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Original article

Characterization of early onset neurofibromatosis type 2

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Abstract

Neurofibromatosis type 2 (NF2) is an autosomal dominant multiple neoplasia syndrome of the central nervous system. The aim of the present study was to characterize the clinical course of early onset NF2. The specific Japanese disease registry for NF2 in 2010 was analyzed retrospectively. The male:female ratio for the 312 patients identified in the database was 1:1.29. The median age at onset was 25 years (range 2–76 years), with 31.3% of patients exhibiting symptoms at <20 years of age. Patients with an age at onset of <20 years were found to have more frequent spinal cord and extravestibular cranial nerve involvement, cutaneous signs, and convulsions than patients with a later age at onset. Of patients younger than 18 years of age, half did not exhibit hearing problems; in contrast, they frequently had other cranial nerve schwannomas, cranial meningioma, spinal cord tumors, and subcutaneous schwannoma. There were weak but significant positive correlations between symptomatic periods and disability scores in patients with an age of onset of $\geqslant$20 years ($R = 0.225$; $P < 0.01$) and those with an earlier age of onset ($R = 0.306$; $P < 0.01$). Although there were no significant differences in disability scores between genders or patients with an age at onset of <20 versus $\geqslant$20 years, patients with an earlier age at onset had significantly higher disability scores for spinal symptoms than patients with an age at onset of $\geqslant$20 years. Atypical extravestibular presentation is common in early onset NF2, with more prominent spinal symptoms.

Keywords: Neurofibromatosis type 2 (NF2); Childhood; Prognosis

1. Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominantly inherited disease characterized by bilateral vestibular schwannomas and multiple other tumors of the central nervous system. The gene responsible for NF2 is *merlin*, which acts as a tumor suppressor and is located on chromosome 22q12 [1,2]. The incidence of NF2 is one in 33,000 births [3] and the condition has an average age of onset of 18–24 years [4]. The clinical course of NF2 is variable and there are at least two subtypes of NF2, namely 'Gardner', a mild form of the disease, and 'Wishart', an intermediate to severe form [5]. Gardner-type NF2 is characterized by a late onset of symptoms (usually hearing loss), with a few associated brain or spinal tumors. In contrast, Wishart-type NF2 is characterized by an earlier onset, with rapid progression of hearing loss and multiple intracranial and spinal tumors. Although previous studies have reported that the mean age of onset is younger for patients with Wishart-type NF2 [4,5], only a few large-scale studies have investigated the natural course of NF2. Because an understanding of the natural course of the disease is necessary for the proper design and interpretation of clinical trials, in the present study we analyzed data

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from the specific Japanese disease registry for NF2 to characterize early onset NF2.

2. Patients and methods

Data from the disease registry of the Ministry of Health and Welfare of Japan in 2010 were used to determine the clinical characteristics of NF2. Diagnoses of NF2 were made on the basis of the National Institutes of Health NF2 diagnostic criteria [6]. Of the 312 records available in the registry, the age at onset was available for 264 patients only, and these data were used in the analyses in the present study. Patients were divided into two groups according to the age at onset, namely <20 and ⩾20 years. Clinical status was assessed using disability scores, as indicated in Table 1.

Comparisons between the two groups were made using the χ^2 test. Simple regression analysis and Spearman's rank correlation coefficient were used to analyze the relationship between symptomatic periods and disability scores. The Mann–Whitney *U*-test was used to compare disability scores between the two groups. $P < 0.05$ was considered significant.

3. Results

The male:female ratio in the 312 patients identified in the registry was 1:1.29 and the median patient age was 39 years (range 8–81 years). Of the 172 patients for whom information regarding a family history was available, 72 (41.8%) had affected relatives. The median age at onset was 25 years (range 2–76 years), with 20.8% of patients having an age at onset of <16 years. Of all the patients, 31.3% patients experienced symptoms at <20 years of age (Fig. 1A), and the median symptomatic period was 10 years (range 0–65 years; Fig. 1B).

Table 1
Disability scores.

Signs/symptoms	Score
Hearing loss (each side)	
70–100 dB	1
>100 dB	2
Facial nerve palsy (each side)	1
Cerebellar ataxia	1
Decreased facial sensation	1
Dysphagia or dysarthria	2
Double vision	1
Blindness (each side)	2
Hemiplegia	2
Aphasia	2
Memory disturbances	1
Convulsions	1
Spinal symptoms[†]	
Mild/moderate	2
Severe	4

[†] Spinal symptoms were classified as mild/moderate if pain, gait disturbance, weakness of the upper limbs, and urinary/rectal disturbances were present. They were classified as severe when patients were unable to walk and had lost function of the upper limbs on either side.

3.1. Clinical signs and symptoms in patients with age of onset <20 and ⩾20 years of age

As indicated in Table 2, patients with an age of onset <20 years were more likely to have third to sixth cranial nerve schwannoma (52.3% of fifth cranial nerve and 22.1% of others), spinal schwannoma (77.9%), Café-au-lait spots (41.9%), blindness (14.0%), hemiplegia (24.4%), aphasia (5.8%), convulsions (19.8%), and mild to moderate spinal cord symptoms (54.7%).

3.2. Signs and symptoms appearing in pediatric patients

Sixteen patients were less than 19 years of age (range 8–18 years) at the time of the registry. All sixteen patients had bilateral vestibular schwannoma, but only half exhibited an increased hearing threshold (>30 dB). The other signs and symptoms recorded in this group were as follows: other cranial nerve schwannoma ($n = 7$), cranial meningioma ($n = 5$), spinal cord tumor ($n = 11$), subcutaneous schwannoma ($n = 11$), convulsions ($n = 2$), dysphagia ($n = 3$), spinal cord symptoms ($n = 5$), and facial nerve palsy ($n = 2$).

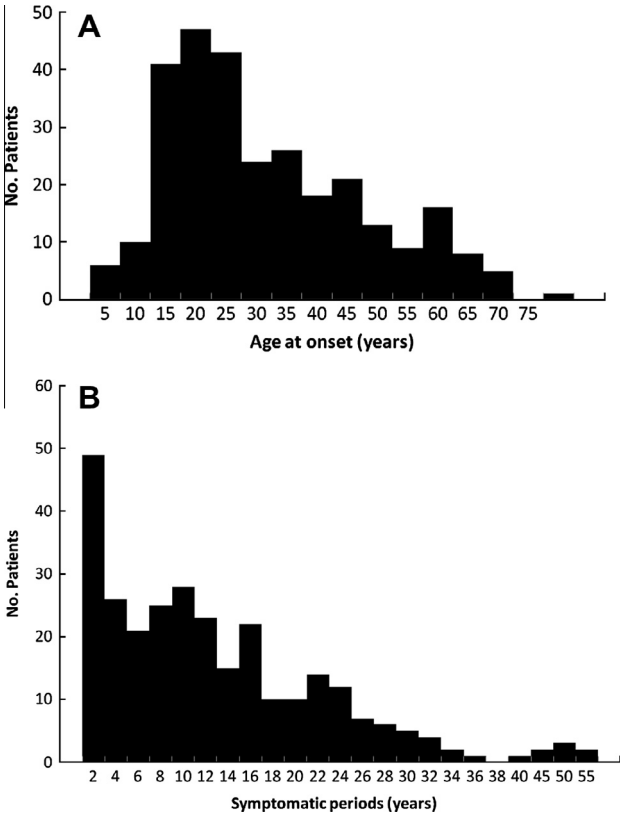

Fig. 1. Distribution of (A) the age at onset and (B) symptomatic periods in patients with neurofibromatosis type 2.