

Imaging Features of Early Diffuse Idiopathic Skeletal Hyperostosis (pre-DISH): Analysis of Progression of Ligament Ossification over 5 Years by Computed Tomography

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Abstract:

Introduction: Some patients who have not been diagnosed with diffuse idiopathic skeletal hyperostosis (DISH) (patients in the preclinical stage of DISH [pre-DISH]) may develop DISH in the future. However, there are currently no clearly defined diagnostic criteria for pre-DISH. This study aims to define pre-DISH by analyzing the change in the ossification extent in each intervertebral space in the thoracic and lumbar spines over time using computed tomography (CT).

Methods: Of the patients who underwent CT of the thoracic to pelvic region at least twice from 2009 to 2018, 188 who underwent CT at an interval of 5 years to 5 years and 2 months were enrolled. The prevalence of DISH during the first and second CT scans was investigated. The pre-DISH feature was defined, and the prevalence of pre-DISH on the first CT and the change after 5 years in patients with pre-DISH was investigated.

Results: Of the 188 patients, 37 (19.7%) and 48 (25.5%) were diagnosed with DISH on the first and second CT scans, respectively. Pre-DISH was defined as the ossification characterized by the modified Mata score of three contiguous intervertebral spaces with a score of ≥ 2 points (222; 2 points, ligament ossification of half or more of the intervertebral disc height but incomplete fusion), and 52 patients were diagnosed with pre-DISH. Of the 52 patients with a score of ≥ 2 , 11 (21.2%) were diagnosed with DISH 5 years later.

Conclusions: Patients who have three contiguous intervertebral spaces with a modified Mata score of 2 or 3 points should be considered pre-DISH.

Keywords:

Diffuse Idiopathic Skeletal Hyperostosis, Pre-DISH, Ligament Ossification, Thoracic and Lumbar Vertebra

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Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by progressive ossification of the ligaments throughout the body. The anterior longitudinal ligament on the vertebral bodies ossifies in the spine. DISH is a condition that gradually makes the spine rigid for unknown reasons^{1,2}.

The anterior longitudinal ligament does not undergo rapid ossification in patients with DISH, but it gradually ossifies. Ligament ossification gradually progresses when a single intervertebral space is concerned as shown by the grading systems developed by Resnick et al.² and Mata et al.³. Eventual bridging of intervertebral spaces results in loss of intervertebral mobility. The increase in bridged intervertebral spaces causes spine rigidity when the entire spine is concerned, de-

spite differences among individual patients. Bridging may occur along the contiguous intervertebral spaces or at separate intervertebral spaces. DISH is diagnosed when three contiguous intervertebral spaces are bridged with the intervertebral disc height relatively maintained and without the rigidity of the sacroiliac joint¹. Although bridging is not observed in most people in their 30s or younger, the prevalence of DISH increases in their 50s. Moreover, DISH is detected in more than 50% of men in their 80s⁴. Ossification also more rapidly progresses in younger people⁵. Based on these findings, ligament ossification in DISH appears to be a pathological condition that gradually progresses.

The presence of DISH affects the treatment outcomes of other spinal diseases as described above, and the presence or absence of DISH should be considered when treatment

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strategies are determined. The diagnosis of DISH requires the presence of bridging of three or more contiguous intervertebral spaces, following the diagnostic criteria developed by Resnik and Niwayama¹⁾. Clinically, many patients who cannot be diagnosed with DISH but are susceptible to developing DISH in the future (patients in the preclinical stage of DISH [pre-DISH]) were encountered. For example, patients with bridging of two contiguous intervertebral spaces and patients with three or more contiguous intervertebral spaces almost bridged (2 points on the Mata scoring system) were noted. Considering that one report shows that the mobility of intervertebral discs decreases with ossification progression despite the absence of completely bridged intervertebral spaces⁶⁾, treatment of other spinal diseases even in patients with pre-DISH should be undertaken cautiously, similar to that in patients with DISH. However, there are no clearly defined diagnostic criteria for pre-DISH.

Images of computed tomography (CT) performed from the thoracic to the pelvis in the same patients at an interval of approximately 5 years were used in this study to analyze the change in ossification extent in each intervertebral space in the thoracic and lumbar spines over time. Based on this analysis, this study attempted to define pre-DISH.

Materials and Methods

1. Subjects

This study enrolled 8,216 patients who underwent CT of an area from the thoracic to the pelvis at the hospital of the present study at least twice between January 2009 and December 2018, regardless of primary diseases. Of these patients, 188 with images taken at intervals of 5 years and 0-2 months (87 men and 101 women with a mean age of 61.6 years at the time of the first CT) were examined. The first and second CT scans were defined as the CT images recorded at baseline and after 5 years, respectively. The patients with an interval of <5 or >5 years and 2 months were excluded, even if they had undergone CT imaging more than once. Of the patients included in this study, 76.1% had CT scans to follow-up on their cancer treatment. The patients who could not be followed up due to underlying disease were not included in this study.

2. Diagnosis of DISH and evaluation of the extent of progression of ossification

The presence or absence of DISH was separately determined on the first and second CT images. DISH was diagnosed when three diagnostic criteria developed by Resnik and Niwayama¹⁾ were met: (1) the presence of osseous bridging of four contiguous vertebral bodies on the anterior or lateral aspect, (2) the presence of relatively preserved intervertebral disc spaces, and (3) the absence of the rigid sacroiliac joint. Subsequently, the extent of the progression of ligament ossification in each intervertebral space was evaluated using the modified Mata scoring system⁶⁾. Scores were

assigned as follows: 0 point, no ligament ossification; 1 point, ligament ossification of less than half of the intervertebral disc height; 2 points, ligament ossification of half or more of the intervertebral disc height but incomplete fusion; and 3 points, complete bridging (Fig. 1). Each intervertebral space in the thoracic and lumbar spines (T1/2-L5/S) was evaluated. Three spinal surgeons with ≥5 years' experience evaluated the spaces. The scores that appeared to be most appropriate for each intervertebral space were adopted through consensus.

To indicate the extent of ossification in three contiguous intervertebral spaces, the scores were expressed as (333) for a combination of three contiguous intervertebral spaces with a score of 3 points, (332) for a combination of two intervertebral spaces with a score of 3 points and one intervertebral space with a score of 2 points, (322) for a combination of one intervertebral space with a score of 3 points and two intervertebral spaces with a score of 2 points, and (222) for a combination of three intervertebral spaces with a score of 2 points (Fig. 2).

3. Study 1 (determination of imaging features of pre-DISH)

First, the prevalence of DISH during the first and second CT scans was evaluated and examined according to age and sex. Second, patients who were not diagnosed with DISH by the first CT but were diagnosed with DISH by the second CT were selected. The characterization of the scores on the first CT images (recorded 5 years earlier) was examined in patients with complete bridging (3 points) of three or more contiguous intervertebral spaces (333) on the second CT image.

4. Study 2 (prevalence of pre-DISH and extent of progression of ossification)

Based on the results of Study 1, none of the patients with a score of less than [222] in three contiguous vertebral spaces developed DISH [333] after 5 years. Therefore, the feature of pre-DISH was defined as the presence of three contiguous intervertebral spaces with a modified Mata score of ≥2 points ([222], [322], or [332]). The prevalence of pre-DISH on the first CT images was evaluated. Subsequently, the change in the scores after 5 years in patients with three contiguous intervertebral spaces with a modified Mata score of ≥2 points was examined.

5. Statistical analysis

IBM SPSS for Mac ver. 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. A chi-square test was performed for categorical analyses. Student's t-test was performed for continuous variables (e.g., age). A P-value of <0.05 was considered statistically significant.

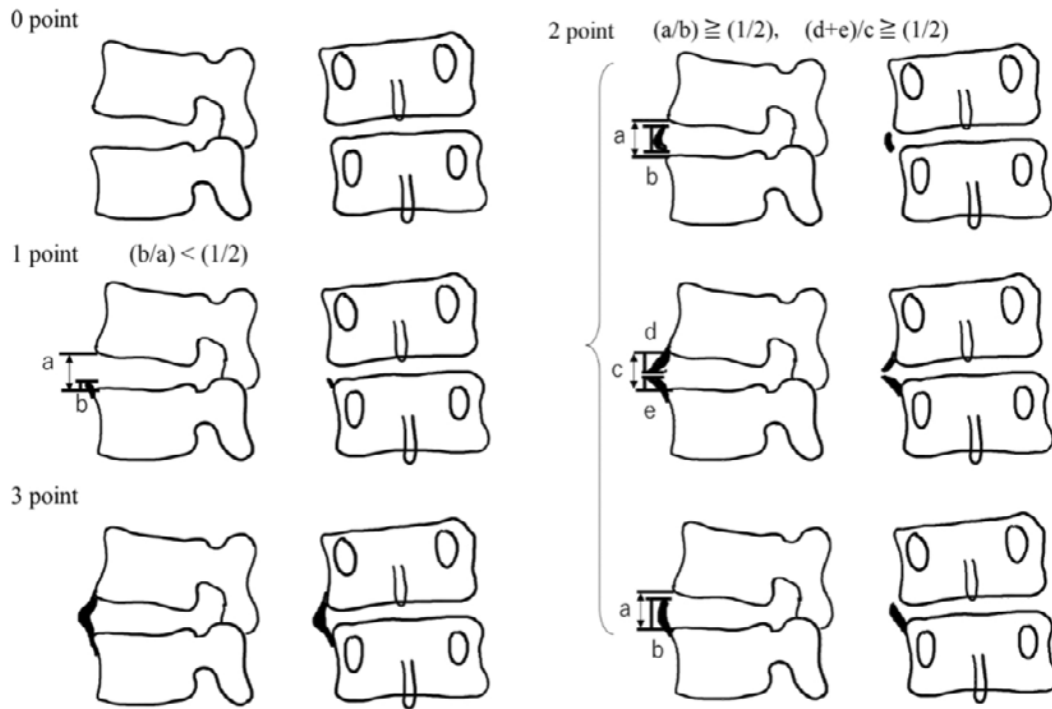


Figure 1. Modified Mata score. 0 point, no ligament ossification; 1 point, ligament ossification of less than half of the intervertebral disc height; 2 points, ligament ossification of half or more of the intervertebral disc height but incomplete fusion; 3 points, complete bridging.

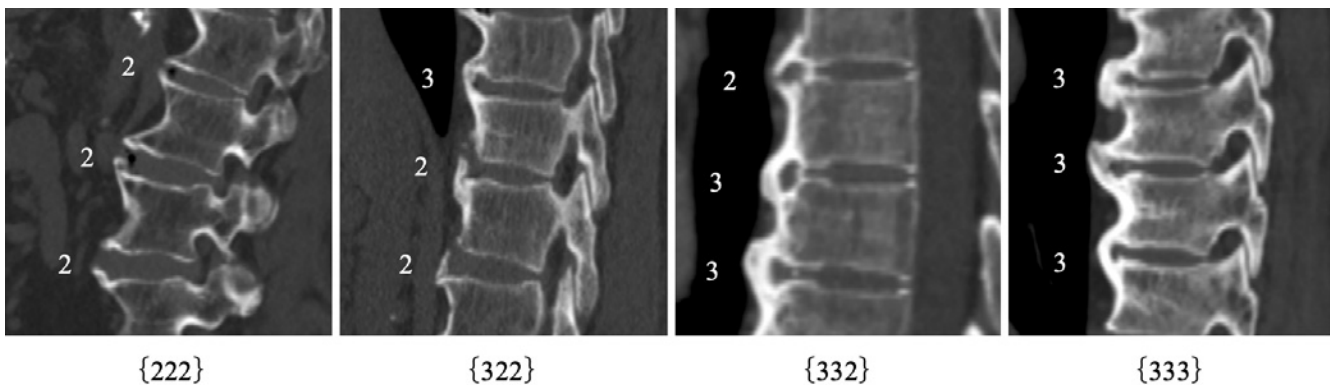


Figure 2. Figure of ossification using the modified Mata score in three contiguous intervertebral spaces. A combination of three contiguous intervertebral spaces with a score of 2 points was expressed as {222}. A combination of one intervertebral space with a score of 3 points and two intervertebral spaces with a score of 2 points was expressed as {322}. A combination of two intervertebral spaces with a score of 3 points and one intervertebral space with a score of 2 points was expressed as {332}. A combination of three contiguous intervertebral spaces with a score of 3 points was expressed as {333}.

Results

1. Study 1

DISH was diagnosed in 37 (19.7%) and 48 (25.5%) of the 188 patients on the first and second CT scans, respectively. During the 5-year interval, 11 patients developed DISH. At either time point, the prevalence was significantly higher in men and elderly patients (Table 1, 2). Of the 48 patients diagnosed as DISH on the second CT, 32 had ligament ossification only in the thoracic spine, 15 in the thoracolumbar spine, and 1 in the lumbar spine, and the bone

bridging was present especially in the thoracic spine. There was a significant difference in the history of hypertension and diabetes mellitus. In addition, there was no significant difference in heart failure, stroke, thyroid dysfunction, chronic kidney disease, or immunological diseases (Table 3).

Fig. 3 shows the modified Mata scores of each intervertebral space in 11 patients who developed DISH during the 5-year interval. While the scores on the first CT were examined in the sites consisting of three or more contiguous intervertebral spaces with a score of 3 points that led to the diagnosis of DISH on the second CT, most sites on the first CT consisted of three contiguous intervertebral spaces with

Table 1. Demographic Data on 1st and 2nd CT with and without DISH.

Variable	Total case	1 st CT			2 nd CT		
		DISH (+)	DISH (-)	p-value	DISH (+)	DISH (-)	p-value
Total	188	37 (19.7%)	151		48 (25.5%)	140	
Sex				<.05			<.05
Male	87	28	59		30	57	
Female	101	9	92		18	83	
Age (years)		70.6±8.1	59.4±14.9	<.05	75.0±8.5	63.7±15.0	<.05

DISH: Diffuse Idiopathic Skeletal Hyperostosis

Table 2. Age Distribution of DISH and Pre-DISH.

Age	All cases	DISH (n)	%	Pre-DISH (n)	%
≤50	37	0	0	0	0
51-60	40	3	7.5	3	7.5
61-70	56	14	25	3	5.4
71-80	44	13	29.5	2	4.5
81-90	11	7	63.6	3	27.3

DISH: Diffuse Idiopathic Skeletal Hyperostosis

a score of ≥2 points. Therefore, Study 2 was conducted on the assumption that pre-DISH is associated with ossification characterized by three contiguous intervertebral spaces with a score of ≥(222).

2. Study 2

DISH was not diagnosed on the first CT in 151 (80.3%, patients without DISH) of the 188 patients. Of these 151 patients, 52 were diagnosed as pre-DISH (patients with a score of ≥[222]). None of the 99 patients with a score of <(222) was diagnosed with DISH after 5 years. Of the 38 patients with a score of (222), 2 (5.2%) were diagnosed with DISH 5 years later (progression to a score of [333]). After 5 years, DISH was also diagnosed in three of the seven patients with a score of (322) (42.8%) and six of the seven patients with a score of (332) (85.7%) (Fig. 4, 5). There was no difference in gender, age, or past history between pre-DISH cases with and without the development of DISH. Two pre-DISH cases with and without the development of DISH are presented (Fig. 6).

Discussion

Pre-DISH was assumed to be diagnosed if the modified Mata score is ≥2 in at least three contiguous intervertebral spaces based on the results. When pre-DISH is diagnosed (i. e., when there are three contiguous intervertebral spaces with a modified Mata score of 2 or 3 points), those intervertebral spaces are highly probable to be bridged and to cause DISH in 5 years. Therefore, selecting treatment strategies in consideration of DISH may be necessary when decompression or fusion is performed.

Kuperus et al.⁷⁾ used CT images taken over time to de-

Table 3. Medical Comorbidities with or without DISH.

	DISH (+) n=48	DISH (-) n=140	P
Cancer	39	104	.329
Hypertension	27	35	<.05
Diabetes mellitus	15	19	<.05
Hyperlipidemia	10	13	.351
Stroke	6	18	.425
Thyroid abnormalities	3	14	.434
COPD	1	2	.755
Immunological disease	1	4	.182
Heart failure	0	4	.236
Hepatitis	0	2	.405
Chronic kidney disease	0	1	.557

DISH: Diffuse Idiopathic Skeletal Hyperostosis

COPD: Chronic Obstructive Pulmonary Disease

velop and validate the diagnostic criteria for early DISH. When their diagnostic criteria were applied, 22.6% of the patients diagnosed with early DISH were diagnosed with DISH 5 years later, whereas almost 100% of the patients diagnosed without DISH did not develop DISH. In this study, most sites of advanced ligament ossification along three or more intervertebral spaces showed a modified Mata score of (222), (322), or (332) 5 years earlier. These sites would also be diagnosed as lesions of early DISH according to the diagnostic criteria developed by Kuperus et al.⁷⁾. We believe that the definition of pre-DISH set in Study 1 is appropriate. After 5 years, the scores were (333) in 5.4% of the sites with a score of (222), 42.8% of the sites with a score of (322), and 85.7% of the sites with a score of (332). DISH was more prevalent in sites with more bridged intervertebral spaces or sites with more intervertebral spaces with a score of 3 points.

Progression occurs gradually, although ligament ossification in DISH is progressive^{5,7,8)}. Murakami et al.⁵⁾ examined the progression of ligament ossification by age group, reporting that the progression was faster in young patients. This suggests that young patients are more susceptible to DISH even when there are contiguous intervertebral spaces with a score of 2 or 3 points. Thus, attention should be focused not only on imaging findings but also on age, but we could not clarify predictive factors such as age, metabolic

	First CT															Second CT																		
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	L1	L2	L3	L4	L5	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	L1	L2	L3	L4	L5
case 1	0	0	0	0	0	0	0	1	1	2	3	3	0	1	1	1	1	0	0	0	0	0	0	0	1	2	3	3	3	0	1	1	1	1
case 2	2	2	2	1	2	2	2	2	2	3	2	2	2	0	0	0	0	2	2	2	1	2	2	2	2	3	3	3	2	2	0	0	0	0
case 3	2	3	2	3	2	2	3	2	3	0	0	0	0	0	0	0	0	2	3	3	3	2	2	3	2	3	0	0	0	0	0	0	0	0
case 4	2	2	2	3	2	2	3	2	2	2	2	0	0	0	0	0	0	3	2	2	3	3	3	3	3	2	2	2	0	0	0	0	0	0
case 5	2	2	2	2	2	2	2	2	2	2	0	0	2	3	3	2	0	2	2	2	2	2	2	2	2	2	2	0	0	3	3	3	2	0
case 6	0	0	3	2	2	0	0	2	0	0	2	2	1	0	0	0	0	0	0	3	3	3	0	0	2	0	0	2	2	1	0	0	0	0
case 7	0	0	0	3	2	3	3	2	2	2	2	3	2	0	1	1	3	0	0	0	3	3	3	3	2	2	2	2	3	2	1	1	1	3
case 8	2	2	3	3	2	2	1	2	3	3	2	0	0	0	0	1	1	2	2	3	3	2	2	1	2	3	3	3	0	1	0	0	1	1
case 9	0	2	3	2	0	2	3	2	3	0	0	0	0	0	0	0	0	0	2	3	2	2	2	3	3	3	2	1	0	0	0	0	0	0
case 10	0	2	2	2	2	2	2	2	2	0	0	0	1	0	0	0	1	0	2	2	2	3	3	3	2	3	1	0	0	2	0	1	1	2
case 11	2	0	2	2	2	2	2	2	1	2	2	2	1	2	2	1	0	2	0	3	3	3	2	3	2	2	3	2	3	1	2	2	1	0

: Modified Mata's Score 3 points
 : the areas of three or more contiguous intervertebral spaces

Figure 3. Modified Mata scores of each intervertebral space on the first and second computed tomographic images. Intervertebral spaces with a score of 3 points are shaded, and the areas of three or more contiguous intervertebral spaces with a score of 3 points are enclosed with a thick line. Most of the sites with three or more contiguous intervertebral spaces with a score of 3 points on the second computed tomography (CT) consisted of three contiguous intervertebral spaces with a score of ≥ 2 points on the first CT.

151/188 patients (80.3%) were not diagnosed as DISH on the first CT.

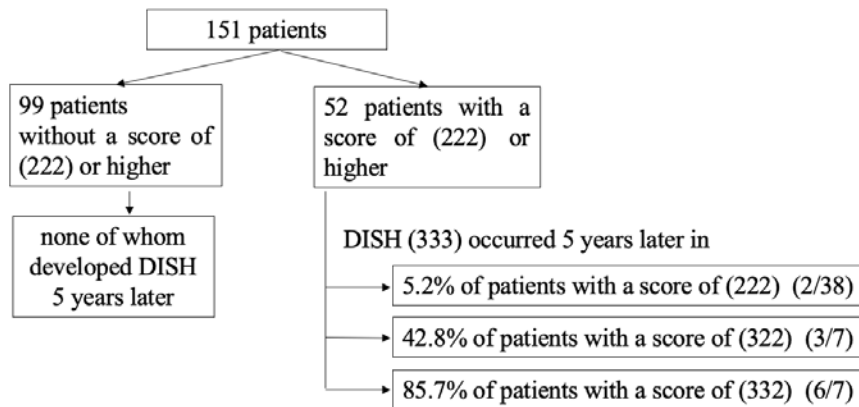


Figure 4. The changes after 5 years in patients diagnosed as diffuse idiopathic skeletal hyperostosis (DISH) (-) on the first computed tomography (CT). Based on the first CT images, 151/188 patients (80.3%) were diagnosed as DISH (-). There were 99 patients without a score of (222) or higher, none of whom developed DISH 5 years later. There were 52 patients with a score of (222) or higher. DISH (333) occurred 5 years later in 5.3% of patients with a score of (222), in 42.8% of patients with a score of (322), and in 85.7% of patients with a score of (332).

disease, and so on in this study.

Murakami et al.⁶⁾ quantified ligament ossification in the lumbar spine and found a correlation between the total score and the range of motion of the lumbar spine. They reported that the range of motion decreased with an increasing score. Decreased spinal flexibility is a risk for thoracic myelopathy and may contribute to poor treatment outcomes for spinal canal stenosis or the development of nonunion after fusion⁹⁻¹¹⁾. Therefore, it is important to evaluate not only ossified lesions of DISH but also sites with a modified Mata score of 2 points and the extent of pre-DISH. Surgical procedures also need to be selected in consideration of the

probability of developing DISH.

In terms of age and sex, the risk factors for DISH include advanced age and male sex⁴⁾. In this study, patients who developed DISH were older and more likely to be men than patients who did not develop DISH. The prevalence of hypertension and diabetes mellitus was higher in DISH patients. These were consistent with the previously reported results.

This study has several limitations. First, the sample size was small, and 76.1% of the patients are cancer patients. Although there were no reports of an association between cancer and DISH and it is believed that this does not have any

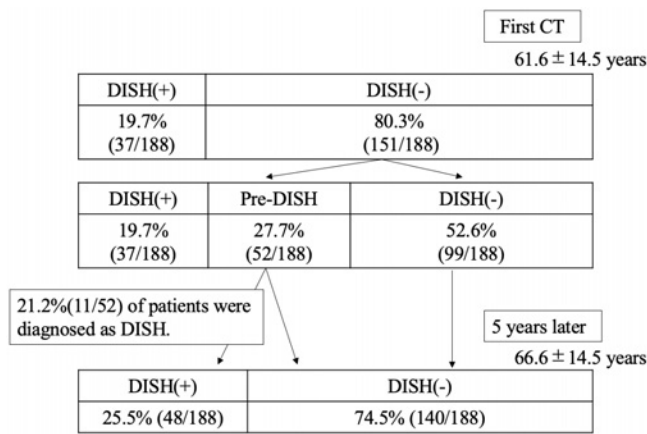


Figure 5. The prevalence of diffuse idiopathic skeletal hyperostosis (DISH), pre-DISH, and DISH (-) and the changes after 5 years. Pre-DISH was included in the ones diagnosed as DISH (-) so far, and pre-DISH was diagnosed as DISH with a probability of 21.2% after 5 years. Values are presented as mean±standard deviation or percentage (number). CT, computed tomography

effect on ossification development, it was desirable to enter and follow healthy patients if possible. Second, the interval between CT scans was 5 years. Consequently, only 5 years of clinical courses were evaluated and the state of the spine at the time before this interval was not evaluated. In addition, since a longer period is necessary for the progression of ligament ossification, studies need to be conducted in patients who underwent imaging with a longer interval. In this study, the database used provided the largest sample size when the interval was set at 5 years. An imaging interval of 5 years was adopted because the sample size was smaller with a longer interval.

Conclusions

This study used CT images taken at a 5-year interval to investigate the imaging features of patients who developed DISH. Patients who have three contiguous intervertebral spaces with a modified Mata score of 2 or 3 points should be considered pre-DISH. Caution should presumably be exercised while treating such patients because they have a high predilection to develop DISH in the future.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions: Yusuke Murakami, Tadao Morino, Masayuki Hino, Hiroshi Misaki, and Tomofumi Kinoshita designed the study; Yusuke Murakami and Tadao Morino analyzed the data; Masaki Takao supervised the experiments; and Yusuke Murakami and Tadao Morino wrote the manuscript.

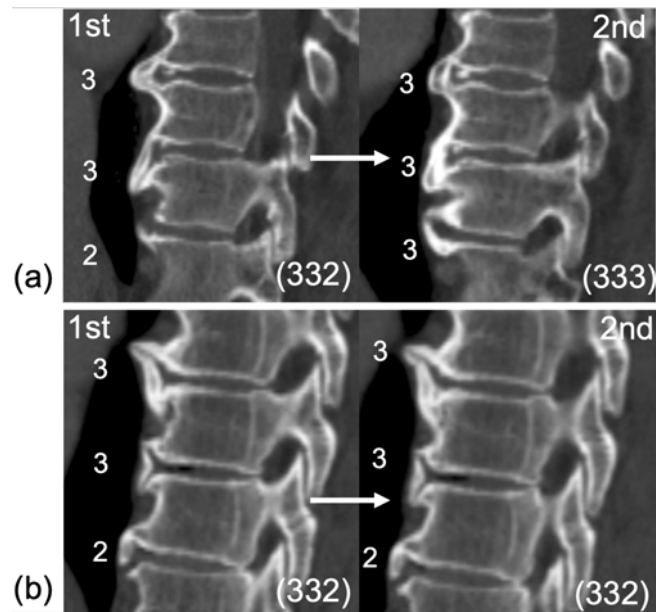


Figure 6. (a) shows a case where the most caudal intervertebral space has fused, and the pre-DISH (332) has developed DISH (333) in 5 years. (b) shows a case where the most caudal intervertebral space has not fused and remained pre-DISH 5 years later.

Ethical Approval: This study was approved by the institutional review board at our University Hospital (IRB approval no., 2207011).

Informed Consent: Informed consent was obtained from all individual participants included in the study by posting the opt-out information in our hospital.

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