An Open Letter on Ehlers-Danlos Syndromes, Child Abuse, and Bone Fractures

Concerns have been expressed that infants with Ehlers-Danlos syndrome (EDS) may present with features that are interpreted as signs of child abuse [Anderst et al., 2013; Morais et al., 2013; Castori, 2015]. Unexplained bruising, skin tears, and unusual scars that can be seen in multiple EDS types, perhaps especially vascular EDS, may lead to accusations of child abuse [Roberts et al., 1984].

More recently, it has been argued that (hypermobile) EDS, not abuse, is a reason for unexplained bone fractures in infants. Many such cases have been described, mostly in the lay press, publicized worldwide, and propagated by a few individuals with little scientific merit. Below, we will review the scientific data surrounding bone health in EDS. Our opinion is that there is not scientific validity to the argument and therefore should not be used in defense arguments.

Bone

Bone is made up of living cells and the bone matrix. The matrix is composed primarily of type I collagen and various chemical compounds such as calcium phosphate that help harden the matrix. The quality of bone is often measured as bone mineral density (BMD) and compared either to peak bone mass that occurs around 25-30 years of age (T-score) or to age-specific normal ranges (Z-score). Osteopenia refers to bone that has a density less than average but not osteoporosis. This is still "normal". A similar analogy is height; 5'3" (160 cm) is less than average height but is still normal. Osteoporosis is defined by having a reduced bone mass with a T-score of -2.5 or lower. Several risk factors contribute further to the calculation that predicts risk of fragility fractures because a diagnosis of osteoporosis is not the sole factor. That said, these risks for fracture have been mostly worked out for post-menopausal women (see the National Osteoporosis Foundation website at www.nof.org).

Genetic defects in bone

Osteogenesis imperfecta (OI) is a genetic condition that has "brittle" (i.e. easily breakable) bones. The genetic defect is in collagen type I for the majority, but like EDS, OI has several types. Some of the rarer types involve other proteins and enzymes that affect the production and processing of type I collagen or the maturation of bone. There are several EDS types that are also caused by defects in type I collagen such as a variant of classic EDS (formerly classic-like EDS with propensity for arterial rupture), cardiac-valvular, and arthrochalasia, in addition to dermatosporaxis, whose defect alters the removal of the amino-terminal propeptide from type I procollagen [Malfait et al., 2017]. These rarer types of EDS more often have associated osteoporosis and bone fragility and can be differentiated from a normal newborn in the vast majority of cases and, most importantly, confirmed by genetic testing [Brady et al., 2017].

Bone properties in EDS

A search of the medical literature produces a few dozen primary articles on this subject. Some were described before the 1980s prior to a modern description of EDS. Some are

reviews that capture these original data. The following is a brief summary of the literature as it relates to bone and EDS involving either the classic type or the hypermobile type.

Coelho et al. [1994] studied four adult patients they termed classic EDS. In looking at the lumbar spine, one of the four had bone density in the osteoporotic range while the other three were more consistent with being osteopenic. Bone density measured in the proximal femur was normal for all four patients. There was no genetic testing (or, at that time collagen, protein analysis) confirming the diagnosis of classic EDS. We know now that there is a rare type of classic EDS that is due to type I collagen (the bone collagen). No further information is available.

Deodhar and Woolf [1994] described a series of seven adult patients with reported osteoporosis. All were diagnosed with EDS (type not specified) after bone density analysis. With modern criteria, only two of the seven would qualify as having osteoporosis, both males of 70 and 55 years of age. How the diagnosis was made on males over 50 was not discussed and, if based on clinical features alone, still remains difficult at best today.

Dolan et al. [1998] studied 23 adult patients with EDS (10 cEDS; 13 hEDS) and 23 age-matched controls. They adjusted for such factors as weight, age, gender, and height which are known factors in bone density. They measured bone density in three locations. The bone density measured was lower in the EDS group but not in the osteoporotic range. The incidence of fractures was different in that 78% of the EDS patients had had at least one fracture compared to 13% of controls. The majority were in the foot and wrist, not typical of fragility fractures but more typical of a person twisting an ankle and/or falling.

Carbone et al. [2000] studied an additional 23 adults with hEDS. They also showed differences in bone density that disappeared once corrected for age, weight and activity-level. The authors of this study were critical of Dolan et al. [1998] for not correcting for activity and suggested that the differences in the Dolan study would likely NOT be significant.

Gulbahar et al. [2006] looked at 23 pre-menopausal women with joint hypermobility and found that this population more often had mild osteopenia as compared to the controls.

Yen et al. [2006] studied 16 people with EDS. While the study showed overwhelmingly lower bone density in children, the study had several major issues. It used the incorrect bone density values for children and, in the US for example, these measures have not been established for some of the age groups. EDS was also diagnosed in several under 4 years of age which is not typical of the hypermobile type of EDS and no genetic testing was done. Several individuals had features also not typical of EDS which may represent other genetic disorders including the bone fragility disorder, osteogenesis imperfecta. So, unfortunately, through its various faults, no real information can be used from this.

In the first of two Italian studies published in 2016, Eller-Vainicher et al. looked at 50 consecutive adult patients with cEDS or hEDS. This group of 50 had controls matched for age, gender, activity level and body mass. About 10% of the EDS population scored in the osteoporosis range compared to 4% of the controls. Using another radiologic marker (vertebral height), 10% of the EDS group was considered positive for occult vertebral fractures of the lower back whereas no controls were. The marker is used to determine that a vertebral fracture likely had occurred. None of the EDS individuals recalled a traumatic event. However, all of EDS patients who had this marker for vertebral fracture had normal bone density. These types of asymptomatic fractures do occur in people who hyperextend their

spine such as gymnasts, ballet dancers, divers, and contortionists. It is more likely due to the mechanical stress placed on the spine and not related to decreased bone density.

In the second study, Mazzioti et al. [2016] looked at 52 adult patients with EDS (12 cEDS; 37hEDS; 3 other). The majority of EDS patients also had normal bone density. They too found a higher occurrence of this radiologic marker in the spine of this EDS population, finding that those with this marker were no different than the control group in their bone density.

Child abuse and unexplained fractures

In 1993, Paterson proposed the term "temporary brittle bone disease" in infants with multiple unexplained fractures [Paterson, Burns, McAllion, 1993]. In part, this was proposed because of the observation that very premature infants occasionally had fractures while in the nursery. These premature infants did have "poor bones" but it was found that the then current infant formulas were deficient in calcium and copper as well as other factors and that changes in nutrition were required (now we use preemie formula to mimic what happens in the womb towards the end of the pregnancy when the bones harden in the fetus). These changes largely eliminated fractures in these premature infants. However, this idea of "temporary brittle bones" was applied to healthy newborns who suffered fractures in the first year of life. Laboratory evaluations never documented a problem with bone metabolism in such cases. In 2005, the Society for Pediatric Radiology [Mendelson, 2005] and in 2006, the American Academy of Pediatrics determined that this "theory" had no scientific validity [Jenny, 2006].

Paterson and Mole [2012] studied 162 parents of 81 infants with multiple unexplained fractures. Of the 162 parents, 40 of the 162 (24.7%) parents had joint laxity. They defined joint laxity as having a Beighton score of 4 or greater. General population studies have suggested that approximately 15% have joint laxity as defined as Beighton score of 5 or greater [Bridges et al., 1992]. Therefore, a prevalence of 25% is not unexpected using a Beighton score of 4 or greater. In addition, he gave each parent a diagnosis of EDS based solely on joint hypermobility using a Beighton score of 4 or more. This is NOT consistent with the diagnostic criteria of EDS then or now [Beighton et al., 1998; Juul-Kristensen et al., 2017].

Holick et al. [2017] published a series of 72 infants whose parents were accused of child abuse. In this series, 100% of the infants had vitamin D deficiency and/or Ehlers-Danlos syndrome as the reason for fractures. The clinical criteria used for the diagnosis of EDS in the infants are not clear. They did not examine approximately one-third of infants, yet assigned a diagnosis of EDS. He stated that the parents had joint laxity and used this to diagnose EDS in the parents and, therefore, the infants. The infants diagnosed with vitamin D deficiency often did not have blood values to suggest vitamin D deficiency nor signs of rickets on x-rays [Misra et al., 2008; Shore and Chesney, 2013]. Chronic vitamin D deficiency can result in bone changes called rickets. As mentioned previously, joint laxity alone does not define Ehlers-Danlos syndrome. Although most forms of EDS, including the hypermobile type of EDS, are thought to be autosomal dominant conditions, diagnosis in a parent is not a surrogate for diagnosis in the child—it simply defines a risk. In sum, this study did not have clear criteria for the diagnosis of EDS and could not document abnormalities in vitamin D metabolism or levels. As such, it does not scientifically support the hypothesis that either or both factors are a cause of unexplained fractures in infancy.

The experience

Castori [2015], addressed this controversy in a recent paper "Ehlers-Danlos syndrome(s) mimicking child abuse". The cases put forth in the media and in courts primarily involve what is described as hypermobile EDS. Castori states that in his experience of more than 420 cases, mostly hypermobile EDS, he was concerned in only one case that EDS may have contributed to a fracture.

None of us want to believe the worst of people and certainly not of parents. But the stark reality is that child abuse is the most common cause of unexplained bone fractures in infants from shortly after birth to age 3 years [Leventhal et al., 2008; Servaes et al., 2016]. We see similar stories in domestic violence where some can't believe it is happening and even the victims hide the consequences. Our jobs as medical professionals and the child protection teams are to assure the safety of the infant. No one wants to make a mistake but sometimes it happens, which is unfortunate. Use of unproven models (and this includes an assertion that it "will be proven in the future") does not meet current medical, legal or ethical standards for use in court. Expert witnesses should be held to this standard. Professional societies are asking the states to do such a thing in recognizing "experts" and it is hoped that this will not allow unfounded ideas to confuse the courts and place children at risk [Moreno, 2013; Narang et al., 2017].

"The court is not an appropriate forum for the presentation of new or unsubstantiated theories of causation of disease. Rather, the court must ensure the accuracy of legal decisions." -Servaes et al., 2016

Summary

In summary, while there is some concern for bone health in various forms of EDS, there is little evidence to substantiate unexplained fractures in EDS, much less in infants. According to the American Academy of Pediatrics and other professional societies, any infant with unexplained multiple fractures should undergo the appropriate evaluation including genetic testing that would reveal the rare instances of EDS due to type I collagen abnormalities [Flaherty et al., 2014; Christian et al., 2015; Pepin and Byers, 2015; Pereira, 2015]. **It is our opinion, based on the summary above, that there is no evidence to support the hypermobile and classic EDS (due to type V collagen abnormalities) as a cause of multiple fractures in infants [Tinkle et al., 2017].**

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On Behalf of the Ehlers-Danlos Society

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