Signal changes of the alar ligament in a healthy population: a dispositional or degenerative consequence?

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OBJECT The alar ligaments (ALs) are vital for stabilizing the craniocervical junction. In terms of morphology, their appearance varies and is visible on MRI. Dark signal of the AL on proton-density (PD)–weighted images is generally considered the norm, but the etiology of frequently observed signal hyperintensities is poorly understood. Using spectral fat suppression, signal hyperintensities can be differentiated into fat- and nonfat-related hyperintensities (NFH). Although signal hyperintensities have no evident association with whiplash-associated disorder, age-related degeneration has often been theorized. Therefore, this study investigates the signal intensities of the ALs on 3.0-T MRI with special reference to age. Expanding thereon, the authors investigated the relationship between signal hyperintensities and patient characteristics, such as height, weight, and sex.

METHODS Sixty-six healthy volunteers were scanned using 3.0-T PD-weighted MRI, including spectral fat suppression of the craniocervical junction. The study population was separated into 2 groups (old vs young) using 2 approaches: dichotomization at the median age (40.0 years) and the calculated threshold (28.5 years) using receiver operating characteristics (ROC). The AL was independently characterized with respect to continuity, course, shape, signal intensity, and graduation of homogeneity by 2 experienced neuroradiologists. Signal intensity was differentiated into fat-related hyperintensity and NFH. Univariate and multivariate logistic regression models were employed to investigate the relationship between patient characteristics and signal intensities.

RESULTS Two different AL patterns were observed: inhomogeneous (33.3%) and homogeneous (66.7%). The latter pattern was mostly surrounded by a small dark rim (56.8%). Fat could be identified in 15.9% of all ALs (21 of 132 patients), and NFH was identified in 17.4% of all ALs (23 of 132 patients). Here, 28.5 years was the preferred threshold, demonstrating a relatively high sensitivity for dichotomizing the population based on the ROC of NFH. The most relevant factor for having NFH was being older than the calculated threshold (odds ratio [OR] 3.420, $p = 0.051$). Fat-related hyperintensities occurred significantly more frequently in men than women (OR 0.110 and $p = 0.007$ for women; OR 9.075 and $p = 0.007$ for men). Height was the second most significant factor: for every 1-cm increase, the odds of having fat lesions increased by approximately 10% (OR 1.102; $p = 0.017$).

CONCLUSIONS This study shows that AL signal hyperintensities are substantially influenced by age, sex, and height in healthy individuals. Regarding fat-related hyperintensities, the most relevant factors proved to be sex and height. The odds of detecting NFH increased almost significantly after a relatively young age (> 28.5 years) and were remarkably more frequent in individuals older than 28.5 years. The authors caution presumptions equating signal alterations with age-related deterioration. Instead, they suggest that dispositional factors such as sex and height are more relevant in the AL constitution. Signal alterations in ALs naturally occur in healthy symptom-free individuals, underscoring the importance of cautiously interpreting such lesions on posttraumatic MRI scans.

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ABBREVIATIONS AL = alar ligament; FPR = false-positive rate; NFH = nonfat-related hyperintensity; PD = proton density; PD/T2-TSE0 = PD-weighted images/T2-weighted double-echo turbo spin-echo images; ROC = receiver operating characteristics; SD = standard deviation; T2-SPACE = T2-weighted sampling perfection with application optimized contrasts using different flip angle evolution; TPR = true-positive rate; WAD = whiplash-associated disorder.

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ALAR ligaments (ALs) are vital for stabilizing the craniocervical junction.^{6,33} They connect the dens of the axis to the occipital condyles and inhibit excessive rotation, lateral flexion, as well as anterior dislocation of the atlas on the axis during flexion.^{4,8,9,13,22,28} Substantial variability in the morphology of the upper cervical ligaments has been shown in various studies using MRI.^{16,20,24,29,32,35}

Dark signals on proton-density (PD)-weighted images of the ALs are generally considered the norm.¹⁹ However, high signal alterations of the ALs have frequently been reported in patients with (chronic) whiplash-associated disorder (WAD),^{1,5,11,26,28,31} and also in uninjured individuals.^{14,16,34} This high signal intensity of the ALs was previously suggested by some authors to be correlated with the clinical symptoms caused by the mechanism of whiplash.^{17,19} However, these findings have been contradicted by several investigators who found no direct correlation to trauma or clinical symptoms.^{2,21,24,25,29,30} Instead, as an alternative explanation, degeneration has been put forward as the source of these high signal changes.³⁷

This hypothesis was put to the test. Are signal changes of the ALs evidence of age-related degeneration? Or are there other influences on AL composition? To test this, 2 neuroradiologists assessed the ALs in healthy volunteers with respect to continuity, course, shape, and graded signal intensity. To the best of our knowledge, this is the first study that evaluates the relationship between physical characteristics such as weight, height, age, and sex, and their respective influences on signal intensities.

Methods

Study Cohort

Sixty-six healthy volunteers who had provided written informed consent were included (53.0% were female [35 of 66 participants]). Exclusion criteria included neck pain, restricted mobility of the cervical spine, history of trauma to the cervical spine, traumatic brain injury, motor vehicle accident, and medical history of neurological or spine-related diseases. Furthermore, patients with a history of connective tissue disorders, such as Marfan syndrome and Ehler-Danlos syndrome, were excluded.

To investigate age-related AL deterioration, the study population was separated into 2 groups: old and young. Two different approaches were used: 1) classic dichotomization at the median age (40.0 years); and 2) dichotomization at the optimal threshold (with high sensitivity and specificity) based on the receiver operating characteristic (ROC) for age (28.5 years). This study was performed according to local institutional guidelines and approved by the local ethics committee.

MRI Protocol

MRI was performed using a 3.0-T magnetic field scanner (Magnetom Trio, Siemens Healthcare). A standard 12-channel head and neck coil was used, and all images were acquired with the participant's head and neck in a neutral position.

The imaging protocol consisted of T2-SPACE (T2-weighted sampling perfection with application optimized

contrasts using different flip angle evolution) sequences, PD/T2-TSE (PD-weighted images/T2-weighted double-echo turbo spin-echo images) with and without fat saturation angulated parallel to the left and right AL, and 1 axial PD/T2-TSE sequence (for details see Table 1).

Image Evaluation

All viewing and analysis of the acquired data sets were electronically performed on a DICOM workstation using OsiriX Imaging Software (<http://www.osirix-viewer.com/index.html>).

Two neuroradiologists, who were blind to all clinical data, independently analyzed each data set. These raters were allowed to freely adjust the window/level settings, but no automatic preprocessing was applied. For optimal evaluation of ligamental continuity, the T2-SPACE sequence was used. The subsequently acquired semicoronal PD-weighted images of the AL were used to evaluate the signal characteristics and determine AL morphology.

With regard to AL morphology, the parameters of continuity, course, and shape from the dens to the occipital condyle were evaluated. These parameters were determined in the axial and coronal reconstructed T2-SPACE (anterolaterally/laterally/dorsolaterally, ascending, strictly horizontally, descending).

Regarding the signal characteristics, homogeneity and signal intensity were determined. AL homogeneity was categorized, on semicoronal PD-weighted images, as homogeneous (Fig. 1) or inhomogeneous (Fig. 2) patterns. The homogeneous pattern included ALs with a hypointense dark rim (Fig. 1C, D). In contrast, the inhomoge-

TABLE 1. MRI parameters for each sequence used in this study

Parameter	T2-SPACE*	PD-T2-TSE†	PD-T2-TSE-FS‡
Voxel size (mm)	0.9 × 0.9 × 0.9	0.7 × 0.5 × 2.0	0.7 × 0.5 × 2.0
FOV-read (mm)	280	180	180
FOV-phase (%)	100	100	100
Base resolution (pixel)	230	384	384
Slices	52	20	20
Slice thickness (mm)	0.9	2	2
Averages	14	3	3
TR (msec)	1500	4550	4550
TE (msec)	121	25/116	25/116
Flip angle (°)	140	150	150
Echo-train length		8	8
Fat saturation	No	No	Yes
TA (min)	05:53	04:12	04:16
PAT	3	2	2

FOV = field of view; PAT = parallel acquisition technique; TA = acquisition time; TE = echo time; TR = repetition time.

* SPACE, Sampling Perfection with Application optimized Contrasts using different flip angle Evolution.

† PD-T2-TSE, Proton-Density weighted images/T2-weighted double echo Turbo Spin Echo images.

‡ PD-T2-TSE-FS, Proton-Density weighted images/T2-weighted double echo Turbo Spin Echo images with fat saturation.

FIG. 1. Courses and signal patterns of the AL on PD-weighted images. White bars reveal the location of the AL. **A and B:** Axial images showing that the course (arrows) of the AL was either strictly lateral (A) or dorsolateral (B). **C and D:** Oblique images parallel to the course of the left AL, which is laterally ascending, and spectral fat suppression (D). Note the homogeneous signal pattern with the clear dark rim of the AL in both C and D. **E and F:** Oblique images parallel to the course of the right AL, which is strictly horizontal, and fat suppression (F). Note the homogeneous signal pattern of the AL in both.

neous pattern was further graded based on the extent of inhomogeneity according to Kråkenes et al.¹⁶ (Table 2). Importantly, signal intensity was further differentiated into either fat-related hyperintensity or nonfat-related hyperintensity (NFH). This differentiation was achieved using spectral fat suppression.

Statistical Analysis

The statistical analyses were descriptive and performed using SPSS software (Statistical Package for the Social Sciences, version 19.0; IBM Corporation). The distributions of age, height, and weight were tested against the normal distributions using the Shapiro-Wilk test and Q-Q plots. We defined the following binary outcome parameters: the presence of 1) high signal intensity; 2) fat signal; and 3) NFH, either in the left or right AL.

ROC was plotted to measure sensitivity and the false-positive rate at the possible thresholds for the clinical features of age, height, and weight. The best-performing age threshold was used to dichotomize the data set in further analyses.

Univariate logistic regression was used to assess the relationship between the patient characteristics (age, weight, height, and sex) and the 3 aforementioned outcome parameters. We also used multivariate-adjusted models to isolate the effects of certain clinical features. To evaluate signal differences between age groups, the chi-square or Fisher exact test was used. We applied Pearson's correlation to assess the relationship between weight and height. To

FIG. 2. Hyperintensity types ([A and B] and fat [C–F]) in PD-weighted images. **A and B:** Oblique images of the right AL obtained in a 20-year-old male, including spectral fat suppression (B). There are linear hyperintensities (arrows) along the course of the ligament (both A and B), which cannot be suppressed by spectral fat suppression (B) and hence are NFH. The left ligament was homogeneously dark. **C–F:** Fat signal of left AL insertion at the occipital condyle in a 52-year-old male. Panels C (oblique) and E (axial) show bright signal hyperintensities, while D (oblique) and F (axial) illustrate the corresponding decreased signal after spectral fat suppression and, hence, are fat-related hyperintensities. Asymmetrical signal of both ALs (multiplanar coronal reconstruction of a SPACE data set) is shown in panel F.

compare the age, weight, and height distributions between men and women, the Wilcoxon-Mann-Whitney U-test or unpaired t-test was applied, respectively. In this study, p values < 0.05 were considered statistically significant.

Results

Study Cohort

The ages of the volunteers ranged between 18 and 65 years, with a median of 40.0 years (lower–upper quartile 25.75–52.25 years) and peaks around 20–25 and 55–60 years. Both height (range 149–198 cm; mean 172.9 ± 9.3 cm [SD]) and weight (range 51–105 kg; mean 74 ± 12.5 kg) approximately followed a normal distribution.

TABLE 2. Grading criteria for the extent of inhomogeneity of ALs

Grade	Criteria
0	Low signal intensity throughout the entire cross-section
1	High signal intensity in one-third or less of cross-section
2	High signal intensity in one-third to two-thirds of cross-section
3	High signal intensity in two-thirds or more of cross-section

Continuity, Course, and Shape of ALs

All 132 ALs (66 volunteers; 1 AL on each side) showed a continuous course on the T2-SPACE sequences. In 1 case, the PD-weighted sequences were equivocal concerning 1 AL. In this case, continuity was confirmed with the T2-SPACE sequences. Symmetry, in terms of shape and size, was present in 91% of participants (60 of 66); asymmetrical AL was found in 9% of participants (6 of 66).

The course of the AL in the coronal plane was laterally ascending in 62.1% (41 of 66) (Fig. 1C and D) and horizontally oriented in 37.9% of participants (25 of 66) (Fig. 1E and F). No laterally descending course was observed. The course of the AL in the axial plane was strictly laterally oriented in 40.9% (27 of 66) (Fig. 1A) and dorsolaterally in 59.1% of participants (39 of 66) (Fig. 1B). Anterolateral orientation was not detected.

Patterns of Signal Characteristics of the ALs

Concerning the signal characteristics of ALs, 2 different patterns were observed: homogeneous (with or without a dark rim) and inhomogeneous.

A homogeneous signal pattern for the AL presented in 66.7% (88 of 132) of participants. This pattern, however, was subdivided into the completely homogeneous pattern (Fig. 1E and F) and the homogeneous pattern with a small dark rim (Fig. 1C and D). Only a minority of ALs were completely homogeneous (9.9%; 13 of 132 participants; 7 left- and 6 right-sided AL). In 56.8% of all homogeneous cases (75 of 132 participants; 35 left- and 40 right-sided AL), an intermediate to bright signal surrounded by a small dark rim of various thicknesses was seen.

The inhomogeneous signal pattern of the ALs (Fig. 2) was observed in one-third of all participants (44 of 132 participants; 24 left- and 20 right-sided ALs). In the vast majority of these participants (93.18%; 41 of 44 participants; 21 left-sided and 20 right-sided ALs), the extent of inhomogeneity was less than one-third of the AL cross-section. An inhomogeneity of more than one-third was rare (6.81%; 3 of 44 participants; 3 left- and 0 right-sided AL). Moreover, an extended inhomogeneity of more than two-thirds was not found.

Fat could be identified in 21 ALs (9 right- and 12 left-sided ALs) using spectral fat suppression, reflecting 15.9% (21 of 132) of all ligaments (Fig. 2C and D). All of these 21 cases belonged to the inhomogeneous AL subgroup, representing 47.7% of participants (21 of 44). Likewise, NFH could be detected in 17.4% of participants (23 of 132) (Fig. 2A and B).

Receiver Operating Characteristics

ROC analysis was used to identify an ideal age threshold. The ROC of the age for showing NFH demonstrated a weak tendency, with an area under the curve of 0.573 (95% CI 0.434–0.713; $p = 0.334$). A suitable age threshold was set at 28.5 years (23 of 66 participants were < 28.5 years; 43 of 66 participants were ≥ 28.5 years) in order to achieve a relatively high sensitivity of 81.8% (i.e., true-positive rate [TPR]) with a corresponding acceptable specificity of 43.2% (i.e., relatively low false-positive rate [FPR] of 56.8%). In comparison with the ROC approach,

classic dichotomization at the median age (40.0 years) resulted in a sensitivity (i.e., TPR) of 59.1% and a specificity (FPR) of 45.5%.

Relationship Between Signal Hyperintensity Types and Patient Characteristics

General Signal Hyperintensity

Men had a tendency ($p = 0.137$) for 111% increased odds of having nonspecific hyperintensity in AL (OR 2.111 [95% CI 0.022–0.549]) in comparison with women. Bodyweight showed a similar trend; with every 1-kg increase the odds of having an AL-hyperintensity increased by approximately 2.9% (OR 1.029 [95% CI 0.988–1.072], $p = 0.173$).

Nonfat-Related Hyperintensity

In the univariate logistic regression, age showed only a weak tendency with NFH (OR 1.020 [95% CI 0.982–1.059], $p = 0.315$). However, when comparing the ROC values for the age thresholds, the older subgroup (≥ 28.5 years) had an almost statistically significant ($p = 0.051$) and clinically highly relevant ($\sim 240\%$ increased odds) (OR 3.420 [95% CI 0.993–11.780]) of having NFH in their ALs. Cross-tabulation showed similar results ($p = 0.057$). In contrast, classic dichotomization at the median age resulted only in a weak tendency toward an increased odds of having NFH (OR 1.733 [95% CI 0.615–4.887], $p = 0.298$).

In the multivariate logistic regression model adjusted for sex, height, and weight, patients ≥ 28.5 years had a clinically relevant tendency for an increased chance of having NFH (OR 2.849 [95% CI 0.742–10.948], $p = 0.127$). The other markers showed no relevant trend or interaction.

Fat-Related Hyperintensity

The univariate logistic regression analyses were used to elucidate the occurrence of fat-related hyperintensities (i.e., fat lesions). Men and women presented opposite tendencies in their odd ratios for having fat lesions: women had a statistically and highly significant decreased 0.110 OR for having fat lesions (95% CI 0.022–0.549, $p = 0.007$). In contrast, men had a statistically highly significant increased 9.075 OR for having fat lesions (95% CI 1.822–45.208, $p = 0.007$). Moreover, in the multivariate model adjusted for age, height, and weight, men had an almost significant trend for an approximately 590% increased odds for having fat signals in ALs (OR 6.910 [95% CI 0.855–55.861]; $df = 1$; $p = 0.070$). No other factor showed a relevant association.

Height had an impact on the occurrence of fat lesions; for every 1-cm increase in height, the odds of having fat lesions increased statistically significantly by approximately 10% (OR 1.102 [95% CI 1.018–1.192], $p = 0.017$). In contrast, weight presented an insignificant tendency (OR 1.037 [95% CI 0.986–1.091], $p = 0.155$). The data proved the well-known correlation between height and weight at a statistically highly significant level (Pearson $r = 0.582$; $n = 65$; $p < 0.01$). Furthermore, it is noteworthy that men were significantly taller ($p < 0.001$) and weighed ($p < 0.001$, t -test) more than women without any relevant age differences ($p = 0.634$, Mann-Whitney U-test) in the study.

cohort. There was no significant interaction between sex and weight or height; similarly, there was no significant interaction between age and the aforementioned factors, or between height and weight.

Discussion

Substantial morphological variability of the upper cervical ligaments has been shown in various MRI studies, including the ALs.^{10,16,20,24,29,32,35} Signal changes in the ALs associated with trauma were initially reported by Volle^{38,39} and Krakenes^{16,17} and their colleagues in patients with chronic WAD. Furthermore, clinical symptoms were reported in patients with WAD and AL signal alterations.^{16–18,39} However, the clinical significance of these signal changes has been disputed since the 1990s: various MRI studies showed that there is a broad range of variations in interindividual signal intensity and morphology in AL, both in patients with WAD^{36–40} and healthy volunteers.^{23,24,29} As a cautionary note, MRI should generally be accompanied in WAD, and especially in suspected upper spinal instability, with multimodal imaging procedures depending on the clinical setting of the patient. Especially for suspected upper spinal injuries and trauma, it is crucial to evaluate the status of the tectorial membrane, in particular, as it is the single most important stabilizing structure at the craniocervical junction.^{12,27}

While direct associations between trauma, clinical symptoms, and signal alterations of the AL were ruled out in recent years,^{2,21,24,25,29,30} age-related degenerative changes have been assumed as an alternative explanation for signal changes.³⁷ However, to date, concrete evidence that substantiates these claims is lacking. The goal of this cross-sectional study was to explore if signal intensity and signal changes are influenced by age. Accordingly, we assessed the morphological variations and signal intensity of the ALs in an asymptomatic cohort of 2 groups of different ages (young vs old). Moreover, we statistically evaluated the relationship between other patient characteristics, such as weight, height, and sex, and their respective signal intensities.

Morphologically, our results are consistent with prior *in vitro*⁸ and *in vivo*^{20,24,29} studies regarding AL orientation. On coronal images, 62.1% were laterally ascending and 37.9% were horizontally orientated. In accordance with our results, Lummel et al.²⁴ described a laterally ascending orientation in 58.5% and a horizontal orientation in 40.5% of patients.

Regarding the features of the signal patterns, we observed 2 different kinds. On one hand, a homogeneous intermediate to bright signal pattern, usually surrounded by a small dark rim of various thicknesses, was noted in 66.7% of all AL. On the other hand, we observed an inhomogeneous signal pattern in one-third of patients.

The signal alterations' origin may have different causes. First, it could be due to the misinterpretation of the partial volume effects from the surrounding fatty tissues. Second, it may be due to scars from severe craniocervical injuries in patients with high-energy traumata. This type of population was excluded from our study. Third, it could be caused by dispersed interstitial fat within the AL, which

was shown by Koch in 2008 in her autopsy study.¹⁵ Lastly, AL signal alterations may presumably be due to age-related degeneration. Investigating this presumption, the hyperintensities were either categorized as fat-related hypersensitivity (interstitial fat in ALs) or NFH, depending on the signal in the fat-suppressed PD-weighted sequences.

Using the fat suppression sequences, we found NFH in 23 of 132 ALs. Our analysis showed that the older age group (≥ 28.5 years) had an almost significant and relevant increased odds by approximately 240% for having NFH. Setting the age threshold at a relatively young age of 28.5 years, we emphasized higher sensitivity at the price of slightly lower specificity for detecting NFH lesions. Nonetheless, the specificity was almost as good as the general approach using the median age. No other factor seemed to significantly influence the occurrence of NFH in our patients.

Regarding fat-related hyperintensities, we found that age did not play a significant factor, neither did classical dichotomization at the median age of 40 years nor for the threshold age of 28.5 years. Surprisingly, the factors most relevant to having fat-related hyperintensity appeared to be sex followed by height. Female patients had a significantly decreased odds ratio of having fat lesions, while men had statistically highly increased odds of having fat lesions. For men, the odds of having fat lesions in the multivariate model were increased by approximately 590%, and in the univariate model the odds were increased by approximately 800%. In contrast, females had a 90% decreased odds of having fat lesions. Moreover, counterintuitively, weight did not significantly impact the odds of having fat-related hyperintensity, while height did. For every 1-cm increase in height, the odds of having fat lesions significantly increased by approximately 10%. However, it is noteworthy that, as expected, men were significantly taller and weighed more than female participants, which could bias the perceived frequency of the signal alterations.

To recapitulate, the most relevant factor for having NFH was older age, as calculated by the ROC analysis. In contrast, for fat-related hyperintensities, sex and height seemed to influence fat lesion occurrence the most, with men being more likely and females being less likely to demonstrate fat lesions.

Because we are the first to show that the aforementioned factors affect AL constitution, one might argue that a limitation of our study is that the findings might be somewhat incidental due to the moderate population size ($n = 66$). However, comparison with other studies shows that our findings are indeed viable. Using fat suppression, Dullerud et al.⁷ was among the first to differentiate between NFH and intraligamentous fat of the AL. In Dullerud and colleagues' control population of healthy volunteers ($n = 27$), the observed frequency of signal alterations of the AL without fat suppression was 54%; with fat-suppression (i.e., NFH) the frequency was 37%. Therefore, in 17% of the control population, fat was detectable within the AL. These results are very similar to our results that about 16% of ALs contain fat. In our study, NFH was detectable in 52.3% of all ligaments with bright signal alterations. Therefore, indeed, our results appear to be reproducible.

Another possible limitation of our study might be the

impediment of evaluating small structures due to partial volume effects. However, an autopsy series³ of relatively small AL reported the dimensions to be about 8.8 ± 2.6 mm in length and 7.3 ± 1.3 mm in diameter. Therefore, applying 2-mm-thick PD-weighted images without a gap is reliable and well established.^{20,23,24} Furthermore, one could further argue that higher MRI field strength could improve AL delineation, increase AL signal intensities, and, thus, adulterate imaging evaluations. This, however, was ruled out before.²³

Lastly, in the clinical setting of assessing craniocervical junction integrity and the resulting decision-making management, it is crucial to rely on various examinations in context. This encompasses multimodal imaging procedures of the bony and soft tissue, according to the patient's clinical picture and anamnesis, and also entails not focusing on a single ligamentous structure but evaluating the craniocervical junction as a whole.

Conclusions

We show that the ALs have signal variability, which is likely influenced by age, sex, and height. The impact on fat-related hyperintensities by sex and height is significant and highly relevant, and therefore crucial to consider when evaluating the patient's clinical status. Moreover, the impact of age on NFH is highly relevant and edges very closely to the significance level. The question of whether AL signal alterations are evidence for age-related degeneration must be answered in 2 ways. First, regarding fat-related hyperintensities, these signal changes are not evidence of age-related deterioration. Second, regarding NFH, these signal changes show a trend toward an increased likelihood of being more prevalent in older individuals.

Therefore, we caution against presumptions equating signal alterations with age-related deterioration for fat-related hyperintensity, and instead suggest that dispositional factors such as sex and height are more important. In contrast, NFH seem to be an age-related occurrence. In general, signal alterations in AL seem to naturally occur in healthy symptom-free individuals, underscoring the importance of the cautious interpretation of such lesions on posttraumatic MRI scans.

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