Is Routine Spine MRI Necessary in Skeletally Immature Patients With MHE? Identifying Patients at Risk for Spinal Osteochondromas

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Background: Multiple hereditary exostoses (MHE) is an autosomal dominant condition leading to development of osteochondromas throughout the body. Although long bones are most often affected, spine involvement may occur and usually requires advanced imaging for diagnosis. However, the high cost of detection, infrequent occurrence, and very low likelihood of spinal cord compression and neurological injury, create a management conundrum. The purpose of our investigation is to identify patients at greatest risk for spinal lesions and refine indications for advanced imaging.

Methods: All MHE patients in a 24-year period were retrospectively reviewed. Skeletally immature patients with advanced imaging of the spine were further evaluated. The demographic characteristics, family history, clinical presentation, past surgical history, tumor burden, and distribution of patients with spinal lesions were compared with those without.

Results: In total, 227 MHE patients were identified and 21 underwent advanced spinal imaging. Spinal lesions were found in 8 of the 21 screened patients (38.1%, 3.5% overall), of which 4 were intracanal and 1 was symptomatic (4.8%, 0.4% overall). Only the symptomatic patient underwent excision of the spinal lesion. Patients with spinal lesions had higher tumor burden than those without (median, 28.5 vs. 19 locations; $P = 0.010$). There was a significant association with rib ($P = 0.018$) and pelvic ($P = 0.007$) lesions, which may serve as "harbinger" lesions. The presence of both a rib and a pelvic lesion used as a screening tool for spinal lesions produces a sensitivity of 100% and specificity of 69%.

Conclusions: Symptomatic spinal involvement in children with MHE is rare and tends to occur in patients with higher tumor burden. We recommend limiting advanced spine imaging to children with neurological symptoms or with rib and pelvic "harbinger" lesions. Patients without these findings are unlikely to have spine involvement needing intervention. This approach offers an opportunity to avoid unnecessary testing and substantially reduce costs of diagnostic imaging.

Level of Evidence: Level III.

Key Words: multiple hereditary exostosis, skeletally immature, spinal osteochondroma, spinal cord compression, MRI, cost-effectiveness, screening

(*J Pediatr Orthop* 2017;00:000–000)

Multiple hereditary exostoses (MHE) is an autosomal dominant genetic disorder manifesting as multiple benign, cartilage-capped bony tumors (aka osteochondromas) throughout the skeleton.[1,2] It most commonly results from mutations in the *EXT 1* or *EXT 2* genes[3,4] and affects children and adolescents with an estimated incidence of 1 per 50,000 individuals.[5]

Although osteochondromas most commonly arise in the metaphyses of long bones,[1,2] spinal osteochondromas also occur at a widely varying reported incidence ranging from 3% to 68%.[2,6–8] Spinal osteochondromas are most often asymptomatic, but may rarely cause spinal cord compression and serious neurological compromise.[2,6,9–11] Symptomatic intracanal osteochondromas must undergo prompt surgical excision, generally with excellent neurological functional outcome.[9–13] Conversely, treatment of asymptomatic lesions is controversial. Although some recommend excision of all spinal osteochondromas due to risk of growth and cord compression,[6] most asymptomatic spinal osteochondromas can be safely observed.[6,11,14] However, appropriate safety standards for detection and management of spinal lesions have not been formulated. Plain radiographs are unreliable due to the complex anatomy, overlapping structures, and cartilaginous content of the tumors.[6,13] This has led some investigators to advocate routine screening, with magnetic resonance imagine (MRI) or computed tomography, before skeletal maturity in all MHE patients.[6,7] However, the clinical need and cost-effectiveness of this approach is debatable given unresolved questions regarding appropriate follow-up and management of asymptomatic lesions, generally good prognosis following surgical excision of symptomatic lesions, and potential overutilization of health care resources.

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The authors have no sources of financial support to report.

The authors declare no conflicts of interest.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.pedorthopaedics.com.

DOI: 10.1097/BPO.0000000000001084

There is no prior report on the clinical characteristics of MHE patients with spinal lesions; and therefore, it remains unclear which children would benefit most from screening. The purpose of our investigation is to discern differences in clinical characteristics of patients with spinal lesions and those without. Given, the current recommendations for routine MRI in all MHE patients,[6,7,15,16] but lack of clear indications for treatment, we sought to develop a simple, cost-effective means of identifying patients at highest risk for spinal lesions to reduce the cost of unnecessary diagnostic imaging.

METHODS

Sample and Patient Comparisons

After Institutional Review Board approval, we retrospectively reviewed our prospectively collected musculoskeletal tumor database and identified all MHE patients between 1990 and 2014 at our institution. Skeletally immature patients 18 years or younger, with MRI or computed tomography of the spine, were included in the investigation. Patients did not undergo routine screening at our institution, and the decision for advanced imaging was at the treating surgeons discretion. Patients were divided into 2 groups, those with and those without spinal lesions identified on advanced imaging. Demographic characteristics, age at imaging, height percentile, family history, back pain, neurological symptoms, past surgical history, number of involved sites, and pattern of involvement were compared.

Counting Lesions

Lesions were clinically and radiographically counted as the number of unique anatomic locations affected, regardless of size or number of lesions per region. Each small bone of the hands and feet, clavicles, scapulae, and each rib were counted as unique locations. Long bones were divided into distal and proximal segments. Each component of the innominate bone (ilium, ischium, pubis) was considered separately. Spinal lesions were not factored into total lesion counts. Images were reviewed retrospectively, and no additionally imaging was taken beyond that deemed clinically necessary by the treating surgeon.

Development of a Screening Tool and Cost Analysis

The presence of both a rib and a pelvic lesion was evaluated as a potential screening tool for spinal lesions. A 2×2 paired contingency table was constructed to calculate sensitivity and specificity of the presence of both pelvic and rib lesions compared with presence or absence of spinal lesion on advanced spine imaging.

Literature Review

PubMed and bibliographies of published manuscripts were searched for all cases of spinal osteochondromas or spinal cord compression in pediatric (18 y and below) MHE patients. For each case the year, age, sex, family history, level and origin of lesions, neurological symptom duration, lesion excision (yes/no), and outcome were recorded.

Statistical Analysis

Standard descriptive summaries were used to summarize demographic variables. Comparisons of categorical variables between patients with spinal lesions and those without were made using the χ^2 test or the Fisher exact test for expected cell counts <5. Comparisons of continuous variables were made using the student t test or the Mann-Whitney test depending on normality. Alpha was set at a significance level of $P < 0.05$. Statistics were performed utilizing SPSS version 22 (2013; IBM Corp., Armonk, NY).

RESULTS

Overall, 227 MHE patients were identified over the 24-year period, of which 21 underwent advanced spinal imaging. Advanced imaging revealed 8 patients with spinal lesions (8/21, 38% with imaging; 8/227, 3.5% overall), 4 of which (4/21, 19%) were intracanal lesions. All 4 intracanal lesions were in the cervical spine. Of these, only 1 was symptomatic (1/21, 4.8% with imaging; 1/227, 0.4% overall). Of patients with spinal exostoses, the average was 2.25 spinal lesions per patient (range, 1 to 4 lesions), and 6 (75%) patients had multiple lesions. Lesions were found throughout the spine, 7 (39%) cervical, 6 (33%) thoracic, and 5 (28%) lumbar.

Patients with spinal lesions had similar rates of back pain (63% vs. 69%), but more frequent neurological symptoms (50% vs. 15%, $P = 0.146$); however, these were not statistical significant. Common neurological symptoms included weakness, gait disturbance, and radicular pain. Upon further work-up, only 1 (16.7%) patient's neurological symptoms was thought to relate to a spinal osteochondroma, all others were due to confounding issues, such as peripheral nerve compression. Only 1 patient with spinal lesion and neurological symptoms underwent excision of a spinal lesion. None of the other 7 patients with known spine involvement required excision and none developed neurological symptoms during the follow-up period (average, 8.2 y; range, 3.0 to 12.7 y). Patients with spinal lesions also had

TABLE 1. Baseline Demographics

	No Spine Involvement (n = 13)	Spine Involvement (n = 8)	*P*
Sex (% male)	54	75	0.400
Family history (%)	62	67	0.999
Height (cm)	147.8	148.7	0.922
Height percentile for age*	52.2	68.8	0.902
Weight*	45	50.3	0.536
BMI*	18.9	21.1	0.171
Age at imaging	10.9	12.6	0.349
Back pain (%)	69	63	0.999
Neurological symptoms (%)	15	50	0.146
No. prior surgical procedures*	0	2.5	**0.046**
Total lesion count*	19	28.5	**0.010**

*Median.
The bold values indicate statistical significance (*P*-value <0.05).
BMI indicates body mass index.

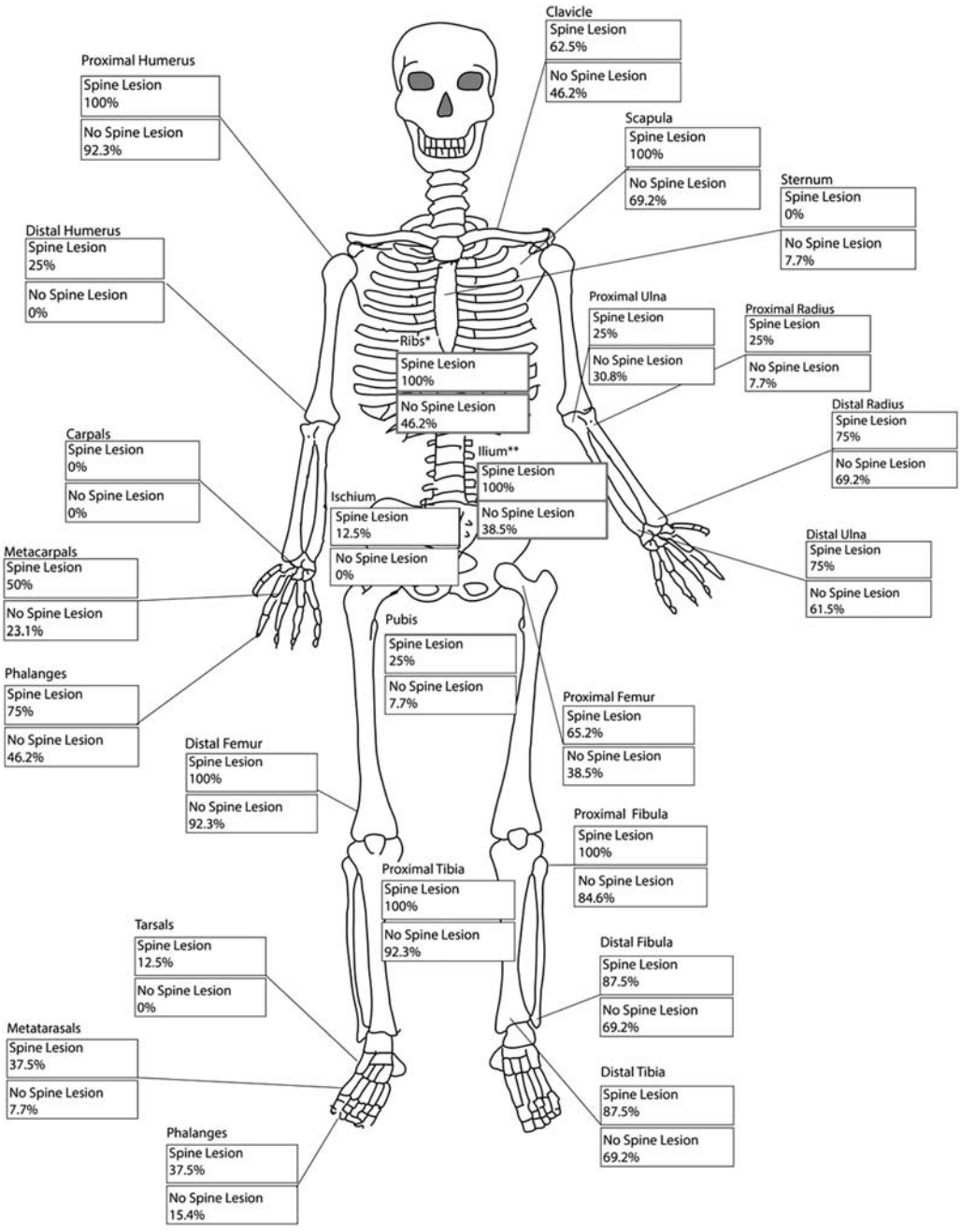

FIGURE 1. Comparison of the percentage of patients affected in each of the anatomic regions (*$P = 0.018$; **$P = 0.007$).

undergone a greater number of procedures for excision of extremity osteochondromas (median, 2.5 vs. 0; $P = 0.046$), reflective of their higher disease burden. Table 1 summarizes the baseline characteristics and compares those with spinal lesions to those without. Table A1 (electronic appendix, Supplemental Digital Content 1, http://links.lww.com/BPO/A130) summarizes the clinical data for all patients.

The distribution of lesions and comparison of involvement between groups are summarized in Figure 1. Patients with spinal lesions were more likely to have rib (100% vs. 46.2%, $P = 0.018$) and the iliac (100% vs. 38.5%, $P = 0.007$) involvement. There were no significant differences for all other locations. They also had overall significantly more lesions (median, 28.5 vs. 19; $P = 0.010$) (Fig. 2). The presence of both a rib and a pelvic lesion used as a screening tool for spinal lesions produces a sensitivity of 100% and specificity of 69% (Fig. 3).

DISCUSSION

The true prevalence of spinal lesions in MHE is unknown, with wide-ranging estimates ranging from 3%

		Spine Lesion on MRI/CT		
		Positive	Negative	
Presence of Both Rib and Pelvic Lesions	Positive	8	4	PPV= 66.7%
	Negative	0	9	NPV= 100%
		Sn=100%	Sp=69.2%	

FIGURE 2. Sensitivity and specificity of pelvic and rib lesions for spine lesions. CT indicates computed tomography; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

to 9%[1,2] to as high as 22% to 68%[6,7] in more recent studies. We estimate an overall prevalence between 3.5% and 38%. Although 38% of those with imaging had spinal lesions, this rate is likely an overestimation, as routine imaging was not performed in all MHE patients. Symptomatic lesions are quite rare, as we report only 1 patient, 0.4% overall. Others estimate only 0.5% to 1% of all spine osteochondromas are symptomatic,[17] although symptomatic lesions are more often reported in MHE patients compared with solitary osteochondromas[13] (Figs. 4, 5).

Our results strongly suggest differences/peculiarities in the clinical picture of MHE patients who develop spinal lesions. Patients with spinal lesions have more severe involvement overall, with higher total lesion counts (median, 28.5 vs. 19; $P=0.010$) and a greater number of prior surgeries (median, 2.5 vs. 0; $P=0.046$), which suggests more extensive involvement. Others have anecdotally noticed spinal lesions in patients with more extensive disease,[18] though unfortunately, discerning which patients have most severe involvement may be difficult as there is no agreed upon classification systems.[18–20] However, the present study is the first to identify strong association between spinal lesions and the presence of pelvic and rib osteochondromas, which can aid the determining patients at greatest risk. In contrast to other involved sites, the rib and pelvic lesions were most suited to serve as "harbinger lesions," as they were statistically associated with spinal lesions, and simultaneously ubiquitous in patients with spinal lesions while being found in only the minority of patients without spine lesions. The presence of both and pelvic and rib lesions, used as a screening criteria, had 100% sensitivity and 69% specificity for identifying patients with spinal lesions. Although the lack of a "harbinger" lesions does not guarantee the absence of spine involvement, it should be reassuring that patients without "harbinger" lesions are at low-risk and unlikely to have spine involvement. On the basis of this finding, we would not recommend routine imaging of the spine in this low-risk group, unless there are symptoms concerning for spine involvement.

It is unclear if spinal lesions occur in patients with greatest severity of disease, and pelvic and rib lesions are a proxy for severity, or if there is a subtype of MHE with greater propensity for axial skeleton involvement. Several studies demonstrate differing degrees of involvement and distribution of lesions based on genotype and sex.[8,21–24] However, the clinical presentation of MHE is quite variable, even within families, making clear genotype-phenotype correlations difficult to ascertain.[19] This is in part explained by the growing understanding that MHE requires a "second hit" for the phenotype to arise, with worse disease severity the earlier the hit.[25,26]

Although we did not have genotypic data to make comparisons, there is some basis for a genetic correlation between "harbinger," spinal lesions, and severity of disease[8,21,22,24] Clement and Porter[8] found more extensive disease and higher rates of pelvic and spine lesions in

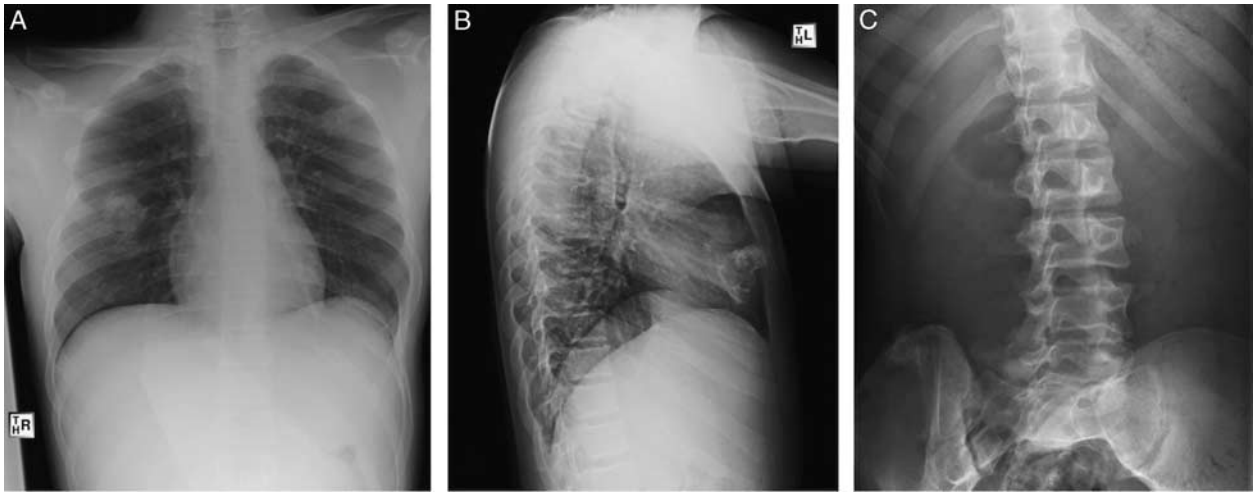

FIGURE 3. A, The 14-year-old boy with left third rib and right sixth rib osteochondromas visible in an anteroposterior view of the chest. B, The same sixth rib osteochondroma visible on a lateral view of the chest. C, The same child with a right iliac crest osteochondroma. This child was also found to have an intracanal osteochondroma of the C2 vertebra.

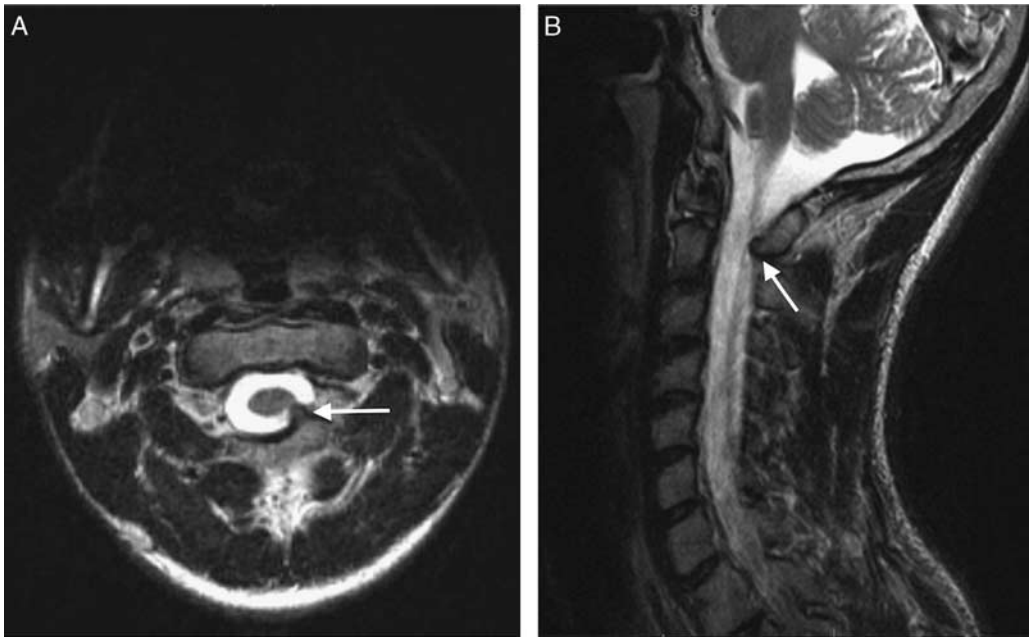

FIGURE 4. A 14-year-old child with an intracanal osteochondroma of the C2 lamina (arrows) visible on axial (A) and sagittal (B) T2-weighted noncontrast magnetic resonance imaging. This child was also found to have a pelvic osteochondroma and 2 rib osteochondromas.

patients with *EXT 1* than *EXT 2* gene mutations. Prior studies have also linked the EXT 1 mutation with greater tumor burden and predilection for the pelvis and other flat bones, though the spine was not specifically evaluated.[21,22] Male sex has also been linked to the development of more extensive disease,[8,23,27] and a higher incidence of spinal lesions.[6,13] Likewise, we found a higher proportion of males in patients with spinal lesions (75% vs. 54%, $P = 0.400$); however, this was not significant.

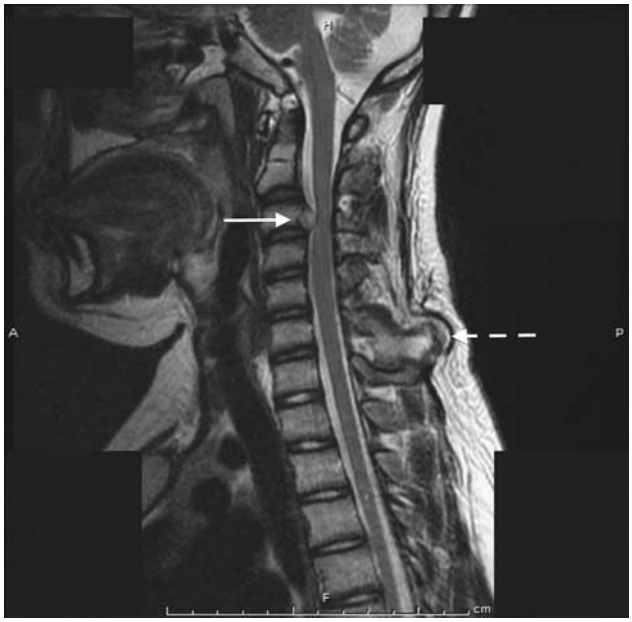

FIGURE 5. A 15-year-old boy with a palpable osteochondroma of the spine at the level of C6. The lesion was planned for excision due to pain. A preoperative sagittal T1-weighted noncontract magnetic resonance imaging demonstrated the large, C6 osteochondroma (dashed arrow) as well as an incidental, asymptomatic C3 osteochondroma (solid arrow) on the posterior vertebral body. The symptomatic C6 lesion was removed, whereas the asymptomatic C3 lesion was not.

Review of the literature revealed 67 cases of spinal osteochondromas or spinal cord compression in MHE patients 18 years and below (Table A2, Electronic Appendix, Supplemental Digital Content 2, http://links.lww.com/BPO/A131). Nearly all (92%) with neurological symptoms completely recovered, and it is argued that residual deficits may continue to improve with time.[13] It should be noted that 1 case reported the death of a child with a C2 lesion.[28] However, his symptoms developed slowly over the course of years, progressing from weakness and eventually to quadriplegia. He was finally brought to medical attention due to recurrent pneumonia, subsequently requiring mechanical ventilation, and ultimately succumbing to respiratory complications. Most lesions in reported cases occurred in males (64%) and in the cervical spine (57%), rarely involving the lumbar spine (4%). However, there is likely reporting bias as, compared with lumbar lesions, cervical lesions are more often symptomatic, thus coming to medical attention, given the reduced anatomic space and increased mobility.[13] Our patients, however, revealed fairly even distribution of lesions throughout the spine, although the only symptomatic lesion was of the cervical spine.

Once discovered, it is unclear how best to proceed for asymptomatic lesions. How often repeat imaging is needed, which require prophylactically excision, and if activity modification is necessary, remain unanswered questions. Fukushi et al[14] recommend follow-up for all until skeletal maturity, although the frequency and method were not specified.

Roach et al[6] recommend excision of all lesions compressing the dural sac, and did not recommend activity modification for patients being observed. Despite MRIs being performed in all patients, this recommendation only altered care for 3 of the 44 MRIs (7%). Even still, it is unclear if these prophylactic excisions improve outcomes. Thus, further prospective studies are needed to better characterize which lesions become symptomatic and determine if proactive treatment (ie, prophylactic excision) improves outcomes over reactive treatment (ie, excision of symptomatic lesions).

Because of the rarity of MHE, small sample size is a limitation of our study. However, it is still among the largest cohorts to specifically evaluate spinal lesions in MHE patients, and the only to do so exclusively in skeletally immature patients. The true prevalence of these lesions is not known as patients were not universally screened at our institution and only a small portion underwent imaging. As such, our sample may be biased toward more severely involved patients, limiting generalizability. In addition, counting of the lesions was performed retrospectively and relied on reported physical examination findings and the availability of radiographs. No additional images were taken beyond that necessary for medical care, thus, patients did not all have identical radiographic evaluations. However, the counting method used places less need for repeated radiographs, as once a region was affected it did not need to be reevaluated to assess for the development of new lesions.

Spinal lesions in MHE patients are uncommon and symptomatic lesions even more so, yet seem to have a good prognosis when treated promptly. Given high cost to the health care system, uncertainty regarding management of asymptomatic lesions, and the likelihood patients will not become symptomatic, we argue against routine imaging for all MHE patients. Rather, we recommend patient education regarding symptoms of spinal cord compression, emphasizing the need for timely medical attention. We recommend limiting advanced imaging to patients who present with concerning neurological symptoms and those with "harbinger" lesions of the rib and pelvis. These may be easily detected on physical examination or plain radiographs, and patients without these findings appear to be at very low-risk for spinal exostosis.

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