Self-rated non motor symptoms burden grading identifies landmarks and nonmotor subtypes of Parkinson's disease: First reports from a Moscow-Madrid-London collaboration

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OBJECTIVE

To evaluate clinical and surrogate imaging biomarkers of nonmotor symptoms (NMS) burden (NMSB) as defined by NMS questionnaire (NMSQ) scores in an ongoing prospective international cohort study of Parkinson's disease (PD).

METHODS

179 consecutive patients (68.5±11.4 yrs) have been studied (disease duration 7.29±6.85 yrs, 7% drug-naive, median Hoehn & Yahr [HY], 2) as part of an international collaboration. Measures of motor state, sleep, depression, anxiety, health-related quality of life (HRQoL), dopamine transporter scan (DaTscan in a subset) and olfaction (Sniffin sticks) were collected.

BACKGROUND

NMS are integral to PD and NMSB grading is now validated using NMSQ which is recommended by the MDS and other learned societies and PD charities (Chaudhuri et al., PRD 2013) (Table 1). Relationship of self-declared NMSB with objective surrogate biomarkers of PD to help define subtypes has not been studied before.

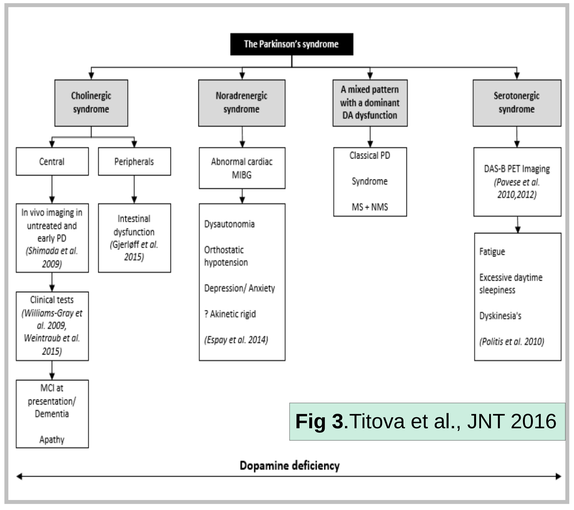

Fig 3.Titova et al., JNT 2016

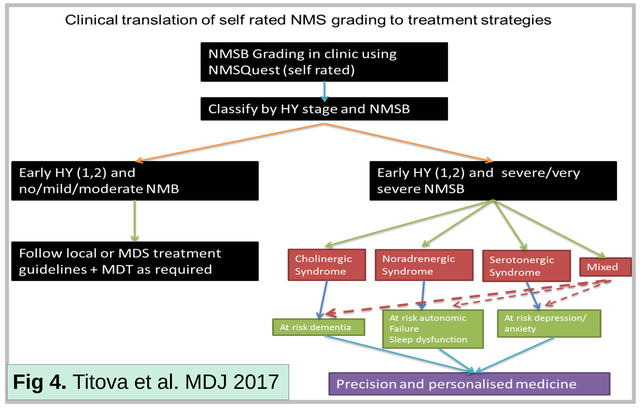

Fig 4. Titova et al. MDJ 2017

Editorial Parkinson's Disease — Titova et al. ENR. 2017

The Future of Parkinson's Treatment – Personalised and Precision Medicine

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References:
Chaudhuri et al. PRD. 2013
Ttova et al. J Neural Trans 2016
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Sauerbier et al. PRD 2015

RESULTS

17% were NMSB mild, 30% moderate, 26% severe, and 26% very severe NMSB. 12% had very severe and 16% severe NMSB in spite of mild HY state. Motor dysfunction (HY) was worse in very severe NMSB. Significant deterioration of NMSB was seen with anxiety (mild 6.1 vs very severe 11) and QoL (mild 5.1 vs very severe 16). PD sleep scale total score worsened significantly with increasing NMSB. However, DATscan putamen uptake ratios were not significantly different between NMSB (Table 1) in contrast to HY (Table 2). Olfaction was significantly worse in very severe (70%) vs severe (32%), moderate (17%) and mild (13%) (Fig 2). Autonomic domain NMSQ was abnormal in severe and very severe NMSB.

RESULTS

Table 1: Putamen binding ratios and NMSB showing no correlation

NMSQ burden score	NMSB	N	DATscan Uptake ratio (normal King's Range>2)	
			Right Putamen	Left Putamen
0-5	Mild	31(17%)	0.93	0.96
6-9	Moderate	54(30%)	1.06	1.14
10-13	Severe	47(26%)	0.75	0.70
>13	Very Severe	47(26%)	0.92	1.01

NMS = *nonmotor symptoms;* NMSB = *NMS Burden*

Table 2: Hoehn & Yahr (HY) and Dat binding ratios. Lower scores with advancing HY

	HY 1-2	HY 3	HY 4
Right Striatum	1.79	1.16	0.39
Left Striatum	1.81	1.62	0.64
Right Caudate	2.55	1.53	0.56
Left Caudate	2.22	1.84	0.80
Right Putamen	1.09	0.77	0.26
Left Putamen	1.37	1.34	0.50

Figure 1: Motor and nonmotor characteristics in Severe (S-NMSB) and very severe (VS-NMSB) NMS burden cases with mild HY stage.

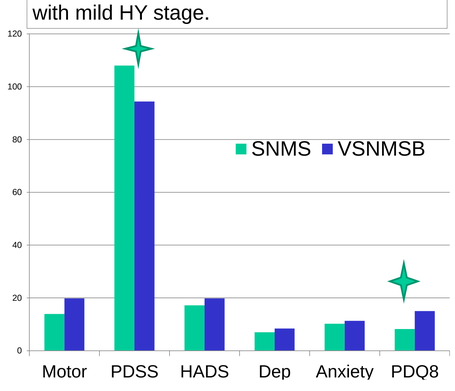
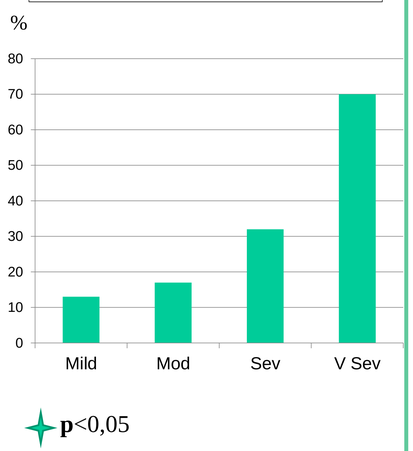


Figure 2: NMSB and Olfaction



CONCLUSION

- This ongoing prospective cohort study using self reported NMSQuest supports the concept of heterogeneous non motor presentation of PD. Early motor state (indicated by HY stages 1,2) but with severe or very severe NMSB (Fig 1) indicate endophenotypes of PD driven by NMS. Mild HY with very severe NMSB have worse QoL, sleep, anxiety and depression and olfaction with dysautonomia (Fig 1).
- While HY stage correlates with DaT putaminal binding ratio, NMSB grading appears not to correlate (Table 2) further supporting a nondopaminergic origin of the NMS.
- Clinical and imaging biomarker supported specific neurotransmitter driven subtypes have been proposed (Fig 3) and our subtype (early HY with very severe NMSB) may belong to the noradrenergic subtypes described by Sauerbier et al, 2016 and Titova et al., 2016. (Fig 3)
- In such patients subtype specific personalised medicine based treatment strategies need to be considered (Titova and Chaudhuri, 2017) (Fig 4).

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