Familial Risks for Main Neurological Diseases in Siblings Based on Hospitalizations in Sweden

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Recent successes in identifying the underlying genetic mechanisms for neurological diseases, particularly for their Mendelian forms, have had profound implications for their diagnostics, treatment and classification. However, there has never been an attempt to compare familial risks in a systematic way among and between the main neurological diseases. Familial risks were here defined for siblings who were hospitalized because of a neurological disease in Sweden. A nationwide database for neurological diseases was constructed by linking the Multigeneration Register of 0- to 69-year-old siblings to the Hospital Discharge Register for the years 1987 to 2001. Standardized risk ratios were calculated for affected sibling pairs by comparing them to those whose siblings had no neurological disease. There were three main results. First, it was shown that all disease groups had a familial risk, with the exception of transient ischemic attacks, and the risks could be ranked from the highest (3451) for Huntington's disease to the lowest (2.1) for inflammatory diseases. Second, increased familial risks were shown for disease subtypes for which susceptibility genes or familial clustering have not been demonstrated previously, including multiple sclerosis, sleep apnea, nerve, nerve root and plexus disorders, and cerebral palsy. Third, based on the available sample size there was no convincing evidence for familial comorbidity between the disease groups, suggesting that the factors causing familial aggregation, probably usually heritable genes, are distinct for each subtype. The high familial risks for neurological disease imply heritable etiology and opportunities for identification of further susceptibility genes.

Neurological diseases are medical conditions for which molecular genetic techniques have probably achieved the greatest success, contributing to the characterization of disease etiology and mechanisms and to improvements in diagnostics and disease classification (Bertram & Tanzi, 2005; Ropper & Brown, 2005). In the course of these studies entirely novel disease mechanisms have been discovered, including DNA repeat expansions in coding and noncoding sequences, now found in over 40 neurological diseases (Gatchel & Zoghbi, 2005). Other achievements include molecular and pathophysiological characterization of severe diseases such as Huntington's chorea, hereditary ataxias, muscular dystrophies and myotonic disorders, all with a main heritable etiology (Bertram & Tanzi, 2005; Dalkilic & Kunkel, 2003; Day & Ranum, 2005; Muntoni & Voit, 2004; Ropper & Brown, 2005; Taroni & DiDonato, 2004). In the major neurological diseases including Alzheimer's disease, Parkinson's disease, epilepsy and migraine, some heritable subtypes have been noted, but these explain only a small proportion of the etiology of these diseases (Bertram & Tanzi, 2005; Estevez & Gardner, 2004; Guerrini et al., 2003; Robinson & Gardiner, 2004; Ropper & Brown, 2005; Scheffer & Berkovic, 2003; Wessman et al., 2004). In multiple sclerosis, familial aggregation is recognized but high penetrant susceptibility genes remain to be identified (Kalman & Leist, 2004; Nielsen et al., 2005).

Familial clustering of a disease is a measure of its heritability, provided that shared environmental factors can be excluded. For some high penetrant neurological diseases familial aggregation has been striking, and pedigrees of index cases have shown typical Mendelian segregation. However, for the most common neurological diseases, such as Alzheimer's disease, Parkinson's disease, epilepsy, migraine and multiple sclerosis, most patients lack a family history, although familial aggregation has been demonstrated in twin and other types of family studies (Bertram & Tanzi, 2005; Kalman & Leist, 2004; Mulder et al., 2003; Nielsen et al., 2005; Robinson & Gardiner, 2004; Svensson et al., 2003; Wessman et al., 2004). Moreover, most of the family studies have been small case-control studies that have relied on reports of

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neurological diseases in family members, the accuracy of which may be highly variable. There has never been an attempt to compare familial risks in a systematic way among and between the main neurological diseases. Heritable comorbidity between neurological diseases would have mechanistic implications regarding the specificity of the gene defect to damage certain nerve cell functions but not others. Almost all the genes that have been linked to neurological diseases are expressed in most nerve cells, and the present pathophysiologial understanding does not explain disease specificity; for example, why superoxide dismutase 1 (SOD1) mutations only cause amyotrophic lateral sclerosis, or why the epsilon 4 allele of the apolipoprotein E gene primarily affects Alzheimer's disease (Bertram & Tanzi, 2005). Certain specific forms of epilepsy are due to mutations in genes coding for ion channel proteins in nerve cells, hence the term channelopathy (Robinson & Gardiner, 2004; Wessman et al., 2004). Familial hemiplegic migraine, episodic ataxias and spinocerebellar ataxia type 6 are also channelopathies (Kors et al., 2004). Mutations in a single gene, CACNA1A encoding a calcium channel pore subunit gene, predispose to these three diseases (Kors et al., 2004). So far, however, the evidence for such shared phenotypic effects is limited.

The availability of disease-specific data on all hospitalizations in Sweden prompted us to analyze familial risks in siblings aged 0 to 69 years between the main neurological diseases with the particular aim of observing how the familial risks compare and whether they are shared between the individual diagnostic groups. The usefulness of the Swedish family dataset has been demonstrated earlier in studies of familial migraine and aortic aneurysms (Hemminki et al., 2005, 2006).

Materials and Methods

The research database used for this study, the neurological database, is a subset of the national MigraMed database at Karolinska Institute, Centre for Family and Community Medicine. The MigMed database was compiled using data from several national Swedish registers provided by Statistics Sweden, including the Multigeneration Register in which persons (second generation) born in Sweden in 1932 and thereafter are registered shortly after birth and are linked to their parents (first generation). Sibships could only be defined for the second generation, which was the present study population. National Census Data (1960–1990) and the Swedish population register (1990–2001) were incorporated into the database to obtain information on individuals' socioeconomic status. Dates of hospitalization for neurological diseases were obtained during the study period from the Swedish Hospital Discharge Register. Since 1986, complete data on all discharges, with dates of hospitalization and diagnoses, have been recorded in this register. All patients registered for hospitalization stayed at least one night in the hospital, usually in wards with neurology consultants or in neurology departments; the Register does not include outpatients in hospitals or healthcare centers. Diagnoses were reported according to the 9th (1987–1996) and 10th (1997–2001) versions of the *International Classification of Diseases* (ICD; World Health Organization, 1977, 2004), classified in 17 groups of diseases. All linkages were performed using the national 10-digit civic identification number that is assigned to each person in Sweden for his or her lifetime. This number was replaced by a serial number for each person in order to provide anonymity and to check that each individual was only entered once, for his or her first hospitalization for a neurological disease. Over 6.9 million individuals were included in the second generation of the neurological database.

Person-years were calculated from start of follow-up on January 1, 1987, until hospitalization for the first neurological disease, death, emigration, or closing date, December 31, 2001. Age-specific incidence rates were calculated for the whole follow-up period, divided into five 5-year periods, and they were standardized to the European population. Standardized incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases. The expected number of cases was calculated for age (5-year groups), sex, period (5-year groups), region and socioeconomic status–specific standard incidence rates derived from the MigMed database. Sibling risks were calculated for men and women with siblings affected with concordant (same) or discordant (different) neurological diseases, compared with men and women whose siblings were not affected by these conditions, using the cohort methods as described (Hemminki et al., 2001). In rare families where more than two siblings were affected, each was counted as an individual patient. Confidence intervals (95% CI) were calculated assuming a Poisson distribution, and they were adjusted for dependence between the sibling pairs (Hemminki et al., 2001).

Results

We analyzed risks for siblings aged 0 to 69 years to be hospitalized for a neurological disease, divided into 17 subtypes, in Sweden between 1987 and 2001. Only the first hospitalization was considered. The numbers of cases and their hospitalization rates are shown in Table 1 for male and female subjects. Epilepsy, sleep apnea and transient cerebral ischemic attacks show the highest hospitalization rates. Multiple sclerosis and migraine had a large female excess in contrast to sleep apnea and transient cerebral ischemic attacks with a male excess.

To make the sibling risk results readable we present the subtypes in two tables; the subtypes were selected so that none of the SIRs for discordant disease types were significant between the two tables. Table 2 shows sibling risks for multiple sclerosis and

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Table 1

Number of Cases and Hospitalization Rates of Subtypes of Nervous System Disease in Siblings Aged 0 to 69 Years

	Men		Women	
Subtype	No. of case	Rate (per 100,000 person years)*	No. of case	Rate (per 100,000 person years)*
Multiple sclerosis	1405	2.9	3002	6.5
Huntington's disease	94	0.2	103	0.3
Hereditary ataxia	315	0.7	271	0.6
Anterior horn cell disease	447	1.6	291	1.1
Parkinson's disease	633	2.8	409	1.9
Other extrapyramidal and movement disorders	611	1.6	680	1.8
Alzheimer's disease	119	0.9	191	1.4
Other degenerative disease of nervous systems	978	2.3	746	1.8
Inflammatory diseases of the central nervous system	4905	10.3	4663	10.1
Epilepsy	15,394	34.9	11,405	25.7
Migraine	4869	10.2	9254	20.2
Transient cerebral ischemic attacks	3739	20.8	2315	12.7
Sleep apnea	9051	27.7	2378	7.7
Nerve, nerve root and plexus disorders	6827	15.4	8950	20.1
Polyneuropathies and other disorders of the peripheral nervous system	1468	3.9	1063	2.7
Diseases of myoneural junction and muscle	1177	2.6	1023	2.3
Cerebral palsy and other paralytic syndromes	3800	8.2	2814	6.1

Note: *Incidence rate was adjusted for European standard population.

degenerative diseases of the nervous system. A total of 76 siblings were hospitalized for multiple sclerosis, giving an SIR of 8.3. Huntington's disease showed a huge familial risk of 3451 and was also associated with other extrapyramidal and movement disorders with an SIR of 27.3; however, only one family with two siblings affected with Huntington's disease was included. SIRs for all other concordant diseases in siblings were also significant, ranging from 471 for hereditary ataxias to 6.8 for Parkinson's disease. The SIR for the discordant diseases Parkinson's-Alzheimer's (8.3/10.9) was higher than for Parkinson's disease alone.

Data for other neurological diseases are shown in Table 3. All concordant SIRs were significant except for transient cerebral ischemic attacks. Diseases of the myoneural junction and muscle showed the highest SIR (137), followed by polyneuropathies and other disorders of the peripheral nerves (8.5), sleep apnea (4.7) and cerebral palsy and other paralytic syndromes (4.4). The only discordant associations were between migraine and polyneuropathies, and other disorders of the peripheral nerves and nerve, nerve root and plexus disorders, but both were of borderline significance.

Discussion

In the present study we used SIR as a measure of familial risk, as it expresses the likelihood of an individual being affected, given a diagnosed disease of the nervous system in a sibling. As a comparison to the sibling SIRs for neurological diseases, most types of cancer show sibling risks of about 2.0 (Hemminki & Li, 2004). Familial SIRs are high if the concordance of disease between siblings is high, that is, when few sporadic cases occur (Risch, 2001). Thus, SIRs are very high for highly penetrant heritable diseases if they account for the majority of the cases. In the present analysis, Huntington's disease, known to be almost fully penetrant, showed the highest risk (3451; Ropper & Brown, 2005). Many types of hereditary taxias are also caused by penetrant genes and thus the high SIR of 471. If one or many genes contribute to the disease and if, in addition, there are apparent sporadic cases, with negligible concordance between siblings, the SIRs become a weighted measure of the high heritable risk and the low sporadic risk. This was the case for many of the disease categories studied, including anterior horn cell disease (including amyotrophic lateral sclerosis), epilepsy, migraine, polyneuropathies and diseases of the myoneural junction and muscle (Bertram & Tanzi, 2005; Estevez & Gardner, 2004; Guerrini et al., 2003; Robinson & Gardiner, 2004; Ropper & Brown, 2005; Scheffer & Berkovic, 2003; Wessman et al., 2004). Thus a low SIR may hide rare high-risk syndromes, which show up when pedigrees are inspected. However, because the national Hospital Discharge Register has only been in operation since 1987, the present study covered a time period of no longer than 15 years and thus two-generational data or pedigrees would not be very informative.

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Table 2

Sibling Risks for Hospitalization for Multiple Sclerosis and Degenerative Disease of Nervous System

Subtypes of nervous system disease in siblings	Multiple sclerosis				Huntington's disease				Hereditary ataxia				Anterior horn cell disease				Parkinson's disease				Other extrapyramidal and movement disorders				Alzheimer's disease				Other degenerative disease of nervous systems			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Multiple sclerosis	76	**8.3**	**4.6**	**14.8**	0				3	3.1	0.4	13.0	1	0.7	0.0	5.8	0				1	0.5	0.0	3.9	1	1.9	0.0	15.4	4	1.6	0.3	6.0
Huntington's disease	0				39	**3451.3**	**1734.6**	**6677.7**	0				0				0				1	12.5	0.0	101.7	0				1	10.1	0.0	81.5
Hereditary ataxia	3	4.1	0.5	17.1	0				54	**471.2**	**250.2**	**870.0**	1	7.7	0.0	62.5	0				2	10.6	0.7	54.9	1	22.4	0.0	181.4	0			
Anterior horn cell disease	1	0.6	0.0	5.1	0				1	5.1	0.0	41.7	22	**66.8**	**29.5**	**143.2**	0				1	2.5	0.0	20.0	0				2	3.9	0.3	20.5
Parkinson's disease	0				0				0				0				8	**6.8**	**2.0**	**18.9**	2	2.8	0.2	14.6	3	**10.9**	**1.5**	**45.5**	0			
Other extrapyramidal and movement disorders	1	0.4	0.0	3.3	2	**27.3**	**1.8**	**142.1**	2	6.8	0.5	35.4	1	2.4	0.0	19.6	2	2.7	0.2	14.1	16	**27.5**	**11.1**	**63.2**	0				1	1.3	0.0	10.9
Alzheimer's disease	1	1.4	0.0	11.1	0				1	10.1	0.0	81.6	0				3	**8.3**	**1.1**	**34.6**	0				2	**21.4**	**1.4**	**111.1**	0			
Other degenerative disease of nervous systems	4	1.6	0.3	6.0	1	14.3	0.0	115.6	0				2	4.5	0.3	23.6	0				2	3.2	0.2	16.5	0				14	**14.2**	**5.5**	**33.7**

Note: O: observed number of cases; SIR: standardized incidence ratio; CI: confidence interval.

Bold type: 95%CI does not include 1.00.

Another limitation of the present study is that it covered a period of vast diagnostic improvements in neurological diseases, and since this was a nationwide study, diagnostic accuracy could have varied within the study period and within the country. However, diagnostic accuracy was probably good overall as hospitalization normally involved a diagnosis made by several physicians, including a neurologist. Many neurological diseases result in multiple hospitalizations, and we could confirm the diagnostic accuracy through the consistency of discharge diagnoses used on consecutive occasions. A recent Danish study based on a specific multiple sclerosis register reported a sibling risk of 8.6, which was very close to the present SIR of 8.3 (Nielsen et al., 2005), supporting the high diagnostic accuracy of the present data. Another potential problem could be a selective hospitalization; when one sibling is hospitalized, other siblings may preferentially also seek care. Such a selection would be likely for conditions that do not invariably lead to hospitalization, such as migraine. We have previously estimated the potential for such a selection by comparing risks for hospitalization because of migraine between spouses, and found no evidence supporting bias (Hemminki et al., 2005). The above limitations have to be kept in mind when interpreting the hospitalization rates, shown in Table 1.

An advantage of a nationwide, fully register-based study is that selection biases are minimized and both the probands and the cases are medically diagnosed. The previous literature on sibling risks for multiple sclerosis, cited by Nielsen and coworkers (Nielsen et al., 2005), gives a range from 12 to 38, considerably higher than 8.3 and 8.6 in the present study and in the Danish study, respectively. These kinds of systematic differences between case-control and register-based studies have been repeatedly observed in studies of familial cancer; case-control studies tend to exaggerate risks because of false reporting and other biases (Hemminki et al., 2004). Thus we believe that the range of sibling SIRs, produced here in a uniform way for all neurological diseases, gives the order of their familial aggregation, which should be related to their heritability. Shared habits may also cause familial aggregation of a disease, but such environmental factors are unlikely to contribute much to the present results, since they would need to be very strong to have an effect (Lorenzo Bermejo & Hemminki, 2005). Moreover, such factors have not been determined for neurological diseases, with the exception of inflammatory conditions.

Although the present data cannot distinguish between the contribution of the known susceptibility genes to the observed familial aggregation, they clearly indicate familial diseases for which no major heritable genes have yet been found. Multiple sclerosis is one example. Numerous positive linkage regions have been mapped for this disease, but high penetrant genes

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Table 3

Sibling Risks for Hospitalization for Other Nervous System Disease

Subtypes of nervous system disease in siblings	Inflammatory diseases of the central nervous system				Epilepsy				Migraine				Transient cerebral ischemic attacks				Sleep apnea				Nerve, nerve root and plexus disorders				Polyneuropathies and other disorders of the peripheral nervous system				Diseases of myoneural junction and muscle				Cerebral palsy and other paralytic syndromes			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Inflammatory diseases of the central nervous system	55	**2.1**	**1.1**	**3.8**	84	1.0	0.6	1.8	46	1.2	0.6	2.3	24	1.7	0.8	3.5	25	1.1	0.5	2.2	39	1.1	0.5	2.1	6	0.9	0.2	2.7	2	0.4	0.0	2.0	17	0.8	0.3	1.7
Epilepsy	85	1.2	0.7	2.1	588	**2.4**	**1.6**	**3.7**	123	1.1	0.6	1.8	51	0.9	0.5	1.7	106	1.3	0.8	2.2	154	1.4	0.8	2.2	29	1.3	0.6	2.7	20	1.3	0.6	2.8	47	0.8	0.4	1.5
Migraine	47	1.2	0.6	2.2	125	0.9	0.5	1.5	193	**2.8**	**1.7**	**4.5**	37	1.3	0.6	2.5	74	1.7	0.9	3.0	110	**1.7**	**1.0**	**2.9**	23	1.8	0.8	3.9	14	1.7	0.7	4.1	35	1.1	0.6	2.3
Transient cerebral ischemic attacks	24	1.7	0.8	3.6	53	0.8	0.4	1.5	38	1.3	0.6	2.5	48	1.5	0.8	2.8	50	1.4	0.8	2.7	53	1.4	0.7	2.6	8	1.0	0.3	2.7	1	0.2	0.0	1.8	14	1.2	0.5	2.8
Sleep apnea	25	0.9	0.4	1.9	108	0.9	0.5	1.6	77	1.4	0.8	2.5	52	1.3	0.7	2.3	253	**4.7**	**3.0**	**7.6**	99	1.6	0.9	2.7	17	1.4	0.6	3.1	10	1.3	0.4	3.5	25	1.2	0.5	2.4
Nerve, nerve root and plexus disorders	42	0.9	0.5	1.8	165	1.0	0.6	1.6	116	1.4	0.8	2.4	55	1.1	0.6	2.1	101	1.5	0.9	2.6	217	**2.5**	**1.6**	**4.1**	22	1.3	0.6	2.8	9	0.9	0.3	2.3	30	0.9	0.4	1.8
Polyneuropathies and other disorders of the peripheral nervous system	6	0.9	0.2	2.8	32	1.3	0.6	2.5	25	**2.1**	**1.0**	**4.4**	9	1.2	0.4	3.1	17	1.7	0.7	3.8	22	1.7	0.8	3.7	22	**8.5**	**3.8**	**18.3**	4	2.5	0.5	9.2	9	1.7	0.5	4.6
Diseases of myoneural junction and muscle	2	0.4	0.0	2.0	22	1.2	0.5	2.6	14	1.7	0.7	4.1	1	0.2	0.0	1.9	13	2.2	0.8	5.3	9	1.1	0.3	2.9	4	2.5	0.5	9.0	159	**137.2**	**82.5**	**226.7**	4	0.9	0.2	3.3
Cerebral palsy and other paralytic syndromes	18	1.0	0.4	2.2	51	0.9	0.5	1.7	39	1.6	0.8	3.1	14	1.5	0.6	3.6	26	1.7	0.8	3.6	30	1.3	0.6	2.6	9	2.0	0.7	5.5	4	1.1	0.2	4.0	72	**4.4**	**2.4**	**7.8**

Note: O: observed number of cases; SIR: standardized incidence ratio; CI: confidence interval.

Bold type: 95%CI does not include 1.00.

have not been identified despite considerable effort (Dyment et al., 2004); human leukocyte antigen class II alleles remain the strongest genetic risk factors (Lincoln et al., 2005). Another common disease with a reasonably high familial risk of 4.7 is sleep apnea, which is second only to epilepsy regarding the number of affected siblings. A lower familial risk (2.0) for this disease has been reported in Iceland (Gislason et al., 2002). Other common neurological diseases showing clearly increased familial risks were nerve, nerve root and plexus disorders (SIR = 2.5) and cerebral palsy and other paralytic syndromes (SIR = 4.4). The major causes of these diseases are environmental, and thus the increased familial risks may indicate a substantial heritable contribution, provided that environmental factors are excluded.

Based on the sample size of the present study, little evidence was found for familial comorbidity for neurological diseases. The noted association between Alzheimer's and Parkinson's diseases may be due to related conditions, such as Lewy body dementia and frontotemporal dementia, both of which may show an Alzheimer's type of dementia and Parkinsonian features (Bertram & Tanzi, 2005; Ropper & Brown, 2005). Migraine was associated with both polyneuropathies (SIR = 2.1) and nerve, nerve root and plexus disorders (SIR = 1.7). The associations were of borderline significance, and in both discordant disease pairs there were two individuals hospitalized for both diagnoses at various times, leaving the familial associations tentative.

The remarkable achievements attained in the past 20 years in characterizing gene defects for the various neurological diseases constitute an outstanding success story for molecular medicine (Ropper & Brown, 2005). The present technologies are capable of identifying genes for monogenic forms of disease. A challenge for the future will be to dissect the molecular basis of the common, multifactorial forms of diseases for which both genes and the environment are likely to play a role (Bertram & Tanzi, 2005). Large, unbiased family studies are needed to delineate the most likely underlying heritable mechanisms for disease clustering and to define the most optimal family structures for study. Even for whole genome association studies familial cases would be preferable, if available. For success in multifactorial diseases, the present power of genomics needs to be matched with a thorough understanding of disease clustering in the population under study.

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