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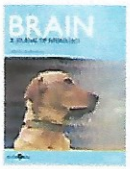
A Journal of Neurology



Editor
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IMPACT FACTOR 9.196
5 YEAR IMPACT FACTOR 10.418

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Prevalence of hereditary ataxia and spastic paraplegia in southeast Norway: a population-based study

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DOI: http://dx.doi.org/10.1093/brain/awp056 1577-1588 First published online: 31 March 2009

Summary

A population-based, cross-sectional study was performed in southeast Norway, between January 2002 and February 2008, to identify subjects with hereditary ataxia and hereditary spastic paraplegia, and to estimate the prevalence of these disorders. Patients were recruited through colleagues, families, searches in computerized hospital archives and the National Patients' Association for Hereditary Ataxia and Spastic Paraplegia. Strict criteria were used for inclusion of familial and isolated subjects. A project neurologist examined all index subjects and clinical and genetic data were registered. The source population on January 1, 2008 was 2.63 million and the prevalence day was set as February 1, 2008. One hundred seventy-one subjects from 87 unrelated families with hereditary ataxia and 194 subjects from 65 unrelated families with hereditary spastic paraplegia were included. The total prevalence was estimated at 13.9/100 000. Hereditary ataxia prevalence in the region was estimated at 6.5/100 000: 4.2/100 000 for autosomal-dominant and 2.3/100 000 for autosomal recessive, 0.15/100 000 for Friedreich's ataxia and 0.4/100 000 for ataxia telangiectasia. Hereditary spastic paraplegia prevalence was 7.4/100 000: 5.5/100 000 for autosomal dominant-hereditary spastic paraplegia, 0.6/100 000 for autosomal recessive-hereditary spastic paraplegia and 1.3/100 000 for isolated subjects. Marked differences were found in the frequencies of hereditary ataxia subtypes compared with other countries, while those of the most common autosomal dominant-hereditary spastic paraplegia genotypes, SPG4, SPG3 and SPG31, were similar to those previously reported. Clear variations between age groups and counties were observed, but no gender differences. Mean age on prevalence day was 48 years, mean age at onset was 24 years. We present the largest population study performed on hereditary ataxia and hereditary spastic paraplegia prevalence and report a higher prevalence than expected. Better inclusion criteria and multiple search strategies may explain the observed differences.

ataxia telangiectasia Friedreich's ataxia hereditary ataxia hereditary spastic paraplegia prevalence SCA SPG3 SPG4 SPG11 SPG31

Introduction

Hereditary ataxias (HA) and hereditary spastic paraplegias (HSP) are heterogeneous neurodegenerative disorders often known as spinocerebellar degenerative disorders. Hereditary ataxia is characterized by progressive gait and limb ataxia, loss of coordination and disturbances of speech and oculomotor control. Hereditary spastic paraplegia is mainly characterized by progressive spasticity and weakness in the lower

limbs. The disorders are classically described as pure or complex, depending on the absence or presence of additional neurological symptoms (Harding, 1983) such as polyneuropathy, dementia, tremor, ataxia for HSP and spasticity for HA. The main symptoms and signs are related to degeneration of the cerebellum, corticospinal tracts, brainstem and spinal cord. Autosomal dominant (AD), autosomal recessive (AR) and some X-linked modes of inheritance are reported. At least 28 genetic loci and 12 genes have been identified for the dominant ataxias, and many genes have been identified for the recessive ataxias. SCA 1,2,3,6 and Friedreich's ataxia are reported to be the most common subtypes (Albin, 2003; Schols *et al.*, 2004; Warrenburg *et al.*, 2005; Duenas *et al.*, 2006; Fogel and Perlman, 2007; Soong and Paulson, 2007; Tsuji *et al.*, 2008). To date 38 genetic loci have been identified for HSP, including 15 for AD-HSP, 20 for AR-HSP and three for X-linked HSP (X-HSP) (Depienne *et al.*, 2007). AD-HSPs account for ~80% of all HSPs, with SPG4 and SPG3A being the most common forms.

Although hereditary ataxia and hereditary spastic paraplegia have a worldwide distribution, few epidemiological studies have been conducted on these disorders. Most studies are from Europe, and a few are from Africa and Asia. The reported prevalence of hereditary ataxia and hereditary spastic paraplegia varies from 1.6 to 18.5/100 000 (Table 1) (Skre, 1974*a*, *b*; Sridharan *et al.*, 1985; Brignolio *et al.*, 1986; Leone *et al.*, 1990; Polo *et al.*, 1991; Filla *et al.*, 1992; van de Hirayama *et al.*, 1994; Lopez-Arlandis *et al.*, 1995; Silva *et al.*, 1997; Moseley *et al.*, 1998; Mori *et al.*, 2001; Juvonen *et al.*, 2002; McMonagle *et al.*, 2002; Zhao *et al.*, 2002; van de Warrenburg *et al.*, 2002; Sasaki *et al.*, 2003; Muzaimi *et al.*, 2004; Zortea *et al.*, 2004; Infante *et al.*, 2005; Tsuji *et al.*, 2008).

Table 1
Prevalence of hereditary ataxia and spastic paraplegia in previous studies: for HA, studies published from 1990; for HSP, studies published from 1970 (with HA data included where available)

References	Country	Study population	Recruitment sources	Included diagnoses	No. of subjects	Total prevalence all included	Total prevalence HA	Tota prev HSP
Skre (1974)	Norway	725 000	Multiple search strategies	HA	37	6.2[a]		
Skre (1974)	Norway	725 000	Multiple search strategies	AD-HSP, AR-HSP	34	12.1[a]		
Sridharan (1985)	Libya	519 000	Regional health institutions	HA, AD-HSP, AR-HSP	25	4.8	2.7	2.1
Brignolio (1986)	Italy	2 327 996	Regional hospital	HA, AD-HSP, AR-HSP, isolated HSP	142	6.1	4.8	1.3
Leone (1990)	Italy	3 617 915	Multiple search strategies	FRDA	44	1.2	NA	
Polo (1991)	Spain	510 000	Regional hospital	HA, HSP (pure)	103	20.2	10.6	9.6
Filla (1992)	Italy	335 211	Mail and phone survey	HA, AD-HSP, AR-HSP	25	7.5	4.8	2.7
Hirayama (1994)	Japan	123 000 000	Hospitals >200 beds, mail survey	HA, HSP, MSA, sporadic ataxia	5050[a]	4.53[a]	NA	NA
Leone (1995)	Italy	115 270	Regional health institutions	HA, AD-HSP, AR-HSP, isolated HSP	17	14.8	10.5	4.3
Lopez-Arlandis (1995)	Spain	3 898 241	Diagnostic centres	FRDA	38	3.83	NA	
Silva (1997)	Portugal	250 061	Multipe search strategies	AD-HA, AR-HA, AD-HSP, AR-HSP	16	6.4	4.4	2
Mori (2001)	Japan	613 349	Multiple search strategies	HA, HSP, MSA, sporadic ataxia	109	17.8	NA	NA

References	Country	Study population	Recruitment sources	Included diagnoses	No. of subjects	Total prevalence all included	Total prevalence HA	Total preval HSP
McMonagle (2002)	Ireland	5 436 000	Multiple search strategies	AD-HSP	69	1.27		NA
van de Warrenburg (2002)	Netherland	15 863 950	Diagnostic centres	AD-HA	391	3.0[a]	NA	
Zhao (2002)	Singapore	3 500 000	Diagnostic centres	AD-HA	204	1/27 000	NA	
Juvonen (2002)	Finland	5 180 000	Diagnostic centres	FRDA	7	[b]	NA	
Zortea, 2004	Italy	845 203	Multiple search strategies	HA	79	9.33	NA	
Muzaimi (2004)	Great Britain	570 000	Multiple search strategies	HA, sporadic ataxia	76	8.4 + 1.8	NA	
Infante (2005)	Spain	527 000	Diagnostic centres	HA	8	1.6	NA	
Tsuji, 2007	Japan	NA	Hospitals >200 beds, mail survey	HA, HSP, MSA, sporadic ataxia	10 487	18.5	NA	NA
Present study	Norway	2 633 893	Multiple search strategies	HA, AD-HSP, AR-HSP, isolated HSP	365	13.9	6.5	7.4

- a Extrapolation.
- b Carrier frequency 1/500.
- c SCA1 and 2.
- FRDA = Friedreich's ataxia; MSA = multisystem atrophy; NA = not available.

Enlarge table

Despite these studies, the true prevalence of hereditary ataxia and hereditary spastic paraplegia remains uncertain. Comparison of the ratios is difficult because of methodological differences. In addition there seem to be geographical variations among different subtypes, especially in the hereditary ataxia group.

One of the first epidemiological studies on these disorders was conducted by Skre in western Norway in 1974, but it has not been followed up. Skre estimated the prevalence of AD-HA at 3.2/100 000, AR-HA at 3.0/100 000, Friedreich's ataxia at 1.0/100 000 and AD-HSP at 12.1/100 000 (Skre, 1974a, *b*). Since then molecular diagnostics have become available and the disorders have been reclassified.

Rare disorders like hereditary ataxia and hereditary spastic paraplegia are important public health issues and a challenge to the medical community. Health authorities need reliable epidemiological data when developing health care strategies. Hereditary ataxia and hereditary spastic paraplegia patients may remain undiagnosed and therefore unaware of new diagnostic and therapeutic resources because symptoms are often mild and disease progression slow, and the disorder may become accepted as a family characteristic. However, these patients also need regular follow-up and genetic counselling, and in view of new treatment possibilities it is important to identify them. Our aims were to identify subjects with hereditary ataxia and hereditary spastic paraplegia in southeast Norway and estimate the prevalence of the disorders in a cross-sectional population-based study using multiple search strategies.

Materials and Methods

Study design

The study was a cross-sectional population-based study in accordance with the STROBE statement (vonElm *et al.*, 2007).

Study area and population

A power analysis was performed (see Statistical methods section) to determine the population size required to obtain reliable prevalences. We chose southeast Norway (Fig. 1), which covers 111 000 sq km^2 and includes 10 of the 18 Norwegian counties: Oslo, Akershus, Hedmark, Oppland, Østfold, Buskerud, Vestfold, Telemark, Aust-Agder and Vest-Agder. The population is well-defined and mobility is

low. The most recent national census, of January 1 2008, listed 2 633 893 inhabitants or 55% of the Norwegian population. The region has nine neurological and paediatric wards, three of which are at university clinics.

County	Population	No. of subjects HA (AD/AR)	Prevalence HA x 10^{-5}	No. of subjects HSP (AD\AR\iso)	Prevalence HSP x 10^{-5}	Prevalence HA and HSP x 10^{-5}
Oslo	560 484	39 (17/21)	6.7	24 (16/3/5)	4.3	11.0
Akershus	515 567	27 (21/6)	5.2	38 (31/1/6)	7.3	12.5
Hedmark	189 289	17 (11/6)	9.0	9 (9/0/0)	4.7	13.7
Oppland	183 637	15 (7/8)	8.2	15 (6/4/3)	8.2	16.4
Østfold	283 459	15 (12/3)	5.6	22 (16/1/5)	8.3	13.9
Buskerud	251 229	10 (8/2)	4.0	24 (20/1/3)	9.5	13.5
Vestfold	226 433	12 (6/6)	5.3	25 (20/2/3)	11.0	16.3
Telemark	166 731	27 (23/4)	16.2	12 (11/0/1)	7.2	23.4
Aust-Agder (Aust+Vest)	272 074	10 (6/4)	3.7	25 (14/3/8)	9.2	12.9
Total	**2 633 893**	**171 (111/60)**	**6.5**	**194 (145/15/34)**	**7.4**	**13.9**

Figure 1
Study area and regional prevalences of HA and HSP in Norway. Iso = isolated.

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Subject collection

The following search strategies were used to identify and examine subjects and families with confirmed or suspected hereditary ataxia and hereditary spastic paraplegia (Fig. 2).

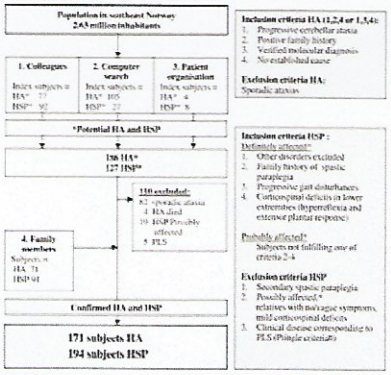

Figure 2
Flow chart of patient collection, inclusion and exclusion criteria and data on the study population. *Ref.: Fink *et al.* (1996). **Ref: Pringle, C.E., Primary lateral sclerosis, Clinical features, neuropathology and diagnostic criteria, *Brain* 1992. PLS = primary lateral sclerosis.

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Colleagues

Neurologists in Norway were asked to refer patients with known or suspected HA and HSP to the Department of Neurology, Ullevål University Hospital, Oslo, from 2002. Information about the project was disseminated through national meetings, letters to all neurologists and paediatricians and visits to neurological and paediatric departments.

Computer searches

A. In 2003–04, as part of a pilot study at Ullevål Hospital, we searched the hospital's electronic coding system using the international classification system for diseases (ICD) to determine the most relevant codes for identifying HA and HSP patients. The search covered ICD-9 code 334.0-9 (spinocerebellar diseases), ICD-10 code G11.0-9 (hereditary ataxia and spastic paraplegia), and codes for the non-specific diagnoses of paraplegia and tetraplegia (G82.0-5), gait and coordination disturbances (R26.0-8 and R27.0-8), and cerebral palsy (G80.0-8) for the period 1996–2003.

B. In January 2007–August 2007, systematic searches of the electronic coding systems of the nine neurological and paediatric departments in the study region were conducted for the period 1992–2007, in collaboration with in-house physicians. Because the pilot study had shown that little was to be gained from the additional non-specific codes, only ICD-9 code 334.0-9 and ICD-10 code G11.0-9 were used.

C. The genetic databases of the medical genetics departments in Oslo, Bergen and Tromsø were searched for subjects who had tested positive for SCA1, 2, 3, 6, 7 or Friedreich's ataxia.

Patients' association

The National Patients' Association for Hereditary Ataxia and Spastic Paraplegia (NASPA) was established in 2003. All members of the association were informed about the study, and family members and others with suspected HA or HSP who had not been examined were invited to contact one of the project neurologists.

Families

Index subjects in each newly identified family were invited to ask affected or potentially affected family members to contact a project neurologist for examination.

Examination of subjects

All identified subjects with a tentative diagnosis of hereditary ataxia or hereditary spastic paraplegia were invited to participate. Clinical data were systematically registered according to the protocol established by SPATAX, the European and Mediterranean network for analysis of spinocerebellar degenerations (Tallaksen, 2003). Hereditary ataxia and hereditary spastic paraplegia were classified as pure or complex according to Harding's classification (Harding, 1983). Pure forms presented with predominant cerebellar for HA and pyramidal signs for HSP, and complex forms presented with additional features such as neuropathy, cognitive impairment and extrapyramidal signs. Motor disability was assessed by a four-stage functional scale: (i) mild symptoms and signs at examination, walking without aid; (ii) walking without aid but unable to run; (iii) walking with aid; and (iv) wheelchair-dependent.

Family subjects

At least one affected subject from each newly identified family was examined by one of the project neurologists. Children were examined in cooperation with paediatricians. At least one symptomatic individual from each family underwent neurological examination, genetic testing and supplementary examinations and tests. Most families not initially diagnosed by our group were re-examined and re-evaluated by a project neurologist (C.T., J.K., A.K.E.) to confirm diagnosis. Pedigrees for at least three generations were drawn for each proband. Recessive inheritance was presumed when two or more siblings were affected or when consanguinity was present. For a few isolated subjects, recessive inheritance was revealed after positive genetic testing. Dominant inheritance was presumed in cases of parent-to-child transmission, but father-to-son transmission was not always present. Subjects in the region who were unable to attend our out-patient clinic were examined at the local neurological department or at home. Twenty-one HA- and 29 HSP-affected relatives investigated by other neurologists were unable to attend an examination and their data were collected from telephone interviews and medical charts.

Isolated subjects

Hereditary ataxia

The first 29 of the referred sporadic ataxia subjects were thoroughly examined for symptomatic causes of ataxia according to the recommendations of Abele *et al.* (2002, 2007). A simplified examination protocol was used for the remaining 53 because a full examination was extremely time-consuming and proved uninformative in the 29 first subjects. Sporadic subjects were excluded after (i) telephone interviews (pedigrees drawn) and clinical assessments based on medical charts by a neurologist; or (ii) new clinical and genetic examinations by our group. Subjects with complex recessive forms and sporadic forms with early onset (<20 years) were screened for metabolic disorders (Sandhoff disease, Tay Sachs disease, Niemann-Pick disease, cerebrotendinous xanthomatosis and congenital disorders of glycosylation).

Hereditary spastic paraplegia

Subjects with HSP and unknown family history were given regular clinical follow-ups for several years. Supplementary examinations, including cerebral and medullar MRI, spinal fluid tests and laboratory screening (including very long chain fatty acids) and, when indicated, neurophysiological and neurourological examinations, were performed to exclude other diagnoses.

Inclusion and exclusion criteria

All subjects with confirmed hereditary ataxia and hereditary spastic paraplegia according to the inclusion criteria living in the region and alive on February 1, 2008 were included in the study (Fig. 2).

Criteria for hereditary ataxia

The following groups were included: subjects with progressive cerebellar ataxia and positive family history or confirmed genetic diagnosis; ataxia due to metabolic defects; early-onset ataxia (<20 years); late onset ataxia (>20 years); and episodic ataxias. Sporadic subjects were excluded (Harding, 1983, 1993; Albin, 2003; Schols *et al.*, 2004; Klockgether, 2005; Warrenburg *et al.*, 2005; Duenas *et al.*, 2006; Fogel and Perlman, 2007; Soong and Paulson, 2007; Tsuji *et al.*, 2008).

Criteria for hereditary spastic paraplegia

Family and sporadic subjects were included according to Fink's criteria (Fink *et al.*, 1996). Subjects classified as 'definitely affected' and 'probably affected' were included. Subjects with diffuse or no symptoms or mild pyramidal tract deficits and members of a known HSP family were classified as 'possibly affected' and excluded from the prevalence data. Isolated subjects were included only after careful exclusion of all other known causes of spastic paraplegia. All the included isolated subjects fulfilled the progression criteria after observation for at least 3 years.

Genetic analyses

DNA was extracted from peripheral blood lymphocytes using standard techniques.

Hereditary ataxia

Standard diagnostic tests were performed for SCA1, 2, 3, 6, 7 and Friedreich's ataxia, respectively, in all dominant and recessive subjects. Half the recessive index subjects without genetic diagnosis were tested for SCA1, 2, 3, 6 and 7. Additional molecular tests were performed depending on the clinical findings and pedigrees [dentatorubral-pallidoluysian atrophy (DRPLA), fragile X premutations, DNA polymerase γ disorders (POLG mutations), SCA 8, SPG 4, AOA1 and AOA2, A-T, and metabolic tests]. Available markers were used to screen for rare disorders [carbohydrate-deficient transferrin (CDT), albumin

cholesterol, gammaglobulins, α-fetoprotein and vitamin E]. All children with elevated α-fetoprotein were tested for ataxia telangiectasia (Stray-Pedersen *et al.*, 2007) and all adults with elevated α-fetoprotein for AOA2.

Hereditary spastic paraplegia

Molecular testing was performed for *SPG4* and *SPG3A*. The presence of point mutations and deletions was assessed by direct sequencing and MLPA analysis using standard methods. Each proband and sporadic subject was tested for SPG4, SPG3 in all SPG4-negative probands and sporadic subjects with early onset (before age 25 years). Direct sequencing and MLPA analyses of *SPG31* were performed for all SPG3- and SPG4-negative probands and sporadic subjects with a pure form of disease. SPG11 was investigated in all probands/sporadic subjects presenting with a thin corpus callosum (Stevanin *et al.*, 2007; Erichsen *et al.*, 2008).

Statistical methods

We performed a population-based study of hereditary ataxia and hereditary spastic paraplegia between January 1, 2002 and February 1, 2008. The point prevalence for February 1, 2008 was calculated using the 2008 mid-year population estimate of 2.63 million as the denominator. Age, sex and county-specific rates were calculated with a 95% CI using Fleiss's method (Fleiss, 2003). The difference in prevalence between sex and counties when adjusting for age distribution was estimated *a priori* using the Poisson model (Kleinbaum, 1988).

In light of previous prevalence data on hereditary ataxia and hereditary spastic paraplegia, an *a priori* power analysis was performed. A prevalence of 6/100 000 was hypothesized for HA with a precision of ±1/100 000 and a design effect of two for complex sample survey. A study population of at least 1394 805 was needed to capture this prevalence with 95% probability. For HSP, a prevalence of 4/100 000 was hypothesized and 1 945 171 subjects were needed to capture this prevalence with 95% probability.

Ethics

The study was approved by the regional committee for medical research ethics. Data were registered in accordance with Norwegian guidelines and all subjects in the study gave written informed consent.

Results

Prevalence estimates

All identified HA and HSP subjects (100%) agreed to participate, and 365 subjects (179 women and 186 men) from 152 non-related families were included (Fig.1 and Table 1). The prevalence of HA and HSP in southeast Norway was estimated at 13.9/100 000. There was no gender difference after adjustment for age (HA: rate ratio men versus women = 1.2, 95% CI 0.9–1.6, $P = 0.4$, HSP: rate ratio men versus women = 1.0, 95% CI 0.8–1.4, $P = 0.6$), but there were significant differences between counties (Fig. 1). After adjustment for age, comparisons with other counties pooled together showed a 166%-higher prevalence of HA in Telemark (rate ratio Telemark versus others = 2.7 95% CI 1.8–4.) and a 54%-higher prevalence of HSP in Vestfold (rate ratio Vestfold versus others = 1.5, 95% CI 1.0–2.3). Prevalence increased with age for both disorders. For HA, the highest prevalence (15.0/100 000) was found in the age group 70–79 years, and for HSP the highest prevalence (14.3/100 000) was in the age group 50–59 years.

Hereditary ataxia

One hundred seventy-one affected subjects (82 women, 89 men) from 87 unrelated families were included. Dominant forms were present in 48 families (111 subjects) and recessive forms in 39 families (60 subjects). Prevalence of HA in southeast Norway was estimated at 6.5/100 000, AD-HA at 4.2/100 000, AR-HA at 2.3/100 000, Friedreich's ataxia at 0.15/100 000 and ataxia telangiectasia at 0.4/100 000. Twenty-four of the 111 subjects (four families with ADCA and 11 with ARCA) were of non-Norwegian origin; Iran ($n = 1$), Iraq ($n = 6$), Pakistan ($n = 6$), Morocco ($n = 3$), Portugal ($n = 2$), UK ($n = 2$), Macedonia ($n = 2$) and Denmark ($n = 2$). Consanguinity was present in 11 recessive families (nine non-Norwegian, two Norwegian).

Hereditary spastic paraplegia

A total of 194 subjects from 65 families (97 men and 97 women) fulfilled the inclusion criteria; of these, 81% were familial and 19% sporadic subjects. The HSP prevalence for the region was estimated at 7.4/100 000. Prevalences for the hereditary forms were: 4.5/100 000 for pure AD-HSP, 1.0/100 000 for complex AD-HSP, and 0.6/100 000 for AR-HSP. For the isolated form, the prevalence was 1.3/100 000. All subjects were Caucasian. Seven subjects originated from other countries: Sweden ($n = 4$), Spain ($n = 1$), Italy ($n = 1$) and Iraq ($n = 1$). Consanguinity was present in five recessive families (four Norwegian and one Iraqi).

Genetic diagnoses

Genetic diagnosis was achieved in 34% (59/176) of all index subjects, 25% of HA index subjects and 37% of HSP index subjects.

Hereditary ataxia

Eight per cent (4/48) of AD-HA families and 46% (18/39) of AR-HA families had a genetic diagnosis. Among the dominant forms only one SCA1 family (Pakistan), one SCA2 family (UK) and two SCA3 families (Norway) were diagnosed.

Eleven of the 39 recessive families had elevated α-fetoprotein. Nine of these (11 subjects) had A-T and two (four subjects) had AOA2. Friedreich's ataxia was diagnosed in three families (four subjects) and AVED in one isolated subject. In two unrelated families (three subjects) with Friedreich's ataxia phenotype, an expansion in only one Frataxin gene allele was found; to date no mutation has been found in the other allele. One subject was diagnosed with Sandhoff disease.

Hereditary spastic paraplegia

Fifty-five per cent (30/55) of AD-HSP families, 20% (2/10) of AR-HSP families and 15% (5/34) of isolated subjects (all pure) had a genetic diagnosis. In AD-HSP families the frequency of SPG4 mutations and deletions was estimated at 40% (22/55), SPG3 at 11% (6/55) and SPG31 at 4% (2/55). SPG11 mutations were detected in 20% (2/10) of AR-HSP families.

Clinical data

Mean age on prevalence day for HA and HSP subjects was 49 years (range 4–94), mean disease onset 24 years (range 1–79) and mean disease duration 24 years (range 1–85). Sixty-one per cent of subjects did not use a walking aid (Fig. 3).

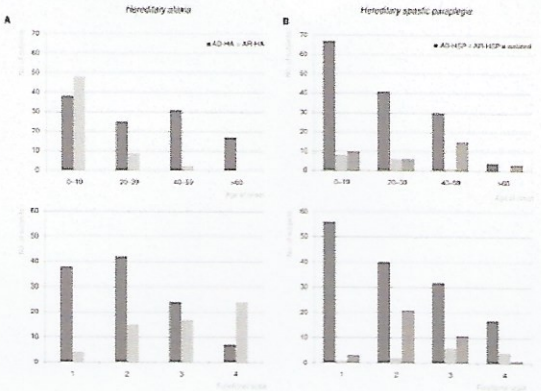

Figure 3
(**A**) Age at onset and severity of disease for inheritance groups of hereditary ataxia; (**B**) age at onset and severity of disease for inheritance groups of hereditary spastic paraplegia. Functional scale: 1 = mild symptoms, walking without aid; 2 = walking without aid but unable to run; 3 = walking with aid; 4 = wheelchair-dependent. iso = isolated.

Hereditary ataxia

Mean age on prevalence day was 57 years (range 13–94) for AD-HA and 32 years (range 4–71) for AR-HA. Mean age at disease onset was 32 years (range 1–79) in the dominant group and nine years (range 1–55) in the recessive group. In the dominant group 66% had onset >20 years but in the recessive group only 19%. Mean disease duration was similar in the two groups, 24 years for AD-HA and 23 years for AR-HA. All subjects in the recessive group but only 25% in the dominant group (28/83) were classified as complex forms. Ataxia telangiectasia subjects were all <18 years and mean disease duration for this group was seven years (range 3–12). Among subjects with dominant forms 6% (7/111) used a wheelchair and of those with recessive forms 43% (26/60).

Hereditary spastic paraplegia

On prevalence day, 64% of subjects were ambulatory without help, 25% were dependent on a walking aid and 11% were wheelchair-bound. AR-HSP subjects had an earlier onset age (mean 17 years, range 1–40) and a more severe disease course (26% were wheelchair-bound) than AD-HSP subjects [mean onset age 23 years (range 1–65), 12% wheelchair-bound]. Isolated subjects had a milder disease course (3% wheelchair-bound) and later disease onset (mean 33 years with the highest prevalence in the 50–80 year age group), than familial subjects. Disease duration was 1–77 years (mean 25). In AD-HSP families, 82% (45/55) were classified as pure and 18% (2/10) as complex. In AR-HSP families, 80% (2/10) were complex. In isolated subjects, the ratio of pure to complex was 68% (23/34) versus 32% (11/34), respectively.

Discussion

This is the first study of hereditary ataxia and hereditary spastic paraplegia prevalence in southeast Norway, and the first hereditary ataxia and hereditary spastic paraplegia prevalence study using stringent methods and inclusion criteria. A higher HSP-prevalence, but with a genetic distribution comparable with other countries, and a surprisingly high AD-HA prevalence, a high A-T prevalence and a high proportion of HA with a still unconfirmed genetic diagnosis was found. The highest prevalence was found among adults, and there was a high proportion of mild disease.

Inclusion and methodology

Norway has a stable population of ~4.73 million (January 2008), with an average life expectancy of 83 years for women and 78 for men. There is low consanguinity and a well-functioning public health system

with standardized systems for coding and patient registration. There are no private neurological in-patient clinics, and collaboration between neurological departments is good. The country is, therefore, highly suitable for cross-sectional population-based studies of rare disorders. All index subjects diagnosed by clinicians agreed to participate. All were given the possibility of being examined close to their home if they could not travel easily, which may have contributed to the high participation. Colleagues at collaborating hospitals were extremely helpful in the recruitment process. For these reasons, we believe that the prevalences estimated in this study are the best possible for diagnostically challenging disorders like HA and HSP.

Great care was taken to avoid including false positive subjects. The borderline between hereditary and secondary neurodegenerative disease is not always clear, and clinical differentiation is often difficult, especially for ataxias and sporadic forms and among children. By using strict inclusion criteria and molecular testing, we believe that we avoided inclusion of subjects with other neurodegenerative diseases, and chose to risk missing subjects rather than including non-hereditary disorders. This means that our results probably underestimate the true prevalence.

Our most important recruitment source was colleagues, who referred 46% (169/365) of the subjects (Fig. 2). The fact that neurologists were informed about the project many years before inclusion was begun, that the number of neurologists in Norway is large compared with many other countries and that subjects could be referred for examination without delay helped to ensure that the number of subjects was optimal.

Subjects from the following groups may have been missed, however.

Sporadic subjects, mild forms and asymptomatic carriers

Sporadic subjects

All sporadic subjects with ataxia were excluded and some AR-HA subjects may have been missed. Phenotypes similar to AOA1, AOA2, Friedreich's ataxia, ataxia telangiectasia, AVED and mitochondrial recessive ataxias were screened by genetic testing, and we also looked for specific markers (albumin, cholesterol, α-fetoprotein and vitamin E) (Koht and Tallaksen, 2007). Sporadic subjects with complex HSP were also excluded, but we tested for SPG11, 7 and 15 where relevant. Sporadic subjects with pure forms, no other known diagnosis and confirmed progression for ≥3 years were included.

Mild forms

Families in Norway today are small and because morbidity generally increases with age, a mild disorder such as very late onset ataxia occurring at or over the age of 60 may not be identified as a neurodegenerative disorder.

Asymptomatic carriers

Expressivity is variable, and up to 20% of SPG4 mutation carriers are reported to remain asymptomatic (Tallaksen *et al.*, 2001). Because SPG4 mutation is present in a substantial group of HSP subjects, the numbers may be underestimated even when there are no asymptomatic carriers for the other HSPs. Thus, there could have been up to 16 undiagnosed HSP subjects in our SPG4 group. A systematic examination of asymptomatic family members might have identified a few more subjects, but this was excluded for ethical reasons.

Misdiagnosed subjects

Subjects examined years ago and no longer in contact with the health system may have been miscoded and therefore not identified. Ataxias that begin with other more prominent symptoms and signs may have been incorrectly diagnosed as non-ataxia disorders, and thus missed in our searches. In line with previous reports, we estimated the number of missed HA subjects at ~10% of our 82 sporadic subjects (Abele *et al.*, 2002; Dragasevic *et al.*, 2006).

The main differential diagnosis for subjects with adult-onset HSP is multiple sclerosis, especially before MRI became a routine investigation. Some subjects with complex early-onset disease may be concealed under the non-specific diagnosis of cerebral palsy if diagnosed in childhood many years ago. We believe that this applies primarily to sporadic cases and older patients in nursing homes, and that the actual number is very small.

Lack of follow-up

A few HA and HSP subjects may have escaped inclusion in the study if not followed up by clinicians, particularly older patients with many years of chronic disease living in nursing homes, the mildly affected, those living in isolated rural areas and those not in touch with the health system during the study or computer search periods. We believe that this number is also very low, particularly because southeast Norway is largely urban, our search of medical records went back to 1992 and the public health system offers good follow-up for these disorders.

If we hypothesize four to six small families with no follow-up and 10 subjects with concealed HA due to incorrect diagnosis or mild forms, the final number is ~20–25 missed subjects. Correspondingly, we estimate the number of missed HSP subjects at ~25. This means that the prevalence of HA and HSP in our study is probably underestimated. We believe, however, that the number of missed subjects is small and that obtaining an exact number is impossible.

Previous studies

Prevalence studies of hereditary ataxia and hereditary spastic paraplegia have been conducted in many countries, but overall our results show a higher prevalence than previously reported (Tables 1 and 2). The type and size of populations, methods of case detection, classification of disorders and diagnoses included vary considerably, however. These and other methodological differences make it difficult to compare reports.

Table 2
Prevalences of hereditary ataxia and spastic paraplegia in southeast Norway

Age (years)	Population	HA total (AD/AR)	Rate	95% CI HA total	HSP total (AD/AR/iso)	Rate	95% CI HSP total
0–9	323 310	6 (0/6)	1.8	0.7–4.0	3 (2/0/1)	0.9	0.2–2.7
10–19	336 180	21 (3/18)	6.2	3.9–9.5	10 (10/0/0)	2.9	1.4–5.5
20–29	318 585	13 (5/8)	4.1	2.2–7.0	18 (13/4/1)	5.6	3.4–8.9
30–39	392 921	14 (10/4)	3.6	1.9–6.0	26 (19/3/4)	6.6	4.3–9.7
40–49	382 249	25 (15/10)	6.5	4.2–9.7	34 (27/4/3)	8.9	6.1–12.4
50–59	335 710	27 (21/6)	8.0	5.3–11.7	48 (38/1/9)	14.3	10.5–18
60–69	263 597	32 (26/6)	12.1	8.3–17.1	29 (16/3/10)	12.2	7.4–15.8
70–79	159 380	24 (22/2)	15.0	9.6–22.4	21 (15/0/6)	13.2	8.1–20.1
>80	121 961	9 (9/0)	7.4	3.4–14.0	5 (5/0/0)	4.1	1.3–9.6
Total	2 633 893	171 (111/60)	6.5	5.6–7.6	194 (145/15/34)	7.4	6.4–8.5

Skre's results from western Norway (Skre, 1974*a*) were based solely on clinical criteria, were calculated using an extrapolation method, and according to our statistical calculations were based on a limited population. The estimated prevalence of AD-HSP in Skre's study was 12.1/100 000, which, due to extrapolation, is far from the crude prevalence of 3.2/100 000 (23/725 000) and lower than the 5.5/100 000 found in our study. For AR-HSP the crude prevalence would have been 1.5/100 000 (11/725 000) versus 0.6/100 000 in our study. The problem is the same for his estimated HA prevalence of 6.2/100 000, which otherwise appears to be comparable to our estimated figure of 6.5. Differences in crude prevalence may be mostly related to diagnostic differences, while changes in consanguinity in the population may account for the differences between the autosomal recessive subjects.

A recent HSP study from Ireland (McMonagle *et al.*, 2002) is comparable to ours with respect to patient inclusion strategies and source population size. The prevalence of pure AD-HSP in this study was, however, markedly lower than in our study (1.17/100 000 versus 4.5/100 000) considering that the subject ascertainment methods and geographical and cultural conditions are comparable with ours. One reason for the discrepancy may be that, as the authors themselves state, a lack of neurologists outside the capital leads to missed subjects due to misdiagnosis and lack of subject identification.

The highest HA prevalence (17.8/100 000) is reported in Japan. However, these studies included sporadic ataxia, hereditary spastic paraparesis and multi-system atrophy diagnoses (Sasaki *et al.*, 2003; Tsuji *et al.*, 2008). This illustrates how difficult it is to compare prevalences when classification and included diagnoses differ. If we had included all sporadic subjects in addition to HA and HSP in our estimated prevalence, this would have raised it to 17/100 000, which is the same as that reported in the above studies.

The size of the study population is important in prevalence studies, and many previous studies (Table 1) have been conducted on small populations, which can bias the results. According to the power analysis we performed before defining our study area, a sample size of at least 1 394 805 is required to estimate a precise prevalence for these rare diseases. The importance of this condition is illustrated by the significant difference in prevalences found between our counties (Fig. 1), which ranged from 3.7 to 16.2 for HA and 4.3 to 11.0/100 000 for HSP. The presence of one large family in a region will influence the prevalence; for example, HA had a high prevalence in Telemark and HSP in Vestfold, where there were large families. Small or few families were found in counties with the lowest prevalence.

In a few studies where the population size was comparable with ours or larger (Brignolio *et al.*, 1986; Silva *et al.*, 1997; Mori *et al.*, 2001; McMonagle *et al.*, 2002; van de Warrenburg *et al.*, 2002; Zhao *et al.*, 2002; Sasaki *et al.*, 2003; Tsuji *et al.*, 2008), prevalences were still lower than our estimates, possibly due to differences in case detection methods. Studies based mainly on index subjects from diagnostic centres may miss subjects and underestimate true prevalence (Silva *et al.*, 1997; Zhao *et al.*, 2002). The use of multiple search strategies ensures inclusion of more subjects; 44% of our subjects were included through other family members and might otherwise have been missed (Fig. 2). In Norway, HA and HSP patients are not often hospitalized and, until recently, follow-up has not been systematic. Assuming a similar situation in other western countries, many patients may be missed when hospital archives are used as the only recruitment channel.

Clinical and genetic aspects

Hereditary ataxia

A specific molecular diagnosis was found in 40% of AR-HA families but only 8% of AD-HA families. For dominant forms this is much lower than in previous reports (Schols *et al.*, 2004; Lima *et al.*, 2005; van de Warrenburg *et al.*, 2005; Soong and Paulson, 2007). In our neighbour countries, SCA8 is the most common form reported in Finland (Juvonen *et al.*, 2000) and SCA7 in Sweden (Jonasson *et al.*, 2000). Neither of these subtypes was found in our population, nor was SCA6, the most common form reported in England (Craig *et al.*, 2004). This leaves us with a high number of undiagnosed subjects with AD-HA and may indicate a genetic specificity in Norway that still remains to be identified.

The prevalence of Friedreich's ataxia in our study was low compared with central Europe (Skre, 1975; Leone *et al.*, 1990; Polo *et al.*, 1991; Filla *et al.*, 1992; Lopez-Arlandis *et al.*, 1995), but similar to Finland (Juvonen *et al.*, 2002). The difference may be due to differences in origin between populations and restricted or other genetic variants in our population. Until genetic testing became available, Friedreich's ataxia was a clinical diagnosis. Revision of the diagnoses in line with new insights in molecular genetics (Schols *et al.*, 1997) and reduced consanguinity may explain the lower prevalence than that reported by Skre.

Ataxia telangiectasia was the most common recessive form of HA in our population, and is the only form of ataxia recently genetically described in Norway (Laake *et al.*, 2000; Stray-Pedersen *et al.*, 2004; Riise *et al.*, 2007). Nine of our 33 ataxia telangiectasia subjects were born in Hedmark, which has an annual birth rate of 1800. On this basis the incidence of ataxia telangiectasia in Hedmark is 1:10 000 live births. The nine patients from Hedmark were either homozygous or compound heterozygous for the Norwegian founder mutation, which originated in the Rendalen valley in northern Hedmark. The common ancestor identified for six of the Norwegian ataxia telangiectasia families with the founder mutation was born in 1495 in Rendalen.

AOA2, AVED and Sandhoff disease were identified in our population, but remain rare disorders, as reported elsewhere (Ouahchi *et al.*, 1995; Sasaki *et al.*, 2003; Fogel and Perlman, 2007). It is important, however, to establish a diagnosis because of the therapeutic and genetic consequences.

Hereditary ataxia prevalence increased with age and was highest among those over 60 and AD-HA subjects. AR-HA subjects had, as expected, a shorter life-expectancy and therefore a lower prevalence in higher age groups (Crawford *et al.*, 2006; Fogel and Perlman, 2007). The increasing prevalence with age among AD-HA subjects may indicate that there are many mild forms in this group. The fact that only 6.3% of the AD-HA subjects were wheelchair-dependent supports this observation. We identified several small families with pure forms and very late onset. Whether they are a genetic subgroup in our population remains to be determined.

Hereditary spastic paraplegia

The prevalences of SPG4, SPG3 and SPG11 in our study are similar to previous reports (Depienne *et al.*, 2007; Stevanin *et al.*, 2007; Erichsen *et al.*, 2008), confirming previous evidence of low phenotypic and genotypic variation between different countries for these HSP forms. The ratio of AR-HSP to AD-HSP in our study is lower than in other studies (Brignolio *et al.*, 1986; Silva *et al.*, 1997). The reason for this is not known, but again it may be partly due to the low consanguinity in today's Norwegian population and differences in population origins.

With only 10% of subjects wheelchair-dependent, HSP seems to have mild symptoms for most patients, although there were clear differences between familial, especially recessive and sporadic patients. The mean onset was later (33 years) in sporadic than in familial patients (AD = 23 years/AR = 17 years) and 40% of AD-HSP patients had disease onset before the age of 15. However, disease onset is to some extent subjective, and late recognition of symptoms is a well-known bias where there is a lack of family history. Further studies are, therefore, needed to clarify whether the disease is indeed milder in sporadic cases. The prevalence of HSP in our population increased with age, as expected for a disease with reported onset at all ages and normal life expectancy (Fink, 2006). However, prevalence showed a distinct drop in the age group ≥80. This is consistent with previous findings of decreasing prevalence of HSP with age (Brignolio *et al.*, 1986; Filla *et al.*, 1992; Leone *et al.*, 1995; McMonagle *et al.*, 2002). One reason for this could be that the number of missed subjects is higher in this age group owing to miscoding and mild symptoms. Alternatively, the figures may reflect a shorter life expectancy for HSP patients due to disease-related complications, and this should be investigated more closely.

Conclusion

Hereditary ataxia and hereditary spastic paraplegia are rare disorders with a heterogeneous presentation, and in most patients genetic diagnosis is still unconfirmed. This study is the first population-based study using stringent clinical and methodological criteria to estimate the prevalence of HA and HSP. We found a higher prevalence than previously reported, which may indicate that previous studies have underestimated the true prevalence. We also found a high prevalence of late-onset and mild disease in both groups, and a high percentage of genetically undiagnosed AD-HA subjects in this Norwegian population.

Funding

The HSP-related part of the study was financed by the Norwegian Foundation for Health and Rehabilitation (project number 28300105).

Acknowledgements

The authors thank all colleagues for referral of patients and especially Dr N.J. Brautaset (Vestfold Hospital), Dr A. Edland (Buskerud Hospital), Dr S. Øygarden, C. Schneider and T. Mørland (Telemark Hospital), Dr S. Larsen (Ullevål University Hospital), Dr A. Dahl, Dr S. Hoven, Dr M. Rasmussen (Akershospitalet), Dr J. Barlin, Dr A. Beiske, Dr T. Tyssvang (Akershus University Hospital), Dr T.

Hognestad (Innlandet Hospital), Dr T. K. Veger (Østfold Hospital), Dr M. Bøe and Dr R. Eikeland (Sørlandet Hospital) who searched for patients in the hospital archives. We also thank the patients' association NASPA for their cooperation, all the patients for participating in the study, and the Department of Medical Genetics (Ullevål University Hospital). Finally we thank all the colleagues and departments who have helped us in genetic diagnostics: A. L. Børresen Dale and L. Jansen at Radiumhospitalet (Oslo) who performed the A-T mutation analyses, Professor L. Bindoff at Haukeland University Hospital (Bergen) for the POLG analyses, University Hospital Northern Norway (Tromsø), Professor J. Nielsen (Denmark), M. Koenig (Strasbourg, France), the the Molecular Genetics Department, University of Antwerpen, Belgium and Inserm U679, Departement de Génétique, Cytogénétique et Embryologie, INSERM/UPMC UMR_S975 CRicm, Hôpital Pitié-Salpêtrière, Paris.

Footnotes

*These authors contributed equally to this work.
Abbreviations:
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AD = autosomal dominant
AR = autosomal recessive
AOA1 and AOA2 = ataxia with ocular apraxia type 1 and 2
FRDA = Friedreich's ataxia
A-T = ataxia telangiectasia
HA = hereditary ataxia
HSP = hereditary spastic paraplegia
MLPA = multiplex ligation probe amplification
RR = rate ratio
SCA = spinocerebellar ataxias

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Online ISSN 1460-2156 Print ISSN 0006-8950