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Critical review of 'temporary brittle bone disease'

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Introduction

The Society for Pediatric Radiology (SPR) and the European Society of Paediatric Radiology (ESPR) are the professional organizations in North America and Europe for physicians specializing and board certified in the diagnostic imaging of children. The SPR and ESPR are committed to ensuring excellence in diagnostic imaging, promoting scientific inquiry, and providing information to health care providers and governmental agencies that are involved with the health of children.

Pediatric radiologists are frequently called upon to educate lawyers and judges on the diagnostic imaging of child abuse. The testimony of pediatric radiologists can be crucial in the differentiation of child abuse from accidental fractures, metabolic diseases, and other bone disorders. In cases where child abuse is suspected, a physician's opinion will often be determinative, particularly when the child is unable to speak for himself. Thus, members of the SPR and ESPR should endeavor to instruct the courts on the most current and widely accepted imaging methods and to refute expert testimony that lacks a sound medical basis. The SPR and ESPR believe that the time has come to initiate a process that will expose irresponsible medical expert testimony in the field of pediatric diagnostic imaging based upon unique theories of causation, unreliable methodology, omission of facts or knowledge significant to the opinion, or unusual interpretations and conclusions.

Child abuse is a frequent cause of fractures in the first year of life [1, 2]. Abusive fractures are also frequently seen in association with other forms of severe trauma in infancy [3]. Nevertheless, a sound approach to evaluation of the origin of fractures in young infants must foster the identification of natural conditions that increase the likelihood of skeletal injury from otherwise minor trauma. Many such conditions have been identified (see Table 1), and other disorders may exist that have not yet been discovered. Several good references are available to assist the physician in pursuing a reasonable course of differential diagnosis [4–8].

Such a course, however, is not possible for a recently proposed entity called "temporary brittle bone disease" ("TBBD"). The key concept in this alleged condition is that a young infant had a problem that made the bones susceptible to fracture for a short period of time, but the condition resolved spontaneously, leaving no pathology to identify. Two proponents advance different and contradictory mechanisms for this alleged condition. Each of these hypotheses is discussed in detail below.

As experts in the field of pediatric diagnostic imaging, SPR and ESPR members have the professional responsibility to provide the courts with reliable scientific information. As shown below, a diagnosis of "TBBD" does not meet this standard because it lacks appropriate grounding in scientific methods and procedures and because it is based on the unsupported speculation and subjective beliefs of a small number of medical professionals. Testimonial conjecture regarding "TBBD" cannot assist a judge or jury in understanding the relevant medical evidence or determining the cause of a particular injury. Thus, presentation of evidence of "TBBD" creates a grave risk that non-scientist fact-finders will be

This statement is the work product of the Society for Pediatric Radiology (SPR) ad hoc Committee on Child Abuse. The SPR and European Society for Paediatric Radiology (ESPR) Board of Directors endorsed this statement at their Board meetings in 2005. The members of the committee are: Drs. Kenneth Mendelson, Chair; Melissa Spevak, Sandra Gorges, Marguerite Care, Gael Longergan, Richard Patterson, Debra Pennington, Mark Finkelstein, Peter Strouse, and Martin Reed. The committee is advised by Dr. John Miller, Dr. Paul Kleinman, Dr. Charles Fitz, Dr. Stephen Chapman ESPR, Mr. Brian Holmgren (Nashville, TN. District Attorney), Dr. Andrew Baker (Forensic Pathologist, Minneapolis, MN), Ms. Pat Kleinman (Epidemiology), Ms. Joelle Moreno (Professor, New England School of Law), and Dr. Betty Spivack (Forensic Pediatrician, Louisville, KY, USA).

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Table 1 Medical conditions in infancy predisposing to fracture or mimicking abuse

Disorders of collagen formation	Disorders of mineralization	Non-fracture mimics
Osteogenesis imperfecta	Rickets	Congenital syphilis
Copper deficiency	Neuromuscular disorders	Osteomyelitis
Menkes syndrome	Prematurity	Leukemia
	Liver failure	Scurvy
	Malabsorption	Caffey disease
	Loop diuretic usage	Vitamin A toxicity
	Glucocorticoid usage	Prostaglandin E therapy
	Methotrexate usage	

misled or confused by unreliable and/or irrelevant expert opinions. This danger threatens the quality of contingent legal decisions and, more significantly, poses an unacceptable risk to the safety of children.

"TBBD" version #1 (temporary collagen synthesis defect)

The initial description of "TBBD" was by Paterson et al. in 1993 [9]. They described a group of 39 children who had multiple fractures in the first year of life but none thereafter. The fractures were principally of ribs (72% of cases) and metaphyses (76% of cases), but included diaphyseal fractures as well. They identified several features reminiscent of osteogenesis imperfecta, including lack of history of significant trauma, diminished external evidence of injury, and "accidental" discovery of the fractures on radiographs taken for other purposes. They also noted that two-thirds of the patients had one parent with "striking joint laxity," suggesting an inherited component of this condition, and the possibility that "collagen defects could be responsible."

Paterson et al. also described other features of these patients, noting that many of the children were premature (33% $<$37 weeks' gestation, 21% $<$33 weeks' gestation), products of multiple gestations (28%) and were fed formula rather than breast-fed (93%). They correlated these factors with the known entity of copper deficiency in prematurity, and proposed that "TBBD" was caused by copper deficiency, causing temporary problems in collagen synthesis by decreased activity of lysyl oxidase, a cuproenzyme. They noted that symptoms of copper deficiency, including hemoglobin $<$10 g/dl and neutrophil count $<$39% , and overt osteopenia, each occurred in more than 25% of their cases. Three of the 39 children were still having fractures at the time of Dr. Paterson's involvement; levels of serum copper and red cell superoxide dismutase, a cuproenzyme, were evaluated in these children. One had undetectable copper levels at 8 weeks of age. Two 8-week-old twins had normal copper and red cell superoxide dismutase levels. He proposed that copper deficiency could still account for their "TBBD," as "a period of copper deficiency, which was self-limiting, could lead to the deposition of an abnormal collagen and therefore a period of bone fragility that outlived the copper deficiency."

The issue of copper deficiency and infant fractures was well reviewed by Shaw in 1988 [8]. Shaw indicates that healthy full-term infants are born with a 5-month store of copper, and low-birth-weight infants with a mean of 2 months' store. Copper status after these periods will depend upon the relative degrees of growth and copper intake. Since premature infants grow at a higher proportional rate, they require a larger concentration of copper to maintain normal copper status. The mean age of presentation with copper deficiency was 8.3 months (range 5–18 months) for full-term infants and 3.0 months (range 2.2–15 months) for premature infants. Virtually all of the affected infants had a significant sideroblastic anemia with hemoglobin less than 10 g/dl (92% full-term, 85% preterm). Severe neutropenia ($<1{,}000\times10^6$/dl) was present in 84% of affected infants; all affected infants had neutrophil counts less than $2{,}000\times10^6$/dl. Psychomotor retardation, hypotonia, and rash are described as symptoms, but no frequencies are given. Fractures occurred in 22%, with radiographic bone changes in 55%. The radiographic changes preceded fracture and included symmetric cupping and fraying of the metaphyses, osteopenia, subperiosteal new bone, and delay in bone age. Shaw notes that skull fracture has never been reported in copper deficiency, and rib fractures have never been reported in full term infants with copper deficiency. He further states that treatment with copper leads to full resolution of skeletal abnormalities, and that "fractures have never been reported as a late sequel to copper deficiency," i.e., after copper levels return to normal.

It is disturbing that this extensive review was published 5 years prior to the publication of Paterson's paper, in a major journal in his home country, and was not referenced by Paterson. The Shaw review provides a strong argument against Paterson's principal theory, that copper deficiency is a cause of "TBBD," since 33 of the 39 patients had their first fracture before 4 months of age, and 2 of the 3 patients who had copper levels tested had normal copper and red cell superoxide dismutase. Paterson et al. suggest it had previously been low, and the collagen was still abnormal, but fails to provide a single case of known copper deficiency where fractures continued after treatment and resolution of the deficiency. Shaw indicates that no such case exists in the literature, and our review has failed to find one published previously or subsequently. Insistence on this explanation for normal copper levels transforms Paterson's "TBBD" into an unfalsifiable hypothesis, and therefore a non-scientific hypothesis by definition [10].

Paterson's criteria for determining that bone pathology is the cause of fractures in their series also have serious methodological flaws. In particular, they cite lack of superficial evidence of trauma, i.e., absence of bruising, as an indication that minimal trauma was needed to cause the fracture. He states that this is a common fea-

ture of patients with osteogenesis imperfecta, implying that superficial bruising is common or universal in fracture patients without bone pathology. This hypothesis was tested by Mathew et al. [11] in a prospective evaluation of 93 fractures in 88 normal children. Prevalence of bruising was assessed at initial presentation, and, when the opportunity offered, at the time of surgery or cast change. Only eight fractures (8.6%) were associated with bruising at the time of initial treatment. Initial bruising was not seen at all in undisplaced fractures or in those well covered by soft tissues. Thirteen out of 73 fractures re-examined within 24 h under anesthesia (17.8%) had developed bruising that had not been present at prior examination. Four out of 16 fractures re-examined in the first week (25%) had developed bruising. In all, 25 fractures (28%) had associated bruising noted at any time after presentation. This demonstrates that rarity of bruising is the expected situation after pediatric fracture, rather than an indication of bone pathology as a cause of fracture. The frequency of bruising would be expected to be even lower in fractures detected in an advanced healing phase or in those that resulted from the application of indirect forces. Both of these factors are especially relevant in the interpretation of posterior rib fractures and classic metaphyseal lesions, which are well-recognized indicators of abuse.

Paterson et al. also cited the absence of pain associated with many of these fractures. They made no distinction between diaphyseal fractures and rib or metaphyseal fractures in the frequency of symptoms, though he noted that diaphyseal fractures were frequently the presenting injury. This implies that the diaphyseal fractures caused symptoms severe enough to lead to medical intervention.

Infantile rib fractures generally involve only one side of the cortex [12]. Posterior fractures are in a position where the ribs do not move much with respiration. This will decrease pain and splinting. The non-specific tenderness will decrease markedly as soon as soft callus develops. Most rib fractures are first detected in the healing phase [13], leading to an expectation of lack of associated symptoms. Metaphyseal fractures in young infants with limited mobility and weight bearing would not be expected to cause significant symptoms. The most frequent fractures recognized in Paterson's patients were rib and metaphyseal fractures. The frequent absence of associated symptoms, therefore, is expected in Paterson's patient population, and is not an indication of underlying bone pathology.

In summary then, there is no basis for hypothesizing bone or collagen pathology as an etiology for the fractures seen in Paterson's patients, nor is there evidence of copper deficiency as a causal agent in their fractures.

"TBBD" Version #2 (temporary defect in mineralization)

A more recent version of the "TBBD" hypothesis was proposed by Miller and Hangartner [14]. They report on 26 children who fit their criteria for "TBBD." These criteria were denial of wrongdoing by the parents, absence of history of trauma, absence of history of external bruising, absence of other injuries associated with child abuse, absence of radiographic evidence of metabolic bone disease, normal values of serum calcium and phosphorus, and normal collagen analysis or osteogenesis imperfecta considered unlikely on clinical grounds. None of the children had a fracture after 18 weeks of age. All of these children were self-referred by the parents or by the parents' attorneys. Mothers were interviewed as to whether the child's intrauterine movement was normal: increased or decreased. The authors used radiographic (7 children) or CT densitometry (5 children) to assess bone density in 9 of the 26 children at ages ranging from 5 months to 24 months of age. Radiographic densitometry of phalanges was performed using an ad hoc DXA device. The CT densitometry was performed in a manner that could determine cortical or trabecular bone density individually. The CT densitometry values of the tibia were compared with data from 7 normal controls; 6 controls were 10 months old, the other was 27 months old. The DXA densitometry values cite comparison with two reference sources [15, 16] for age and sex-matched controls.

The authors reported that 25 out of 26 children experienced intrauterine confinement due to twin pregnancy, fetopelvic disproportion, structural uterine abnormality, oligohydramnios, uterine scarring from previous cesarean deliveries or a subplacental hemorrhage. They also found that 20 out of 21 mothers with singleton pregnancies reported decreased fetal movement.

The DXA evaluations revealed that 4 out of 7 children had bone densities more than two standard deviations below the reference range; all had bone densities at least one standard deviation below the reference range. The CT densitometry evaluation showed that all five children tested were more than two standard deviations below the reference mean in either trabecular or cortical bone density, though none of the children had abnormal results in both of these regions.

The authors concluded that "TBBD" resulted from decreased intrauterine movement associated with intrauterine confinement, leading to disuse osteopenia and increased susceptibility to fracture.

Analysis of this study shows that the authors do not justify this claim. The criteria do not establish the presence of bone pathology. We have already analyzed the data on the absence of bruising in pediatric fractures. Denial of responsibility is the rule rather than the exception in cases of child abuse, as in all types of criminal behavior. The other criteria used by Miller et al. merely establish the absence of definable pathology. There is nothing inherent in these criteria which would exclude non-accidental trauma as the cause of the fractures, or establish the existence of "TBBD." Furthermore, the patients reached Miller through knowledge of his hypothesis. Therefore, it is expected that an

extremely high proportion would fit the premise of intrauterine confinement. None of the mothers' obstetric or prenatal records were reviewed to corroborate descriptions of decreased fetal movement or other obstetric problems.

The analysis of decreased bone density arising from decreased intrauterine movement (or any other source) as a contributing factor to fractures in these patients is also not convincing. None of the children had bone densitometry performed at a time when fractures had recently occurred. Intervals between last fracture and testing ranged from 8 weeks to 21 months. None of the children was tested at less than 5 months of age, and 3 of the 9 children were at least 12 months of age. This delay makes any correlation of findings with intrauterine confinement unlikely, since unrestricted postnatal movement, especially after onset of rolling, crawling, and walking, would be expected to obliterate the effects of the prenatal restriction.

Furthermore, the validity of the data is impaired by the nature of the control populations that were used, and the lack of a mention of raw data in addition to the *z*-scores, which were unmatched to mean and standard deviation norms. Despite submission for publication in 1998, no references to neonatal or infant densitometry standards previously published in the peer-reviewed medical literature were cited [17–20]. All published standards for newborns and infants, both CT [20] and DXA [17–19], use densitometry of the lumbar vertebrae, so even if it were the case that raw data for the patients and controls had been published, they could not be compared with data from other sources. The authors cite two references [15, 16] for their DXA reference values. The first [15] is unavailable in the peer-reviewed medical literature, the latter [16] deals with the reproducibility of values in adults. The CT control population consisted of six 10-month-olds, and one 27-month-old. Published data on newborn bone mineralization [17] indicates that bone mineral content (BMC) and bone mineral density (BMD) correlate with birth weight, length, body surface area and gestational age (r range 0.6–0.73). Data from the same source on infants indicates that BMC and BMD correlate even more strongly with weight, age, length, and body surface area ($r \geq 0.94$ for all listed parameters) over the first 2 years of life. The six 10-month-olds might be useful in starting to generate a data point for 10-month-olds, though six subjects is small for the purposes of establishing standard deviations relative to a much larger population. The 27-month-old should not be included in the same set. The data should only be used to evaluate infants in roughly the same age group; this would only apply to one 11-month old infant out of the five children who underwent CT densitometry.

The basic premise that intrauterine confinement would lead to disuse osteopenia appears flawed as well. Miller and Hangartner cite Rodriguez et al. [21] in support of their hypothesis. In the cited work, Rodriguez et al. evaluated postmortem radiographs and radiomicrographs of infants with congenital neuromuscular diseases. They found that, compared with a control group without neuromuscular disorders, the affected infants had reduced external bone diameter, cortical thickness, and cortical area. The same group had found similar findings in an animal model in which fetal rats were paralyzed with curare [22]. However, the authors specifically state: "Previous clinical studies have suggested that muscular strength is more important than movement in the regulation of fetal long bone development. This suggestion is based in the observation that long bone hypoplasia is a usual finding in newborns with congenital neuromuscular diseases *but not in newborns with oligohydramnios sequence who also had intrauterine limitation of motion but normal muscular activity*" (emphasis ours). Hence, Rodriguez et al. contradict the central premise of Miller and Hangartner's hypothesis. None of the patients in the latter's study group had neuromuscular disorders. In fact, a child with normal musculature who is confined due to small or shared uterus is engaged in isometric exercise as it attempts to move. It is more likely that this will lead to increased, rather than decreased bone density at birth, though this too is a hypothesis that should be tested rather than asserted in the absence of appropriate data.

A scientific test of the hypothesis that twin pregnancy, or other causes of intrauterine confinement, lead to decreased neonatal bone density would require prospective comparison of measured bone densitometry in healthy twin neonates and healthy controls matched for gestational age and birth weight. This might require dual sets of controls since twins generally weigh less than singleton neonates of equivalent gestational age. If a significant difference in bone mineralization was demonstrated between the two groups, the two groups could be followed over the first 2 years of life to see how long differences persisted, and if differences in initial bone mineralization correlated with the appearance of fractures in the first year of life.

We conclude that Miller and Hangartner fail to demonstrate the existence of a syndrome of "TBBD" or to demonstrate the relationship of fracture patterns to intrauterine confinement or to decreased bone density.

Conclusion

The existence of "TBBD" has not been effectively demonstrated by either Paterson et al. or Miller and Hangartner. The two hypotheses are also contradictory and do not support each other. Intrauterine confinement and decreased movement would not explain increased parental joint laxity, or problems in collagen synthesis as asserted by Paterson et al. Disorders of collagen formation, especially associated with genetic predisposition, would not be associated with intrauterine confinement as asserted by Miller and Hangartner. Both hypotheses are based on flawed premises, and bolstered by poorly

designed scientific studies or misinterpretation of well-performed studies. Because the existence of "TBBD" has not been established and because legal accuracy often depends on scientific legitimacy, this unreliable medical diagnosis should have no place in the courts. Presentation of evidence of "TBBD" creates the serious risk that non-scientist fact-finders will rely on unreliable, irrelevant, confusing, and misleading opinion testimony, rather than on relevant and reliable medical evidence to determine the cause of a particular child's injuries.

As experts in the field of pediatric diagnostic imaging, SPR and ESPR members have the professional responsibility to provide the courts with reliable scientific information. The evidence must be based on sufficient data and a physician's conclusions must be the product of reliable principles and methods applied reliably to the facts. A diagnosis of "TBBD" cannot meet this basic legal evidentiary standard because it lacks appropriate grounding in scientific methods and procedures. As the review of the facts and data contained in this statement reveal, a "TBBD" diagnosis is not generally accepted within the field of radiology, but is instead based on the unsupported speculation and subjective beliefs of a very small number of medical professionals. This type of testimonial conjecture cannot satisfy the professional standards of the Society for Pediatric Radiology or the European Society of Paediatric Radiology.

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