J Neural Transm (2009) 116:861–866
DOI 10.1007/s00702-009-0234-9

MOVEMENT DISORDERS - ORIGINAL ARTICLE

Eye of the tiger-like MRI in parkinsonian variant of multiple system atrophy

Ming-Hong Chang · Wan-Ling Hung · Yi-Chu Liao · Yi-Chung Lee · Peiyuan F. Hsieh

Received: 4 December 2008 / Accepted: 21 April 2009 / Published online: 7 May 2009

Abstract Parkinsonian variant of multiple system atrophy (MSA-P) clinically presents as autonomic dysfunction with parkinsonian features. Parkinsonian features include bradykinesia, rigidity, tremor, postural instability and poor levo-dopa response. Neuropathologically, MSA-P is characterized by selective neuronal loss and gliosis mainly affecting the putamen and caudate nucleus, substantia nigra, olivopontocerebellar pathway and intermediolateral cell column of the spinal cord. Therefore, the target of magnetic resonance imaging (MRI) is focused on signal changes or volume reduction on putamen, including putaminal slit, gliosis by diffusion studies and reduction of putaminal volume. There have been no reports describing clinical manifestations of MSA-P with imaging abnormalities over globus pallidus. Here, we describe three patients with typical presentations of MSA-P with autonomic dysfunction and disturbances of axial motor function with minimal appendicular symptoms, including postural instability and gait difficulties. MRI showed symmetrical hyperintensity over the center of globus pallidus surrounded by a mild low-signal rims at T2-weighted image that is similar to that of eye of the tiger sign except for the marked hypointense rims. Dopamine transporter scans showed symmetric reduction of uptake over bilateral basal ganglia. This is the first report concerning these unusual imaging findings in MSA-P patients and we believe there is a subgroup of MSA-P with clinical presentation of axial impairment and symmetrically abnormal signal changes of globus pallidus in MRI.

Keywords Multiple system atrophy · MSA · Magnetic resonance imaging · MRI parkinsonism · Globus pallidus

M.-H. Chang (✉) · W.-L. Hung · Y.-C. Liao · Y.-C. Lee · P. F. Hsieh
Section of Neurology, Taichung Veterans General Hospital, No 160, Chung-Kang Road, Section 3, Taichung 40705, Taiwan
e-mail: cmh50@ms10.hinet.net

M.-H. Chang · Y.-C. Liao · Y.-C. Lee · P. F. Hsieh
Department of Neurology, National Yang-Ming University, Taipei, Taiwan

Introduction

Multiple system atrophy (MSA) is an adult-onset sporadic and progressive neurodegenerative disease. Clinical manifestations are variable, featuring autonomic failure with either poorly levo-dopa-responsive parkinsonian symptoms, or cerebellar syndrome or in any combination. According to consensus criteria, patients with MSA are clinically divided based on their motor presentation into parkinsonian (MSA-P) and cerebellar subtypes (MSA-C) (Gilman et al. 1999, 2008). MSA-P was formerly called striatonigral degeneration (Gilman et al. 1999; Graham and Oppenheimer 1969; Papp et al. 1989; Quinn 2005; Wenning et al. 2004). The gross neuropathologies of MSA-P or MSA-C are characterized by selective neuronal loss and gliosis involving the striatum, substantia nigra, olivopontocerebellar pathways, and intermediolateral cell column of the spinal cord; while microscopically, glial cytoplasmic inclusions were found in the brain tissue from patients with MSA (Papp et al. 1989). However, there are few pathognomonic features to differentiate MSA-P from Parkinson's disease (PD), thereby resulting in a considerable under-recognition of MSA-P during early disease states (Kollensperger et al. 2008). Nevertheless, modern imaging

techniques can clearly detect the differences in these subtle abnormalities and partially replace the role of a pathological examination. Therefore, an early confirmatory diagnosis of MSA-P can be made possible with MRI studies of the striatum, which would include analyses with conventional T2-weighted images for the hypointense putamen (possibly reflecting iron deposition) (Lang et al. 1994; Schrag et al. 1998; Schwartz et al. 1996), hyperintense rims over the lateral putamen (Horimoto et al. 2002; Schocke et al. 2002), and a reduction of putaminal volume (Schulz et al. 1999; Seppi et al. 2005) Here, we describe three patients presenting clinical manifestations of autonomic failure with a rapid progressive imbalance, gait difficulties and parkinsonian features; in all of whom, the MRI showed unusual findings in the globus pallidus that have never been reported in MSA-P patients.

Illustrative patient 1

A 74-year-old woman was referred for evaluation of gait disturbances and a severely bent neck and trunk for more than 20 months. In late 2003, she visited a neurologist due to short-stepped gait and difficulty in turning. PD was diagnosed and she received L-dopa and anticholinergic treatment, but the effect was minimal. Brain MRI at that time only revealed aging change. Afterward, she experienced a progressive worsening of gait, especially during the turning and eventually, this condition caused her to fall easily. Then, she exhibited poor urine control and difficulty in defecation. However, the function of upper limbs was relatively spared and she could independently eat, brush teeth and wash face slowly. On examination, significant imbalance and gait difficulty let her sit in the wheelchair with a mild flexor posture. Passive movement of the neck showed resistance in neck extending. Although rising from the wheelchair, she could stand-up independently. A worsening in the flexion of the neck (antecollis) and trunk (camptocormia) with a mild deviation of the trunk (Pisa syndrome) and neck to the right occurred during walking. The steps were short and she had hesitation with obviously motor blockade during turning, typical presentation of freezing of gait (FOG). No dizziness or orthostatic hypotension occurred. Unified Parkinson's disease rating scale (UPDRS) for item 27, 28, 29 and 30 was 11. The tilting table test showed normal results. Urodynamic study showed hyporeflexic bladder with 100 cm^3 of residual urine. Anticholinergics showed no benefit for the severely flexed neck and trunk. Botulinum toxin injection for the treatment of neck flexion was also ineffective. After conservative and rehabilitation treatment for 2 years, the gait difficulty and bending posture progressively worsened; however, cognitive function was still intact.

Patient 2

A 74-year-old man was referred for the evaluation of gait disturbances, severe orthostatic dizziness and intermittent palpitations for 4 years. In early 2003, he saw a cardiologist due to the persistent dizziness, intermittent palpitations and night dyspnea, whereby orthostatic hypotension was suspected. One year later, difficulty in gait initiation occurred. This was followed by additional gait disturbances, palpitations and gradually worsening dizziness. On examination, he sat in an upright posture. Cognitive function and memory were normal. A masked face and hypophonic dysarthria were found. Eye movement in every direction was free. There was neck rigidity with a bending posture and mild limb rigidity. Finger tapping was slow with decreased amplitude. Muscle strength, DTR and sensory examination were normal. A finger–nose–finger test was normal. Foot tapping and leg agility were impaired. During standing up, he needed partial support from family members. There was a marked impairment in the initiation of a first step with a tendency to fall with dizziness. When he walked, steps were short as if his feet were glued to the ground without any increase of step-speed. UPDRS for item 27, 28, 29 and 30 was nine. There was obviously orthostatic hypotension and a nocturnal inspiratory stridor occasionally occurred. The tilting table test showed marked orthostatic hypotension with the drop of systolic/diastolic pressure of 54/22 mmHg, indicating autonomic failure. At clinical follow-up, the unpredictable syncope with falls occurred frequently and gait difficulty progressed and worsened. Now, his daily activity is dependent on care givers.

Patient 3

A 68-year-old woman visited our clinic due to an inability to walk with severe difficulty in the initiation of steps without support and also suffered from urine incontinence for 3 years. In 2003, she visited an urologist due to urine dripping. Urodynamic study showed hyporeflexic bladder with around 120 cm^3 residual urine. In late of 2004, she saw a neurologist due to gait disturbance, especially with regards to half turn. Primary progressive freezing gait or atypical Parkinson's disease was suspected and anti-PD medication was given. Improvement of gait was found, but with short duration of effect for 4–5 months and then the gait worsened gradually. One year later, she needed to wear adult diapers for the urine incontinence and was confined to wheelchair because of severe gait disturbance. There was no accompanying impairment of cognitive function or gaze palsy in the following years. On examination, she sat in a wheelchair. Although, a masked face was observed, eye movement in every direction was free. There was a rigidity

over the wrist and free of neck. Finger tapping was slow with decreased amplitude. Muscle strength, DTR and sensory examination were normal. The finger–nose–finger test was normal. During rising from wheelchair and standing up, she could stand independently without support, but severe FOG with propulsion was observed. UPDRS for item 27, 28, 29 and 30 was 12. There was no obviously orthostatic hypotension. For clinical follow-up for 2.5 years, the clinical features are similar with urine problem and FOG; however, the severity is worse.

Methods

MRI of brain

Conventional brain MRI for a differential diagnosis was performed on a 1.5 T superconducting system (Sigma, GE Medical systems). The imaging studies included (1) axial and coronal T1-weighted spin-echo, repetition time/echo time/excitation time (450/10/2), (2) axial and coronal T2-weighted fast spin-echo, repetition time/echo time/excitation time (4200/110/2) with echo train length 8 and (3) axial fast fluid-attenuated inversion recovery, repetition time/inversion time/echo time/number of excitations (9000/2200/133/1) sequences. Sections (5 mm thick) with 2.5-mm interslice gaps, 24 cm field-of-view and 256 × 192 matrix were used for all scans.

Dopamine transporter (DAT) scan

Radiopharmaceutical preparation

The[2-[[-[[[3-(4-Chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]-methyl] (2-mercaptoethyl)amino]ethyl]amino]ethanethiolato(3-)-N2,N2′,S2,S2′]oxo-[1R-(exo-exo0)-^{99m}Tc-technetium ($^{99m}T_c$-TRODAT-1) was obtained in a 1-vial kit formulation from the INER. The final sterilized product was produced by autoclaving the mixture for 30 min. Radiochemical purity was 97 ± 2%, as measured with high-performance liquid chromatography.

Imaging acquisition protocol

All medication was discontinued at least 12 h before the test. After the clinical evaluation, patients were brought to the Nuclear Medicine Department. A dose of 925 MB_q (25 mCi) $^{99m}T_c$-TRODAT-1 was injected intravenously. SPECT images were acquired 4 h later using a MULTI-SPECT triple-head γ-camera, with fan beam collimators and 120 equally spaced projections over 360°, taking 20 s per step and using a 128 × 128 matrix size. Individual images were reconstructed with back-projection using a ramp-Butterworth filter, with a cutoff of 0.3 cm^{-1} and an order of 10. The slice thickness and in-plane size was 2.9 mm. Three reconstructed transaxial slices were summed together and reoriented to be parallel to the orbitomeatal (OM) line with the highest signal in the region of the basal ganglia as the central slice (Lu et al. 2004; Weng et al. 2004). All images underwent a blind review and the diminished uptake of TRODAT-1 was divided into four degrees by visual analysis: (1) normal, (2) mildly decreased, (3) moderately decreased and (4) severely decreased.

Results

Magnetic resonance imaging (3 years after symptoms) of the illustrated patient showed normal axial T1-weighted imaging for ages and T2-weighted images revealed symmetric high-signal intensity over the globus pallidus bilaterally on axial and coronal view (Fig. 1*1A, 1B, 1C*). The high-signal intensity was located in the center of the globus pallidus with mildly low intense peripheral rims, unlike the typical eye of the tiger pattern with a surrounding rim of extremely low intensity due to abnormal deposition of iron.

Magnetic resonance imaging scans for patients 2 and 3 (3 and 4 years after symptoms first appeared, respectively) showed similar findings to those described in the illustrated patient (Fig. 1, *2A*, *2B, 2C*, *3A, 3B, 3C*).

Dopamine transporter activity measured with TRODAT-1 was scanned with patient 2 showing symmetrically and moderately decreased uptake and patient 3 showing severe depletion of uptake over the striatum bilaterally. The images of patient 2 and an age-matched control are shown in Fig. 2.

Discussion

The diagnosis of MSA-P of our patients is based on their poorly levo-dopa-responsive parkinsonism and typical autonomic failure with either cardiovascular or urogenital dysfunction (Kollensperger et al. 2008; Seppi et al. 2005). Marked postural instability with gait disturbance and axial rigidity or dystonia also occurred in all patients. These findings are consistent with a clinical diagnosis of probable MSA-P based on the consensus criteria (Gilman et al. 1999, 2008; Wenning et al. 2004). Recently, a standardized checklist summarizing six categories of presentations has been developed with high sensitivity and specificity for discriminating between MSA-P and PD (Kollensperger et al. 2008). These six categories are the following: (1) early instability with recurrent falls within 3 years of disease onset; (2) rapid progression to a wheelchair bound

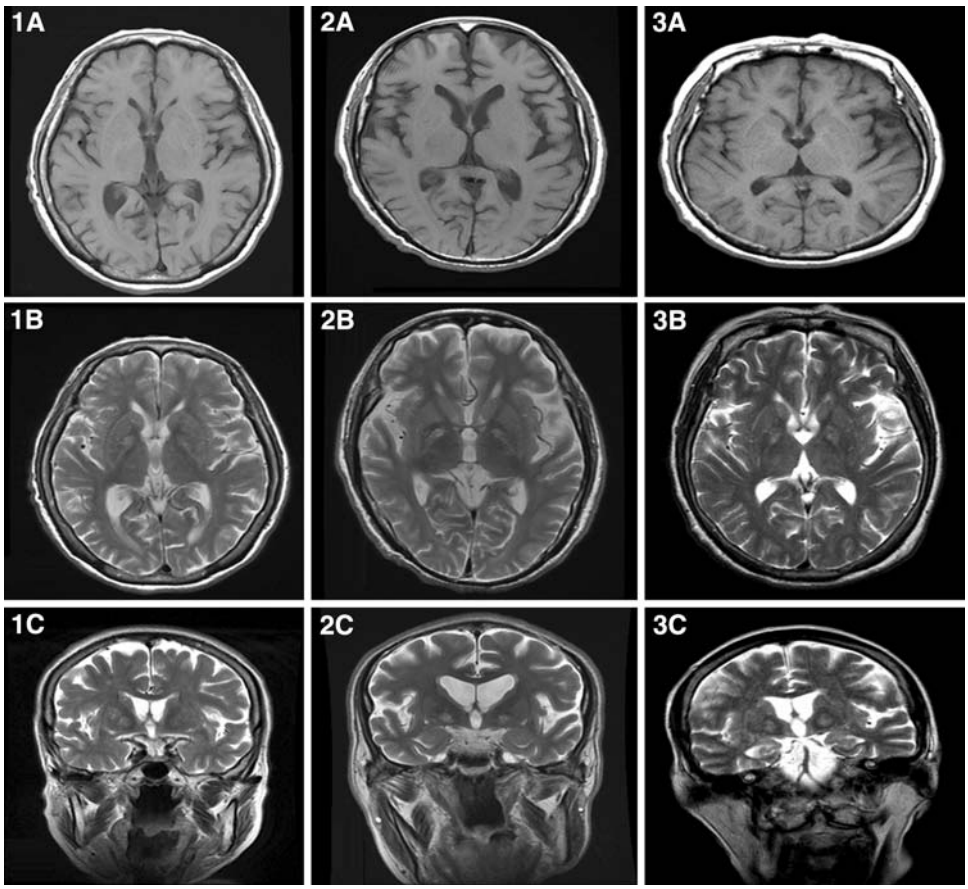

Fig. 1 Axial T1-weighted (*A*) and axial T2-weighted (*B*) and coronal T2-weighted (*C*) images from illustrated, patients 2 and 3 are shown in Fig. 1. The axial and coronal views of T2-weighted images show symmetric high-signal intense lesions over central globus pallidus surrounded by a mildly low-signal rims with normal T1-weighted images (*1A*, *1B* and *1C* from illustrated patient; *2A*, *2B* and *2C* from patient 2; *3A*, *3B* and *3C* from patient 3)

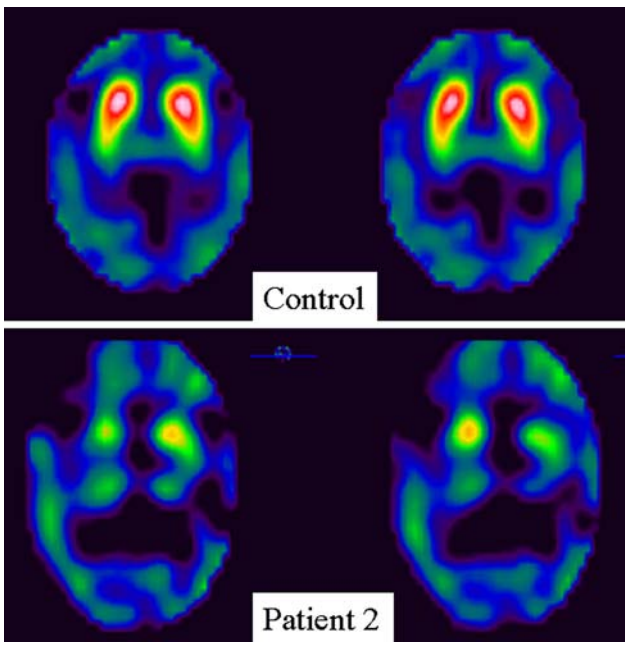

Fig. 2 Dopamine transporter (DAT) scans show symmetrical decreases of the TRODAT uptake over bilateral basal ganglia in patient 2

state within 10 years; (3) abnormal posture with disproportionate antecollis, camptocormia and Pisa syndrome; (4) bulbar dysfunction; (5) respiratory dysfunction and (6) emotional incontinence. All our patients had at least two categories considered red flags for MSA. For example, early instability and rapid progression occurred in all patients. Abnormal posture with disproportionate antecollis, camptocormia and Pisa syndrome occurred in the illustrated patient. Bulbar and respiratory dysfunction occurred in patient 2 and early onset of FOG with postural instability occurred in patient 3 (Kollensperger et al. 2008). Therefore, the diagnosis of probable MSA-P for our patients is supported by the clinical criteria (Gilman et al. 2008) Recently, TRODAT SPECT has been used to determine the concentration of DATs on dopaminergic nerve terminals as a possible biomarker for dopaminergic degeneration (Poewe and Scherfler 2003). The scans of our patient 2 and 3 showed a relatively symmetrical decrease of uptake, suggesting that their parkinsonian features come from impairment of nigrostriatal pathway (Lu et al. 2004; Poewe and Scherfler 2003; Pricker et al. 2000; Varrone et al. 2001). Although a symmetrical decrease of TRODAT uptake was consistent but non-specific for MSA-P, it was

not in favor of the diagnosis of PD or corticobasal degeneration that usually showed a relative asymmetry in the decrease of uptake (Lu et al. 2004; Pricker et al. 2000) However, it may be argued that our patients really have MSA-P or other neurodegenerative disease because there was no pathological confirmation currently. In any case, there is no alternative diagnosis of neurodegenerative diseases, characterized by elderly onset and progressive courses with obvious autonomic impairment and parkinsonian features besides MSA-P.

The globus pallidus may have a role in controlling axial movement (Bhatt et al. 1993; Feve et al. 1993; Bucher et al. 1996). It has been suggested that the globus pallidus is responsible for the FOG and posture instability. By contrast, typical features of parkinsonism, for example, limb rigidity, bradykinesia and tremor are minimal in patients with globus pallidus lesions. The typical syndromes of globus pallidus lesion are hypoxic encephalopathy (Bhatt et al. 1993; Li et al. 2000) and carbon monoxide intoxication (Davis 1986; Hsiao et al. 2004). The clinical features of our patients are consistent with presentations of axial motor impairment, for example, rigidity and dystonia of neck, postural impairment and marked disturbance of gait with freezing and with mild or minimal features of appendicular signs. Although the clinical presentations and imaging studies of our patients have similar appearances to hypoxia and CO intoxication, marked autonomic failure is not an obvious feature of hypoxia and CO intoxication. Furthermore, our patients did not have a history of hypoxia and CO intoxication and they had a progressive course of gradual deterioration.

Age-dependent signal loss in T2-weighted images commonly occurs in the globus pallidus due to iron deposition (Schenker et al. 1993). Therefore, the globus pallidus always has low-signal intensity as compared to neostriatum during aging. An abnormally marked accumulation of iron over bilateral globus pallidus occurs in pantothenate kinase-associated neurodegeneration (PKAN), which results in very low-signal intensity over the globus pallidus bilaterally on T2-weighted images (Antonini et al. 2006; Thomas et al. 2004; Valentino et al. 2006). Usually, an area of exclusively high-signal intensity in T2-weighted images may be evident in the central pallidus, which is surrounded by a region of extremely low-signal intensity. Accordingly, this MRI finding has been referred to as the eye of the tiger sign that is similar to those of MRI findings in our patients (Thomas et al. 2004). However, the T1-weighted images from PKAN patients show typical hyperintensity over the globus pallidus, which is quite different from our MRI findings. Furthermore, the clinical features of PKAN are quite different from ours, such as the age of onset. The age of onset for PKAN is rarely after 50 years of age, although the clinical presentations of parkinsonian symptoms and gait difficulties are common features of late adult-onset of PKAN. However, the more important difference is the marked autonomic failure in our patients that is a rare and only a late feature in PKAN (Schocke et al. 2002).

In conclusion, we propose that MSA-P patients can be divided into a novel subgroup with axial motor impairment that has the eye of the tiger-like appearance of T2-weighted images bilaterally and symmetrically over the globus pallidus.

References

Antonini A, Goldwurm S, Benti R, Prokisch H, Ebhardt M, Cilia R et al (2006) Genetic, clinical and imaging characterization of one patients with late-onset slowly progressive pantothenate kinase-associated neurodegeneration. Mov Disord 21:417–418

Bhatt MH, Obeso JA, Marsden CD (1993) Time course of postanoxic akinetic-rigid and dystonic syndrome. Neurology 43:314–317

Bucher SF, Seelos KC, Dodel RC, Paulus W, Maximilian R, Oertel WH (1996) Pallidal lesions: structural and functional magnetic resonance imaging. Arch Neurol 53:682–686

Davis PL (1986) The magnetic resonance imaging appearance of basal ganglia lesions in carbon monoxide poisoning. Magn Res Imaging 4:489–490

Feve AP, Fenelon G, Wallays C, Remy P, Guillard A (1993) Axial motor disturbances after hypoxic lesions of the globus pallidus. Mov Disord 8:321–326

Gilman S, Low P, Quinn N, Albanese A, Ben-Shlomo Y, Flower CJ et al (1999) Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 163:94–98

Gilman S, Wenning GK, Low PA et al (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology 71:670–676

Graham JG, Oppenheimer DR (1969) Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy. J Neurol Neurosurg Psychiatry 32:28–34

Horimoto Y, Aiba I, Yasuda T, Ohkawa Y, Katayama T, Yokokawa Y et al (2002) Longitudinal MRI study of multiple system atrophy—when do the finding appear, and what is the course? J Neurol 249:847–854

Hsiao CL, Kuo HC, Huang CC (2004) Delayed encephalopathy after carbon monoxide intoxication-long term prognosis and correlation of clinical manifestations and neuroimages. Acta Neurol Taiwan 13:64–70

Kollensperger M, Geser F, Seppi K, Stampfer-Kountchev M, Sawires M, Scherfler C (2008) Red flags for multiple system atrophy. Mov Disord 23:1093–1099

Lang AE, Curran T, Provias J, Bergeron C (1994) Striatonigral degeneration: iron deposition in putamen correlates with the slit-like void signal of magnetic resonance imaging. Can J Neurol Sci 21:311–318

Li JY, Lai PH, Chen CY, Wang JS, Lo YK (2000) Postanoxic parkinsonism: clinical radiologic, and pathologic correlation. Neurology 55:591–593

Lu CS, Weng YH, Chen MC, Chen RS, Tzen KY, Wey SP et al (2004) 99mTC-TRODAT-1 imaging of multiple system atrophy. J Nucl Med 45:49–55

Papp MI, Kahn JE, Lantos PL (1989) Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral

degeneration, olivopontocerebellar atrophy and Shy–Drager syndrome). J Neurol Sci 94:79–100

Poewe W, Scherfler C (2003) Role of dopamine transporter imaging in investigation of Parkinsonian syndromes in routine clinical practice. Mov Disord 18(Suppl 7):S16–S21

Pricker W, Asenbaum S, Bencsits G et al (2000) [123I] β-CIT/SPECT in multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. Mov Disord 15:1158–1167

Quinn NP (2005) How to diagnose multiple system atrophy. Mov Disord 20(Suppl 12):S5–S10

Schenker C, Meier D, Wichmann W, Boesiger P (1993) Valavanis: age distribution and iron dependency of the T2 relaxation time in globus pallidus and putamen. Neuroradiology 35:119–124

Schocke MF, Seppi K, Esterhammer R, Kremser C, Jaschke W, Poewe W et al (2002) Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD. Neurology 58:575–580

Schrag A, Good CD, Miszkiel K, Morris HR, Mathias CJ, Lee AJ et al (1998) Clinical usefulness of magnetic resonance imaging in multiple system atrophy. J Neurol Neurosurg Psychiatry 65:65–71

Schulz JB, Skalej M, Wedekind D, Luft AR, Abele M, Voigt K et al (1999) Magnetic resonance imaging-based volumetry differentiate idiopathic Parkinson's syndrome from multiple system atrophy and progressive supranuclear palsy. Ann Neurol 45:65–74

Schwartz J, Weis S, Kraft E, Tatsch K, Bandmann O, Mehraein P, Vogl T, Oertel WH (1996) Signal changes on MRI and increase in reactive microgliosis, astrogliosis and iron in the putamen of two patients with multiple system atrophy. J Neurol Neurosurg Psychiatry 60:98–101

Seppi K, Schocke MFH, Wenning GK, Poewe W (2005) How to diagnose MSA early: the role of magnetic resonance imaging. J Neural Transm 112:1625–1634

Thomas M, Hayflick SJ, Jankovic J (2004) Clinical heterogeneity of neurodegeneration with brain iron accumulation (Hallervoden–Spatz syndrome) and pantothenate kinase-associated neurodegeneration. Mov Disord 19:36–42

Valentino P, Annesi G, Ciro Candiano IC, Annesi F, Civitelli D, Tarantino P et al (2006) Genetic heterogeneity in patients with pantothenate kinase-associated neurodegeneration and classic magnetic resonance imaging: eye of the tiger pattern. Mov Disord 21:252–254

Varrone A, Marek KL, Jennings D, Innis RB, Seibyl JP (2001) [123I] Beta-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy. Mov Disord 16:1023–1032

Weng YH, Yen TZ, Chen MC, Kao PF, Tzen KY, Chen RS et al (2004) Sensitivity and specificity of ^{99m}TC-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. J Nucl Med 45:393–400

Wenning GK, Colosimo C, Geser F, Poewe W (2004) Multiple system atrophy. Lancet Neurol 3:93–103