UK PARKINSON'S Excellence Network

Which neurogenetic parkinsonian conditions produce an abnormal DaTSCAN?

Appraised by Kevin Galbraith, 11 February 2016

Update due 2019

Clinical question

Among the genetic conditions presenting with parkinsonian symptoms, which of them are associated with an abnormal DaTSCAN?

Background

5% to 10% of Parkinson's cases are associated with mutations in a range of genes.[1]

Furthermore, with recent advances in genetics, new atypical parkinsonian conditions are emerging that may share some clinical features with the classical presentation of progressive supranuclear palsy (PSP), corticobasilar degeneration (CBD), and multiple system atrophy (MSA), and have been described as PSP, CBD, or MSA look-alikes. This CAT looks at which of these genetic conditions we would expect to produce an abnormal DaTSCAN.

Clinical bottom line

A number of genetic conditions present with parkinsonian symptoms. The literature provides few attempts to collate the DaTSCAN findings. Only two such studies were found – one based on strong evidence, and the other dependent on the opinion of the authors. Both are summarised and appraised here.

Search terms

(Ioflupane OR FP-CIT OR DaTSCAN OR DaTscan OR DaT-SPECT OR dopaminergic imaging) AND (prognosis OR therapeutic response)

Search strategy

Ovid Medline, adapted for Embase and Cochrane Library from 1996 to February 2016.

Evidence

The search yielded 103 articles. Of these, two were relevant: a chart review to assess DaTSCAN findings in a large sample of patients with genetic Parkinson's,[1] and a narrative review characterising the features of genetic PSP/CBD/MSA look-alike conditions.[2] Both articles were critically appraised:

McNeill A, Wu R-M, Tzen K-Y, Aguiar PC, Arbelo JM, Barone P, et al. Dopaminergic neuronal imaging in genetic Parkinson's disease: insights into pathogenesis. PloS one. 2013;8(7):e69190.

Summary

The previous DaTSCANs of 37 patients with genetic Parkinson's were reanalysed. The aim was to test the hypothesis that mutations in GBA and LRRK2 would have asymmetrical loss of radioligand, reflecting initially focal neurodegeneration due to interactions with additional endogenous or exogenous pathogenic factors. Parkinson's with bi-allelic PINK1 or Parkin mutations would show a more symmetrical loss of uptake, since mutation in these genes alone is sufficient to induce neurodegeneration. The study addresses our question in that DaTSCANs were described for GBA, LRRK2, alpha synuclein, PINK1 and Parkin mutations. DaTSCANS in all of these conditions showed reduced uptake. The asymmetry of radioligand uptake for Parkinson's with GBA or LRRK2 mutations was greater than that for Parkinson's with alpha synuclein, PINK1 or Parkin mutations. It was proposed that the asymmetry of uptake in Parkinson's associated with GBA or LRRK2 mutations might be due to interactions with additional genetic or environmental factors associated with dopaminergic neuronal loss. The following points should be noted:

- Standard clinical protocols were used to identify gene mutations. It is therefore likely that the patients had a correct genetic diagnosis.
- A standard method and standard settings were used for all DaTSCANS, and they were reported by a single investigator, apart from those of patients with a mutation of the SNCA gene, which were reported by a second investigator. We can therefore expect good reliability of the test.
- Images were analysed blind to the genetic diagnosis, which reduces the potential for ascertainment bias.
- Findings were consistent with those of existing studies.

Strength of evidence

level 2 (1=strongest; 5=weakest)*

*OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. www.cebm.net/index.aspx?o=5653

Stamelou M, Quinn NP, Bhatia KP. "Atypical" atypical parkinsonism: New genetic conditions presenting with features of progressive supranuclear palsy, corticobasal degeneration, or multiple system atrophy-A diagnostic guide. Movement Disorders. 2013;28(9):1184-99.

Summary

A narrative review based on articles and case reports presenting patients with PSP, CBD, and MSA look-alikes. These were selected according to defining criteria determined in advance. The authors present an outline of the different genetic conditions that may present as PSP, CBD or MSA look-alikes, dividing them, according to aetiology, into neurodegenerative, neurometabolic (including mitochondrial), and prion disorders. The characteristic DaTSCAN findings for each condition have been copied to the abridged table below:

Genetic conditions that have been reported more commonly to may [sic] present with atypical parkinsonism and PSP-like, CBD-like or MSA-like features

Genetic disorders most commonly described to cause look-alikes	Gene	PSP look-alike[a]	CBD look-alike[a]	MSA look-alike[a]	DaTSCAN (in patients with look-alikes)
Heredodegenerative					
Frontotemporal lobar degeneration	MAPT	+	+	-	Abnormal
	PGRN	+	+	-	Abnormal
	C9ORF72	+	+	-	Abnormal
Alzheimer's dementia	PSEN1	-	+	-	May be abnormal
Perry syndrome	DCTN1	+	+	+	Abnormal
PARK-related parkinsonism					
PARK8	LRRK2	(+)	(+)	-	Abnormal
PARK9 (Kufor-Rakeb)	ATP13A2	+[b]	-	-	Abnormal
Spinocerebellar ataxias	ATXN2	(+)	-	+	Abnormal
	ATXN3	(+)	-	+	Abnormal
Fragile X tremor ataxia syndrome	FMR1	-	-	+	~47% abnormal
Neurometabolic					
Cerebrotendinous xanthomatosis	CYP27A1	(+)	(+)	(+)	Abnormal
Gaucher's disease	GBA	(+)[b]	(+)[b]	-	Abnormal
Niemann-Pick-C	NPC	+	-	-	Unknown
Mitochondrial	Various	+	+	(+)	Abnormal
Genetic prion	PRNP	+	+	-	Abnormal

[a] +, reported; (+), rarely reported (only in 1 or 2 case reports); -, never reported
[b] No pathology available.

The following points should be noted:

- Although this is a narrative rather than systematic review, some helpful details were provided about the literature search. Only a single bibliographic database was searched (PubMed), so some important studies might have been missed. The search terms were appropriate however, and would be expected to produce a sensitive search, albeit within the single database. Inclusion criteria were explicitly set out.
- Studies were included if the subjects fit a number of diagnostic criteria (determined in advance) for each look-alike condition. This was a systematic, consistent way of selecting appropriate case reports and studies, but as the authors acknowledged, failed to account for the overlap of symptoms between conditions. However, the criteria ensured that patients were classified according to the predominant symptoms, as would normally occur in clinical practice.

Strength of evidence:

level 5 (1 =strongest; 5 =weakest)*

* OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

References

1. McNeill A, Wu R-M, Tzen K-Y, Aguiar PC, Arbelo JM, Barone P, et al. Dopaminergic neuronal imaging in genetic Parkinson's disease: insights into pathogenesis. PloS one. 2013;8(7):e69190.

2. Stamelou M, Quinn NP, Bhatia KP. "Atypical" atypical parkinsonism: New genetic conditions presenting with features of progressive supranuclear palsy, corticobasal degeneration, or multiple system atrophy-A diagnostic guide. Movement Disorders. 2013;28(9):1184-99.