[123I]IOFLUPANE SPECT AND CLINICAL FEATURES IN EARLY IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS: COMPARISON WITH NEWLY DIAGNOSED PARKINSON'S DISEASE

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Background: Idiopathic normal pressure hydrocephalus (iNPH) is a chronic neurological disorder typically affecting the elderly population and usually presenting with dementia, urinary incontinence, and gait/balance disturbances in the classic description made by Hakim and Adams. However, not all patients show this triad of symptoms. The phenotypic spectrum of iNPH may also be wider, including extrapyramidal parkinsonian-like features. Although a nigrostriatal dopaminergic impairment evaluated by [123I]Ioflupane ([123I]FP-CIT) SPECT is considered absent in iNPH, in many patients it can be present. To date, it is still unknown whether this is an inevitable event in the evolution of iNPH or it identifies a particular subtype of pathology. There is a conspicuous lack of information concerning the outcome and mostly the proper therapy in this group of patients. This condition is probably understimated because the diagnosis is challenging and requires skilled specialists. The pathophysiology of parkinsonian symptoms in iNPH has not been conclusively understood. The abnormal pulsation of cerebrospinal fluid flow occurring in iNPH may produce secondary damage to the nigrostriatal dopaminergic pathway and a downregulation of dopamine 2 receptors in the striatum.
We compared [123I]FP-CIT SPECT and clinical findings in early iNPH versus newly diagnosed Parkinson's disease (PD) to detect possible differences.

Methods: We examined thirty early iNPH patients with positive [123I]FP-CIT SPECT and thirty patients with newly diagnosed PD. We then evaluated [123I]FP-CIT SPECT tracer uptake values, MDS-UPDRS part 3 total and single items scores, and levodopa response between the two patients groups.
The scintigraphic images were obtained by tomographic acquisition three hours after intravenous administration of the radiopharmaceutical. The investigation was performed by FAN-BEAM collimator, with 360° rotation arc (1 fr/4° /45 sec). 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.
The following normal [123I]FP-CIT SPECT tracer uptake values were employed: 3.02 ± 0.56 for putamen; 3.64 ± 0.53 for caudate nucleus; 0.83 ± 0.07 for putamen/caudate ratio.

Results: Compared to newly diagnosed PD, early iNPH patients with positive [123I] FP-CIT SPECT have:

- **not significant asymmetric** (p=0.226 for putamen, p=0.273 for caudate nucleus in early iNPH; p=0.008 for putamen, p=0.012 for caudate nucleus in newly diagnosed PD) **and generally lower nigrostriatal dopaminergic impairment** (p=0.017 for more affected putamen, p=0.024 for contralateral putamen; p=0.018 for more affected caudate nucleus, p=0.027 for contralateral caudate nucleus);
- **lower difference in [123I]FP-CIT SPECT tracer uptake values between putamen and caudate nucleus** (p=0.017 for putamen/caudate ratio);
- **a prevalent bradykinetic-rigid phenotype** (93%), with tremor-dominant subtype in the remaining patients;
- **more symmetric extrapyramidal motor signs**;
- **no correlation between MDS-UPDRS part 3 total score and nigrostriatal dopaminergic impairment** (rho: 0.132, p=0.259 in early iNPH; rho: 0.642, p=0.022 in newly diagnosed PD);
- **no significant levodopa response** (under 30% improvement).

Finally, we underlined a predominant PD-like gait phenotype in 17 (57%) early iNPH patients with positive [123I]FP-CIT SPECT, whereas a typical gait apraxia is more relevant in the remaining iNPH cases.

	EARLY INPH WITH POSITIVE [123I]FP-CIT SPECT	NEWLY DIAGNOSED PD
[123I]FP-CIT SPECT TRACER UPTAKE VALUES	***Lower difference between putamen and caudate nucleus, not significant asymmetric and generally higher***	***Higher difference between putamen and caudate nucleus, significant asymmetric and generally lower***
more affected putamen	*1.96 ± 0.48*	*1.51 ± 0.17*
contralateral putamen	*2.09 ± 0.40*	*1.81 ± 0.19*
more affected caudate	*2.59 ± 0.39*	*2.27 ± 0.38*
contralateral caudate	*2.69 ± 0.37*	*2.51 ± 0.41*
putamen/caudate ratio	*0.79 ± 0.12*	*0.68 ± 0.09*
EXTRAPYRAMIDAL MOTOR PHENOTYPE	***Prevalent bradykinetic-rigid phenotype (93%), more symmetric***	***Bradykinetic-rigid (67%) or Tremor-dominant (33%) subtypes, asymmetric***
CORRELATION BETWEEN MDS-UPDRS PART 3 SCORE AND [123I]FP-CIT SPECT TRACER UPTAKE VALUES	***No***	***Yes***
MDS-UPDRS part 3 score	*17.17 ± 8.34*	*7.21 ± 3.19*
SIGNIFICANT LEVODOPA RESPONSE	***No***	***Yes***
GAIT PHENOTYPE	***Predominant PD-like in 57%, and more relevant gait apraxia in the remaining cases***	***Predominant PD-like***

Conclusions: Our preliminary findings of a distinct pattern of nigrostriatal impairment in early iNPH, compared to newly diagnosed PD, might suggest a different significance of the neurodegenerative dopaminergic component and/or a pathogenesis other than truly degenerative one.
Despite greater global motor clinical deficits, early iNPH patients with positive [123I]FP-CIT SPECT have lower nigrostriatal impairment. This feature could be explained by a severe and direct involvement of corticostriatal pathway, primarily causing clinical manifestations. In this view, the secondary impairment of nigrostriatal network could be related to a symmetric axonal "dying-back" degeneration starting from striatum. The dopaminergic deficiency would then be secondary, not primitive.
iNPH patients with positive [123I]FP-CIT SPECT don't significantly benefit from dopamine oral therapy. Their outcome of shunt surgery may be different. Therefore, an accurate clinical examination and a baseline [123I]FP-CIT SPECT are of primary emphasis. The identification of a possible neurodegenerative process should always be sought in the clinical practice.
Clinical phenotype and integrity/damage of the nigrostriatal pathway could be important variables to evaluate and predict the effects deriving from shunt surgery, then correct diagnosis and treatment can become more challenging in iNPH patients with positive [123I]FP-CIT SPECT.

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XLVIII CONGRESSO NAZIONALE
14-17 OTTOBRE 2017 – NAPOLI
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