SHORT REPORT

Probable multiple system atrophy in a German family

U Wüllner, M Abele, T Schmitz-Huebsch, K Wilhelm, R Benecke, G Deuschl, T Klockgether

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Multiple system atrophy (MSA) is a neurodegenerative disorder of unknown aetiology. A possible underlying genetic component has not yet been identified. A family is reported with phenotypic MSA and probable autosomal dominant inheritance. The patients presented initially with either parkinsonian or cerebellar signs, and developed severe autonomic failure and typical atrophy of the brain stem and cerebellum in the course of the disease.

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder of unknown aetiology, clinically characterised by poorly levodopa responsive parkinsonism with or without cerebellar dysfunction, in combination with autonomic failure.[1] α-Synuclein positive oligodendroglial inclusions are the specific neuropathological hallmark of MSA. Like idiopathic Parkinson's disease, MSA might therefore be classified as a sporadic synucleinopathy.[2] While both autosomal dominant and recessive traits have been identified in Parkinson's disease, no familial cases of MSA have yet been reported. We describe a family with a phenotype typical of MSA in two successive generations.

METHODS

All family members were examined by two of us (UW and TSH), using the unified multiple system atrophy rating scale (UMSARS) and the unified Parkinson's disease rating scale (UPDRS). All had standardised autonomic testing, and magnetic resonance imaging (MRI) was undertaken in nine family members, the protocol including T1-TSE three dimensional volume datasets and T2 weighted images, as described previously.[3] The two affected patients underwent additional single photon emission computed tomography (SPECT) with ^{123}I-FP-CIT and ^{123}I-IBZM.

RESULTS

The family comes from northern Germany. There are 14 living members in three generations, without any history of consanguinity (fig 1).

I_1 first presented at age 68 years with akinetic parkinsonism which responded well to levodopa treatment for approximately eight years. Urinary incontinence and orthostatic dysfunction developed within two years, and ataxia of gait and stance within six years after the initial diagnosis. On examination (aged 77), she showed no cognitive impairment. Ataxia of gait and stance was severe and she was unable to walk unaided. She had a smooth expressionless face, severe dysarthria, upper and lower limb ataxia, symmetrical brisk tendon reflexes, and cogwheel rigidity, but no plantar responses (UMSARS scores: I (activities of daily living), 35; II (motor examination), 43; UPDRS III, 39). Blood pressure was 140/100 mm Hg recumbent and 100/60 mm Hg upright, the change of posture producing giddiness. MRI showed severe brain stem and cerebellar atrophy with a hot cross bun sign (fig 2). Only moderate changes where present in the putamen.

II_1 first presented at age 46 years with ataxia of gait. A partial (urge) incontinence, orthostatic dysfunction, and mild right sided parkinsonism developed within two years after the occurrence of ataxia. On examination (age 49), she showed no cognitive impairment. She had mild ataxia of gait and stance and mild upper and lower limb ataxia, moderate dysarthria, symmetrical brisk tendon reflexes, and mild cogwheel rigidity of the right arm, but no plantar responses (UMSARS scores: I (activities of daily living), 11; II (motor examination), 18; UPDRS III, 19). Blood pressure was 130/90 mm Hg recumbent and 100/90 mm Hg upright. MRI showed predominant cerebellar and moderate brain stem atrophy with a hot cross bun sign (fig 2).

Subjects $II_{2–4}$ (aged 48–55) all had completely normal neurological examinations except for a minimal ataxia of gait in II_2 when walking in tandem with eyes closed, and a corresponding discrete atrophy of the upper vermis on MRI (not shown).

Subjects $III_{1–3}$ (aged 21–28), the three children of II_1, had completely normal neurological examinations and MRIs (not shown).

I_1 and II_1 underwent SPECT with ^{123}I-FP-CIT and ^{123}I-IBZM. Both showed an asymmetrical massive reduction of the presynaptic dopamine transporter and a moderate loss of dopamine D2 receptors (data not shown). Extensive laboratory testing was undertaken in I_1 and II_1; all routine variables, including caeruloplasmin and urine copper, were within the normal range; CSF samples were normal, without oligoclonal bands. Genetic testing excluded spinocerebellar ataxia (SCA) types 1–3, 6, 7, and 17 in I_1 and II_1.

DISCUSSION

This is the first description of a family with the clinical phenotype of probable MSA, corresponding morphological changes on MRI, and a probable autosomal dominant inheritance. In 1964, before the recognition of MSA as a disease entity, Lewis described a family with orthostatic hypotension as the leading symptom.[4] However, while two family members had ataxia and parkinsonism and might have fulfilled the current criteria of probable or possible MSA, a common feature in that family seemed to be prominent amyotrophy and rather slow disease progression, with a disease duration of more than 30 years in one case.[4] In addition, the predominant symptom in two cases was diarrhoea, which could point to coeliac disease. Diarrhoea, autonomic failure, and cerebellar degeneration are also observed in hereditary neuronal nuclear inclusion disease (NIID), even though at least in some cases NIID symptoms may start in childhood.[5]

Although a multigenic aetiology of MSA is often suspected, the evidence for a genetic component is rather weak, and families with MSA have not been described up to now. A family with necropsy proven Parkinson's disease and necropsy proven MSA was reported by Shimo *et al*,[6] but the significance of that combination remains unclear. The

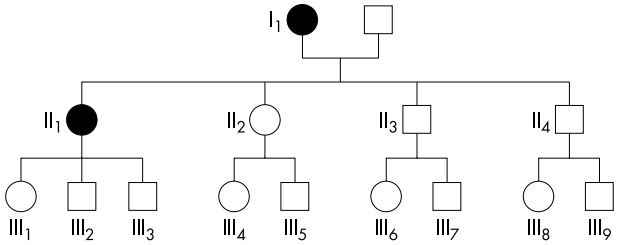

Figure 1 Patient pedigree.

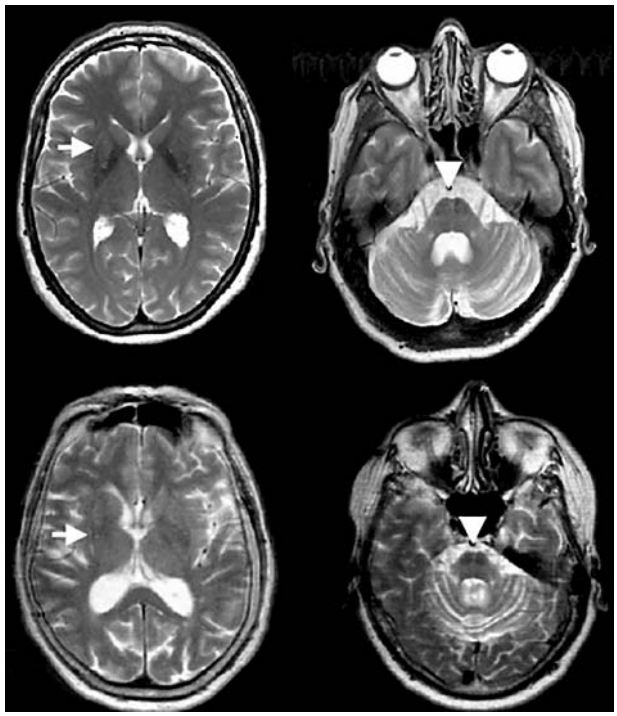

Figure 2 T2 weighted horizontal magnetic resonance images at the level of the basal ganglia (left) and the brain stem (right): bottom, I_1; top, II_1. Note the atrophy of the cerebellar peduncle with gliosis and the hot cross bun sign in the brain stem (arrowheads). Only moderate gliosis is present at the outer rim of the putamen (arrows).

probability that the cases encountered occurred by chance alone is rather low. The standardised prevalence rates of MSA are estimated to be 4 or 5 in 100 000.[7] Thus the probability of finding two patients with probable MSA in a family of 14 members by chance alone is as low as 0.0006. A genetic predisposition for MSA was suggested by an epidemiological study by Nee *et al*, who reported a higher frequency of symptoms and neurological diseases in first degree relatives of 60 MSA cases than in controls (23% in MSA cases *v* 10% in controls).[8] Although a small study reported an association between MSA and a mutant allele of the CYPIID6 gene, a subsequent analysis did not find an association between MSA and genetic variants of the genes coding for CYPIID6, apoE, the receptor for IGF-1, ciliary neurotrophic factor (CNTF), the H5 pore region of the human homologue of the weaver mouse gene, or HLA-A32.[9 10] Also, no mutations were identified in the coding region of the α-synuclein gene.[11 12] Neither CAG trinucleotide repeat expansions of spinocerebellar ataxia types 1–3, 6–8, and 12, nor frataxin mutations were found in 20 patients with possible or probable MSA.[13] In our family none of the known SCA mutations was found, although the marked difference in age at disease onset in the two affected family members (*anticipation*) could point to an as yet unidentified trinucleotide repeat disorder.

Identification of the present family suggests that MSA—although considered a sporadic disease—may be inherited in rare instances. As with Parkinson's disease, genetic analysis of larger families might provide clues to the suspected genetic basis of MSA.

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Authors' affiliations
U Wüllner, M Abele, T Schmitz-Huebsch, T Klockgether, Department of Neurology, UKB, Sigmund Freud Strasse, Bonn, Germany
K Wilhelm, Department of Radiology, UKB, Bonn
R Benecke, Department of Neurology, UKR, Rostock, Germany
G Deuschl, Department of Neurology, UKK, Kiel, Germany

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Correspondence to: PD Dr med U Wüllner, Department of Neurology, University Bonn (UKB), Sigmund Freud Str 25, D-53105 Bonn, Germany; wuellner@uni-bonn.de

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