Predictors of normal and abnormal outcome in clinical brain dopamine transporter imaging

Elina Jaakkola[1,2], Juho Joutsa[1, 3, 4], Valtteri Kaasinen[1, 3]

[1]Division of Clinical Neurosciences, Turku University Hospital and University of Turku, Turku, Finland

[2]Department of Nuclear Medicine, Turku University Hospital and University of Turku, Finland

[3]Turku PET Centre, Turku University Hospital and University of Turku, Turku, Finland

[4]Department of Clinical Neurophysiology, Turku University Hospital and University of Turku, Finland

Correspondence:

Dr. Elina Jaakkola

Department of Nuclear Medicine, Turku University Hospital

Kiinamyllynkatu 4-8

FIN-20521 Turku Finland

E-mail: elanja@utu.fi

Phone: +358-2-3138721

Fax: +358-2-2318191

Keywords: DAT – SPECT – Parkinson's disease - parkinsonism

Abstract

Brain dopamine transporter (DAT) imaging with [^{123}I]FP-CIT SPECT can be used to evaluate the integrity of the mesostriatal dopaminergic system in patients with clinically uncertain parkinsonism. To evaluate whether scanning a patient is clinically necessary, it is vital to understand possible factors that affect the scanning result. Therefore, we investigated an unselected sample of 538 consecutively scanned patients from a six-year period, and the demographic data and indications for DAT SPECT were recorded. After scanning, the patients were divided into groups according to the scanning outcome. Multivariate binary logistic regression analyses were performed to investigate whether the pre-imaging variables had independent associations with the outcome of the scan. Three hundred and three (56.3%) patients had abnormal scans showing a dopaminergic deficit. The independent factors associated with abnormal scans were older age ($p = 0.002$), asymmetry of motor symptoms ($p = 0.005$) and shorter symptom duration ($p < 0.001$). Re-evaluation of the previously established Parkinson's disease diagnosis was associated with a higher probability of an abnormal scan (74.4 % abnormal, $p = 0.004$), whereas the possibility of medication-induced parkinsonism was associated with a higher probability of a normal scan (35.4 %, $p = 0.036$). The probability of an abnormal outcome in clinical brain DAT imaging increases with known risk factors of neurodegenerative parkinsonism. However, a long duration of uncertain motor symptoms and suspicion of medication-induced parkinsonism are associated with a higher probability of a normal outcome. The findings reflect epidemiological factors in parkinsonism together with referral biases that may be used to improve the clinical use of DAT imaging.

Introduction

The degeneration of nigral dopaminergic neurons in Parkinson's disease (PD) leads to decreased presynaptic dopamine transporter (DAT) levels in striatal projection areas (Niznik et al. 1991; Kraemmer et al. 2014). Recent neuropathological studies suggest that the loss of striatal DAT is a surrogate marker of nigral dopaminergic neuronal death (Walker et al. 2007; Kraemmer et al. 2014). In clinical practice, brain DAT imaging is used to differentiate patients who present with parkinsonism in association with dopaminergic degeneration from those who have intact dopamine systems (Bajaj et al. 2013). [^{123}I]FP-CIT SPECT has been approved by the European Medicines Agency (EMA) for the differentiation between parkinsonian tremor and essential tremor (ET) and for the differentiation between Lewy Body Dementia and Alzheimer's disease. The US Food and Drug Administration (FDA) has approved the method for the differentiation of ET from tremor due to idiopathic PD, multiple system atrophy (MSA) or progressive supranuclear palsy (PSP). Apart from the official indications, clinical DAT imaging is used for several other conditions that present as clinically uncertain parkinsonian syndrome (CUPS) (Bajaj et al. 2013).

Within the context of increasing mixed clinical use of brain DAT imaging, the method-related risks, limitations and costs are relevant. For example, there is a small but noteworthy cancer risk (1/5000-7500) (de la Fuente-Fernández 2012) associated with radioactivity. In addition, although a DAT scan can be used to differentiate between ET and degenerative parkinsonian syndromes, it has not been validated for the differentiation between different dopaminergic parkinsonian syndromes, i.e., PD, PSP, and MSA (Bajaj et al. 2013). DAT scans are also affected by several factors that need to be considered in the interpretation such as age, gender and type of motor symptoms (Kaasinen et al. 2014; Kaasinen et al. 2015). Therefore, to evaluate whether a DAT scan is necessary at a given time point, it is important to fully understand the factors that predict the outcome. If there are factors that have high predictive value for normal or abnormal scanning results, this knowledge could assist the

clinician when the necessity of the scan is weighted. The present study was carried out to investigate these factors in an unselected heterogeneous sample of patients.

Methods

We investigated a sample of 538 consecutive patients referred to diagnostic [^{123}I]FP-CIT SPECT imaging from a single centre (Department of Nuclear Medicine, Turku University Hospital, Finland) during a 6-year period (2007-2012).

The demographic and clinical data, as well as indications for SPECT scanning, were obtained from hospital records as described previously (Kaasinen et al. 2014). These included age at scan, gender, motor symptom duration before imaging, asymmetry (asymmetric/symmetric presentation of motor symptoms), predominant side of motor symptoms (left/right), symptom type (tremor or no tremor), possible medications affecting the dopamine system (antiparkinsonian dopaminergic or antipsychotic), and the type of scanner (Table 1). In addition, indications for scanning were recorded in detail, including the EMA- and FDA-approved indications together with other possible reasons.

Patients were scanned using the GE Infinia II Hawkeye SPECT/CT (GE Medical Systems, Milwaukee, WI, USA) or Picker Irix gamma camera (Picker International, Uniontown, OH, USA). Oral $KClO_4$ (250 mg, 1% solution) was administered one hour before the injections to protect the thyroid gland. A 185 MBq bolus of [^{123}I]FP-CIT was injected, and scanning was performed four hours post-injection as described in detail previously (Kaasinen et al. 2014). The classification of the outcome of the scan—normal or abnormal—was formed based on the original clinical evaluation of striatal DAT binding made by a nuclear medicine physician according to the current guidelines (Darcourt et al. 2010).

Statistical analyses were performed using IBM SPSS Statistics (version 22; SPSS Inc., Chicago, Illinois, USA). The comparisons of patients with different scanning outcomes were performed using independent samples *t*-tests or Chi-squared tests, as appropriate. Multivariate binary logistic

regression analyses were performed to investigate which scanning indications and demographical/clinical variables were independently associated with the outcome of the scan. Only variables that showed significant differences between patients with normal and abnormal outcome ($p < 0.05$) were included in the multivariate analysis. Scanning indications with at least 30 patients were included in the regression analyses. For the multivariate regression analysis, suspected MSA and PSP were grouped with suspected parkinsonism plus syndromes due to the low number of subjects in each category. CUPS as the standard scanning indication, was used as the reference category. Patients with unclear parkinsonism without specific diagnostic questions were classified as CUPS, whereas other patients were classified according to the clinical problem outlined by the clinician (e.g. 'ET or PD?' and 'drug-induced or PD?'). Medication was not used as a variable in multivariate analysis because of high intercorrelation (e.g., patients scanned for suspected drug-induced parkinsonism frequently used antidopaminergic medications). The level of statistical significance was set at $p < 0.05$.

Results

Several different clinical indications for scanning were identified (Figure 1). The most common reasons for scanning were clinically uncertain parkinsonian syndrome (CUPS, n = 190) or CUPS with PD as the primary diagnostic option (n = 175). Of all patients, 67.8 % were scanned for CUPS or suspected PD. Additionally, drug-induced parkinsonism (n = 48), re-evaluation of PD diagnosis because of atypical progression (n = 39), and the differentiation between PD and ET (n = 31) were common. Less common reasons for scanning were suspected LBD (n = 19), suspected PSP (n = 11), suspected MSA (n = 10), suspected parkinsonism plus (n = 9), suspected vascular parkinsonism (n = 3), akinetic crisis (n = 2), and suspected corticobasal syndrome (n = 2).

In 303 (56.3 %) patients, the scanning outcome was abnormal. The scanning indication was associated with the outcome of the scan (p = 0.001). When adjusted for the demographic and clinical factors, the re-evaluation of PD diagnosis (p = 0.004) was independently associated with an abnormal outcome, and the differentiation between PD and drug-induced parkinsonism (p = 0.036) was associated with a normal outcome (Figure 1). The type of scanner had no effect on the outcome (p = 0.60).

Compared with patients with normal scans, patients with abnormal scans were older (p = 0.002), had shorter symptom duration (p < 0.001), and had more often asymmetrical motor symptoms (p = 0.005) (Table 2; Figure 2). Although gender difference was significant using Chi-squared test (Table 1), it was not independently associated with the outcome in multivariate analysis.

Discussion

The results of the present study demonstrate that age, symptom asymmetry, and symptom duration are associated with the outcome of clinical brain DAT imaging. In addition, the indication for scanning is associated with the outcome, as patients who are scanned due to possible drug-induced parkinsonism tend to have a higher proportion of normal scans, and patients scanned for PD diagnosis confirmation have a high proportion of abnormal scans. Although women and tremor-dominant PD patients generally show higher [^{123}I]FP-CIT binding (Kaasinen et al. 2014; Kaasinen et al. 2015), gender or the lack/presence of tremor does not seem to influence the outcome of clinical DAT SPECT in an unselected sample of patients.

Notably, age appears to be an independent factor associated with abnormal DAT SPECT. Clinical semiquantitative automated calculations of striatal tracer binding are typically corrected with healthy age-matched samples, and the normal age-related decline in FP-CIT binding (Varrone et al. 2013; Kaasinen et al. 2015) does not explain the increasing number of abnormal scans in older individuals. Instead, ageing is the most important risk factor for Parkinson's disease (Collier et al. 2011), and the increasing proportion of abnormal scans in older populations probably reflects this robust age-dependent PD epidemiology. Unlike ageing, the relationship between long symptom duration and increased likelihood of normal DAT binding can be considered paradoxical. We interpret this result to be a reflection of a clinical selection bias as degenerative parkinsonisms progress clinically, and diagnostic imaging often becomes unnecessary after the first few years of follow-up. After several years, diagnostic imaging may be mostly needed in patients who do not have progressive neurodegeneration, resulting in a higher proportion of normal scanning outcomes. It is also possible that CIT-SPECT represents just an additional tool in the large diagnostic battery of patients with unclear long-lasting motor symptoms and CIT-SPECT, as an auxiliary investigation is probably associated with a higher number of normal scans. The present results further indicate

that patients with asymmetric motor symptoms are more likely to have an abnormal scan. This finding is expected because motor symptoms are nearly always asymmetric in the early stages of PD (Djaldetti et al. 2006). The effect was significant, although parkinsonism plus syndromes such as PSP and MSA are generally more symmetric than PD (Colosimo et al. 1995; Djaldetti et al. 2006; Seppi et al. 2006; Wüllner et al. 2007), and they are also associated with a clear decline in DAT binding.

Although most patients were scanned for CUPS or suspected PD, one-third of patients were scanned for other reasons, such as drug-induced parkinsonism and the re-evaluation of PD diagnosis. In a recent study from France, 516 patients were scanned with clinical [^{123}I]FP-CIT SPECT, and only 18 % of scans were in agreement with the license (Thiriez et al. 2015). As much as 37 % were classified as inappropriate, i.e., scanning provided no new information concerning patient care or did not answer the diagnostic question (Thiriez et al. 2015). Our results are generally in line with this discrepancy because they demonstrate that the EMA- and FDA-approved official indication of the differentiation between ET and PD represented only 5.8 % of all scans. The indication of the differential diagnosis between LBD and AD was even less common (3.5 %).

Conclusion

To conclude, as less than 10 % of scans were performed for official indications, the current clinical use of DAT imaging is much broader than the official recommendations for use. Although it is possible that a proportion of scans is performed without sufficient clinical benefit, our study could not directly address this issue without post-scan value ratings from the clinicians or neuropathological verification of diagnoses. However, with current knowledge, the differential diagnostics between neurodegenerative conditions similarly affecting the dopamine system, such as PD and PSP, is questionable. Accordingly, the proportion of abnormal scans was 100 % in patients with suspected PSP. Further controlled prospective work is required to confirm the diagnostic value of the method in various unofficial indications together with neuropathological verification. In any case, the results of the present study demonstrate that not only the scanning indication but also age, symptom asymmetry and duration are independent determinants of clinical brain DAT scan outcome. These findings likely partially reflect prescription biases that come into play when neurologists refer patients for DAT imaging (e.g., patients with a long duration of unexplained motor symptoms). Although demographic factors have little significance in clinical decision-making and the necessity of a clinical scan should always be evaluated on an individual basis, the clinician should be aware of these factors and possible biases that influence the outcome of a diagnostic test.

Acknowledgements

The staff of the Department of Nuclear Medicine, Turku University Hospital, is gratefully acknowledged.

Conflicts of interest

None.

Ethical approval

The local ethical committee accepted this retrospective study protocol, and the requirement to obtain informed consent was waived. The study was conducted according to the principles of the Declaration of Helsinki.

References

Bajaj N, Hauser RA, Grachev ID (2013) Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J Neurol Neurosurg Psychiatry 84(11): 1288-1295.

Collier TJ, Kanaan NM, Kordower JH (2011) Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. Nat Rev Neurosci 12(6): 359-366.

Colosimo C, Albanese A, Hughes AJ, de Bruin VM, Lees AJ (1995) Some specific clinical features differentiate multiple system atrophy (striatonigral variety) from Parkinson's disease. Arch Neurol 52(3): 294-298.

Darcourt J, Booij J, Tatsch K, Varrone A, Vander Borght T, Kapucu OL, Någren K, Nobili F, Walker Z, Van Laere K (2010) EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging 37(2): 443-450.

de la Fuente-Fernández R (2012) Role of DaTSCAN and clinical diagnosis in Parkinson disease. Neurology 78(10): 696-701.

Djaldetti R, Ziv I, Melamed E (2006) The mystery of motor asymmetry in Parkinson's disease. Lancet Neurol 5(9): 796-802.

Kaasinen V, Joutsa J, Noponen T, Johansson J, Seppänen M (2015) Effects of aging and gender on striatal and extrastriatal [123I]FP-CIT binding in Parkinson's disease. Neurobiol Aging 36(4): 1757-1763.

Kaasinen V, Kinos M, Joutsa J, Seppänen M, Noponen T (2014) Differences in striatal dopamine transporter density between tremor dominant and non-tremor Parkinson's disease. Eur J Nucl Med Mol Imaging 41(10): 1931-1937.

Kraemmer J, Kovacs GG, Perju-Dumbrava L, Pirker S, Traub-Weidinger T, Pirker W (2014) Correlation of striatal dopamine transporter imaging with post mortem substantia nigra cell counts. Mov Disord 29(14): 1767-1773.

Niznik HB, Fogel EF, Fassos FF, Seeman P (1991) The dopamine transporter is absent in parkinsonian putamen and reduced in the caudate nucleus. J Neurochem 56(1): 192-198.

Seppi K, Scherfler C, Donnemiller E, Virgolini I, Schocke MF, Goebel G, Mair KJ, Boesch S, Brenneis C, Wenning GK, Poewe W (2006) Topography of dopamine transporter availability in progressive supranuclear palsy: a voxelwise [123I]beta-CIT SPECT analysis. Arch Neurol 63(8): 1154-1160.

Thiriez C, Itti E, Fénelon G,Evangelista E, Meignan M,Cesaro P, Remy P (2015) Clinical routine use of dopamine transporter imaging in 516 consecutive patients. J Neurol 2015 Apr;262(4):909-15

Varrone A, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Booij J, Kapucu OL, Kluge A, Knudsen GM, Koulibaly PM, Nobili F, Pagani M, Sabri O, Vander Borght T, Van Laere K, Tatsch K (2013) European multicentre database of healthy controls for [123I]FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis. Eur J Nucl Med Mol Imaging 40(2): 213-227.

Walker Z, Jaros E, Walker RW, Lee L, Costa DC, Livingston G, Ince PG, Perry R, McKeith I, Katona CL (2007) Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. J Neurol Neurosurg Psychiatry 78(11): 1176-1181.

Wüllner U, Schmitz-Hübsch T, Abele M, Antony G, Bauer P, Eggert K (2007) Features of probable multiple system atrophy patients identified among 4770 patients with parkinsonism enrolled in the multicentre registry of the German Competence Network on Parkinson's disease. J Neural Transm 114(9): 1161-1165.

Table 1. Main demographic and clinical characteristics of the studied sample according to the outcome in SPECT (normal/abnormal).

	Normal	**Abnormal**	***p* value[1]**
n	235	303	
Age at scan (years)	64.3 (12.0)	66.8 (10.7)	0.012
Symptom duration (years)	4.4 (7.2)	2.2 (3.0)	<0.001
Sex (m/f)	113/122	178/125	0.014
Asymmetrical/symmetrical motor symptoms	168/67	243/60	0.024
Tremor/no-tremor	153/82	184/119	0.30
Dopaminergic medication	28 (11.9 %)	52 (17.2 %)	0.11
Antipsychotic medication	49 (20.9 %)	18 (5.9 %)	<0.001

Variables that showed significant differences between the groups ($P<0.05$) were selected for multivariate binary logistic analysis.
[1]Independent samples *t*-test or Chi-Squared test, as appropriate.

Table 2. Independent effects associated with scanning outcome.

Factor	**OR (95 % CI)**	***p* value**
Symptom duration (years)	0.87 (0.81-0.93)	<0.001
Age at scan (years)	1.3 (1.1-1.55)	0.002
Asymmetry of symptoms	1.97 (1.23-3.15)	0.005
Female gender	1.42 (0.97-2.07)	n.s.
Indication for imaging[2]		0.001
Re-evaluation of PD diagnosis	3.56 (1.5-8.46)	0.004
PD or medication related	0.48 (0.24-0.95)	0.036
Suspected parkinsonism plus[1]	2.34 (0.96-5.7)	n.s.
PD or essential tremor	0.93 (0.34-2.22)	n.s.
Suspected PD	1.37 (0.88-2.13)	n.s.

Results of multivariate binary logistic regression analysis
[1]includes patients with suspected PSP or MSA.
[2]compared with CUPS.
n.s. = non-significant, OR = odds ratio.

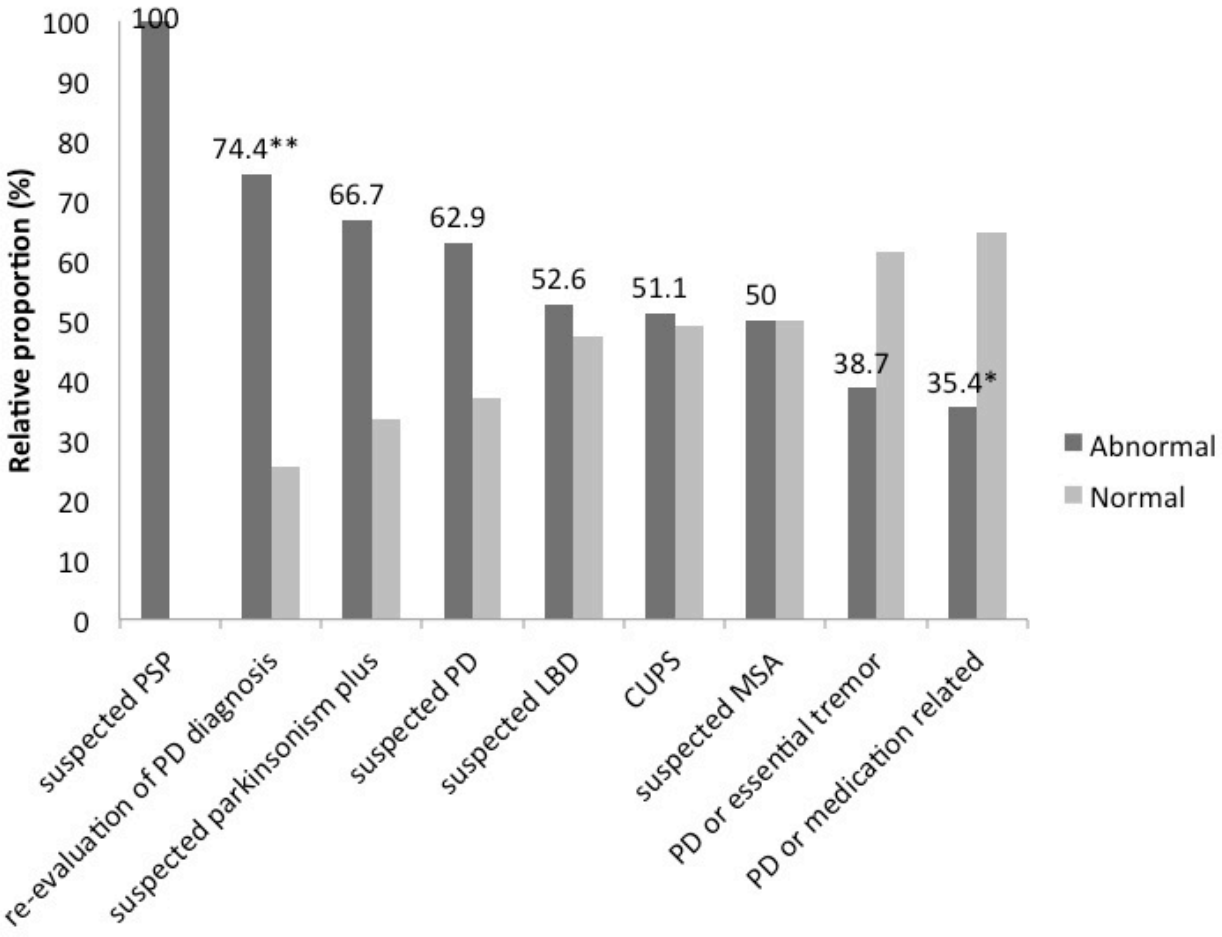

Figure 1. Relative distribution of normal and abnormal scans according to scanning indication. The effect of scanning indication (p = 0.001) was significant in multivariate analyses. CUPS = clinically uncertain parkinsonian syndrome, LBD = Lewy body dementia, MSA = multiple system atrophy, PSP = progressive supranuclear palsy, PD = Parkinson's disease. *$p < 0.05$, **$p < 0.01$.

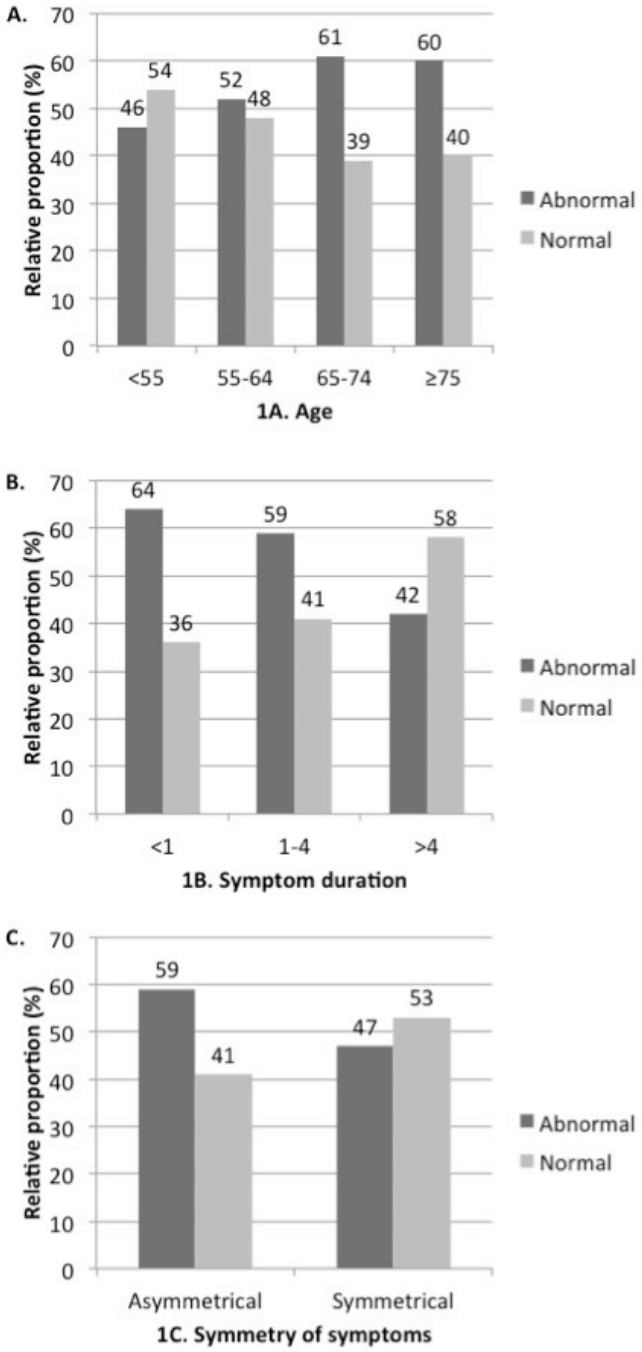

Figure 2. Relative distribution of normal and abnormal scans according to age, symptom duration and symmetry of motor symptoms. A. Increasing age-related proportion of abnormal outcome ($p = 0.002$ in multivariate analysis). B. Long duration of motor symptoms associated with a normal outcome ($p < 0.001$). C. Asymmetrical symptoms associated with abnormal scans ($p = 0.005$).