Brain (1998), **121,** 589–600

The natural history of degenerative ataxia: a retrospective study in 466 patients

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Summary

The aim of the present study was (i) to compare disease progression and survival in different types of degenerative ataxia, and (ii) to identify variables that may modify the rate of disease progression. We included patients suffering from Friedreich's ataxia (FRDA, n *= 83), early onset cerebellar ataxia (EOCA,* n *= 30), autosomal dominant cerebellar ataxia (ADCA) type I (ADCA-I,* n *= 273), ADCA-III (*n *= 13) and multiple system atrophy (MSA,* n *= 67). Molecular genetic testing allowed us to assign 202 ADCA-I patients to one of the following subgroups: spinocerebellar ataxia type 1 (SCA1,* n *= 36), SCA2 (*n *= 56) and SCA3 (*n *= 110). To assess disease progression 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; stage 3 = confinement to wheelchair; stage 4 = death. Disease progression was most rapid in MSA, intermediate in FRDA, ADCA-I and ADCA-III and slowest in EOCA. The rate of progression was similar in SCA1, SCA2 and SCA3. The CAG repeat length was a significant risk factor for faster progression in SCA2 and SCA3, but not in SCA1. In FRDA, the time until confinement to wheelchair was shorter in patients with earlier disease onset, suggesting that patients with long GAA repeats and early disease onset have a poor prognosis. Female gender increased the risk of becoming dependent on walking aids or a wheelchair, but it did not influence survival in FRDA, SCA3 and MSA. In SCA2, female gender was associated with shortened survival. In MSA, later age of onset increased the risk of rapid progression and death.*

Keywords: Friedreich's ataxia; disease progression; multiple system atrophy; spinocerebellar ataxia; trinucleotide repeat

Abbreviations: ADCA = autosomal dominant cerebellar ataxia; CI = confidence interval; EOCA = early onset cerebellar ataxia; FRDA = Friedreich's ataxia; MSA = multiple system atrophy; SCA1 (2 or 3) = spinocerebellar ataxia type 1 (2 or 3)

Introduction

The degenerative ataxias are a group of diseases that are clinically characterized by progressive ataxia resulting from degeneration of the cerebellar cortex and spinal pathways. Classification of degenerative ataxias distinguishes between hereditary and idiopathic ataxias (Harding, 1983). Hereditary ataxias are further subdivided into ataxias with autosomal recessive inheritance such as Friedreich's ataxia (FRDA) and early onset cerebellar ataxia with retained tendon reflexes (EOCA), and the autosomal dominant cerebellar ataxias (ADCA). The idiopathic ataxias are sporadically occurring adult onset disorders of unknown aetiology which may resemble ADCA phenotypically. In many cases of idiopathic ataxia the underlying disease is multiple system atrophy (MSA) (Quinn, 1989).

FRDA usually begins around puberty, presenting as progressive ataxia accompanied by areflexia, posterior column signs and dysarthria. In addition, non-neurologic symptoms such as hypertrophic cardiomyopathy and diabetes mellitus may be associated with FRDA. The highly characteristic clinical presentation of FRDA led to the definition of essential diagnostic criteria which, among others, include areflexia and age of onset before the age of 25 years. The neuropathological abnormalities of FRDA include axonal neuropathy and degeneration of spinal tracts resulting in spinal atrophy (Geoffroy *et al.*, 1976; Harding, 1981*a*).

Recent molecular studies have shown that 94% of FRDA patients are homozygous for an expanded intronic trinucleotide (GAA) repeat in a novel gene, *X25*, while the remaining 6% are compound heterozygotes with an expanded repeat on one allele and a point mutation on the other allele (Campuzano *et al.*, 1996). Demonstration of the GAA repeat expansion in patients with retained tendon reflexes or disease onset after 25 years shows that the clinical spectrum of FRDA is broader than that defined by the classical diagnostic criteria (Dürr *et al.*, 1996*a*).

EOCA is another type of early onset ataxia that was originally distinguished from FRDA by the preservation of tendon reflexes (Harding, 1981*b*). Although recent studies show that tendon reflexes may also sometimes be preserved in FRDA (Dürr *et al.*, 1996*a*; Klockgether *et al.*, 1996*b*), it has been convincingly shown that EOCA represents a distinctive clinical syndrome. In contrast to FRDA, EOCA is associated with cerebellar degeneration. In addition, cardiomyopathy and diabetes mellitus do not occur in EOCA (Harding, 1981*b*; Klockgether *et al.*, 1991). Segregation analysis in EOCA suggests that this disorder is not genetically homogeneous, with autosomal recessive inheritance in only a subset of EOCA patients (Klockgether *et al.*, 1991).

The ADCAs are a heterogeneous group of dominantly inherited disorders with progressive ataxia as the leading symptom. ADCAs are seperated into several clinical types, the most common of which, ADCA-I, is characterized by progressive ataxia associated with various non-cerebellar neurological symptoms. In contrast, ADCA-III is characterized by a persisting purely cerebellar syndrome in all affected family members (Harding, 1982). While the neuropathological abnormality underlying ADCA-III is usually cerebellar cortical atrophy, olivopontocerebellar atrophy is often found in ADCA-I.

Genetic heterogeneity of ADCA-I has been established, with disease loci assigned to chromosome 6p (spinocerebellar ataxia type 1, SCA1), 12q (SCA2), 14q (SCA3), 19p (SCA6) and 16q (SCA4). Four of the genes (SCA1, SCA2, SCA3, SCA6) have been isolated, and the mutations have been shown to be unstable trinucleotide (CAG) repeat expansions present within coding regions of the respective genes (Orr *et al.*, 1993; Kawaguchi *et al.*, 1994; Imbert *et al.*, 1996; Pulst *et al.*, 1996; Sanpei *et al.*, 1996; Zhuchenko *et al.*, 1997). In contrast to SCA1, SCA2 and SCA3, the clinical phenotpye of SCA6 is often purely cerebellar so that SCA6 patients may be also classified as ADCA-III.

MSA is an adult onset sporadic disorder presenting with progressive cerebellar ataxia, parkinsonism or autonomic failure, or with variable combinations of these syndromes (Quinn, 1989). Neuropathologically, MSA is characterized by olivopontocerebellar atrophy, striatonigral degeneration and degeneration of the intermediolateral cell columns of the spinal cord. As a distinguishing feature, glial intracytoplasmatic inclusions are found in MSA brains (Lantos and Papp, 1994).

All types of degenerative ataxia take a progressive course and may lead to severe disability and premature death. There is, however, considerable variability of the rate of disease progression and survival between individual patients. Although precise knowledge of disease progression is essential for counselling of patients and design of future therapeutic trials, the natural history of the different types of degenerative ataxia has not been studied systematically, and risk factors influencing the rate of disease progression are largely unknown.

We therefore undertook the present study (i) to compare disease progression and survival in the different types of degenerative ataxia, and (ii) to identify variables that may modify the rate of disease progression. We included patients suffering from FRDA, EOCA, ADCA-I, ADCA-III and MSA. Genotyping was used to assign ADCA-I patients to one of the presently identified gene loci. These disorders are clinically and genetically well defined and represent the vast majority of ataxia patients in the setting of an adult neurological clinic.

Patients and methods

Patients

The medical records of all ataxia patients referred to the Departments of Neurology at the Universities of Tübingen and Bochum were reviewed and 543 patients with a diagnosis of FRDA, EOCA, ADCA-I, ADCA-III or MSA were identified. Of these, 466 were available and agreed to participate in the study, which was approved by the ethics committees of the Universities of Tübingen and Bochum.

Diagnoses

Diagnoses were based on the following criteria.

FRDA. (i) Progressive, otherwise unexplained ataxia with an age at disease onset of <25 years; (ii) autosomal recessive inheritance; (iii) loss of tendon reflexes in the legs; (iv) impaired vibration or position sense at the lower legs; and (v) dysarthria within 5 years of disease onset

(Geoffroy *et al*., 1976; Harding, 1981*a*). In many of the FRDA patients the results of genetic tests were available showing homozygosity for GAA expansion in *X25*. We also included patients homozygous for the GAA expansion who had retained tendon reflexes or disease onset after 25 years. Molecular genetic tests for FRDA were done using standard laboratory protocols (Campuzano *et al*., 1996).

EOCA. (i) Progressive, otherwise unexplained ataxia with an age at disease onset of <25 years; (ii) family history compatible with autosomal recessive inheritance; (iii) tendon reflexes of the legs normal or increased; (iv) absence of pigmentary retinal degeneration, hypogonadism, optic atrophy, cataract, myoclonus, cardiomyopathy or diabetes mellitus; and (v) MRI or CT evidence of cerebellar atrophy untypical for FRDA (Harding, 1981*b*; Klockgether *et al*., 1991).

ADCA. (i) Progressive, otherwise unexplained, ataxia; and (ii) autosomal dominant inheritance. Families with ADCA were further subdivided into families with a purely cerebellar syndrome (ADCA-III) and families with additional non-cerebellar symptoms (ADCA-I). Molecular genetic tests for SCA1, SCA2, SCA3 and SCA6 were done using standard laboratory protocols (Orr *et al*., 1993; Kawaguchi *et al*., 1994; Imbert *et al*., 1996; Zhuchenko *et al*., 1997).

MSA. (i) Progressive, otherwise unexplained ataxia and/or non or poorly levodopa-responsive parkinsonism; (ii) severe symptomatic autonomic failure with at least postural syncope or presyncope and/or marked urinary incontinence or retention not due to other causes; (iii) no evidence of inheritance; (iv) absence of dementia, generalized tendon areflexia or predominant downgaze supranuclear palsy (Quinn, 1989).

Data collection

To study disease progression 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; 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. If patients were deceased, were unable to take part in the interview or had difficulty in recalling the desired information, identical questions were posed to spouses or first-degree relatives. All information obtained by interview was compared with that from medical records. If there were only minor dicrepancies of <2 years, the interview data were used for further analysis. If the discrepancies exceeded 2 years, the patients or relatives were contacted a second time and the data taken from the medical records were discussed with them. A second interview was required in ~10% of the patients. If discrepancies remained after the second interview we usually selected the interview data, except when the patient or his relatives admitted that they had difficulty recalling the correct data or when two independent sources from medical records agreed upon a particular date.

Data analysis

Disease progression was modelled by a multi-state first order Markov process that allows only progressive transitions (Andersen *et al*., 1993). Each transition probability was assumed to follow a Cox regression model (Cox, 1972). All analyses were done separately on two time scales: (i) a time scale starting with disease onset (disease scale) and (ii) a time scale starting with birth (age scale). The following covariables were considered: gender; year of birth; age at disease onset; and, in the SCA mutations, CAG repeat length. GAA repeat length was not introduced as a covariable in FRDA because repeat length was measured in different laboratories and quantification was not sufficiently reliable.

The covariables were included into the respective models when they reached a 10% significance level in a forward selection procedure. Continuous covariables were assumed to act linearly on the hazard. When the data were analysed on the age scale, the age at disease onset was modelled as a time-dependent covariable. All results are presented in terms of risk ratios (relative risks) and their 95% confidence intervals (95% CI). Tests on the validity of the proportional hazard assumption were done by including an additional time-dependent covariable as described by Cox (1972). If this assumption was violated, the model was stratified at the median of the covariable and all analyses were recalculated. In this case, the results of the unstratified models have to be interpreted as the relative risks at the mean of all time points, and 95% CI and *P*-values are not estimable.

P-values of <0.05 are reported. We did not perform corrections for multiple testing because it was our aim to select unknown potential risk factors, and not to confirm known risk factors or to study presumed risk factors in depth. Instead, we focused on the size and homogeneity of risk ratios, which can be done best by interpreting the respective confidence intervals. We are aware of the fact that, if only *P* values are considered, this procedure may lead to somewhat over-optimistic results.

Disease progression was compared between groups via weighted means at subsequent time points with the weights based on estimated survival curves, as described by Zilber *et al.* (1994). Due to censored observations at intermediate disease stages the method was slightly modified. Each survival curve was bounded by the survival curve of the following stage. Group comparisons were done with a closed test

procedure of *F* tests in repeated measurement ANOVAs (analyses of variance).

Results

Patients

The study population consisted of 466 patients, 231 males and 235 females. At the time of data collection, 366 of the patients were living and 100 deceased. There were 83 patients with FRDA, 30 with EOCA, 273 with ADCA-I, 13 with ADCA-III and 67 with MSA. Forty-three of the the MSA patients had a cerebellar phenotype and 24 a predominantly parkinsonian phenotype. Molecular genetic testing allowed us to assign 206 ADCA-I patients to one of the following subgroups: SCA1 (n = 36), SCA2 (n = 56), SCA3 (n = 110) and SCA6 (n = 4). Due to the small number of patients, SCA6 was not further analysed as a separate group. The median CAG repeat number was 50 in SCA1 (range, 42–57), 40 in SCA2 (36–52) and 73 in SCA3 (63–82). While the male : female ratio was balanced in most groups, there were significantly more male patients in the EOCA and ADCA-III group (Table 1).

Age of onset

Age of onset ranged from from 3 to 74 years. While FRDA and EOCA usually started before the age of 20 years, age of onset was variable in ADCA-I and ADCA-III with a median age of onset of 39.5 and 41 years, respectively. The median age of onset was 36.5 years in SCA1, 30 years in SCA2 and 42 years in SCA3. As shown previously, the age of onset in SCA mutations was inversely correlated with repeat length (SCA1, r = –0.89; SCA2, r = –0.80; SCA3, r = –0.78; Spearman rank correlation). MSA typically started between the ages of 50 and 60 years with a median age of onset of 56 years (Table 1).

Group comparison

To assess disease progression in the various disease groups, we calculated the mean disease stage at subsequent time points for each group (Zilber *et al.*, 1994). To estimate the rate of disease progression we first analysed the data on a time scale starting with disease onset (disease scale). As shown in Fig. 1, disease progression was fastest in MSA, intermediate in FRDA, ADCA-I and ADCA-III, and slowest in EOCA. Statistical analysis showed that the progression rates in MSA and FRDA were significantly faster than in all other groups ($P < 0.05$). The rate of progression tended to be faster in SCA1 than in SCA2 and SCA3. However, this difference did not reach the level of statistical significance.

A different picture emerged when we analysed the data using a time scale starting with birth (age scale). This analysis revealed that patients with the early onset recessive ataxias, FRDA and EOCA, reached advanced disease stages at an earlier age than patients with ADCA-I, ADCA-III and MSA. Statistical analysis showed differences between all groups ($P < 0.05$). Similarly, disease progression on the age scale differed between the SCA groups ($P < 0.05$); SCA2 started earlier than SCA1 and SCA3, while disease progression was faster in SCA1 compared with SCA2 and SCA3. On average, SCA2 patients <40 years old were more severely disabled than SCA1 and SCA3 patients of a similar age. Beyond the age of 50 years, however, SCA1 patients were more severely disabled than SCA2 and SCA3 patients (Fig. 2).

Variables influencing disease progression

We used multiple Cox regression models to analyse whether gender, year of birth, age of onset and (in SCA1, SCA2 and SCA3), CAG repeat length influence disease progression and survival in the various disease groups. A summary of the data is given in Table 2 (disease scale) and Table 3 (age scale).

FRDA

Female patients had an increased risk of becoming dependent on walking aids or of becoming wheelchair-bound compared with male patients. The relative risks ranged from 1.7 to 2.0 depending on whether the data were analysed on the age or disease scale. In contrast, survival was not influenced by gender. More recent year of birth slightly increased the risk of becoming dependent on walking aids and of becoming wheelchair-bound (walking aid risk on the disease scale = 1.03, 95% CI = 1.00–1.05; walking aid risk on the age scale = 1.05, 95% CI = 1.02–1.09; wheelchair risk on the age scale = 1.04, 95% CI = 1.01–1.07), but it did not significantly influence survival.

At a given age, each additional year of age at disease onset decreased the risk of entering advanced disease stages (walking aid risk = 0.85, 95% CI = 0.79–0.93; wheelchair risk = 0.80, 95% CI = 0.74–0.86). When the data were analysed on a disease scale, age of onset decreased the risk of becoming wheelchair-bound by a factor of 0.92 (95% CI = 0.88–0.96) indicating faster progression to wheelchair-dependence in patients with earlier disease onset.

EOCA

Gender, year of birth and age of onset did not have a significant influence on disease progression and survival in EOCA (data not shown).

SCA1

Gender did not significantly influence disease progression and survival in SCA1 patients. The risk of death slightly

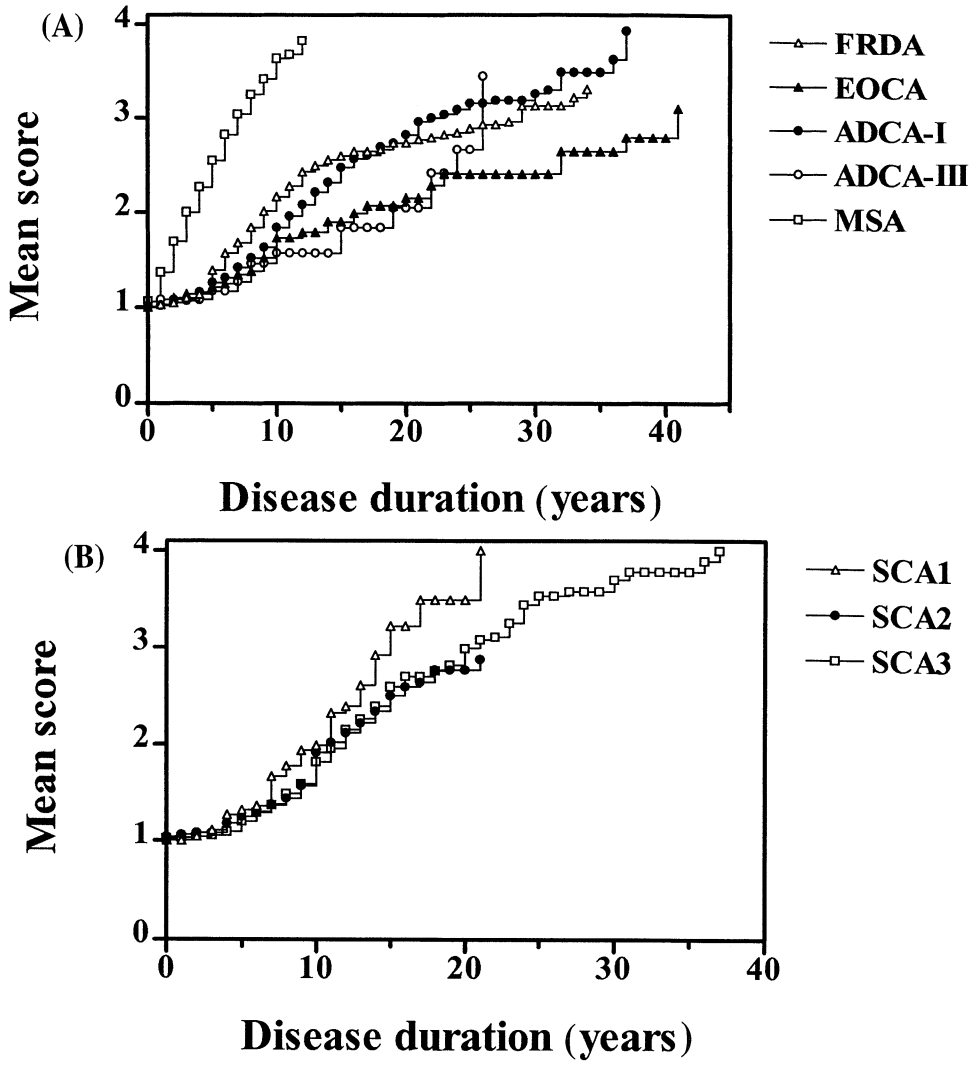

Fig. 1 Mean disease score of (**A**) FRDA, EOCA, ADCA-I, ADCA-III and MSA and (**B**) SCA1, SCA2 and SCA3, calculated on a time scale starting with disease onset (disease scale).

Table 1 *Patient data (*n = *466)*

	Group/subgroup							
	FRDA	EOCA	ADCA-I	SCA1	SCA2	SCA3	ADCA-III	MSA
n	83	30	273	36	56	110	13	67
Living/deceased	77/6	28/2	213/60	27/9	43/13	84/26	10/3	38/29
Male/female	35/48	20/10	131/142	18/18	27/29	50/60	9/4	36/31
Median age at onset (years)	14	17	39.5	36.5	30	42	41	56
Interquartile range (years)	10–18	14–24	30–49	31–41.5	23–40	31–50	26–46	49–61

FRDA = Friedreich's ataxia; EOCA = early onset cerebellar ataxia; ADCA-I/III = autosomal dominant cerebellar ataxia type I/III; SCA1/2/3 = spinocerebellar ataxia type 1/2/3; MSA = multiple system atrophy.

decreased with more recent year of birth (risk on the disease scale = 0.96, 95% CI = 0.91–1.00; risk on the age scale = 0.93, 95% CI = 0.87–0.99).

At a given age, each additional year of age at disease onset decreased the risk of entering advanced disease stages (walking aid risk = 0.82, 95% CI = 0.67–1.00; wheelchair risk = 0.72, 95% CI = 0.57–0.89; death risk = 0.76, 95% CI = 0.62–0.94). On the other hand, there was no effect of the age of onset on disease progression and survival, when the data were analysed on

Table 2 *Risk factors influencing disease progression and survival calculated on a time scale starting with disease onset (disease scale)*

	FRDA			SCA1			SCA2			SCA3			MSA		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Stage 2															
Gender	1.8*	–	–	–	–	–	3.6*	–	–	3.0*	–	–	3.0*	–	–
Year of birth	1.03	1.00–1.05	0.0180	0.95	0.90–1.00	0.0669	–	–	–	–	–	–	–	–	–
Age of onset	–	–	–	–	–	–	1.09	1.01–1.18	0.0348	–	–	–	1.12	1.03–1.22	0.0057
Repeat length	–	–	–	–	–	–	1.47	1.08–2.02	0.0158	–	–	–	–	–	–
Stage 3															
Gender	1.7*	–	–	–	–	–	–	–	–	2.9*	–	–	3.5*	–	–
Year of birth	–	–	–	–	–	–	1.29	0.98–1.71	0.0713		–	–	–	–	–
Age of onset	0.92	0.88–0.96	0.0001	–	–	–	1.65	1.14–2.38	0.0081	1.09	0.98–1.20	0.1112	1.05	1.01–1.10	0.0197
Repeat length	–	–	–	–	–	–	3.37	1.64–6.94	0.0010	1.29	1.02–1.63	0.0320	–	–	–
Stage 4															
Gender	–	–	–	–	–	–	4.9*	–	–	–	–	–	–	–	–
Year of birth	–	–	–	0.96	0.91–1.00	0.0621	0.93	0.88–1.00	0.0442	0.98	0.96–0.99	0.0002	1.12	0.99–1.28	0.0758
Age of onset	–	–	–	–	–	–	0.90	0.83–0.97	0.0046	–	–	–	1.19	1.04–1.37	0.0094
Repeat length	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

RR = relative risk. Covariables were only included when they reached a 10% significance level in a forward selection procedure. *Assumption of proportional hazards was violated; in this case, 95% CI and *P*-values are not estimable.

Table 3 *Risk factors influencing disease progression and survival calculated on a time scale starting with birth (age scale)*

	FRDA			SCA1			SCA2			SCA3			MSA		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Stage 2															
Gender	2.0*	–	–	–	–	–	4.5	1.36–14.81	0.0137	2.1*	–	–	2.0	1.07–3.71	0.0292
Year of birth	1.05	1.02–1.09	0.0021	–	–	–	–	–	–	–	–	–	1.09	1.01–1.18	0.0236
Age of onset	0.85	0.79–0.93	0.0001	0.82	0.67–1.00	0.0560	0.87	0.78–0.99	0.0298	0.82	0.75–0.90	0.0001	0.81	0.69–0.94	0.0076
Repeat length	–	–	–	–	–	–	1.20	0.99–1.45	0.0580	1.28	1.10–1.50	0.0019	–	–	–
Stage 3															
Gender	–	–	–	–	–	–	–	–	–	3.0*	–	–	–	–	–
Year of birth	1.04	1.01–1.07	0.0171	–	–	–	1.21	1.03–1.44	0.0237		–	–	–	–	–
Age of onset	0.80	0.74–0.86	0.0001	0.72	0.57–0.89	0.0030	–	–	–	0.69	0.56–0.85	0.0005	0.81	0.72–0.91	0.0006
Repeat length	–	–	–	–	–	–	1.44	1.04–2.00	0.0300	1.27	0.98–1.64	0.0703	–	–	–
Stage 4															
Gender	–	–	–	–	–	–	12.08	1.36–106.83	–	–	–	–	–	–	–
Year of birth	–	–	–	0.93	0.87–0.99	0.0334	0.94	0.87–1.01	0.0997	0.98	0.96–1.00	0.0172	1.15	1.01–1.32	0.0405
Age of onset	–	–	–	0.76	0.62–0.94	0.0132	0.74	0.62–0.88	0.0007	0.89	0.84–0.94	0.0001	0.90	0.83–0.99	0.0289
Repeat length	–	–	–	–	–	–	–	–	–	–	–	–		–	–

RR = relative risk. Covariables were only included when they reached a 10% significance level in a forward selection procedure. *Assumption of proportional hazards was violated; in this case, 95% CI and *P*-values are not estimable.

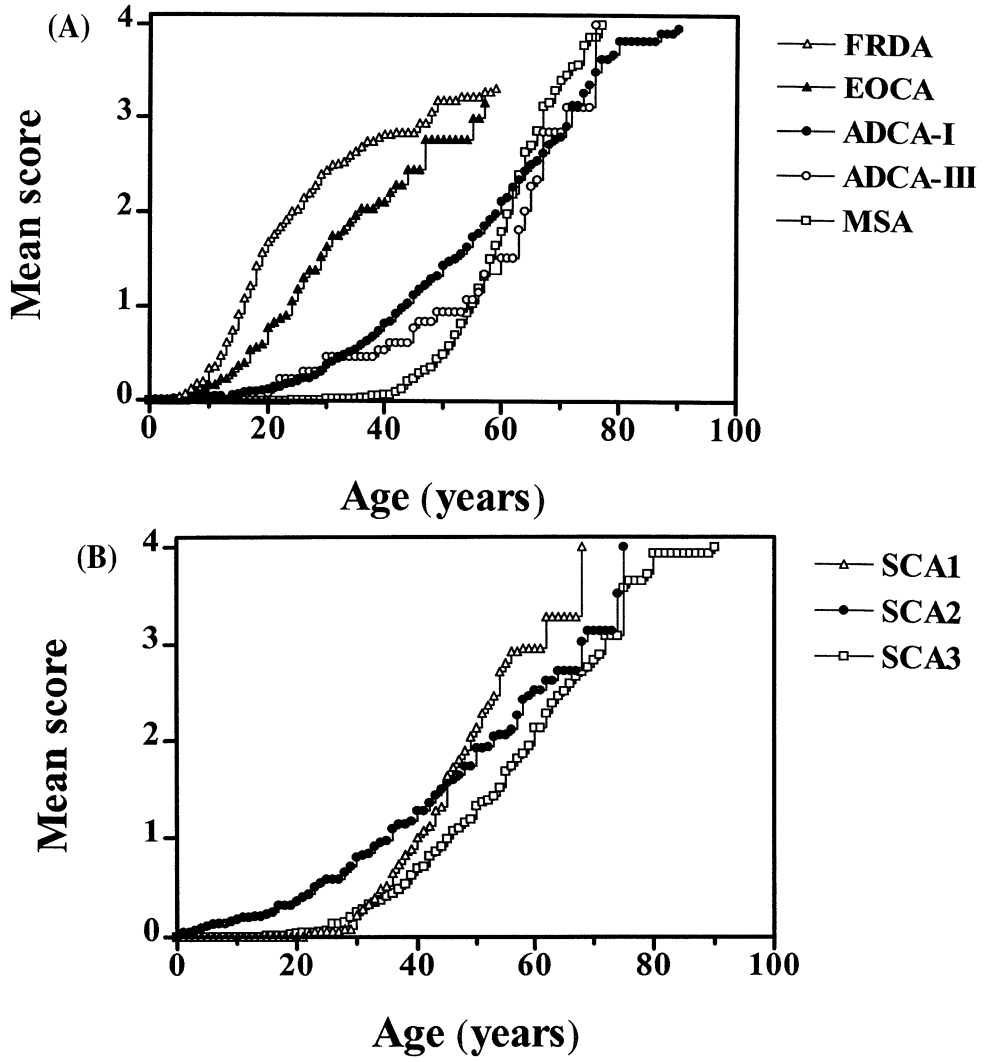

Fig. 2 Mean disease score of (**A**) FRDA, EOCA, ADCA-I, ADCA-III and MSA and (**B**) SCA1, SCA2 and SCA3, calculated on a time scale starting with birth (age scale).

the disease scale. Similarly, CAG repeat length had no significant influence on disease progression and survival in SCA1.

SCA2

Female gender markedly increased the risk of entering advanced disease stages or of death, irrespective of whether the data were analysed on the age or disease scale. The relative risks ranged from 3.6 to 12.08. The year of birth and age of onset had inconsistent effects on the risks of entering advanced disease stages. In contrast, repeat length significantly increased the risk of becoming dependent on walking aids (risk on the disease scale = 1.47, 95% CI = 1.08–2.02; risk on the age scale = 1.20, 95% CI = 0.99–1.45) or wheelchair-bound (risk on the disease scale = 3.37, 95% CI = 1.64–6.94; risk on the age scale = 1.44, 95% CI = 1.04–2.00). Since repeat length was not available for most deceased patients the effect of repeat length on survival could not be analysed.

SCA3

Female sex increased the risk of entering advanced disease stages (walking aid risk on the disease scale = 3.0; wheelchair risk on the disease scale = 2.9; walking aid on the age scale = 2.1; wheelchair on the age scale = 3.0), but had no significant influence on survival. A more recent year of birth slightly decreased the risk of death (disease scale: 0.98, 95% CI = 0.96–0.99; age scale: 0.98, 95% CI = 0.96–1.00).

At a given age, each additional year of age at disease onset reduced the risk of entering advanced disease stages or of death by a factor of 0.82 (95% CI = 0.75–0.90), 0.69 (95% CI = 0.56–0.85) and 0.89 (95% CI = 0.84–0.94) for

stages 2, 3 and 4, respectively. In contrast, data analysis on the disease scale did not show a significant effect of age of onset on disease progression and survival.

Increase in CAG repeat length significantly increased the risk of becoming dependent on walking aids (age scale = 1.28, 95% CI = 1.10–1.50) or wheelchair-bound (risk on the disease scale = 1.29, 95% CI = 1.02–1.63; risk on the age scale = 1.27, 95% CI = 0.98–1.64). Since repeat length was not available for most deceased patients the effect of repeat length on survival could not be analysed.

ADCA-III

Gender, year of birth and age of onset did not have a significant influence on disease progression and survival in ADCA-III (data not shown).

MSA

Female sex increased the risk of entering advanced disease stages (walking aid risk on the disease scale = 3.0; wheelchair risk on the disease scale = 3.5; walking aid risk on the age scale = 2.0, 95% CI = 1.07–3.71), but had no influence on survival. The year of birth slightly increased the risk of becoming dependent on a walking aid (risk on the age scale = 1.09, 95% CI = 1.01–1.18) or of death (risk on the disease scale = 1.12, 95% CI = 0.99–1.28; risk on the age scale = 1.15, 95% CI = 1.01–1.32).

On the age scale, each additional year of age at disease onset reduced the risk of becoming dependent on walking aids (0.81, 95% CI = 0.69–0.94), of becoming wheelchair-bound (0.81, 95% CI = 0.72–0.91) or of death (0.90, 95% CI = 0.83–0.99). On the other hand, when the data were analysed on the disease scale, age of onset increased the risk of entering advanced disease stages (walking aid risk = 1.12, 95% CI = 1.03–1.22; wheelchair risk = 1.05, 95% CI = 1.01–1.10) or of death (1.19, 95% CI = 1.04–1.37).

Discussion

This is the first systematic study of the natural history of the various types of degenerative ataxia. In this study, we included patients with FRDA, EOCA, ADCA and MSA. We show here that these disorders differ not only with respect to age of disease onset but also with respect to rate of disease progression and survival. In addition, we have identified a number of potential risk factors that modify the natural course of the respective disorders.

FRDA and EOCA

These disorders share the clinical features of early disease onset and progressive ataxia. Although recent studies in patients with molecularly proven FRDA have shown that FRDA may start after the age of 25 years, the majority of patients have a disease onset in the second decade of life (Klockgether *et al.*, 1993; Dürr *et al.*, 1996*a*). Confirming results of earlier studies (Harding, 1981*a*, *b*; Klockgether *et al.*, 1991), there was a tendency towards later disease onset in EOCA than in FRDA, although this difference did not reach statistical significance. However, progression was significantly faster in FRDA compared with EOCA. For example, the median latency to confinement to wheelchair was 11 years in FRDA and 22 years in EOCA. Unfortunately, the limited access to data from deceased patients did not allow us to calculate median latencies to death. However, the data show that 75% of FRDA patients survive for >34 years after disease onset. The corresponding value for EOCA patients was 41 years. Our study indicates slightly better survival than two studies based on Italian populations that reported a 30-year survival rate of 61% in FRDA (Leone *et al.*, 1988) and 77% a in EOCA (Chio *et al.*, 1993). Although survival in FRDA appears to be better than often assumed, FRDA patients spend more than two decades of their lives in a severely disabled state with confinement to wheelchair.

We found an increased risk of female FRDA patients of becoming dependent on walking aids or of becoming wheelchair-bound compared with male patients. Although difficult to interpret, we believe that the apparently faster progression in females does not reflect a biological difference but is rather due to a reduced capacity of female FRDA patients to cope with physical disability. This view is supported by the observation that gender had no influence on survival. Similarly, Leone *et al.* (1988) did not observe reduced survival in female patients. However, the argument that survival was not affected by female gender must be used with caution because calculation of the risk of death is based on a large proportion of incomplete observations. Earlier use of walking aids and wheelchair without shortened survival in female patients was also observed in SCA3 and MSA, suggesting that the effect of female gender is not specific for FRDA but may reflect a more general phenomenon in degenerative ataxia.

Year of birth was introduced as a covariable in our analysis to search for factors that might modify the natural history of ataxia in the longterm. A novel therapy or a more effective health care system might represent factors that would lead to slower progression and better survival in patients with later birth. Unexpectedly, we found that progression was slightly faster in FRDA patients with more recent dates of birth, although there was no significant difference with respect to survival. These findings show that prognosis of FRDA has not improved over the years. A possible explanation of the apparently faster progression is that wider availability of medical care may lead to earlier prescription of walking aids and wheelchairs. Again, this phenomenon was not specific for FRDA, but was also observed in SCA2 and MSA.

When interpreting the influence of age of onset on disease progression and survival, it is important to consider whether the data were analysed on the disease scale or the age scale. The risk-decreasing effect of age of onset observed in

FRDA and a number of other degenerative ataxias is simply explained by fact that, at a given rate of progression, patients with later disease onset reach advanced disease stages at later age. In contrast, risk-modifying effects of age of onset on the disease scale reflect direct effects of this variable on the rate of disease progression. Because GAA repeat length was not used as a covariable in FRDA, the data are not adjusted for repeat length. Given the inverse correlation of age of onset and repeat length in FRDA, a suspected risk-increasing effect of repeat length would lead to a risk-decreasing effect of age of onset in our analysis. Indeed, we found an 8% decreased risk of becoming wheelchair-bound with each additional year of age at disease onset. These data confirm the recent finding of De Michele *et al.* (1996) that onset before the age of 20 years was associated with a shorter time before becoming wheelchair-bound. The hypothesis that the effect of age of onset on progression reflects an effect of GAA repeat length is supported by the observation that the size of the smaller GAA expansion and the time until confinement to wheelchair are inversely correlated in FRDA (Dürr *et al.*, 1996*a*).

ADCA

It is generally assumed that the purely cerebellar type of ADCA, ADCA-III, has a later disease onset and slower progression than the more frequent subtype, ADCA-I, that is characterized by the occurrence of various non-cerebellar symptoms (Harding, 1982). This was only partially confirmed in the present study. Median age of onset was similar in both groups (for ADCA-I, 39.5 years; for ADCA-III, 41 years). However, the analysis of disease progression showed differences between both groups with faster progression in ADCA-I. The time until confinement to a wheelchair was 17 years in ADCA-I and 26 years in ADCA-III.

Disease progression and survival were similar in SCA1, SCA2 and SCA3. Compared with SCA1 and SCA3, SCA2 patients had slightly earlier disease onset, while progression tended to be faster in SCA1 compared with SCA2 and SCA3. Life expectancy was shortest in SCA1, with a median age at death of 56 years. The data may have been influenced by the composition of the patient groups and the distribution of the CAG repeat length. For example, our SCA1 group did not include patients with very large expansions of more than 60 units. There are only very limited survival data in the literature. Most of these data come from small series of autopsied patients and do not appear to be representative. Nevertheless, Genis *et al.* (1995) reported a mean age at death in a series of 14 autopsied SCA1 cases of 54.1 years that is almost identical to the calculated median age of death of 56 years in the present study. While survival after disease onset ranged from 21 to 25 years in SCA1, SCA2 and SCA3 in our study, shorter survival times have been reported (Orozco *et al.*, 1989; Takiyama *et al.*, 1994; Dürr *et al.*, 1996*b*).

In SCA2, female gender markedly increased the risk of reaching advanced disease stages and of death. In SCA3, female gender only increased the risk of losing independent gait or of becoming wheelchair-bound, but not to die, while an effect of gender could not be ascertained in SCA1. The negative influence of female gender on disease progression is a novel and unexpected finding. The increased risk of death in female SCA2 patients makes it improbable that the observed gender effect is due to different attitudes towards disease-related disability, as we suggested for FRDA. Rather, the data suggest that there are biological factors that accelerate progression in females. At present, the underlying mechanisms are completely unknown. However, improved understanding of this phenomenon appears to be of considerable pathophysiological importance and might lead to the development of novel therapeutic interventions.

Year of birth had a weak, albeit significant, negative effect on the risk of death in the SCA mutations, indicating longer survival of SCA patients with later birth. This finding is in line with the general assumption that development of modern public health care systems may lead to improved survival in neurodegenerative disease, even in the absence of effective therapies.

In SCA2 and SCA3, progression was faster with increasing CAG repeat length, while such an effect was not ascertained in SCA1. These observations confirm and extend earlier results obtained in a subset of the present SCA3 patients (Klockgether *et al.*, 1996*a*). Although we were unable to demonstrate an effect of CAG repeat length on survival because repeat length was not available in deceased patients, our data suggest that the number of CAG repeats has a direct impact on the timing and dynamics of neuronal cell death in SCA3. Whether the negative finding in SCA1 is due to different disease mechanisms in SCA1 or whether it is simply due to the smaller number of patients, is difficult to decide. Age of onset was introduced as an independent covariable in the analysis, but did not have consistent effects on progression and survival in ADCA.

MSA

Although MSA and hereditary ataxias share a number of clinical and neuropathological features, the natural history of these latter disorders is fundamentally different. Among the diseases studied, MSA had the latest disease onset with a median age of 56 years. On the other hand, disease progression was much faster than in the hereditary ataxias. On average, from onset of gait difficulties, MSA patients remained ambulant for only 6 years and survived for 9 years. These data are in good agreement with those of earlier studies (Schulz *et al.*, 1994; Wenning *et al.*, 1994).

In contrast to the weak and variable effects of gender and year of birth on disease progression in MSA, higher age of onset consistently accelerated progression and increased the risk of death. In a meta-analysis of 433 pathologically proven cases of MSA, Ben-Shlomo *et al.* (1997) found that age of onset beyond 60 years was associated with shorter survival.

We did not observe comparable effects in the other types of degenerative ataxias. However, a similar effect of age of onset with poor prognosis in patients with later disease onset has been noted in amyotrophic lateral sclerosis, another sporadic neurodegenerative disorder (Norris *et al.*, 1993; Preux *et al.*, 1996).

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Received July 14, 1997. Revised October 22, 1997.
Accepted November 12, 1997