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ABSTRACTS

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HOW TO DIAGNOSE MSA EARLY - CLINICAL SKILLS

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The diagnosis of MSA remains clinical. This is particularly so in early MSA, before abnormalities may be evident on imaging, autonomic tests, or sphincter EMG.

A high index of suspicion helps, particularly if the patient is in their 50s. REM sleep behaviour disorder is very common as an initial feature in MSA (and Lewy body diseases), but uncommon in PSP. Ask about increased snoring, stridor, sleep apnoea and inspiratory sighs or gasps. As well as questioning about postural faintness, note any change in colour or temperature of hands or feet. Always ask about nocturia, frequency, urgency and incontinence, and double micturition or retention as symptoms of incomplete bladder emptying. Also enquire about erectile dysfunction in males.

Does the patient have a tremor that is jerky and irregular, and is there myoclonus (often stimulus-sensitive) of the extremities? If the patients tremor is classic pill-rolling, it makes MSA unlikely, only being present in less than 10% of cases. Has levodopa been ineffective or poorly tolerated? Are there atypical dystonic movements of the face or neck?

Is there incoordination, unsteadiness or slurred speech, square wave jerks, saccadic pursuit or nystagmus?

Emotional incontinence is often present in MSA and PSP. Significant cognitive impairment, or drug-induced hallucinations, are uncommon in MSA.

Even when core diagnostic criteria are not reached, many of these “red” or “pink” flags may point towards a diagnosis of MSA.

HOW TO DIAGNOSE MSA EARLY - AUTONOMIC TESTING

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Impairment of the autonomic nervous system is an integral component of multiple system atrophy, and is likely to provide information to help diagnosis, and also to aid management, both of which are ideally obtained early in the course of the disease. However, the multi-faceted involvement of the autonomic nervous system causes difficulties as a variety of systems can be involved. Autonomic involvement may also occur in other parkinsonian syndromes, and is being increasingly recognised in idiopathic Parkinson’s disease.

Autonomic testing is directed at obtaining information on activity, or function (dependent on target organs), or both. This overview will outline the current approaches to the evaluation of autonomic function in early MSA. There will be an emphasis on cardiovascular and sudomotor testing. The descriptions will include physiological tests that evaluate autonomic function, autonomic neurohormonal approaches including those which are dependent on the use of neuropharmacological probes, and autonomic neuroimaging.

HOW TO DIAGNOSE MSA EARLY – MAGNETIC RESONANCE IMAGING

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Multiple system atrophy (MSA) is a sporadic, progressive, adult onset disorder associated with varying degrees of parkinsonism, autonomic dysfunction, and cerebellar ataxia. Neuropathologically, MSA is characterized by selective neuronal loss and gliosis predominantly affecting the basal ganglia, substantia nigra, olivopontocerebellar pathways, and the intermediolateral cell column of the spinal cord. Diagnosis in life is often difficult, especially in early stages of the disease, and differentiation from Parkinson’s disease (PD) carries a high rate of misdiagnosis. Brain magnetic resonance imaging (MRI) offers the potential for objective criteria in the differential diagnosis of MSA, since it frequently shows characteristic abnormalities in the striatum, brainstem, and cerebellum in patients with MSA and is believed to be normal in patients with PD.

Abnormalities on routine MRI in patients with MSA, may include not only putaminal abnormalities (atrophy, T2 hypointensity and “slit-like” marginal hyperintensity), but also atrophy of the lower brainstem, middle cerebellar peduncles, and cerebellum, as well as hyperintensities in the pons, middle cerebellar peduncles, and cerebellum. Signal hyperintensities within the pons and middle cerebellar peduncles are thought to reflect degeneration of pontocerebellar fibres, these changes may occasionally resemble a hot cross bun.

Non-specific putaminal hypointensities may occur in patients with classical PD. However, hypointense putaminal signal changes were reported to be more frequent in MSA than in PD patients using T2-weighted gradient echo (GE) instead of T2-weighted fast spin echo images, indicating that T2-weighted GE sequences are of better diagnostic value for patients with parkinsonism.

MR spectroscopy (MRS) studies have shown reduced but overlapping n-acetylaspartate (NAA) to creatine and NAA to choline ratios in the lentiform nucleus of MSA-P versus PD patients and normal controls.

Diffusion-weighted imaging (DWI) may represent a useful diagnostic tool that can provide additional support for a diagnosis of MSA-P (Parkinson variant of MSA). DWI is able to discriminate MSA-P and both patients with PD and healthy volunteers on the basis of putaminal ADC (apparent diffusion coefficients) and Trace(D) (trace of diffusion tensor) values. The increased putaminal diffusivity in MSA-P is likely to reflect ongoing striatal degeneration, whereas most neuropathologic studies reveal intact striatum in PD. But, since in progressive supranuclear palsy (PSP) compared to PD, rADCs were also
significantly increased in both putamen and globus pallidus, increased putaminal rADC values do not discriminating MSA-P from PSP.

Significant reductions in mean striatal and brainstem volumes were found in patients with MSA-P, MSA-C (cerebellar variant of MSA), and PSP, whereas patients with MSA-C and MSA-P also showed a reduction in cerebellar volume. More recently, voxel-based morphometry confirmed previous region of interest (ROI)-based volumetric studies showing basal ganglia and infratentorial volume loss in MSA-P patients. These data also revealed prominent cortical volume loss in MSA-P mainly comprising the cortical targets of striatal projections such as the primary sensorimotor, lateral premotor cortices and the prefrontal cortex. MR-based volumetry is a helpful tool to investigate the progression of cortical and subcortical atrophy patterns in MSA compared to other disorders, however, it cannot be applied for routine diagnostic work-up of individual patients.

In conclusion, it is often difficult to distinguish clinically between patients with MSA and PD. Magnetic resonance imaging including routine, spectroscopic, and volumetric MRI as well as DWI may be helpful in the differential diagnosis of MSA versus PD and may thus increase the diagnostic accuracy of the neurologist’s assessment. However, the value of the MR abnormalities have to be confirmed prospectively in larger patient cohorts, especially in very early stages when the clinical diagnosis remains uncertain.

SPECT IMAGING IN MULTIPLE SYSTEM ATROPHY

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Neuropathological studies have shown that approximately 20% of patients diagnosed in life with Parkinson’s disease (PD) may prove at post-mortem to have another form of parkinsonism, particularly multiple system atrophy (MSA). Diagnostic errors may occur because MSA patients, particularly those with the striatonigral type, often present with clinical features that are classically ascribed to PD. The identification of MSA patients in life, possibly early in the disease course, has clinical relevance, both therapeutically and clinically.

Currently, no definite diagnostic tests are available to help the clinician when the clinical diagnosis between PD and MSA is uncertain.

Functional studies with single photon emission computed tomography (SPECT) may provide a means to detect early parkinsonism as well as to discriminate between MSA and PD. Abnormalities detected by neuroimaging studies are consistent with neuropathological findings in the two diseases: degeneration mainly confined to the substantia nigra and locus ceruleus in the midbrain in PD, more widespread degeneration with involvement of striatal projection neurons in MSA. SPECT studies with dopamine transporter tracers like 123I-Ioflupane have generally reported decrements in the striatum similar to PD. By contrast, functional studies with 99mTc-ethylene-dicyesteine dihydroxyphenylalanine (ECD/SPECT) and of striatal dopaminergic receptors (IBZM/SPECT) have shown involvement of the post-synaptic dopaminergic system particularly in patients with MSA-P. Given the greater diffusion and practicability of those studies possibly in combination with MRI we think that SPECT imaging may prove a useful tool to help the neurologist in the identification of patients with atypical parkinsonism.

POSITRON EMISSION TOMOGRAPHY AND SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IN THE DIAGNOSIS OF MULTIPLE SYSTEM ATROPHY

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The clinical criteria established for the diagnosis of multiple system atrophy (MSA) do not require structural or functional imaging. Nevertheless, positron emission tomography (PET) imaging may contribute to clinical diagnosis by differentiating MSA from pure autonomic failure (PAF) and from idiopathic Parkinson’s disease (IPD), and by predicting the future course of sporadic olivopontocerebellar atrophy (sOPCA). Both PET and SPECT have also been used to characterize subgroups of MSA, detect involvement of other organ systems, and examine the pathogenesis of the sleep disturbances, REM sleep behavior disorder (RBD) and obstructive sleep apnea (OSA). Fulham et al. found that PET-[18F]fluorodopa (FDG) could differentiate clearly between MSA and PAF. Otsuka et al. reported that [18F]fluorodopa (FDA) was more useful than [18F]FDG in differentiating between Parkinson’s disease and MSA. Rinne et al. found decreased striatal [18F]FDA binding in seven and decreased striatal [11C]diprenorphine binding in four out of 10 patients with sOPCA, all of whom had autonomic failure. (By definition, however, all had MSA-C). Multiple studies utilizing SPECT-[123I]MBG have shown markedly decreased cardiac uptake in IPD patients with Hoehn-Yahr stages 3-5, and some investigations report normal but others find reduced uptake in MSA. Using PET-[18C]fluorodopa (FED), Berding et al. found reduced cardiac uptake in IPD but normal uptake in MSA. My colleagues and I have carried out several related studies. Initially, we compared MSA with sOPCA (without autonomic failure) using [18F]FDG and found markedly decreased ICMRglc in the brainstem, cerebellum, putamen, thalamus and cerebral cortex in both disorders as compared to normal controls, but lower ICMRglc in the basal ganglia and thalamus in MSA than in sOPCA. Later, we examined striatal binding of (±) [11C]dihydroxytetabenazine (DTBZ), the type-2 vesicular monoamine transporter in MSA and sOPCA (without autonomic failure), finding significantly decreased binding in both patient groups compared to controls, but greater deficits in MSA than in sOPCA. Subsequently we used the (+) enantiomer of [11C]DTBZ in MSA patients divided into those with prin-
Multiple system atrophy (MSA) is a degenerative disease manifesting a combination of parkinsonism, cerebellar, pyramidal, and autonomic (including urinary, sexual and anorectal) dysfunction. It is pathomorphologically defined, but lacks a definitive clinical diagnostic test. Sphincter EMG, reflecting Onuf’s nucleus degeneration, has been proposed as a helpful test, but the issue is controversial.

In patients with probable MSA, abnormal sphincter EMG, as compared to control subjects, has been found in the majority of patients in all the different forms of the disease in most studies, including patients who, as yet, have no urological or anorectal problems.

Technically, an important issue to determine the abnormality of sphincter EMG seems to be the way the EMG signal is analysed: the distinguishing feature of MSA seems to be motor unit potentials (MUPs) with late components (thus being of very long duration). The traditional method (“single MUP” analysis of the EMG signal) is good at recognizing such MUPs (with so-called satellite potentials), the recently standardized, more efficient and less biased “multi-MUP” technique, however, is not.

(SPHINCTER EMG IN DIFFERENTIAL DIAGNOSIS OF MULTIPLE SYSTEM ATROPHY)

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Multiple system atrophy (MSA) is a degenerative disorder characterized by progressive autonomic failure with cerebellar, pyramidal and extrapyramidal signs due to a diffuse neurodegenerative process. The latter results in a more aggressive course, dopaminergic drug resistance, and more frequent sleep disorders and excessive daytime sleepiness compared to patients with Parkinson’s disease (PD). In fact, at the same disease duration, we found a higher incidence and variety of sleep disorders in patients with MSA than in those with PD. This paralleled the increasing severity of motor signs and the wider diffusion of the underlying degenerativ process, which involves neuronal substrates for sleep organisation and maintenance, such as the brainstem nuclei and/or basal ganglia. Among these sleep disorders, sleep-related breathing disturbances and REM sleep behaviour disorder (RBD) are prominent features in MSA patients with RBD sometimes preceding motor signs, as has been shown in alpha-synucleinopathies. However, whereas RBD represents the most common and most easily treatable clinical sleep manifestation and polysomnographic (PSG) finding in those patients, inspiratory nocturnal stridor appears to be a typical poor prognosis condition associated with sudden death during sleep in MSA. Often associated with sleep-breathing disorders of various types, its management is not yet well established. Results from audio and video monitored PSG in twenty-one MSA patients in whom stridor and/or sleep related respiratory disturbances were clinically suspected, showed abnormal baseline PSG in all patients with augmented sleep latencies, reduction of total sleep time, sleep fragmentation, and reduction of slow wave
sleep (stages 3 and 4) and REM sleep, thus confirming our previous findings in the questionnaire-based study. Of the total group, 3 patients (14%) presented with a typical obstructive sleep apnoea syndrome (mean apnoea-hypopnoea index = 37) without stridor, whereas 14 (67%) presented stridor occurring alone (apnoea-hypopnoea index ≥ 10) or accompanied by apnoea (apnoea-hypopnoea index ≥ 10). Six out of these 14 patients with stridor presented predominantly obstructive apnoeas whereas apnoeas of the central type were predominantly seen in 1 patient and mixed apnoeas in another. Mixed apnoeas were seen only in patients with stridor and were always preceded by prolonged inspiratory effort suggestive of upper airway resistance, although inspiratory oesophageal pressure was not monitored. Among the 12 patients (71%) who agreed to initiate CPAP, only 4 (33%) are still undergoing treatment. These 4 patients showed good compliance with CPAP (≥ 3 h/night) and had a significantly less severe disease at the time of CPAP initiation compared to those who discontinued CPAP (mean Hoehn & Yahr stage = 2.7±1 vs 4.9±0.4, p=0.0005). Age, disease duration and apnoea-hypopnoea index did not differ significantly between the two groups. The mean duration of follow-up for these 4 remaining patients was 20.5 months (range 7-35 months) and the mean nightly use was 4h42. Both patients and their spouses reported more efficacious nocturnal sleep and improved daytime alertness after CPAP initiation. Although depression may cause lack of motivation and lead to poor compliance and/or treatment discontinuity, particularly when the inevitable worsening of motor status leads patients to question the usefulness of the treatment, the presence of isolated stridor and the severity of motor impairment appear to be the most significant limiting factors for CPAP usage and acceptance especially at the beginning of treatment. Giving intensive support to both families and patients may improve CPAP compliance in MSA patients with sleep-related breathing disorders. Meeting this condition would seem to be mandatory before conducting further studies to assess the role of CPAP in the survival of these patients.

**THE EUROPEAN MSA STUDY GROUP**

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The EMSA-SG is an academic network comprising 20 centres across Europe and Israel set up in January 1999. This international forum of established experts under the guidance of the University Hospital of Innsbruck as coordinating center has been supported by the 5th framework program of the European Union since March 2001 (QLK6-CT-2000-00661).

The primary goals of the network include a central registry for European MSA patients, a central DNA bank, and the development and validation of a novel Unified MSA Rating Scale (UMSARS) using a multicentre cross-sectional as well as a prospective approach by means of a natural history study (NHS). The latter will yield rates of progression of both motor and non-motor symptoms or signs using UMSARS as well as other serial clinical and para-clinical assessments.

The EMSA-SG registry is a computerized data base located at the coordinating centre in Innsbruck. The data base collects diagnostic and therapeutic data from 20 centres using a “minimal data set”, which was adopted from the German Competence Network Parkinson. MSA patients and controls are recruited into the decentralized EMSA-SG DNA bank.

UMSARS is a novel specific rating instrument that has been developed and validated by EMSA-SG to standardize severity assessments in specialized clinics and research programs world-wide. The assessment of NHS patients comprises basic demographic and clinical data as well as a range of scales including UMSARS, UPDRS, measures of global disability, Red Flag list, Mini-Mental-State Examination, quality of life measures (EQ-5D and SF-36) as well as the Beck Depression Inventory. In a subgroup of patients dysautonomic features are recorded in detail using the Queen Square Cardiovascular Autonomic Function Test Battery, the Composite Autonomic Symptom Scale as well as serial measurements of residual urinary volume. Most of these measures are repeated at 6-monthly follow-up visits for a total study period of 24 months. Surrogate markers of the disease process (progression indices) are identified by the EMSA-SG using structural neuroimaging (MRI) and diffusion weighted imaging (DWI) and are correlated with the clinical data.

More than 300 patients have been recruited into the EMSA registry and more than 200 have donated DNA for research. The first candidate gene studies were launched in 2003. A preliminary NHS baseline analysis of 131 patients with a clinical diagnosis of MSA recruited into the NHS at 14 EMSA-SG sites (Aarhus, Barcelona, Bonn, Innsbruck, Kiel, Lisbon, London, Lund, Marburg, Milan, Naples, Petach-Tiqva, Tel-Aviv, Tübingen) further corroborates the utility of the novel rating scale UMSARS. Dysautonomia and motor impairment clearly impair HR-QoL and in particular perceived physical well-being. Depression appears to be more common in MSA than previously recognized. Further, there are common warning signs of MSA to be included as supportive clinical features in a revised set of clinical diagnostic criteria.

For the first time, prospective data concerning disease progression will become available allowing us to reliably identify predictors of survival. Such data about the natural history and prognosis of MSA as well as surrogate markers of the disease process will enable more effective planning and implementation of future multicentre phase II/III neuroprotective intervention trials within the next few years. Future therapeutic trials across Europe are also promoted by the EMSA-SG registry. Indeed, a trial on growth hormone in MSA is just being completed, and another on minocycline has just been launched. Moreover, the EMSA-SG registry will be helpful for refining current diagnostic and therapeutic standards. The EMSA-SG DNA Bank facilitates further ecogenetic studies in MSA in order to identify genetic risk factors for MSA.
OVERVIEW OF THE NORTH AMERICAN MSA STUDY GROUP (NAMSA-SG)

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In the autumn of 2003, the National Institutes of Health awarded our group a program project grant – “Pathogenesis and Diagnosis of Multiple System Atrophy.” The work involves four projects and four cores, which interact to elucidate the causes of MSA and to improve the diagnosis of MSA. Core A will orchestrate the enrollment of 175 subjects with clinically probable MSA and 350 case control subjects at 11 of the leading centers for MSA research in the USA. Data on the subjects is entered into a web-based data entry system in Core B, which was developed by Drs Susanne May and Ron Thomas at UCSD. Project 1, which is led by Dr Caroline Tanner at the Parkinson’s Institute, will conduct structured telephone interviews with the subjects to identify environmental risk factors. In Core D, Dr Laurie Ozelius’ laboratory at Albert Einstein College of Medicine will analyze DNA collected from the subjects to identify genetic risk factors. Core D, which is led by Dr John Trojanowski at the University of Pennsylvania, will provide pathological assessment of MSA brains. Project 2, which is led by Dr Virginia Lee at the University of Pennsylvania, will perform biochemical and molecular biological studies of alpha-synuclein in the autopsy samples. Project 3, which will be carried out by Drs Cliff Shults and Eliezer Masliah at UCSD, will study transgenic mice in which alpha-synuclein is over-expressed under the control of the myelin basic protein promoter or the platelet-derived growth factor promoter. Project 4, which is led by Dr Phillip Low at the Mayo Clinic, will further characterize the autonomic deficits in MSA.

MANAGEMENT OF MULTIPLE SYSTEM ATROPHY: STATE OF THE ART

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Symptomatic treatment of multiple system atrophy (MSA) is largely aimed at alleviating parkinsonism and dysautonomia, since there is virtually no effective treatment for the cerebellar features of the disease.

Parkinsonism - The commonly held belief that patients with MSA are non- or poorly levodopa-responsive is misleading. Clinical series have documented levodopa efficacy in up to 40% of patients with MSA, while data obtained from series with pathological confirmation are even more variable, with rates of beneficial response ranging between 30% and 80%. However, whatever response there is, it usually declines after a few years of treatment and dyskinesia, often dystonic and predominant in the orofacial district, emerges in half of the patients. Results with dopamine agonists are also variable, but these compounds are no more effective than levodopa and often poorly tolerated. Despite anecdotal benefit in single cases, a short-term open trial with amantadine in patients with MSA was negative, while results from a small placebo-controlled trial are awaited soon. Anticholinergics do not usually improve motor symptoms, but they may be helpful when sialorrhoea is severe and disturbing. Ablative neurosurgical procedures such as pallidotomy failed to improve parkinsonian motor disturbance in MSA. However, beneficial short-term effects of bilateral subthalamic high-frequency stimulation have recently been reported in a few patients with MSA. Further studies are needed to establish the role of deep brain stimulation in MSA. Because the results of pharmacological treatment for MSA motor disorder are often poor, supportive therapies are particularly important. Physiotherapy helps maintain mobility and prevent contractures, and speech therapy can improve speech and swallowing and provide communication aids. Dysphagia may require feeding via a nasogastric tube or, better, percutaneous endoscopic gastrostomy (PEG). These palliative management decisions should be based on careful clinical judgement, taking into account the expectations of both patient and caregivers.

Autonomic dysfunction - Treatment of orthostatic hypotension (OH) is crucial to improve the quality of life in patients with MSA and autonomic dysfunction. The treating physician should not to be excessively concerned about a low standing blood pressure when the patient is asymptomatic. Indeed, patients with MSA may tolerate well a decreased standing systolic blood pressure, probably because their cerebral blood flow is kept at an adequate level thanks to autoregulation. When OH becomes disabling it can often be alleviated by avoiding precipitating factors, such as the effects of large meals, alcohol, drugs, straining during micturition and defecation, and exposure to a warm environment. Other non-pharmacological strategies also recommended are elastic stockings, head-up tilt of the bed at night, and increasing salt intake. A variety of pharmacological agents with different mechanisms of action, such as fludrocortisone, desmopressin, clonidine, yohimbine, midodrine, L-threodihydroxyphenylserine (L-DOPS), and ergot derivatives, have been used to reduce OH. Most specialists consider fludrocortisone and midodrine as the first-choice drugs for this condition; unfortunately, trials comparing drugs used to treat OH are not available, and the choice among them should be made according to the experience of the treating physician and the individual characteristics of the patient. Urinary symptoms in MSA are due to a complex mixture of central and peripheral neurological problems, sometimes superimposed on local pathology such as prostatic hypertrophy and perineal laxity. Peripherally acting anticholinergic drugs may help incontinence, but often at the expense of inducing retention; the administration of desmopressin at night may reverse nocturia. Intermittent self-catheterisation or even an indwelling catheter may be needed in the presence of incomplete bladder emptying. Male impotence can be effectively circumvented by the use of phosphodiesterase inhibitors. A recent placebo-controlled study showed that sildenafil is efficacious in the treatment of erectile dysfunction in MSA, but it may unmask or exacerbate orthostatic hypotension. Therefore, careful measurement of lying and standing blood pressure is recommended before prescribing this compound.
THIN SECTION MR STUDY OF THE BASAL GANGLIA IN THE DIFFERENTIAL DIAGNOSIS BETWEEN MSA-P AND PARKINSON’S DISEASE


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Signal abnormalities within the putamen in MRI have been related to tissue degeneration in the striatonigral variant of multiple system atrophy (MSA-P). While previous work demonstrated the high specificity of these MR findings, sensitivity rates were unsatisfactory. We evaluated the specificity and sensitivity of an acquisition protocol using thin section MRI to differentiate MSA-P from Parkinson disease (PD).

Axial 3-mm-thick conventional T2 and proton density spin echo images at the level of basal ganglia were acquired at 1.5 T in 24 patients with MSA-P and 27 patients with PD.

We found an abnormal putaminal T2 hypointensity in 21 out of 24 MSA-P patients (87.5% sensitivity) and a proton density hyperintensity in 20 out of 24 MSA-P patients (83.3% sensitivity). Three out of 27 PD patients had an abnormal putaminal T2 hypointensity (88.8% specificity) and there were no proton density abnormalities (100% specificity).

Our thin section conventional spin echo protocol showed a substantial increase in MR sensitivity compared with previous reports. We believe that a better depiction of even mild signs of degeneration in the putamen may allow a more widespread use of this technique in the differential diagnosis of parkinsonisms.

ECD/SPECT STRIATAL PERFUSION AND MRI SIGNAL MEASUREMENTS IN THE EARLY DETECTION OF MULTIPLE SYSTEM ATROPHY

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The aim of this study was to study sensitivity of neuroimaging markers of MSA at early disease stage.

Previous neuroimaging studies of striatal function with PET and SPECT have revealed a characteristic pattern associated with atypical parkinsonism. Those studies focused mostly on patients at an advanced disease stage. However, diagnostic uncertainties are more common as soon as levodopa response starts declining or impairment of the autonomic system complicates symptoms.

ECD/SPECT and MRI scanning was performed in 12 patients with multiple system atrophy (striatonigral type) at H&Y stage II (age: 59±8 years). MSA patients were investigated as soon as the physician had expressed the clinical suspicion of MSA. Clinical diagnosis had been confirmed in all cases during a follow-up of at least 2 years. Data were compared with those of a group of 18 other MSA patients (age: 60±4 years; H&Y stage III-IV) with more advanced disease and with 30 patients with classical Parkinson’s disease (PD) (age: 63±5 years; H&Y stage II-III). For ECD/SPECT standardized elliptical regions of interest (ROIs) were determined in three adjacent transaxial slices in the basal ganglia (caudate nucleus and lentiform).

In the putamen two regions were identified after individual MRI matching: one in the anterior and the other in the posterior part of the structure. For MRI we evaluated the presence of putaminal T2 hypointensity relative to globus pallidus and of a hyperintense band in the lateral putamen on proton density images. Striatal MRI signal was visually evaluated on T2 and proton density scans. An investigator blind to the status of the patient analyzed all scans. Sensitivity and specificity were calculated in detecting MSA vs PD.

We found significant perfusion decrements in the putamen of early MSA compared to PD (p<0.001). Reductions were more pronounced in the posterior part of the putamen compared to the anterior part (p<0.01). Putamen values in advanced MSA patients were lower than in their early MSA counterparts (p<0.01) Discriminant analysis revealed that 11/12 early MSA had been correctly categorized with a sensitivity of 92%.

By contrast MRI showed signal abnormalities only in 9/12 patients with a sensitivity of 75%.

ECD/SPECT imaging can reliably identify MSA patients at an early disease stage based on their striatal perfusion values. Perfusion decrements appear more pronounced in the posterior than the anterior portion of the putamen. Sensitivity of MRI scanning appears to be lower at early stage. Perfusion and signal abnormalities are likely to be related to degeneration of striatal projection neurons.

EFFECTS OF RILUZOLE AS “RESCUE THERAPY” IN AN MPTP + 3-NP MOUSE MODEL OF STRIATONIGRAL DEGENERATION: EXPERIMENTAL RATIONALE FOR ITS USE IN MULTIPLE SYSTEM ATROPHY


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Only symptomatic treatments of limited efficacy are available in striatoniagral degeneration (SND)/multiple system atrophy-parkinsonism (MSA-P). We investigated the potency of riluzole, an anti-glutamatergic drug, to jam the neuronal death process in a phenotypic MPTP + 3-nitropropionic acid mouse model of SND/MSA-P.
The study design was an experimental study in mice. We used a “neuronal rescue” strategy by administering riluzole (for 7 days) only after the end of intoxication. The motor disorder, its recovery, behavioral performances at motor and sensorimotor integration tests (rotarod, pole test, traversing a beam, open-field), and histopathological outcome were compared in the control (saline, n=7) and riluzole groups (10 mg/kg, n=7; 20 mg/kg, n=7), matched by triplets for motor severity.

While riluzole did not produce any effect on the gross motor disorder or on rotarod task or open-field kinetic variables, riluzole allowed better recovery on the beam-traversing task and the pole test. Accordingly, the histopathological outcome was significantly better in the riluzole-treated mice regarding both nigral and dorsolateral striatal cell loss and astrogial activation, with a dose-effect relationship.

Thus, riluzole induces subtle symptomatic effects but has “neuronal rescue” properties in an SND/MSA-P phenotypic animal model.

The study was supported by Université Victor Segalen-Bordeaux2, France Parkinson.

DEPRESSION IN MULTIPLE SYSTEM ATROPHY (MSA) – A PRELIMINARY CROSS-SECTIONAL ANALYSIS OF 95 EUROPEAN MSA PATIENTS

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The EMSA-SG is an academic network comprising 23 centres across Europe and Israel that has been supported by the 5th framework program of the European Union since March 2001 (QLK6-CT-2000-00661). The primary goal of the network is to validate the novel Unified MSA Rating Scale (UMSARS) using a multicentre cross-sectional as well as prospective study approach.

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterised clinically by any combination of parkinsonian, autonomic, cerebellar, or pyramidal signs. MSA is associated with marked disability and handicap, however, the likely occurrence of depression has never been determined in a large patient cohort.

The aims of the current study were: 1) to assess the frequency and severity of depression, and 2) to examine the relationship of depressive symptoms with global disability, motor symptoms, activities of daily living using the Beck Depression Inventory (BDI) as well as a range of additional scales.

The BDI is a widely used self-administered 21-item depression inventory comprising answer options from 0-3 and a maximum score of 63 with defined cut-off scores (normal range: 0-9; minimal, mild to moderate or severe depression: 10-15, 16-19 and 20-29 respectively). The overall severity of depression was correlated with the global disability using a 3-point severity scale (SS3) and UMSARS IV as well as with a range of scales including the Unified Parkinson’s Disease Rating Scale (UPDRS) I (Mentation, Behaviour, and Mood), UPDRS II (Activities of Daily Living – ADL), Unified MSA Rating Scale (UMSARS) I (ADL), Schwab & England ADL, UMSARS Part II (Motor Examination scale – ME), and Hoehn and Yahr Parkinson’s Staging (H&Y).

95 MSA patients (MSA-P: 61%, MSA-C: 39%, male:female ratio: 1:0.6) were analysed. Mean age at symptom onset was 57 years; age or disease duration at the time of analysis was 62 years and 5 years respectively.

The mean BDI score was 15±9 with no significant differences in sex, motor subtype, or diagnostic categories. Some degree of depression was present in 78% of subjects (minimal 30%, mild to moderate 23%, moderate to severe 18%, severe 7%). Mean BDI scores correlated with global disability measures as well as with UMSARS I and II, and UPDRS I and II. BDI scores did not correlate with age at symptom onset or disease duration.

Depression appears to be more common in MSA than in Parkinson’s disease.
Previously recognized. Motor impairment seems to determine the degree of depression regardless of age, disease duration, and cerebellar or parkinsonian presentation. Depression should be recognized as a therapeutic target in the management of MSA.

### WARNING SIGNS (‘RED FLAGS’) IN POSSIBLE MSA: A PRELIMINARY CROSS-SECTIONAL ANALYSIS OF THE EUROPEAN MSA STUDY GROUP (EMSA-SG)

F. Geser, M. Stampfer-Kountchev, K. Seppi, J.P. Ndayisaba, C. Frick, W. Poewe, G.K. Wenning and the EMSA-SG

In spite of advances in recent years, the diagnosis of MSA remains problematic. Besides the poor response to levodopa, and the additional presence of pyramidal or cerebellar signs (ataxia) or autonomic failure as cardinal diagnostic features, certain other features may raise the clinical suspicion of MSA. Recently, these diagnostic pointers towards MSA, so-called ‘red flags’, have been defined operationally excluding cardinal diagnostic features and non-specific features suggesting atypical parkinsonism (such as rapid progression or early instability and falls) for use in daily clinical practice and prospective clinicopathological studies.

The frequency and diagnostic role of red flags in possible MSA has never been determined prospectively. Therefore EMSA-SG has launched a natural history study incorporating a serial red flag screening throughout a 2-year study period. Here we present a preliminary baseline analysis of European MSA patients for the most salient red flags that have been associated with early MSA.

48 patients were classified as possible MSA according to the Gilman clinical diagnostic criteria. Mean age at symptom onset was 57 years; age and disease duration at the time of analysis were 63 and 6 years, respectively.

Motor red flags: Severe atypical dysarthria occurred in 59% of cases. Axial deformity was present in 48% of patients including atypical spontaneous or L-Dopa induced dystonia predominantly affecting orofacial muscles (21%), prolonged episodes of lateral trunk flexion (Pisa syndrome) (28%), and a disproportionate antecollis comprising a severe neck flexion with minor flexion elsewhere (22%). Furthermore, irregular (jerky-myoclonic) postural or action tremor of the hands and/or fingers developed in 27% of cases.

Non-motor red flags: Abnormal respiration occurred in almost 42% of patients including inspiratory stridor (19%), involuntarily deep sighs/gasps (34%), sleep apnoea (13%), and excessive snoring (22%). Further non-motor red flags included REM sleep behavior disorder (39%), and emotional incontinence (inappropriate crying or laughing [27%]). Cold hands/feet were present in 26%, whereas Raynaud’s phenomenon was noted just in 7% of patients.

The present study suggests that atypical dysarthria, axial deformity and abnormal respiration are the most common red flags in possible MSA and they may therefore be included as supportive clinical features in a revised set of diagnostic criteria to be developed by EMSA-SG.

### NON-INVASIVE CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) IN MULTIPLE SYSTEM ATROPHY (MSA) PATIENTS: LONG TERM ACCEPTANCE

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The aim of the study was to assess the long-term acceptance of nasal CPAP in MSA patients with PSG-confirmed sleep apneas and/or nocturnal stridor.

Inspiratory nocturnal stridor is a typical poor prognosis condition associated with sudden death during sleep in MSA. Often associated with sleep-breathing disorders of various types, its management is not yet well established.

Twenty-one MSA patients with clinical suspicion of stridor and sleep-related respiratory disturbances were investigated by means of audio-video monitored PSG. Patients in whom the first PSG disclosed either a sleep apnea/hypopnea index (AHI) of > 10, or inspiratory stridor without apneas, or both, underwent a second PSG for CPAP titration.

Two patients presented with a typical obstructive sleep apnea syndrome without stridor, whereas 15 patients presented stridor occurring alone or accompanied by apneas (AHI ≥ 10). Seven out of these 15 patients with stridor presented predominantly obstructive apneas. Eleven patients agreed to pursue CPAP at home. Two patients died 2 to 3 days after CPAP initiation, 3 discontinued CPAP usage after the first week and 1 after 10 months of follow up because of discomfort. One patient died after 17 months of follow up. The 4 remaining patients reported more efficacious sleep and improved daytime alertness. The mean duration of follow up after CPAP treatment initiation for these patients was 20.5 months and the mean nightly usage was 5h15. Patients showing good compliance with CPAP had significantly less severe disease at the time of CPAP initiation. Age, disease duration and AHI did not differ significantly between the two groups.

The presence of isolated stridor and the severity of motor impairment at treatment initiation appear to be the most significant limiting factors for CPAP usage and acceptance. It is difficult to draw firm conclusions about CPAP direct involvement in the fatal outcome in 2 of our patients. Efforts should be made to improve support of MSA patients and their compliance to treatment before further studies are conducted to assess the role of CPAP in the survival of these patients.

This study was supported by a PHRC 97 grant and a CHU de Bordeaux-CNRS fellowship.
SLEEP DISORDERS IN MULTIPLE SYSTEM ATROPHY: A POLYSOMNOGRAPHIC STUDY


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The aim of this study was to assess the type and extent of breathing, heart and motor abnormalities during sleep in multiple system atrophy (MSA).

Nineteen consecutive patients with MSA referred to our neurological department were examined for sleep disturbances.

All patients underwent a video-polysomnographic recording. A comparative analysis was performed versus 10 patients with obstructive sleep apnoea syndrome (OSAS).

All MSA patients displayed snoring, 42% stridor, and 37% OSAS. Paradoxical breathing was present in 53%. Mean sleep SaO₂ was 92.7%, with lowest value of 86%. A significant increase in breathing rate from wakeful state to NREM and REM sleep and higher heart rate during sleep were detected in patients with stridor. Intercostalis and tibialis anterior EMG activity in the form of continuous muscle recruitment pattern and repetitive motor unit potential discharges was found in MSA patients, more often in those with stridor. 88% had periodic limb movements during sleep (PLMS), and 100% had REM sleep behaviour disorders (RBD). None of the OSAS patients had RBD, and none exhibited respiratory muscle and tibialis anterior EMG tonic activity, PLMS recurring in 60%.

Abnormal autonomic and motor overactivity during sleep, involving respiratory and limb muscles is characteristic of MSA patients and suggests a general impairment of sleep homeostatic integration. These features should be looked for in the diagnostic work up of the disease.

EXPRESSION OF ALPHA-SYNUCLEIN MRNA IN MULTIPLE SYSTEM ATROPHY

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Alpha-synuclein (ASYN) is a major constituent of glial cytoplasmic inclusions (GCIs), which are pathognomonic for multiple system atrophy (MSA). We have previously demonstrated that in the normal human brain, ASYN mRNA has a restricted pattern of neuronal expression and no apparent glial expression. The current study used in situ hybridization to determine whether ASYN mRNA is expressed by the oligodendroglia of MSA cases. Film autoradiography confirmed the restricted pattern of ASYN mRNA expression in the brain. Cellular analyses focused on melanin-containing dopamine neurons of substantia nigra and on parafascicular oligodendroglia of crus cerebri, a GCI-rich region ventral to the substantia nigra. In our first analysis, oligodendroglia that were identified by the presence of the transcript for proteolipid protein had negligible levels of ASYN mRNA relative to the abundance of this transcript detected in nigral dopamine neurons. Another analysis tested for a possible correlation between ASYN mRNA levels and GCI presence in oligodendroglia. In MSA-P (parkinsonian phenotype), similar low levels of ASYN mRNA were observed in GCI-positive and GCI-negative oligodendroglia, while in MSA-C cases (cerebellar phenotype) ASYN mRNA was elevated.
in GCI-positive oligodendroglia relative to nearby GCI-negative oligodendroglia. This suggests that ASYN mRNA overexpression may play a role in GCI formation of MSA.

EVIDENCE FOR DOPAMINERGIC RE-INNERRATION BY EMBRYONIC ALLOGRAFTS IN AN OPTIMIZED RAT MODEL OF THE PARKINSON VARIANT OF MULTIPLE SYSTEM ATROPHY

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Failure of conservative drug treatment to ameliorate disabling parkinsonism associated with multiple system atrophy (MSA) creates a strong need for alternative treatment strategies. In order to test neurorestorative and neuroprotective approaches our group has created a number of animal models of striatonigral degeneration (SND) the core pathology underlying progressive parkinsonism associated with MSA (MSA-P) using either intracerebral or systemic injections of established nigral and striatal toxins (6-hydroxydopamine, quinolinic acid, 3-nitropropionic acid, MPTP).

Using embryonic allografts of either nigral, striatal or combined striatonigral tissue we were able to consistently show graft survival in a denervated and lesioned striatum using both histological and autoradiographic analyses as well as improvement of rotational behaviour. However, due to severe lesions of the striatum and the chosen time window of 3-6 weeks between lesion and grafting, severe gliosis led to demarcation of the graft and prevented re-innervation of the remaining adult striatum. The aim of the present study was to modify our “double toxin-double lesion” rat model by reducing the dose of quinolinic acid injected into the striatum from 150 nmol to 75 nmol (thereby creating a model of minimal change MSA-P) and shortening the interval between lesion and grafting to 1-2 weeks.

Male Wistar rats received sequential unilateral injections of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle and after 4 weeks quinolinic acid (QA) into the dorsolateral striatum of the same side. Dopaminergic denervation was confirmed by amphetamine-induced rotation tests.

Animals were randomly divided into 2 treatment groups receiving either mesencephalic grafts or implantation medium. In order to optimize graft survival a caspase inhibitor (AcYVAD) and a spintrapping agent (Tirilazad) were added into the implantation medium. 23-24 weeks after the grafting procedure animals were perfused and processed for immunohistochemistry. The number of remaining tyrosinehydroxylase (TH)-positive neurons in the substantia nigra pars compacta (SNC), striatal lesion volume and cell loss of DARPP-32 positive striatal neurons as well as graft volume and number of TH-positive grafted cells were defined stereologically.

6-OHDA injection resulted in a significant cell loss of TH-positive neurons in SNC (p<0.0001), 75 nmol QA led to a significant reduction of DARPP-32 positive neurons (p<0.005) and volume (p<0.0001) in the striatum.

Analysis of embryonic mesencephalic grafts showed graft survival in all animals, mean number of surviving neurons was 7832±3123, mean graft volume 2.45 µm\textsuperscript{2}±0.97. Outgrowth of embryonic mesencephalic neurons and re-innervation of adult striatum was observed.

Modification of our established 6-OHDA and QA double lesion model by reducing the amount of QA injected improves the capacity for graft-outgrowth and dopaminergic re-innervation. Considering embryonic transplantation as a possible future antiparkinson therapeutic intervention in MSA-P patients our preliminary data stress the need for optimal patient selection, i.e., early disease stage with limited striatal dysfunction.

ANNULAR ALPHA-SYNUCLEIN OLIGOMERS RELEASED FROM GLIAL INCLUSIONS ISOLATED FROM MULTIPLE SYSTEM ATROPHY BRAINS

D.L. Pountney, R. Lowe, N.H. Voelcker, W. Ping Gai

Flinders University, Adelaide, Australia

Multiple system atrophy (MSA) is an alpha-synucleinopathy characterized by the formation of oligodendroglial inclusions that contain abundant alpha-synuclein filaments. Although strong evidence indicates that abnormal alpha-synuclein contributes to the pathogenesis of alpha-synucleinopathies via a gain of toxic function, the precise mechanism by which alpha-synuclein is linked to neural cell death is unclear. Previous in vitro studies show that the assembly of alpha-synuclein filaments proceeds via spherical and annular oligomeric species. The annular alpha-synuclein species permeabilized lipid vesicles and may exhibit cytotoxicity by a mechanism analogous to bacterial pore-forming toxins. We therefore examined whether such alpha-synuclein species could be demonstrated from pathological material.

We used an immuno-affinity purification procedure to isolate glial cytoplasmic inclusions (GCIs) from post-mortem MSA brains and dissociated the inclusions with wild bacterial pore-forming toxins. We therefore examined whether such alpha-synuclein species could be demonstrated from pathological material.

Using embryonic allografts of either nigral, striatal or combined striatonigral tissue we were able to consistently show graft survival in a denervated and lesioned striatum using both histological and autoradiographic analyses as well as improvement of rotational behaviour. However, due to severe lesions of the striatum and the chosen time window of 3-6 weeks between lesion and grafting, severe gliosis led to demarcation of the graft and prevented re-innervation of the remaining adult striatum. The aim of the present study was to modify our “double toxin-double lesion” rat model by reducing the dose of quinolinic acid injected into the striatum from 150 nmol to 75 nmol (thereby creating a model of minimal change MSA-P) and shortening the interval between lesion and grafting to 1-2 weeks.

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sions can be a source of annular alpha-synuclein species. If these species are cytotoxic, then blocking their formation, mobilization or action could delay disease progression.

TILTING TEST AND MIBG MYOCARDIAL SCINTIGRAPHY IN DIFFERENTIATION BETWEEN PARKINSON’S DISEASE AND MULTIPLE SYSTEM ATROPHY

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This study aimed to assess the most useful examination in differentiation between Parkinson’s disease (PD) and multiple system atrophy (MSA) from their early clinical course.

Four cases with MSA (mean age: 56.5±10.1 years, mean disease duration: 1.5±1.0 years) and four cases with PD (mean age: 69.8±1.7 years, mean disease duration: 4.0±0.8 years).

All subject underwent 60° tilting test, isoproterenol and norepinephrine infusion tests, and MIBG myocardial scintigraphy. We measured plasma norepinephrine concentration (PNE) levels before and after the 60° tilting test. Chronotropic dose 25 (CD25) and Δ systolic blood pressure change (ΔSBP) were calculated during infusion tests. Heart/mediastinum ratio (H/M ratio) was calculated from MIBG myocardial scintigraphy, late image.

Only H/M ratio showed significant difference between MSA and PD (2.03±0.49 vs 1.29±0.94, p<0.05). PNE ratio (PNE after tilting / PNE before tilting) showed non-significant trend to lower values in MSA than PD (1.22±0.32 vs 2.06±0.72, p=0.08). Other values did not show significance.

Although the number is small in this study, H/M ratio, calculated from Metaiodobenzyl guanidine (MIBG) myocardial scintigraphy, is the most useful to differentiate MSA from PD in the early clinical stage.

LEVODOPA-INDUCED HYPOTENSION IN MULTIPLE SYSTEM ATROPHY AND PARKINSON’S DISEASE: CHARACTERISTICS AND FACTORS THAT PREDICT ITS OCCURRENCE

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This study set out to determine characteristics and factors predicting dopa-induced hypotension (DIH) in MSA and PD.

189 parkinsonian patients were clinically categorized into PD (141), MSA-P (28) and “unclassified (UP)” parkinsonism (20). Two pills of carbidopa/levodopa (25/100) were administered in a practical ’off’ state and motor response, blood pressure (BP) and heart rate assessed hourly. OH was defined according to Consensus statement 1996.

Patients were similar in age at presentation and duration of parkinsonism. Prior to levodopa: symptoms of OH and significant fall in BP occurred more frequently in MSA-P than in PD and UP. After levodopa: a fall in BP was observed an hour later in PD, MSA and UP while supine, and worsened after two hours. OH occurred more frequently in MSA. Fall in BP on standing was higher in MSA than in PD and UP. In MSA, DIH was maximum at end of 1-hr and lasted for more than two hours (p<0.005). Patients with DIH were symptomatic and often older than 50 yrs. DIH occurred similarly in the three groups. Most PD patients with OH (75%) were dopa responsive.

Symptomatic DIH is common above the age of 50 yrs. OH was more common in MSA-P and lasted for over 2 hours. Duration of Parkinsonism and systolic hypotension prior to levodopa predicted DIH. Measurement of OH is essential in patients over 50 yrs, prior to starting and optimizing dose of levodopa.

This study was supported by a Collaborative Grant from the Wellcome Trust, UK.

VOXEL BASED ANALYSIS OF \([^{123}\text{I} ]\) IBZM SPECT DIFFERENTIATES IDIOPATHIC PARKINSON’S DISEASE FROM MULTIPLE SYSTEM ATROPHY

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Until recently, region of interest (ROI) analysis, which is based on sampling brain volumes with a priori categorical assumptions as to their size and shape, was applied to \([^{123}\text{I} ]\) IBZM SPECT in order to measure striatal dopamine D2 receptor (D2R) function. In contrast, no a priori hypothesis regarding the localization of SPECT signal change is required by statistical parametric mapping (SPM), allowing exploratory voxel-by-voxel group comparisons throughout the entire brain volume. SPM was applied to compare D2R function, measured by \([^{123}\text{I} ]\) IBZM SPECT in patients with idiopathic Parkinson’s disease (IPD) and multiple system atrophy (MSA) of similar disease duration.

Ten patients with IPD (mean age 64.8±6.7 yrs; mean disease duration 2.2±0.8 yrs; UPDRS motor score 25.4±11.5), nine patients with MSA (mean age 62.2±8.9 yrs; disease duration 2.7±0.9 yrs; UPDRS motor score 39.67) underwent \([^{123}\text{I} ]\) IBZM SPECT. Drugs with the potential to interfere with the \([^{123}\text{I} ]\) IBZM uptake were withdrawn 5 days prior to scanning. Because of the very low density of D2R in neocortical areas, the frontal cortex
Patients were matched for disease duration and age. ROI analysis showed significant decreases in IBZM uptake of the more affected caudate in patients with MSA compared to IPD patients (1±0.14; 1.22±0.12; p<0.05). Voxel based analysis confirmed the finding of ROI analysis. Additionally, in contrast to patients with IPD, MSA patients showed significant decreases of IBZM uptake in the rostral more affected caudate (p<0.001; talairach coordinates:[-8; 6; 9]).

Compared with the ROI approach, SPM interrogation of [123I] IBZM uptake appears to be more sensitive in differentiating MSA patients from IPD patients. A possible explanation may be that the ROI approach is based on an a priori hypothesis sampling only the dorsal head of the caudate, whereas SPM localises relative reductions in the entire caudate on a voxel-by-voxel basis. The area within the rostral caudate identified by SPM, should be considered in the individual analysis of patients with uncertain parkinsonism undergoing IBZM-SPECT.

IMPACT OF DYSAUTONOMIA VERSUS MOTOR IMPAIRMENT ON QUALITY OF LIFE IN MSA: A CROSS-SECTIONAL BASELINE ANALYSIS OF THE EMSA-SG NATURAL HISTORY STUDY

M. Stampfer-Kountchev, M. Köllensperger, F. Geser, W. Poewe, G.K. Wenning, on behalf of the European MSA Study Group (EMSA-SG)

The EMSA-SG is an academic network comprising 23 centres across Europe and Israel that has been supported by the 5th framework program of the European Union since March 2001 (QLK6-CT-2000-00661). The primary goal of the network is to validate the novel Unified MSA Rating Scale (UMSARS) using a multicentre cross-sectional as well as prospective study approach.

One of the secondary goals is to identify determinants of health related quality of life (HR-QoL), which is clearly impaired in this multifaceted disorder.

The aim of the current study was to assess the impact of perceived dysautonomia (using COMPASS) and motor impairment (using UMSARS II - motor examination) on HR-QoL in both the parkinsonian (MSA-P) and cerebellar (MSA-C) variants of MSA. Quality of life was assessed by using the Medical Outcomes Study 36 Item Short Form (SF-36) health survey questionnaire.

A total of 32 MSA patients with either possible or probable MSA (19 MSA-P, 13 MSA-C; mean age 63±7.7 years; mean disease duration 6.5±4.2 years) fulfilling the Consensus diagnostic criteria (Gilman et al. 1998) have been studied. The SF-36 is a widely established generic HR-QoL scale comprising measures of eight health dimensions (i.e., physical functioning, role limitation due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perception). Each dimension was coded by an arbitrary scale with 0 being the worst and 100 the best imaginable state.

The Composite Autonomic Symptom Scale (COMPASS) is a self-administered 169 item questionnaire including nine domains of autonomic symptoms: orthostatic; secretomotor; male sexual dysfunction; urinary; gastrointestinal; pupillomotor; vasomotor; reflex syncope; and sleep function.

The UMSARS II motor examination scale comprises 14 items. In contrast to the UPDRS only the worst limb is rated. Each item is rated from 0 (no impairment) to 4 (severe impairment).

In MSA-P, both COMPASS and UMSARS scores correlated with two SF36 domains [low bodily pain (p<0.01) and general health perception (p<0.01)]. In MSA-C, COMPASS and UMSARS scores correlated with one SF36 (COMPASS: vitality (p<0.01); UMSARS II: physical function (p<0.05)). In patients with probable MSA, COMPASS and UMSARS II correlated with more SF-36 domains than in patients with possible MSA.

The current data show for the first time that dysautonomia and motor impairment clearly impair HR-QoL and in particular perceived physical well-being. In general, dysautonomia and motor impairment affected HR-QoL more in MSA-P than in MSA-C. The more likely the diagnosis according to the Gilman criteria the more strongly dysautonomia and motor impairment appear to impact on HR-QoL. Both dysautonomia and motor impairment need to be targeted by future therapeutic strategies to improve HR-QoL in MSA.

ANTIAPOPTOTIC AGENTS ARE NOT NEUROPROTECTIVE IN A DOUBLE LESION RAT MODEL OF STRIATONIGRAL DEGENERATION (MULTIPLE SYSTEM ATROPHY)

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Department of Neurology, University of Innsbruck, Austria

The aim of this study was to investigate neuroprotective effects of antiapoptotic agents in a rat model of striatonigral degeneration (SND).

Antia apoptotic agents such as caspase inhibitors and minocycline have been shown to be neuroprotective in rat or mouse models of striatal and nigral degeneration. Combined striatonigral degeneration (SND) is the core pathology underlying MSA associated parkinsonism. We have developed rodent models of SND using systemic or local administration of neurotoxins. We here addressed the question of whether antiapoptotic agents are neuroprotective in a combined SND double lesion rat model.

SND rats were generated by inducing stereotactic lesions of the substantia nigra pars compacta (SNC) using 6-hydroxydopamine (6-OHDA) and of striatum using qui-
This study aimed to determine whether the first symptoms differ between Parkinson's disease (PD) and multiple system atrophy (MSA).

162 parkinsonian patients (men: 117, women: 45) were clinically evaluated and categorized into PD and MSA using established criteria. Onset and duration of symptoms of motor, urogenital dysfunction and orthostatic hypotension (OH) were recorded.

The 132 PD (81.5%) and 30 (18.5%) MSA patients had similar ages at presentation. Duration of motor symptoms in PD and MSA was similar. Symptomatic dysautonomia in the form of urinary, genital and orthostatic hypotension only without the typical oligodendroglial pathology of MSA. Whether the agents tested here are beneficial in the transgenic (PLP)-α-synuclein mouse model of MSA remains to be determined.

DIFFERENCES IN FIRST SYMPTOMS BETWEEN PARKINSON'S DISEASE AND MULTIPLE SYSTEM ATROPHY


National Institute of Mental Health & Neurosciences, Bangalore, India

This study was supported by a Collaborative Grant from the Wellcome Trust, UK.

Multiple system atrophy (MSA) is a neurodegenerative disease marked by variable combination of parkinsonism, orthostatic hypotension and cerebellar dysfunction. Pharmacotherapeutic options are very limited for MSA, but some response to levodopa can be observed. Deep brain stimulation (DBS) is well established for advanced levodopa-responsive idiopathic Parkinson’s disease (PD).

We successfully implanted bilateral DBS leads in the subthalamic nucleus (STN) of two MSA patients with severe medically refractory parkinsonism.

Patient 1 is a 64-year-old woman with a 9-year history of progressive rigidity, focal dystonia (blepharospasm), orthostatic hypotension (OH), gait and balance abnormalities resulting in frequent falls. She initially received some benefit from levodopa, which deteriorated over time.

Patient 2 is a 63-year-old woman with a 4-year history of rapidly progressive bradykinesia, rigidity, OH and prominent balance and gait abnormalities, causing frequent falls. Initially diagnosed as PD, she responded sufficiently well to levodopa, which over time became progressively less efficacious. In both cases, pre-operative glucose PET scan was consistent with the diagnosis of MSA. Intraoperative microelectrode recordings, fluoroscopy and MRI were used to locate final target. Patients were videotaped and evaluated with the UPDRS before and after surgery. DBS settings were systematically adjusted to achieve best clinical effect. Follow up was at least 18 months in both cases.

Both patients initially showed mild but subjectively satisfactory improvement of their parkinsonism. Patient 1 reported reduced fluctuation of her symptoms when ‘ON’ or ‘OFF levodopa. The ‘OFF’ medication motor UPDRS (part III) showed a 26% improvement. However, her speech was negatively affected and gait was progressively worse. Persistent blepharospasm and limb dystonia needed treatment with periodic injections of botulinum toxin. Patient 2 reported improved posture and gait two months after STN DBS, but her speech was slightly slurred. The ‘OFF’ medication motor UPDRS (part III) showed a 58% improvement at 3 months. Stimulation parameters were not different from those routinely used for patients with idiopathic PD. Daily doses of levodopa were not significantly affected by STN DBS. Long-term follow up showed progressive deterioration of the initially observed clinical benefit. Motor UPDRS scores indicated a 32% worsening in patient 1 and a much-reduced gain (22%) in patient 2.

Subthalamic DBS may provide mild-to-moderate short-term benefits in selected patients with advanced atypical parkinsonism with a history of beneficial response to levodopa. However, such benefits are short lasting. Extrapyramidal symptoms rapidly deteriorate after a few months, in contrast to what is usually observed in idiopathic PD.
VASOMOTOR RESPONSES TO PRESSOR STIMULI IN MSA AND PURE AUTONOMIC FAILURE (PAF)

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Pressor stimuli produce skin vasomotor reflexes (SVRs) via peripheral autonomic nerves in healthy subjects. Laser Doppler studies have found preserved SVRs in multiple system atrophy (MSA). Due to the post-ganglionic lesion site in PAF, we anticipated that SVRs would be diminished.

A total of 16 subjects (9 MSA and 7 PAF) were studied. SVRs were recorded from the index finger (pulp) in the supine position. Measurements were obtained at baseline and after each of the following stimuli: 1) gasp (single voluntary gasp); 2) mental arithmetic (MA); 3) bilateral leg raise for 10 seconds; 4) cold pressor.

All stimuli were then repeated once and means of the 2 minimum values taken for each stimulus. The vasomotor reduction ratio was then calculated as: (reduction in flow/baseline flow) X 100% for each stimulus.

The table compares SVR ratios in MSA and PAF.

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<th>Gasp</th>
<th>MA</th>
<th>Leg raise</th>
<th>Cold Pressor</th>
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<tr>
<td>MSA</td>
<td>52.1 (16.3)</td>
<td>40.8 (11.7)</td>
<td>57.4 (14.4)</td>
<td>50.1 (19.0)</td>
</tr>
<tr>
<td>PAF</td>
<td>0.004**</td>
<td>0.03*</td>
<td>0.044*</td>
<td>0.1</td>
</tr>
</tbody>
</table>

SVR reduction ratios (%) as mean ± (SD); *=p<0.05

We found SVRs reduced in PAF compared with MSA, which may reflect the underlying lesion site. However, the MSA subjects had a markedly attenuated pressor response to MA. This may reflect proposed alternative sites of central generation of SVR and pressor response.

Testing for SVR ratios is quick and non-invasive. Our findings suggest that this method may provide a useful tool in helping differentiate MSA from PAF.

HAEMODYNAMIC AND ORTHOSTATIC RESPONSES IN MSA AND PURE AUTONOMIC FAILURE AFTER WATER INGESTION

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As water increases the seated blood pressure (BP) of patients with autonomic failure (AF), and has been postulated to help orthostatic hypotension in these subjects, we studied the effects of 480ml water ingestion on seated and standing BP in AF.

We studied 7 subjects with multiple system atrophy (MSA) and 7 subjects with pure autonomic failure (PAF). All subjects had documented AF and orthostatic hypotension.

On the morning of the study the fasted subject (with vasoactive medication omitted) underwent a total of 3, 5 minute stands (stand 0 before water; stand 1, 15 minutes after drinking 480 ml of distilled water; stand 2, 35 minutes after the water), sitting down between stands. BP and HR were recorded intermittently, with a Dynamap (Critikon) every 3 minutes, and continuously with the Portapres II. Comparisons were made between the stands before and after water ingestion.

The table compares SVR ratios in MSA and PAF.

<table>
<thead>
<tr>
<th></th>
<th>Stand 0</th>
<th>Stand 1</th>
<th>Stand 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasp SBP</td>
<td>110.6±25.1</td>
<td>122.9±29.0</td>
<td>133.9±25.5</td>
</tr>
<tr>
<td>Gasp DBP</td>
<td>69.6±12.9</td>
<td>76.4±13.9</td>
<td>80.4±14.1</td>
</tr>
<tr>
<td>MA SBP</td>
<td>79.5±21.5**</td>
<td>101.0**±23.3</td>
<td>99.6**±24.0</td>
</tr>
<tr>
<td>MA DBP</td>
<td>51.5±15.0**</td>
<td>63.6±13.0</td>
<td>64.0±14.0</td>
</tr>
<tr>
<td>Leg raise SBP</td>
<td>77.4±25.6**</td>
<td>95.3±23.0</td>
<td>95.4±22.9</td>
</tr>
<tr>
<td>Leg raise DBP</td>
<td>49.6±16.3**</td>
<td>63.4±16.1</td>
<td>60.4±16.1</td>
</tr>
</tbody>
</table>

Systolic and diastolic blood pressure (SBP and DBP) compared before and after drinking compared in 14 AF subjects. Values given are BP in mmHg±SD; *=p<0.01; **=p<0.001; p values refer to stand 2 or stand 3 BP compared with baseline (stand 1) obtained with paired 2-tail t-test; Results show Dynamap data.

All AF patients symptomatic on stand 0 (11/14) noted an improvement in symptoms on stands 1 & 2.

We have thus shown that water ingestion can alleviate orthostatic hypotension in AF as early as 15 minutes after drinking, leading to subjective and objective improvements.

THE ORGANISATION OF A SPECIALISED UNIT FOR ATYPTHICAL PARKINSONISM

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A specialised unit has been set up having the following objectives: to ensure fast and specific diagnosis of patients suspected of having atypical parkinsonism; to ensure continued evaluation of clinical status and appropriate identification and treatment of risk factors; to ensure optimal investigation of symptoms and treatment in all stages of the disease, medically as well as non-medically and to create an environment where all aspects of the diseased person are accepted and cared for; to enable patients to contact known health care professionals when needed; to
obtain steady improvement in diagnostic measures and treatment options and continued education of health care professionals; to obtain recruitment for scientific investigations and trials.

This multi-disciplinary unit works as an integrated team and coordinates its activities through frequent meetings and continued education.

The figure outlines the structure of the unit.

Patients are diagnosed according to diagnostic criteria, and neurologists work closely with specially trained nurses, who coordinate investigations, medication, and care of the patients.

All professionals working with the patients refer to the neurologist and specialist nurse, and the status of the patient is continually evaluated by relevant staff.

The patients are seen in our day centre, and patients can telephone the unit during the day-time. An e-mail service for patients is being set up. Patients are admitted to the ward when necessary, and 2 beds are allocated to the unit.

All patients fulfilling diagnostic criteria are offered enrolment into clinical research.

1 month after opening the unit for referrals, 20 new patients have been referred. Approximately two-thirds of these patients fulfil diagnostic criteria for an atypical parkinsonian syndrome. The patients present with different needs, ranging from the need to reach a diagnosis, to the need for evaluation or specific treatment of symptoms, or palliative care. A need for specific diagnosis and information is evident.

Printed material is much needed to support the information given orally.

The unit is important for the coordination and execution of the specialised evaluation and treatment of the complex symptoms of patients with atypical parkinsonism in order to secure an improved quality of treatment and information of patients and caregivers. A detailed evaluation after 1 year will address the specific needs of the patients.