学位論文

Population Characteristics and Progressive Disability in Neuofibromatosis Type 2

神経線維腫症２型の日本における現状と悪化因子の解明

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脳神経外科学分野

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論　文　内　容　要　旨

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学位論文題名	Population Characteristics and Progressive Disability in Neuofibromatosis Type 2

背景と目的

神経線維腫症２型（NF2）は、神経鞘腫や髄膜腫が多発するために治療困難な遺伝性疾患である。
NF2 の疫学、病態、予後因子などが充分に解明されていないため、世界的にみても未だ治療指針が確立されていない疾患である。日本における NF2 の現状把握と今後の治療指針確立に向けて、全国から集められた臨床調査個人票の解析(後ろ向きコホート研究)を行った。

方法

2009 年～2013 年に登録された 807 名の臨床調査個人票を解析した。臨床調査個人票に記載必要の項目は、疫学的項目４つ、 腫瘍性状に関する項目５つ、神経症状に関する項目１３、計２２の項目である。その中で、神経症状に関する項目に対して点数が付与され、その合計点(0～25 点)で重症度を反映する重症度スコアというものが国により制定されている。この NF2 患者の症状（臨床重症度スコア）を悪化させる因子解明のために、ロジスティック回帰分析を用いて解析を行った。

結果

日本における NF2 患者は、年齢 1～80 歳（平均 24 歳）、男性と女性の比 1:1.29、発症年齢 25 歳未満の Wishart type45%、25 歳以上の Gardner type42%と若年発症がやや多かった。家族歴有り 24%、無し 48%、不明 28%、国内では家族歴無しが有りの倍を占めた。
NF2 患者の症状(臨床重症度スコア)を悪化させた因子としては、若年発症(25 歳未満の Wishart type)($p<0.015$)， 家族歴($p<0.007$)， 治療歴($p<0.026$)， 難聴 ($p<0.014$)， 顔面神経麻痺 ($p<0.015$)， 全盲($p<0.011$)， 半身麻痺 ($p<0.025$)を有しているという結果であった。

結論

日本における NF2 の臨床症状を悪化させる因子として、若年発症、家族歴、治療介入、特定の神経所見を有する患者であることが解明された。

Population Characteristics and Progressive Disability in Neuofibromatosis Type 2

Original Research

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key words: Neurofibromatosis Type 2; Population Characteristics; Scoring System; Cohort study; Natural history study

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Population Characteristics and Progressive Disability in Neurofibromatosis Type 2

Original Research

Abstract

Objective: To characterize the clinical features of the NF2 population and determine prognostic risk factors for progressive disabilities.

Methods: In this retrospective cohort study of the Japanese national NF2 registry between 2009-2013, various clinical data (demographic, history, oncological, and neurological) of 807 patients with diagnosis of NF2 were analyzed. The overall severity of neurological disability was assessed using a comprehensive 25-point scoring system encompassing a wide variety of neurological deficits. In 587 patients in whom longitudinal disability data were available, multivariate logistic regression was performed to identify risk factors of significant disability progression.

Results: The clinical characteristics of the Japanese NF2 population were heterogeneous Median onset age [range] of 24 years [1-80]; male-to-female ratio 1:1.29; initial severity score 4 [0-22] out of 25-points. Family history was present in 33%. Most frequent clinical features were bilateral cranial nerve VIII nerve sheath tumor (CN8 NST, 87%), spinal NST (80%), hearing loss (65%), spinal dysfunction (50%), intracranial meningioma (49%), and facial paresis (36%). Disability score progressed by ≥5-points in 6.1% of patients over the study period. Based on multivariate logistic regression analyses, the significant independent risk factors of progression (p-value) included: onset age <25 years (p=0.015), positive family history (p=0.007), positive treatment history (p=0.026) hearing loss (p=0.014), facial paresis (p=0.015), blindness (p=0.011), hemiparesis (p=0.025).

Conclusions: The NF2 population in Japan is heterogeneous in clinical features. Risk factors of progressive disability include younger age of onset, positive family history, positive treatment history, and specific neurological deficits.

Abbreviation

NF = Neurofibromatosis; NF2 = Neurofibromatosis type 2; NST = nerve sheath tumor; CNS = central nervous system; CN8 NST = cranial nerve VIII nerve sheath tumor; NIH = National Institutes of Health; QoL = quality of life; REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis; IQR = interquartile range

Introduction

Neurofibromatosis type 2 (NF2) is a rare autosomal-dominant inherited disease classically associated with bilateral auditory canal schwannomas. NF2 is caused by a mutation of a tumor suppressor gene NF2 encoding a protein called merlin, losing function of which leads to the development of multiple tumors in the central nervous system (CNS), including schwannomas, meningiomas and ependymomas[2,27,30]. The clinical course is highly variable and depends on the tumor location, size, number, and mass effect(s) onto surrounding structures. Neurological disturbances in auditory, visual, swallow, and/or gait functions are most common clinical manifestations[9].

NF2 is a progressive multifocal disease with invariably unfavorable outcome. Estimated overall 10-year survival is 67%[24]. There is no known cure for NF2 and available therapies (e.g. surgical, radiation, pharmacological) are intended for symptomatic control at best. Therapeutic failure due to tumor recurrence is common[5] and so are therapy-related complications and co-morbidities[3,5,6,11,15,28]. The clinical manifestation and natural history are highly variable and therefore NF2 comprises a heterogeneous patient population, with limited data available to inform optimal management decisions. Prognostic factors of mortality[4,17,32] have been previously suggested and include disease onset at a young age, genetic non-mosaicism, intracranial meningioma, presence of lower cranial nerve tumors and type of treatment centers[4,17,32]. However, NF2 mutation (split-site or missense mutations) were associated with reduced mortality[17]. On the other hand, prognostic factors of neurological deterioration (or progressive disability thereafter) have not yet been elucidated. This is a critical knowledge gap, as progressive disability profoundly impacts quality of life[7,12,18] and preservation or restoration of neurological function remains one of the primary goals for NF2 management[10].

Therefore, the purpose of this study was to characterize the clinical features of the NF2 patient population and identify prognostic risk factors of progressive disability. We hypothesized that patients with certain clinical features are more prone to rapid neurological deterioration. Knowledge of such prognostic factors may influence treatment decision-making and inform future clinical trial

design as well as development of management guidelines.

METHODS

Study Design and Population

In this retrospective cohort study, longitudinally-collected national NF2 registry data of the Japanese Ministry of Health and Welfare between 2009 and 2013 were analyzed. Each patient record was entered by the patient's treating clinician and reported annually to the Ministry's central database. Registration was mandatory for patients to receive supplemental healthcare insurance coverage under the "Rare Disease" status. NF2 diagnoses were made according to National Institutes of Health (NIH) diagnostic criteria[1]. Forty-six out of 47 prefectures of Japan contributed to the central database. With approval of the Ministry, anonymized registry records was made available to the investigators.

Data Collection

The registry data consisted of 23 clinical features included in the Japanese NF2 disability scoring system[21] divided into three broad categories recorded at the time of initial evaluation as summarized in **Table 1**: 5 demographic/history, 5 oncological, and 13 neurological features. The overall severity of neurological disability was calculated according to a 25-point scoring system (**Table 2**) by summing the disability score of each neurological function as previously described [21]. Any duplicated data were removed and unique 807 patient records were identified.

In the cross-sectional analysis of baseline clinical features, all 807 patients were included. For the longitudinal-analysis of disability progression, only those with follow-up disability data were available were included. Progressive disability was defined as ≥5-point worsening during the 5-year study period. Those without longitudinal records were considered lost to follow-up (n=262) and excluded from the longitudinal analysis. Patients with missing initial disability data (n=2), or contradictory diagnostic criteria and family history (n=5) were also excluded. The remaining 538 patients formed the study group for the longitudinal analysis.

Statistical Analysis

Statistical analysis was performed using STATA version 13·1 (StataCorp, College Station, TX USA). In the cross-sectional analysis (n=807), summary statistics of each baseline clinical feature were calculated. Chi-squared test was performed for binary/ordinal variables, and Mann-Whitney test for continuous variables. Longitudinal analysis was performed only in whom longitudinal disability data were available (n=538). Multivariate logistic regression was performed to identify independent risk factor of progressive disability. To account for obvious correlation between features across categories (e.g. diagnostic criteria and presence of bilateral CN8 NST), separate analyses were performed for the demographic/history, oncological, and neurological categories. The logistic regression algorithm used Firth penalized likelihood ratio method to calculate robust odds-ratio (OR) and 95% confidence

interval estimates, in anticipation of potential complete or quasi-complete separation of the data [16]. Finally, to assess for potential selection bias introduced by the exclusion of missing longitudinal data, the included and excluded cohorts were compared in terms of onset age and initial disability score using Mann-Whitney test and chi-squared goodness-of-fit test. P-values <0·05 were considered statistically significant for all analyses.

Role of the Funding Source

The funder of the study provided anonymized registry records, but had no role in further data collection, analysis, interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Standard protocol approvals, registrations, and patient consents

All data were provided to the investigators with approval of the Japanese Ministry of Health and Welfare. The following study was exempt from institutional Ethics Committee review.

Results

The population characteristics of the entire NF2 patient cohort (n=807) are summarized in **Table 1**. For illustrative purposes, the frequency histograms of the onset age and initial disability score are shown in **Figure 1**. The onset age ranged from 0 to 80 years, with median of 24 years with interquartile range of [16-38] years. The estimated population prevalence was 807 cases per 127·6 million (Population Reference Bureau estimate, www.prb.org), or 6·32 cases per million. There was small but statistically significant gender predilection, with male-to-female proportion of 1:1·29 (p<0·001). Most frequent oncological features were bilateral VIII cranial nerve sheath tumor (CN8 NST, 87%), spinal NST (80%) intracranial meningioma (49%). Most frequent neurological features were: hearing loss (65%), spinal dysfunction (50%), and facial paresis (36%). The disability score ranged from 0 to 22 (out of 25 total points), with median of 4 and IQR of [0-22]. During the study period, disability score progressed by 0-2, 3-4, and ≥5 points in 471 (86%), 41 (7·5%), and 33 (6·1%) patients, respectively. The median [IQR] of follow up period was 2.5 years [2].

The results of the multivariate logistic regression of the included 538 patients are summarized in **Table 3**. The significant and independent risk factors for clinical progression were younger age of onset (<25 years; OR 3·8, p=0·015), positive family history (first-degree relative; OR 3.6, p=0·007), positive treatment history (stereotactic radiation, surgery or drugs) (OR 4·6, p=0·026), unilateral hearing loss (70-100 dB; OR 6·7, p=0·014) or worse, facial paralysis (OR 4·0, p=0·015), blindness (OR 6·4, p=0·011), and hemiparesis (OR 6·0, p=0·025).

Finally, there was no significant difference between the included and excluded cohorts in disability score or onset age. The median [IQR] of the onset age was 24 years [15-37] vs. 24 years [16-40] for

the two cohorts, respectively (p=0·735). Similarly, the median [IQR] of the initial disability scores were 4 [2-8] vs. 4 [2-9] respectively (p=0·708). Similarly, no significant difference in the shape of the histogram was found between the included and the excluded cohorts, in onset age (p=0·153) or initial disability score (p=0·488).

Discussion

Neurofibromatosis type 2 is a progressive multiple neoplasia syndrome with variable clinical presentation, natural course, treatment response, and outcome. Management of NF2 patients is aimed at preservation of neurological functions, but prognostication of patients at risk for rapid functional deterioration has been challenging. The purpose of this population-scale retrospective cohort study was to characterize the baseline clinical features of NF2 and identify independent prognostic risk factors of functional deterioration.

We found that early-onset disease, positive family history, and positive treatment history, are independent risk factors of progressive disability. In addition, certain neurological features, including hearing loss, facial paralysis, blindness, and hemiparesis were also associated with progression. In particular, our finding of onset age is consistent with previous reports on NF2 subtype classifications: late-onset mild Gardner subtype and early-onset intermediate-to-severe Wishart subtype[25]. The apparent association between treatment history and progressive disability also underscores the current challenges in NF2 therapy

In this analysis, one of the significant and independent risk factors for clinical disability progression was treatment. However, the treatment timing, modality, technique, or target region/tumor information, immediate post-therapy outcome data were not included in the database. While it is conceivable, for example, that progression of hearing loss and facial paresis could occur more frequently after surgery compared to observation, the registry data did not allow for any meaningful sub-analysis of the treatment data. It therefore remains unclear whether disability progression was the cause or the effect of treatment, and we plan to further investigate in a follow-up study.

In this study, we utilized the Japanese national NF2 registry records, developed in 1988 based on the NIH consensus recommendations[2]. Our clinician-rated disability scoring system was intended to summarize all NF2-related findings on a comprehensive neurological examination. Our choice of ≥5-point deterioration to define significant progression was motivated by the fact that it would imply deterioration in more than one neurological function. In contrast to simple CN8 NST's with plausible focused outcome metrics (e.g. tumor size, auditory and facial nerve functions), a multi-focal disease such as NF2 would require a multi-functional scoring system such as ours to assess overall severity of disease burden. Tumor size and growth rate have been shown to be a poor indicator of neurofunctional deterioration[8,13,29]. Therefore, a holistic evaluation of neurological function would

be particularly useful in evaluating systemic therapy response, e.g. bevacizman, everolimus, and lapatinib[14,19,20,22,26]. While this scoring system has not been directly validated against quality of life (QoL), many individual elements of the scoring system have been shown to correlate with QoL in NF2 patients, including facial weakness, balance disturbance, and hearing loss[7,12,18,23]. The registry database has since incorporated a focused QoL questionnaire in 2015, which will enable a formal comparison of our scoring system to QoL in near future. While comprehensive, we note that this clinician-rated scoring system does not include patients' perceived pain scale. While pain was likely reflected in patient's "self-reported wellness" data captured in the registry, it may be worthwhile to explicitly include pain scale in future studies of disease severity assessment.

Finally, we note that a consensus system for disease severity assessment was recently developed by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) Collaboration[31], and now recommended for future prospective clinical trials (Wolters et al 2016). We were unable to use REiNS for this retrospective study because the registry data were collected prior to the development of REiNS. However, the Japanese scoring system used in this study appears to be in partial alignment with REiNS response categories (4 out of 7 categories covered by our system).

ther notable limitations of the study are as follows. As with any retrospective study, various forms of selection bias are possible. For example, our registry data may be subject to verification bias. Patients most likely to register are those with clinically-significant disease requiring frequent medical attention through the national health insurance program. Since those with subclinical NF2 not requiring extensive diagnostic workup or frequent medical care may not be included, the disease prevalence in the present data may be underestimated. Nonetheless, the estimated NF2 prevalence in Japan was 1:158,000, comparable to previous reports (1:100,000-210,000) in United Kingdom[9,11]. Our analysis of the longitudinal data also excluded approximately 1/3 of the total records because of loss to follow up. This in principal could have resulted in under-representation of those with very mild disease and/or those who died due to severe disease, but this database included no information about mortality. However, our analysis of the initial disability score distribution did not show statistically significant difference between the included and excluded cohorts, suggesting that the bias, if any, is likely insignificant. Finally, imaging characteristics other than the presence/absence of certain tumor types and laterality were not recorded in this study. While the tumor size may be a reasonable surrogate of the tumor burden and therapeutic response, size itself is often a poor indicator of disability[3,6,11,15,28]. Because the main goal NF2 management is the maintenance of function, comprehensive disability scoring would be an important complimentary method to tumor volumetrics for assessment of clinical outcome.

In summary, this retrospective study of the Japanese national NF2 registry assessed the population characteristics and prognostic risk factors of progressive disability. Certain clinical features, including early disease onset, bilateral CN VIII NST, positive treatment history, and positive family history, were

found to be independent risk factors of progressive disability. The knowledge of these prognostic factors may inform clinicians to improve patient counselling and better guide treatment strategies.

AUTHOR CONTRIBUTIONS

K Iwatae wrote the manuscript and assisted data analysis. T Yokoo and E Iwatate performed data analysis and assisted manuscript preparation. K Saito served as the principal investigator, conceptualized the study and supervised K Iwatate. M Ichikawa, T Sato, M Fujii and J Sakuma assisted the manuscript preparation. All authors approved the final version of the manuscript.

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DISCLOSURE

The authors reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Figures and Tables

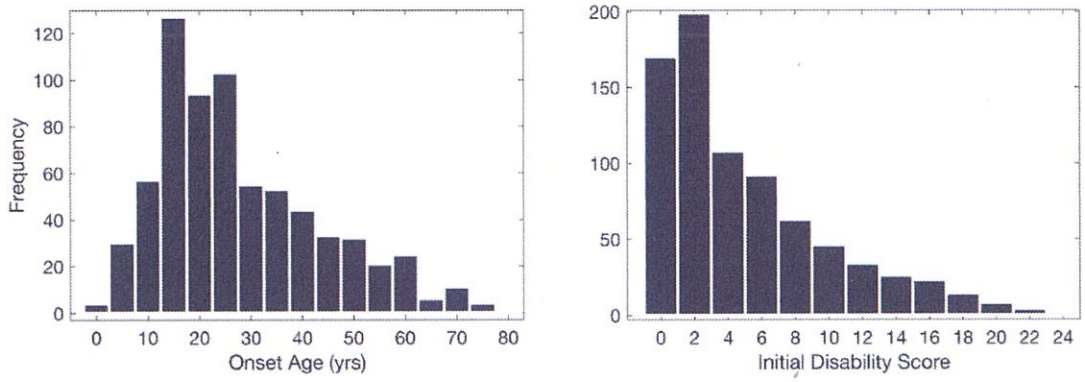

Figure1: Distribution of Onset Age and Initial Disability Score

Frequency histograms of the onset age (left) and initial disability score (right) of the entire NF2 population (n=807). The onset age distribution was skewed towards young age, with median and interquartile range [IQR] of 24 [16-38] years. The initial disability score (0-25 points) was skewed towards mild disease, with median score and IQR of 4 [2-8].

Table1: Population Characteristics

Demographic / History								
1	Sex	Total	Male	Female	-	-	-	Unknown
		805	352 (44%)	453 (56%)				2
2	Age of first onset	Total	≥25 yrs 338	<25 yrs 362	-	-	-	Unknown
		700	(48%)	(52%)				107
3	Family history	Total	None	Present	-	-	-	Unknown
		585	390 (67%)	195 (33%)				110
4	Diagnostic criteria*	Total	A	B	C	-	-	Unknown
		710	626 (88%)	24 (3%)	60(8%)			97
5	Self-reported wellness	Total	improved2	stable	Slow prog.	Rapid prog.	-	Unknown
		783	4 (3%)	305 (39%)	424 (54%)	30 (4%)		24
Oncological								
6	CN8 NST	Total	None	Unilateral	Bilateral	-	-	Unknown
		751	50 (7%)	45 (6%)	656 (87%)			56
7	CN5 NST	Total	None	Unilateral	Bilateral	-	-	Unknown
		667	369 (55%)	103 (15%)	195 (29%)			140
8	Intracranial meningioma	Total	None	Present		-	-	Unknown
		715	367 (51%)	348 (49%)				92
9	Spinal NST	Total	None	Present		-	-	Unknown
		621	122 (20%)	499 (80%)				186
10	Treatment history	Total	None	Present		-	-	Unknown

		565	224 (40%)	341 (60%)				242
Neurological								
11	Hearing loss score[†]	Total	1	2	3	4	5	Unknown
		756	265 (35%)	70 (9%)	170 (22%)	86 (11%)	165 (22%)	51
12	Facial paresis	Total	None	Unilateral	Bilateral	-	-	Unknown
		769	496 (64%)	241 (31%)	32 (4%)			38
13	Cerebellar dysfunction	Total	None	Present	-	-	-	Unknown
		765	543 (71%)	222 (29%)				42
14	Facial hyperesthesia	Total	None	Present	-	-	-	Unknown
		752	529 (70%)	223 (30%)				55
15	Dysphagia dysarthria	Total	None	Present	-	-	-	Unknown
		770	582 (76%)	188 (24%)				37
16	Double vision	Total	None	Present	-	-	-	Unknown
		760	651 (86%)	109 (14%)				47
17	Blindness	Total	None	Unilateral	Bilateral	-	-	Unknown
		758	691 (91%)	67 (9%)	0 (0%)			49
18	Hemiparesis	Total	None	Present	-	-	-	Unknown
		767	642 (84%)	125 (16%)				40
19	Aphasia	Total	None	Present	-	-	-	Unknown
		764	737 (97%)	27 (4%)				43
20	Memory loss	Total	None	Present	-	-	-	Unknown
		765	710 (92%)	55 (7%)				42
21	Seizure	Total	None	Present	-	-	-	Unknown

	[none, present]	760	690 (91%)	70 (9%)				47
22	Spinal dysfunction	Total	Mild	Moderate	Severe	-	-	Unknown
		767	382 (50%)	311 (40%)	74 (10%)			40

* NIH diagnostic criteria A – bilateral CN VIII NST; B – NF2 in 1° relative and unilateral CN VIII NST; C – NF2 in 1° relative and two of the following (schwannoma, meningioma, juvenile glaucoma). Spinal dysfunction (Mild spinal – gait disturbance, weakness of upper extremities, or disturbance of urination or defecation; Severe – unable to walk or complete paralysis of unilateral or bilateral upper extremities). NST – nerve sheet tumor. [†]Hearing loss is scored as none 0; mild 1; moderate 2; severe 3 per side and summed for both side

Table2: Japanese NF2 Disability Scoring System

Neurological Features	Point
Hearing loss (each side)	
70-100 dB	1
≥100 dB	2
Facial nerve palsy (each side)	1
Cerebellar Dysfunction	1
Decreased facial sensation (each side)	1
Dysphagia / Dysarthria	2
Double Vision	1
Blindness (each side)	2
Hemiplegia	2
Aphasia	2
Memory disturbance	1
Convulsions	1
Spinal symptoms	
mild/moderate	1
severe	2

Table 3: Risk Factors of Progressive Disability

	Risk Factor	Levels	No Prog. Grp	Prog. Grp	OR (p-value)	95% CI
Demographic / History						
1	Sex	Male	293	19	1·029 (0·950)	[0·420-2·523]
		Female	212	14		
2	Age of first onset	≥25 years	228	7	3·800 (0·015)	[1·295-11·148]
		<25 years	232	23		
3	Family history	Absent	249	11	3·593 (0·007)	[1·429-9·038]
		Present	133	14		
4a	Diagnostic criteria*	A	422	31	0·191 (0·279)	[0·010-3·592]
		B	15	0		
4b	Diagnostic criteria*	A	422	31	0·318 (0·249)	[0·053-1·915]
		C	34	1		
5a	Self-reported wellness	No change	212	5	1·995 (0·655)	[0·096-41·301]
		Improved	17	0		
5b	Self-reported wellness	No change	212	5	2·805 (0·063)	[0·946-8·314]
		Slow prog.	258	25		
5c	Self-reported wellness	Slow prog.	258	25	1·280 (0·875)	[0·058-28·047]
		Rapid prog.	13	1		
Oncological						
6a	CN VIII NST	None	31	0	0·871 (0·946)	[0·016-47·079]
		Unilateral	28	0		
6b	CN VIII NST	Unilateral	28	0	2·998 (0·457)	[0·166-54·070]
		Bilateral	423	33		
7a	CN V NST	None	241	13	1·903 (0·294)	[0·572-6·335]
		Unilateral	53	7		
7b	CN V NST	Unilateral	53	7	1·111 (0·862)	[0·337-3·672]
		Bilateral	128	11		
8	Intracranial meningioma	None	238	9	1·990 (0·172)	[0·741-5·350]
		Present	220	21		
9	Spinal NST	None	320	25	0·884 (0·852)	[0·241-3·237]
		Present	85	3		
10	Treatment	None	209	5	4·622 (0·026)	[1·197-17·849]
		Present	154	21		
Neurological						
11a	Hearing loss	Score 0	178	3	6·727 (0·014)	[1·481-30·560]

		Score 1	38	5		
11b	Hearing loss	Score 1	38	5	0·745 (0·639)	[0·219-2·543]
		Score 2	112	9		
11c	Hearing loss	Score 2	112	9	1·760 (0·381)	[0·497-6·230]
		Score 3	58	6		
11d	Hearing loss	Score 3	58	6	0·984 (0·983)	[0·278-3·499]
		Score 4	104	7		
12a	Facial paresis	None	321	12	4·004 (0·015)	[1·307-12·270]
		Unilateral	153	18		
12b	Facial paresis	Unilateral	153	18	1·159 (0·589)	[0·301-8·283]
		Bilateral	21	2		
13	Cerebellar dysfunction	None	349	21	0·730 (0·573)	[0·245-2·175]
		Present	143	11		
14	Decreased facial sensation	None	331	21	0·888 (0·816)	[0·328-2·406]
		Present	151	11		
15	Dysphagia / dysarthria	None	380	21	2·440 (0·182)	[0·658-9·045]
		Present	115	11		
16	Double vision	None	418	28	0·901 (0·868)	[0·264-3·083]
		Present	69	4		
17a	Blindness	None	449	24	6·409 (0·011)	[1·526-26·922]
		Unilateral	40	8		
17b	Blindness	Unilateral	40	8	n.a.	n.a.
		Bilateral	3	0		
18	Hemiparesis	None	423	23	5·996 (0·025)	[1·256-28·611]
		Present	69	9		
19	Aphasia	None	481	31	2·053 (0·581)	[0·160-26·388]
		Present	10	1		
20	Memory loss	None	464	30	1·010 (0·990)	[0·203-5·018]
		Present	28	2		
21	Seizure	None	446	28	1·548 (0·496)	[0·439-5·460]
		Present	44	4		
22a	Spinal dysfunction	None	256	14	1·941 (0·268)	[0·601-6·273]
		Mild/mod	194	15		
22b	Spinal dysfunction	Mild/mod	194	15	1·133 (0·879)	[0·227-5·659]
		Severe	42	4		
23	Initial severity score		see text		0·730 (0·146)	[0·477-1·116]

Multivariate logistic regression analysis was performed with categorical or ordinal predictors. Each multi-level ordinal variable (self-reported wellness, CN V and VIII NST, hearing loss, facial paresis, blindness, spinal dysfunction) was treated as a nominal variable by discretizing for each incremental change in its value using the dummy variable method. *Legends*: *NIH diagnostic criteria A – bilateral CN VIII NST; B – NF2 in 1° relative and unilateral CN VIII NST; C – NF2 in 1° relative and two of the following (schwannoma, meningioma, juvenile glaucoma). Spinal dysfunction (Mild spinal – gait disturbance, weakness of upper extremities, or disturbance of urination or defecation; Severe – unable to walk or complete paralysis of unilateral or bilateral upper extremities). NST – nerve sheet tumor. Unk – unknown or missing data entry.