

# Characteristic Reconstitution of the Spinal Langerhans Cell Histiocytosis in Young Children

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**Background:** Pediatric Langerhans cell histiocytosis (LCH) often results in vertebral compression fracture. However, few reports have reported vertebral remodeling during the course of LCH. We aimed to investigate the longitudinal reconstitution and transformation of the affected vertebrae and the adjacent structures in young children with spinal LCH.

**Methods:** We recruited 13 patients, including 16 affected vertebrae, diagnosed with LCH via biopsy. The average age at first visit was 3.6 years. The average follow-up period was 10.2 years. Vertebral lesions involved L2 in 3 cases; T12, L1, or L5 in 2 cases; and C4, C5, C7, T5, T8, T9, or L3 in 1 case. We measured the ratios of the height of the affected vertebra and 1 vertebra above the affected one to that of the second vertebra above the affected one, local kyphotic angles, and the ratio of the height of the center of the adjacent disk to that of one disk above it.

**Results:** The collapse of the affected vertebra was most severe after 1 year of disease onset. The rate of reconstitution accelerated at 2 years or later of disease onset. The recovery speed of the anterior wall was faster than that of the center height. While the height of the affected vertebrae was restored, the thickness of the adjacent disk also increased. Further, the height of the adjacent vertebrae increased in a similar manner. The average local kyphosis angle shifted to lordosis within the first 3 years.

**Conclusions:** The heights of not only the disk but also the adjacent vertebra increased during the vertebral collapse phase in pediatric spinal LCH patients. These transformations may affect the realignment of the sagittal spinal balance at the earlier stage of the disease. During the collapse phase, the heights of the adjacent vertebrae and

disks increase but after the affected vertebrae reconstituted, the augmentation of adjacent vertebrae and disks diminished.

**Level of Evidence:** Level IV.

**Key Words:** Langerhans cell histiocytosis, spine, young children, reconstitution, realignment, remodeling, kyphosis, lordosis

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Letterer-Siwe disease, Hand-Schuller-Christian disease, and Eosinophilic granuloma, previously believed to be 3 different diseases, are now known to be different presentations of a single disease process [Langerhans cell histiocytosis (LCH)] distinguished by the clonal proliferation of Langerhans cells.<sup>1,2</sup> Many reports on patients with LCH of the spine are well described in the literature, and the clinical findings were first reported by Calve in 1925. The incidence of LCH with spine lesions in children is ~20% to 30%.<sup>3</sup> However, vertebral collapse commonly occurs in pediatric LCH patients and induces local kyphosis of the sagittal alignment at the affected site during early stages. Spontaneous recovery of the compression fracture is a characteristic of this disease. Most previous studies have focused on the results at discontinuous timing including onset and final visit. Few reports have demonstrated in detail the longitudinal assessment for vertebral remodeling. Therefore, this study aimed to investigate the longitudinal changes in the affected vertebrae and the adjacent disk and vertebrae in children with spinal LCH, aged below 8 years, within the first 7 years after disease onset.

## METHODS

We recruited 13 patients (9 girls and 4 boys) including 16 affected vertebrae. All patients were aged below 8 years. They were diagnosed with LCH by histologic assessment via biopsy. Biopsy is not always necessary to diagnose this condition. However, in this study, we recruited only patients with pathologic diagnosis via biopsy to maintain a high accuracy of diagnosis for research purposes. Children with C1 lesions were excluded from this study. The average age at first visit was 3.6 years (range, 1.4 to 7.8 y), and the average follow-up period was 10.2 years (range, 5 to 21 y). A single lesion was observed in 5 patients, whereas multiple lesions were observed in the remaining 8 patients who received chemotherapeutic treatment, including 2 patients with organ involvement. Nine patients used a brace for 3 months to 6 years, and 4 patients were treated with supervised neglect. Vertebral

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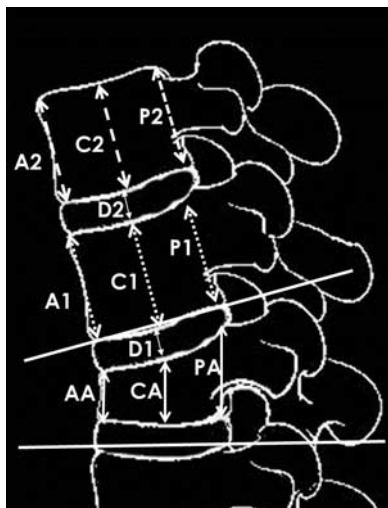
The authors declare no conflicts of interest.

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**FIGURE 1.** Radiographic measurements. AA/A2 indicates the ratio of the height of the anterior wall of the affected vertebra to that of the 2 above vertebra; A1/A2, the ratio of the height of the anterior wall of the 1 above vertebra to that of the 2 above vertebra; CA/C2, the ratio of the height of the center of the affected vertebra to that of the 2 above vertebra; C1/C2, the ratio of the height of the center of the 1 above vertebra to that of the 2 above vertebra; DD, the ratio of the adjacent disk (D1) to the one above disk (D2); LKA, local kyphosis angle; PA/P2, the ratio of the height of the posterior wall of the affected vertebra to that of the 2 above vertebra; P1/P2, the ratio of the height of the posterior wall of the 1 above vertebra to that of the 2 above vertebra.

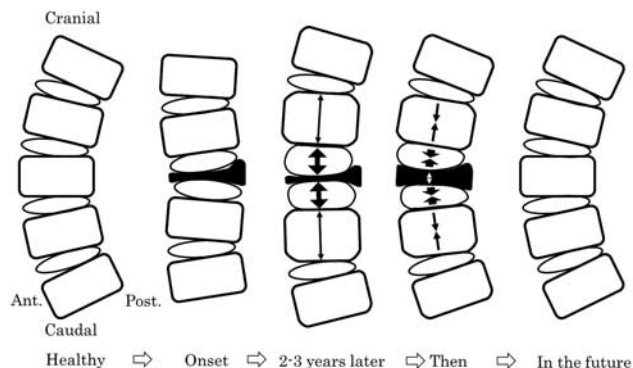
lesions involved L2 in 3 cases; T12, L1, or L5 in 2 cases; and C4, C5, C7, T5, T8, T9, or L3 in 1 case.

First, we measured the ratios of the height of the affected vertebra and one vertebra above the affected one to that of the second vertebra above the affected one (AA/A2, CA/C2, PA/P2, A1/A2, C1/C2, and P1/P2), as the indices of the collapse and reconstitution of the affected vertebra and the influence of adjacent vertebra. Next, we measured the ratio of the height of the center of the adjacent disk to that of the one disk above it (DD) and the local kyphosis angle to define the transformation of the adjacent disk and the shift in the sagittal alignment. We made these radiographic measurements using sagittal x-ray films obtained with the patient in a standing position (Fig. 1). In addition, we assessed the influence of chemotherapy and brace treatment on the recovery of vertebral collapse using CA/C2.

We examined patient data until 7 years after disease onset as the data for this period had only few missing entries. Statistical differences between first visit and other timings were analyzed using the Wilcoxon signed-rank test. A probability value of <0.05 was considered statistically significant. Data analysis was performed using SPSS package version 24 (IBM Corporation, Armonk, NY).

## RESULTS

Tables (Supplemental Digital Content 1, <http://links.lww.com/BPO/A186>) show the data of the collapsed vertebra, local kyphosis angle, and the adjacent structures.



**FIGURE 2.** The schema of the reconstitution of spinal Langerhans cell histiocytosis at the lumbar site. After disease onset, the transformations of the adjacent structures occurred to recover the spinal alignment. As the affected vertebra reconstituted, the augmentation of the adjacent disk and vertebra gradually diminished.

## The Index of Vertebral Collapse and Local Kyphosis

In the affected vertebra, the posterior wall height remained in the collapse phase and the most severe collapse was noted not at the first visit but 1 year after disease onset. The recovery speed of the anterior wall tended to be faster than that of the center. The rate of reconstitution accelerated at 2 years or later. However, complete reconstitution was not achieved at the final visit (7 years after onset). Patients acquired lordosis alignment within the first 3 years.

Patients who received chemotherapy had a tendency to show a lower rate of vertebral collapse of the affected vertebra and the faster recovery ( $P < 0.05$  at 5 and 6 y after onset) (Supplemental Digital Content 2, <http://links.lww.com/BPO/A187>). There was no statistical difference between the patients with and without brace treatment (Supplemental Digital Content 3, <http://links.lww.com/BPO/A188>).

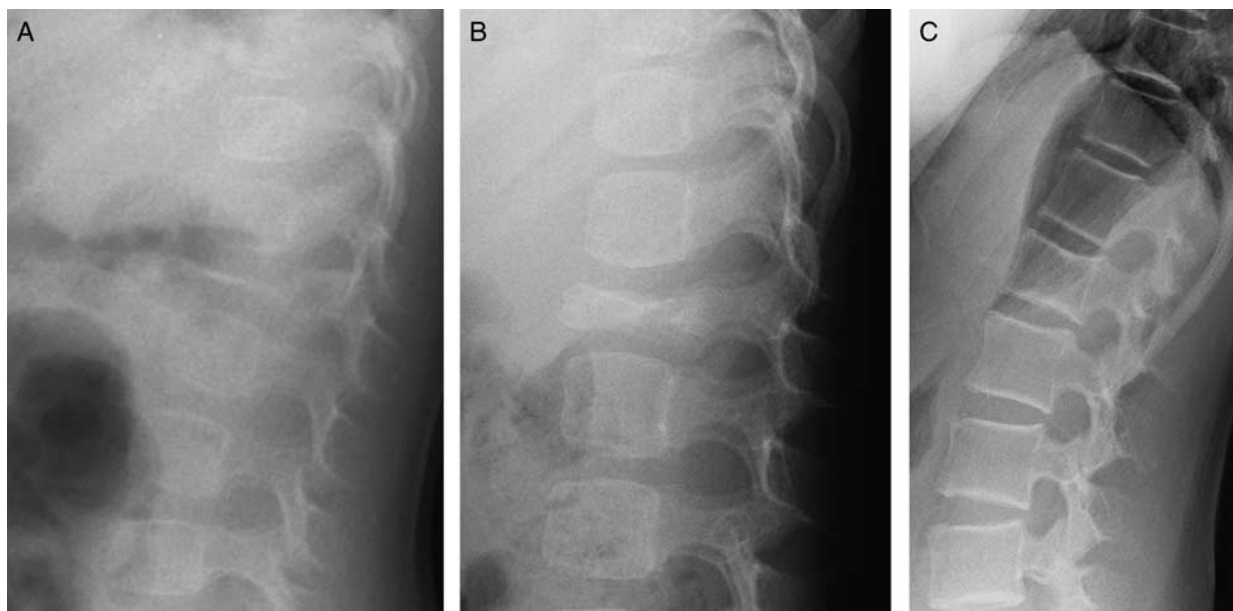
## The Index of the Transformation of the Adjacent Structures

The height of the adjacent disk increased during a severe collapse phase of the affected vertebra. In addition, the height of adjacent vertebra increased in the same phase. Figure 2 shows the schema of the reconstitution of spinal LCH in this series (Fig. 3).

## DISCUSSION

The vertebral height in children with spinal LCH gradually recovered, despite the almost complete collapse of the affected vertebra at disease onset.<sup>4,5</sup>

Several treatments for bony LCH lesions have been reported including supervised observation, steroid injections, curettage with/without a bone graft, chemotherapy, and irradiation. With a variety of treatment options, most of the patients responded well, and there is no evidence suggesting that one treatment is more advantageous than another.<sup>6</sup> In the present study, the patients who were treated with



**FIGURE 3.** Case presentation. Spinal Langerhans cell histiocytosis at L1 in a 3-year-old girl. A, First visit: the affected vertebra showed severe collapse and caused local kyphosis. The heights of the adjacent disks had already increased. B, After 2 years, the affected vertebra had shown a tendency to recover and the heights of the adjacent disks and vertebrae were increased. C, At final visit (12 y old), the height of the affected vertebra was comparable to the other healthy vertebra. The heights of adjacent disks and vertebrae were almost normal.

chemotherapy tended to show a lower percentage of vertebral collapse at an early stage and faster recovery. To the best of our knowledge, there is no study reporting the effect of chemotherapy on the recovery of collapsed vertebrae. We believe that bed rest may be one of the factors preventing vertebral collapse because chemotherapy requires in-hospital treatment. The other factor may be the site of the affected vertebra. The nonchemotherapy cases included 3 vertebrae in thoracic spine. The resilience of cervical and lumbar vertebrae, which represent lordosis alignment, was better than that of thoracic vertebrae, which represent kyphosis alignment. However, the small sample size is a limitation of this study, and we need further research to explain this result. Specifically, for the treatment of spinal LCH, most physicians seem to consider immobilization with a brace as the initial treatment. Several studies have reported that immobilization is adequate for most patients.<sup>7</sup> We agreed with Greenlee et al's<sup>8</sup> suggestion that the brace can be removed after the pain is resolved. Although we tried to compare outcomes between the groups with and without brace treatment in this series, there was no significant difference in the reconstitution of the affected vertebrae and the spinal alignment. Thus, we believe that there are no advantages of long-term use of braces.

Several studies have reported that the best reconstitution of vertebral height was noted after skeletal maturity, and adolescence or at least 4 years before the development of skeletal maturity is an appropriate time for vertebral remodeling.<sup>9,10</sup> Raab et al<sup>11</sup> reported that the degree of reconstitution does not change based on the involved site: cervical, thoracic, or lumbar portion. In our study, 13 of 16

affected vertebrae were located at the physiological lordosis site (cervical and lumbar portion). The collapse of the affected vertebra was most severe 1 year after disease onset. Then, the affected vertebra gradually recovered. Finally, overall results of this series headed toward lordosis alignment. Meanwhile, the final recovery height of the affected vertebrae reported in previous studies<sup>9-11</sup> was better than that reported in this study. Therefore, our results only indicate reconstitution at the early stage of the disease (only 7 years after onset).

Local kyphosis also improved in the same manner. Intriguingly, the recovery speed from kyphosis to lordosis was faster than the recovery speed of the affected vertebral height. Thus, we investigated the transformation of the adjacent disks and vertebrae. As a result, 1 and 2 years after onset, the period with the maximum collapse of the affected vertebra, the heights of not only the adjacent disk but also the adjacent vertebra increased. We could not determine whether it was overgrowth or an augmentation change. We often see the similar phenomenon in early-onset scoliosis children with implanted growing rods, who show vertebral body growth by the growth-stimulating effect of the distraction force that the growing rod produces based on Hueter-Volkman principle.<sup>12-15</sup> Similarly, considering that the final alignment in this series leads toward lordosis alignment, there is a possibility of a small effect of reduced axial pressure or the relative distraction force at the adjacent site of the collapsed vertebrae. We need more bioengineering studies in the future to validate this hypothesis. After the onset, the transformations of the adjacent structures occurred as if to augment the spinal alignment. These transformations affected the positive realignment of the sagittal balance at the earlier stage of the

disease. Then, based on the reconstitution of the affected vertebra, the augmentation of the adjacent disk and vertebra gradually diminished. There are no reports that have discussed the changes of the adjacent disks and vertebrae in detail.

In this study, the average age at disease onset was 3.6 years. Moreover, very young children have better bone remodeling potential. Greenlee et al<sup>8</sup> suggested that younger patients have greater potential for recovery of vertebral height. However, Levine et al<sup>13</sup> reported varying degrees of reconstitution of vertebral height and noted no correlation between age and the degree of reconstitution. With regard to this point, the results of the present study remained controversial. Hence, further studies are needed to determine the transformation of the adjacent disk and vertebrae among adolescents.

### REFERENCES

1. Lichtenstein L. Histiocytosis X (eosinophilic granuloma of bone, Letterer-Siwe disease, and Schuller-Christian disease). Further observations of pathological and clinical importance. *J Bone Joint Surg Am.* 1964;46:76–90.
2. Schajowicz F, Stullitel J. Eosinophilic granuloma of bone and its relationship to Hand-Schuller-Christian and Letterer-Siwe syndromes. *J Bone Joint Surg Br.* 1973;55:545–565.
3. Sessa S, Sommelet D, Lascombes P, et al. Treatment of Langerhans-cell histiocytosis in children. Experience at the Children's Hospital of Nancy. *J Bone Joint Surg Am.* 1994;76:1513–1525.
4. Bavbek M, Atalay B, Altinors N, et al. Spontaneous resolution of lumbar vertebral eosinophilic granuloma. *Acta Neurochir (Wien).* 2004;146:165–167.
5. Kamimura M, Kinoshita T, Itoh H, et al. Eosinophilic granuloma of the spine: early spontaneous disappearance of tumor detected on magnetic resonance imaging. Case report. *J Neurosurg.* 2000;93 (suppl):312–316.
6. Kilpatrick SE, Wenger DE, Gilchrist GS, et al. Langerhans' cell histiocytosis (histiocytosis X) of bone. A clinicopathologic analysis of 263 pediatric and adult cases. *Cancer.* 1995;76:2471–2484.
7. Mammano S, Candiotti S, Balsano M. Cast and brace treatment of eosinophilic granuloma of the spine: long-term follow-up. *J Pediatr Orthop.* 1997;17:821–827.
8. Greenlee JD, Fenoy AJ, Donovan KA, et al. Eosinophilic granuloma in the pediatric spine. *Pediatr Neurosurg.* 2007;43:285–292.
9. Ippolito E, Farsetti P, Tudisco C. Vertebra plana. Long-term follow-up in five patients. *J Bone Joint Surg Am.* 1984;66:1364–1368.
10. Nesbit ME, Kieffer S, D'Angio GJ. Reconstitution of vertebral height in histiocytosis X: a long-term follow-up. *J Bone Joint Surg Am.* 1969;51:1360–1368.
11. Raab P, Hohmann F, Kuhl J, et al. Vertebral remodeling in eosinophilic granuloma of the spine. A long-term follow-up. *Spine (Phila Pa 1976).* 1998;23:1351–1354.
12. Akbarnia BA, Breakwell LM, Marks DS, et al. Dual growing rod technique followed for three to eleven years until final fusion: the effect of frequency of lengthening. *Spine (Phila Pa 1976).* 2008;33:984–990.
13. Levine SE, Dormans JP, Meyer JS, et al. Langerhans' cell histiocytosis of the spine in children. *Clin Orthop Relat Res.* 1996;323:288–293.
14. Olgun ZD, Ahmadiadli H, Alanay A, et al. Vertebral body growth during growing rod instrumentation: growth preservation or stimulation? *J Pediatr Orthop.* 2012;32:184–189.
15. Yilmaz G, Huri G, Demirkran G, et al. The effect of posterior distraction on vertebral growth in immature pigs: an experimental simulation of growing rod technique. *Spine (Phila Pa 1976).* 2010;35:730–733.