Development of an X-ray–Based Bone Oxalosis Grading Scale to Assess Oxalate Accumulation in Patients with Primary Hyperoxaluria Type 1

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INTRODUCTION

- Primary hyperoxaluria type 1 (PH1) is a rare genetic disease in which hepatic oxalate overproduction can lead to kidney stones, nephrocalcinosis, kidney failure, and systemic oxalosis, a condition in which calcium oxalate is deposited in various tissues, including bone[1,2]

- Radiological signs of bone oxalosis include dense and radiolucent metaphyseal bands, coarse trabeculation, vertebral "bone within a bone" appearance, and bulbous growth of rib ends[3,4]

- Previously, no scale existed to grade the severity of bone oxalosis using x-rays

METHODS

- An x-ray grading scale to evaluate systemic oxalosis in specific bones was developed based on expert opinion

- Areas evaluated included the bilateral hands and wrists, hips (proximal femur), knees (distal femur, tibia, and fibula), and humeri (proximal only) as well as the spine and ribs

- Scores on individual items ranged from 0 to 4, except for spine and ribs, which ranged from 0 to 2 (higher values represent more advanced oxalosis)

- Fracture assessment was not included in the scale

- Eighty-five x-ray images from 5 pediatric patients with PH1 who had developed bone oxalosis were collected from charts at Shaare Zedek Medical Center (Jerusalem, Israel) and de-identified

- Two blinded, independent raters evaluated each x-ray image twice and assigned a numerical score to each applicable item on the scale

- Inter-rater and intra-rater reliability analyses were conducted using the weighted Cohen's kappa statistic[5] (Table 1)[6]; total weighted kappa estimates were generated by pooling all observed ratings for each evaluated area

Table 1. Reliability Interpretation[6] of Kappa Statistic

Kappa	Strength of Agreement
<0.00	Poor
≥0.00–0.20	Slight
>0.20–0.40	Fair
>0.40–0.60	Moderate
>0.60–0.80	Substantial
>0.80–1.00	Almost perfect

RESULTS

- Total overall inter-rater and intra-rater kappa estimates demonstrated almost perfect agreement (Table 2)

- Overall inter-rater kappa estimates demonstrated the following:

  - Almost perfect agreement (kappa estimates of >0.80–1.0) was observed for the left hand/wrist, left hip, left knee (femur), and left humerus

    - An example of scoring results for the left hand/wrist is shown in Table 3. An example x-ray is shown in the Figure

  - Substantial agreement (kappa estimates of >0.60–0.80) was observed for the right hip, right knee (tibia), right humerus, spine, and ribs

  - Moderate agreement (kappa estimates of >0.40–0.60) was observed for the right knee (femur) and right knee (fibula)

  - The overall inter-rater kappa estimate for the left knee (fibula) demonstrated poor agreement (−0.08 [95% CI: −0.27 to 0.10])

  - Overall inter-rater kappa estimates for the right hand/wrist and left knee (tibia) were considered unreliable due to lack of variability in the data, and the standard errors were not estimable

- Overall intra-rater kappa estimates demonstrated the following:

  - Almost perfect agreement (kappa estimates of >0.80–1.00) was observed for the spine

  - Substantial agreement (kappa estimates of >0.60–0.80) was observed for the right knee (femur) and right knee (fibula)

- Most other overall intra-rater kappa estimates could not be calculated due to lack of variability in the estimates for one or both raters. In these instances, intra-rater kappa estimates for the first and second raters demonstrated moderate to almost perfect agreement (>0.40–1.00; left hand/wrist, right hip, left hip, left knee [femur], right knee [tibia], left knee [tibia], right humerus, left humerus, and ribs). For the left knee (fibula), intra-rater kappa estimates for the first and second raters were −0.14 (−0.34 to 0.05) and 1.00, respectively, and for the right hand/wrist, they were 1.00 and 0.00

Table 2. Total Overall Kappa Estimates[a]

	Weighted Kappa (95% CI)/N[b]
Inter-rater	
Overall	**0.83 (0.79–0.87)/479**
First rating	0.82 (0.77–0.87)/242
Second rating	0.84 (0.79–0.89)/237
Intra-rater	
Overall	**0.95 (0.93–0.97)/482**
First rater	0.82 (0.77–0.87)/237
Second rater	0.97 (0.95–0.99)/245

CI, confidence interval.
[a]Total kappa estimates were generated by pooling all observed ratings across all questions.
[b]Number of paired observations.

Table 3. Scoring for the Left Hand/Wrist[a,b]

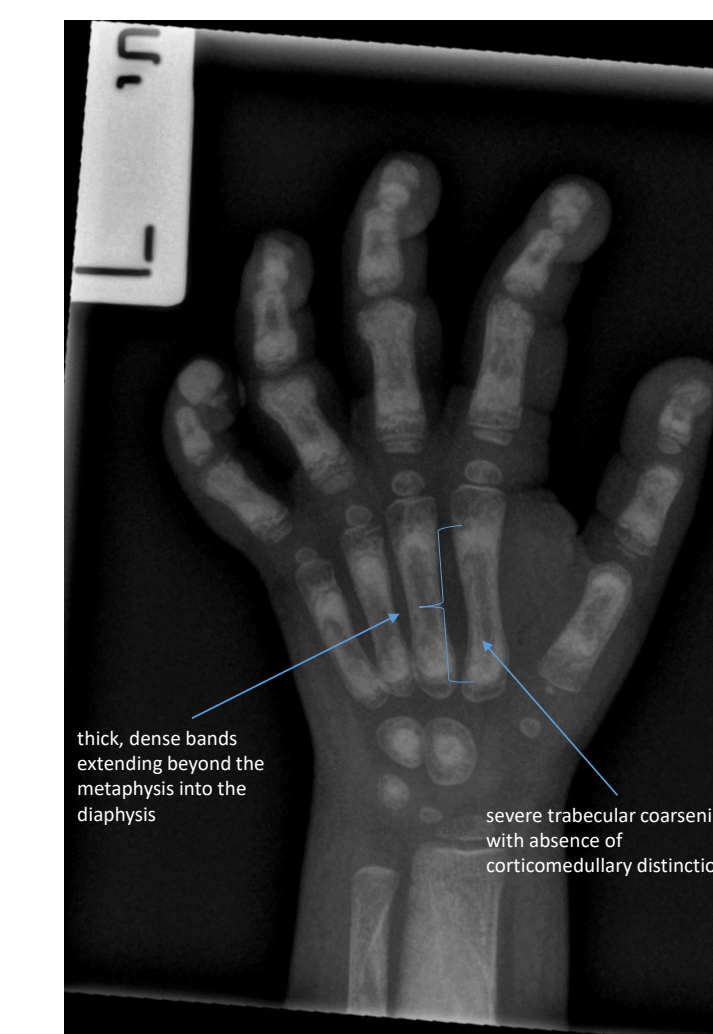|	Weighted Kappa (95% CI)/N[c]
Inter-rater	
Overall	**0.83 (0.72–0.93)/54**
First rating	0.76 (0.58–0.94)/27
Second rating	0.86 (0.73–0.99)/27
Intra-rater	
Overall	**N/A (N/A)/54**
First rater	0.76 (0.58–0.94)/27
Second rater	1.00 (N/A)/27

CI, confidence interval; N/A, not adequate.
[a]Twenty-seven images contained the targeted bone. Overall intra-rater kappa estimate and asymptotic CI could not be calculated.
[b]Right hand/wrist was assessed separately using the same criteria.
[c]Number of paired observations.

Figure. Left Hand/Wrist X-ray.
Bone Oxalosis Grading Scale Score: 4

thick, dense bands extending beyond the metaphysis into the diaphysis

severe trabecular coarsening with absence of corticomedullary distinction

CONCLUSIONS

- We developed a novel x-ray–based bone oxalosis grading scale for patients with PH1

- Total overall weighted kappa estimates for inter-rater and intra-rater reliability demonstrated almost perfect strength of agreement

- Most individual items demonstrated reliable kappa estimates (in some cases, sample sizes were limited)

- The right and left knee (fibula) were removed from the scale due to poor reliability

DISCLOSURES

J Baker: Consulting fees from Alnylam Pharmaceuticals.
J Bacchetta: Consulting fees from Alnylam Pharmaceuticals, Dicerna and Biocodex.
LC: Former employee of Alnylam Pharmaceuticals; currently employed with Alexion Pharmaceuticals.
JMG & RW: Employees of Alnylam Pharmaceuticals and hold shares in Alnylam Pharmaceuticals.
YF: Consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee.
RC-K: Consulting fees from Alnylam Pharmaceuticals and Medpace.

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