Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pathology – Research and Practice 201 (2005) 305–312
PATHOLOGY RESEARCH AND PRACTICE
www.elsevier.de/prp

ORIGINAL ARTICLE

Vascular changes in the periosteum of congenital pseudarthrosis of the tibia ☆

Benita Hermanns-Sachweh[a,*], Jan Senderek[a], Joachim Alfer[a], Bernd Klosterhalfen[a], Reinhard Büttner[a], Laszlo Füzesi[b], Michael Weber[c]

[a]*Institute of Pathology, University Hospital, RWTH Aachen, Pauwelsstr. 30, D-52057 Aachen, Germany*
[b]*Institute of Pathology, Georg-August-University Göttingen, Germany*
[c]*Department of Orthopedics, Medical School of the Technical University of Aachen, Germany*

Received 6 October 2003; accepted 28 September 2004

Abstract

The etiology and the pathogenesis of congenital pseudarthrosis of the tibia (CPT) are still unknown. The affected tibia exhibits insufficient mechanical strength and osteogenetic capability. CPT is frequently associated with neurofibromatosis type 1 (NF1; von Recklinghausen's disease); however, both diseases have not yet been linked pathogenetically. This study presents the pathomorphologic findings of CPT under special consideration of NF1. Therefore, samples from patients operated on for CPT ($n = 4$) with ($n = 3$) and without ($n = 1$) neurofibromatosis were investigated by light microscopy, immunohistochemistry, and electron microscopy. The most striking finding in all patients was thickened periosteum with accumulation of nerval cells surrounding small arteries, causing subtotal or complete obliteration.

In conclusion, impaired vascularization can result in decreased osteogenic capabilities. The similarity of ultrastructural findings in the abnormal periosteum and in skin neurofibromas of neurofibromatosis patients may indicate a pathogenetic association of both diseases.

Keywords: Congenital pseudarthrosis; Neurofibromatosis; Periosteum; Electron microscopy

Introduction

Congenital pseudarthrosis of the tibia (CPT) is characterized by recurrent pathologic fractures of the lower leg in early childhood. Callus formation fails, and bone healing tends to be insufficient [5,6,28]. Usually, the first symptom of CPT is antero-lateral bowing of the tibia and secondary bowing of the fibula. X-ray examination reveals focal cortical sclerosis and broadening of the tibia and the fibula, with the apex of the bowing between the middle and the lower third of the diaphysis (prefracture state). The periosteum is markedly thickened in the region where the pseudarthrosis develops. Fracture of either the tibia or the fibula occurs spontaneously or follows a minor trauma. Consecutive bone healing is insufficient, with development of fibrous tissue forming the pseudarthrosis.

Numerous models of pathogenesis such as mechanical stress [9,24], neurofibroma interfering with bone union [12], or abnormalities of the blood vessels feeding the

☆The study was supported by the START programme of the Medical Faculty, RWTH Aachen (14/2000).
*Corresponding author. Tel.: +49 241 8089280; fax: +49 241 8082439.
E-mail address: hermanns@ukaachen.de (B. Hermanns-Sachweh).

0344-0338/$ - see front matter © 2004 Elsevier GmbH. All rights reserved.
doi:10.1016/j.prp.2004.09.013

tibia [34] have been proposed. However, these features were neither found consistently in CPT patients nor could they conclusively explain the clinical and pathologic properties of CPT. The periosteal cuff surrounding the CPT may play a major role in the advent of the bone lesion [23]. Pseudarthrosis was induced in rats by cellophane stripes [19] and in the rabbit by placing a synthetic Marlex-Mesh® around the tibia, mimicking the thickened periosteum in CPT [33]. In agreement with these findings, CPT healing rates were higher when the pathologic periosteum and fibromatous tissue were entirely removed [2,32].

Up to 50–75% of patients with CPT show clinical symptoms of neurofibromatosis type I (NF1; von Recklinghausen's disease) [16,18]. The character of the correlation between both diseases is unknown. NF1 is caused by germline mutations (one out of two is sporadic) or somatic mosaicism in the neurofibromin gene on the long arm of chromosome 17 [11,29]. The phenotype of NF1 mutations varies considerably, including typical benign skin tumors and café au lait spots, as well as gliomas of the optic and acoustic nerves [22].

The purpose of this study was to analyze and compare the pathomorphology of the periosteum and tibial pseudarthrosis of CPT patients with and without NF. In addition, we attempted to evaluate the role of the thickened periosteum in the set up of CPT.

Materials and methods

Patients

We investigated four children (one female and three males) with CPT, their age ranging between 8 and 13 years. The initial fracture of the tibia was noted during the first 3 years of life. Three patients were diagnosed with NF1 based on clinical diagnostic criteria defined by the National Neurofibromatosis Foundation (www.nf.org), whereas one patient did not have NF1, but was affected by additional fibrous dysplasia.

As a control case, we used operation specimens from a 2-year-old girl suffering from osteomyelitis complicated by development of a pseudarthrosis.

Case 1: An 8-year-old boy with CPT of the right leg, type 2 (in Boyd classification, 1982) [2], and NF1. He endured the first fracture at the age of 6 months. Two operations performed alio loco were unsuccessful. The samples were taken during operation in our hospital. After resection of the pseudarthrosis and sclerotic bone, a callus distraction of 11 cm was then performed using a technique described by Weber [30], consisting of internal bone segment transport with flexible wires and pulleys. This procedure resulted in the complete healing of the tibia.

Case 2: A 12-year-old girl with CPT of the left tibia and fibula, type 2 (in Boyd classification, 1982) [6] (Fig. 1), and NF1 with multiple foci of hamartomas or gliomatosis diagnosed by cranial MRT. Further manifestations of the NF1 were not observed. The first fracture of the lower leg was noted at the age of 2 years and 10 months. Four operations performed alio loco and one in our hospital were not successful; therefore, the lower leg had to be amputated using a technique according to Weber [31]. Tissue samples for pathologic examination were taken during surgery.

Case 3: A 12-year-old male with CPT of the right tibia, type 2 (in Boyd classification, 1982) [2], and NF1. He sustained his first fracture at the age of 2. Ten unsuccessful operations alio loco followed. The samples were taken during amputation of the lower leg using the same special technique as described in Case 2.

Case 4: A 13-year-old male with CPT of the right tibia, type 6 (according to Boyd classification, 1982) [2], and without NF1, but suffering from fibrous dysplasia of the right tibia. He had his first fracture at the age of 3 years. Ten operations alio loco were unsuccessful. Specimens were taken in our hospital during surgery. The tibia healed completely after resection of the pseudarthrosis and sclerotic bone, internal bone segment transport of 20 cm, and autologous bone grafting.

Pathologic examination

Specimens were taken from tissue excised during surgery in our orthopedic department. Light microscopic, immunohistochemical, and ultrastructural investigations were performed on samples of the altered periosteum and of the pseudarthrosis obtained by surgery for CPT and for pseudarthrosis after osteomyelitis. The formalin-fixed, paraffin-embedded material was stained by hematoxylin & eosin (H&E) and van-Gieson. Immunohistochemical staining was performed with antibodies against S100 (dilution: 1:500; DAKO, Hamburg, Germany), synaptophysin (dilution: 1:10; DAKO, Hamburg, Germany), GFAP (dilution: 1:100; DAKO, Hamburg, Germany), chromogranin (undiluted; Camon, Wiesbaden, Germany), and Ki67 (dilution: 1:10; Dianova, Hamburg, Germany). For electron microscopy, specimens were embedded in epoxy resin according to routine procedures. Semithin sections were stained with toluidine blue for light microscopy. Ultrathin sections were contrast-enhanced with uranyl acetate and lead citrate, and examined with a Philips T400 electron microscope.