Parkinsonism and Related Disorders 58 (2019) 1–2

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Is neuromelanin the imaging biomarker for the early diagnosis of Parkinson's disease that we were looking for?

Neuromelanin is a granular dark pigment that is normally found in the human brain in the dopaminergic neurons of the substantia nigra pars compacta (SNc) and noradrenergic neurons of the locus coeruleus (LC). It is thought to result from the autooxidation process of dopamine derivatives in these neurons, although other alternative mechanisms have been proposed [1].

While in healthy brain neuromelanin concentration in the SNc and LC neurons increases over time [2], numerous neuropathological studies have demonstrated that the content of this pigment in these regions is reduced in neurodegenerative diseases, such as Parkinson's disease (PD) and other parkinsonian syndromes characterised by nigral neuronal loss [1,3]. Additionally, in patients with PD, the concentration of neuromelanin in the SNc appears to further decrease with disease progression [1]. Therefore, in recent years, there has been a growing interest in developing novel imaging techniques to enable the *in vivo* assessment of brain neuromelanin content with the hope that this could serve as a robust imaging biomarker to improve the early diagnosis of PD and possibly to allow longitudinal assessments of disease progression.

Since neuromelanin exhibits paramagnetic properties when combined with metals such as copper and iron, neuromelanin containing regions are detected as distinct high-intensity areas on MRI T1-weighted fast spin-echo sequences acquired at high magnetic fields. These neuromelanin sensitive MRI sequences are easily implemented also on 3 T MRI scanners and, therefore, in the last ten years, neuromelanin-sensitive MRI (NM-MRI) has been increasingly employed to assess patients with PD in several research centres worldwide. The published studies have reliably demonstrated significant reductions in the neuromelanin-related signal in the SNc of PD brains, providing high diagnostic accuracy for differentiating PD patients from healthy controls [4]. Furthermore, NM-MRI could also be potentially useful in the differentiation of idiopathic PD from Essential Tremor (ET), as well as other types of Parkinsonism. However, there have been only a few studies performed in patients with atypical Parkinsonism, which have demonstrated conflicting results [4], and only one study has compared PD with ET patients [5].

In the clinical setting, differentiating between PD, especially tremor-dominant PD (PDT), and ET can be particularly challenging in early stages of disease, even in specialist Movement Disorder Clinics. One clinical study has reported that one-third of patients who received an initial diagnosis of ET were misdiagnosed, with PD being the most common final diagnosis [6]. Several factors can explain this diagnostic uncertainty. PDT patients often have very mild or absent bradykinesia and rigidity, and a recent investigation of the clinical characteristics of a large cohort of recently diagnosed PD cases with abnormal DaTSCAN has shown that over 20% of patients presenting with tremor did not exhibit resting tremor [7].

To make matters more complicated, about 18% of ET patients, especially those with long disease duration, experience tremor at rest, and bradykinesia and rigidity can also be detected in these patients [8]. Additionally, a community-based study has shown that patients with ET had a fourfold to fivefold increased risk of developing PD compared with controls over a 3.3-year follow-up, suggesting that patients with long-standing ET might have co-occurrence of the two diseases [9].

The advent of a commercially available SPECT ligand ([^{123}I]-FP-CIT, DaTSCAN) to visualize dopamine transporter function in the striatum has increased our diagnostic accuracy in patients with an uncertain diagnosis. [^{123}I]-FP-CIT SPECT imaging has been reported to have 97% sensitivity for the clinical diagnosis of Parkinsonism and 100% specificity for ET [10]. However, [^{123}I]-FP-CIT SPECT has a number of limitations. It is still not available worldwide and there are risks associated to the exposure to ionising radiation. Additionally, it has low specificity and sensitivity to differentiate PD from atypical parkinsonian syndromes, such as multiple system atrophy and progressive supranuclear palsy [11], and it is still debated if it is a suitable surrogate marker of disease progression [12]. NM-RMI could overcome all these limitations and this explains why this technique has recently raised so much interest in both research and clinical settings.

Wang and colleagues [13] used NM-MRI to assess whether PDT patients and patients with ET have different patterns of neuromelanin content in the SNc compared with age-matched controls and whether this could be useful in differentiating these two conditions early is the disease process. Importantly, both groups of patients were untreated, thus eliminating the risk of potential confounding effects of medications on the MRI findings. Another strength of the study is that the authors performed both quantitative measurements (SNc width and contrast-to-noise ratio, CNR) and visual analysis of the SNc high signal intensity on NM-MRI images. Receiver Operating Characteristic (ROC) analysis and the more sensitive Net Reclassification Improvement (NRI) were then used to investigate which NM-MRI parameters better discriminated the PDT group from the ET group.

In line with previous published studies [4], three different SNc sub-regions (lateral, central and medial) were identified. Compared with age-matched controls and the ET patients, PDT patients, as a group, were found to have a significant decrease in the width and in the contrast-to-noise ratio (CNR) values of the lateral and central sub-regions of the SNc. Similarly, when using the visual approach, the total visual score of all SNc sub-regions was significantly reduced in PDT compared with controls, but this was not the case in the ET group.

The best differentiation between ET and PDT was achieved with the

https://doi.org/10.1016/j.parkreldis.2018.12.013
Received 12 December 2018; Accepted 12 December 2018

width of the lateral sub-region SNc. However, a good diagnostic value was also achieved with visual analysis alone. In fact, NRI analysis indicated that visual analysis and the width of the lateral SNc sub-region had similar diagnostic power.

The sample size of this study is relatively small with approximately 20 patients included in each group. Additionally, the analysis of individual patients was not performed and it is, therefore, unclear if this technique is able to identify patients with an abnormal SNc neuromelanin pattern at an individual level. Nevertheless, if confirmed in larger cohorts of patients, the results of this study are very promising, as they suggest that patients with ET and PDT can be differentiated on the basis of their SNc neuromelanin pattern on NM-MRI imaging. Moreover, it appears that a simple visual analysis of NM-MRI images is nearly as good as the quantitative measures to provide high diagnostic accuracy for distinguishing ET from the PDT subtype, making it a relatively simple tool to be used in clinical practice.

It has to be acknowledged that this is not the first NM-MRI study to compare SNc neuromelanin patterns in patients with PD and ET. Reimao and colleagues [5] have previously reported that, compared with age-matched healthy controls, PD patients, but not ET patients, had marked decreases in the area and width of the T1 high signal in the SN region, particularly in its ventrolateral segment. However, the study by Wang and colleagues is the first to compare ET patients with PD patients with a tremor-predominant phenotype who in the clinical setting pose the most difficult diagnostic challenge in the early stages of disease often leading to misdiagnosis.

One possible weakness of this study is that patients were enrolled in the study based on their current clinical diagnosis and there was no gold standard for the final diagnosis. Therefore, there is a potential risk of misdiagnosis. If performed in these patients, molecular imaging of the striatal pre-synaptic dopaminergic function would have strengthened the clinical diagnostic accuracy of these patients and could have been an appropriate comparator to assess the diagnostic value of NM-MRI. Further studies are requested to address this issue. However, when compared with data available in the medical literature, NM-MRI seems to have slightly lower diagnostic sensitivity and specificity than DaTSCAN [10] to differentiate PD from ET (NM-MRI: sensitivity and specificity 90.5% and 83.3%, respectively, when the cutoff value for the width of lateral sub-region was set as 0.525 mm; DaTSCAN overall sensitivity and specificity of 96%), but slightly higher than transcranial sonography (sensitivity and specificity 78% and 85% respectively) [14]. Transcranial sonography has the further limitation that 10% of people have no temporal bone window and, therefore, the examination cannot be carried out. Additionally, the typical midbrain hyperechogenicity observed in PD patients does not change with disease progression, and therefore cannot be used as a marker of disease progression.

In conclusion, the study by Wang and colleagues [13] adds further weight to the view that NM-MRI could provide a reliable imaging biomarker of nigral pathology/abnormalities in PD. This could not only be potentially useful to differentiate PD from ET, but also in distinguishing PD from other Parkinsonian syndromes. However, it should be acknowledged that further investigations are required in the field. In particular NM-MRI should be tested in large longitudinal cohorts of patients. It is quite surprising that so far only small cohorts of patients have been published, despite NM-MRI having been available in a number of centres for more than a decade. It is also essential to reach expert consensus on technical guidelines for the use of NM-MRI as diagnostic and progression markers in PD, including technical standards, imaging protocols, and methods of analysis. This will allow multicenter data collection and lead to a better validation of NM-MRI as an effective marker of dopamine cell loss in PD and related disorders.

References

[1] L. Zecca, D. Tampellini, M. Gerlach, P. Riederer, R.G. Fariello, D. Sulzer, Substantia nigra neuromelanin: structure, synthesis, and molecular behaviour, Mol. Pathol. 54 (6) (2001 Dec) 414–418.

[2] D.M.A. Mann, P.O. Yates, Lipoprotein pigments—their relationship to ageing in the human nervous system. II. The melanin content of pigmented nerve cells, Brain 97 (1974) 489–498.

[3] B. Pakkenberg, A. Møller, H.J. Gundersen, A. Mouritzen Dam, H. Pakkenberg, The absolute number of nerve cells in substantia nigra in normal subjects and in patients with Parkinson's disease estimated with an unbiased stereological method, J. Neurol. Neurosurg. Psychiatry 54 (1) (1991) 30–33.

[4] N. Pavese, Y.F. Tai, Nigrosome imaging and neuromelanin sensitive MRI in diagnostic evaluation of parkinsonism, Mov. Disord. Clin. Pract. 5 (2) (2018 Feb 22) 131–140.

[5] S. Reimão, P. Pita Lobo, D. Neutel, L.C. Guedes, M. Coelho, M.M. Rosa, P. Azevedo, J. Ferreira, D. Abreu, N. Gonçalves, R.G. Nunes, J. Campos, J.J. Ferreira, Substantia nigra neuromelanin-MR imaging differentiates essential tremor from Parkinson's disease, Mov. Disord. 30 (7) (2015) 953–959.

[6] S. Jain, S.E. Lo, E.D. Louis, Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? Arch. Neurol. 63 (8) (2006) 1100–1104.

[7] J. Pasquini, R. Ceravolo, Z. Qamhawi, J.Y. Lee, G. Deuschl, D.J. Brooks, U. Bonuccelli, N. Pavese, Progression of tremor in early stages of Parkinson's disease: a clinical and neuroimaging study, Brain (2018 Jan 22), https://doi.org/10.1093/brain/awx376.

[8] 0 Cohen, S. Pullman, E. Jurewicz, D. Watner, E.D. Louis, Rest tremor in patients with essential tremor: prevalence, clinical correlates, and electrophysiologic characteristics, Arch. Neurol. 60 (3) (2003) 405–410.

[9] J. Benito-León, E.D. Louis, F. Bermejo-Pareja, Neurological Disorders in Central Spain Study Group Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study, J. Neurol. Neurosurg. Psychiatr. 80 (4) (2009) 423–425.

[10] H.T.S. Benamer, J. Patterson, D.G. Grosset, J. Booij, K. de Bruin, E. van Royen, J.D. Speelman, M.H.I.M. Horstink, H.J.W.A. Sips, R.A. Dierckx, J. Versijpt, D. Decoo, C. Van Der Linden, D.M. Hadley, M. Doder, A.J. Lees, D.C. Costa, S. Gacinovic, W.H. Oertel, O. Pogarell, H. Hoeffken, K. Joseph, K. Tatsch, J. Schwarz, V. Ries, Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123 I]-FP-CIT SPECT imaging: the [123 I]-FP-CIT study group, Mov. Disord. 15 (3) (2000) 503–510.

[11] A.M. Vlaar, M.J. van Kroonenburgh, A.G. Kessels, W.E. Weber, Meta-analysis of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes, BMC Neurol. 7 (2007) 27.

[12] G. Pagano, N. Ferrara, D.J. Brooks, N. Pavese, Age at onset and Parkinson disease phenotype, Neurology 86 (15) (2016) 1400–1407.

[13] J. Wang, Z. Huang, Y. Li, F. Ye, C. Wang, Y. Zhang, X. Cheng, G. Fei, K. Liu, M. Zeng, C. Zhong, L. Jin, Neuromelanin-sensitive MRI of the substantia nigra: an imaging biomarker to differentiate essential tremor from tremor-dominant Parkinson's disease, Parkinsonism Relat Disord, 2018.

[14] A. Shafieesabet, S.M. Fereshtehnejad, A. Shafieesabet, A. Delbari, H.R. Baradaran, R.B. Postuma, J. Lökk, Hyperechogenicity of substantia nigra for differential diagnosis of Parkinson's disease: a meta-analysis, Park. Relat. Disord. 42 (2017) 1–11.

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