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Original Article

Prevalence of Obesity in Japanese Individuals with Neurofibromatosis 1

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Abstract

Background : Although much research on the clinical features of neurofibromatosis 1 (NF1) has been published, few studies have investigated the body size of adults with NF1. Additionally, there are very few reports of metabolic syndromes, such as diabetic mellitus, occurring as comorbidities in individuals with NF1. In a previous single institution study, we found that adults with NF1 had a lower body mass index (BMI) than control subjects.

Materials and Methods : The study cohort comprised 146 adults with NF1 (61 men, 85 women ; age range 20–79 years [mean $\pm$ standard deviation] {SD} 42.2 ± 16.1 years) from two institutions. As a control, we retrieved national reference data (NFD) on BMI from epidemiologic research performed by the Ministry of Health, Labour and Welfare in Japan in 2011–2012. We used the Mantel–Haenszel test to compare the prevalence of obesity ($25 \text{ kg/m}^2 < \text{BMI}$) between individuals with NF1 and those drawn from NFD.

Results : The prevalence of $\text{BMI} > 25 \text{ kg/m}^2$ was significantly lower in men with NF1 than in the cohort drawn from NFD ($p=0.012$) ; however, this difference was not significant for women ($p=0.288$).

Conclusions : Our findings indicate that most men with NF1 are of normal body size and that they have a lower prevalence of obesity than a control group.

Key words : neurofibromatosis 1, obesity, body mass index, weight

Introduction

Neurofibromatosis 1 (NF1) is an autosomal dominant disorder, is characterized clinically by café-au-lait macules and multiple neurofibromas. Many other clinical findings and associated comorbidities have been reported¹⁾²⁾. It is well established that, apart from individuals with a 17q11 microdeletion (i.e., deletion of the whole *NF1* gene), individuals with NF1 are of short stature³⁾. However, little research on the body mass index (BMI) of individuals with NF1 has been reported ; thus, there is currently no consensus on their BMI. Additionally, there have been very few reports of metabolic syndrome

such as diabetic mellitus type 2 or hyperlipidemia occurring as comorbidities with NF1. Because obesity is known to be the strongest risk factor for the occurrence and exacerbation for these disorders, we speculated that most patients with NF1 are of normal body size with a low prevalence of obesity. We have already reported a single institution study in which we found that individuals with NF1 (especially in men) are shorter and have lower BMIs than other persons with dermatological disorders⁴⁾. The aim of the present study was to ascertain the prevalence of obesity in individuals with NF1 and compare it with the prevalence in the general population of Japan.

Materials and Methods

This study was a retrospective. The diagnosis of NF1 was established according to clinical manifestations, using the diagnostic criteria set by the National Institutes of Health in 1988⁵⁾. Relevant clinical variables, including age, sex, and height at initial visit of individuals diagnosed with NF1 at Fukuoka University Hospital (FUH) and Tottori university hospital (TUH) from 1990 to 2014, were extracted from hospital records. The data from FUH included the previously reported cohort⁴⁾ plus an additional five individuals. National reference data (NFD) for height and BMI were retrieved from the results of epidemiologic research performed by the Ministry of Health, Labour and Welfare in Japan in 2011–2012⁶⁾⁷⁾. The individuals with NF1 and controls from the NFD were allocated to various groups according to sex, age, and BMI. The age groups were each 10 years and ranged from 20 to 79 years. As to BMI, study individuals were allocated to a normal or obese ($\text{BMI} > 25 \text{ kg/m}^2$). The difference in prevalence of obesity between individuals with NF1 and those from the NFD were then compared by the Mantel-Haenszel test. A Statcel3 software package (OMS publishing Co., Saitama, Japan) was used. Statistical significance

was set at $P < 0.05$ for all results. This study was approved by the Ethics Committee of the Institutional Review Board of FUH and TUH. The requirement for informed consent was waived because the data were anonymized.

Results

Subjects

Relevant characteristics of the study cohort of 147 adults (61 men, 86 women ; mean age 42.2 ± 16.1 years ; range : 20–79 years) with NF1 were compared with those of the NFD controls ; these are summarized in Table 1. The study cohort comprised 100 individuals (38 men, 62 women) from FUH and 47 (23 men, 24 women) from TUH. Data on height were available for all patients ; however, information on weight was missing for one female patient from FUH. The heights and BMIs did not differ significantly for either sex between these two cohorts of patients from the two institutions (data not shown).

Height

The mean heights of study subjects were 162.3 ± 7.44 cm for men and 153.3 ± 6.66 cm for women. The mean national reference values for heights of men and women were 167.3 ± 7.0 cm and 154.2 ± 6.8 cm, respectively, both of which

Table 1 Summary of data from all subjects and control

			NF1*	National reference data**
age	Median (minimum–maximum)		42 (20 – 79)	
height (cm)	men	mean $\pm$ SD (n)	162.3 ± 7.44 (n=61)	167.3 ± 7.0
	women	mean $\pm$ SD (n)	153.3 ± 6.66 (n=86)	154.2 ± 6.8
BMI (kg/m^2)	men	mean $\pm$ SD (n)	22.5 ± 3.93 (n=61)	23.6 ± 3.3
	women	mean $\pm$ SD (n)	21.5 ± 2.81 (n=85)	22.3 ± 3.6

BMI : body mass index, * includes previously published data, ** Ministry of Health, Labour and Welfare, Japan. The National Health and Nutrition Survey in Japan, 2012 (in Japanese). Available at : <http://www.mhlw.go.jp/bunya/kenkou/eiyou/h24-houkoku.html>.

Table 2 Prevalence of obesity in men with NF1 and men in the National Reference Data.

		Number of Individuals with NF1	Number of individuals in National reference data
20~29yrs	Obesity (BMI > 25)	1	154
	Without obesity	9	605
30~39yrs	Obesity (BMI > 25)	1	371
	Without obesity	13	957
40~49yrs	Obesity (BMI > 25)	3	518
	Without obesity	6	880
50~59yrs	Obesity (BMI > 25)	3	460
	Without obesity	8	971
60~69yrs	Obesity (BMI > 25)	0	682
	Without obesity	12	1,584
70~79yrs	Obesity (BMI > 25)	1	706
	Without obesity	4	1,800

According to the Mantel-Haenszel test, significantly fewer men with NF1 had BMI > 25 kg/m² than control men ($p=0.012$).

Table 3 Prevalence of obesity in women with NF1 and women in the National Reference Data.

		Number of Individuals with NF1	Number of individuals in National reference data
20~29yrs	Obesity (BMI > 25)	4	70
	Without obesity	23	749
30~39yrs	Obesity (BMI > 25)	2	199
	Without obesity	25	1,374
40~49yrs	Obesity (BMI > 25)	0	274
	Without obesity	9	1,463
50~59yrs	Obesity (BMI > 25)	1	427
	Without obesity	10	1,508
60~69yrs	Obesity (BMI > 25)	0	696
	Without obesity	5	2,078
70~79yrs	Obesity (BMI > 25)	2	833
	Without obesity	4	2,402

According to the Mantel-Haenszel test, these values did not differ significantly ($p=0.288$).

are higher than in the individuals with NF1.

BMI

The mean BMIs in this study cohort were 22.5 ± 3.93 kg/m² for men, and 21.5 ± 2.81 kg/m² for women, whereas the mean reference BMIs were 23.6 ± 3.3 kg/m² and 22.3 ± 3.6 kg/m², respectively. The prevalence of obesity was significantly smaller in men with NF1 than in men from the NFD ($p=0.012$). However, the prevalence of obesity, though trending toward being lower in

the former group, did not differ significantly between women with NF1 and women from the NFD ($p=0.288$) (Table. 2, 3)

Discussion

Although there have been previous reports of an association between NF1 and height⁽³⁾⁸⁾⁹⁾, there is no consensus about a relationship between adults with NF1 and BMI. Some researchers have stated that individuals with extremely large plexiform neurofibroma tend to weight

more¹⁰⁾¹¹⁾. However, it has also been reported that the body weight of individuals with NF1 is lower than that of control subjects, although this difference was not significant in that study¹²⁾.

In a previous investigation, we found that individuals with NF1 of both sexes, especially men, had lower BMIs than controls⁴⁾. However, we did not ascertain the prevalence of obesity in that study. In the present study, we compared the prevalence of obesity in individuals with NF1 with that in a control group drawn from the NFD and found that it was lower in the men with NF1. This result was consistent with the tendency toward lower BMIs that we identified in individuals with NF1 in our previous single institution study⁴⁾. For female patients with NF1, the prevalence of obesity seemed lower in the 20s to the 60s age group; however, these differences were not statistically significant.

There are several interesting reports concerning BMI in individuals with NF1. One study stated that they have a tendency toward less adequate nutrition intake than a control group¹³⁾. Another study suggested that they have a specific metabolism in the patients with NF1¹⁴⁾. Because the pathoetiology are currently unclear, we plan to address these aspects in another study.

This study has several limitations. First, because the number cohort was relatively small, there were insufficient participants in each group to compare their data with those of the age-group categories in the NFD. We therefore used the overall data for individuals with NF1. Second, we selected the NFD as a source of control data because of its large size. However, these data were of limited usefulness for the statistical analysis because they do not include details of individuals. Third, because we studied only Japanese subjects, we cannot exclude the possibility that ethnicity and life styles affects the studied variables. Forth, the inferior socioeconomic status stemming from the physical inferiority of individuals with NF1 in their adolescence may affect their subsequent BMIs.

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Disclosure Statement

The authors have no conflicts of interest to declare in relation to this article.

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神経線維腫症 1 型患者の体形についての検討

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神経線維腫症 1 型（以下 NF1）患者は、一部を除き低身長であることが知られる。しかしながら、体重（body mass index：以下 BMI）については現在までほとんど検討されていない。一方で、NF1 患者では、肥満が risk factor となる 2 型糖尿病、高脂血症などの報告が極めて少ない。そこで以前に我々は、単施設の調査であるが、NF1 患者の体形について調査を行い、BMI が低値である傾向を明らかにした。本研究では 2 施設の成人の NF1 患者を対象に、2011 年～2012 年に行われた厚生労働省の身長、BMI に関するデータを用い、両者を比較することで NF1 患者の体形について更に詳細な検討を行った。手法としては NF1 群、一般国民のデータを痩せ形～普通体形（BMI 25 kg/m^2 以下）と肥満体形（ $25\text{ kg/m}^2 < \text{BMI}$ ）の 2 群に分けて、さらに性別、年齢別に層別化し Mantel-Haenszel test を用いて統計学的に解析した。その結果、NF1 の男性患者は、対照群と比較して肥満体型が少ないことがわかったが、女性に関しては有意差はみられなかった。

キーワード：神経線維腫症 1 型，肥満，BMI，体重