Epidemiological Analysis of Major Complications Requiring Medical Intervention in Patients with Neurofibromatosis 1

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Neurofibromatosis 1 has various complications. To elucidate the frequency of neurofibromatosis 1-related major complications requiring medical intervention, a nationwide retrospective study was conducted of 3,530 patients with neurofibromatosis 1 registered from 2001 to 2014 in Japan. The ratio of certified patients requiring medical intervention (>stage 3) was 82%. Patients classified in the most severe grade experienced dermatological complications (71.8% of patients), neurological complications (38.1%) and bone complications (33.3%). In patients with dermatological manifestations, medical treatment was needed for cutaneous neurofibromas (58%), diffuse plexiform neurofibromas (31%) and malignant peripheral nerve sheath tumours (10%). Patients with neurological manifestations needed medical treatment mainly for brain tumours (53%) and intellectual disability (26%). Patients with bone manifestations needed medical treatment for pseudoarthrosis (9%), scoliosis (55%) and bone defects (16%). It is necessary for physicians to be aware of neurofibromatosis 1-related complications requiring medical intervention in order to provide appropriate care for patients with neurofibromatosis 1.

Key words: neurofibromatosis 1; epidemiology; treatment; survey.

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Neurofibromatosis 1 (NF1) is an autosomal dominant genetic disorder with a birth incidence of 1 in 3,000–4,000 individuals (1). NF1 is caused by a mutation of the *NF1* gene (2) and has various complications, including dermatological, neurological and bone manifestations (3). We recently performed an epidemiological survey of patients with NF1 at the Division of Dermatology of Tottori University Hospital in Japan for assessment of disease severity. The survey found that 37.1% of patients had major health impairments requiring medical treatment (4). In addition, two-thirds of patients classified in the most severe grade of NF1 experienced diffuse plexiform neurofibromas with secondary problems. However, the number of patients in that study was relatively small ($n = 124$) and the survey was limited to the field of dermatology. Since patients with a severe grade of NF1 have been supported by the public medical expenses subsidy system in Japan, we investigated the details of complications in cases requiring medical intervention that were registered in a national database. The aim of this nationwide study was to elucidate the clinical characteristics of NF1 and to determine the frequencies of complications requiring medical intervention.

SIGNIFICANCE

Neurofibromatosis 1 is a genetic disease characterized by various symptoms such as dermatological, neurological and bone complications. This study presents the frequencies of complications requiring medical treatment in patients with neurofibromatosis. Our data suggest that most frequently treated symptoms were dermatological complications. It is important to know the characteristic complications requiring treatment in order to provide appropriate care for patients suffering from neurofibromatosis.

PATIENTS AND METHODS

This retrospective study investigated clinical information for patients with NF1 registered at the Ministry of Health, Labour and Welfare from 2001 to 2014 from all over Japan. Patients with NF1 with a certain grade of severity are registered for research and exemption of medical fees as a government's healthcare policy in Japan. Anonymous data for patients who met the diagnostic criteria of NF1 by the National Institutes of Health in 1988 (5) were analysed (patients for whom essential information, such as age or sex, was missing were excluded). Clinical information, including sex, age, family history and complications, was investigated. Clinical severity was also assessed by both the Japanese severity classification (DNB classification) (4) and Riccardi's severity grade (6), as shown in Appendices S1[1] and S2[1]. The study protocol was approved by the ethics committees of Tottori University Hospital (number 1704A005) and Fukuoka University Hospital (17-4-03).

RESULTS

Patients' characteristics

Of the 3,530 registered patients, 25 were excluded from the study due to missing essential data. Finally, data for

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Table I. Characteristics of patients with neurofibromatosis 1 (NF1) in this study population

Characteristics	*n*	
Sex		Age, years (mean±SD)
Male	1,595	37.6±20.9
Female	1,910	38.8±19.7
Total	3,505	38.3±20.3
Family history		
Yes	1,484	
No	1,312	
Unknown	709	
DNB classification		Riccardi's classification, *n*
Stage 1	175	175
Stage 2	447	447
Stage 3	309	1,354
Stage 4	663	1,529
Stage 5	1,911	–

SD: standard deviation.

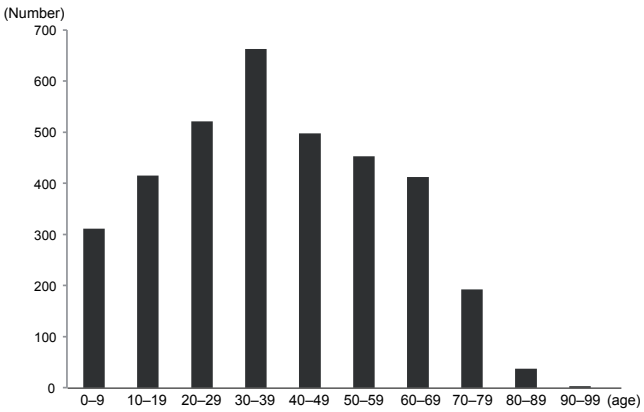

Fig. 1. Age of 3,505 individuals in this study population.

3,505 patients (1,595 males and 1,910 females) were analysed (**Table I**). The ages of patients ranged from 0 to 93 years, with a mean age of 38.3 years. The distribution of patients by decade of life is shown in **Fig. 1**. The prevalence peak was between 30 and 39 years of age. There was a family history of NF1 in 42.3% of patients.

Grade of severity

Grades of severity of NF1 evaluated by the DNB classification in Japan and Riccardi's classification are shown in Table I. The ratio of patients with stage 1 or 2 (mild manifestations not requiring treatment) was 18% in both classifications. Since the definitions of stages 1 and 2 were almost the same in both classifications, the percentages of patients were the same. The ratio of certified patients requiring medical intervention (> stage 3) was 82%. In the DNB classification, 55% of patients were classified as the most severe grade. The ratio of patients with grade 4 in Riccardi's classification was 44%, because patients with severe bone manifestations were categorized as stage 3 in that classification.

Frequencies of complications requiring medical intervention

In Japan, patients with NF1 with major health impairments (stages 3–5) have been supported by the public medical expenses subsidy system. At first, we focused on patients classified in the most severe grade (stage 5). The patients experienced dermatological complications (71.8% of patients), neurological complications (38.1%) and bone complications (33.3%). Next, we investigated the frequencies of each complication in detail (stages 3–5). In patients with dermatological manifestations, medical treatment was needed for cutaneous neurofibromas (58%), diffuse plexiform neurofibromas (31%) and malignant peripheral nerve sheath tumours (10%) (**Fig. 2**A). Patients with neurological manifestations needed medical treatment mainly for intellectual disability (26%) and brain tumours (53%) (Fig. 2B). Patients with bone manifestations needed medical treatment mainly for long-bone bowing with pseudoarthrosis (9%), scoliosis (55%) and bone defects (16%) (Fig. 2C).

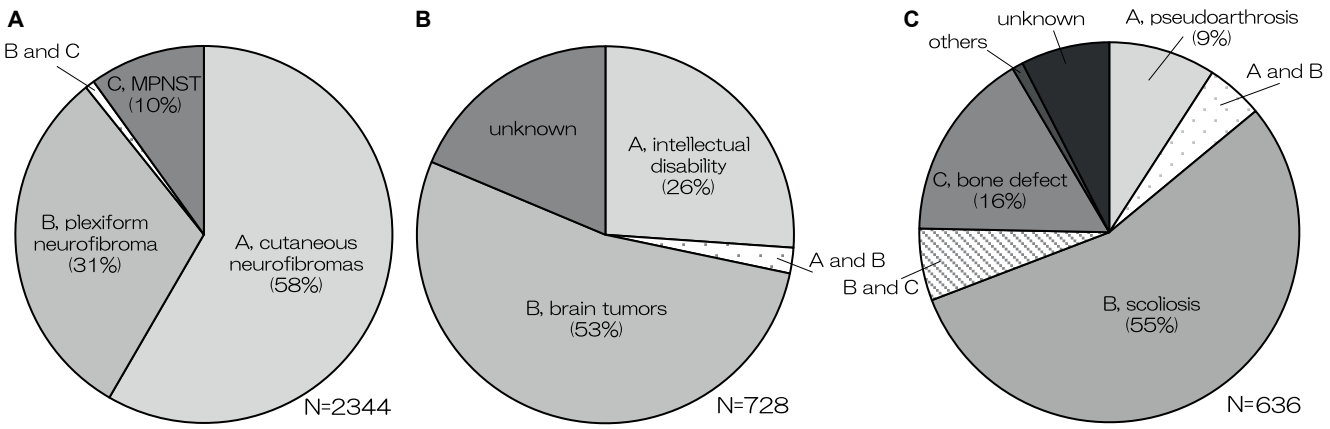

Fig. 2. (A) Dermatological manifestations requiring medical treatment (A, cutaneous neurofibromas; B, large plexiform neurofibroma with severe secondary problems; C, malignant peripheral nerve sheath tumour (MPNST). (B) Neurological manifestations requiring medical treatment (A, severe intellectual disability; B, brain tumours). (C) Bone manifestations requiring medical treatment (A, pseudoarthrosis; B, scoliosis; C, bone defect).

Frequencies of other complications

Cardiovascular diseases (arterial aneurysm, pulmonary stenosis, arterial hypertension, moyamoya disease and cerebral infarction) were seen in 48 patients (1.4%). Endocrinological diseases (pheochromocytoma and thyroid dysfunction) were seen in 7 patients (0.2%). Malignant neoplasms (breast cancer and gastrointestinal stromal tumour) were seen in 16 patients (0.5%). The frequency of patients with osteoporosis was unknown.

DISCUSSION

NF1 has various complications, including dermatological, neurological and bone manifestations (7). However, clinical expression is variable in each individual and the degree of severity is not predictable. There have been a number of reports on the incidences of NF1-related complications (8–10). We have reported previously that approximately two-thirds of patients with NF1 had a relatively mild phenotype, and life-threatening complications were shown to be less common in a recent epidemiological study (4). Patients with NF1 are usually followed clinically with no medical or surgical intervention. However, it has been reported that the overall risk of malignancies in patients with NF1 is 2.7-times higher than that in the general population (11). In addition, the mean age at death in patients with NF1 is approximately 15 years younger than that in healthy individuals (12). Therefore, medical treatment is necessary for patients with serious complications. To provide appropriate care, it is important to be aware of the frequencies of NF1-related major complications requiring medical intervention. In our study, the ratio of patients with a severe grade was higher than that in a past study (13). It is likely that patients with a severe grade in our study tended to be registered in the system.

More than 70% of the patients with NF1 in the most severe grade had dermatological manifestations requiring medical treatment. It is notable that 58% of the patients supported by the public medical expenses subsidy system needed treatment for cutaneous neurofibromas. Cutaneous neurofibromas usually develop during puberty and the incidence increases with age (14). They are always benign, but they influence the quality of life in patients with NF1 (15). These tumours can be removed if they cause problems in daily life or social activity. Diffuse plexiform neurofibromas are seen in approximately 20% of patients with NF1, and they can also cause serious disfigurement (4). They have a risk of malignant transformation, and sometimes cause life-threatening massive intra-tumour haemorrhage. Although a large diffuse plexiform neurofibroma is a therapeutic challenge, treatment by surgery or embolization is preferable (16). Indeed, 31% of the patients with dermatological manifestations in the present study needed treatment for diffuse plexiform neurofibromas. Clinical trials for treatment of diffuse plexiform neurofibromas are ongoing (17). In the future, novel medical therapies with recent targeted strategies may be useful for treatment of diffuse plexiform neurofibromas.

In our study population, the prevalence peak was between 30 and 39 years of age. We assume that those patients presented with cosmetic and social problems due to the above dermatological manifestations. In contrast, the ratio of patients with malignant peripheral nerve sheath tumours, the most frequent malignant neoplasm associated with NF1, was relatively low (18).

Neurological manifestations are also commonly seen in individuals with NF1 (3). Treatment for neurological complications was needed in 38.1% of patients in the most severe grade. Approximately half of the patients had brain tumours. In addition, one-quarter of the patients needed medical care for severe intellectual disability. Neurological examinations should be performed during annual monitoring in patients with NF1.

The ratio of patients with bone manifestations in need of medical treatment was 33.3% in the most severe grade. Specific bone manifestations associated with NF1 include long-bone bowing with pseudoarthrosis (19) and sphenoid wing dysplasia (20). However, the frequencies were not high. In contrast, scoliosis affects approximately 10% of patients with NF1 (21), even though it is not included in established diagnostic criteria for NF1 (5). Since more than half of the patients with bone manifestations needed medical treatment for scoliosis, attention must be paid to this complication. The frequency in patients with osteoporosis has not been elucidated in this study.

This nationwide survey revealed, for the first time, the frequency of major complications requiring medical intervention in patients with NF1 based on the DNB classification. In agreement with a previous report (13), the priority for medical intervention seems to be dermatological manifestations, especially cutaneous neurofibromas.

This study has a number of limitations. The study population is not totally representative of the general NF1 population, because patients without severe complications may not be registered in the public medical expenses subsidy system. In addition, there is a possibility that clinicians who are not familiar with management of NF1 do not recommend registration in the system to patients. The outcome may be biased by the selection of severe complications. In Japan, several NF1-related complications, including cardiovascular diseases, endocrinological diseases and malignant neoplasms except malignant peripheral nerve sheath tumours, have not been included in the DNB classification. Therefore, those complications could be overlooked in the system.

In addition, the medical costs of each manifestation in this study could not be assessed. In 2000 it was reported that the mean cost per patient per year was approximately

900 EUR in France, and that the costs for moderate and severe cases were higher than the costs for less severe cases (13). However, it is not easy to assess the financial cost because the insurance system or economic scale is different in each country. Despite these limitations, the current study provides important information for medical and social management of NF1.

In conclusion, once NF1-related complications progress, much effort is needed to improve the impaired quality of life of patients with NF1. It is important for physicians to be aware of the priority of NF1-related major complications requiring medical intervention.

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The authors have no conflicts of interest to declare.

REFERENCES

1. Lammert M, Friedman JM, Kluwe L, Mautner VF. Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. Arch Dermatol 2005; 141: 71–74.
2. Viskochil D, Buchberg AM, Xu G, Cawthon RM, Stevens J, Wolff RK, et al. Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. Cell 1990; 62: 187–192.
3. Yoshida Y. 71 Neurofibromatosis. In: Kelly AP, Taylor SC, editors. Taylor and Kelly's dermatology for skin of color. 2nd edn. McGrawHill Press, New York, USA. 2016: p. 499–504.
4. Ehara Y, Yamamoto O, Kosaki K, Yoshida Y. Clinical severity in Japanese patients with neurofibromatosis 1 based on DNB classification. J Dermatol 2017; 44: 1262–1267.
5. National Institutes of Health Consensus Development Conference. Neurofibromatosis: Conference statement. Arch Neurol 1988; 45: 575–578.
6. Riccardi VM, Kleiner B. Neurofibromatosis: a neoplastic birth defect with two age peaks of severe problems. Birth Defects Orig Artic Ser 1977; 13: 131–138.
7. Anderson JL, Gutmann DH. Neurofibromatosis 1. Handb Clin Neurol 2015; 132: 75–86.
8. Friedman JM, Birch PH. Type 1 neurofibromatosis: a descriptive analysis of the disorder in 1728 patients. Am J Med Genet 1997; 70: 138–143.
9. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007; 44: 81–88.
10. Niimura M. Neurofibromatosis in Japan, In: Ishibashi Y, Hori Y, editors. Tuberous sclerosis and neurofibromatosis epidemiology, pathophysiology, biology and management. Amsterdam: Excerpta Medica, Elsevier Science Publishers, 1990: p. 22–31.
11. Walker L, Thompson D, Easton D, Ponder B, Ponder M, Frayling I, Baralle D. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. Br J Cancer 2006; 95: 233–238.
12. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. Am J Hum Genet 2001; 68: 1110–1118.
13. Wolkenstein P, Durand-Zaleski I, Moreno JC, Zeller J, Hemery F, Revuz J. Cost evaluation of the medical management of neurofibromatosis 1: a prospective study on 201 patients. Br J Dermatol 2000; 142: 1166–1170.
14. Ehara Y, Yamamoto O, Kosaki K, Yoshida Y. Natural course and characteristics of cutaneous neurofibromas in neurofibromatosis 1 based on DNB classification. J Dermatol 2018; 45: 53–57.
15. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplège A. Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. Arch Dermatol 2001; 137: 1421–1425.
16. Kolker S, Wunder JS, Roche-Nagle G. Hybrid resection of a giant thigh plexiform neurofibroma. Int J Surg Case Rep 2015; 8C: 1–4.
17. ClinicalTrials.gov. A service of the U.S. National Institutes of Health. Available from: http://www.clinicaltrials.gov. Accessed May 1, 2018.
18. Bradford D, Kim A. Current treatment for malignant peripheral nerve sheath tumors. Curr Treat Options Oncol 2015; 16: 328.
19. Pannier S. Congenital pseudoarthrosis of the tibia. Orthop Traumatol Surg Res 2011; 97: 750–761.
20. Alwan S, Tredwell SJ, Friedman JM. Is osseous dysplasia a primary feature of neurofibromatosis 1(NF1)? Clin Genet 2005; 67: 378–390.
21. Akbarnia BA, Gabriel KR, Beckman E, Chalk D. Prevalence of scoliosis in neurofibromatosis. Spine 1992; 17: S224–228.