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ORIGINAL COMMUNICATION

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Sporadic adult onset ataxia of unknown etiology

A clinical, electrophysiological and imaging study

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Abstract *Background* The sporadic adult onset ataxias of unknown etiology (SAOA) denote the non-hereditary degenerative adult onset ataxias that are distinct from multiple system atrophy (MSA). *Objective* To define and characterize the clinical phenotype of sporadic adult onset ataxia of unknown etiology (SAOA). *Design* A survey of clinical features, nerve conduction and evoked potentials, autonomic tests, and magnetic resonance imaging (MRI)-based brain morphometry was conducted in patients with SAOA. *Patients* Study subjects were a consecutive sample of 27 patients (11 male, 16 female) who met the diagnostic criteria for SAOA (age 55 ± 13 years; age at disease onset 47 ± 14 years; disease duration 8 ± 7 years). *Results* All patients presented with a cerebellar syndrome. The most frequent extracerebellar symptoms were decreased vibration sense in 70 % and decreased or absent ankle reflexes in 33 % of the patients. Nerve conduction studies revealed a polyneuropathy in 26 % of the patients. Somatosensory evoked potentials were abnormal in 44 %, and central motor conduction time in 17 % of patients. Autonomic testing revealed an affected autonomic nervous system in 58 % of patients. Voxel-based brain morphometry showed a predominant reduction of gray matter in the cerebellum which was significantly correlated with disease stages. A loss of white matter was found in both middle cerebellar peduncles and the outer edge of the pons. *Conclusions* The data show that SAOA is a predominantly, but not exclusively cerebellar disorder. Clinical, electrophysiological, and imaging findings showed some similarities with multiple system atrophy which raises the question of an overlap of these two disorders.

Key words ataxia · voxel-based morphometry · electrophysiology · clinical characteristics

Introduction

Anita Harding introduced the term idiopathic late onset cerebellar ataxia (ILOCA) to denote non-hereditary adult onset ataxias [16]. Subsequent work showed that approximately one-third of ILOCA patients suffered from multiple system atrophy (MSA) and that a small subgroup of apparently sporadic late-onset ataxias were due to mutations of the Friedreich's ataxia (FRDA) or one of the spinocerebellar ataxia (SCA) genes [3, 13]. Based on these findings, we delineated a non-hereditary degenerative adult onset ataxia disorder distinct from MSA that we named sporadic adult onset ataxia of unknown etiology (SAOA) [3].

The aim of this study was to characterize the clinical phenotype of SAOA.

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Methods

Patients

Twenty-seven unselected ataxia patients who were consecutively seen at our department between January 2001 and October 2003 were included in the study. All patients gave informed consent to participate in the study which was approved by the local ethics committee. Inclusion criteria were as follows [3]: (1) progressive ataxia, (2) disease onset after the age of 20 years, (3) informative and negative family history (no similar disorders in first- and second-degree relatives; parents older than 50 years, or, if not alive, age at death of more than 50 years; no consanguinity of parents), (4) no established symptomatic cause (normal CSF studies; no ischemia, hemorrhage or tumor of the posterior fossa; no alcohol abuse; no chronic intake of anticonvulsant drugs; no other toxic causes; no malignancies; anti-Hu and -Yo negative; glutamic acid decarboxylase antibodies negative; normal levels of vitamin B12 and E; VDRL negative; no evidence of onset of ataxia in association with encephalitis, sepsis, hyperthermia or heat stroke; normal thyroid function), (5) no subacute onset of ataxia; (6) negative molecular genetic testing for SCA1–3, 6, 17, FMR1 premutation and FRDA; (7) no possible or probable MSA according to established clinical criteria [14].

Disease stages were defined as follows: stage 0: no gait difficulties, stage 1: disease onset, as defined by onset of gait difficulties, stage 2: loss of independent gait, as defined by permanent use of a walking aid or reliance on a supporting arm, stage 3: confinement to wheelchair, as defined by permanent use of a wheelchair.

Electrophysiological studies

Nerve conduction and evoked potential studies were performed using standard electrophysiological procedures. Values beyond established age-adapted thresholds from our laboratory were considered abnormal.

A diagnosis of polyneuropathy was made when abnormal nerve conduction velocities, compound muscle action potentials, sensory nerve action potentials, or F-waves were present in three or more nerves.

Motor evoked potentials (MEP) were recorded from the abductor digiti minimi and anterior tibial muscle after transcranial magnetic stimulation of the brain. Central motor conduction time (CMCT) was determined using the F-wave technique.

Cortical somatosensory evoked potentials were recorded following tibial and median nerve stimulation at ankles and wrists. Latency of P40, N9, N13, and N20 was measured.

Autonomic testing

Autonomic tests included determination of heart rate variability during quiet wakefulness, during forced breathing at 6/min (respiratory sinus arrythmia), during and after an exspiratory pressure of 40 mmHg (Valsalva test), and after change from supine to upright position (30/15 ratio). Established age-adapted normative data were used for comparison [22]. Blood pressure was recorded in supine and for 5 min after active change to upright position. According to the MSA diagnostic criteria, an orthostatic drop of systolic blood pressure of > 20 mmHg or diastolic blood pressure > 10 mm Hg was considered abnormal.

None of the included patients suffered from diabetes mellitus or took medication affecting the autonomic nervous system at the time of examination.

Statistical analysis

Group comparisons were performed using the χ^2 test or student's t-test. Disease stages were evaluated using Kaplan-Meier statistics.

Magnetic resonance imaging (MRI)-based brain morphometry

T1-weighted, turbo field echo (TFE) sequences were acquired from 14 of the patients and 14 age- and sex-matched controls in a 1.5-T scanner (Philips Gyroscan Intera). Repetition time was 15.4 ms; echo time 3.6 ms; flip angle 30°; number of excitations 1; field of view 256 mm; acquisition matrix 256x256 pixels; and slice thickness 1 mm yielding 140 sagittal slices and a voxel size of 1x1x1 mm^3. The pre-processing of the T1 images followed the protocol for optimized voxel-based morphometry (VBM), as described elsewhere [5, 15, 26]. The processed data were corrected for deformations applied during the normalization procedure ('modulated data') and smoothed (Gaussian kernel 12 mm). Data were analyzed using an ANCOVA model by including the total brain volume as a confounding covariate. Separate analyses were performed for gray and white matter. In addition, a correlation between disease stages and reduction in gray- and white matter volume was estimated.

Statistical comparisons were thresholded at a voxel-wise value of $p < 0.05$, controlled for false-discovery rate [12]. However, the discussion will mainly be based on those areas, which additionally survived a corrected extension threshold of at least 500 voxels.

A transformation from MNI to Talairach coordinates was performed for anatomical localization (www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml). Regions were anatomically characterized with Talairach Daemon (http://ric.uthscsa.edu/resources) and Talairach atlas [27].

Results

Patients

Sixteen of the 27 patients were female and 11 male. Mean age at examination was 55 ± 13 years, age at disease onset 47 ± 14 years, and disease duration 8 ± 7 years. Age of onset in women was 10 years earlier than in men (43 ± 12 vs. 53 ± 15 years). Eight of the patients (37 %) were dependent on walking aids and two wheelchair-bound (7 %). Median time to become dependent on walking aids was 12 years after disease onset.

Clinical presentation

All patients presented with ataxia of stance and gait. Irregularity of fast alternating hand movements and abnormal heel-shin slide was found in 26 (96 %), dysmetria and intention tremor of upper limbs in 25 (93 %), and ataxic speech in 23 (85 %) of the patients. Oculomotor abnormalities were found in all patients and included broken-up smooth pursuit in 26 (96 %), gaze-evoked horizontal nystagmus in 15 (56 %), impaired suppression of the vestibuloocular reflex in 20 (74 %), and saccade dysmetria in 24 (89 %).

Extracerebellar symptoms included decreased vibration sense in 19 (70 %), decreased or absent ankle reflexes in 9 (33 %), increased ankle reflexes in 6 (22 %),

and extensor plantar responses in 4 (15 %). A pure cerebellar syndrome was found in only 4 (15 %) patients whereas three of them had abnormal autonomic testing. Mini-Mental State Examination scores ranged from 25 to 30 with a median of 29.

Nine patients (33 %) complained of bladder urgency, 9 (32 %) of swallowing difficulties, and 6 (22 %) of double vision. Snoring was reported in 11 (41 %), restless legs syndrome in 6 (15 %), and symptoms of REM sleep behavioral disorder in 2 (7 %) of the patients. Only one of the 11 male patients (9 %) complained of erectile dysfunction.

Gait ataxia was more severe in patients with decreased or absent ankle reflexes ($p < 0.05$). No further significant correlations of the presence of extracerebellar symptoms and severity of ataxia symptoms as measured with an ordinal scale were found [18].

Electrophysiological studies and autonomic testing

A predominant sensorimotor and mixed axonal-demyelinating polyneuropathy was found in 7 out of 27 patients (26 %) with no significant correlation to other clinical findings.

Delayed or absent cortical SEPs after tibial nerve stimulation were found in 12 out of 27 patients (44 %). Five of these patients (19 %) had delayed responses after median nerve stimulation (one N9, N13, and N20; two N13 and N20; two N20). Abnormal cortical SEPs were correlated with a decreased vibration sense ($p < 0.05$). Only four of the 12 patients (33 %) with abnormal cortical SEPs had a polyneuropathy.

MEPs were abnormal in 4 out of 23 patients (17 %). Abnormalities consisted of increased CMCT to the upper extremities in 3 patients (13 %) and to the lower extremities in 1 patient (4 %) as well as absent responses with normal F-waves to the lower extremities in 2 patients (9 %). Two of the three patients with increased CMCT to the upper limbs had also increased CMCT to the lower limbs, whereas CMCT to the lower limbs could not be assessed in the third one due to absent F-waves.

There was no correlation of SEPs and MEPs with nerve conduction parameters, age, age of onset, and disease duration.

Autonomic testing was abnormal in 15 out of 26 patients (58 %). Short-term HRV and Valsalva test were abnormal in 2 out of 26 patients (8 %), respiratory sinus arrhythmia in 12 out of 26 patients (46 %), and 30/15 ratio in 5 out of 26 patients (19 %). None of the patients showed relevant orthostatic dysregulation. There was no significant correlation of the presence of autonomic abnormalities with bladder dysfunction, neuropathy, sex, age, age of onset, and disease duration.

Magnetic resonance imaging

Routine MRI

Routine MRI was available from all 27 patients and showed an isolated cerebellar atrophy in 17, an additional brainstem atrophy in 5, and no atrophy in another 5 patients. No signal abnormalities in brainstem, medial cerebellar peduncles, and basal ganglia were found.

MRI-based brain morphometry

Mean age at examination in the MRI substudy was 60 ± 11 years in patients (6 male; 8 female) and 61 ± 10 years in controls (6 male; 8 female). Age at disease onset was 53 ± 12 years and disease duration 7 ± 6 years.

At a corrected extension threshold of $p < 0.05$ we found a reduction of gray matter in the vermis, in both anterior lobes, the upper part of both posterior lobes and both tonsils of the cerebellum. There was additional significant but less extended gray matter loss in the left hippocampus and the upper left occipital lobe (cuneus). An inverted comparison did not reveal any gray matter increases (Table 1 and Fig. 1).

At a corrected extension threshold of $p < 0.05$, white matter was reduced in both middle cerebellar peduncles and the outer edge of the pons. An additional, less extended white matter loss was found in the left subcortical precentral region, straight above of the cingulate gyrus (Fig. 2). Again, an inverted comparison did not re-

Table 1 Morphometric analysis of magnetic resonance imaging density changes in 14 patients with SAOA compared to 14 healthy controls. The coordinates refer to the Talairach coordinates

	cluster-level		voxel level			coordinates			
	p	size	p FDR	t	z	X	Y	Z	Area
Gray matter (decrease)	0.000	119785	0.000	7.26	5.28	−7	−46	−28	Vermis, R/L ant. and post. lobes, tonsils
White matter (decrease)	0.000	13003	0.029	6.00	4.68	−27	−39	−33	R/L middle cerebellar peduncles, pons
Correlation between stadium and gray matter loss	0.000	50348	0.010	8.22	4.68	−20	−55	−10	L anterior and posterior lobe
	0.001	8931	0.010	6.56	4.20	17	−71	−7	R posterior lobe

p p-value; *size* number of voxels; *p FDR* p-value controlled for false discovery rate; *t* t-value; *z* z-value

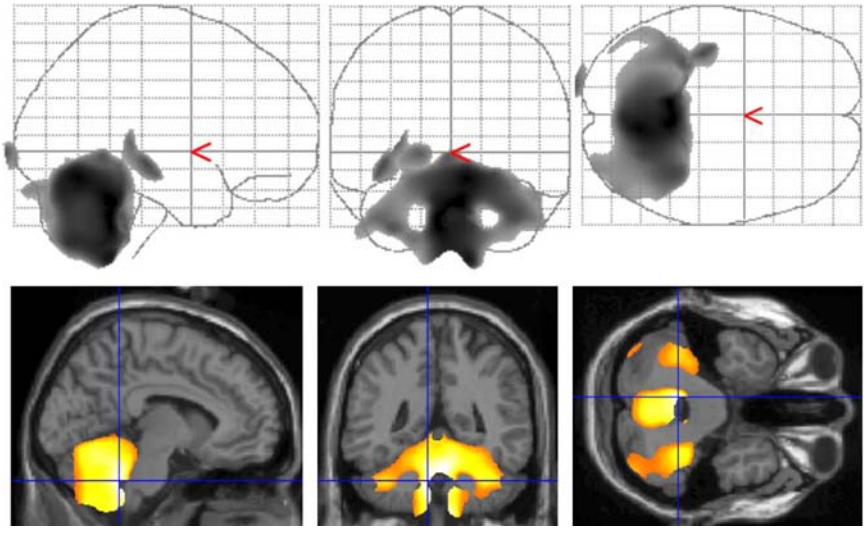

Fig. 1 Gray matter decrease in SAOA (n = 14) as compared to controls (n = 14). *Top:* Standard glass slide view. *Bottom:* Three representative images displayed on a T1-weighted template

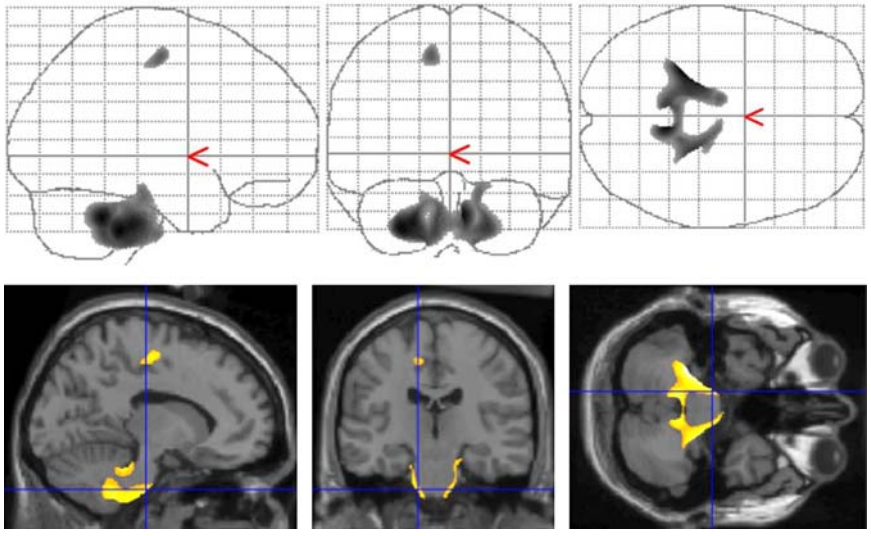

Fig. 2 White matter decrease in SAOA (n = 14) as compared to controls (n = 14). *Top:* Standard glass slide view. *Bottom:* Three representative images displayed on a T1-weighted template

veal any increases of white matter in patients with sporadic ataxia.

At a corrected extension threshold of $p < 0.05$ we found a significant correlation of gray matter reduction with disease stages in the left anterior lobe and in both posterior lobes of the cerebellum. There was additional, less extended gray matter reduction in the right anterior cerebellar lobe and adjacent to the right gyrus rectus. There was no significant correlation of disease stages with white matter decrease or gray and white matter increase.

Discussion

A comparison of the SAOA phenotype with earlier studies of sporadic ataxia patients is difficult as this is the first study that used a strict definition of sporadic ataxia and excluded patients carrying causative gene mutations or met diagnostic criteria of MSA [16, 18]. Although a number of SCA mutations have a clinical phenotype that overlaps with that of SAOA, it is very unlikely that our sample still includes unrecognized SCA patients because the untested SCA mutations are extremely rare and all patients had an informative and negative family history. Harding (1981) subdivided ILOCA patients into a group with severe ataxia of gait, another group with prominent resting and postural tremor and a larger group comprising patients who did not fit into one of both groups [16]. The clinical phenotype of our patients fits best in Harding's first and last group. However, on the basis of our present and recent clinical data, we could not define specific subgroups in SAOA and doubt that a further clinical subdivision is

justified [3]. In addition, statistical analysis comparing Hardings' groups did not show any relevant differences and it is likely that a considerable fraction of her ILOCA patients suffered from MSA or hereditary ataxia [3, 13].

Electrophysiological examination revealed a polyneuropathy in 26 % and abnormal SEPs in 44 % of the patients. Abnormal SEPs occurred in patients with normal peripheral nerve conduction and were correlated with decreased vibration sense indicating involvement of central somatosensory pathways in a subset of SAOA patients. A minority of patients without peripheral neuropathy but delayed N13 responses might have a more proximal or radicular affection of peripheral nerves. The combined degeneration of the cerebellum and afferent somatosensory pathways in SAOA is in accordance with the frequently made observation that different neurodegenerative diseases affect functionally connected anatomical systems [2, 4, 30].

Abnormal MEPs were present in 17 % of our patients. Previous studies in smaller, less strictly defined groups of patients reported higher frequencies of MEP abnormalities ranging from 25 to 43 % [7, 10, 11, 20]. As in a previous study in MSA, we failed to find a correlation between MEP abnormalities and clinical signs of pyramidal tract involvement [4].

Autonomic testing revealed abnormalities in 58 % of our patients, reflecting a predominantly reduced parasympathetic function [21, 23]. In MSA, similar abnormalities were reported to be more frequent with abnormal respiratory sinus arrhythmia in up to 85 % [24]. In addition, 68 % of MSA patients have orthostatic hypotension reflecting disturbed sympathetic function [28]. As we performed no further tests of the sympathetic nervous system, we cannot exclude a less severe sympathetic dysfunction in our patients. The presence of autonomic abnormalities was not statistically correlated with disease duration and age at examination. This might point to a subgroup of patients with an affected autonomic nervous system.

Routine MRI revealed MSA-like brainstem atrophy in 5 patients which is consistent with recent data on MRI in a small group of sporadic ataxia patients [8]. We cannot completely rule out that the clinical diagnosis of MSA might be missed in some of these patients due to a short disease duration. However, at least two of them had a disease duration of 10 and 11 years, respectively, which makes a future evolution in MSA quite unlikely.

The major findings of VBM were a prominent loss of cerebellar gray matter, a reduction of white matter in the middle cerebellar peduncles, and a less significant gray and white matter loss in the hippocampus and some of its efferent projections. In particular the infratentorial changes showed some similarities with earlier reports of VBM in MSA of the cerebellar type [6, 17, 25]. Cerebellar atrophy has been previously reported in morphometric MRI studies of sporadic ataxia patients that used region-guided approaches [8, 9, 31]. The cerebellar gray matter loss was not diffuse, suggesting a differential vulnerability of cerebellar gray tissue in SAOA. Correlation with disease duration indicates that degeneration of cerebellar cortex is directly related to the disease process. The observation of tissue loss in the hippocampus and adjacent regions of the cingulate gyrus and the gyrus rectus raises the question whether SAOA is associated with impaired memory or other cognitive disturbances. Despite normal MMSE scores in all but one patient in the MRI substudy, a definite answer to this question cannot be given as detailed neuropsychological examinations were not part of this study.

Although SAOA is a predominantly cerebellar disorder, our clinical, electrophysiological and morphological data show that there is additional extracerebellar involvement in a considerable part of SAOA patients. Our data do not allow to decide whether the heterogeneity of extracerebellar findings reflects the clinical range of a single clinical entity or whether SAOA represents a heterogeneous group of disorders with yet unrecognized different causes.

The findings of this study showed some similarities with multiple system atrophy which raises the question of an overlap of these two disorders. Some of the diagnostic criteria that we applied to exclude MSA patients have a high negative predictive value suggesting that the probability to include MSA patients was low [28]. In addition, basal ganglia symptoms which are typical for MSA were completely lacking in our patients and disease progression was markedly slower than in MSA. Recently, Abdo et al. found different CSF biomarker levels in a retrospective study of MSA and SAOA patients [1]. Although this should be confirmed in a prospective study, their findings support the view that MSA and SAOA are two distinct disease entities.

However, all clinico-pathological studies that examined the validity of the diagnostic criteria of MSA focussed on the distinction of MSA and basal ganglia disorders [19, 29]. We can therefore not completely rule out that SAOA patients suffer from a milder variant of MSA. This question can only be answered with future neuropathological studies systematically looking for ultrastructural markers of MSA in sporadic cerebellar degenerations.

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