



## Pisa syndrome in Idiopathic Normal Pressure Hydrocephalus

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### ABSTRACT

**Introduction:** Idiopathic Normal Pressure Hydrocephalus (iNPH) is a complex syndrome of ventriculomegaly that can include parkinsonian-like features besides the classical triad of cognitive decline, urinary incontinence, and gait/balance disturbances. Pisa syndrome (PS) is a postural abnormality often associated with parkinsonism and defined as lateral trunk flexion greater than 10° while standing that resolves in the supine position. We reported a case series of classical “fixed” PS and one case of “Metronome” recurrent side-alternating PS in iNPH, displaying opposite electromyographic patterns of paraspinal muscles.

**Methods:** Eighty-five iNPH patients were followed longitudinally for at least one year through scheduled clinical and neuropsychological visits.

**Results:** Five (5.9%) subjects revealed PS. None of them had nigrostriatal dopaminergic involvement detected by [123I]FP-CIT SPECT. Among these patients, four had “fixed” PS, whereas one showed a recurrent side-alternating PS which repeatedly improved after ventriculo-peritoneal shunt and following adjustments of the valve-opening pressure of the shunt system.

**Discussion:** This is the first case series of PS in iNPH and the first report of “Metronome” PS in iNPH. The prompt response of the abnormal trunk postures through cerebrospinal fluid (CSF) shunt surgery suggests a causative role of an altered CSF dynamics. PS and gait disorders in iNPH could be explained by a direct involvement of cortico-subcortical pathways and subsequent secondary brainstem involvement, with also a possible direct functional damage of the basal ganglia at the postsynaptic level, due to enlargement of the ventricular system and impaired CSF dynamics. The early detection of these cases supports a proper surgical management.

### 1. Introduction

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a complex syndrome of ventriculomegaly that typically affects the elderly population and is diagnosed by means of clinical and neuroradiological criteria [1,2]. Gait and balance disorders are the leading presentations whereas cognitive decline and urinary incontinence usually appear as disease progresses [1,2]. It is known that motor signs of iNPH can improve after cerebrospinal fluid (CSF) shunt surgery [3,4]. The phenotypic spectrum of iNPH may also be wider, including parkinsonian-like features [5]. It is still unclear whether the latter findings are directly related to iNPH itself or otherwise they are expression of an underlying

neurodegenerative process [6,7]. Nevertheless, the differential diagnosis becomes challenging as it makes difficult to proceed to CSF shunt if iNPH mimics neurodegenerative parkinsonisms such as Lewy Body Dementia or Progressive Supranuclear Palsy [8,9].

The pleurothotonus, commonly referred as Pisa syndrome (PS), is defined as lateral trunk flexion greater than 10° while standing that resolves in the supine position [10]. It is found in advanced Parkinson's disease (PD) and atypical parkinsonisms, above all Multiple System Atrophy (MSA), as well as in iatrogenic forms, e.g. secondary to dopamine receptor blocker drugs, such it is often considered a form of trunk dystonia [11–13]. The pathophysiology of PS remains poorly understood and can probably be multifactorial, involving dysfunction

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of sensorimotor integration, abnormal basal ganglia function, and peripheral abnormalities [12,14]. For instance, in PD there are reports that the asymmetric trunk postures can depend on the asymmetry in the nigrostriatal dopaminergic impairment, so the lateral flexion can result towards the least affected body side and contralateral to the least denervated striatum [15]. Instead, other authors reported no difference in bending between more affected and less affected side [11] or lateral flexion even in the absence of clear asymmetry of parkinsonian signs [16]. The early recognition of PS is crucial to limit the development of structural deformities that can cause severe and irreversible mechanical constraints affecting respiration, mobility, and postural stability [12]. Nevertheless, the management of PS represents a clinical challenge mainly owing to the absence of high-quality and long-lasting response to pharmacological and non-pharmacological treatments, e.g. revision of drug regimen, injection of botulinum toxin type A into the hyperactive trunk muscles, and rehabilitation program [12,14].

Based on our clinical experience on iNPH patients, we report a case series of four classical “fixed” PS and an unusual case of “Metronome” recurrent side-alternating PS in iNPH. Of note, the latter benefited from ventriculo-peritoneal shunt and following adjustments of the valve-opening pressure of the shunt system.

## 2. Methods

Between January 2016 and May 2018, eighty-five iNPH patients were investigated at Parkinson's Disease and Movement Disorders Unit of “Casimiro Mondino” National Neurological Institute in Pavia (Italy). All subjects were followed longitudinally for at least one year through scheduled clinical and neuropsychological visits, which were adapted to clinical needs of the patients. In particular, the one-year follow-up started from baseline visit for iNPH patients who did not undergo shunt and from surgery date for iNPH patients who underwent shunt. The former subjects were followed every six months for the first year and then every year. Instead, the latter patients were visited one, three, six, and twelve months after shunt and then every year. In particular, forty-eight (56.5%) subjects underwent shunt surgery (lumbo-peritoneal shunt in forty patients and ventriculo-peritoneal shunt in eight patients). The impairment in gait, balance, cognitive functions, and sphincter continence was evaluated through iNPH rating scale [17], whereas the severity of eventual contextual parkinsonism was assessed by means of MDS-UPDRS motor section (third part). A response to levodopa (defined as at least 30% improvement in MDS-UPDRS motor section) at the daily dose of 600 mg (t.i.d.) for at least three months was tested in all the subjects. Eventual lateral flexion of the trunk was measured with a wall goniometer. The clinical and demographic characteristics of iNPH patients are displayed in Table 1.

**Table 1**  
Clinical and demographic characteristics of iNPH patients (\*data refer to the first clinical and neuropsychological evaluation). In the iNPH rating scale items, a value of 100 represents normal function and 0 the most severe level of dysfunction. Cognitive impairment was defined by deficit in more than two cognitive domains.

Number	85
Male/Female	47/38
Age at onset (years), mean $\pm$ SD	72.5 $\pm$ 7.7
Motor presentation with higher-level gait disorder and balance disturbances	59 (69.4%)
Motor presentation with parkinsonian-like features	26 (30.6%)
MDS-UPDRS motor section (third part), mean $\pm$ SD*	17.7 $\pm$ 9.2
iNPH rating scale GAIT item, mean $\pm$ SD*	66.8 $\pm$ 17.9
iNPH rating scale BALANCE item, mean $\pm$ SD*	59.4 $\pm$ 15.1
iNPH rating scale NEUROPSYCHOLOGY item, mean $\pm$ SD*	72.3 $\pm$ 14.8
iNPH rating scale CONTINENCE item, mean $\pm$ SD*	59.5 $\pm$ 20.9
Cognitive impairment*	60 (70.6%)
Urinary urgency/incontinence*	65 (76.4%)
Not responders to levodopa	85 (100%)

## 3. Results

In our sample, five (5.9%) subjects revealed PS. Among these patients, four had classical “fixed” PS. In particular, two subjects showed a higher-level gait disorder without appendicular rigidity or bradykinesia, whereas the other two also presented freezing of gait and mild asymmetric hypokinesia/bradykinesia. The degree, orientation, and duration of the “fixed” lateral trunk flexion were respectively: 25°, rightward, lasting for about two years in one subject; 20°, leftward, lasting for about three years in two patients; 15°, rightward, lasting for about two years in the remaining case. Three subjects underwent electromyographic (EMG) analysis of the paraspinal muscles during standing, which demonstrated a hyperactivity of the thoraco-lumbar muscles contralateral to the leaning side (Fig. 1). None of the iNPH patients with PS had nigrostriatal dopaminergic involvement detected by [123I]FP-CIT SPECT. Two subjects underwent lumbo-peritoneal shunt that was followed by gait improvement in both cases and mild PS amelioration in one patient. Particularly, the degree of the rightward lateral trunk flexion changed from 25° to 15°. The shunt response persisted at last follow-up visit, two years after surgery, for both patients. The remaining two subjects refused CSF diversion.

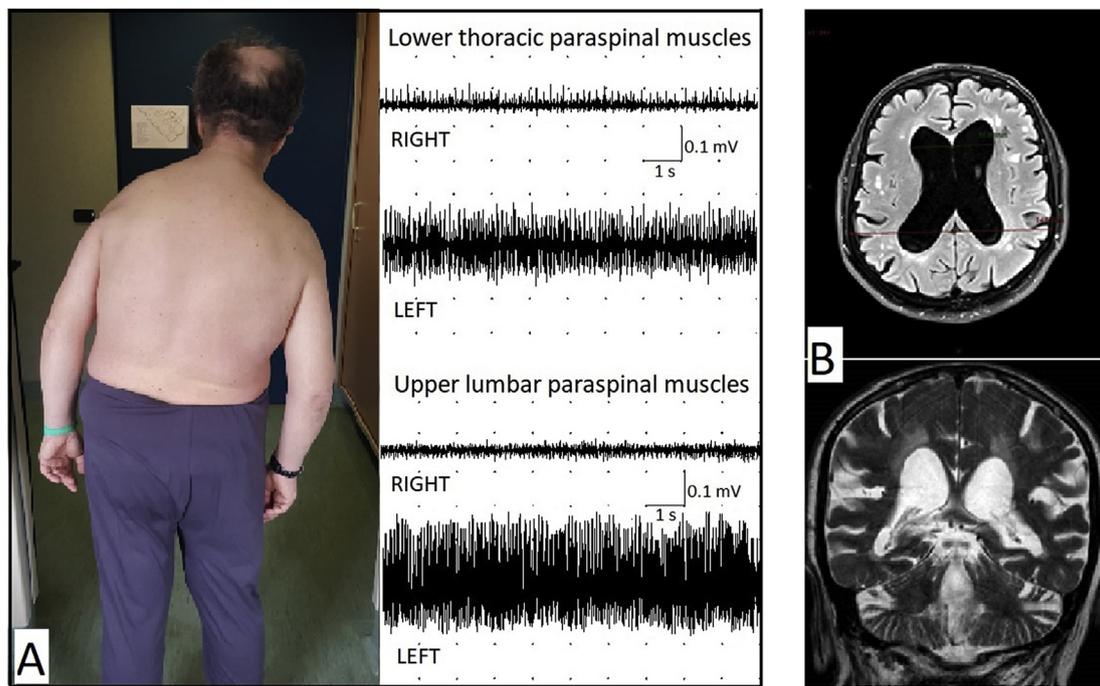
Among iNPH patients with PS, one showed an uncommon PS, which was characterized by recurrent side-alternating lateral trunk flexion. The details of this case are reported below.

### 3.1. Case report

In September 2016, an 81-year-old Italian man came to our attention. Recurrent falls without loss of consciousness or overt epileptic or hypotensive findings were reported for about five years, with recent increase in frequency. In the past two years, the patient showed progressive development of motor slowdown and cognitive deficits, without urinary urgency or incontinence. In the last months, his caregiver noticed fluctuating abnormal upright trunk postures with lateral bending most often rightward, but also leftward. These postural disturbances initially lasted for some minutes, becoming later more prominent and persisting for several hours and days, being present during standing and resolving in supine position. The patient presented well-controlled systemic arterial hypertension and moderate carotid stenosis. He was on antiplatelet therapy in primary prevention. No other pharmacological treatments were ongoing or formerly used.

The neurological examination revealed a parkinsonism, particularly mild hypomimia, moderate rigidity in the neck and symmetrically in the limbs, moderate symmetric hypokinesia and bradykinesia. Gait was wide-based and characterized by symmetric small shuffling steps with reduced arms swing. Occasional evidence of freezing of gait during turning and starting was also noticed. Posture was characterized by moderate PS and mild camptocormia. Repeated clinical evaluations disclosed side-alternating lateral trunk bending during upright position. The trunk deviation was mainly rightward, reaching 20° and lasted for several days during standing, and it was interspersed with leftward trunk bending up to 15° that could last for several hours.

The EMG study of the paraspinal muscles was performed during standing and was characterized by asymmetrical hyperactivity of the thoraco-lumbar muscles on the bending side, i.e. right EMG hyperactivity when bending rightward (Fig. 2A) and left EMG hyperactivity when bending leftward (Fig. 2B). Radiograph scans excluded scoliosis or other important abnormalities of the spine. Due to multiple metallic chips (consequence of an explosion exposure during adolescence without any considerable consequences) he could not perform magnetic resonance imaging. Brain computed tomography scan displayed an enlargement of the supratentorial ventricular system, especially in the posterior portions of the lateral ventricles, in the context of mesial frontal atrophy and moderate cerebral small vessel disease, with Evans' index equal to 0.45, narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface with dilatation of the sylvian

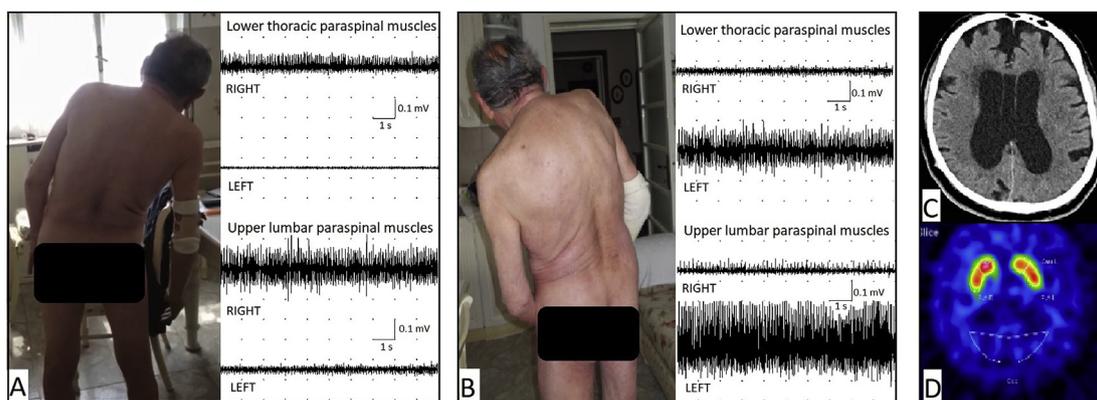


**Fig. 1.** iNPH patient with “fixed” Pisa syndrome, presenting a rightward trunk bending. **A** Two-channels needle EMG recording of lower thoracic paraspinal muscles (top panel) and upper lumbar paraspinal muscles (bottom panel), showing hyperactivity on the left side (hyperactivity of trunk muscles contralateral to the leaning side). **B** Axial FLAIR MRI scan (top panel), displaying dilated lateral ventricles (Evans’ index 0.41), and coronal T2 MRI scan (bottom panel), revealing acute callosal angle and disproportionately enlarged subarachnoid space hydrocephalus (DESH).

fissures (i.e. disproportionately enlarged subarachnoid spaces), an acute callosal angle (78°), no macroscopic obstruction to CSF flow (Fig. 2C). The patient also underwent [123I]FP-CIT SPECT scan, which was performed by FAN-BEAM collimator, with 360° rotation arc (1fr/4°/45sec). Transaxial sections (with 5.79 mm slice thickness) parallel to the orbitomeatal plan were obtained by the tomographic images. Qualitative analysis of the scintigraphic examination was confirmed by semiquantitative investigation. It did not show presynaptic nigrostriatal dopaminergic depletion (Fig. 2D). The neuropsychological evaluation showed multiple-domain cognitive impairment, mainly involving the logical, executive, and attentive functions.

No significant response during three months therapy with levodopa 600 mg per day was obtained. Instead, an improvement of motor performances, freezing of gait, and a clear reduction of PS were achieved after CSF tap-test (large volume lumbar puncture) (Fig. 3A). The CSF opening pressure was 150 mmH<sub>2</sub>O. In keeping with iNPH International

Guidelines [1] and iNPH Japanese Guidelines [2], a probable diagnosis of iNPH was made. A month later, the patient underwent ventriculo-peritoneal shunt with the Codman-Hakim programmable valve system, set to 140 mmH<sub>2</sub>O. After surgery, he showed a marked motor improvement, in terms of increase of the step width without freezing of gait and reduced lateral trunk bending until almost normalization of the upright posture (Fig. 3B). No other falls were reported since. By contrast, no cognitive gain was observed during the following neuropsychological evaluations. Six months later, the patient exhibited postural and gait worsening, with recurrence of side-alternating PS and freezing of gait. After evaluation of the correct functioning of the shunt system, the valve-opening pressure was lowered to 120 mmH<sub>2</sub>O, with subsequent almost immediate improvement of gait and reduction until disappearance of PS. This motor benefit lasted for five months. Later, a gradual worsening of gait and posture was reported, with the re-appearance of freezing of gait and side-alternating PS. Once more these



**Fig. 2.** iNPH patient with “Metronome” Pisa syndrome. **A-B** Two-channels needle EMG recording of lower thoracic paraspinal muscles (top panel) and upper lumbar paraspinal muscles (bottom panel), showing right hyperactivity when bending rightward (**A**) and left hyperactivity when bending leftward (**B**) (hyperactivity of trunk muscles ipsilateral to the bending side). **C** Axial CT scan, displaying dilated lateral ventricles (Evans’ index 0.45). **D** [123I]FP-CIT SPECT scan, showing preserved presynaptic nigrostriatal dopaminergic system.



**Fig. 3.** iNPH patient with “Metronome” Pisa syndrome. Clear reduction of Pisa syndrome until almost normalization of the upright posture after CSF tap-test (A) and after ventriculo-peritoneal shunt (B).

features were responsive to the lowering of the valve-opening pressure of the shunt system, which was set to 110 mmH<sub>2</sub>O. After this adjustment the patient displayed a sustained clinical benefit, which carried on the last follow-up visit (thirteen months after last change of the valve-opening pressure).

#### 4. Discussion

To the best of our knowledge, this is the first case series of PS in iNPH patients. Moreover, we described the first report of side-alternating PS, the so-called “Metronome syndrome”, in iNPH, with optimal response to CSF tap-test and subsequent ventriculo-peritoneal shunt, whereas successive recurrences of PS were well treated with lowering of the valve-opening pressure of the shunt system. PS disappearance after CSF tap-test or shunt surgery with further gait, balance and behavioral improvement was so far only described in two “juvenile cases” of Normal Pressure Hydrocephalus [18,19]. These two young patients also presented parkinsonism, which was instead detected in two out of four subjects with “fixed” PS and in the patient with “Metronome” PS in our case series. Of note, the age of the two juvenile case reports is rather atypical and it does not support a diagnosis of iNPH [1,2]. Moreover, the age of our patients with PS was comparable to that of subjects without PS. In our case series iNPH patients revealed PS in 5.9%. This occurrence is only slightly lower than the prevalence rate of PS in PD (8.8% as reported by Tinazzi and colleagues [11]) and definitely lower than revealed in MSA with a predominant parkinsonian phenotype (42% as indicated by Köllensperger and collaborators [13]). There are reports of Metronome PS as a form of tardive dystonia under clozapine treatment [20] and in PD [21,22].

In our case report of iNPH patient with “Metronome” PS the EMG assessment of the paraspinal muscles disclosed an alternating asymmetric hyperactivity on the bending side, which is not the sole EMG pattern identified in PS. In fact, within our case series of iNPH subjects with classical “fixed” PS, three presented an opposite EMG paraspinal pattern, i.e. hyperactivity of the thoraco-lumbar muscles contralateral to the leaning side, a probable compensation for the trunk deviation. These different EMG patterns have been reported in several studies and they overlap with data concerning PS in different neurological diseases, above all PD [15,23,24]. A possible explanation could be based on the chronological course of PS. When it is acute, subacute or intermittent, the prevalent EMG paraspinal pattern could be the hyperactivity on the bending side. Conversely when it is chronic, the dominant EMG paraspinal pattern could be the opposite, i.e. hyperactivity contralateral to the leaning side, thus possibly underlying a compensatory mechanism. In our case report the EMG hyperactivity on the bending side could be

indeed explained by the side-alternating course of PS, then transient considering each trunk side.

The pathogenesis of PS is unclear. In PD, PS development has been correlated to an imbalance in the dopaminergic-cholinergic system and to the progression of the underlying disease [12,14]. This hypothesis is based on the observation of a correspondence between the side of the lateral trunk bending, the contralateral most affected body side and the ipsilateral dominant nigrostriatal denervation [12,14,15]. However, such explanation cannot be taken into account in our cases series of iNPH with PS because of their preserved dopaminergic nigrostriatal system.

The prompt response of the abnormal trunk postures of the iNPH patient with “Metronome” PS through CSF shunt surgery and reductions of the valve-opening pressure suggests a causative role of an altered CSF dynamics. Sudden sharp fluctuations in the intraventricular CSF pressure could explain the wide and variable phenomenology, including side-alternating PS.

A possible direct functional involvement of the supplementary motor area with a consequent impairment of cortical motor programming was suggested in the development of the postural and gait disturbances in iNPH [25]. A possible direct damage of the basal ganglia at the postsynaptic level, as seen in studies revealing striatal hypometabolism through [18F]FDG PET-CT [26] and postsynaptic D2 receptor reduction through [11C]raclopride PET-CT [27], due to enlargement of the ventricular system and altered CSF dynamics in iNPH, was thought to be another underlying pathophysiological mechanism [21].

An impaired CSF dynamics can result in excessive mechanical tension of periventricular fibers, which contribute to cortico-spinal and cortico-striato-thalamic pathways. Such mechanical stress may also alter the activity of deep subcortical structures, such as the pedunculo-pontine nucleus (PPN). Thereby in iNPH a severe and direct involvement of cortico-subcortical circuits, primarily causing typical clinical manifestations, can subsequently induce a secondary brainstem involvement, e.g. parkinsonian-like features and postural abnormalities such as PS. According to the role played by PPN in postural settings [28], its strategic position in the dorsal tegmentum of the midbrain and upper pons, and its diffuse innervations, the mechanical overstretch determined by the impaired CSF dynamics might alter PPN axons activity, thus possibly affecting its function. In particular, the dysfunction of ascending thalamic cholinergic projections from PPN could impair postural control, therefore possibly explaining the peculiar postural abnormalities seen in our case series of iNPH patients with PS. In line, the alteration of PPN connections with the spine and the basal ganglia might account for gait impairment and other parkinsonian-like features. According to a possible role of the mesencephalic locomotor region in the phenomenology of gait and postural abnormalities in iNPH, there are reports of increase of the diameters of the midbrain [29] and disappearance of the “hummingbird sign” [30] in iNPH after shunt surgery. These features can be explained by an improvement of the CSF dynamics with a reduction in the CSF in the lateral and third ventricles, then a lower compression of the superior surface of the midbrain tegmentum.

Whatever the mechanisms that cause PS in iNPH, its early detection supports a proper surgical management that can lead to a stable resolution of the postural abnormalities.

#### Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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parkinsonism and dementia: improving the accuracy of diagnosis and the patient care to reverse the symptomatology. Neurodegeneration, phenotypes and outcome measures”).

None of the funding sources had any influences on the study protocol, interpretation of results, writing of this paper or decision to submit the paper for publication.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Author contributions

Massimiliano Todisco: study concept and design; acquisition of data; analysis and interpretation; drafting the manuscript; final approval of the version to be submitted.

Nicolò Gabriele Pozzi: critical revision of the manuscript for important intellectual content; final approval of the version to be submitted.

Roberta Zangaglia: acquisition of data; final approval of the version to be submitted.

Brigida Minafra: acquisition of data; final approval of the version to be submitted.

Domenico Servello: acquisition of data; final approval of the version to be submitted.

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Enrico Alfonsi: acquisition of data; critical revision of the manuscript for important intellectual content; final approval of the version to be submitted.

Alfonso Fasano: critical revision of the manuscript for important intellectual content; final approval of the version to be submitted.

Claudio Pacchetti: study concept and design; study supervision; analysis and interpretation; critical revision of the manuscript for important intellectual content; final approval of the version to be submitted.

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