

# The aetiology of sporadic adult-onset ataxia

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## Summary

The nosology and aetiology of sporadic adult-onset ataxia are poorly understood. The aim of the present study was to answer the following questions: (i) How many sporadic ataxia patients have a genetic cause? (ii) How many sporadic ataxia patients suffer from multiple system atrophy (MSA)? (iii) Is there a specific association between sporadic ataxia and serum anti-glutamic acid decarboxylase (GAD) or antigliadin antibodies? and (iv) What are the clinical features of patients with unexplained sporadic ataxia? The study was performed in 112 patients who met the following inclusion criteria: (i) progressive ataxia; (ii) onset after 20 years; (iii) informative and negative family history (no similar disorders in first- and second-degree relatives; parents older than 50 years); and (iv) no established symptomatic cause. Thirty-two patients (29%) met the clinical criteria of possible (7%) or probable (22%) MSA. The

Friedreich's ataxia mutation was found in five patients (4%), the spinocerebellar ataxia (SCA) 2 mutation in one (1%), the SCA3 mutation in two (2%) and the SCA6 mutation in seven (6%). The disease remained unexplained in 65 patients (58%). We did not detect anti-GAD antibodies in any of our patients. Antigliadin antibodies were present in 14 patients, 10 patients with unexplained ataxia (15%) and 4 patients with an established diagnosis (9%). Patients with unexplained sporadic ataxia had a median disease onset of 56.0 years. Decreased vibration sense (62%), decreased or absent ankle reflexes (40%), increased ankle reflexes (39%), dysphagia (38%) and extensor plantar responses and/or spasticity (34%) were the most frequent extracerebellar symptoms. Compared with MSA, disease progression was significantly slower.

**Keywords:** antigliadin antibodies; Friedreich's ataxia; multiple system atrophy; spinocerebellar ataxia

**Abbreviations:** FRDA = Friedreich's ataxia; GAD = glutamic acid decarboxylase; IDCA = idiopathic late onset cerebellar ataxia; IgA = immunoglobulin A; IgG = immunoglobulin G; MSA = multiple system atrophy; OPCA = olivopontocerebellar atrophy; SCA = spinocerebellar ataxia

## Introduction

Despite the enormous progress that has been made in the understanding of the genetic basis of hereditary ataxia, the origin of many sporadic ataxias remains obscure. In 1981, Harding proposed labelling the sporadic adult-onset ataxias of unknown aetiology as idiopathic late onset cerebellar ataxias (IDCA) (Harding, 1981). IDCA is thus distinguished from symptomatic ataxias due to identified exogenous and endogenous causes. The most frequent established causes of sporadic ataxias are chronic alcoholism, remote malignancies (paraneoplastic cerebellar degeneration), vitamin deficiency, various toxic agents and hypothyroidism.

Clinical and radiological studies suggest that IDCA is heterogeneous. In a previous study of 28 IDCA patients (Klockgether *et al.*, 1990), we tentatively divided IDCA into two groups with distinct clinical, radiological and prognostic features. IDCA-plus patients had accompanying extracerebellar features such as parkinsonism, bulbar symptoms, urinary incontinence and pyramidal tract signs. MRI showed cerebellar and brainstem atrophy typical for olivopontocerebellar atrophy (OPCA). Progression was fast with a median survival of only 7.7 years. In contrast, IDCA-cerebellar patients suffered from a lasting purely cerebellar syndrome.

They had isolated cerebellar atrophy on MRI and survived for more than 20 years. Subsequent clinical studies showed that many if not all IDCA-plus patients suffered from multiple system atrophy (MSA) (Schulz *et al.*, 1994; Wenning *et al.*, 1994). MSA is a sporadic, adult-onset disease characterized by neurodegeneration in the basal ganglia, brainstem, cerebellum and intermediolateral cell columns of the spinal cord encompassing the former disease categories striatonigral degeneration, sporadic OPCA and Shy-Drager syndrome (Quinn, 1989). The ultrastructural hallmark of MSA is the presence of oligodendroglial cytoplasmic inclusions (Papp and Lantos, 1994). Based on clinicopathological correlation studies, sensitive criteria have been established which allow a highly specific clinical diagnosis of MSA (Gilman *et al.*, 1999).

While sporadic ataxia patients presenting with autonomic failure can be assigned to MSA, the aetiology in many other patients suffering from sporadic ataxia remains unclear. One hypothesis is that these disorders represent monogenic diseases, either late onset autosomal recessive ataxias or new dominant mutations. In contrast to earlier assumptions, recessive ataxias such as Friedreich's ataxia (FRDA) may start after the age of 30 years (Klockgether *et al.*, 1993). In a clinical genetic study of 140 FRDA patients, 19 had a disease onset later than 25 years (Dürr *et al.*, 1996). Since recessively inherited disorders are more likely to occur sporadically than clustered in families, sporadic late onset ataxias might represent late onset variants of FRDA or other recessive ataxias. The occurrence of new dominant mutations in spinocerebellar ataxia (SCA) genes is possible, but appears to be rare. However, the parent who transmitted the disease may have died before clinical symptoms became apparent making the family history uninformative. This is particularly probable for SCA6 because average disease onset of SCA6 occurs in late adulthood (Ikeuchi *et al.*, 1997; Schöls *et al.*, 1998). In addition, autosomal dominant disorders may be apparently sporadic due to false fatherhood.

Recently, an association of ataxia with serum anti-glutamic acid decarboxylase (GAD) and antigliadin antibodies has been reported suggesting that some types of sporadic ataxia may have an immunological cause (Hadjivassiliou *et al.*, 1996; Saiz *et al.*, 1997; Hadjivassiliou *et al.*, 1998). However, for antigliadin antibodies, the specificity of the association with sporadic ataxia has been challenged (Bushara *et al.*, 2001).

The aim of the present study was to clarify the nosology of sporadic adult-onset progressive ataxia. To this end, we performed a clinical and laboratory study of 112 ataxia patients. In particular, we aimed to answer the following questions: (i) How many patients with an ataxia of hitherto unknown aetiology have a genetic cause? (ii) How many sporadic ataxia patients suffer from MSA? (iii) Is there a specific association between sporadic ataxia and serum anti-GAD or antigliadin antibodies? and (iv) How many patients have an unexplained ataxia, and what are their clinical features?

## Methods

### *Inclusion criteria and study population*

The medical records of all ataxia patients referred to the Departments of Neurology at the Universities of Bonn and Tübingen (Germany) and the St Josef Hospital in Bochum (Germany) between January 1996 and December 1998 were reviewed and patients with sporadic adult-onset progressive ataxia of unknown aetiology were identified. Inclusion criteria were as follows: (i) progressive ataxia; (ii) disease onset after the age of 20 years; (iii) 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 >50 years), (iv) no established symptomatic cause [(a) normal CSF studies; (b) no ischaemia, haemorrhage or tumour of the posterior fossa; (c) no alcohol abuse; (d) no chronic intake of anticonvulsant drugs; (e) no other toxic causes; (f) no malignancies; (g) anti-Hu and anti-Yo negative; (h) normal levels of vitamin B12 and E; (i) Venereal Disease Research Laboratories (VDRL) test negative; (j) no evidence of onset of ataxia in association with encephalitis, sepsis, hyperthermia or heat stroke; and (k) normal thyroid function]; and (v) no subacute onset of ataxia [subacute onset of ataxia was defined as progression to stage 2 (see below) within less than 4 months].

One hundred and twelve of the 132 patients who met the inclusion criteria agreed to participate in the study. These patients were seen at our ataxia clinics or visited at home. All subjects gave informed consent. The study was approved by the Ethical Committee of the Medical Faculty at the University of Bonn.

### *Data collection*

In all patients, a detailed history including questions for disease onset and disease progression (see below), urinary symptoms and erectile dysfunction (in males) was taken. All patients were asked whether there was consanguinity of their parents. Bladder dysfunction was assumed when patients complained of urinary urgency, incontinence or retention. Cystometrograms were not performed systematically.

All patients were clinically examined by M.A. (Bonn), K.B. (Tübingen) or L.S. (Bochum) using generally acknowledged definitions of clinical symptoms. Decreased ankle reflexes were defined as barely elicitable or elicitable only with facilitation manoeuvres. Spasticity was defined as an increase of muscle tone related to the velocity of passive stretch. The severity of ataxia was rated as described previously (Klockgether *et al.*, 1990), while the severity of other clinical symptoms was not rated. Examination included repeated measurements of systolic and diastolic blood pressure in recumbent position and within 3 min of standing from the recumbent position. A blood sample was taken in all patients.

A clinical diagnosis of possible or probable MSA was made following the consensus statement published by Gilman

**Table 1** Patient characteristics

	All patients	Disease duration ≥4 years
Affected examined ( <i>n</i> )	112	81
Gender ( <i>n</i> ; male/female)	61/51	44/37
Age at examination (years)	61 (25–84)	62 (25–82)
Age of onset (years)	56.5 (20–82)	54 (20–75)
Disease duration (years)	6 (0–25)	8 (4–25)

Age at examination, age of onset and disease duration are given as median and range.

and colleagues (Gilman *et al.*, 1999). In this consensus statement, a distinction is made between features which represent clinical symptoms characteristic of MSA and criteria which are defining features or a composite of several features required for the diagnosis of MSA. Features belong to one of four domains: (i) autonomic/urinary dysfunction; (ii) parkinsonism; (iii) cerebellar dysfunction; and (iv) corticospinal tract dysfunction. All our patients met the criterion of cerebellar dysfunction (gait ataxia and at least one of ataxic dysarthria, limb ataxia and sustained gaze-evoked nystagmus). According to Gilman and colleagues (Gilman *et al.*, 1999), a diagnosis of possible MSA can be made when patients have two additional features from separate domains, such as orthostatic hypotension with drop of systolic blood pressure by at least 20 mm Hg, rigidity or extensor plantar responses. For the diagnosis of probable MSA, patients have to meet the criterion of autonomic failure in addition to that of cerebellar ataxia. Autonomic failure is defined as an orthostatic fall in systolic blood pressure by at least 30 mm Hg or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men) or both.

Disease progression was studied as described previously (Klockgether *et al.*, 1998). Briefly, we defined the following disease stages: 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; and stage 4: death. For each patient, we determined the year of birth, the age at disease onset in years, the current disease stage and the latencies from disease onset in years after which subsequent disease stages were reached. Data were obtained from living patients by a personal structured interview. Patients were allowed to use their own diaries and notes. All information obtained by interview was compared with that from medical records.

### Laboratory studies

For determination of anti-GAD antibodies, a photometric immunoassay (Diaplets Anti-GAD, Boehringer Mannheim, Mannheim, Germany) was used. Results were referred to the

GAD-specific human monoclonal islet cell antibody clone 3 (MICA3) and calibrated to human immunoglobulin G (IgG) concentration. Samples with an anti-GAD concentration of less than 32 ng/ml were considered negative. The lower detection limit was 20 ng/ml.

Detection of antigliadin IgG and immunoglobulin A (IgA) antibodies in serum samples was performed using a solid phase enzyme immunoassay (Gluten IgG/IgA EIA, Pharmacia, Erlangen, Germany) following the manufacturer's instructions. To quantify the absorbance of each serum sample, a human reference serum sample containing a high concentration of antigliadin antibodies was used. Absorbance of the reference sample was set to 100 AU (arbitrary units/100 µl). One AU was equal to 1% absorbance of the reference. Serum samples with values above a threshold of 20 AU were considered positive. The lower detection limit was 6 AU. Endomysial antibodies were measured using indirect immunofluorescence (Viro-Immun Labor Diagnostika, Oberursel, Germany).

Molecular genetic tests were performed using standard laboratory protocols for FRDA (Epplen *et al.*, 1997), SCA1 (Schöls *et al.*, 1995a), SCA2 (Riess *et al.*, 1997a), SCA3 (Schöls *et al.*, 1995b), SCA6 (Riess *et al.*, 1997b), SCA8 (Koob *et al.*, 1999) and TATA-binding protein (Zühlke *et al.*, 2001).

### Statistical evaluation

To compare the frequency of clinical symptoms and the prevalence of antigliadin antibodies in different patient groups we used the  $\chi^2$ -test. The Mann-Whitney *U*-test was used to compare age of onset, age at examination, disease duration and severity of cerebellar ataxia. Disease progression was evaluated using Kaplan-Meier statistics.

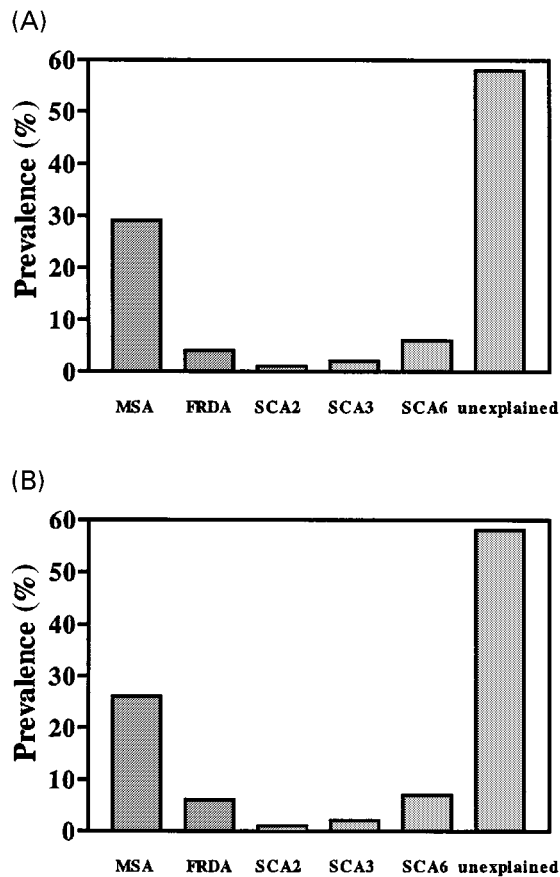
## Results

### Patients

The study population consisted of 112 patients, 61 males and 51 females. Age at examination ranged from 25 to 84 years with a median of 61 years, age at disease onset from 20 to 82 years with a median of 56.5 years (Table 1). Eighty-one patients had a disease duration of ≥4 years. Age at examination in this subgroup ranged from 25 to 82 years with a median of 62 years, age at disease onset from 20 to 75 years with a median of 54 years (Table 1). None of the patients was aware of consanguinity of their parents.

### Prevalence of MSA and genetically defined ataxias

Thirty-two patients (29%) met the clinical criteria of possible (7%) or probable (22%) MSA. The FRDA mutation was found in five patients (4%), the SCA2 mutation in one (1%), the SCA3 mutation in two (2%) and the SCA6 mutation in



**Fig. 1** Prevalence of MSA, FRDA, SCA2, SCA3 and SCA6. (A) Whole study population ( $n = 112$ ). (B) Subgroup of patients with a disease duration of  $\geq 4$  years ( $n = 81$ ).

seven (6%) (Fig. 1A). Thus, a diagnosis could be established in 47 patients (42%), while ataxia remained unexplained in the remaining patients (58%).

Since extracerebellar symptoms establishing a clinical diagnosis of MSA may develop up to 4 years after onset of ataxia (Klockgether *et al.*, 1990), we analysed the subgroup of patients with a disease duration of  $\geq 4$  years separately. The distribution of diagnoses in this subgroup was similar to that in the whole study population: 21 (26%) had MSA (possible: 2%, probable: 23%), five FRDA (6%), one SCA2 (1%), three SCA3 (2%) and six SCA6 (7%) (Fig. 1B).

### Serological findings

Since anti-GAD and antigliadin antibodies have been reported to occur in association with ataxia, we searched for these antibodies in our study population. We did not detect anti-GAD antibodies in any of our patients. Antigliadin antibodies were found in 14 patients: IgG antibodies in seven patients, IgA antibodies in nine patients and endomysial antibodies in one patient. Two of the patients had both IgG and IgA antibodies and one patient had IgA and endomysial antibodies. Antigliadin antibodies were present both in patients with unexplained ataxia (10 patients; 15%) and in patients with an established diagnosis (four patients; 9%). Of these four patients, three had MSA and 1 FRDA. There was no statistical difference between the frequency of antigliadin antibodies in patients with unexplained ataxia and in patients with an established diagnosis.

**Table 2** Clinical features of patients with unexplained ataxia and MSA

	Unexplained ataxia	MSA
Affected examined ( $n$ )	65	32
Gender ( $n$ ; male/female)	40/25	12/20*
Age at examination (years)	61 (25–84)	61.5 (33–77)
Age of onset (years)	56 (20–82)	57 (24–68)
Disease duration (years)	6 (1–25)	5.5 (0–20)
Associated signs (%)		
Ankle reflexes decreased or absent	40	9**
Ankle clonus	39	42
Extensor plantar response/spasticity	34	47
Muscular rigidity	9	53**
Tremor	5	25*
Amyotrophy	6	3
Muscle fasciculation-like movements	9	3
Decreased vibration sense	62	47
Gaze palsy	11	13
Double vision	17	31
Dysphagia	38	72*
Bladder dysfunction	34	91**
Dystonia	9	9

Age at examination, age at onset and disease duration are given as median and range. There were no statistically significant differences (Mann–Whitney  $U$ -test). The prevalence of clinical signs is given in percentages. \* $P < 0.01$ , \*\* $P < 0.001$  versus unexplained ataxia,  $\chi^2$ -test.

### Clinical characteristics of patients with unexplained ataxia

Forty of the 65 patients with unexplained sporadic ataxia were male and 25 female. Median age of onset was 56 years (range: 20–82 years) in patients with unexplained ataxia compared with 57 years (range: 24–68 years) in MSA. This difference was not statistically significant.

All patients with unexplained sporadic ataxia presented with a cerebellar syndrome. Severity of ataxia of gait ( $P < 0.001$ ), ataxia of upper limbs ( $P < 0.01$ ), dysdiadochokinesis ( $P < 0.01$ ), ataxia of lower limbs ( $P < 0.05$ ) and dysarthria ( $P < 0.001$ ) were less severe than in MSA. Although ataxia was the prominent symptom in patients with unexplained disease, extracerebellar symptoms were observed frequently (Table 2). The most frequent additional symptoms were: decreased vibration sense (62%); decreased or absent ankle reflexes (40%); increased ankle reflexes (39%); dysphagia (38%); bladder dysfunction (34%); and extensor plantar responses and/or spasticity (34%). Decreased or absent ankle reflexes were more frequent in patients with unexplained ataxia than in MSA (40% versus 9%,  $P < 0.001$ ). In contrast, bladder dysfunction (34% versus 91%,  $P < 0.001$ ), muscular rigidity (9% versus 53%,  $P < 0.001$ ), tremor (5 versus 25%,  $P < 0.01$ ) and dysphagia (38% versus 72%,  $P < 0.01$ ) were encountered less frequently than in MSA. A comparison of the age of onset and clinical features of anti-gliadin-positive and anti-gliadin-negative patients with unexplained ataxia did not reveal any significant differences (data not shown).

Disease progression was significantly slower in patients with unexplained ataxia compared with MSA. The median latency to become dependent on walking aids after disease

onset was 11.1 years compared with 4.7 years in MSA ( $P < 0.01$ ) (Fig. 2).

### Clinical characteristics of SCA and FRDA patients

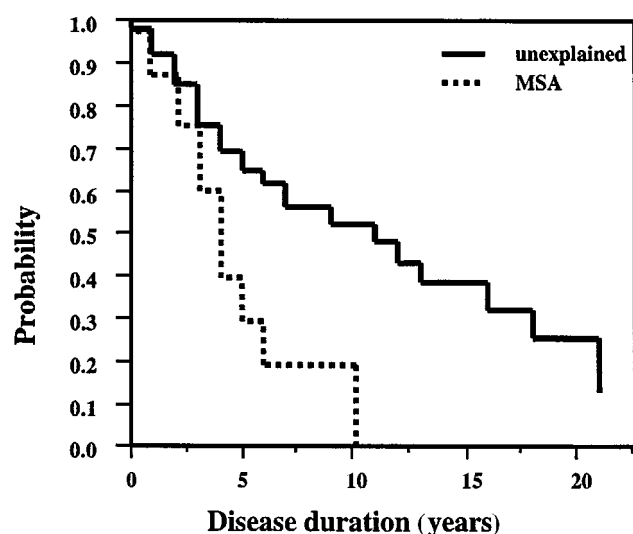
Ten patients were found to have an SCA mutation even though their family history was informative and negative. The parents of the SCA patients had died at a median age of 77 years (range: 55–96 years). Median age of death of the mothers was 78 years (range: 55–96 years) and of the fathers 75 years (range: 63–83 years). Seven out of 10 SCA patients carried the SCA6 mutation. Median age of onset was 59 years (range: 53–71 years) compared with 56 years (range: 20–82 years) in patients with unexplained ataxia. This difference was not statistically significant. Although SCA6 patients tended to have less severe ataxia of the upper and lower extremities, the clinical presentation was similar to that of patients with unexplained ataxia.

Five patients had the FRDA mutation. Not unexpectedly, they had a younger age of onset than all other groups (median: 27 years, range: 25–36 years). Ankle reflexes were preserved in one patient, while they were absent in the other four. Two had extensor plantar responses, two amyotrophy and four reduced vibration sense. The FRDA group was too small to make meaningful statistical comparisons with other patient groups.

### Discussion

The principal findings of this study can be summarized, as follows: (i) MSA is a frequent cause of sporadic adult-onset ataxia; (ii) mutations of the FRDA or SCA genes account for less than 15% of sporadic adult-onset ataxia patients; (iii) anti-gliadin antibodies are found in the serum of both patients with unexplained ataxia and patients with MSA or a genetic cause; and (iv) compared with MSA, patients suffering from unexplained sporadic ataxia have a milder phenotype and a better prognosis.

Our finding that 29% of sporadic ataxia patients suffer from MSA corresponds well to data of a recently published study of sporadic OPCA patients who were followed for 3 months to 10 years (Gilman *et al.*, 2000). Within this period, 17 out of 51 patients developed autonomic failure or parkinsonism indicating a diagnosis of MSA. Since these symptoms may develop years after onset of ataxia, a diagnosis of MSA might be missed in patients with a short disease duration. We therefore analysed patients with a disease duration of  $\geq 4$  years separately. A latency of 4 years was chosen because we had found previously (Klockgether *et al.*, 1990) that, if extracerebellar symptoms occur in sporadic ataxia, these symptoms usually develop within the first four years after ataxia onset. The prevalence of MSA in the subgroup of patients with a disease duration of  $\geq 4$  years was not different from that of the whole study population.



**Fig. 2** Kaplan-Meier graph showing the latency to become dependent on walking aids after disease onset in patients with unexplained ataxia ( $n = 65$ ) and MSA ( $n = 32$ ). The median latency was 11.1 years in patients with unexplained ataxia compared with 4.7 years in MSA ( $P < 0.01$ ).

This finding strongly argues against the possibility that we overlooked a considerable number of MSA cases because patients were examined before typical symptoms of MSA had evolved.

The percentage of sporadic ataxia patients with positive genetic tests was 13%: 4% carried the FRDA mutation, 1% the SCA2 mutation, 2% the SCA3 mutation and 6% the SCA6 mutation. A number of previous studies also looked for gene mutations in sporadic ataxia. In our own earlier study (Klockgether *et al.*, 1994), we failed to identify any SCA1 mutations in 61 IDCA patients. In other studies, the frequency of positive genetic tests in apparently sporadic ataxia patients ranged from 2% to 22% (Matsumura *et al.*, 1997; Moseley *et al.*, 1998; Pujana *et al.*, 1999; Schöls *et al.*, 2000). The discrepancies between the studies are probably due to variable genetic background and to different sub-sets of the study populations. In our study, all patients were examined personally and a careful family history was taken. Patients were included only if their parents were >50 years old or if parents had died when >50 years old. This reduces the likelihood of including patients with dominant ataxia whose parents had died before onset of the disease.

It may be possible that known gene mutations that were not tested, or presently unknown gene mutations may underlie some of the unexplained cases of sporadic ataxia. Both possibilities cannot be ruled out completely. However, there are several reasons that strongly argue against the idea that one or both of these mechanisms account for the disease in a considerable number of our patients. Although we tested only for the FRDA mutation and not for other recessive mutations, we do not believe that patients included in this study suffered from one of the recessive ataxias with known gene mutation or gene locus such as ataxia telangiectasia, ataxia with isolated vitamin E deficiency, abetalipoproteinaemia, autosomal recessive spastic ataxia of Charlevoix–Saguenay or recessive ataxia with ocular apraxia. Ataxia telangiectasia typically begins in early childhood and, although milder variants with later disease onset are possible, a disease onset after the age of 20 years is highly improbable. A recent study failed to find abnormal levels of  $\alpha$ -foetoprotein or mutations of the coding region of the ataxia telangiectasia mutated gene in a group of 34 sporadic ataxia patients aged three to 77 years (Hassin-Baer *et al.*, 1999). Ataxia with isolated vitamin E deficiency and abetalipoproteinaemia can be ruled out because all our patients had been screened for vitamin E deficiency before entry into the study. Autosomal recessive spastic ataxia of Charlevoix–Saguenay patients develop first signs of lower limb spasticity within the first years of life—in most cases observed at gait initiation between 12 and 18 months (Bouchard *et al.*, 1998). It is therefore highly improbable that our series of ataxia patients with a disease onset after 20 years included autosomal recessive spastic ataxia of Charlevoix–Saguenay patients. Recessive ataxia with ocular apraxia has a highly characteristic clinical phenotype which was not encountered among our patients (Barbot *et al.*, 2001). SCA1, SCA2, SCA3 and SCA6 account

for 86% of all families suffering from dominant ataxia in Germany (Riess *et al.*, 1997b). In addition, we tested for SCA8 and the TATA-binding protein. If one assumes that the distribution of SCA mutations in German sporadic ataxia patients is similar to that in dominant families, one can estimate that only a negligible number of patients in this study suffered from an SCA mutation other than one of the mutations tested.

The term ‘gluten ataxia’ has been coined to denote sporadic ataxia in patients with cryptic gluten sensitivity as indicated by circulating antigliadin antibodies in the absence of gastrointestinal symptoms (Hadjivassiliou *et al.*, 1998). In one study, 17 out of 25 patients suffering from unexplained sporadic ataxia had raised titres of antigliadin antibodies (Hadjivassiliou *et al.*, 1996). Positive duodenal biopsies were obtained in 35%. Demonstration of inflammatory infiltrates in the cerebellar white matter and posterior column of one gliadin-positive patient further corroborated the idea of a specific association of antigliadin antibodies and sporadic ataxia. In other studies, the prevalence of antigliadin antibodies was lower. Pellecchia and colleagues found antigliadin antibodies in 12.5% (Pellecchia *et al.*, 1999), Bürk and colleagues in 11.5% (Bürk *et al.*, 2001) and Combarros and colleagues in none of their sporadic ataxia patients (Combarros *et al.*, 2000). Quite unexpectedly, a recent study also found a high prevalence of gluten sensitivity (37%) in patients with dominant ataxias including patients with known SCA mutations (Bushara *et al.*, 2001). In our study population, antigliadin antibodies were present not only in patients with unexplained sporadic ataxia (15%), but also in patients with an established diagnosis (9%). The prevalence of antigliadin antibodies in healthy German blood donors is 5% (Bürk *et al.*, 2001). These observations raise the question of whether positive antigliadin antibodies are a consequence rather than the cause of cerebellar degeneration. Further studies are needed to clarify the importance of antigliadin antibodies in sporadic and hereditary ataxis.

A number of studies reported an association of cerebellar ataxia with anti-GAD antibodies (Saiz *et al.*, 1997; Abele *et al.*, 1999; Trivedi *et al.*, 2000; Honnorat *et al.*, 2001). Most of the GAD-positive patients had also insulin-dependent diabetes mellitus or other autoimmune endocrine manifestations. Our present search for anti-GAD antibodies was completely negative, showing that the association of sporadic ataxia with anti-GAD antibodies is rare.

In the largest subgroup of our study population, ataxia remained unexplained. As in MSA, age of onset is between 50 and 60 years. Compared with MSA, however, these patients have a milder phenotype and slower disease progression. Although cerebellar ataxia is the prominent symptom in these patients, many have clinical features suggesting additional involvement of pyramidal tracts, posterior columns and peripheral nervous system. The clinical phenotype of the present patients with unexplained ataxia broadly resembles that of the patients labelled as IDCA by Harding (1981). Harding subdivided

her 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 either of these groups. However, statistical analysis comparing the frequency of clinical symptoms in her three groups did not show any relevant differences. In most of our patients, ataxia of gait and stance was the prominent symptom, whereas tremor was an infrequent finding. Although it is not possible to prove clinical homogeneity of our patients with unexplained ataxia, our data give no rational basis for further subdivision into subgroups.

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*Received August 20, 2001. Revised November 22, 2001.*

*Accepted December 12, 2001*