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Bone fractures in children with trisomy 13 and 18

Meaghann S. Weaver[1] | Kelly Hauschild[2] | Angela J. Beavers[3] | Nicole Birge[4] | Elizabeth Lisowyj[5] | Bridget M. Norton[6] | Valerie K. Shostrom[7] | Suzanne Haney[8]

[1]Division of Palliative Care, Department of Pediatrics, Children's Hospital and Medical Center and the University of Nebraska Medical Center, Omaha, Nebraska

[2]Division of Cardiac Care, Department of Pediatrics, Children's Hospital and Medical Center and the University of Nebraska Medical Center, Omaha, Nebraska

[3]Division of Pediatric Radiology, Department of Radiology, Children's Hospital and Medical Center and the University of Nebraska Medical Center, Omaha, Nebraska

[4]Division of Neonatology, Department of Pediatrics, Children's Hospital and Medical Center and the University of Nebraska Medical Center, Omaha, Nebraska

[5]Division of Nutrition, Department of Pediatrics, Children's Hospital and Medical Center and the University of Nebraska Medical Center, Omaha, Nebraska

[6]Division of Critical Care, Department of Pediatrics, Children's Hospital and Medical Center and the University of Nebraska Medical Center, Omaha, Nebraska

[7]Division of Biostatistics, College of Public Health, University of Nebraska Medical Center, Omaha, Nebraska

[8]Division of Child Abuse Pediatrics, Department of Pediatrics, Children's Hospital and Medical Center and the University of Nebraska Medical Center, Omaha, Nebraska

Correspondence
Meaghann S. Weaver, Division of Palliative Care; Children's Hospital and Medical Center; 8200 Dodge Street; Omaha, NE 68114.
Email: meweaver@childrensomaha.org

To the Editor:

Bone fractures have been found on routine radiographic imaging for multiple infants with trisomy 13 and 18 in our care setting. Bone health for infants and children with trisomy 13 and 18 has received little attention in the literature. We completed a descriptive case series using retrospective chart review to assess for osteopenia and bone fractures for children with these genetic diagnoses seen at our free-standing children's hospital from 2016 to 2019. The frequency of fracture findings was 13/29 (45%). Sharing information about the characterization of fractures in terms of natural history and association with prognostic factors may result in osteopenia prevention interventions for these children, may help geneticists and general pediatricians not miss fractures on exam, and may led to future causation studies.

Trisomy 13 and 18 are often discussed together. Both genetic diagnoses have poor prognoses, are associated with major cardiac malformations and significant neurodevelopmental disabilities, and are identifiable by similar methods of ultrasound and genetic testing (Parker et al., 2010). While the conditions may be difficult to diagnose with lack of "cardinal" signs, manifestations differ between the two disorders. For example, patients with trisomy 13 may be noted to have features such as cutis aplasia, orofacial clefts, polydactyly, and detectable structural brain abnormalities. Patients with trisomy 18 may be more likely to demonstrate distinctive hand and foot anomalies of clenched or overriding fingers and rocker-bottom feet, and may have characteristic facial features. Assessment of bone health has not been reported for infants with either of these genetic diagnoses, although we have noted concerning rates of osteopenia and fractures. Here, we provide summary of a patient case which led to a descriptive case series.

The initial case that led to our case series was a 4-month-old girl with trisomy 18 noted to have multiple healing rib fractures and a clavicular fracture (Figure 1) at the time of transfer from a referring facility. Retinal exam and head imaging were normal. Calcium, phosphorus, Vitamin D_3, liver and renal labs were within normal limits for age. There was no reported history of trauma and the infant had never left the hospital setting. She received supportive care with maximized nutrition and evidence of bone healing over time.

Our study team obtained local Institutional Review Board approval for medical record review utilizing trisomy 13 and trisomy 18 diagnostic codes for all patient encounters from 2016 through 2020. Prior to development of record data abstractors, the interdisciplinary study team completed a literature review on infant fracture risks to operationalize reporting (Faienza et al., 2019; Sethi, Priyadarshi, & Agarwal, 2020). Study variables queried from the medical record were: karyotype; fracture presence and location; age at time of fracture; birth age and weight; prolonged (>4 weeks) total parental nutrition (TPN) use; diuretic use; corticosteroid therapy; and calcium, phosphorus, and Vitamin D_3 lab values.

A data abstraction form was developed for chart extraction for the two blinded study team members who reviewed each medical record (KH, MW). The form was organized with responses simplified to allow only specific code responses for the variable. A small pilot test occurred on the first five charts to ensure that all of the coded
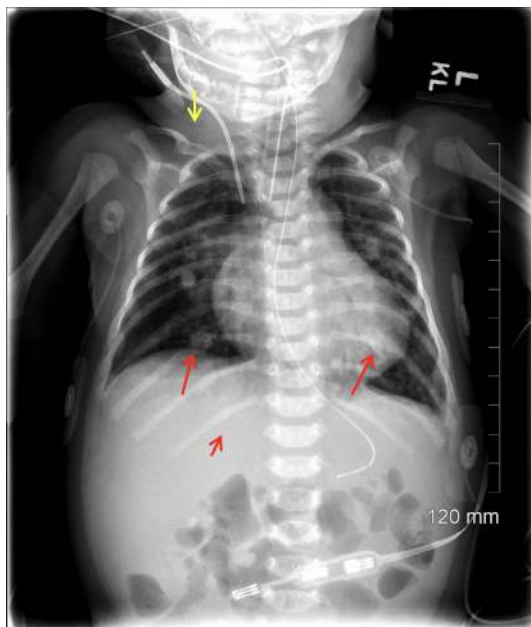
FIGURE 1 Supine chest radiograph, demonstrating multiple healing rib fractures (red arrows) and a healed right clavicular fracture (yellow arrow) [Color figure can be viewed at wileyonlinelibrary.com]

elements could be populated with accuracy and consistency (Vassar & Holzmann, 2013). Inter-rater reliability was noted to be consistently >90% and intra-rater reliability >95%.

PC SAS version 9.4 was used for all count summaries and analyses. Categorical variables were analyzed using Fisher's exact tests to examine a relationship to fracture. The statistical level of significance was set at 0.05 for all correlation analyses.

Out of 29 patients (two with mosaic trisomy 18, three with full trisomy 13, and 24 with non-mosaic trisomy 18) who received care at our center, a total of $n = 13$ (45%) had a bone fracture noted on plain film imaging. Diffuse osteopenia was noted in 25/29 plain films (86%). Age at the time of fracture was mean 5.8 months (range birth to 3 years). None of the children were weight-bearing at time of fracture.

Birth weight less than 1,500 g, gestational age at time of birth, prolonged TPN use, steroid use, diuretic use, and diet type were not statistically significantly correlational with fractures for this cohort.

Fracture locations included: seven clavicular fractures, 13 rib fractures with lower posterior rib predominance, and one humerus fracture. Six children were noted to have more than one fracture on plain film imaging (Figure 1).

Total calcium values at the time of fracture were within normal limits for age for all subjects with mean 10.3 mg/dl (range 9.9–11.7 mg/dl), phosphorus mean value was 5.7 mg/dl (range 3.7–6.6 mg/dl), and Vitamin D_3 mean value was 49.2 pg/ml (range 36.2–87 pg/ml).

The high incidence of osteopenia and bone fractures in children with trisomy 13 and 18 discovered by this case series offers a cautious description of bone health in these genetic diagnoses. The

diffuse pattern of osteopenia is striking. Radiologists often use the term osteopenia generically to convey decreased bone mineral density perceived on radiographs. There is no current manner to quantify bone mineral density on radiograph alone though the radiologist may suggest the diagnosis based on decreased bony trabeculae and cortical thinning in otherwise morphologically normal appearing bone. Radiographs have been shown to have a low sensitivity for detection of bone demineralization, with 30–50% bone mineral density loss needed for the findings to be radiographically perceptible (Done, 2012).

In infants with metabolic bone disturbance, such as premature infants and chronically ill infants, radiographic changes of metabolic bone disease may be identified in addition to findings of demineralization. Imaging findings suggestive of metabolic bone disease can include metaphyseal fraying, long bone bowing, and loss of the zone of provisional calcification, among others. Although radiographs can suggest demineralization or metabolic bone disease, given the low radiographic sensitivity for demineralization, biochemical evaluation is utilized in these vulnerable populations (Bozzetti & Tagliabue, 2009). DEXA scans can provide quantitative data on bone mineral density; although these scans are not often used in the infant population given the lack of portability, the use of ionizing radiation, and the lack of normative data (Done, 2012).

The exact timing of fracture occurrence in these patients is uncertain. Multiple studies have proposed fracture staging criteria such as periosteal reaction, callus development, bridging callus, and fracture remodeling, though these studies vary in fracture location, patient demographics, and other fracture characteristics that may affect timing of healing (Messer, Adler, Brink, Xiang, & Agnew, 2020). Dating of fractures is an imprecise process given the multitude of factors influencing fracture healing such as immobilization, nutritional status, patient demographic and fracture location (Messer et al., 2020). A proposed rib fracture dating guideline by Sanchez et al. suggests five stages of healing ranging from a barely visible fracture line to progressive callous formation and thickening (Sanchez, Nguyen, Palacios, Doherty, & Coulter, 2013). Ultimately, fracture healing has been shown to be a continuum.

The hospital child protection team was consulted for many of these cases due to fracture finding in a non-weight bearing infant. Child abuse is described as the cause of 12% percent of fractures in children under 3 years of age (Leventhal, Martin, & Asnes, 2008). Therefore, it is reasonable to consider an abuse evaluation for any young child who presents with a fracture, especially if there is little to no history of injury and if the child is non-ambulatory. This evaluation for suspected child abuse is well-defined and begins with a thorough history from the caregiver, especially if the caregiver can give a detailed explanation of any trauma. Past medical history should include questions about vitamin supplementation, risks for a metabolic bone disorder, such as extreme prematurity, and any possible medical conditions that could contribute to bony fragility. Family history of suggestive findings such as bony fragility (e.g., frequent or unusual fractures), hearing loss, or abnormal dentition should be included. A thorough physical examination should include observation for

bruising, with particular attention paid to the TEN (torso, ears and neck) locations as well as frenula. In children under 2 years of age, a skeletal survey as delineated by the American College of Radiology is recommended (Paine & Wood, 2018). Finally, a laboratory evaluation (complete blood count; renal function tests and urinalysis; serum calcium, phosphate, alkaline phosphatase; parathyroid- hormone, 25-hydroxy-vitamin D, serum copper, and ceruloplasmin when clinically indicated) should be done to look for skeletal conditions as well as to assess for other signs of inflicted injury such as elevated liver enzymes. Consultation with a pediatrician certified in child abuse pediatrics through the American Board of Pediatrics can help with the differential and work up. The presence of a medical condition for which there is little information on the propensity for fracture should warrant a closer look, as we have done with these infants with trisomy 13 and 18. However, children who have significant medical conditions are also at risk for inflicted injury and abuse cannot be completely ruled out just by presence of a medical condition (Brodie, McColgan, Spector, & Turchi, 2017; Hibbard, Desch, and the American Academy of Pediatrics Committee on Child Abuse and Neglect and the Council on Children With Disabilities, 2007). If there is reasonable concern for abuse, a report should be made to authorities to allow for proper evaluation of the child's environment.

Based on these clinical findings, we have initiated the osteopenia protocol for all children with trisomy 13 or 18 in our care setting. The osteopenia protocol initiates "fragile bone" signage at the bedside and on the door regarding safe handling precautions for staff and family caregivers. Physical and occupational therapists are consulted for gentle strengthening and safe handling. The pediatric dietitian optimizes vitamin D, calcium and phosphorus intake. If the family's goals of care are medical management, then alkaline phosphatase is monitored every 2 weeks. If alkaline phosphatase remains higher than 500 U/L, further work-up is completed including measurement of urine calcium, serum 25-hydroxyvitamin D, serum calcium and intact parathyroid hormone. If alkaline phosphatase remains above 500 U/L for greater than 30 days, the metabolic bone team is consulted for consideration of pamidronate.

A select cohort of families choose to continue pregnancies and pursue biomedical interventions for children with these genetic diagnoses (Lantos, 2016; Weaver et al., 2020). In 2019, the 5-year survival rates revealed trisomy 13 at 7.7% and trisomy 18 at 7.7% (Goel et al., 2019). There is emerging evidence that surgical and medical interventions may potentially further improve the survival rates of children with trisomy 13 and 18 (Carey, 2019; Kosho & Carey, 2016; Lorenz & Hardart, 2014; Nelson, Rosella, Mahant, & Guttmann, 2016). With increased access to biomedical interventions and life-prolonging technologies, under-reported medical issues such as osteopenia and bone fragility may become increasingly relevant. This case series points to the need for a national registry for these diagnoses.

A strength of this study was the inclusion of alive and decedent children with different characteristics and comorbidities, resulting in a sample size representative of children with these genetic diagnoses. The lack of children with trisomy 13 in this case series represents a study limitation. While a case series methodology limits the ability to make causal inferences about the relation between exposures and fracture outcomes, this case series may be helpful in generating hypothesis about bone health in these unique genetic diagnoses which could be tested in further analytic studies.

This case series resulted in our care setting committing to bone health precautions for all children with these genetic diagnoses in an effort to maximize bone health and minimize fracture incidence.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS
Meaghann S. Weaver: Designed the paper, collected data, drafted the initial manuscripts, and revised the manuscript. **Kelly Hauschild:** Designed the data collection instruments and collected data. **Nicole Birge**, **Elizabeth Lisowyj**, **Angela J. Beavers**, and **Bridget M. Norton:** Reviewed and thoughtfully revised the manuscript for key content. **Valerie K. Shostrom:** Carried out the initial analyses. **Suzanne Haney:** Conceptualized the manuscript and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ORCID
Meaghann S. Weaver https://orcid.org/0000-0003-2310-0111

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