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Descriptive Analysis of Tibial Pseudarthrosis in Patients With Neurofibromatosis 1

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Five percent of individuals with neurofibromatosis type 1 (NF1) present with congenital long bone pseudarthrosis (PA). In large series, 50–80% of patients with congenital long bone PA also have NF1. Very little information exists on the natural history and pathogenesis of PA in NF1. This report is a descriptive analysis of a large series of patients with NF1 and tibial bowing or PA. Study A is a case-control study using the National Neurofibromatosis Foundation International Database (NNFFID). Eighty-five patients with PA were compared to a control group from the same database. There was a statistically significant male predominance of NF1 cases with PA (54 males to 31 females), compared to controls (85 males to 87 females) ($\chi^2 = 4.0$, $P = 0.046$, using a two-tailed test with Yates' correction). There was no significant difference in the clinical presentation of NF1 manifestations in NF1 patients with PA than in NF1 patients without PA. Of the affected individuals with PA, there were 24 de novo cases and 21 familial cases (9 through maternal and 12 through paternal inheritance). Questions that could not be answered by Study A were addressed by a partially overlapping case-series report, Study B, in which data on 75 cases ascertained through questionnaires completed by NF center directors were collected. From Study B we determined that half of the patients who had a fracture sustained it before age 2, and approximately 16% of the pseudarthrosis patients had an amputation. Our data indicate a male predominance and no parent-of-origin effect. Male gender may be a susceptibility factor for pseudarthrosis in NF1. Am. J. Med. Genet. 84:413–419, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: neurofibromatosis type 1; pseudarthrosis; tibial bowing; bone dysplasia

INTRODUCTION

Neurofibromatosis type 1 (NF1) is one of the most common genetic disorders of childhood. Among the many associated manifestations of NF1 is the orthopedic complication of long bone pseudarthrosis, usually tibial pseudarthrosis. Ducroquet [1937] first observed that tibial pseudarthrosis is related to NF1. Approximately 5% of patients with NF1, from NF clinics that reported to an international database, have this osseous dysplasia [Friedman and Birch, 1997] and about 50–80% of all reported cases of pseudarthrosis have NF1 [Gilbert and Brockman, 1995; Morrissy et al., 1981; Sofield, 1971]. The literature indicates that NF1 patients with this condition initially present with an-

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terolateral bowing of the long bone [Crawford and Bagamery, 1986; Rudicel, 1987]. Therefore, this type of bowing can be easily distinguished from the mild lateral bowing commonly present in the pediatric population. While the term congenital is usually applied, most patients with or without NF1 present with bowing later than birth, usually in the first year of life. Very little information exists on the natural history and pathogenesis of NF1-related pseudarthrosis, a biologically intriguing and medically challenging condition.

The biologic basis of long bone bowing and pseudarthrosis in NF1 is not known. The bony defects are primary dysplasias and presumably not secondary responses to neurofibromas. While most of the medical manifestations of NF1 involve cells derived from the neural crest, there is no easy explanation for the mesodermally derived osseous defect in NF1.

Our understanding of the natural history of NF1 patients with long bone dysplasia and pseudarthrosis is limited. Such information, if it were available, would be helpful for the management and counseling of these patients. There is no detailed large series study on the natural history of pseudarthrosis in NF1 patients. Some of the questions regarding the biology and natural history of PA in NF1 can be addressed using the National Neurofibromatosis Foundation International Database (NNFFID) [Friedman et al., 1993] and a network of clinic directors. Three specific questions are posed: 1) Are the demographics, clinical manifestations, and developmental history of patients with NF1 different in patients with and without pseudarthrosis? 2) Is there an affected parent-of-origin effect? 3) What is the natural history of tibial bowing and PA in NF1 (i.e., age of onset, age at fracture, number of operations, and rate of amputation)?

METHODS

Information on patients with NF1 is available through the NNFFID. Contributors to the database contribute standard information regarding their NF patients. These data were reviewed and evaluated. In addition, we investigated several natural history questions that are not addressed by the database. A questionnaire was designed to collect information on the natural history of NF1 patients with long bone dysplasia. Thus, this investigation includes two different methods for ascertainment of data. The two components of the study are designated Study A (using the NNFFID) and Study B (using a questionnaire sent to NF clinic directors).

Patient Selection

Study A, the database component, is a case-control study using the NNFFID [Friedman et al., 1993]. This database is a system for collecting comprehensive information on the clinical manifestations of NF. The database currently contains detailed clinical information on individuals contributed by 25 clinics throughout the world. Information is collated in a central database. Confidentiality is maintained by identifying patients by a database number. Local clinics can identify individual patients by linking this database number to the patient's name. Cases with osseous dysplasia of the tibia and/or fibula were selected from the database.

Of the 1,479 unrelated individuals with NF1 included in the database at the time of this analysis, 85 individuals or 5.7% had long bone bowing or pseudarthrosis. Of these, 52 or 3.5% of reported NF1 patients are described as having pseudarthrosis, with the remainder having long bone bowing.

Study B, the questionnaire component, is a case series intended to obtain information on the natural history of pseudarthrosis that was not available in the database. Patient selection consisted of personally contacting NF centers around the world to obtain more specific data on their patients with tibial bowing and pseudarthrosis. Invitations to contribute information on patients were sent to 21 NF centers, of which 10 responded with completed questionnaires.

For confidentiality, centers were asked to use identification numbers instead of names. Thirty patients identified in this survey had identification numbers identical to those of Study A. Using this approach demographic, genetic, and clinical data on 75 patients from various international NF clinics were collected. The data were evaluated for aspects of disease presentation and the presence or absence of certain variables relating to NF1 and pseudarthrosis.

Diagnosis Criteria

Cases with long bone dysplasia who did not meet the NIH criteria for NF1 [Stumpf et al., 1988], were excluded. NIH criteria for the diagnosis of NF1 include at least two of the following findings: six or more café-au-lait spots greater than 5 mm in diameter in prepubertal subjects and greater than 15 mm in postpubertal subjects, two or more neurofibromas or one plexiform neurofibroma, intertriginous freckling, distinctive bone lesions (sphenoid wing dysplasia or pseudarthrosis), two or more Lisch nodules, an optic glioma, or a first-degree relative diagnosed with NF1.

One problem encountered was the difficulty of defining pseudarthrosis and the wide spectrum of associated osseous abnormalities. The classic presentation is tibial bowing (Fig. 1) leading to fracture that results in non-union. However, the spectrum of severity includes simple anterolateral bowing with cortical thickening, hairline fractures, fracture with and without healing after varying times, fibular involvement, amputations, bone grafts, and surgeries before fracture. Various classifications of pseudarthrosis have been published, including Boyd's classification and the more recent classification system by Crawford. None has been widely adopted [Andersen, 1973, 1976a, 1976b; Bassett et al., 1980; Boyd and Sage, 1958; Crawford, 1986; Masserman et al., 1974; McFarland, 1951; Morrissy, 1981; Rathgeb et al., 1974; Sofield, 1971]. The clinician at each referring center determined if cases had any of the above mentioned forms of osseous dysplasia of the tibia and/or fibula. Such cases were included in both Studies A and B.

For this study, two groups were delineated: Group 1 and Group 2. Cases with only simple anterolateral bowing of the tibia or fibula were placed in Group 1.

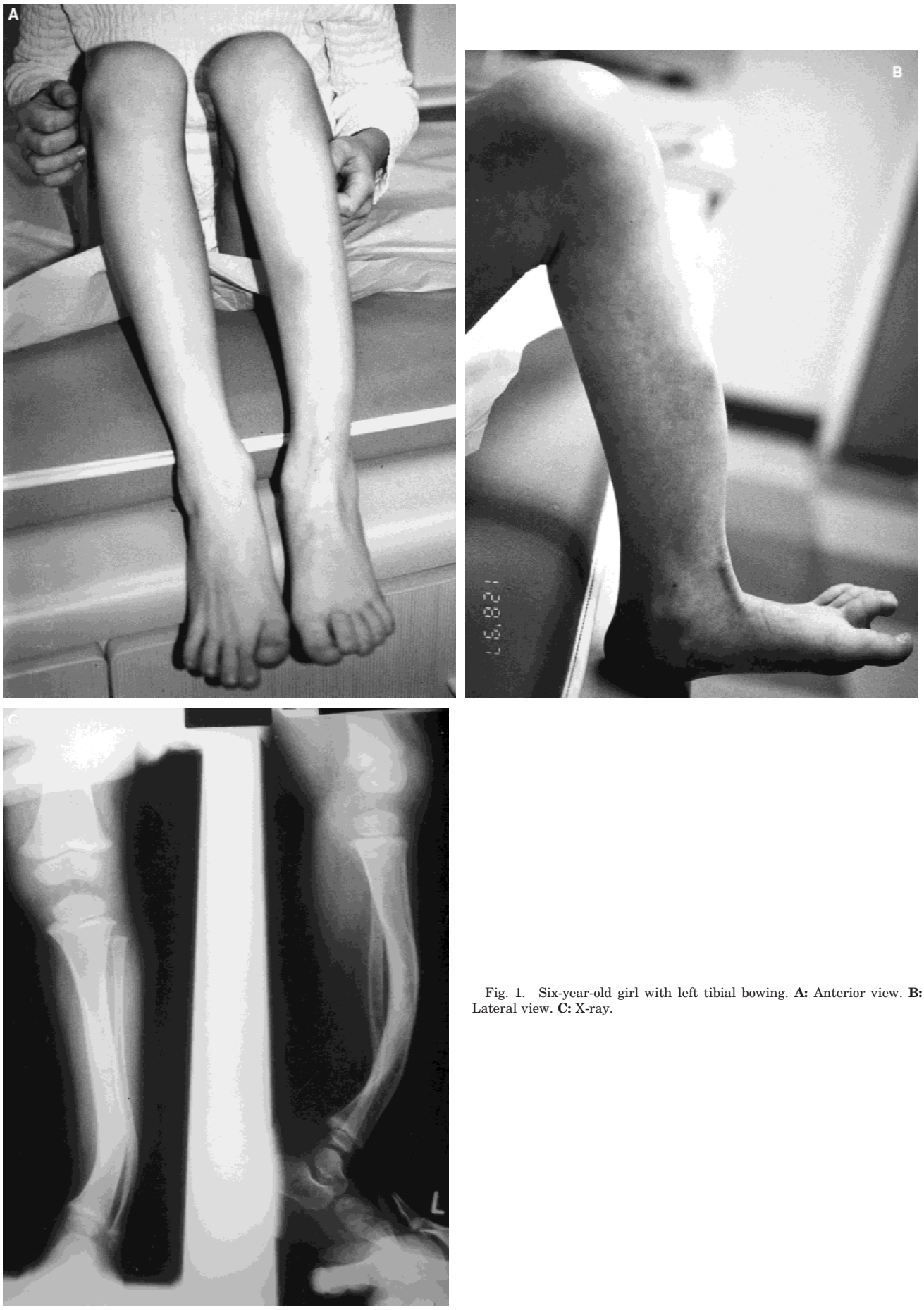

Fig. 1. Six-year-old girl with left tibial bowing. **A:** Anterior view. **B:** Lateral view. **C:** X-ray.

Cases with complications of fracture, pseudarthrosis, surgery, and/or amputation secondary to the bowing were placed in Group 2.

Selection of Control Individuals

Control subjects were only used in Study A. Initially each of the affected individuals from the database was age- and clinic-matched to two control subjects (NF1 patients without bowing/pseudarthrosis). Control subjects were age-matched to pseudarthrosis-affected individuals within 1 year in all cases under 40 years of age. Cases over 40 years of age were matched to within 4 years of control subjects (the oldest individual was 54 years old). Evaluation of the affected patients and their selected matched control subjects identified a few individuals who did not fulfill the NF1 diagnostic criteria. They were eliminated from the study leaving 172 NF1 controls and 85 NF1 individuals affected with pseudarthrosis.

Statistical Analysis

In Study A, NF1 patients with pseudarthrosis were compared to matched NF1 control subjects for gender, mode of inheritance, and associated manifestations. Analysis included Fisher exact tests, Mann-Whitney U tests, and chi-squared calculations using SYSTAT version 5.0.

RESULTS

Study A

Study A analyzed the frequency of 40 different manifestations of NF1 in the control and pseudarthrosis-affected groups. Some include café-au-lait macules, Lisch nodules, discrete neurofibromas, plexiform neurofibromas, optic gliomas, seizures, hydrocephalus, developmental abnormalities, heart disease, endocrine abnormalities, Noonan phenotype, other minor anomalies, and asymmetry unrelated to pseudarthrosis or bowing. Table I summarizes results from a representative sample of some of the more common findings in NF1. When the patients with long bone dysplasia were compared to the NF1 control subjects there was no statistically significant difference in the frequency of any of the 40 features. Likewise, there was no significant difference between trait frequency in Group 1 and Group 2.

Information on whether or not the patient had an affected parent was available in the database on only 53% of cases and 34% of control subjects. Information on maternal versus paternal inheritance was available on all of these familial cases. In Study A, nine people inherited NF1 from their mothers and 12 from their fathers. In the control group, the numbers were 21 and 16 respectively. In this small group there is no statistically significant parent-of-origin effect ($P = 0.41$; Table II).

Most patients were Caucasian in both the control group (82.2%) and the pseudarthrosis-affected group (81.2%); 0.6% of controls and 5.9% of pseudarthrosis-affected cases were of African descent and 6.9% of controls and 9.4% of pseudarthrosis-affected cases were of Asian descent.

There was an excess of affected males (54 males to 31 females). This differed significantly from the control group, in which there were 85 males and 87 females ($\chi^2 = 4.0$, $P = 0.046$, using a two-tailed test with Yates' correction; Fig. 2). Almost the entire difference comes from the male predominance in Group 2 (36 males to 16 females). Group 1 had 18 affected males and 15 affected females.

Study B

The natural history of NF1 patients with long bone dysplasia was addressed through data from a questionnaire. Often the health care provider either did not completely fill out the questionnaire or indicated that the information was not available. For this reason, denominators are not consistent in all categories. Study B included 75 patients. The average age of cases was 11.9 years (N = 72; range = 0.5–54 years, median = 8.6 years). In 53 of the 75 cases the age of bone deformity recognition by a health care provider was established. The mean age of presentation of the osseous problem was 15.3 months (N = 18; range = 0–108 months, median = 8.5 months) in Group 1 and 25.7 months (N = 35; range = 0–228 months, median = 8 months) in Group 2. The combined age of presentation of all cases was 22.2 months (N = 53; range = 0–228 months, median = 8 months). In 36 of 53 patients, in whom the age of recognition of the bone deformity was recognized, the abnormality was identified before one year of age (Table III).

Females averaged fewer operations than males (Table IV). One patient underwent 13 operations while others achieved union with simple casting. In Group 2,

TABLE I. Study A: Common Clinical Manifestations of NF1 With and Without Pseudarthrosis (From NNFFID in Vancouver, BC)

Clinical manifestation	Prevalence in Group 1 (N)	Prevalence in Group 2 (N)	Prevalence in control group (N)	*P*-Value[a]
≥6 Café-au-lait macules	0.79 (33)	0.88 (52)	0.88 (172)	$P = 0.35$
Intertriginous freckling	0.48 (33)	0.37 (52)	0.29 (172)	$P = 0.08$
Scoliosis	0.18 (33)	0.33 (52)	0.23 (172)	$P = 0.23$
Dysplastic vertebrae	0.09 (33)	0.02 (52)	0.08 (172)	$P = 0.27$
Dysplastic sphenoid wing	0.00 (11)	0.00 (11)	0.07 (45)	$P = 0.55$
Plexiform neurofibroma	0.21 (33)	0.19 (52)	0.24 (172)	$P = 0.71$
Lisch nodules	0.21 (33)	0.35 (52)	0.36 (172)	$P = 0.25$
Glioma	0.03 (33)	0.06 (52)	0.12 (172)	$P = 0.18$
Seizures	0.00 (33)	0.06 (52)	0.05 (172)	$P = 0.40$

[a]2 × 3 Chi-squared analysis looking at differences in distribution across three categories: bowing, complicated, and controls.

TABLE II. Parent of Origin (Study A: Database Component)*

	Familial		
	Maternal	Paternal	De novo
NF1 control (N = 59)	21	6	22
Total affected (N = 45)	9	12	24
Group 1 (N = 18)	2	7	9
Group 2 (N = 27)	7	5	15

*No information available on 153 individuals (cases plus control subjects). Familial vs. de novo: (Group 1/Group 2): Fisher exact test (two-tailed) $P = 0.77$; (Control/total affected): Fisher exact test (two-tailed) $P = 0.12$. Maternal vs. Paternal: Fisher exact test $P = 0.41$.

TABLE III. Age Bony Deformity Recognized (Study B: Questionnaire Component)

	No. of cases	
Age (years)	Group 1	Group 2
At birth	3	7
0–1	10	15
1–2	3	4
2–3	1	3
>3	1	6
Total (N = 532)	18	35

16% (8/50) had an amputation. The average number of operations in Group 2 was 2.9 (range 0–13).

The average age of fracture in pseudarthrosis-affected cases was 4.61 years (N = 32) with a range of 0–28 years with females fracturing an average of 1.06 years later than males (Table IV). In Group 2, 53% fractured before the age of 2 years (Table V).

It was noted that 43% of cases had fibular dysplasia. Two patients had fibular dysplasia without tibial dysplasia. The spectrum of fibular dysplasia ranged from simple bowing to frank pseudarthrosis. Three patients had forearm deformities. They consisted of left ulnar pseudarthrosis with left radial bowing, isolated right radial pseudarthrosis, and right radial and ulnar bowing without pseudarthrosis. The remainder of cases had unilateral tibial and/or fibular deformities. Data analysis was restricted to long bone dysplasia of the tibia and fibula excluding ulnar and radius pseudarthroses.

Laterality of the affected bone was evenly distributed with 35 patients presenting on the left side and 34 patients presenting on the right side. All subjects presented unilaterally. Only three patients out of 71 had a neurofibroma near the site of the deformity.

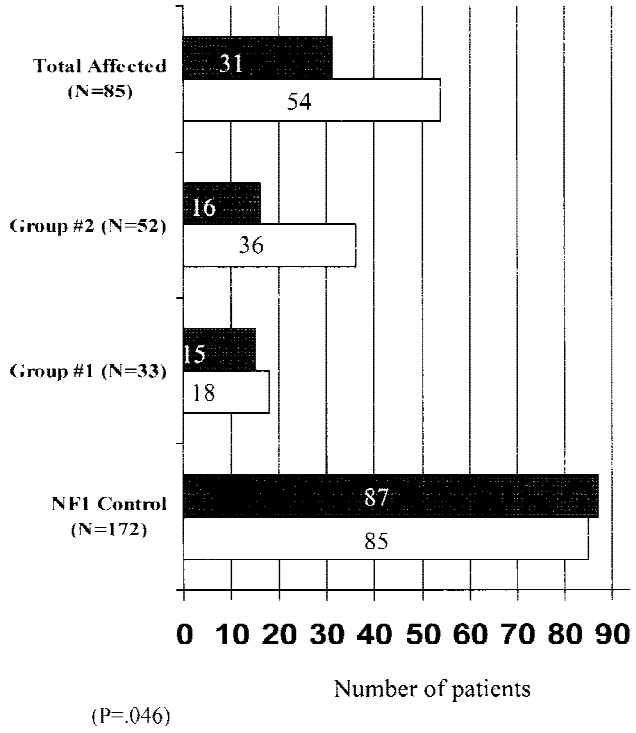

Fig. 2. Study A (database component) gender distribution (females, solid bars; males, open bars).

DISCUSSION

It is known that patients with NF1 exhibit a wide variety of manifestations. This study examined a number of variables with respect to pseudarthrosis (Table I). In Study A, there was no significant difference in the frequency of other clinical manifestations between pseudarthrosis-affected individuals and the control NF1 group. Morrissy et al. [1981] reported an increased observation of gliomas of the central nervous system among individuals with NF1 and pseudarthrosis. This study did not find an association of optic gliomas or neoplasms of any kind among patients.

We identified certain aspects of the natural history of pseudarthrosis in NF1, which may help practitioners more appropriately advise their patients on the potential complications. There are controversies concerning treatment of bowing/pseudarthrosis, and various investigators report different approaches to therapy. Some report one surgical procedure to be better than other procedures [Boyd and Sage, 1958; Charnley, 1956; Farmer, 1952; McFarland, 1951; Moore, 1949; Morrissy et al., 1981; Paterson et al., 1980; Wilson, 1941]. Some claim that amputation should not be done [Sofield, 1971; Van Nes, 1966] while others recommend amputation [Aitken, 1959; Boyd and Fox, 1948; Rathgeb et al., 1974; Rudicel, 1987]. Some patients seek amputation for therapy [Andersen, 1976b; Morrissy, 1981; Van Nes, 1966] due to the many complications that leave them incapacitated and disabled. Orthopedic surgeons remain frustrated on how best to handle this difficult condition. There has been much discussion on the various surgical procedures available to the orthopedist for management of long bone pseudarthrosis. With respect to bowing, the prevention of a fracture seems paramount. Some patients elected to have the bowed bone operated on before a fracture occurs, making it difficult to readily assess when or if a fracture would occur. Several surgical procedures including bone grafting, osteotomy, and vascularized autogenous grafts have been performed. Chronic bracing with a knee-ankle-foot orthosis (KAFO) is advocated by some orthopedists as a modality to prevent bowing from progressing to frank pseudarthrosis [Crawford, 1986]. At the present time there is no standardized protocol or

TABLE IV. Gender Observation of Fracture Age and Operations (Study B: Questionnaire Component)*

	Male	Female	Total	
Average age at fracture (years)	4.4	5.4	4.6	(Range = 0–28 yrs)
	(N = 24)	(N = 8)	(N = 32)	
	(Median = 2.0)	(Median = 2.5)	(Median = 2.0)	
Average no. of operations	3.3	1.8	2.9	(Range = 0–13)
	(N = 28)	(N = 10)	(N = 38)	
	(Median = 2.5)	(Median = 2.0)	(Median = 2.0)	

*Mann-Whitney U test: age at fracture: $P = 0.67$; number of operations: $P = 0.15$.

controlled clinical trial that has rigorously shown to be of value.

This study showed that half of the cases that fractured did so before the age of 2 years. However, the age was highly variable, ranging from prenatal to 28 years. Fifty-nine percent of Group 1 (patients with simple anterolateral bowing) were over the age of 4.61 years (our calculated average age of first fracture) with the oldest being 15.3 years old. This leaves nine patients with bowing who had not reached the average age at which fractures occurred.

It is commonly thought that NF1 patients with tibial bowing will inevitably sustain a fracture. Since this is a retrospective cross-sectional investigation, we were unable to determine from our data if these patients will fracture, but our data suggests that there are patients with significant bowing who may never fracture.

Fibular dysplasia often occurred with tibial dysplasia. In Study B, 43% of cases had fibular dysplasia. Two patients had fibular dysplasia without tibial dysplasia. Long bone dysplasia in NF1 is commonly referred to as tibial pseudarthrosis, but the fibula is often concurrently involved. Pseudarthroses of other long bones besides the tibia and fibula have been reported in NF1 patients. Other affected bones include the ulna, radius, humerus, femur, and clavicle [Rudicel, 1987]. Only a few isolated cases of these pseudarthroses have been reported.

We observed three patients with forearm deformities. They consisted of a case with left ulnar pseudarthrosis and left radial bowing, a case with right radial pseudarthrosis, and a case with right radial and ulnar bowing. None of these three cases had involvement of the tibia.

All cases presented with unilateral deformities. Laterality of the affected bone was evenly distributed in Study B. This observation suggests that other factors play a role in the development of this skeletal dysplasia, and that the NF1 mutant allele is not sufficient to cause the osseous dysplasia. These other factors could likely be somatic mutations of modifier genes.

The pathophysiology of pseudarthrosis is unknown. It has been postulated that a neurofibroma at the site of the deformity actually causes the deformity. Green and Rudo [1943] reported a histological specimen with a neurofibroma growing in the pseudarthrosis segment. Another study by Aegeter [1950] claimed that the tissue surrounding the site of the pseudarthrosis was the cause of the bony deformity. Brooks and Lehman [1924] proposed that the neurofibromas may arise from the nerves of the periosteum, erode into the bone, and then become covered by a shell of bone. However, Crawford and Bagamery [1986] stated that few surgical specimens have neurofibromatous tissue at the pseudarthrosis site and Moore [1941] found no report of actual invasion of the shaft by the neurofibroma. Our study confirms the latter observations. Only three patients of 71 had a neurofibroma near the site of the deformity. These may be incidental or part of the intrinsic dysplasia. Our data do not support the notion of a neurofibroma causing this osseous dysplasia.

There has been some speculation about a parent-of-origin effect. Miller and Hall [1978] noted an increased occurrence of serious complications such as pseudarthrosis when NF1 had been inherited from the mother as opposed to the father. These serious complications included pseudarthrosis. From their study it was postulated that there may be a parent-of-origin effect in the development of pseudarthrosis in patients with NF1. Study A did not suggest a maternal influence, but the numbers are small. There may be a maternal influence in other severe manifestations of NF1; however, these data do not support a parent-of-origin effect in the occurrence of pseudarthrosis (Table II).

Regarding racial distribution, it has been noted that few black Americans have NF1-associated optic nerve gliomas [Saal et al., 1995]. Therefore, there may be a correlation between ethnic origin and various NF1 manifestations. Due to the small number of non-Caucasians (17.8% of controls and 18.8% of affected individuals were non-Caucasian or "unknown"), no statistically significant conclusions could be made regarding racial distribution in this study. It is important to evaluate a larger number of patients of African and Asian descent to determine if the prevalence of pseudarthrosis in NF1 individuals from different ethnic backgrounds varies.

The most striking and singular observation of this study was the gender difference. In Study A, the control group showed an equal distribution of males and

TABLE V. Age at Fracture in Group 2 (Study B: Questionnaire Component)*

Age (years)	No. of cases
At birth	2
0–1	9
1–2	6
2–3	4
3–6	3
6–13	5
>13	3

*(N = 32); range, 0–28 years; mean, 4.6 years.

females, which is consistent with the literature on NF1 patients. In contrast, we found a significant excess of males with long bone dysplasia, especially in Group 2. The natural history study showed that male patients in Group 2 averaged more surgeries with an earlier age of fracture than females (Table IV).

This series is the largest investigation of patients with pseudarthrosis and NF1 reported to date. Previous studies do not provide information on gender, or include fewer patients. Although Gilbert and Brockman [1995] reported that males had a longer healing time than females, and Moore [1957] reported a slight male predominance in pseudarthrosis, neither study differentiated pseudarthrosis patients with NF1 and those without. We found no evidence in the literature to refute our findings.

The observation of a male predominance in the complicated group suggests that male gender could be a susceptibility factor for pseudarthrosis in patients with tibial bowing and NF1. This observation is also noted in NF1-associated leukemias. An increased proportion of males has also been observed among NF1 patients with myelogenous dysplasia [Shannon et al., 1992]. Conceivably, the mesodermal derivation of the tissue of origin of bone marrow cells and skeleton plays a role in the male susceptibility.

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REFERENCES

Aegeter E. 1950. The possible relationship of neurofibromatosis, congenital pseudarthrosis and fibrous dysplasia. J Bone Joint Surg Am 32:618–626.

Aitken GT. 1959. Amputation as a treatment for certain lower extremity congenital abnormalities. J Bone Joint Surg Am 41:1267.

Andersen KS. 1973. Radiological classification of congenital pseudarthrosis of the tibia. Acta Orthop Scand 44:719–727.

Andersen KS. 1976a. Congenital pseudarthrosis of the tibia and neurofibromatosis. Acta Orthop Scand 47:108–111.

Andersen KS. 1976b. Congenital pseudarthrosis of the leg. J Bone Joint Surg Am 58:657–662.

Bassett CAL, Caulo N, Korte GJ. 1980. Congenital pseudarthrosis of the tibia: treatment with pulsing electromagnetic fields. Clin Orthop 154: 136–149.

Boyd HB, Fox KW. 1948. Congenital pseudarthrosis. J Bone Joint Surg 30:274–283.

Boyd HB, Sage FP. 1958. Congenital pseudarthrosis of the tibia. J Bone Joint Surg Am 40:1245–1270.

Brooks B, Lehman EP. 1924. The bone changes in Recklinghausen's neurofibromatosis. Surg Gynecol Obstet 38:587–595.

Charnley J. 1956. Congenital pseudarthrosis of the tibia treated by the intramedullary nail. J Bone Joint Surg Am 38:283–290.

Crawford AH. 1986. Neurofibromatosis in children. Acta Orthop Scand 57:7–60.

Crawford AH, Bagamery N. 1986. Osseous manifestations of neurofibromatosis in childhood. J Pediatric Orthop 6:72–88.

Ducroquet RL. 1937. A propos des pseudoarthroses et inflexions congénitales du tibia. Mem Acad Chir (Paris) 63:863–868.

Farmer AW. 1952. The use of a composite pedicle graft for pseudarthrosis of the tibia. J Bone Joint Surg Am 34:591–600.

Friedman JM, Birch P. 1997. Type 1 neurofibromatosis: a descriptive analysis of the disease in 1728 patients. Am J Med Genet 70:138–143.

Friedman JM, Birch P, Greene C, NNFF International Database Participants. 1993. National neurofibromatosis foundation international database. Am J Med Genet 45:88–91.

Gilbert A, Brockman R. 1995. Congenital pseudarthrosis of the tibia. Clin Orthop 314:37–44.

Green WT, Rudo N. 1943. Pseudarthrosis and neurofibromatosis. Arch Surg 46:639–651.

Masserman RL, Peterson HA, Bianco AJ. 1974. Congenital pseudarthrosis of the tibia: a review of the literature and 52 cases from the Mayo Clinic. Clin Orthop 99:140–145.

McFarland B. 1951. Pseudarthrosis of the tibia in childhood. J Bone Joint Surg Br 33:36–46.

Miller M, Hall JG. 1978. Possible maternal effect on severity of neurofibromatosis. Lancet 2:1071–1073.

Moore BH. 1941. Some orthopaedic relationships of neurofibromatosis. J Bone Joint Surg 43:109–140.

Moore JR. 1949. Delayed autogenous bone graft in the treatment of congenital pseudarthrosis. J Bone Joint Surg Am 31:23–29.

Moore JR. 1957. Congenital pseudarthrosis of the tibia. Instr Course Lect 14:222–237.

Morrissy RT, Riseborough EJ, Hall JE. 1981. Congenital pseudarthrosis of the tibia. J Bone Joint Surg Br 63:367–375.

Paterson DC, Lewis GN, Cass CA. 1980. Treatment of congenital pseudarthrosis of the tibia with direct current stimulation. Clin Orthop 148: 129–135.

Rathgeb JM, Ramsey PL, Cowell HR. 1974. Congenital kyphoscoliosis of the tibia. Clin Orthop 103:178–190.

Rudicel S. 1987. The orthopaedic manifestations of neurofibromatosis. Conn Med 51:221–222.

Saal HM, Schorry EK, Lovell AM, Ball W, Egelhoff J, Koch B, Samango-Sprouse CA, Rosenbaum KN, Stern HJ, Tifft CJ, Vezina LG. 1995. Racial differences in the prevalence of optic gliomas in neurofibromatosis. Am J Med Genet Suppl 57:A54.

Shannon KM, Watterson J, Johnson P, O'Connell P, Shah N, Steinherz P, Kan YW, Priest JR. 1992. Monosomy 7 myeloproliferative disease in children with neurofibromatosis, type 1: epidemiology and molecular analysis. Blood 79:1311–1318.

Sofield HA. 1971. Congenital pseudarthrosis of the tibia. Clin Orthop 76: 33–42.

Stumpf DA, Alksne JF, Annegers JF, Brown SS, Conneally PM, Housman D, Leppert MF, Miller JP, Moss ML, Pileggi AJ, Rapin I, Strohman RC, Swanson LW, Zimmerman A. 1988. Neurofibromatosis conference statement national institutes of health consensus development conference. Arch Neurol 45:575–578.

Van Nes CP. 1966. Congenital pseudarthrosis of the leg. J Bone Joint Surg Am 48:1467–1483.

Wilson PD. 1941. A simple method of two-stage transplantation of the fibula for use in cases of complicated and congenital pseudarthrosis of the tibia. J Bone Joint Surg 23:639–675.