Fracture Healing in Pediatric Patients with Neurofibromatosis Type 1: A Case Series and Review of the Literature

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Introduction

Neurofibromatosis type 1 (NF-1) is an autosomal dominant genetic disorder that affects 1 in 3,000 persons worldwide.[1] Approximately 50% of patients with NF-1 will demonstrate one or more musculoskeletal conditions such as congenital pseudarthrosis of the tibia (CPT), scoliosis, or plexiform neurofibromata during childhood.[2] Patients with NF-1 frequently demonstrate a generalized abnormality of bone metabolism and management of the musculoskeletal manifestations of NF-1 is often challenging.[1,3]

The treatment of CPT is complicated by a high rate of re-fracture, malunion, and nonunion (up to 65%). Dystrophic and nondystrophic forms of scoliosis are common in patients with NF-1 and are associated with an increased risk of pseudarthrosis following instrumented spinal fusion when compared to patients with idiopathic scoliosis. Although significant attention has been paid to treatment of CPT and spinal deformity in NF-1, fracture healing in patients with NF-1 is relatively poorly understood. While it is accepted that patients with NF-1 have a higher incidence of metabolic bone disease, the significance of this with respect to fracture incidence and healing is controversial.[3]

The purpose of this study was to examine fracture healing in pediatric patients with NF-1 treated at our tertiary care center. We hypothesized that patients with NF-1 demonstrate normal healing in response to traumatic fractures in normal, non-dysplastic long bones.

Methods

Following internal review board (IRB) approval, a retrospective review was performed of all subjects 20 years or younger who presented to an orthopaedic provider between 2008 and 2016 at our tertiary referral center with a diagnosis of NF-1 (ICD 10 code Q85.01, ICD9 code 237.71). Charts, billing records, and radiographs were reviewed to identify all cases of long bone fractures within this cohort. For the purposes of this study, we defined long bones as the humerus, radius, ulna, clavicle, femur, tibia, and fibula. Cases were included if they had clinical follow-up until evidence of radiographic healing. Subject with a long bone dysplasia (defined as dysplastic tibial bowing with or without pseudarthrosis) were included as potential subjects. Fractures in these subjects were included if the fracture bone appeared radiologically normal. Management (operative and non-operative) of fractures in dysplastic bone and/or pseudarthroses was excluded.

For each fracture, we recorded patient demographics (age, sex), fracture characteristics (location, pattern, mechanism of injury, open vs. closed), fracture treatment, and outcomes (including time to radiographic union, time to return to full activities, and presence of delayed union). Radiographic union was defined as visible fracture callus on at least three of four cortices of all involved bones as assessed on biplanar imaging. Delayed union was defined as union occurring at more than 12 weeks after initial treatment. Descriptive statistics were calculated utilizing SPSS Statistics, version 24.0 (IBM Corp., Armonk, N.Y., USA),

Results

Between 2008 and 2016, 1259 unique pediatric patients with NF-1 were evaluated and treated by an orthopaedic surgeon at our institution. Sixty patients were identified as having fractures based on billing codes.Twenty-four patients were identified as having CPT and were excluded. Seventeen patients were excluded from analysis because they had fractures of non-long bone (e.g. phalangeal fracture, metacarpal fractures, or metatarsal fractures). This study included the remaining 19 fractures (Table 1) which occurred in 18 patients (11 males, 7 females). No patients were lost to follow up. Mean age at the time of fracture was 9 years (1 to 15 y). Mechanisms of injury included ground level fall (13 cases), fall from a height $>$ 3 feet (4 cases), motor vehicle accident (1 case), and non-contact rotational injury (1 case).

Ninety-five percent (18/19) of fractures were closed injuries and were treated non-operatively. In these patients, the mean time to radiographic union was 46 days (range 27-76 days) and the mean time to full activities was 67 days (range 27-97 days). Complete healing occurred in all patients. There were no instances of re-fracture at most recent follow up. One patient presented with a Gustilo and Anderson type 1 open mid-shaft both bone forearm fracture after a fall

Table 1: Fracture patterns and characteristics for patients with NF-1 treated between 2008 and 2016. GLF = ground level fall; FFH = fall from height; MVA = motor vehicle accident.

Sex	Age at Injury (years)	Fracture (bone)	Location within Bone	Mechanism of Injury	Fracture Pattern	Open vs Closed	Time to Union (days)
M	7.5	Radius + Ulna	Distal 1/3	GLF	Transverse	Closed	42
F	9.9	Radius + Ulna	Middle 1/3	GLF	Oblique	Closed	64
M	13.3	Ulna	Distal 1/3	GLF	Transverse	Closed	40
M	15.2	Tibia + Fibula	Proximal 1/3	FFH	Transverse	Closed	61
F	8.1	Radius	Distal 1/3	GLF	Transverse	Closed	30
F	1.3	Tibia	Distal 1/3	GLF	Buckle	Closed	30
M	1.8	Femur	Middle 1/3	GLF	Spiral	Closed	43
F	6.3	Tibia	Proximal Physeal	FFH	Physeal, SH-II	Closed	58
M	12.6	Clavicle	Middle 1/3	GLF	Oblique	Closed	34
M	12.2	Tibia	Distal Physeal	MVA	Physeal, SH-I	Closed	28
F	12.0	Radius + Ulna	Middle 1/3	FFH	Oblique	Closed	76
F	9.4	Radius + Ulna	Middle 1/3	GLF	Oblique	Closed	50
F	9.9	Radius	Distal 1/3	GLF	Torus	Closed	34
M	13.5	Radius + Ulna	Distal 1/3	GLF	Oblique	Closed	43
M	11.3	Tibia	Medial Mall	Rotational	Transverse	Closed	78
M	7.7	Fibula	distal physeal	GLF	Physeal SH-I	Closed	27
M	9.5	Radius + Ulna	distal 1/3	GLF	Oblique	Closed	54
M	1.9	Tibia	Distal 1/3	GLF	Spiral	Closed	39
F	11.0	Radius + Ulna	Middle 1/3	FFH	Oblique	Open (Type 1)	220

from a height. This patient was treated with irrigation and debridement and internal fixation with compression plates. The post op course was complicated by a deep surgical site infection requiring repeat irrigation and debridement and partial hardware removal. This patient had a delayed union, with eventual radiographic healing at 31 weeks.

Discussion

The purpose of this study was to examine fracture healing in pediatric patients with NF-1. In this case series, we found that routine healing of traumatic fractures in non-dysplastic bone was observed in 95% of cases in patients with NF-1. The one fracture that went on to delayed union in this series was an open both-bone forearm fracture which was complicated by deep surgical site infection.

Although a substantial amount of research has been devoted to nature and treatment of osseous manifestations of NF-1, few studies have examined fracture incidence and healing in patients with NF-1.Tucker *et al* performed laboratory analyses of various measures of bone metabolism in 72 adult patients with NF-1 and found that over half had low serum 25-hydroxy-vitamin D levels and a third of the group had elevated levels of serum parathyroid hormone.[3] They found that patients with NF-1 had a comparatively higher frequency of fractures when compared to unaffected siblings or spouses.[3] This study did not examine characteristics of fracture healing in the NF-1 population.

In contrast, George-Abraham *et al* surveyed children at two multidisciplinary NF clinics and found an equivalent prevalence rate of a fracture history compared to age matched controls.[4] They did note that patients with NF-1 tended to have lower rates of physical activity than controls which may have had a protective effect against fracture. Again, this study did not examine characteristics of fracture healing in the NF-1 population. Heerva *et al* examined a cohort of 460 Finnish patients with NF-1 and compared them to a group of 3988 appendectomy patients as age and sex matched controls.[5] They found that patients with NF-1 had a significantly higher risk for fractures (relative risk 3.8, $p < 0.001$). 98% (59/60) of fractures in patients with NF-1 went on to heal with one patient developing a pseudarthrosis of an ulnar fracture.[5] This study did not comment on fracture or injury characteristics nor did it discuss the type of management (operative vs non-operative) employed.

To date, there is only one report of a delayed union in a patient with NF-1. Kaempffe *et al* presented a case report of a pseudarthrosis of the radius after fracture through non-dysplastic bone in a child with NF-1.[6] This fracture ultimately

went on to union following open reduction and internal fixation.[6]The strengths of this paper include a large population of patients with NF-1 and follow up to union in all cases. To our knowledge, this is the first series to examine traumatic fracture healing in patients with NF-1 from an orthopaedic viewpoint.

This study has several limitations. First and foremost, we relied on billing records to identify patients with NF-1 and fractures, which is susceptible to misclassification and information bias. Although patients with NF-1 present to our tertiary multidisciplinary center from a wide geographic area, it is certainly possible that they could seek routine fracture care at outside institutions. As such, it is impossible for us to determine the true incidence of fractures in the NF-1 population based on this data. Additionally, this study is retrospective in nature and as such is subject to the limitations inherent to that study design.

In conclusion, based on this series, fractures of non-dysplastic bone in patients with NF-1 can be expected to heal in routine fashion when treated according to general pediatric orthopaedic trauma principles. We believe that it is important to recognize features of dysplastic bone that may increase the risk of fracture and/or delayed union. Practitioners should remain cognizant of the increased prevalence of metabolic bone disease in this population and should be concurrently evaluating patients for other manifestations of NF-1, such as spinal deformity.

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