Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. ■, no. ■, 1–6, 2017

1094-6950/■:1–6/$36.00
http://dx.doi.org/10.1016/j.jocd.2017.03.004

Quantitative Ultrasound and Tibial Dysplasia in Neurofibromatosis Type 1

David A. Stevenson,[1,2] Heather Hanson,[1] Austin Stevens,[1] John Carey,[1] David Viskochil,[1] Xiaoming Sheng,[1] Karen Wheeler,[1] and Hillarie Slater[1]*

[1]*Department of Pediatrics, University of Utah, Salt Lake City, UT, USA; and* [2]*Department of Pediatrics, Division of Medical Genetics, Stanford University, Stanford, CA, USA*

Abstract

Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder associated with unilateral anterolateral bowing with subsequent fracture and nonunion. In infancy, physiologic bowing of the lower leg can be confused with pathologic tibial dysplasia in NF1. Little is known about the bone physiology of the tibiae prior to fracture or predictors of fracture. The aim of this study was to characterize bone quality of bowed tibiae prior to fracture in NF1 using quantitative ultrasound (QUS). Bone quality was assessed on both tibiae (the non-bowed and bowed tibiae) using QUS to measure speed of sound (SOS) at the midshaft in 23 individuals with NF1. SOS (m/s) was determined and Z-scores generated using cross-sectional reference data of the same sex and age. The mean difference in SOS Z-scores when comparing the bowed tibia vs the individual's contralateral unaffected tibia was statistically significant with lower mean Z-scores in the bowed tibia ($p = 0.001$). Radiographs of all individuals with a clinical diagnosis of anterolateral bowing were reviewed, and in 2 individuals the radiographs showed minimal bowing with absence of characteristic cortical thickening and medullary canal narrowing in NF1-related tibial dysplasia, suggesting physiologic bowing. In both individuals, the Z-scores of the bowed leg were not lower than the unaffected leg supporting the suggestion of physiologic bowing rather than pathologic tibial dysplasia. These data show that dysplastic tibiae in NF1 prior to fracture and nonunion have abnormal bone quality with significant decreases in SOS even though radiographically the tibiae show a thickened cortex. These data also suggest that QUS can help distinguish dysplastic bowing vs physiologic bowing in infancy in NF1. QUS is an effective quantitative outcome measure for trials aimed at improving tibial bowing to prevent fracture, and it is a potential aid in diagnosis and clinical management in NF1.

Key Words: Bone; bone ultrasound; bowing; neurofibromatosis type 1; pseudarthrosis.

Introduction

Neurofibromatosis type 1 (NF1, OMIM#162200) is an autosomal dominant disorder affecting 1 in 3000–4000 individuals *(1)*. It is caused by mutations in *NF1* found on chromosome 17q11.2, which encodes the protein neurofibromin that regulates the Ras-MAPK pathway. Individuals with NF1 have multisystem manifestations (e.g., café au lait macules, neurofibromas, learning disabilities, short stature, malignancies, distinctive osseous lesions), but there is a high degree of clinical variability.

Orthopedic complications affect approximately 38% of individuals with NF1 *(2)*, including tibial dysplasia. Tibial dysplasia typically presents as anterolateral bowing progressing to fracture and nonunion (i.e., pseudarthrosis) and is almost universally unilateral *(3)*. However, the degree of bowing is variable and not all individuals with NF1 and tibial bowing progress to fracture and nonunion (pseud-

Received 12/30/16; Accepted 03/23/17.
*Address correspondence to: David A. Stevenson, MD, Department of Pediatrics, Division of Medical Genetics, Stanford University, 300 Pasteur Dr., H315, Stanford, CA 94305. E-mail: dasteven@stanford.edu

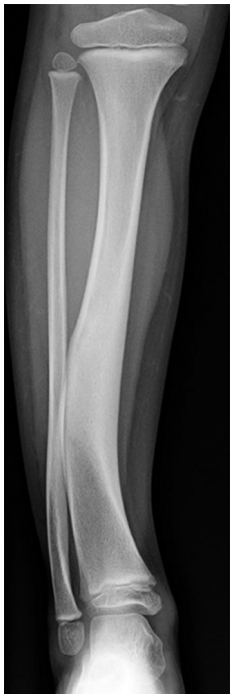

Fig. 1. Example of radiograph of participant with anterolateral bowing of the leg with tibial dysplasia. Radiograph shows the typical cortical thickening with medullary canal narrowing at the apex of the bowing.

arthrosis). Fracture of the bowed tibia frequently occurs in early childhood *(2)*, and bracing is currently considered the standard of care although efficacy is not known *(4)*.

Clinical evaluation for anterolateral bowing in NF1 can be difficult given the frequency of physiologic bowing of the legs in infancy, and modalities to clarify affected status are lacking, which in some instances lead to confusion and angst for families. The radiographic features of dysplastic tibias in NF1 have been described and typically involve cortical thickening with medullary canal narrowing at the apex of the bowing (Fig. 1) *(5)*. Several therapeutic agents have been suggested for use in tibial pseudarthrosis *(3,4,6–9)* raising the question of potential translation to treat tibial bowing prior to fracture. However, the development of clinical trials for NF1 bone manifestations is limited because of the lack of appropriate endpoints and surrogate markers.

Modalities to assess bone quality specifically of the tibia in infants and young children are limited, but quantitative bone ultrasound has several suitable aspects to investigate the tibia in this population. Ultrasound is portable, rapid in measurement, and there is no ionizing radiation. Quantitative ultrasound (QUS) measures speed of sound (SOS) through bone by axial transmission and provides an estimate of bone quality, which can be impacted by bone mineralization and micro-architecture *(10)*. The purpose of this study was to utilize QUS to measure SOS and quantify tibia bone quality in individuals with NF1 with tibial bowing.

Materials and Methods

Participants

Participants were recruited from across North America and evaluated at a single center at the University of Utah. Inclusion criteria included fulfilling the clinical diagnostic criteria for NF1 based on National Institutes of Health guidelines *(1)*, and a clinical diagnosis of unilateral tibial bowing without pseudarthrosis of the tibia by a physician. Informed consent was obtained and the study was approved by the University of Utah Institutional Review Board.

After enrollment, all individuals were personally examined by one medical geneticist (DAS) and detailed phenotypic information was obtained. Medical records and radiographs performed clinically in the past were obtained and reviewed.

The time from enrollment of the first individual to end of funding for follow-up phone interviews was 3 yr. Phone interviews were performed every 6 mo after enrollment through the duration of the study to obtain information relating to surgical procedures or fracture.

Bone Ultrasound

Measurements were obtained using an ultrasound bone sonometer (Sunlight Omnisense 8000; BeamMed Ltd, Petah Tikva, Israel) with the optional pediatric software installed. Measurements were obtained on both legs of individuals with NF1 with unilateral tibial bowing. Quality verification, limb positioning, and measurement gauges were performed/utilized as per manufacturer guidelines. One of 2 trained technicians performed patient measurements (HS and KW). Mid-shaft tibia (measurement point) was marked utilizing a waterproof white eyeliner pencil. The mark ran perpendicular to the direction of the bone and was extended across the tibia to half the diameter of the leg so that it could be followed easily with the probe. The 2.5 cm "CS" probe was used for children under 1 yr of age; the 4.2 cm "CM" probe was used for children of all other ages. Parker gel was applied to the probe head and the probe was positioned parallel to the bone axis, with the center mark of the probe aligned with the skin marker on the patient. Measurements were taken by sweeping the probe laterally and then medially along the axis of the bone, following the contour of the bone. A minimum of 2 sets of measurements, with a set being defined as at least 3 statistically similar measurement cycles, were taken at the mid-shaft on each leg to yield 2 final SOS values. If the final SOS values did not fall within 50 m/s of one another, additional measurement sets were repeated until this criterion had been satisfied. Then the mean of the 2 SOS values were calculated.