ORIGINAL ARTICLE doi: 10.2176/nmc.oa.2020-0106

Neurol Med Chir (Tokyo) 60, 450–457, 2020 Online August 15, 2020

Social Independence of Patients with Neurofibromatosis Type 2 in Japan: Analysis of a National Registry of Patients Receiving Medical Expense Subsidies, 2004–2013

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Abstract

Although it is important for patients with neurofibromatosis type 2 (NF2) to live independently and maintain good quality of life (QOL), no study has examined the social independence status in this patient population. This study aimed to examine the state of social independence and its contributing factors in patients with NF2 using data from a national registry in Japan during the past decade. A database provided by the Ministry of Health, Labour and Welfare of Japan that contained information about all patients with newly submitted claims for medical expense subsidies for NF2 in Japan between fiscal years 2004 and 2013 was analyzed. Individuals aged 6 to 64 years were deemed eligible for the present study. Categories of "employed," "studying," and "housekeeping" were classified as "socially independent." Multivariate logistic regression analysis was performed to examine associations between demographic variables, neurological features, and social independence status. Of 334 participants, 79% were socially independent at the time of registration. Socially dependent participants had more neurological features than those who were socially independent, whereas sex, age, and family history had no significant associations with social independence status. Multivariate logistic regression analysis revealed that participants with bilateral hearing loss, unilateral hearing loss, blindness, hemiplegia, or seizures had significantly higher odd ratios for being socially dependent compared to participants without these features. Our findings, which suggest that these neurological features could restrict social independence, could contribute to the maintenance of better social functioning and QOL in patients with NF2.

Keywords: neurofibromatosis type 2, social independence, neurological features, patient registry, medical expense subsidies

Introduction

Neurofibromatosis type 2 (NF2) is a rare autosomal dominant inherited disease that involves multiple neoplasias, such as schwannomas, meningiomas, and ependymomas.[1)] The disease is caused by a mutation in a tumor-suppressor gene located on chromosome 22q. There is no known cure for NF2, although several therapies (e.g., surgical, radiation, pharmacotherapy) are available to manage the disease. The distinctive feature of NF2 is bilateral vestibular nerve schwannomas, and the most common symptom is hearing loss. Schwannomas can develop in other cranial, spinal, and peripheral nerves, and the clinical course of this disease is highly variable. It can include hemiparesis, seizures, or spinal dysfunction. The quality of life (QOL) of patients with NF2 often declines as a result of these symptoms,[2)] which may negatively impact social independence.

Several epidemiological studies have analyzed the characteristics of patients with NF2 using data from national registries in Western countries,[3,4)] including an Internet-based patient-entered database.[5)] For example, Hexter et al. reported that a younger

Received April 2, 2020; Accepted June 2, 2020

Table 1 Disability scoring of neurological features in patients with neurofibromatosis type 2 who received medical expense subsidies in Japan

Neurological features	Score
Hearing loss (each side) (dB)	
70–100	1
>100	2
Facial paresis	
Unilateral	1
Bilateral	2
Cerebellar dysfunction	1
Decreased facial sensation	1
Dysphagia or dysarthria	2
Aphasia	2
Double vision	1
Blindness	
Unilateral	2
Bilateral	4
Hemiplegia	2
Memory loss	1
Seizures	1
Spinal dysfunction	
Mild/moderate	2
Severe	4

age at diagnosis, the presence of intracranial meningiomas, and the presence of a non-mosaic NF2 mutation affect mortality of patients with NF2.[3] That study, however, did not include information about neurological features for each patient. To date, no study has examined social independence status and its contributing factors, such as neurological features, in patients with NF2 using data from a national registry.

In Japan, several studies have reported on the characteristics of patients with NF2, including clinical course, using a national registry. Patients who are diagnosed as NF2 become eligible for medical expense subsidies in Japan (Table 1).[6] To receive subsidies, applicants must submit claims to the prefectural government. Applicant information, such as sex, age at onset/registration, and the presence/absence of clinical features, is accumulated in a registry developed by Japan's Ministry of Health, Labour and Welfare (MHLW). Using data from this national registry, Matsuo et al.[7] reported that patients with a NF2 age of onset <20 years were more likely to have several tumors, cutaneous symptoms, and neurological features. They also found that patients with an earlier age at onset had more severe spinal symptoms than those with an age at onset ≥20 years. Despite using the national registry, the study included only data from 2010. Iwatate et al. also reported that younger age of onset, positive family history, positive treatment history, and specific neurological deficits were risk factors for progressive disability in NF2.[8] These studies, however, did not analyze social independence levels of the patients using data from the national registry.

The purpose of the present study was to analyze social independence in patients with NF2 using a national registry of patients who submitted claims to receive NF2 medical expense subsidies in Japan. Understanding the biopsychosocial factors that affect social independence in patients with NF2 could contribute to the promotion of better social functioning and QOL for those living with the disease.

Materials and Methods

Study population and data source

This cross-sectional study used a registry database containing information about all patients who submitted initial claims to receive NF2 medical expense subsidies in Japan between fiscal years 2004 and 2013. The Intractable/Rare Disease Control Division within the MHLW provided access to database information following approval of the research protocol. The Division removed all personally identifiable information, such as names and addresses, from the database and coded a unique identification (ID) number for each patient. Each ID number was made up of seven digits that were not associated with any identifiable personal information. Medical certificates, which are required to receive medical expense subsidies for NF2 in Japan, were documented for all participating patients. All NF2 diagnoses were made by physicians according to the National Institutes of Health's diagnostic criteria.[9] Between fiscal years 2004 and 2013, there were 409 initial claims submitted for NF2 medical expense subsidies (Fig. 1).

The database used for data collection included the following information: [1] sex, [2] age at registration, [3] family history of NF2, [4] activities of daily living (ADLs), [5] social independence status, and [6] neurological features (hearing loss, facial paresis, cerebellar dysfunction, decreased facial sensation, speech dysfunction, blindness, hemiparesis, memory loss, seizures, or spinal dysfunction). Social independence status was classified into the groups of "socially independent" (which included the categories of "employed," "studying," and "housekeeping") and "socially dependent" (which included the categories of "cared for at home," "cared for at a hospital," and "cared for at a nursing home"). Since the number

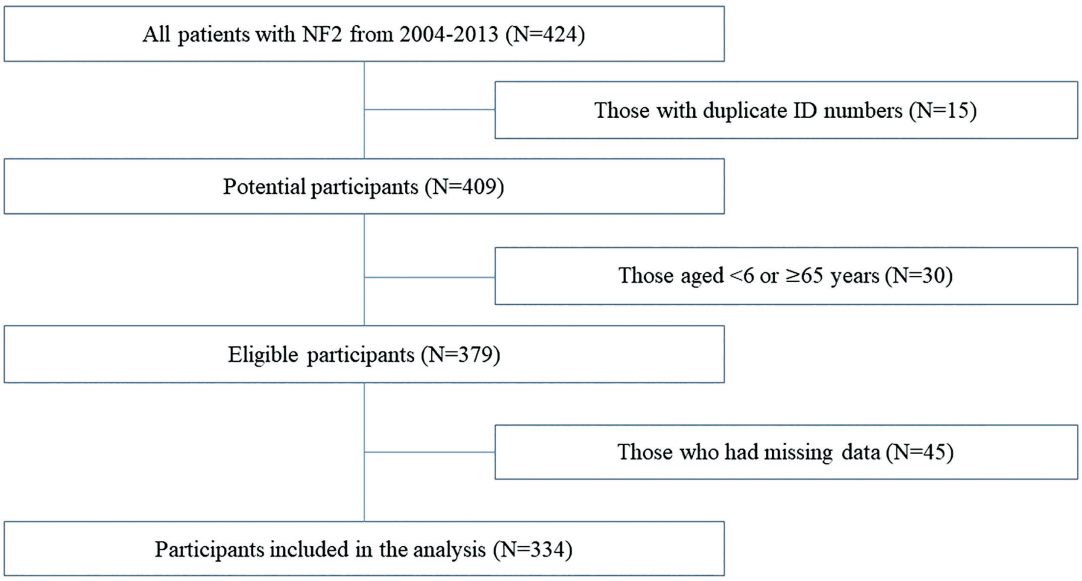

Fig. 1 Flowchart for participant selection. ID: identification

of patients with bilateral facial paresis and blindness was small, we aggregated "unilateral" and "bilateral" as one category for each neurological feature.

Participants who were eligible for inclusion in the study were those aged 6 to 64 years who did not have missing data regarding age. Children in Japan begin attending elementary school at age 6 years and adults generally retire from working at age 65 years.

Ethical approval was not required for this study, in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" set forth by the Japanese government. The present study used a fully anonymous database that was provided by the MHLW, which did not contain any personally identifiable information.

Statistical analysis

The chi-square test and Fisher's exact test were used to examine whether social independence status differed by sex, age, family history, ADLs, or neurological features in patients with NF2. Multivariate logistic regression analysis was performed to examine the associations between demographic variables, neurological features, and social independence status. We used social independence status as the outcome variable, whereas sex, age (6–24 years, 25–44 years, 45–64 years), and neurological features were used as explanatory variables. The category of ADLs was removed from the independent variable grouping in logistic regression analysis due to its multicollinearity with other independent variables that concerned clinical features of NF2. The presence or absence of a family history of NF2 was also removed from the statistical analyses, since 20.1% of participants were categorized as "unknown" on this variable. As shown in Table 1, total disability score of neurological features can be calculated for each participant. However, in the present study, to examine which specific neurological feature contributes to social independence status more strongly than other features do, we included each of 11 neurological features as explanatory variables in logistic regression analysis. Logistic regression coefficients were transformed to odds ratios (ORs) with 95% confidence intervals (CIs). For all analyses, $P < 0.05$ was considered as statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of the 409 unique registrants between fiscal years 2004 and 2013, 30 patients were ineligible for inclusion due to their age at registration. An additional 45 patients were removed from the analysis due to missing data regarding ADLs, neurological features, or social independence status. The final study population consisted of 334 participants (162 males and 172 females; mean age [standard deviation] at registration, 35.4 years [15.1]) (Fig. 1).

As detailed in Table 2, 79% (264/334) of participants were classified as socially independent at the time of registration. The most common ages were from 25 to 44 years, with 138 (41.3%) participants in this age group. Hearing loss was the most frequently observed neurological feature (51.8%), while blindness was

Table 2 Frequency distribution of variables by social independence status

Demographic/ Neurological factors	Socially independent (n = 264)	Socially dependent (n = 70)	Chi-square test/ Fisher's exact test
	n (%)	n (%)	
Sex			
Male	127 (48.1)	35 (50.0)	$P = 0.883$
Female	137 (51.9)	35 (50.0)	
Age (yrs)			
6–24	81 (30.7)	16 (22.9)	$P = 0.208$
25–44	110 (41.7)	28 (40.0)	
45–64	72 (27.3)	25 (35.7)	
Family history			
Present	78 (29.5)	15 (21.4)	$P = 0.402$
Absent	134 (50.8)	40 (57.1)	
Unknown	52 (19.7)	15 (21.4)	
Activities of daily living			
Living normally	123 (46.6)	4 (5.7)	$P < 0.001$
Living with disability	129 (48.9)	18 (25.7)	
Partially cared for	12 (4.5)	36 (51.4)	
Completely cared for	0 (0.0)	12 (17.1)	
Hearing loss			
Bilateral	38 (14.4)	37 (52.9)	$P < 0.001$
Unilateral	78 (29.5)	20 (28.6)	
Absent	148 (56.1)	13 (18.6)	
Facial paresis			
Present	46 (17.4)	36 (51.4)	$P < 0.001$
Absent	218 (82.6)	34 (48.6)	
Cerebellar dysfunction			
Present	40 (15.2)	34 (48.6)	$P < 0.001$
Absent	224 (84.8)	36 (51.4)	
Decreased facial sensation			
Present	41 (15.5)	32 (45.7)	$P < 0.001$
Absent	223 (84.5)	38 (54.3)	
Speech dysfunction			
Present	27 (10.2)	28 (40.0)	$P < 0.001$
Absent	237 (89.8)	42 (60.0)	
Double vision			
Present	19 (7.2)	21 (30.0)	$P < 0.001$
Absent	245 (92.8)	49 (70.0)	
Blindness			
Present	4 (1.5)	14 (20.0)	$P < 0.001$
Absent	260 (98.5)	56 (80.0)	
Hemiplegia			
Present	9 (3.4)	25 (35.7)	$P < 0.001$
Absent	255 (96.6)	45 (64.3)	

Demographic/ Neurological factors	Socially independent (n = 264)	Socially dependent (n = 70)	Chi-square test/ Fisher's exact test
	n (%)	n (%)	
Memory loss			
Present	5 (1.9)	18 (25.7)	P <0.001
Absent	259 (98.1)	52 (74.3)	
Seizures			
Present	9 (3.4)	17 (24.3)	P <0.001
Absent	255 (96.6)	53 (75.7)	
Spinal dysfunction			
Present	86 (32.6)	44 (62.9)	P <0.001
Absent	178 (67.4)	26 (37.1)	

observed least frequently (5.4%). Socially dependent participants had more neurological features and lower ADL scores than those who were socially independent. Sex, age, and family history had no significant relationships with social independence status.

Table 3 shows the results of multivariate logistic regression analysis, with social independence status defined as the dependent variable. After adjusting for sex and age at registration, participants with bilateral hearing loss (OR 4.6; 95% CI, 1.7–12.9), unilateral hearing loss (OR 2.6; 95% CI, 1.1–6.4), blindness (OR 5.2; 95% CI, 1.2–23.3), hemiplegia (OR 6.6; 95% CI, 2.2–19.9), or seizures (OR 4.3; 95% CI, 1.3–13.5) had significantly higher ORs for being socially dependent, as compared to those without these neurological features.

Discussion

The present study examined social independence, as well as its contributing factors, in patients with NF2 using data from a national registry of patients who submitted initial claims to receive NF2 medical expense subsidies in Japan over the past decade. Approximately 80% of patients were determined to be socially independent. Neurological features that were frequently observed in patients who were socially dependent included bilateral/unilateral hearing loss, blindness, hemiplegia, and seizures.

Among neurological features, the most frequently observed was hearing loss (52%) and the least frequently observed was blindness (5%). Hearing loss and tinnitus (often unilateral at onset) are the presenting symptoms of NF2 in 60% of adults.[1] There are, however, very few studies about symptoms other than hearing loss and tinnitus. Neurological features such as seizures or blindness were infrequently observed in previous studies.[10,11] In the present study, the most frequently observed neurological feature was hearing loss, and the number of patients with blindness or seizures was comparatively small. While direct comparisons cannot be made, our findings regarding neurological features appear to be similar to those of previous studies.

In the present study, participants with unilateral hearing loss had significantly higher ORs for being socially dependent, as compared to those without this neurological feature. Relevant neurological features other than unilateral hearing loss, such as vertigo, tinnitus, and sequela of surgery, might have correlated to social independence status, although these information were not available in the national registry of NF2 used in the present study.

Two studies have analyzed MHLW national registry data regarding NF2. Iwatate et al. identified prognostic risk factors for progressive disability with NF2.[8] In that study, significant independent risk factors for progressive disability included age of onset <25 years, positive family history of NF2, positive treatment history, hearing loss, facial paresis, blindness, and hemiparesis. The present study found that, among these neurological features, hearing loss, blindness, and hemiparesis were more frequent in patients who were socially dependent. These findings imply that patients with NF2 tend to be forced to abandon their work or study because of progressive disability regarding these neurological features.

Matsuo et al. characterized the age of NF2 onset according to two groups (<20 years and ≥20 years)[7] and found that patients with an age of onset <20 years were more likely to have blindness, hemiplegia, aphasia, convulsions, or mild to moderate spinal cord symptoms. The clinical course of NF2 is variable, and there are at least two NF2 subtypes[12,13]: [1] (mild) Gardner-type NF2, which presents in adulthood (mean age, 22–27 years) with bilateral

Table 3 Multivariate logistic regression analysis using social independence status as the dependent variable

Explanatory variables	Univariate analysis	Multivariate analysis
	Odds ratio (95% CI)	Odds ratio (95% CI)
Sex		
Male	1.08 (0.6–1.8)	1.04 (0.5–2.1)
Female	(Reference)	(Reference)
Age (yrs)		
6–24	0.77 (0.4–1.5)	1.56 (0.6–3.9)
25–44	(Reference)	(Reference)
45–64	1.42 (0.8–2.6)	1.80 (0.8–4.0)
Hearing loss		
Bilateral	11.09 (5.4–22.9)	4.63 (1.7–12.9)
Unilateral	2.92 (1.4–6.2)	2.59 (1.1–6.4)
Absent	(Reference)	(Reference)
Facial paresis		
Present	5.02 (2.8–8.8)	0.99 (0.4–2.4)
Absent	(Reference)	(Reference)
Cerebellar dysfunction		
Present	5.29 (3.0–9.4)	2.03 (0.9–4.7)
Absent	(Reference)	(Reference)
Decreased facial sensation		
Present	4.58 (2.6–8.2)	1.35 (0.6–3.2)
Absent	(Reference)	(Reference)
Speech dysfunction		
Present	5.85 (3.1–10.9)	0.89 (0.3–2.4)
Absent	(Reference)	(Reference)
Double vision		
Present	5.53 (2.8–11.0)	0.85 (0.3–2.6)
Absent	(Reference)	(Reference)
Blindness		
Present	16.25 (5.2–51.2)	5.19 (1.2–23.3)
Absent	(Reference)	(Reference)
Hemiparesis		
Present	15.74 (6.9–35.9)	6.56 (2.2–19.9)
Absent	(Reference)	(Reference)
Memory loss		
Present	17.93 (6.4–50.4)	1.63 (0.4–6.5)
Absent	(Reference)	(Reference)
Seizures		
Present	9.09 (3.8–21.5)	4.25 (1.3–13.5)
Absent	(Reference)	(Reference)
Spinal dysfunction		
Present	3.5 (2.0–6.1)	1.37 (0.7–2.9)
Absent	(Reference)	(Reference)

CI: confidence interval

vestibular schwannomas (VSs) often being the only feature, and [2] (severe) Wishart-type NF2, which often presents initially with multiple (and rapidly progressive) central nervous system tumors other than VSs. They require repeated surgical intervention, and many patients with these subtypes often do not survive beyond the age of 50 years. Given the results of previous studies[7,8] and the definition of NF2 subtypes, the neurological features associated with social independence observed in the present study may correspond to those of Wishart-type NF2.

To our knowledge, this is the first study to examine social independence status in patients with NF2 using national registry data. The registry used in the present study included all patients who submitted medical certificates that were filled out by physicians to receive NF2 medical expense subsidies in Japan over the past decade. This study, however, has several limitations. First, various forms of selection bias are possible. Specifically, participants were limited to patients with NF2 who submitted initial claims for medical expense subsidies. Individuals with subclinical NF2, who did not require extensive diagnostic workup or frequent medical care, may not have submitted claims for subsidies, and therefore may not have been included in the registry. Although nearly 80% of patients with NF2 were found to be socially independent at the time of registration, future studies need to examine the change in social independence status among these patients using a follow-up data. The registry also did not include information about patients who had died, which may have resulted in the exclusion of potentially relevant data. Second, the study design was cross-sectional. Thus, it was not possible to determine causality between clinical features and social independence status. Third, potential confounding factors, such as comorbidities and socioeconomic status, were not adjusted for in the multivariate analysis because these data were not included in the registry. Fourth, we aggregated "unilateral" and "bilateral" as one category for facial paresis and blindness since the number of these neurological features were not sufficient to perform multivariate logistic regression analysis. Finally, study participants were limited to patients with NF2 in Japan, and thus, caution should be exercised when generalizing the present findings to different populations.

Because no cure for NF2 has been identified to date, it is important for individuals with NF2 to maintain good QOL for as long as possible. According to a previous study, psychosocial stress and pain significantly affect QOL of patients with NF2.[14] The present study could not analyze QOL because the database did not include this information. However, the medical certificate (clinical personal record) that physicians complete for applicants with rare diseases (including NF2) was revised in 2015 to include items regarding pain and mental status. Thus, further discussion about the QOL of patients with NF2 may become possible if data after 2015 become available. In addition, although information about treatment, including the presence/absence of surgical operation, for each patient were insufficient in the national registry used in the present study, further studies analyzing more detailed association between treatment and social independence status among patients with NF2 are needed.

In conclusion, the present study examined the social independence of patients with NF2 using data from a national registry of all patients who submitted claims to receive NF2 medical expense subsidies in Japan from 2004 to 2013. Approximately 80% of patients with NF2 were found to be socially independent at the time of registration. Neurological features of hearing loss, blindness, hemiplegia, and seizures were associated with lower social independence. These findings, which suggest that these neurological features could limit social independence in patients with NF2, may contribute to the maintenance of better social functioning and QOL in this patient population.

Acknowledgment

This work was supported by a Grant-in-Aid for Research on Policies for Intractable Rare Diseases from the MHLW of Japan (H29-nanchi-tou(nan)-ippan-021).

Conflicts of Interest Disclosure

The authors declare that they have no competing interests.

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