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THE DISCUSSANTS REPLY: In response to the comments by Shah et al.: we did not overlook the need for lumbar puncture in this patient. Lumbar puncture should be a part of the workup for neonatal seizures, including apneic seizures. However, there are clinical situations in which the cause is obvious, in which case, a lumbar puncture may not be necessary. Since the diagnosis of an infarct of the middle cerebral artery was made expeditiously by means of a magnetic resonance imaging (MRI) scan of the brain, we decided to defer a lumbar puncture. We considered the possibility of HSV encephalitis on the basis of a hypodense lesion on the CT scan. However, the subsequent MRI of the brain made this possibility unlikely.

In our opinion, the utility of cerebrospinal fluid analysis is limited in the diagnosis of neonatal subarachnoid hemorrhage with a negative CT brain scan, because of the confusing cerebrospinal fluid composition in neonates, who normally have xanthochromia (derived from bilirubin), a high cerebrospinal fluid protein level (related to gestation), and a variable number of red cells (presumably derived from leakage of meningeal capillaries during delivery).¹ The use of cerebrospinal fluid analysis (to look for xanthochromia and red cells) for the diagnosis of subarachnoid hemorrhage with a negative CT scan is more applicable to adults in whom the source of bleeding is arterial, often from a leaking aneurysm.

In response to Spadafora, we agree that screening for cocaine or other forms of drug abuse may be appropriate in many cases of perinatal stroke. We did not screen the mother in this case because we considered her to be at low risk. The presence of overt thrombosis in this case (heart valve and placenta), moreover, differs from that which is usually seen in perinatal stroke from cocaine abuse. Although it is well recognized that cocaine causes arterial vasoconstriction,² and although many consider the mechanism of perinatal stroke caused by cocaine to be cerebral vasospasm,³ clear documentation of venous thrombosis due to cocaine abuse is lacking.⁴ In this case, venous thrombosis was the presumed pathway because of the placental pathology, valvular thrombosis, and patent foramen ovale with right-to-left shunt.

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More on Atypical Fractures of the Femoral Diaphysis

TO THE EDITOR: Our experience has been very similar to that described by Lenart et al. (March 20 issue)¹ in their report on atypical fractures of the femoral diaphysis. These fractures have a distinctive pattern and most likely represent completion of a stress fracture (Fig. 1). In our series,² 64.3% of the patients had involvement of the contralateral femur. In addition, 76% of the patients had documented prodromal symptoms of thigh pain, vague discomfort, or subjective weakness; these symptoms were often dismissed or treated

as symptoms of spinal stenosis. "Giving way" of the involved limb immediately preceded the fall in 23.1% of the patients.³ We suggest that any patient receiving bisphosphonates who has thigh pain should undergo radiographic examination of the femur, and patients with a documented fracture should undergo radiographic examination of the contralateral femur. Prefracture diagnosis is challenging, as is defining the need for prophylactic fixation of a lateral cortical stress reaction that has been characterized by means of computed to-

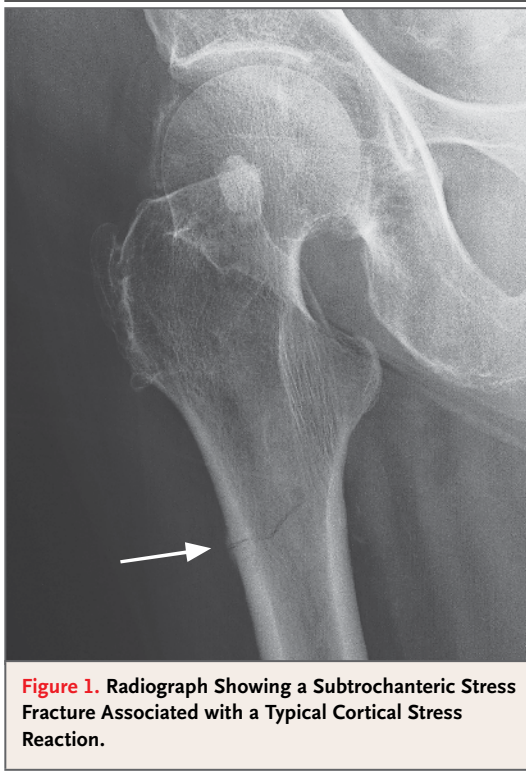


Figure 1. Radiograph Showing a Subtrochanteric Stress Fracture Associated with a Typical Cortical Stress Reaction.

mographic and magnetic resonance imaging (MRI) studies as a callus forming over an incomplete stress fracture.

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TO THE EDITOR: We previously reported a case similar to those reported by Lenart et al. Our patient, a 73-year-old woman, sustained multiple atraumatic femoral insufficiency fractures while receiving alendronate therapy.¹ The bone-specific alkaline phosphatase level was 7.9 μg per liter (range, 3.8 to 22.6), and the ratio of urinary deoxyridinoline to creatinine was suppressed, at

a value of less than 3 nmol per millimole. Although suppressed bone turnover theoretically raises the possibility of bisphosphonate-related “frozen bone,” as previously reported,² histomorphometrically proven suppression of bone formation was incompatible with the demonstration of normal bone-turnover markers in the series reported by Odvina et al.

Femoral insufficiency fractures are associated with increased mortality, and they are probably markers of ill health with multifactorial causes.¹ These fractures are not limited to patients who are receiving bisphosphonates. Nonadherence to prescribed bisphosphonates is associated with a 15 to 20% increase in rates of subsequent fractures. We agree that clinicians should be cautious about the hazards of long-term administration of bisphosphonates. However, until further studies can provide definitive evidence of bisphosphonate-associated fractures, it is premature to attribute atypical fractures to oversuppression of bone turnover alone, while disregarding secondary and patient-related factors. The fractures in our patient healed while alendronate therapy was continued.

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THE AUTHORS REPLY: We agree with Kwek et al. and with Lee and Seibel that stress fractures of the femoral diaphyses commonly occur in association with prolonged bisphosphonate use. We also agree with Kwek et al. that careful scrutiny of the contralateral femur is important, but radiography may not be adequate. A painful limb may require additional imaging. MRI and bone scanning have greater sensitivity than radiography for an incipient stress fracture.

In response to Lee and Seibel: low bone turnover may not be the only cause of stress fractures associated with prolonged bisphosphonate use. In

our series, markers of bone turnover were not directly measured, since diagnosis-related groups did not cover a workup for metabolic bone disease, including markers of bone turnover, for the care of patients with fractures. Microfractures, inadequate mineralization, and outdated collagen are several candidate causes. Although the fractures reported by Lee et al. healed with continued bisphosphonate treatment, an anabolic agent such as parathyroid hormone (1-34) may be preferable. Parathyroid hormone not only has activated bone-formation markers in trials in humans but has also enhanced the healing of fractures in studies in animals.^{1,2}

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Perinatal Deaths in a Family with Autosomal Dominant Polycystic Kidney Disease and a *PKD2* Mutation

TO THE EDITOR: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common mendelian disorders, affecting approximately 12.5 million persons worldwide.^{1,2} Clinical symptoms usually do not arise until adulthood. ADPKD2 is generally considerably milder than ADPKD1. About 2 to 5% of patients have early-onset ADPKD, which at times is clinically indistinguishable from autosomal recessive polycystic kidney disease (ARPKD).³ To date, ADPKD with early manifestations has been thought to be strictly confined to persons with ADPKD1.²

We now report on a four-generation family carrying a mutation in the gene for ADPKD2 (*PKD2*) with previously undetected disease. In the present generation, however, perinatal death due to polycystic kidney disease occurred in the mother's second and third pregnancies, the first having resulted in a healthy girl. The second pregnancy was complicated by oligohydramnios and massively enlarged hyperechogenic fetal kidneys; a boy born at 30 weeks of gestation died shortly after birth from respiratory insufficiency. The third pregnancy was complicated from 20 weeks of gestation forward; a girl born at 34 weeks of gestation died shortly after birth.

Linkage analysis of the gene for ARPKD (*PKHD1*) revealed identical haplotypes in the healthy daughter and the affected daughter, making ARPKD very unlikely (Fig. 1A). Histologic studies unexpectedly

showed glomerular cysts that were suspicious for ADPKD (Fig. 1B). Abdominal ultrasound studies in the parents revealed no cysts in the 31-year-old mother but two cortical cysts in the left kidney and three cysts in the right kidney in the 32-year-old father. Ultrasound studies in other family members showed bilateral renal cysts in the paternal grandmother and in the 80-year-old paternal great-grandmother (Fig. 1C). However, none of these adults had any clinical symptoms. Analysis of the fetal DNA for *PKD1* and *HNF1 β* did not show a pathogenic mutation, but *PKD2* sequencing revealed a novel frameshift mutation, c.1934_1935del insT (p.Asn645fs), in exon 9 (Fig. 1D) that is thought to lead to premature truncation of the encoded polycystin-2 protein and that was not present among 200 ethnically matched control chromosomes. This mutation segregated with the phenotype, further validating its pathogenicity.

These cases emphasize the need for ultrasound studies in the parents and, if the parents are young, the grandparents of a child with polycystic kidney disease of unknown type.⁴ The high risk of recurrence of ADPKD with early manifestations in affected families suggests a common familial modifying background for early and severe disease expression (e.g., mutations or variants in genes encoding other cystoproteins).⁵ Definition of the underlying mechanisms might provide further insights into polycystic kidney disease. This family