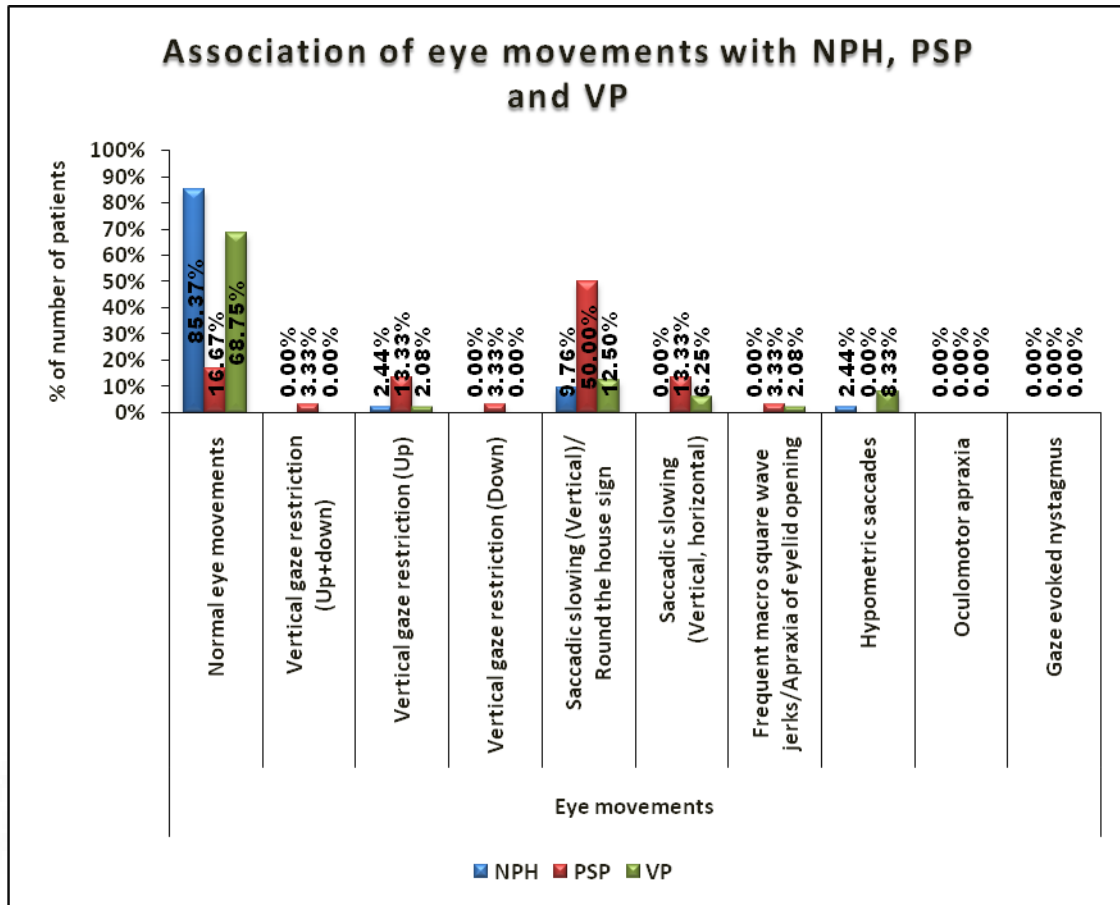


Figure 9.7:-Association of eye movements with NPH, PSP and VP

Proportion of patients with normal eye movements was significantly higher in NPH as compared to PSP and VP. Proportion of subjects with vertical saccadic slowing was significantly higher in PSP as compared to NPH and VP. Similarly, proportion of patients with saccadic slowing was significantly higher in VP as compared to NPH.

Table 7.5:-Association of extra pyramidal examination with NPH, PSP and VP

Extrapyramidal examination	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
Axial rigidity				
Absent	38 (92.68%)	8 (26.67%)	38 (79.17%)	<.0001* NPH vs PSP:<.0001* NPH vs VP:0.194* PSP vs VP:<.0001†
Axial=APP rigidity	2 (4.88%)	7 (23.33%)	8 (16.67%)	
Axial>APP rigidity	1 (2.44%)	15 (50%)	2 (4.17%)	
Limb rigidity				
Absent	7 (17.07%)	1 (3.33%)	3 (6.25%)	0.003* NPH vs PSP:0.0003* NPH vs VP:0.087* PSP vs VP:0.135*
Lower limb only	19 (46.34%)	3 (10%)	15 (31.25%)	
Lower limb>Upper limb	9 (21.95%)	14 (46.67%)	16 (33.33%)	
Lower limb+Upper limb	6 (14.63%)	12 (40%)	14 (29.17%)	
Bradykinesia	11 (26.83%)	26 (86.67%)	29 (60.42%)	<.0001† NPH vs PSP:<.0001* NPH vs VP:0.001† PSP vs VP:0.021*
Experience rest tremor	0 (0%)	3 (10%)	1 (2.08%)	0.086* NPH vs PSP:0.071* NPH vs VP:1* PSP vs VP:0.292*
Experience action tremor	5 (12.20%)	14 (46.67%)	15 (31.25%)	0.006† NPH vs PSP:0.001† NPH vs VP:0.032† PSP vs VP:0.17†
Parkinsonism	10 (24.39%)	26 (86.67%)	28 (58.33%)	<.0001† NPH vs PSP:<.0001* NPH vs VP:0.001† PSP vs VP:0.011*

* Fisher's exact test, † Chi square test

Among, extrapyramidal examination findings, axial rigidity was significantly higher in PSP in comparison with NPH and VP ($p < 0.001$). Bradykinesia and parkinsonism was significantly higher in PSP and VP in comparison with NPH, while there was no significant difference between PSP and VP. Limb rigidity and rest tremor were comparable, while action tremor was more in PSP in comparison with NPH.

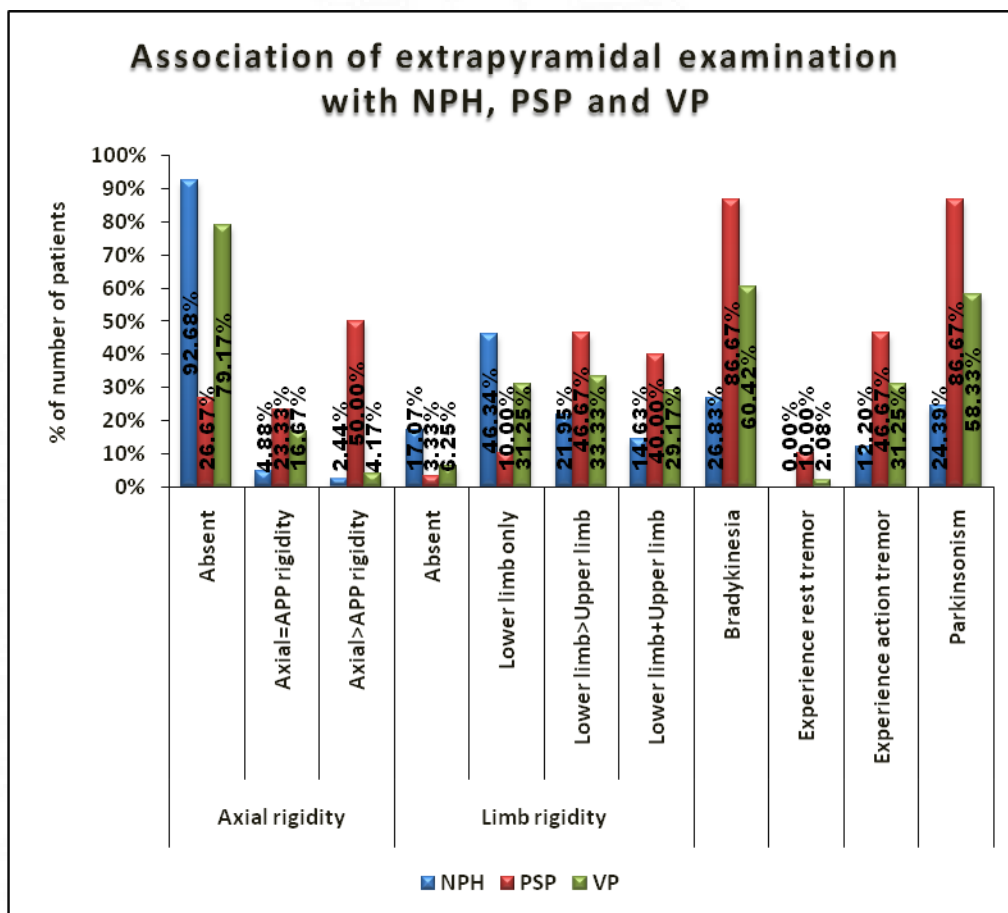


Figure 9.8:-Association of extra pyramidal examination with NPH, PSP and VP

Table 7.6:-Association of gait examination findings with NPH, PSP and VP

Gait examination findings	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
Gait initiation difficulty / failure	13 (31.71%)	26 (86.67%)	34 (70.83%)	<.0001 [†] NPH vs PSP:<.0001* NPH vs VP:0.0002 [†] PSP vs VP:0.167*
Gait apraxia	41 (100%)	30 (100%)	48 (100%)	NA
Freezing of gait finding	12 (29.27%)	29 (96.67%)	25 (52.08%)	<.0001 [†] NPH vs PSP:<.0001* NPH vs VP:0.029 [†] PSP vs VP:<.0001*
Gait variability/distractability	41 (100%)	30 (100%)	48 (100%)	NA
Postural instability				
Absent	17 (41.46%)	1 (3.33%)	12 (25%)	<.0001* NPH vs PSP:<.0001* NPH vs VP:0.206* PSP vs VP:<.0001*
Grade 1	17 (41.46%)	10 (33.33%)	27 (56.25%)	
Grade 2	6 (14.63%)	12 (40%)	9 (18.75%)	
Grade 3	1 (2.44%)	6 (20%)	0 (0%)	
Grade 4	0 (0%)	1 (3.33%)	0 (0%)	

* Fisher's exact test, [†] Chi square test

Postural instability and FOG were significantly higher in PSP in comparison with VP and NPH, while Gait initiation failure was comparable between PSP and VP. Gait initiation failure was significantly higher in PSP in comparison to NPH.

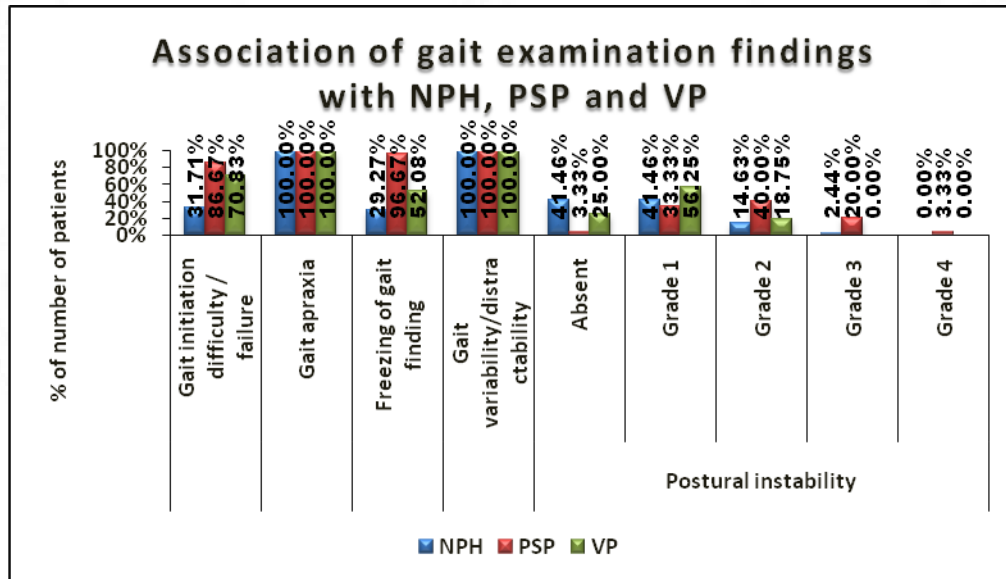


Figure 9.9:-Association of gait examination findings with NPH, PSP and VP

Table 7.7:-Association of hydrocephalus with NPH, PSP and VP

Hydrocephalus	NPH(n=41)	PSP(n=30)	VP(n=48)	P value
Absent	0 (0%)	21 (70%)	22 (45.83%)	$<.0001^*$ NPH vs PSP: $<.0001^*$ NPH vs VP: $<.0001^*$ PSP vs VP:0.066 [*]
Present	40 (97.56%)	5 (16.67%)	19 (39.58%)	
Report only	0 (0%)	2 (6.67%)	6 (12.50%)	
Imaging not done	1 (2.44%)	2 (6.67%)	1 (2.08%)	
Total	41 (100%)	30 (100%)	48 (100%)	

^{*} Fisher's exact test

Hydrocephalus was present in 97.5% of NPH patients, 40% of VP patients, while it was present in 17% of PSP patients. There was statistically significant difference between NPH and PSP and NPH and VP. However, VP and PSP were comparable with respect to hydrocephalus. Proportion of patients with hydrocephalus absent was significantly higher in PSP as compared to NPH and VP.

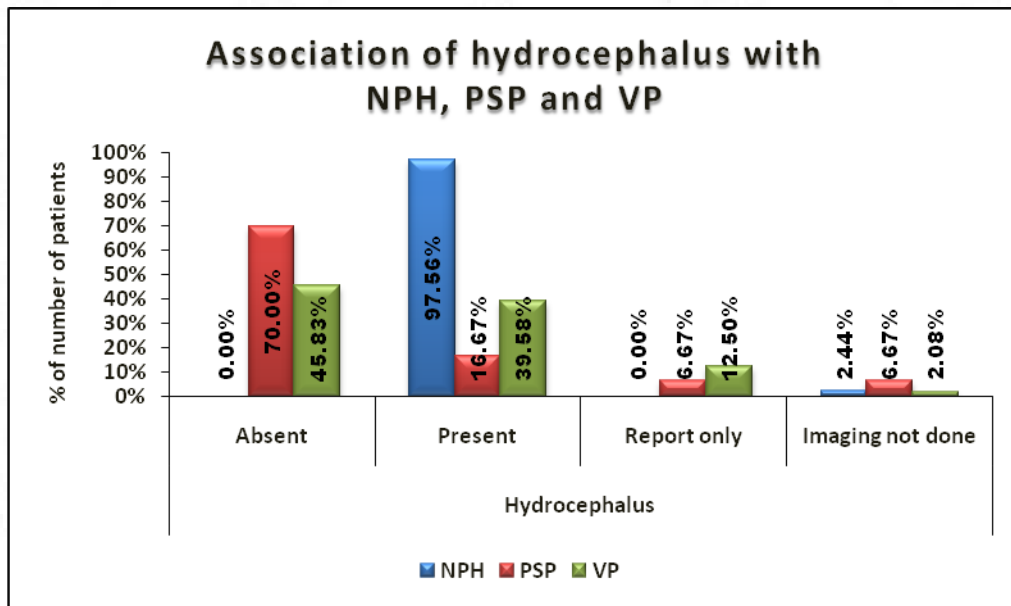


Figure 10:-Association of hydrocephalus with NPH, PSP and VP

Table 7.8:-Association of brainstem imaging changes with NPH, PSP and VP

Brain stem	NPH(n=34)	PSP(n=21)	VP(n=32)	P value
Midbrain to pons ratio				
<0.2	3 (8.82%)	12 (57.14%)	3 (9.38%)	0.0001 [*] NPH vs PSP:0.0001 [*] NPH vs VP:0.782 [*] PSP vs VP:0.0005 [*]
0.2 to 0.22	5 (14.71%)	4 (19.05%)	7 (21.88%)	
>=0.23	26 (76.47%)	5 (23.81%)	22 (68.75%)	
Mean ± SD	0.25 ± 0.03	0.2 ± 0.04	0.25 ± 0.04	<.0001 [‡] NPH vs PSP:<.0001 NPH vs VP:1 PSP vs VP:0.0001
Median(25th-75th percentile)	0.25(0.23-0.27)	0.19(0.17-0.22)	0.24(0.22-0.26)	
Range	0.18-0.31	0.13-0.29	0.18-0.38	
MRPI				
<=13.55	32 (94.12%)	9 (42.86%)	27 (84.38%)	<.0001 [*] NPH vs PSP:<.0001 [*] NPH vs VP:0.251 [*] PSP vs VP:0.002 [†]
>13.55	2 (5.88%)	12 (57.14%)	5 (15.63%)	
Mean ± SD	11.57 ± 1.56	14.49 ± 3.08	11.65 ± 1.85	
Median(25th-75th percentile)	11.8(10.575-12.775)	14.5(12.3-17.1)	12(10.55-12.8)	<.0001 [‡] NPH vs PSP:<.0001 NPH vs VP:1 PSP vs VP:<.0001
Range	6.9-13.9	8.5-19.2	6.9-14.7	

* Fisher's exact test, [†] Chi square test, [‡] ANOVA

The mean midbrain by pons ratio in our study participants among the 3 groups were (0.25 $\pm$ 0.03 vs 0.2 $\pm$ 0.04 vs 0.25 $\pm$ 0.04) and it was significantly lower in PSP group in comparison with VP and NPH. VP and NPH group were comparable to each other. However 24% of PSP patients had a normal midbrain by pons ratio and 9% each of VP and NPH subjects had an abnormal midbrain by pons ratio in our study population.

The mean MRPI in our study participants among the 3 groups were (11.57 $\pm$ 1.56 vs 14.49 $\pm$ 3.08 vs 11.65 $\pm$ 1.85) and it was significantly higher in PSP group in comparison with VP and NPH. VP and NPH group were comparable to each other. However, 43% PSP subjects had normal MRPI and 16% VP and 6% NPH patients had abnormal MRPI in our study.

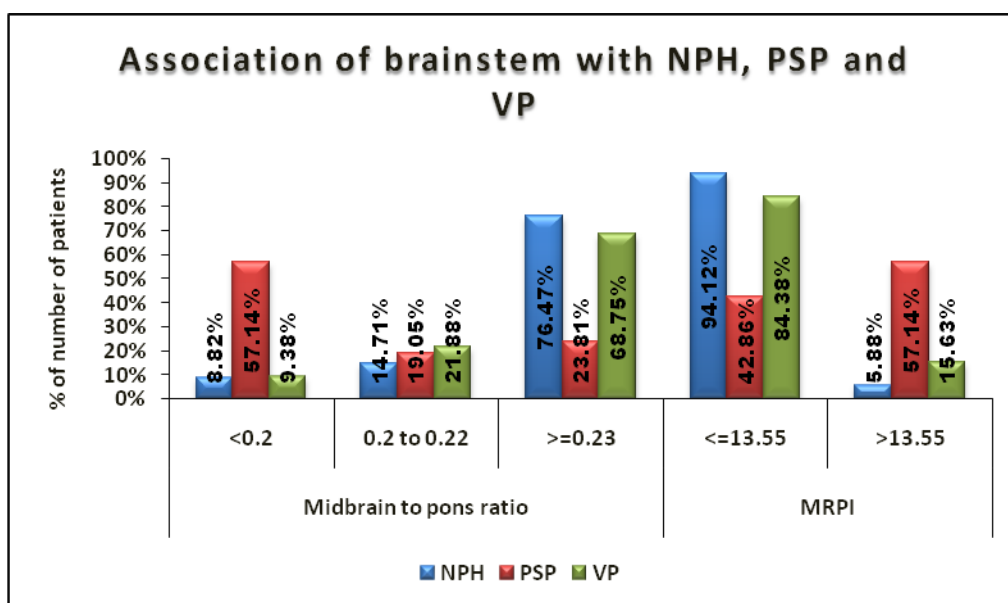


Figure 10.1:-Association of brainstem imaging with NPH, PSP and VP

Table 7.9:-Association of response of gait to initial treatment with NPH, PSP and VP

Response of gait to initial treatment	NPH	PSP	VP	P value
L-Dopa response				
Absent	1 (6.25%)	3 (10%)	5 (10.42%)	0.528* NPH vs PSP:0.248* NPH vs VP:0.588* PSP vs VP:0.588*
Very minimal	9 (56.25%)	9 (30%)	17 (35.42%)	
Moderate	6 (37.50%)	18 (60%)	23 (47.92%)	
Excellent	0 (0%)	0 (0%)	3 (6.25%)	

* Fisher's exact test

A moderate response to levodopa was noted in 60% patients of PSP and 48% patients of VP. However, there was no statistically significant difference in the L-Dopa response rates among the three groups and they were comparable.

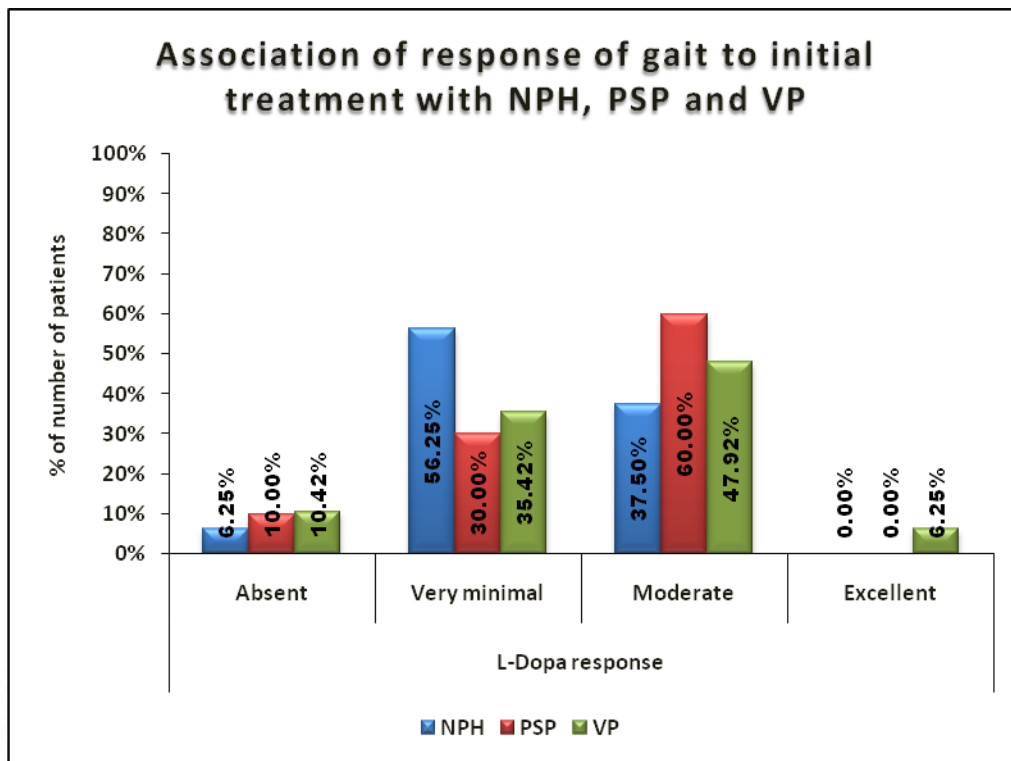
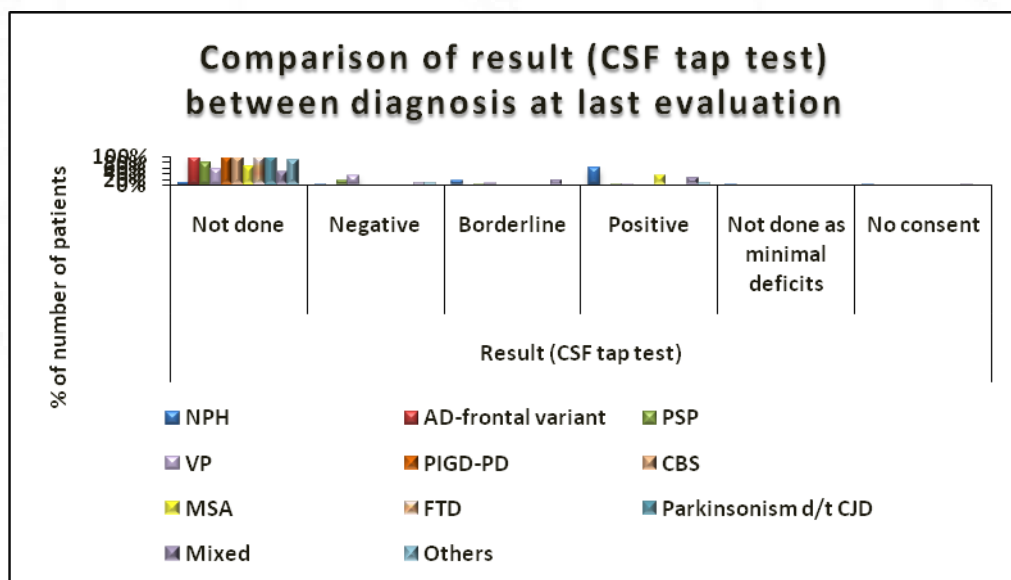


Figure10.2:-Association of response of gait to initial treatment

Figure 10.3:-Comparison of result (CSF tap test) between diagnosis at last evaluation



Among patients with a positive CSF tap test, the diagnosis at last visit was NPH in 16 patients, mixed pathology in 12 patients, VP and PSP in 1 each.

Table 8.0:-Association of MRS with NPH, PSP and VP

MRS	NPH	PSP	VP	P value
Initial MRS				
2	5 (12.20%)	2 (6.67%)	2 (4.17%)	0.013* NPH vs PSP:0.394* NPH vs VP:0.055* PSP vs VP:0.004*
3	26 (63.41%)	16 (53.33%)	41 (85.42%)	
4	10 (24.39%)	12 (40%)	5 (10.42%)	
Functional status at last visit (Final MRS)				
1	5 (14.71%)	0 (0%)	0 (0%)	<.0001* NPH vs PSP:0.0001* NPH vs VP:<.0001* PSP vs VP:0.012*
2	12 (35.29%)	2 (6.90%)	2 (4.44%)	
3	10 (29.41%)	7 (24.14%)	26 (57.78%)	
4	6 (17.65%)	16 (55.17%)	15 (33.33%)	
5	0 (0%)	4 (13.79%)	1 (2.22%)	
6	1 (2.94%)	0 (0%)	1 (2.22%)	

* Fisher's exact test

With respect to initial MRS, a grade 4 disability was seen in 40% PSP subjects, vs. 10% VP subjects and the difference was significant. Otherwise, the groups were comparable.

The final MRS among PSP and VP patients was significantly higher in comparison to NPH, but were comparable to each other. This may be explained by the improvement in symptoms of NPH patients with VPS.

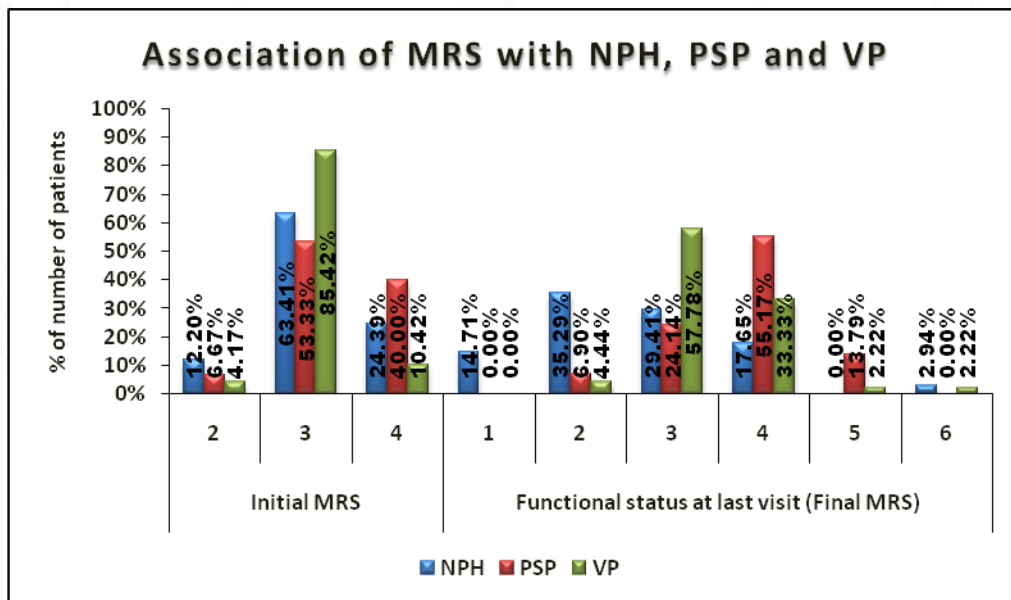


Figure 10.4:-Association of MRS with NPH, PSP and VP

Table 8.1:-Association of change in MRS with NPH, PSP and VP

Change in MRS	NPH(n=34)	PSP(n=29)	VP(n=45)	P value
Mean $\pm$ SD	-0.53 $\pm$ 1.19	0.41 $\pm$ 0.73	0.33 $\pm$ 0.71	0.0003 [§] NPH vs PSP:0.0002 NPH vs VP:0.001 PSP vs VP:0.387
Median(25th-75th percentile)	0(-2-0)	1(0-1)	0(0-1)	
Range	-2-2	-2-1	-1-3	

[§]Kruskal Wallis test

The mean change in MRS in PSP (0.41 $\pm$ 0.73) and VP (0.33 $\pm$ 0.71) was significantly higher in comparison with that of NPH (-0.53 $\pm$ 1.19). Though the mean change of MRS in PSP was higher than that of VP, it was not statistically significant.

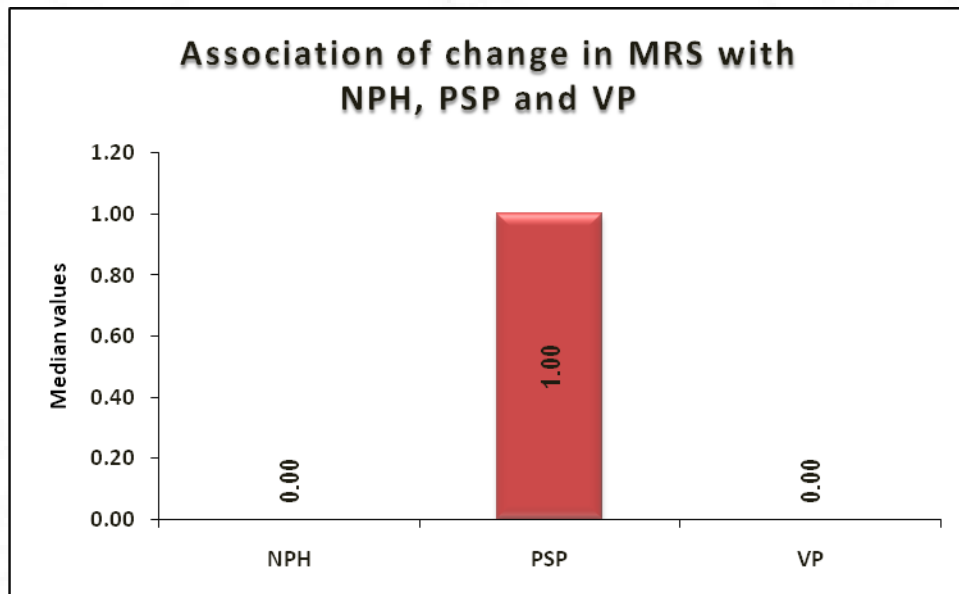


Figure 10.5:-Association of change in MRS with NPH, PSP and VP

Chapter 6

Discussion



DISCUSSION

Lower body parkinsonism is a common, yet poorly defined and understood clinical syndrome. Studies pertaining to its prevalence, diverse etiologies, clinical profile and evaluation protocols are very limited both in India and worldwide. Thus, our study highlights the clinical and radiological profile of patients presenting with lower body parkinsonism, apart from throwing light on etiological profile and phenotypic evolution on follow up.

Demographic characteristics

In our study, the most common age group affected was between 61-70 years who constituted 41.6% of the total subjects, followed by 71-80 years, who constituted 36.6% of the total subjects. LBP was least common in age group less than 40 years (2.5%). Mean value of age at onset of symptoms in our study was 67.4 ± 10.4 years. Though there are no studies on age profile of patients with LBP, it is generally considered to occur at an age later than that of PD. In a community based study, among individuals more than 70 years of age with gait problems, LBP constituted 13% of the neurological gait disorders (22). As VP was considered synonymous with LBP for long time, analysis of age characteristics of patients of VP showed as mean age at symptom onset of 73 years in a study by Sonia et al. (53). The mean age of symptom onset was 72.2 ± 10.0 years in a study of VP patients by Thiago et al. (54), while Zijlman's et al reported age > 60 years for defining VP (5). However, in recent years, NPH and PSP have also been recognized as important causes of LBP. In a study by Carrilho et al, mean age of onset of PSP was 64.7 years (55), while it was 70 years for NPH (56). This might explain the relatively lower mean age of symptom onset in our study participants. 76.2% of our subjects were males. Similar findings were noted in a study by Thiago et al. This may be partly explained by the higher prevalence of vascular risk factors amongst male population (54). NPH however, occurs with equal frequency among males and females (56).

Clinical characteristics

The most common initial manifestation in our patients was gait difficulty, in as much as 66.8 % of the subjects, followed by cognitive decline in (11.4%) and slowness of activities (8%). This is in conjunction with other studies (54). Similar findings were reported by Fitzgerald et al. (18), while in a study by Carrilho et al. in PSP patients (55), postural instability with falls was the most frequent initial feature (62.5%). The mean duration of symptoms at presentation was 25 ± 20 months. Studies describing mean duration of symptoms in patients with LBP at presentation are lacking. However, in a study by Sonia et al. in VP patients, the mean duration was 3 years (2.25-7.5 years) (53). Abrupt onset or step wise progression of parkinsonian symptoms was present in 6% of the subjects in the current study, which is much lesser than 25% that was originally described by Winikates et al. among patients with VP (28). This may be due to the fact that, not all cases of LBP are due to VP and the percentage was calculated including all patients presenting with LBP.

The most common symptom present among the subjects in our study was gait difficulty in 99% of the patients, followed by urinary symptoms in 73.3% and cognitive symptoms in 66.3% cases. Other common symptoms were slowness of activities in 58% and postural instability and falls in 56% cases. Literature in support of the similar frequency of symptoms occurrence in NPH patients exist (85% gait difficulty, 60% cognitive symptoms, 50% urinary symptoms) (34). Among patients with cognitive symptoms, multiple domains were affected in 40% cases, while attention alone was affected in 29%, with a total of 69%. Majority of subjects had MCI and dementia was noted only in 15.9% cases. Our results are in tune with results of PRIAMO study, where attention and memory impairment was reported in 73.5% patients of VP. However, our results are in contrast to the result by Bambuí et al, where dementia was found in 61.5% of VP patients (57).

63% of the study participants had hypertension as a vascular risk factor, which was the commonest, followed by diabetes in 60%, dyslipidemia in 30%, CAD in 21%. 18% had history of smoking, while history of alcohol consumption was present in 7%. Similar results were noted in a study by Thiago et al. among VP patients, where HTN was present in 100% cases, followed by dyslipidemia and diabetes (54). A history of documented ischemic stroke in the past was

present in 14 % patients with recurrent events in around 5% in our study. This is in contrast to findings reported by Deepak gupta et al. in one study among patients with VP, a history of strokes was present in 43.5% of patients (24). The relative low percentage of past strokes in our study may partly be explained due to etiological heterogeneity among our subjects.

The most common general examination finding among our patients was presence of frontal lobe release signs in among 16%, a mask like facies was present in 9.5% and a PSP like staring look in 6.5% of subjects. These results were in agreement with the results noted by Rowe et al. in patients with PSP (58). Similarly, the mean MMSE score in our study group was in the range of 23.85 ± 5.3 with 49% of the values in the range of 26 to 30. The mean MMSE score noted among PSP patients was 21.24 ± 6.5 in a study by Wen et al. (59), while it was around 23.8 in the PRIAMO study among VP patients, which is in agreement with our study finding (60). The mean MMSE was 22.1 in NPH patients in a study by Elobeid et al. (61). In our study, among 62% of LBP patients, eye movements were normal and the most common eye movement abnormality noted was saccadic slowing, vertical > horizontal in 17% of subjects. Vertical gaze restriction was noted in 6.5% subjects. In toto, convincing signs suggestive of PSP were seen in 31% of total subjects presenting with LBP. This is much lesser than the description in other PSP studies and can be explained by the fact that our subjects represent varied etiologies apart from PSP alone. However, in a study by Carrilho et al., among PSP patients, a supranuclear vertical gaze palsy, appeared after 2.3 years of disease onset, and only 12.5% had it at initial evaluation (55). This study highlights the importance of serial evaluations in PSP patients.

Among our study participants, axial rigidity was present in 31%, with axial more than appendicular rigidity in 12% cases. Lower limb predominant rigidity was the most common limb rigidity pattern noted in 34 % subjects, while limb rigidity was absent in 11% subjects. Bradykinesia and parkinsonism were noted in approximately 62% of the patients presenting with LBP in the current study. Rest tremor was present only in 6%, while action tremor was present in 28% of the study participants. Our study findings are coherent with the reports by Gupta et al. (24), who reported rest tremor in only 4% patients of VP and a study by Thanvi et al. (22). Similarly, Carrilho et al. had reported rest tremor in 19% patients of PSP (55). Evidence upper limb parkinsonism was present in 57% of our study participants, and the most common pattern of

parkinsonism was symmetric in 61%, followed by asymmetric pattern in 36% and a hemibody parkinsonism in 3% subjects. Similar reports were made by Chang et al. (27).

Gait apraxia was present in all of our subjects, while gait initiation failure was present in 74% and FOG in 58% of the study participants. Postural instability was present in about 73% of the subjects, of which grade 1 was most commonly observed (41%) among LBP patients, followed by a postural instability of grade 2 in 24% patients. Postural instability was absent in 27% cases. To the best of our knowledge, there are no studies on detailed gait analysis of patients presenting with lower body parkinsonism. Our results go hand in hand with the reports by Raccagni et al., who reported frequency of FOG to be around 57% in VP and with the results of EMSA-PIGD study of 25 PSP-RS patients among whom 75% had postural instability (62). Around 32% of our subjects had pyramidal signs, but only 4% had cerebellar involvement and 0.5% had evidence of orthostatic hypotension. Gupta et al. reported pyramidal signs in 63% of VP patients. The relatively lesser frequency of pyramidal signs in our subjects may be explained by the presence of diverse etiologies in our subjects. Among other miscellaneous examination findings, multifocal myoclonus and dystonia were the commonest and noted in 4.5% of our study participants.

Radiological features

Amongst our subjects, detailed imaging was available for analysis in 163 patients (81%), out of which 12 were only CT scans. In other patients only written report was available. The most common imaging finding among patients with LBP was GCA grade 1 atrophy, noted in around 62.3% subjects. A hydrocephalus was present in 50.5% of our subjects, out of which 95% cases were of a communicating hydrocephalus and in the remaining 5%, an obstructive cause hydrocephalus was noted. The hydrocephalus was disproportionate to the atrophy in 72.5%, of the patients and was ex-vacuo dilation of ventricles in the remainder. There are no studies highlighting the nature and prevalence of hydrocephalus among patients presenting with LBP till date. However, a study by Espay et al., reported various causes of LBP with associated hydrocephalus, other than NPH (62). Amongst the components of iNPH radscale, the most common finding present in patients with hydrocephalus was sylvian fissure enlargement present in 95% subjects, followed by focal enlarged sulci in 70% and grade 1 temporal horn enlargement

in 66% subjects. Periventricular frontal horn capping was seen in 54% and an acute callosal angle (60 to 90 degrees) was noted in 49% subjects. A study by Fallmar et al., reported callosal angle to have highest diagnostic accuracy amongst all components of the iNPH radscale (64). The most common Total iNPH Rad scale score among our study participants was 8 (28%) and the mean score in our study was 7.45 ± 1.77 . A study by Kockum et al., showed, in symptomatic patients with age > 65, an iNPH Radscale score ≥ 8 suggests high probability of NPH with a positive likelihood ratio of 11 and a score of ≤ 4 identified patients without NPH, with a sensitivity of 100%, specificity of 96% with overall accuracy of 98.5% (37).

Midbrain atrophy was present visually among 33.5% of the subjects in our study and this correlated with the Midbrain to pons area ratio which was normal in 62% of our study subjects. The midbrain by pons ratio was < 0.2 in 19.4%, and between 0.20 to 0.22 in the remaining 18.6% of our subjects. Mean value of midbrain to pons ratio of our study subjects was 0.24 ± 0.04 with median of 0.24 (0.21-0.26). There are no studies reporting midbrain by pons ratio of patients presenting with LBP as a whole. However, a study by Quattrone et al. reported that a midbrain pons ratio < 0.2 to 0.22 is highly suggestive of PSP (48). The mean MRPI (n=144) of our study participants 12.09 ± 2.46 with a median of 12 (10.575-12.95). The MRPI was normal (≤ 13.55) in 82% of our subjects and in remaining 18%, it was > 13.55. These values may not be representative of our entire sample, as MRPI was available only in 71% of the total sample size. A study by Morelli et al. reported a MRPI >13.55 to be highly suggestive of PSP (51).

Among patients with LBP, evidence of small vessel ischemic changes were present in 93.5% in our study, out of which Fazekas grade 1 (35%) was the commonest, followed by grade 2 (51%), 3 (7%). Lacunar infarcts were present in 32% subjects and microbleeds were present in 9 %. Evidence of large vessel ischemia or past stroke was present in 16% of the study participants. A strategic infarct in striatal dopaminergic system was noted in 9% subjects, while a bleed was seen in 1 subject. A study by Watson et al, among patients with VP, displayed similar results (65). Other imaging findings among our study participants were bitemporal, asymmetric parietal atrophy and frontotemporal atrophy. In a study by Winikates et al., 95.7% of patients with VP showed ischemic lesions which is matching with our study results. In a study by Sudarsky et al. among 50 elderly patients with gait disorder, 16% had multiple lacunar infarctions (12). In our study, a CSF tap test was done in 81 subjects out of 202 patients presenting with LBP, out of

whom, it was positive in 16.3% and borderline in 9.4% subjects, while no improvement in gait was noted in 14.3% subjects with CSF tap. Among subjects who underwent tap test and had cognitive symptoms, improvement in MMSE with tap test was noted in 45.6% cases in our study.

Initial diagnosis

Vascular parkinsonism (with or without cognitive impairment) was the most common diagnosis at initial visit in our study, which accounted for 24%, followed by NPH (20%) and PSP (15%).

PSP-RS (53.6%) was the most common subtype followed by PAGF (34%) and others. A diagnosis of probable PSP was made in 53.6% and possible in 46.3%. Among NPH patients, probable NPH was diagnosed in 54.6%, while possible in 45.3%. Our results are supported by a study by Espay et al. who reported VP to be the most common cause of LBP (1, 2). However, in a hospital based follow up study Wadia et al. on clinical profile of HLGD among patients presenting with LBP, PSP as the most common cause followed by vascular parkinsonism and NPH (66). This study highlights, PSP to be a more common cause of LBP than it is thought to be, especially in Indian population and highlights the importance of clinical follow up of patients and to study the evolution of disease process. Among other etiologies, in our study, a PIGD variant of PD was noted in 3% subjects, which was concordant with reports by Skodmore et al. (67). A significant proportion of our subjects had features of mixed pathologies, among which combination of VP and NPH was the commonest. This finding is in agreement with reports by Espay et al. 2.5% of our subjects had immune mediated causes (anti Ro, AMA associated). Ju et al. had reported increased risk of PD in patients with Sjogrens disease, which might indirectly support our finding (68). Other etiologies noted were obstructive hydrocephalus (13) and other causes of hydrocephalus, FTD (62), other frontal lobe pathologies (8), AD (62), DLBD (62), MSA (63), CBS (63), vasculitis (69), post radiotherapy sub cortical disease (70), CJD (71) and possible drug induced parkinsonism.

The most common initial disability score (MRS) noted in our subjects was 3.0 (64%), followed by 4 (28%). Levodopa was the most common treatment given to our study participants, in as much as 72%, while VPS was done in 12% of the subjects. Other treatments given were, supportive measures like cholinesterase inhibitors, diuretics, immune therapy, which varied on

case to case basis. Response of gait to levodopa was variable in our study participants (excellent in 5%, moderate in 44%, very minimal in 42% and absent in 9% of subjects). This can be explained by the varied etiological profile of our subjects and variable response of patients with VP and PSP to levodopa, which again depends on multiple factors like stage of disease, subtype of PSP etc. A study by Constantinescu et al. reported L-Dopa response rates in VP to be varying between 20-40% and it to last for about 1-2 years (72). Among patients who underwent VPS, gait improved significantly in 54%, while moderate improvement was noted in 37.5% and only minimal improvement was noted in 8.3% patients. Shaw et al. reported a response rate of 70-85% for VPS among carefully selected patients in NPH (73) with complication rates up to 35%.

Follow up

Among 202 subjects, 25 (12.3%) were lost to follow up after the initial visit. In the remaining patients, the mean duration of follow up was 13.76 ± 17.07 months. Upon follow up, in about 44.6% of the subjects, though initial benefit was there with the treatment, the effect tended to wane with time. This can be explained by the observation made by Constantinescu et al., who opined that effect of dopaminergic therapy usually lasts only 1-2 years in VP. Similarly, Espay et al., made an observation of a so called “honeymoon” period in patients undergoing VPS in suspected NPH, following which there may be symptomatic worsening, which may be an indirect clue of underlying degenerative pathology like PSP (62).

In our study, upon follow up, additional finding of supranuclear gaze palsy was noted in 12%, while saccadic slowing was noted in 5%. This can be explained by the findings in a study by Carrilho et al. in PSP patients, who reported that only around 12.5% patients had eye movement abnormalities at initial presentation and the remaining patients developed eye changes in the subsequent 2-3 years (55). A worsening of gait was noted in 14%, while worsening of cognitive symptoms was noted in 9% of the subjects, which might be explained by the progression of the disease process. In 81% of the subjects, no additional imaging findings were noted in our study upon follow up. In the remaining subjects, worsening of Fazekas ischemic changes without any change in ventricular size was seen in 5%, medial temporal atrophy in 2%, evidence of new vascular event in 1% and evidence of midbrain atrophy (and worsening of MRPI) was noted in 2

patients (1%). These changes suggest either progression of the primary disease process or a development of a mixed pathology depending on the clinical context.

Diagnosis at last visit

VP (includes VP, VP with VCI and VP with CAA) was still the most common diagnosis seen in 22.6%, followed by PSP (19.7%) and NPH (14.1%). The relative decrease in proportion of NPH diagnosis at last visit in comparison to the initial diagnosis and increase in PSP diagnosis highlights the pitfalls in NPH diagnosis and lack of reliable clinical biomarkers in NPH diagnosis. This was followed by mixed pathologies, among which VP with AD was the commonest followed by VP with NPH and VP with PSP. For subjects diagnosed with NPH at initial evaluation, the diagnosis of NPH was retained in 67.5% of patients, while in the remaining 34%, an alternate diagnosis was made (1 was VP, 1 was PSP and in the remaining 9 subjects, a mixed pathology was considered). Similar results were obtained in a study by Starr et al., in 9 patients with suspected NPH, who were subsequently diagnosed as PSP and DLBD based on pathology. Hence, they suggested onset of disease with cognitive symptoms or absence of postural response early in the disease course are relative red flags in the diagnosis of NPH and predicted absence of sustained improvement 3 years from VPS placement (62). In case of patients with PSP, 93.1% retained the diagnosis at final visit, while NPH was diagnosed in 1 and a mixed pathology was diagnosed in other subject. The co-occurrence of NPH as a part of other neurodegenerative disease spectrum was reported by Morariu et al. who reported a PSP-NPH (74) and Cabral et al. who reported an AD-NPH syndrome (75). However, the possibility of NPH being an initial misdiagnosis than co-occurrence of dual pathology could not be ruled out, owing to the practical difficulties.

Among patients diagnosed as VP at initial evaluation, the diagnosis of VP was retained in 77.8% subjects, while in the remainder, a mixed pathology was considered as a diagnosis. This can be due to the fact that VP as a clinical entity is still questioned as lacks standard diagnostic criteria. Its diagnosis is largely based on imaging findings and presence of vascular risk factors, implying patients with an initial diagnosis of VP may later develop features of an unrelated underlying disease with progression. Uehara et al performed MRI brain among asymptomatic individuals and reported silent infarcts in WM and basal ganglia in as high as 40% subjects between 33-82

years (76). These findings re-emphasize the importance of clinical picture and follow up in patients with a diagnosis of VP. The situation is further complicated by the fact that majority of these conditions lack a definitive diagnostic criteria, and require pathological evidence for confirmation. Hence, the diagnosis of mixed or dual pathology may not be always accurate and warrants pathology for confirmation. Among patients with a diagnosis of PIGD variant of PD at initial visit, 1 patient was subsequently diagnosed as PSP, 1 as VP and 1 as a mixed pathology and the original diagnosis of PIGD-PD was retained in only 50% of the subjects (67).

16 subjects, who had no diagnosis of PSP at initial evaluation, were diagnosed as PSP at final visit, out of which RS subtype was diagnosed in 9, PAGF in 4, CBS in 2 and PI in 1 subject and this was significantly higher. Out of 21 subjects, who had diagnosis of a RS subtype of PSP initially, all of them retained the diagnosis at final evaluation. For PAGF subtype, among 13 subjects diagnosed initially, 3 (23%) were diagnosed as RS subtype at final evaluation. 50% of the subjects diagnosed with CBS subtype and 100% of frontal subtype were finally labeled as RS subtype and this change was statistically significant. These findings suggest the rapidly progressive nature of PSP and highlight that classical signs may be absent in the initial phase of the illness. Our results are backed up by the study by Campagnolo et al. (77). Among subjects with NPH at last evaluation, a diagnosis of definite NPH was done in 35%, probable NPH in 39%, while possible NPH was diagnosed in 26% subjects. In 87% of our patients, no new treatment was considered at last visit.

Levodopa was the most common additional treatment considered at last visit (6%) among the study participants. This can be explained by the fact that a new diagnosis of PSP was considered subsequently in some of our subjects upon follow up. VPS was done in 2 (1.13%) cases, External lumbar drain was done in 1 patient, VPS pressure was reset for its malfunction in 1 patient and in 1 patient with PIGD-PD, DBS was planned. The most common disability score (MRS) at last visit was 3 in 39.5% subjects, followed by a score of 4 in 35.5%, 2 in 14.6%, 1 in 5% and 5 in 4% subjects. A MRS of 6 (dead) was noted in 1 subject with VP as diagnosis, secondary to cardiac arrhythmia followed by a fall and SDH. In comparison to the initial scores, the disability scores were higher at last visit.

Etiologies of lower body parkinsonism noted in the current study

(in decreasing order of the frequency of occurrence)

S.No.	Clinical entity
1.	Vascular parkinsonism a) Slowly progressive (subcortical white matter disease or multiple lacunar infarcts or multinfarct state with stepwise progression) b) Acute onset (basal ganglia, brainstem infarct) c) Associated with cerebral amyloid angiopathy
2.	Progressive supranuclear palsy a) RS subtype b) PAGF subtype c) CBS subtype d) Frontal subtype* e) PI subtype
3.	Normal pressure hydrocephalus
4.	Mixed phenotypes a) VP, AD b) VP, NPH c) VP, PSP d) NPH, PSP e) Other less common mixed phenotypes noted were *: • VP, PIGD-PD • VP, DLBD • Immune mediated (Anti Ro) with VP • Immune mediated (AMA) with PSP • PSP, ALS • PSP, ALS complex with VP • PSP, AD • PSP with vascular hemichorea and dystonia • PSP with post radiotherapy subcortical white matter disease • NPH, AD • NPH, PD • NPH, FTD
5.	Other degenerative disorders a) PIGD-PD b) MSA c) FTD d) Less common causes*- CBS, AD-Frontal variant, CJD, DLBD, PLS
6.	Phobic gait/ Functional gait
7.	Other causes of hydrocephalus a) Aqueductal stenosis with obstructive hydrocephalus b) Obstructive hydrocephalus due to tumours (glioma, pituitary macroadenoma) c) Communicating hydrocephalus secondary to CNS TB* d) Neurocysticercosis associated arachnoiditis with communicating

	hydrocephalus* e) Post traumatic communicating hydrocephalus* f) Extraventricular obstructive hydrocephalus*
8.	Other causes* Post radiotherapy subcortical white matter disease Diffuse high grade glioma associated parkinsonism Parkinsonism associated with CNS vasculitis Acquired hepatocerebral degeneration associated with cirrhosis Pallidopyramidal syndrome (PLA2G6) Adult onset Leukodystrophy-Mitochondrial leukoencephalopathy Sphenoid wing meningioma with mass effect on frontal lobe Drug induced Parkinsonism

Note: * represent single cases

ASSOCIATIONS BETWEEN NPH, PSP AND VP

In our study, the mean age of symptom onset was comparable between NPH, PSP and VP (70.29 ± 7.66 vs 66.1 ± 7.17 vs 69.48 ± 7.2). There was no statistically significant difference among the groups with respect to age of onset and symmetry of symptoms at onset. Though VP is classically described to occur in individuals with relatively advanced age (8th decade by Gupta et al.) in comparison with PSP and NPH, our results are backed up by data in similar Indian studies (56, 78, and 79). Among initial symptoms, FOG and postural instability were significantly higher in PSP in comparison with NPH and VP and these findings are supported by Starr et al. (62, 81). Urgency of urine was significantly higher in NPH in comparison with VP and PSP ($p < 0.001$) (56). FOG and postural instability were comparable among VP and NPH in our study (34, 79). Dysphagia, choking spells and cognitive symptoms were comparable among all the groups. This finding in our study is contradictory to the report by Johnson et al., who reported increased swallowing problems in PSP patients. This disparity can be justified by the fact that, we had a significant proportion of subjects with PAGF subtype, the follow up period in our subjects was shorter and probably our patients were in early stage of the disease.

Cognitive symptoms were comparable among the three groups and no statistically significant difference was noted between the groups. However, majority of our subjects had only MCI symptoms unlike in most of the studies, which report higher prevalence of dementia in all the three groups (VP, PSP, NPH) (83, 84). Among the risk factors, hypertension and smoking were found in significantly higher frequencies among VP subjects. Hypertension had been mentioned as the most common risk factor for VP in the literature (as high as 100% in some studies). Though history of documented stroke was present in 5% of NPH patients and 7% of PSP patients in our study, a past history of stroke was significantly higher among VP patients (reported 43% by Winikates et al.) (28). Dyslipidemia was higher in VP in comparison with NPH. Other risk factors were comparable among the study participants.

The mean MMSE score was comparable among the 3 groups (NPH, 24.9 ± 4.6 ; vs PSP, 26 ± 2.6 ; vs VP, 24 ± 5.3), as reported in previous studies (83, 84). In our study, PSP patients had significantly higher proportion of eye movement abnormalities (vertical saccadic slowing), axial rigidity, postural instability, FOG, upper limb parkinsonism in comparison with VP and NPH. Similar observations were made by Kukkle et al. while enrolling subjects into pan India registry for PSP (78). In our study, it was noted that VP subjects had higher proportion of saccadic slowing in comparison to NPH. The possible explanation for this finding could be presence of a brainstem or thalamus vascular insult in the past or an ongoing associated mixed pathology with VP being just an innocent bystander. Clinical follow up may be particularly useful in such situations. Limb rigidity and rest tremor were comparable, while action tremor was more in PSP in comparison with NPH. Gait initiation failure was comparable between PSP and VP, while it was higher in PSP than that in case of NPH (63). Pyramidal signs were present in statistically significant proportions in VP, than in PSP or NPH in our study, as suggested by Gupta et al. in the past (24).

Hydrocephalus was present in 97.5% of NPH patients (1 had borderline ventriculomegaly), 40% of VP patients, while it was present in 17% of PSP patients. There was statistically significant difference between NPH and PSP, NPH and VP. However, VP and PSP were comparable with respect to presence of hydrocephalus. Proportion of patients with hydrocephalus absent was significantly higher in PSP as compared to NPH and VP. These findings in our study go in conjunction with reports by Espay et al., who reported presence of hydrocephalus in patients of

PSP and VP (2, 62). The mean iNPH radscale score was 8.6 ± 1.1 in NPH, while it was 5.8 ± 1.3 in PSP and 5.8 ± 1.2 in VP and there was statistically significant difference between NPH and other 2 groups. There are no reports of iNPH radscale score among patients with VP and NPH, however, Kockum et al., reported that among symptomatic patients, a score of ≥ 8 is highly suggestive of NPH with a specificity of 95% (37). None of our subjects with VP or PSP had an iNPH score > 8 . This implies that iNPH radscale is an important tool in diagnosis of NPH and helps in differentiating NPH from ex-vacuo ventriculomegaly and other causes of hydrocephalus.

The mean midbrain by pons ratio in our study participants among the 3 groups were (0.25 ± 0.03 vs 0.2 ± 0.04 vs 0.25 ± 0.04) and it was significantly lower in PSP group in comparison with VP and NPH, suggesting that this parameter may be used to identify PSP patients among patients presenting with LBP. The value of midbrain by pons area ratio for diagnosis of PSP originally suggested by Oba et al., was <0.16 (49), while it was latter suggested by Quatterone et al., that a ratio of <0.20 may be sufficient to make the diagnosis of PSP (48). In our study, VP and NPH groups had a midbrain by pons area ratio comparable to each other. However 24% of PSP patients had a normal midbrain by pons ratio and 9% each of VP and NPH subjects had an abnormal midbrain by pons ratio in our study population. This may be due to the fact that, early in the course of PSP, it is high likely that a diagnosis of PSP may be missed. This is supported by the mention of limited sensitivity of the NINDS-SPSP criteria for the diagnosis of PSP at 1st visit by Litvan et al. (14-83%) (85). Similarly, Wen et al., had suggested that serial measurements of midbrain by pons ratio and MRPI may help to identify midbrain atrophy among patients with clinical suspicion of PSP (rel Δ Mibrain/pons area noted was 6.52% annually) and also help to delineate among the various subtypes of PSP (86).

The mean midbrain by pons ratio in other diagnosis in our study participants include 0.21 ± 0.04 in mixed pathology subjects, 0.22 ± 0.04 in FTD, 0.24 ± 0 in PIGD-PD, 0.19 ± 0 in DLBD, 0.27 ± 0 in AD, 0.26 ± 0 in CBS, 0.28 ± 0 in MSA. However, these values may not be representative because of their small sample numbers. The mean MRPI in our study participants among the 3 groups was (11.57 ± 1.56 vs 14.49 ± 3.08 vs 11.65 ± 1.85) and it was significantly higher in PSP group in comparison with VP and NPH. Similar results were obtained in the previous studies among PSP patients (48). VP and NPH group were comparable to each other. However, 43% PSP subjects had normal MRPI and 16% VP and 6% NPH patients had abnormal MRPI in our

study. This may again be due to the early stage of the disease and further emphasizes on follow up of the patients. In our study, though both reduced M/P ratio and elevated MRPI were significantly associated with PSP patients, midbrain by pons area ratio was better correlated with PSP patients than with MRPI, which may be partly explained by the complexity of MRPI measurement and inter and intra observer variability in its measurement. In a study by Natalia et al., the mean MRPI for patients of PSP-RS was 19.3 ± 6.9 (9.3-31.3), for PSP-P was 17.3 ± 4.4 (12.0-26.6), for MSA-P was 10.7 ± 2.5 (7.1-17.1) and for controls was 11.2 ± 1.8 (7.7- 15.4) (87). These findings partly match with the findings in our study.

Among subjects with NPH and PSP, around 70% had Fazekas grade 1 small vessel ischemic changes and were higher than that in VP. These findings are contradictory to the conventional belief. This could be a chance occurrence, since silent infarcts are known to occur in as much as 6% of the general population, especially among those with hypertension, as suggested by Lee et al. (88). However, grade 2 (60%) and grade 3 (11%) Fazekas changes were noted in significantly higher proportions in VP than in NPH and PSP ($p < 0.001$). Lacunar infarcts (87%), microbleeds (25%), large vessel ischemic changes (40%) were present in significantly higher numbers in VP patients in comparison with PSP and NPH. Our results are in complete agreement with results of Rampello et al., who reported 100% MRI abnormalities among VP patients (WM lesions in 88%). In the same study, 7% of the PD patients showed WM lesions (89). Similarly, in a study by Demirkiran et al., among VP patients, 100% showed ischemic abnormalities (WM or brainstem or basal ganglia), while 30% of PD patients showed abnormal scans (90). In a study by Winikates et al., in 1994, 23.3% of patients satisfying clinical criteria for PSP, showed evidence of vascular changes, of which sub cortical white matter changes were the commonest (91). Similarly, in a study by Jecmenica et al., among patients with diagnosis of PSP, upon pathological evaluation, AD related pathology was found in 84%, small vessel disease was found in 65%, while pure PSP pathology was present only in 8% of the brain samples. However, the severity of co-pathology was usually mild (92). The prevalence of small vessel ischemic changes in patients with PD have been reported variably among different studies (Demirkiran et al., 30% vs Winikates et al., 22% vs Rampello et al., 7%). The results of the above studies stress up on the increasing recognition of mixed or double pathology among patients presenting with LBP. However, the relative contribution of each pathology to the

patient's disability is difficult to assess, and thus the clinician is often faced with a dilemma and has difficulty in deciding over the treatment modality to be opted.

With respect to initial MRS, a grade 4 disability was seen in 40% of the PSP subjects, vs. 10% VP subjects and the difference was significant. Otherwise, the groups were comparable. The final MRS among PSP and VP patients was significantly higher in comparison to NPH, but was comparable to each other. This may be explained by the improvement in symptoms of NPH patients with VPS. The mean change in MRS in PSP (0.41 ± 0.73) and VP (0.33 ± 0.71) was significantly higher in comparison with that of NPH (-0.53 ± 1.19). Although the mean change of MRS in PSP was higher than that of VP, it was not statistically significant. The results of our study suggest that subjects with PSP have a severe disease and the progression of the disease is faster in comparison to NPH. The worsening of MRS also reflects the treatment refractoriness of PSP and VP, in comparison to NPH. Similar findings were reported by Litvan et al., who reported progressive worsening of symptoms with treatment refractoriness among PSP patients with a median survival of 5.6 years (93). VP is considered to be partly responsive to L-Dopa (and CSF drainage in some) at least during the initial stages (24) of the disease, while NPH has been reported to show a sustained benefit with VPS (34).

The Diagnostic dilemma

Our current study, highlights the diverse etiologies of LBP and the practical difficulties faced in the evaluation of patients presenting with LBP. The drawbacks in the currently available diagnostic criteria's and the difficulties in making an accurate clinical or ante mortem diagnosis, especially at initial presentation are the harsh realities that clinicians often face in current times. In an observation by Caslake et al., the diagnosis of patients presenting with parkinsonism changed in almost 33% of the subjects after a median follow up of 29 months (94). Most of the changes occurred within first 1 year of follow up and PD was the most over diagnosed entity. The change in diagnosis was mainly due to development of atypical clinical or imaging features, variations in response to levodopa and rate of disease progression. Similar insights were put forward by Vizcarra et al., who questioned VP as a clinical entity and opined that parkinsonism resulting from vascular injury is often a rare entity. In clinical practice, a diagnosis of VP is mainly done on the basis of presence of vascular risk factors and much weightage is given to radiology in its diagnosis. However, the exact pathogenic role of the WM hyperintensities

(leukoaraiosis), is often difficult to establish. The patients disability can well be due to an underlying neurodegenerative pathology and this notion is further supported by the fact that severity of leukoaraiosis has no correlation with clinical phenotype. Vizcarra et al., suggested the term pseudo-vascular parkinsonism in such cases. Inzelberg et al., had reported the frequency of “incidental” vascular lesions in pathologically proven PD patients to be around 20% to 30% (95). This suggests, presence of vascular lesions may be a chance occurrence in those patients. Similarly, the nature of some of the WM signal changes in MRI may be of non vascular nature like ischemia or demyelination. They also suggested the terms pseudo-vascular pseudo-parkinsonism for patients with HLGD like NPH and vascular pseudo-parkinsonism for patients with bilateral medial frontal lobe infarcts (1). The situation is further complicated by the observation of subtle extra pyramidal signs reported in as much as 35% of individuals, > 65 years old with multiple co-morbidities, who present with general non specific slowing (often misinterpreted as bradykinesia) (96).

Similar dilemma exists in the diagnosis of NPH. Though presence of classical triad of symptoms and a positive CSF tap test with supportive radiological features was considered sufficient for NPH diagnosis, in a series of cases by Starr et al., out of 9 patients diagnosed as NPH and who underwent VPS, a worsening of gait and cognition was noted on subsequent follow up. 6 out of those 9 had pathological evidence of PSP, while remaining 3 were diagnosed as DLBD (62). They suggested a presence of early cognitive impairment (often predating gait difficulty), or hallucinations and early postural impairment, falls, oculomotor impairment would weigh against the diagnosis of NPH and thus suggested the term “Hydrocephalic Parkinsonism”, highlighting that hydrocephalus can be present in other neurodegenerative conditions like AD, DLBD, other than in NPH. They also made a mention of the presence of a “honeymoon” period in patients with underlying degenerative diseases like PSP after shunting, following which patient progresses further. In our study, we found that iNPH radscale is a reliable tool and a score of ≥ 8 is highly suggestive of NPH. Similarly, Urinary symptoms were significantly higher in NPH patients in comparison to VP in our study. Starr et al., also opined on possibility of dual pathology in NPH patients with secondary worsening after VPS, out of which AD was the commonest consideration.

The boundaries between VP and NPH are often poorly defined and no clinical feature can adequately differentiate between the two, as suggested by Espay et al. (1). This is further reinforced by the fact that significant benefit with CSF tap was noted in VP patients even without significant ventriculomegaly in a report by Ondo et al. (29). In our study, VP patients, had significantly higher vascular risk factors (Hypertension, past stroke, smoking, dyslipidemia), pyramidal signs and Fazekas grade 2, 3 small vessel ischemic changes in comparison to NPH. Early falls, FOG, eye movement abnormalities, Axial predominant rigidity, presence of upper limb parkinsonism and a higher degree of postural instability with a reduced midbrain by pons ratio and increased MRPI differentiated our PSP subjects from VP and NPH. Apart from VP, PSP and NPH, in our current study, we also found a significant proportion of subjects with dual pathologies (especially in conjunction with either VP or NPH). The pathology causing major disability in such patients is often difficult to identify. We propose, that following up the patients for long periods, clinically and radiologically to identify the dominant pathology amongst the mixed phenotype and formulating management protocols accordingly would be the preferable approach.

Chapter 7

Conclusion



CONCLUSION

- Lower body parkinsonism is a common clinical syndrome with diverse etiologies, yet vaguely defined management protocols
- In the current study, the most common cause of LBP noted was vascular parkinsonism, followed by PSP, NPH, mixed pathologies and PIGD variant of PD
- Other causes of LBP among our subjects were, FTD, other causes of obstructive hydrocephalus like tumors, aqueductal stenosis and immunological causes.
- The boundary between VP and NPH is poorly defined and it is often difficult to differentiate them. The situation is further complicated due to frequent presence of vascular changes and silent infarcts among asymptomatic individuals in general population.
- Our study has shown a significantly higher proportion of vascular risk factors (hypertension, past ischemic stroke, smoking, dyslipidemia), pyramidal signs and small vessel ischemic changes in VP in comparison with NPH.
- NPH patients had more urinary symptoms in comparison to VP. A positive CSF tap test alone should not be taken as diagnostic of NPH, as patients with VP can also have transient significant improvement in gait with CSF tap. An iNPH radscale ≥ 8 (often coupled with tap test results) reliably identified NPH patients among our study participants.
- Presence of early falls, significant FOG, convincing eye movement abnormalities, Axial predominant rigidity, upper limb parkinsonism and a greater degree of postural instability was noted in PSP patients in our study. A reduced midbrain by pons area ratio (< 0.2) and increased MRPI (> 13.55) differentiated our PSP subjects from VP and NPH
- Response to treatment was best among patient with NPH, among the 3 groups. VP had variable and transient improvements with L-Dopa, PSP patients had a generally treatment refractory course.
- A more pragmatic approach is needed in the evaluation and management of patients presenting with LBP, owing to its complexity. The importance of clinical follow up of patients cannot be undermined.

Chapter 8

Limitations



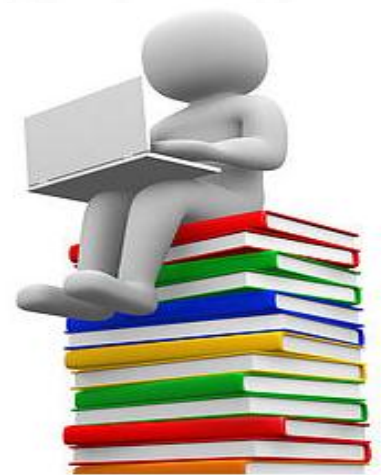
LIMITATIONS

Our study should be interpreted with in context of its limitations.

- Firstly, ours is a retrospective study and the data was collected using a predesigned proforma. Some of the clinical parameters which we aimed to collect were missing and not uniformly available in all the subjects.
- The radiological data collected in our study, like midbrain by pons area ratio and MRPI were calculated by free hand method, with which the possibility of inter and intra observer variability could not be ruled out.
- Out of 202 subjects in our study, follow up data was available only in 177 subjects (25 subjects were lost to follow up after the first visit). The mean duration of follow up in our study was 13.76 ± 17.07 months. However, longer periods of follow up are required to look into the clinical phenotypic evolution of patients with LBP.

Chapter 9

References



REFERENCES

1. Vizcarra JA, Lang AE, Sethi KD, Espay AJ. Vascular Parkinsonism: deconstructing a syndrome. *MovDisord*. 2015 Jun;30(7):886-94.
2. Espay AJ, Narayan RK, Duker AP, Barrett ET, Jr., de Courten-Myers G. Lower-body parkinsonism: reconsidering the threshold for external lumbar drainage. *Nat ClinPractNeurol* 2008;4:50-55.
3. Feve AP, Fenelon G, Wallays C, Remy P, Guillard A (1993) Axial motor disturbances after hypoxic lesions of the globus pallidus. *MovDisord* 8:321–326.
4. Brix MK, Westman E, Simmons A, Ringstad GA, Eide PK, Wagner- Larsen K et al (2017) Evans' index revisited: new cut-off levels for use in radiological assessment of ventricular enlargement in the elderly. *Eur J Radiol* 95:28–32.
5. Zijlmans JC, Daniel SE, Hughes AJ, Révész T, Lees AJ. Clinico-pathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. *MovDisord*. 2004 Jun;19(6):630-40.
6. Casmiro M *et al.* (1989) Risk factors for the syndrome of ventricular enlargement with gait apraxia (idiopathic normal pressure hydrocephalus): a case control study. *J NeurolNeurosurg Psychiatry* **52**: 847–852.
7. Nutt JG, Marsden CD, Thompson PD. Human walking and higher level gait disorders, particularly in the elderly. *Neurology* 1993;43: 268–279.
8. Bruns L (1892). *Über Störungen des Gleichgewichtes bei Stirnhirntumoren*. *Otsch Med Wochenschr* 18: 138–140.
9. Gerstmann J, Schilder P (1926). *Über eine besondere gangstörung bei stirnhirner kranking*. *Wien Med Schr* 76: 97–107.
10. Van Bogaert L, Martin P (1929). *Sur deux signes du syndrome de desequilibration frontale: l'apraxie de la marche et l'atonie statique*. *Encephale* 24: 11–18.
11. Denny-Brown D (1958). The nature of apraxia. *J Nerv Ment Dis* 126: 9–31.
12. Sudarsky L, Ronthal M (1983). Gait disorders among elderly patients: a survey study of 50 patients. *Arch Neurol* 40: 740–743.
13. Adams RD, Fisher CM, Hakim S et al. (1965). Symptomatic occult hydrocephalus with “normal” cerebrospinal fluid pressure: a treatable syndrome. *N Engl J Med* 273: 117–126.
14. Messert B, Baker NH (1966). Symptoms of progressive spastic ataxia and apraxia associated with occult hydrocephalus. *Neurology* 16: 440–452.
15. Critchley M. Arteriosclerotic parkinsonism. *Brain* 1929; 52: 23–83.
16. Thompson PD, Marsden CD. Gait disorder of subcortical arteriosclerotic encephalopathy: Binswanger's disease. *Mov Disord* 1987;2:1e8.
17. Hachinski VC, Potter P, Merskey H. Leuko-araiosis. *Arch Neurol* 1987;44:21e3.
18. FitzGerald PM, Jankovic J. Lower body parkinsonism: evidence for vascular etiology. *Movement Disord*. 1989;4:249-260.

19. Della Sala S, Francescani A, Spinnler H (2002). Gait apraxia after bilateral supplementary motor area lesion. *J Neurol Neurosurg Psychiatry* 72: 77–85.
20. Elble RJ. Gait and dementia: moving beyond the notion of gait apraxia. *J Neural Transm* 2007;114:1253–1258.
21. Baezner H, Hennerici M. From trepidant abasia to motor network failure—gait disorders as a consequence of subcortical vascular encephalopathy (SVE): review of historical and contemporary concepts. *J Neurol Sci* 2005;229-230:81–88.
22. Thanvi B, Lo N, Robinson T. Vascular parkinsonism--an important cause of parkinsonism in older people. *Age Ageing*. 2005 Mar;34(2):114-9.
23. Nutt JG. Higher-level gait disorders: an open frontier. *Mov Disord*. 2013 Sep 15;28(11):1560-5.
24. Gupta D, Kuruvilla A. Vascular parkinsonism: what makes it different? *Postgrad Med J*. 2011 Dec;87(1034):829-36.
25. Van Zagten M, Lodder J, Kessels F. Gait disorder and parkinsonian signs in patients with stroke related to small deep infarcts and white matter lesions. *Mov Disord* 1998; 13: 89–95.
26. Lee SC, Park SJ, Ki HK, et al. Prevalence and risk factors of silent cerebral infarction in apparently normal adults. *Hypertension* 2000;36:73e7.
27. Chang CM, Yu YL, Ng HK, et al. Vascular pseudoparkinsonism. *Acta Neurol Scand* 1992;86:588e92.
28. Winikates J, Jankovic J. Clinical correlates of vascular parkinsonism. *Arch Neurol* (1999) 56(1):98–102.
29. Ondo WG, Chan LL, Levy JK. Vascular parkinsonism: clinical correlates predicting motor improvement after lumbar puncture. *Mov Disord* 2002; 17: 91–7.
30. Hakim S, Adams RD. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. *J Neurol Sci*. 1965;2:307-27.
31. Shenkin HA, Greenberg J, Bouzarth WF, Gutterman P, Morales JO. Ventricular shunting for relief of senile symptoms. *JAMA*. 1973;225:1486-9.
32. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH. Symptomatic occult hydrocephalus with “normal” cerebrospinal-fluid pressure. A treatable syndrome. *N Engl J Med*. 1965;273:117-26,
33. Oliveira LM, Nitrini R, Román GC. Normal-pressure hydrocephalus: A critical review. *Dement Neuropsychol*. 2019 Apr-Jun;13(2):133-143.
34. Kiefer M, Unterberg A. The differential diagnosis and treatment of normal-pressure hydrocephalus. *Dtsch Arztebl Int*. 2012 Jan;109(1-2):15-25; quiz 26.
35. Wang Z, Zhang Y, Hu F, Ding J, Wang X. Pathogenesis and pathophysiology of idiopathic normal pressure hydrocephalus. *CNS Neurosci Ther*. 2020 Dec;26(12):1230-1240.

36. Mori, E., Ishikawa, M., Kato, T., et al. 2012. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. *Neurol. Med. Chir.* 52, 775–809.
37. Kockum K, Virhammar J, Riklund K, Söderström L, Larsson EM, Laurell K. Diagnostic accuracy of the iNPH Radscale in idiopathic normal pressure hydrocephalus. *PLoS One*. 2020 Apr 24;15(4):e0232275.
38. Román GC. Frequent falls in the elderly: Think NPH! *Texas Neurological Society Broca's Area* 2016 (Summer):8-10
39. Junkkari, A., Luikku, A.J., Danner, N. *et al.* The Kuopio idiopathic normal pressure hydrocephalus protocol: initial outcome of 175 patients. *Fluids Barriers CNS* **16**, 21 (2019).
40. Souza R, Rocha S, Martins R, Kowacs P, Ramina R. Gait in normal pressure hydrocephalus: characteristics and effects of the CSF tap test. *Arq Neuropsiquiatr.* 2018;76(5):324-31.
41. Damasceno B. Normal pressure hydrocephalus and the predictive value of presurgical tests. *Arq Neuropsiquiatr.* 2018;76(5):285-6.
42. Meier U, Stengel D, Müller C, et al.: Final results of the SWASONA study in idiopathic normal pressure hydrocephalus. *Acta Neurochir (Wien)* 2011; 153: 1848–9 (Abstract).
43. Richardson JC, Steele J, Olszewski J. Supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia. A clinical report on eight cases of “heterogenous systemdegeneration.” *Trans AmNeurol Assoc* 1963;88:25Y29.
44. Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. *J Neurol Neurosurg Psychiatry* 2006;77(4):468Y473.
45. Respondek G, Stamelou M, Kurz C, et al. The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. *Mov Disord* 2014; 29(14):1758Y1766.
46. Höglinger GU, Respondek G, Stamelou M, Litvan I, et al. Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Mov Disord.* 2017 Jun;32(6):853-864.
47. McFarland NR. Diagnostic Approach to Atypical Parkinsonian Syndromes. *Continuum (Minneap Minn)*. 2016 Aug;22(4 Movement Disorders):1117-42.
48. Quattrone A, Nicoletti G, Messina D et al. MR Imaging Index for Differentiation of Progressive Supranuclear Palsy from Parkinson Disease and the Parkinson Variant of Multiple System Atrophy. *Radiology*. 2008;246(1):214-21.
49. Oba H, Yagishita A, Terada H et al. New and Reliable MRI Diagnosis for Progressive Supranuclear Palsy. *Neurology*. 2005;64(12):2050-5.
50. Massey L, Jager H, Paviour D et al. The Midbrain to Pons Ratio: A Simple and Specific MRI Sign of Progressive Supranuclear Palsy. *Neurology*. 2013;80(20):1856-61.
51. Morelli M, Arabia G, Salsone M et al. Accuracy of magnetic resonance parkinsonism index for differentiation of progressive supranuclear palsy from probable or possible Parkinson disease. *Mov. Disord.* 2011;26 (3): 527-33.

52. Quattrone A, Morelli M, Nigro S, et al. A new MR imaging index for differentiation of progressive supranuclear palsy-parkinsonism from Parkinson's disease. (2018) *Parkinsonism & related disorders*. 54: 3-8.
53. Benítez-Rivero S, Lama MJ, Huertas-Fernández I, et al. Clinical features and neuropsychological profile in vascular parkinsonism. *J Neurol Sci*. 2014 Oct 15;345(1-2):193-7.
54. Vale TC, Caramelli P, Cardoso F. Vascular parkinsonism: a case series of 17 patients. *Arq Neuropsiquiatr*. 2013 Oct;71(10):757-62.
55. Carrilho PE, Barbosa ER. Progressive supranuclear palsy in a sample of Brazilian population: clinical features of 16 patients. *Arq Neuropsiquiatr*. 2002 Dec;60(4): 917-22.
56. M Das J, Biagioni MC. Normal Pressure Hydrocephalus. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
57. Barbosa MT, Caramelli P, Maia DP, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). *Mov Disord* 2006; 21:800-808.
58. Rowe JB, Holland N, Rittman T. Progressive supranuclear palsy: diagnosis and management. *Pract Neurol*. 2021 Oct;21(5):376-383.
59. Wen Y, Yang Q, Jiao B, et al. Clinical features of progressive supranuclear palsy. *Front Aging Neurosci*. 2023 Aug 30;15:1229491.
60. Colosimo C, Morgante L, Antonini A, et al. Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study. *J Neurol* 2010;257:5e14.
61. Adila Elobeid, Katarina Laurell, Kristina Giuliana Cesarini, et al. Correlations Between Mini-Mental State Examination Score, Cerebrospinal Fluid Biomarkers, and Pathology Observed in Brain Biopsies of Patients With Normal-Pressure Hydrocephalus, *Journal of Neuropathology & Experimental Neurology*, Volume 74, Issue 5, May 2015, Pages 470–479.
62. Starr BW, Hagen MC, Espay AJ. Hydrocephalic Parkinsonism: lessons from normal pressure hydrocephalus mimics. *J Clin Mov Disord*. 2014 Oct 29;1:2.
63. Raccagni C, Nonnekes J, Bloem BR, Peball M, Boehme C, Seppi K, Wenning GK. Gait and postural disorders in parkinsonism: a clinical approach. *J Neurol*. 2020 Nov;267(11):3169-3176.
64. Fällmar D, Andersson O, Kilander L, Löwenmark M, Nyholm D, Virhammar J. Imaging features associated with idiopathic normal pressure hydrocephalus have high specificity even when comparing with vascular dementia and atypical parkinsonism. *Fluids Barriers CNS*. 2021 Jul 29;18(1):35.
65. Watson RS, Raji KL, Sabarisree M. A Study on the Clinical and Radiologic Profile of Patients with Vascular Parkinsonism: *J. med. sci. clin.* 2017 Jul; 5(7):24773-24777.

66. A. Alshi, J.D. Desai, P.M. Wadia. Clinical spectrum of higher level gait disorders (HLGD) in a tertiary care movement disorder clinic - A prospective study. *J. Neurol. Sci.* 405S (2019) 104971.
67. Skidmore, F.M., Monroe, W.S., Hurt, C.P. *et al.* The emerging postural instability phenotype in idiopathic Parkinson disease. *npj Parkinsons Dis.* **8**, 28 (2022).
68. Ju UH, Liu FC, Lin CS, Huang WY, Lin TY, Shen CH, Chou YC, Lin CL, Lin KT, Kao CH, Chen CH, Yang TY. Risk of Parkinson disease in Sjögren syndrome administered ineffective immunosuppressant therapies: A nationwide population-based study. *Medicine (Baltimore)*. 2019 Apr;98(14):e14984.
69. Fabiani, G., Teive, H. A., Germiniani, F. M., Sá, D. S. & Werneck, L. C. Reversible parkinsonian syndrome in systemic and brain vasculitis. *Mov. Disord.* **17**, 601–604 (2002).
70. Connor M, Karunamuni R, McDonald C, White N, Pettersson N, Moiseenko V, Seibert T, Marshall D, Cervino L, Bartsch H, Kuperman J, Murzin V, Krishnan A, Farid N, Dale A, Hattangadi-Gluth J. Dose-dependent white matter damage after brain radiotherapy. *Radiother Oncol.* 2016 Nov;121(2):209-216.
71. Corriveau-Lecavalier N, Li W, Ramanan VK, Drubach DA, Day GS, Jones DT. Three cases of Creutzfeldt-Jakob disease presenting with a predominant dysexecutive syndrome. *J Neurol.* 2022 Aug;269(8):4222-4228.
72. Constantinescu R, Richard I, Kurlan R. Levodopa responsiveness in disorders with parkinsonism: a review of the literature. *Mov Disord* 2007;22:2141e8.
73. Clinical outcomes in the surgical treatment of idiopathic normal pressure hydrocephalus. Shaw R, Everingham E, Mahant N, Jacobson E, Owler B. *J Clin Neurosci.* 2016;29:81–86.
74. Morariu MA: Progressive supranuclear palsy and normal-pressure hydrocephalus. *Neurology* 1979, 29(11):1544–1546.
75. Cabral D, Beach TG, Vedders L, Sue LI, Jacobson S, Myers K, Sabbagh MN: Frequency of Alzheimer's disease pathology at autopsy in patients with clinical normal pressure hydrocephalus. *Alzheimers Dement* 2011, 7(5):509–513.
76. Uehara T, Tabuchi M, Mori E. Risk factors for silent cerebral infarcts in subcortical white matter and basal ganglia. *Stroke* 1999;30:378e82.
77. Campagnolo M, Weis L, Fogliano C, Cianci V, Garon M, Fiorenzato E, Carecchio M, Ferreri F, Bisiacchi P, Antonini A, Biundo R. Clinical, cognitive, and morphometric profiles of progressive supranuclear palsy phenotypes. *J Neural Transm (Vienna)*. 2023 Feb;130(2):97-109.
78. P. Kukkle, R. Gupta, S. Desai, S. Mehta, D. Joshi, N. Kumar, R. Kandadai, L. Sahoo, A. Mukherjee, V. Paramanandam, S. Murugan, D. Kp, S. Sundaram, R. Rajan, R. Menon, K. Shetty, P. Samson, S. Krishnan, M. Deshmukh, P. Wadia, C. Sandeep, P. Aggarwal, S. Bhowmick, H. Kumar, A. Biswas, V. Goyal, S. Seshagiri, R. Borgohain, V. Ramprasad.

- Pan India Registry for Progressive Supranuclear Palsy (PAIR-PSP) [abstract]. *Mov Disord*. 2022; 37 (suppl 2).
79. J. Kuragala, J. Murthy, N. Chaudhary, s. Sharma, S. Jaiswal, Y. Reddy. Clinical spectrum of vascular Parkinsonism: A hospital-based study in south India [abstract]. *Mov Disord*. 2018; 33 (suppl 2).
 80. Johnston BT, Castell JA, Stumacher S, Colcher A, Gideon RM, Li Q, Castell DO. Comparison of swallowing function in Parkinson's disease and progressive supranuclear palsy. *Mov Disord*. 1997 May;12(3):322-7.
 81. Osaki Y, Morita Y, Miyamoto Y, Furuta K, Furuya H (2017) Freezing of gait is an early clinical feature of progressive supranuclear palsy. *Neurol Clin Neurosci* 5(3):86–90.
 82. Borm C, Krismer F, Wenning GK, Seppi K, Poewe W, Pallecchia MT et al (2018) Axial motor clues to identify atypical parkinsonism: a multicentre European cohort study. *Parkinsonism Relat Disord*.
 83. Horta-Barba, A., Pagonabarraga, J., Martínez-Horta, S. *et al*. Cognitive and behavioral profile of progressive supranuclear palsy and its phenotypes. *J Neurol* **268**, 3400–3408 (2021).
 84. Saito M, Nishio Y, Kanno S, Uchiyama M, Hayashi A, Takagi M, Kikuchi H, Yamasaki H, Shimomura T, Iizuka O, Mori E. Cognitive profile of idiopathic normal pressure hydrocephalus. *Dement Geriatr Cogn Dis Extra*. 2011 Jan;1(1):202-11.
 85. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. 1996;47:1–9.
 86. Wen Y, Yang Q, Jiao B, Zhang W, Lin J, Zhu Y, Xu Q, Zhou H, Weng L, Liao X, Zhou Y, Wang J, Guo J, Yan X, Jiang H, Tang B, Shen L. Clinical features of progressive supranuclear palsy. *Front Aging Neurosci*. 2023 Aug 30;15:1229491.
 87. Madetko N, Alster P, Kutylowski M, Migda B, Nieciecki M, Koziorowski D, Królicki L. Is MRPI 2.0 More Useful than MRPI and M/P Ratio in Differential Diagnosis of PSP-P with Other Atypical Parkinsonisms? *J Clin Med*. 2022 May 10;11(10):2701.
 88. Lee SC, Park SJ, Ki HK, et al. Prevalence and risk factors of silent cerebral infarction in apparently normal adults. *Hypertension* 2000;36:73e7.
 89. Rampello L, Alvano A, Battaglia G, et al. Different clinical and evolutionary patterns in late idiopathic and vascular parkinsonism. *J Neurol* 2005;252:1045e9.
 90. Demirkiran M, Bozdemir H, Sarica Y. Vascular parkinsonism: a distinct, heterogeneous clinical entity. *Acta Neurol Scand* 2001;104:63e7.
 91. Winikates J, Jankovic J. Vascular progressive supranuclear palsy. *J Neural Transm Suppl*. 1994;42:189-201.
 92. Jecmenica Lukic M, Kurz C, Respondek G, Grau-Rivera O, Compta Y, Gelpi E, Troakes C; Barcelona Brain Bank collaborative group, the MDS-endorsed PSP study group; van Swieten JC, Giese A, Roeber S, Arzberger T, Höglinger G. Copathology in Progressive Supranuclear Palsy: Does It Matter? *Mov Disord*. 2020 Jun;35(6):984-993.

93. Litvan I, Mangone CA, McKee A, Verny M, Parsa A, Jellinger K, D'Olhaberriague L, Chaudhuri KR, Pearce RK. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. *J Neurol Neurosurg Psychiatry*. 1996 Jun;60(6):615-20.
94. Caslake R, Moore JN, Gordon JC, Harris CE, Counsell C. Changes in diagnosis with follow-up in an incident cohort of patients with parkinsonism. *J Neurol Neurosurg Psychiatry*. 2008 Nov;79(11):1202-7.
95. Inzelberg R, Bornstein NM, Reider I, Korczyn AD. Basal ganglia lacunes and parkinsonism. *Neuroepidemiology* 1994;13:108-112.
96. Bennett DA, Beckett LA, Murray AM, et al. Prevalence of parkinsonian signs and associated mortality in a community population of older people. *N Engl J Med* 1996;334:71-6.

Chapter 10

ANNEXURES

ANNEXURE I: ABBREVIATIONS

NPH	: Normal pressure hydrocephalus
PSP	: Progressive supranuclear palsy
VP	: Vascular parkinsonism
VCI	: Vascular cognitive impairment
PGF	: Progressive gait freezing
PAGF	: Pure akinesia with gait freezing
RS	: Richardson syndrome
MCP	: Middle cerebellar peduncle
SCP	: Superior cerebellar peduncle
M/P	: Midbrain by pons area ratio
MRPI	: Magnetic resonance parkinsonism index
PD	: Parkinson's disease
PIGD	: Postural instability and gait dysfunction
MSA	: Multiple system atrophy
CBS	: Corticobasal syndrome
FTD	: Frontotemporal dementia
DLBD	: Diffuse lewy body disease
SNr	: Substantia nigra
STN	: Subthalamic nucleus
AD	: Alzhiemer's disease
ELD	: External lumbar drainage
L-Dopa	: Levodopa
VPS	: Ventriculo-peritoneal shunt

EI	: Evans index
CAA	: Cerebral amyloid angiopathy
LBP	: Lower body parkinsonism
FOG	: Freezing of gait
HLGD	: Higher level gait disorders
GA	: Gait apraxia
DTI	: Diffusion tensor imaging
CPG	: Central pattern generators
PPN	: Pedunculopontine nucleus
DESH	: Disproportionately enlarged subarachnoid space hydrocephalus
ETV	: Endoscopic third ventriculostomy
LP	: Lumbar puncture
CADASIL	: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CSF 1R	: Colony stimulating factor 1 receptor
ACA	: Anterior cerebral artery
CJD	: Creutzfeldt Jakob disease
NCC	: Neurocysticercosis
ATT	: Anti tubercular therapy
AED	: Anti-epileptic drugs
MMSE	: Mini mental state examination
VGR	: Vertical gaze restriction
SS	: Saccadic slowing
Fz	: Fazekas
PV	: Periventricular

DWM	: Deep white matter
OH	: Orthostatic hypotension
GCA	: Global cortical atrophy
MCI	: Minimal cognitive impairment
LEDD	: Levodopa equivalent daily dose
UL	: Upper limb
LL	: Lower limb
OSA	: Obstructive sleep apnoea
PI	: Postural instability
EOM	: Extra ocular movements
CAD	: Coronary artery disease
DM	: Diabetes mellitus
HTN	: Hypertension
ALS	: Amyotrophic lateral sclerosis
PLS	: Primary lateral sclerosis
SDH	: Subdural hemorrhage
SAH	: Subarachnoid hemorrhage
MRS	: Modified Rankin scale

ANNEXURE II: CASE PROFORMA

Master Chart no:

Age:

Sex:

Presenting Complaints:

Walking difficulty/ Freezing/ Falls/ Postural instability

Cognitive symptoms/ Bladder symptoms

Slowness of activities/ tremors of limbs/ Stiffness of limbs

Bulbar symptoms/ Choking spells/ Emotional Lability

Duration of symptoms at initial presentation:

Past history:

Hypertension/ Diabetes/ CAD/ Dyslipidemia/ Sleep Apnoea

History of Ischemic stroke in the past

Family history:

Similar complaints in family

Recurrent ischemic strokes in family

Personal history:

Smoking/ Tobacco consumption/ Alcohol consumption

Treatment History:

Examination

Vital signs: Any postural drop in BP

Examination of Central Nervous System:

Higher mental functions:

Cognitive examination findings reported: MMSE

Cranial nerves:

Eye movements-

Examination of Bulbar muscles-

Other cranial nerve deficits-

Motor system:

Attitude of limbs-

Bulk/Nutrition-

Tone- Axial:

Appendicular:

Power-

Involuntary movements-

Extrapyramidal system:

Bradykinesia-

Postural Instability-

Change in Gait- Cadence, Stride length, Step height, Gait velocity.

Reflexes:

Superficial reflexes-

Abdominal reflex:

Plantar response:

Deep tendon reflexes-

Sensory system:

Cerebellar signs:

Examination of Other Systems:

Investigations:

CT/ MRI Brain findings-

Ventricular size/ Evans index:

Callosal angle/ DESH/ Disproportionate Cerebral atrophy, Inph Radscale:

Small vessel ischemic changes with Fazekas grading (Leukoaraiosis)/ Multinfarct:

Hummingbird sign/ Morning glory sign/ Midbrain pons ratio/ MRPI:

CSF study (as applicable)-

Diagnosis at first evaluation:

Modified Rankin Scale:

Mode of treatment:

Medical Management-

External Lumbar drainage with VP shunt (as applicable) –

Physiotherapy and others (if any)-

Duration of follow up:

Additional neurological examination findings at last visit:

Diagnosis at last visit:

Functional status at last visit:

ANNEXURE III: IEC APPROVAL LETTER



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)

Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/2056/MAY/2023

19.06.2023

Dr. Hema Krishna P
Post Doctoral Fellow
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Hema Krishna,

The Institutional Ethics Committee held on 20th May, 2023, reviewed and discussed your application to conduct the study titled "CLINICAL PROFILE OF LOWER BODY PARKINSONISM IN A TERTIARY CARE HOSPITAL IN SOUTHERN INDIA- A RETROSPECTIVE OBSERVATIONAL STUDY" (IEC/2056).

The following members of the Ethics Sub-committee were present at the meeting held on 20th May, 2023

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
2.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
3.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
4.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
5.	Dr. P. Manickam	BSMS, MSc (Epid), PhD	Male	Health Science Expert/ Social Scientist	No
6.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Responses/Amendments made based on the Reviewer's comments
2. Checklist Form
3. Covering letter addressed to the Chairman, IEC, SCTIMST dated 08.03.2023
4. Covering letter addressed to the Chairman, IEC, SCTIMST dated 25.04.2023
5. Email consent
6. IEC Application Form
7. Declaration form
8. Project Proposal
9. Proforma
10. CV of PI and Co-PIs
11. SRC Recommendation Letter

Revised submission

1. Copy of IEC Recommendation letter dated 06.06.2023
2. Covering letter addressed to Dr. G Srinivas, Member Secretary, IEC, SCTIMST dated 19.06.2023
3. Responses/Amendments made based on the Reviewer's comments
4. Checklist Form
5. Covering letter addressed to the Chairman, IEC, SCTIMST dated 08.03.2023
6. Covering letter addressed to the Chairman, IEC, SCTIMST dated 25.04.2023
7. Email consent
8. IEC Application Form
9. Declaration form
10. Project Proposal
11. Proforma
12. CV of PI and Co-PIs

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

