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Life Expectancy, Mortality and Prognostic Factors in Neurofibromatosis Type 1

A Twelve-year Follow-up of an Epidemiological Study in Göteborg, Sweden

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Neurofibromatosis type 1 (NF1) is a genetic disease with an extremely wide range of manifestations. As yet, the individual course of NF1 cannot be predicted, and it is uncertain to what extent the disorder is associated with increased mortality. In order to gain insights into these aspects, we have conducted a 12-year follow-up study of 70 adult NF1 patients in the city of Göteborg, Sweden, whereby life expectancy, mortality, causes of death and the prognostic value of clinical findings were investigated.

Clinical examinations were made, and all available records, including medical files, death certificates, and autopsy reports were scrutinized. The survival in the NF1 cohort was compared to that in the general Swedish population.

Twenty-two deaths occurred in the NF1 group, whereas 5.1 deaths were expected in the general Swedish population ($p = <0.001$). The mean age at death was 61.6 years. Malignancy was found in 12 (55%) of the deceased (soft tissure sarcomas in 3, and carcinomas in 9). Severe complications related to NF1 were seen in 27%. Hypertension was significantly associated with increased mortality, as 10 out of 12 (83%) patients with hypertension died during the observation period.

NF1 was associated with increased mortality due to malignancy and NF1-related complications. ***Key words: causes and rates of death; malignancy; hypertension.***

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The neurofibromatoses include at least two distinct autosomal dominantly inherited disorders. The most common form is neurofibromatosis type 1 (NF1), with an estimated birth incidence of about one in 3,000, while the estimated birth incidence of neurofibromatosis type 2 (NF2) is about one in 40,000. The diagnosis of NF1 is usually based on cutaneous symptoms, such as café-au-lait spots, axillary freckling, multiple fibromas, whereas NF2 is diagnosed from intracranial tumours, usually bilateral vestibular schwannoma. The diagnostic criteria for NF1 and NF2 are given in Table I. Other forms of neurofibromatosis (NF) are extremely rare.

NF1 shows a wide range of manifestations, even within the same family (1, 2), and the prognosis in the individual patient is impossible to predict today. One of the most severe complications is the development of malignant tumours (3). Other severe complications related to NF1 are osseous dysplasia, causing severe scoliosis (4, 5), and vessel disorders such as bilateral renal arterial stenosis (6) and aneurysm (7). Also hydrocephalus has been reported in NF1 (8).

Long-term follow-up of population-based NF1 studies is likely to provide information about the possible outcome of the disease. In Sweden, the first population-based study of NF1 was made in Göteborg (2) more than 10 years ago. The Göteborg population was comparatively unbiased, since many medical specialties contributed cases of NF1, and 60% were outpatients. Up to now, only one further epidemiological study has included NF1 cases from a circumscribed geographical area (9), and its clinical results were in many ways similar to those in the Göteborg study. In the only long-term follow-up study published so far, the patients were followed during a 39-year period

Table I. *Diagnostic criteria for NF1 and NF2*

NF1	NF2
At least two of the following manifestations:	*Either of the following manifestations:*
Six or more café-au-lait spots with a greatest diameter of over 5 mm in prepubertal and 15 mm in postpubertal individuals	A) Bilateral 8th nerve masses seen with appropriate imaging techniques (e.g. CT or MRI) or
Two or more neurofibromas of any type or one plexiform neurofibroma	B) A first-degree relative with NF2 and either:
freckling in the axillary or inguinal regions	1. Unilateral 8th nerve mass or
Optic nerve tumour	2. Two of the following:
Two or more Lisch nodules (iris hamartomas)	– neurofibroma – meningioma – glioma – schwannoma – juvenile posterior subcapsular lenticular opacity
A distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis	
A first-degree relative (parent, sibling, or offspring) with NF1 by the above criteria	

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Table II. *Clinical sources of participants in the 1978 NF1 study*

Clinical specialty	Number of outpatients	Number of inpatients	Total number of patients
Dermatology	28	0	28
General practice	8	0	8
Surgery	6	11	17
Psychiatry	2	4	6
Internal medicine	0	11	11
Total number of patients	44	26	70
Percentage of patients (%)	63	37	100

(10, 11). That study included 84 inpatients with severe NF and their 128 relatives with NF of milder degrees. However, both NF1 and NF2 cases were included because these disorders were not regarded as separate entities at that time.

The aim of the present study was to determine whether NF1 is associated with reduced life expectancy and to analyse causes of death in the Göteborg NF1 population. We also wanted to explore whether clinical symptoms found in the first study (1978–1980) had prognostic value concerning survival and mortality during the 12-year follow-up period.

SUBJECTS AND METHODS

The follow-up covered the period between January 1, 1978 and January 1, 1990 and involved adults, 20 years and older, with NF1 living in Göteborg on the first of January 1978. The mean age in the study group in 1978 was 43.6 years ± 15.4 years (46.0 years ± 16.7 in the 33 women, and 41.2 years ± 13.7 in the 37 men). Sixty per cent of the patients were recruited from outpatient clinics and 40% from hospitals (Table II). Since the diagnostic criteria for NF1 were not strictly defined until 1987 (12), a diagnostic update, using all available clinical evidence, was made of all the NF patients who participated in the 1978 investigation. Seventy of the 74 original, adult participants fulfilled the diagnostic criteria for NF1 and were included in the present study.

In Sweden, follow-up studies are greatly facilitated by the fact that every individual settled in the country is identified not only by name but

Table III. *Causes of death in 22 patients with NF1*

Code[a]	Age at death (years)	Sex	Main cause of death and contributing factors
			1. Malignancy (55% of all deaths)
32[b]HT	43	Man	Neurofibrosarcoma of the gluteal muscles with with metastases
33	43	Man	Neurofibrosarcoma of the pelvis with metastases
11HT	63	Woman	Leiomyosarcoma of the ovarian vein with metastases
7[b]HT	68	Woman	Ductal breast carcinoma with metastases + adenocarcinoma of the rectum with metastases
30HT	52	Man	Adenocarcinoma of the lung with metastases
58	78	Woman	Adenocarcinoma of the small intestine and colon with metastases
65HT	71	Woman	Adenocarcinoma of the colon with metastases
66	41	Woman	Ductal breast carcinoma with metastases
74[b]	59	Woman	Adenocarcinoma of the biliary tract with metastases
13	65	Woman	Adenopapillary carcinoma of the ovaries with metastases
47	80	Man	Mucoepidermoid carcinoma of the pharynx with metastases
27	44	Man	Squamous cell carcinoma of the lung with metastases
			2. *NF1-related complications (27% of all deaths)*
			Osseous dysplasia
26	61	Woman	Severe scoliosis with medullary compression, paraparesis and respiratory insufficiency
55	54	Man	Severe scoliosis with respiratory insufficiency. Suicide
			Heart and vessel disorders
63HT	81	Woman	Embolus in the superior mesenterial artery and the internal carotoid artery with hemiparesis (bilateral renal artery stenosis)
34HT	79	Woman	Cardiac and cerebral infarction + pulmonary embolism (bilateral renal artery senosis, aneurysm of abdominal aorta, scoliosis and skull bone defect)
29HT	69	Woman	Cerebral infarction with (earlier operated for a phaeochromocytoma and an intracranial aneurysm)
19[b]	58	Woman	Cardiosclerosis with cardiac incompensation, pulmonary embolism (cerebral atrophy and dementia, phaeochromocytoma)
			3. Other causes (18% of all deaths)
71	81	Woman	Cardiac infarction and aorta stenosis with cardiac incompensation
24HT	70	Man	Pulmonary embolism
10HT	57	Man	Pulmonary haematoma (after accidental fall)
45	29	Man	Cerebral contusion (traffic accident)

[a] Case numbers corresponding to previously published case reports (2)
[b] Cases with autopsy
HT Cases with hypertonia

Table IV. *Clinical findings in 1978 as predictors of survival and mortality*

Clinical findings	Number of patients with or without a given symptom who died during the observation period/number of patients with or without the same symptom who were alive in 1991.		Comparison[a] between groups
	Proportion with the symptom	Proportion without the symptom	
Café-au-lait spots (≥10 spots)	8/35	11/30	NS
Skin neurofibromas (>500 noduli)	16/31	6/37	$p<0.005$
Neurofibromas (plexiform type)	5/14	17/54	NS
Axillary freckling	12/43	7/22	NS
Optic nerve tumour	1/2	21/66	–
Osseous dysplasia	5/11	16/56	NS
Positive family history[b]	15/46	4/19	NS
Psychiatric illness	8/21	11/44	NS
Remedial education	9/30	10/35	NS
Hypertension	10/12	12/56	$p<0.001$
Impaired vision	4/10	17/57	NS
Impaired hearing	5/12	16/55	NS
NF1 severity of first grade	1/15	21/53	$p<0.05$
NF1 severity of second grade	15/41	7/27	NS
NF1 severity of third grade	6/12	16/56	NS

[a]Fisher's exact two-tailed test
[b]Affected parent, sibling or offspring
NS = not statistically significant

also by a unique 10-digit »personal code« number. Neither individuals nor their records are thus likely to be lost to follow-up. All living NF1 patients were contacted by letter and asked to participate in a clinical follow-up examination. Every available hospital record was reviewed. Death certificates, with official cause of death, and all available autopsy reports were studied. Cancer registrations in the NF1 cohort were obtained from the Swedish Cancer Registry, which is generally regarded as highly reliable. All microscopical specimens for PAD were reexamined by one of us (Angervall). Survival and life expectancy were estimated by standard life table methods, using Swedish population statistics and taking into account the date of birth, age, sex, and number of follow-up years in every individual, as well as increased risk of death with increasing age. This was done to determine the expected number of deaths in the general population for comparison with the observed number of deaths in the study population. Poisson distribution with two-sided tests was used. Confidence intervals for the risk quotient between patient risk and normal population risk were estimated. Life time expectancy was calculated and compared to that of the general Swedish population.

The causes of death were divided into three groups: 1) malignancy, 2) NF1-related complications, and 3) other causes of death. In agreement with Huson (8), we defined any condition occurring at an increased frequency in NF1 patients as an NF1-related complication. The observed number of tumours in the NF1 patients was compared to the expected number, with the use of statistics from the local cancer register.

Clinical symptoms registered in the 1978 examination were analysed in relation to mortality during the 12-year period. The number of deceased patients with a clinical symptom was thus compared with the number of deceased patients without the symptom. This was done for the purpose of prognostic evaluation. For example, the proportion of patients with hypertension who died was compared with the proportion of patients without hypertension who died. Fisher's exact two-tailed test was used for statistical evaluation.

RESULTS

Life expectancy and mortality

Twenty-two NF1 patients, 13 women and 9 men, had died during the follow-up period. There was a significant difference between the 22 observed deaths in the NF1 cohort and the 5.4 deaths (1.7 women, 3.4 men) expected if the risk coincided with that in the general population of Sweden ($p<0.001$), also when calculated separately for the sexes ($p<0.001$ in the women and $p<0.02$ in the men). The mean age at death was 61.6 (29.1–81.9) years; 67.7 (41.5–81.9) years in the women and 52.8 (29.1–80.7) years in the men. The mean age in the group of patients who died in malignancy was 59.2 (43.1–80.7) years, 64.0 (41.5–77.9) years in the women and 52.6 (43.1–80.7) years in the men.

The estimated risk ratio of death hazard function of patients with NF1 compared to the normal population was 4.3, with a 95% confidence interval of 2.7–6.5.

If the risk ratio was equal to 4.3 for all ages, the mean length of life would decrease from 75 years for the normal population to 59 years for the patient group.

In terms of life time expectancy during the 12-year follow-up period, the life of each matched individual in the general Swedish population was 11 years, compared to only 10 years for the 70 patients in the NF1 cohort.

Causes of death

The causes of death in the 22 patients are given in Table III.

Malignancies. Twelve patients, 7 women and 5 men, died with malignancy (55%). Soft tissure sarcomas were found in 3 patients, 2 of whom had neurofibrosarcomas and 1 leiomyosarcoma.

Nine patients had carcinomas, one of these patients had two carcinomas. Types and locations are presented in Table III.

NF1-related complications. Six of the 22 deaths (27%) were due to complications related to NF1. Two patients had severe scoliosis with respiratory insufficiency; one of these patients committed suicide. Four were found to have diseases of heart and vessels: 2 had bilateral renal artery stenosis, and 1 had a cerebral infarction. She also had a phaeochromocytoma. The fourth patient had a severe myocardial fibrosis and a phaeochromocytoma, which was not operated. She also had severe hydrocephalus. A few of the patients demonstrated a wide variety of NF1-related complications.

Other causes. Four patients (18%) died from causes without known relation to NF1, such as death by accident in 2 cases (Table III).

Prognostic factors

The clinical findings registered in the 70 NF1 patients in the first study (in 1978–80) and their relation to later mortality are given in Table IV.

Among the clinical findings noted as diagnostic criteria for NF1, only that of numerous skin neurofibromas was significantly associated with increased mortality. Psychiatric illness and learning difficulties at school (remedial class attendance) did not contribute to reduced survival, nor did neurological defects in the form of impaired vision or hearing. Among patients with hypertension, the mortality rate was significantly increased compared to patients without hypertension ($p<0.0002$).

There was no association between grade 3 of neurofibromatosis (severe grade causing handicap) and increased mortality (2). However, when the patients with only mild and cosmetic symptoms (grade 1) were compared to those with moderate and severe disease (grade 2 and 3), the difference reached statistical significance ($p<0.05$).

DISCUSSION

The results show considerably reduced life expectancy in the 70 NF1 patients and increased mortality ($p<0.001$). The mean age at death was 61.6 years in the 22 deceased patients, a reduction of about 15 years compared to population statistics. These figures are based on adult cases of NF1 only. Had clinical NF1 cases presenting in childhood been included, this would probably have lowered life time expectancy further, as many cases with severe forms of NF1 present early in childhood (14). Our results suggest that in NF1, women may be more affected than men, but statistical analysis between the sexes is not possible. The reduced life time expectancy is partly explained by the increased risk of developing malignancy in NF1, which may be explained by the NF1 gene being a defect growth regulator and a tumour suppressor gene (15–19).

Compared with the frequency of cancers in the population as reported to the local cancer register the NF1 patients had a significantly increased frequency of cancer, which also supports this explanation. The reduced life time expectancy is also to some extent due to the other complications or diseases related to NF1. Of course, these diseases are also found in patients without NF1. To evaluate the increased risk for reduced survival for all the diverse complications in NF1 is impossible in a single clinical study like this one. More follow-up studies are needed.

We tried to evaluate if NF1-related symptoms in 1978 were of significant importance to the progress of NF1 disease concerning survival. Most of the clinical symptoms of NF1 were not overrepresented among the deceased patients. Positive and somewhat astonishing is the fact that psychiatric illness or intellectual impairment (remedial class attendance) were not significant risk factors for reduced life time expectancy.

Skin neurofibromas (>500), NF1 severity of grade 1 (mild and cosmetic symptoms only) and hypertension were three clinical findings with a significant relation to mortality or survival. This does not necessarily mean that these are of prognostic importance. Two of these findings reflect the disease progress with age; the presence of more than 500 cutaneous neurofibromas is significantly associated with old age, while a mild degree of the NF1 disease is significantly more often seen in younger patients. This suggests that if the progress of the NF1 disease could be arrested by means of future genetic techniques while still in the mild form, life expectancy could be considerably increased. Hypertension was a highly significant prognostic factor of unfavourable outcome in NF1. However, it is difficult to a closer analyse the association on the basis of the present investigation.

In our follow-up study, we had the impression that patients with NF1 often look older than their chronological age, which might be an effect of the NF1 gene being a growth regulator.

This study differs from the follow-up study by Sörensen et al. (11) in patient selection and in focusing only on patients with the NF1 disease. A comparison with the results from the study by Sörensen et al. is still of interest though, as in all probability at least 85% in that study were NF1 patients (20). The earlier study also showed increased mortality, although the causes of death were considered to be the same as in the population in over 70%, but calculation of life expectancy was not made. The age at death was about 57 years among the hospitalized patients and about 68 years among the relatives with NF. If the data for all 113 NF patients who died are put together, the mean age at death was about 62 years, which is to be compared with 61.6 years in the present study. Three of these 113 NF patients died from suicide, compared to 1 in our study. The results from this study can probably be applied also to NF1 in general, and is of clinical relevance since all the NF1 patients in the original epidemiological study were followed up.

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