



Prevalence of plexiform neurofibroma in children and adolescents with type I neurofibromatosis

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Abstract

Objective: To assess prevalence of plexiform neurofibroma in children and adolescents with type I neurofibromatosis and its malignant potential.

Methods: A retrospective study was conducted through analysis of the database at Centro Nacional de Neurofibromatose [Brazilian Neurofibromatosis Center], collected from the following reference services between 1996 and 2004: Instituto de Dermatologia Prof. Rubem David Azulay da Santa Casa de Misericórdia do Rio de Janeiro, Instituto de Pediatria e Puericultura Martagão Gesteira da Universidade Federal do Rio de Janeiro and Department of Immunology and Microbiology at Faculdade de Medicina de Teresópolis.

Results: Over that period, 104 patients aged between 1-17 years were admitted with clinical diagnosis of type I neurofibromatosis. Of these, 53 were male and 51 were female, and 28 patients (15 male and 13 female) had plexiform neurofibroma (26.9%). Division by age group resulted in 21.42% (six) between 1-5 years; 35.71% (10) between 6-12 years and 42.85% (12) between 13-17 years. Of the 104 patients, two developed a malignant peripheral nerve sheath tumor (1.92%).

Conclusions: Plexiform neurofibromas are relatively common manifestations in patients with type I neurofibromatosis and may be a cause of significant increase in morbidity and mortality among patients. In this study, we conclude that frequency of plexiform neurofibroma and its malignant potential in the population studied is in agreement with data from the international literature.

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Introduction

Type I neurofibromatosis (NF1) is a genetic, multisystemic disorder that has major cutaneous manifestations, such as cafe-au-lait spots, ephelides and neurofibromas.^{1,2} NF1 is considered the most common "new" spontaneous, dominant, genetic mutation in human beings, with complete penetrance, despite having variable expression.^{1,3,4} Incidence of

NF1 is approximately 1:2.500 newborns, affecting all races and having identical correlation between men and women.¹ It is estimated that there are today around 80,000 cases of NF1 in Brazil, and around 1.5 million cases worldwide.⁵

NF1 was described in 1882 by Friedrich Daniel von Recklinghausen, who suggested the name neurofibroma for neural tissue tumors present in this disease and

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neurofibromatosis for the condition with multiple neurofibromas.⁶

Diagnosis of NF1, whose criteria were established by the National Institutes of Health (NIH) in 1987 and updated in 1997 (Table 1), depend on a careful clinical examination of patients, on their parents and siblings and on a detailed family history, including clinical information and sometimes complementary examinations.^{7,8}

NIH criteria may be insufficient for NF1 diagnosis in children who represent the only case in the family and only show cafe-au-lait spots, without other manifestations. In this case, annual follow-up of suspected case is recommended, and fluorescent *in situ* hybridization (FISH) or the technique of direct analysis of DNA mutation can be used to clarify possible diagnostic doubts or simply to help establish an earlier diagnosis.⁹ On the contrary, those who inherit the disease from one of the parents can usually be identified during the first year of life, because diagnosis only requires one additional characteristic, besides positive family history.⁷

Plexiform neurofibroma (PN), also called plexiform neuroma, pachydermatocele or neurofibromatous elephantiasis, is classified as a benign peripheral nerve sheath tumor that surrounds multiple nervous fascicles.^{5,10} It is a nonmetastatic, highly vascularized, locally invasive tumor that has slow growth.⁵ PN are one of the significant complications of NF1, which may occur during childhood and rarely develop after adolescence. PN can originate malignant peripheral nerve sheath tumor (MPNST), which occurs in 2-5% of patients with plexiform neurofibroma.⁵ MPNST, previously described as neurofibrossarcomas or malignant schwannomas, are the main cause of death and the most common neoplasia in this group.⁵

This study aims at assessing prevalence of PN in children and adolescents with NF1, as well as the malignant potential of these neurofibromas.

Table 1 - Diagnostic criteria of type I neurofibromatosis (NIH, 1990)*

Six or more cafe-au-lait spots > 5 mm in prepubertal patients or > 15 mm in postpubertal patients
Two or more neurofibromas of any type or a plexiform neurofibroma
Ephelides in axillary and inguinal regions
Optic glioma
Two or more Lisch nodules
A characteristic bone lesion, such as sphenoid bone dysplasia or thinning of cortex long bones, with or without pseudoarthroses.
Incomplete status, but having a first-degree relative (parent, brother or son) who meets NIH criteria

NIH = National Institutes of Health.

* Two or more criteria are needed for diagnostic confirmation.

Methods

Constant observations of the database at Centro Nacional de Neurofibromatose (CNNF) [Brazilian Neurofibromatosis Center], collected from the following reference services between 1996 and 2004: Instituto de Dermatologia Professor Rubem David Azulay da Santa Casa de Misericórdia do Rio de Janeiro, Instituto de Pediatria e Puericultura Martagão Gesteira da Universidade Federal do Rio de Janeiro and Department of Immunology and Microbiology at Faculdade de Medicina de Teresópolis. Over that period, 104 patients aged between 1-17 years were admitted. Patients admitted to CNNF come from different Brazilian states, and some are from neighboring countries, such as Uruguay, Peru, Bolivia and Mexico. All patients were given care by at least one of the authors, and clinical diagnosis of NF1 was performed according to the criteria proposed by NIH Consensus Conference.

The project was approved by the Research Ethics Committee at UNIFESO.

Results

Of the 104 patients aged less than 17 years, 53 were male and 51 were female, which shows gender equity. Of these, 28 patients (26.9%) – 15 male and 13 female – had PN, and the data were in agreement with some studies reporting a 15% prevalence; however, others indicate prevalence between 16-40% in patients with NF1.¹¹ In another study, Huson et al. found prevalence of PN evident on physical examination in 32% of patients with NF1.¹¹

Division by age group resulted in 21.42% (six) between 1-5 years; 35.71% (10) between 6-12 years and 42.85% (12) between 13-17 years. In our study, two patients (1.92%) progressed with MPNST.

Discussion

Although frequent in patients with NF1, PN are not a pathognomonic finding of this syndrome.¹² PN are a major cause of clinical complications in NF1 and develop especially in childhood and adolescence. Their most common location is trunk (43%), followed by head and neck (42%) and limbs (15%).¹³ PN have a much variable natural history, since some lesions can remain quiescent for a long time, whereas others can grow aggressively, especially during childhood and adolescence. PN require clinical follow-up,^{5,10} which should be performed annually through clinical and imaging examinations, such as X-ray, computed tomography (CT) and magnetic resonance (MR), this latter being considered as the gold standard. MR should be used not only to locate PN, but also to measure it, providing useful data for patient follow-up.⁵

During follow-up, one should be alert to occurrence of growth or pain in plexiform neurofibromas, which suggests malignant transformation. In these cases, tumor biopsy is indicated.^{1,5,9} Another laboratory tool available for detection

of MPNST is positron-emission tomography (PET) with glucose analog F-fluorodeoxyglucose (FDG). It is a technique that allows visualization and quantification of glucose metabolism in cells and reflects increased metabolism of malignant tumors.⁵ Risk of MPNST development has been estimated between 2-5%,^{1,5} which are extremely aggressive in these cases with reserved prognosis (5-year survival in 34-52%).^{1,5} Other less frequent neoplastic processes include optic glioma, astrocytoma, pheochromocytoma, rhabdomyosarcoma and juvenile chronic myeloid leukemia.⁵ In these cases, treatment should be the same as that performed in children with neoplasia and without NF1.¹⁴

PN can be surgically treated, despite results being often unsatisfactory, since they are closely involved with nerves and due to their tendency of recurrence.¹ Prognostic factors for recurrence are being less than 10 years in initial surgery, presence of initial tumor after surgery and tumor site (head and neck).⁵

Friedrich et al. suggest that early surgical interventions in small-sized PN in children can be advantageous, especially in the strategy to prevent their progression.¹⁵ Therefore, early diagnosis of a possible malignant transformation followed by surgical resection can positively change prognosis.

PN can be symptomatic at birth or become symptomatic through time. Early occurrence supports the idea that PN are congenital lesions, although there may be patients that develop plexiform neurofibromas after 20 years of age.⁵

PN are relatively common manifestations in patients with NF1 and may be a cause of significant increase in morbidity and mortality among patients.⁵

We conclude that frequency of PN in our population is in agreement with data from the international literature.¹³

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