JSES International 8 (2024) 349–354

Contents lists available at ScienceDirect

JSES International

journal homepage: www.jsesinternational.org

Prevalence of amyloid deposition and cardiac amyloidosis in shoulder disease compared to carpal tunnel syndrome

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ARTICLE INFO

Keywords:
Amyloid
Biceps brachii
Cardiac amyloidosis
Carpal tunnel syndrome
Rotator cuff tear
Shoulder disease
Shoulder surgery

Level of evidence: Level IV; Diagnostic Study

Background: Cardiac amyloidosis is a fatal disease of severe heart failure caused by the accumulation of amyloid in the myocardium. This disease is often advanced by the time cardiac symptoms appear; therefore, early detection and treatment are critical for a good prognosis. Recently, it has been suggested that cardiac amyloidosis is implicated in several orthopedic diseases, including carpal tunnel syndrome (CTS), which is often reported to precede cardiac dysfunction. Shoulder disease has also been suggested to be associated with cardiac amyloidosis; however, there have been no reports investigating the rate of amyloid deposition in shoulder specimens and the simultaneous prevalence of cardiac amyloidosis. Herein, we investigated the prevalence of intraoperative specimen amyloid deposition and cardiac amyloidosis in shoulder disease and CTS to determine the usefulness of shoulder specimen screening as a predictor of cardiac amyloidosis development.

Methods: A total of 41 patients undergoing arthroscopic shoulder surgery and 33 patients undergoing CTS surgery were enrolled in this study. The shoulder group included rotator cuff tears, contracture of the shoulder, synovitis, and calcific tendonitis. In the shoulder group, a small sample of synovium and the long head of the biceps brachii tendon were harvested, while the transverse carpal ligament was harvested from the CTS group. The intraoperative specimens were pathologically examined for amyloid deposition, and patients with amyloid deposition were examined for the presence of cardiac amyloidosis by cardiac evaluation.

Results: In the shoulder group, three cases (7.3%) of transthyretin amyloid deposition were found, all of which involved rotator cuff tears. None of these three cases with amyloid deposition were associated with cardiac amyloidosis. When examining the specimens, the amyloid deposition rate in the long head of the biceps brachii tendon was higher than that in the synovium. In the CTS group, 12 cases (36.4%) of transthyretin amyloid deposition were observed. Of these cases, seven underwent cardiac evaluation and two were identified with cardiac amyloidosis.

Conclusion: While the prevalence of amyloid deposition and cardiac amyloidosis in the CTS group was consistent with previous reports, the shoulder group showed a lower deposition rate and no concomitant cardiac amyloidosis. Therefore, it remains debatable whether investigating amyloid deposition in samples obtained from shoulder surgery is beneficial for the early detection of cardiac amyloidosis.

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https://doi.org/10.1016/j.jseint.2023.11.009

Amyloidosis is a group of disorders caused by the deposition of insoluble amyloid fibrils, which result from the misfolding of discrete secreted proteins, ultimately causing dysfunction in the affected organs.[34] Thirty-six types of precursor proteins associated with amyloid fibrils exist, of which AA (linked to chronic inflammation), AL (involving immunoglobulin light chains), Aβ2M (associated with dialysis), and ATTR (related to transthyretin, either hereditary or age-related) are the most common.[4,34] The AL and ATTR types can lead to cardiomyopathy and polyneuropathy and are associated with musculoskeletal disorders.[8,27,33] AL has a prevalence of approximately 40 cases per million.[24] While there are limited reports on ATTR prevalence, a previous study found that ATTR was identified in 25% of autopsied individuals aged ≥80 years.[31]

Cardiac amyloidosis is a condition of cardiomyopathy caused by the accumulation of ATTR or AL proteins in the myocardium,[16,34] which leads to severe heart failure.[6,13,17] The prognosis of cardiac amyloidosis is poor, with a median survival of 3–5 years from diagnosis for ATTR and 6 months from the onset of heart failure for AL if untreated.[12,18] In recent years, novel treatments for cardiac amyloidosis have been proposed and are expected to improve outcomes.[10,19,20,26,28,35] However, these therapies are only effective when they are applied at an early stage of the disease[19,22,35]; therefore, early detection of the disease is crucial.

Recently, several orthopedic conditions have gained attention as extracardiac manifestations for the early detection of cardiac amyloidosis.[7,10] Carpal tunnel syndrome (CTS) is one of the most common conditions that precede the onset of heart disease.[21,23] A previous study reported that CTS precedes cardiac symptoms by 5–10 years.[27] A study that developed a prediction model for cardiac amyloidosis found CTS to be a major factor for predicting the presence of cardiac amyloidosis.[1] Therefore, CTS has been identified as a predictor of cardiac amyloidosis onset.

Other than CTS, biceps brachii tendon rupture, spinal canal stenosis, and shoulder disease have been reported to be associated with cardiac amyloidosis in several retrospective studies.[2,3,14] Regarding shoulder disease, there are previous reports of pathological amyloid deposition in the rotator cuff[5,29]; however, there are currently no studies reporting the association between specimens collected at the time of shoulder surgery and cardiac amyloidosis.

This cross-sectional study aimed to assess the rate of amyloid deposition in specimens intraoperatively obtained from patients undergoing shoulder and CTS surgery at our institution. We also aimed to determine and compare the incidence of cardiac amyloidosis in the two diseases, postulating that specimens acquired during shoulder surgery may serve as indicators of the emergence of cardiac amyloidosis.

Materials and methods

This is a cross-sectional study that examined the association of amyloid deposition in specimens obtained from shoulder and carpal tunnel surgery and concomitant cardiac amyloidosis. The flow of this study is illustrated in Fig. 1.

Participants

In this study, we included consecutive patients who underwent shoulder or CTS surgery at our institution between June 2021 and January 2023. During the research period, shoulder surgery was performed for rotator cuff tears, contracture of the shoulder, synovitis, and calcific tendonitis of the shoulder. However, we excluded patients who were already diagnosed with systemic amyloidosis or a history of rheumatoid arthritis or dialysis, which can cause amyloid deposition.

This study was approved by the Medical Research Ethics Committee of Tokyo Medical and Dental University (#M2022-010). In accordance with the ethical committee's regulations, informed consent was obtained from all participants prior to their involvement in the study.

Surgical procedures and specimens

In the shoulder group, patients underwent arthroscopic rotator cuff repair for rotator cuff tears, arthroscopic capsular release for shoulder contractures, arthroscopic synovectomy for synovitis, and arthroscopic removal of calcific tendonitis. Small samples of the synovium were excised in all shoulder surgeries. Among cases of rotator cuff tears and shoulder contractures, the long head of the biceps brachii (LHB) tendon was also collected if tenotomy or tenodesis of the LHB was performed. Due to concerns regarding the histological heterogeneity of the sampled specimens, including native tendons, scar tissues of torn tendons, and covering synovium, the stumps of torn rotator cuff tendons were not harvested in cases of rotator cuff tears. In the CTS surgery group, open carpal tunnel release was performed in all patients, and a portion of the transverse carpal ligament was excised during surgery.

Histopathological analysis

All specimens were formalin-fixed and routinely examined for amyloid deposition using Congo red staining and direct fast scarlet staining. In cases with amyloid deposition, immunohistochemistry was performed for subtyping.[20]

Cardiac evaluation

Patients positive for amyloid were subjected to cardiac examination for cardiac amyloidosis by a cardiologist. The evaluations

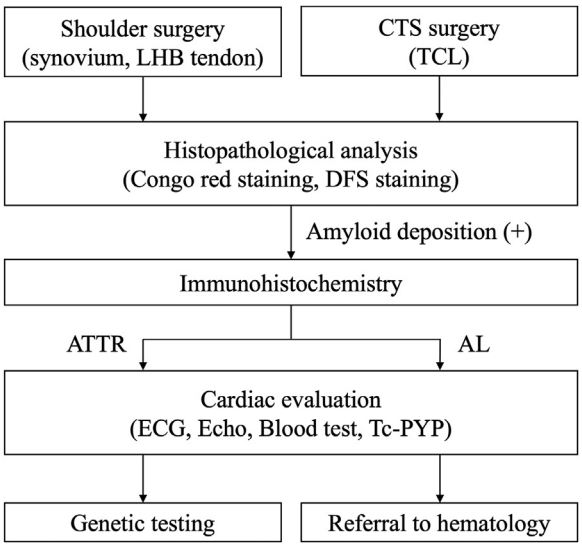

Figure 1 Flow of the evaluation of amyloid deposition in intraoperative specimens and the cardiac evaluation. *AL*, light-chain amyloidosis; *ATTR*, transthyretin amyloidosis; *CTS*, carpal tunnel syndrome; *DFS*, direct fast scarlet; *ECG*, electrocardiography; *LHB*, long head of biceps brachii; *TCL*, transverse carpal ligament; *Tc-PYP*, technetium pyrophosphate scintigraphy.

included electrocardiography, echocardiography, blood tests, and technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy. Electrocardiography was conducted to identify findings characteristic of cardiac amyloidosis, including low voltage, atrioventricular conduction disorders, bundle branch blocks, pseudoinfarct patterns, and atrial fibrillation. Additionally, echocardiography was performed to assess findings characteristic of cardiac amyloidosis, such as left ventricular hypertrophy. Blood tests included troponin I, troponin T, B-type natriuretic peptide, and N-terminal pro-B-type natriuretic peptide. Furthermore, ^{99m}Tc-PYP scintigraphy was performed to confirm cardiac amyloidosis and was evaluated 1 and 3 hours after ^{99m}Tc-PYP administration. At 1 hour, quantitative assessment was performed according to the heart-to-contralateral lung uptake ratio. Subsequently, at 3 hours, visual assessment was performed by referring to the relative tracer uptake in the myocardium relative to the ribs. In accordance with the recommendations of the American Society of Nuclear Cardiology, a heart-to-contralateral ratio $\geq$1.5 in the quantitative assessment was defined as positive, while grade 2 or 3 uptake in the visual assessment was defined as positive.[9]

Genetic testing and referral to hematology

There are two types of ATTR amyloidosis, namely hereditary ATTR amyloidosis and wild-type ATTR amyloidosis (ATTRwt); therefore, patients diagnosed with ATTR cardiac amyloidosis were subjected to genetic testing to determine the type. In contrast, patients diagnosed with AL cardiac amyloidosis were referred to the hematology department for further scrutiny and more specific treatment.

Statistical analysis

Categorical and continuous variables are reported as numbers (percentages) and means ± standard deviations, respectively. Differences between the groups were assessed using the unpaired *t*-test for continuous variables and the chi-square test for categorical variables. Furthermore, the Cochran-Armitage test was used to assess the trends of the amyloid positivity rate by age. All data analyses were performed using EZR (Jichi Medical University, Saitama, Japan),[15] and statistical significance was set at $P < .05$.

Results

All patients who underwent surgery during the study period, did not meet the exclusion criteria, and agreed to participate in the study were included. In total, 41 shoulder surgeries and 33 CTS surgeries were included in this study. Table I presents the characteristics of the patients and the number of amyloid deposits in both groups, while Table II shows the details of the diseases associated with shoulder surgery. A total of 20 LHB tendons were collected, including 19 with rotator cuff tears and 1 with shoulder contractures. The age distribution of the patients in both groups and the amyloid deposition rate by age are shown in Figs. 2 and 3, respectively.

Overall, the shoulder group was significantly younger than the CTS group ($P = .0013$), and the CTS group had a significantly higher proportion of women than the shoulder group ($P = .0071$). Additionally, the amyloid deposition rate was significantly lower in the shoulder group than in the CTS group ($P = .0051$). All three patients that were amyloid-positive in the shoulder group had rotator cuff tears, with a positivity rate of 11.1% when limited to only patients with rotator cuff tears (n = 27).

The deposition rates by age are shown in Fig. 3. In the CTS group, the amyloid deposition rate tended to increase significantly with age ($P = .022$; Cochran-Armitage test). However, the amyloid positivity rate showed no significant trend across ages in the shoulder group ($P = .98$).

Table III shows the details of the amyloid deposition cases in each group. Notably, the subtype of all cases with amyloid deposition was transthyretin (TTR). All three shoulder patients with amyloid deposition underwent cardiac evaluation; however, only 7/12 CTS patients with amyloid deposition underwent the evaluation. The remaining patients in the CTS group either did not request an additional cardiac evaluation or were pending for patient convenience. Of the CTS patients, two were diagnosed with ATTRwt cardiac amyloidosis; however, no patients in the shoulder group were diagnosed with cardiac amyloidosis. Upon cardiac evaluation, two patients in the CTS group met the diagnostic criteria of 99mTc-PYP scintigraphy, while three patients in the shoulder group were in the normal range for 99mTc-PYP scintigraphy (Supplemental Tables I and II).

Table IV lists the number and percentage of positive patients per sampling site. In the shoulder group, only 1 of the 41 synovium showed amyloid deposition. In contrast, amyloid deposition was found in 3/20 patients in which the LHB tendon was examined. Notably, of the three patients in the shoulder group positive for deposits in the LHB, only one had deposits in the synovium.

In the CTS group, 24 of the 33 cases (73%) were diagnosed with bilateral CTS preoperatively, and 10 of the 12 (83%) amyloid deposition cases were bilateral. Furthermore, two cases diagnosed with cardiac amyloidosis had bilateral CTS. In the shoulder group, all cases had unilateral diseases.

Discussion

This study revealed that 7.3% and 36.4% of the patients undergoing shoulder and CTS surgery, respectively, had TTR amyloid deposition. In the CTS group, two of seven cases with amyloid deposits resulted in an identification of cardiac amyloidosis. However, no cases in the shoulder group were identified with cardiac amyloidosis.

Few studies have discussed amyloid deposition in intraoperative specimens of shoulder disease.[5,29] Previously, Cole et al[5] and Sueyoshi et al[29] indicated that patients who underwent rotator cuff repairs had amyloid deposition rates of 57% and 38%, respectively. In this study, we observed considerably lower amyloid-positive rates (7.3% in all cases and 11.1 % in rotator cuff repair cases) than the previous studies. This discrepancy may be related to the difference in sampling sites; for example, the stumps of torn rotator cuff tendons were harvested in previous papers, whereas we examined the synovium or LHB tendon because we assumed that there would be histological heterogeneity in the stumps of the torn rotator cuff tendons. Although the rotator cuff tendon, synovium, and LHB tendon are involved in the shoulder joint, their histological features differ. Therefore, the amyloid affinity of tissues could depend on the type of connective tissue harvested for analysis. Furthermore, the mean age of our cohort (62 years old) was lower than that of previous studies (approximately 65 years old),[5,29] which may have also affected the results.

Regarding the amyloid deposition rate in CTS, a previous Japanese study reported this as 34–37%,[25,29,30] which is consistent with our findings (36.4%). We also found that the amyloid deposition rate of the shoulder was lower than that in CTS. Apart from the aforementioned difference between sampling sites, this difference might be related to the fact that the shoulder group was younger than the CTS group. In fact, previous studies and our results in the CTS group have shown that the rate of amyloid deposition increases with aging.[25,32] However, in this study, the increasing amyloid positivity rate in the shoulder group was not significant across ages. This might be due to the low number of positive cases in the

Table I
Patient demographics and number of amyloid-positive cases.

	CTS surgery (n = 33)	Shoulder surgery (n = 41)	*P* value
Age, mean ± SD (range), years	69.8 ± 10.5 (47–83)	62.0 ± 9.4 (44–80)	.0013
Sex (male:female)	6:27	21:20	.0071
Amyloid deposition-positive, n (%)	12 (36.4%)	3 (7.3%)	.0051

CTS, carpal tunnel syndrome; *SD*, standard deviation.

Table II
Disease types in the shoulder surgery group.

Diagnosis	Cases
Rotator cuff tear	27
Contracture of the shoulder	12
Synovitis	1
Calcific tendonitis of the shoulder	1
Total	41

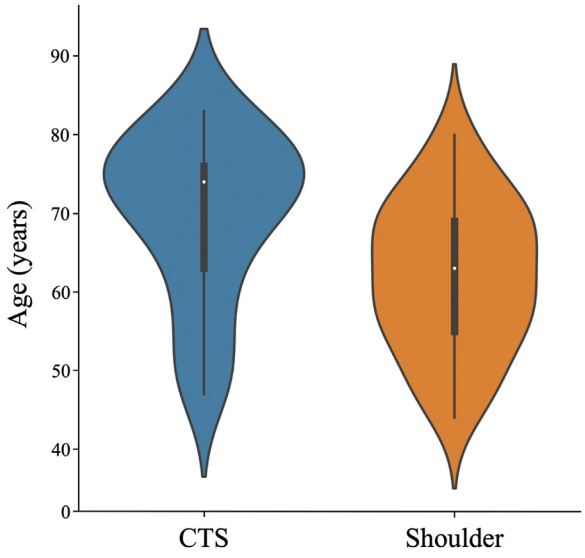

Figure 2 Violin plot of age for the carpal tunnel syndrome and shoulder surgery groups. *CTS*, carpal tunnel syndrome.

shoulder group. However, further analyses are required to correctly define the trend within the shoulder group.

Based on previous reports, approximately 20% of patients with amyloid positivity during CTS surgery demonstrate cardiac amyloidosis complications.[27,30] In the current study, seven TTR amyloid-positive patients in the CTS group underwent cardiac evaluation, and two (28.6%) were diagnosed with ATTRwt cardiac amyloidosis. This is compatible with the previous reports. However, there have been no previous reports investigating cardiac amyloidosis complications in patients with amyloid deposits in intraoperative specimens from shoulder surgery. In the present study, none of the three cases exhibiting amyloid deposition in the shoulder group had a diagnosis of cardiac amyloidosis. Consequently, it is uncertain whether the analysis of amyloid deposition in samples obtained from shoulder surgery is advantageous for the early detection of cardiac amyloidosis.

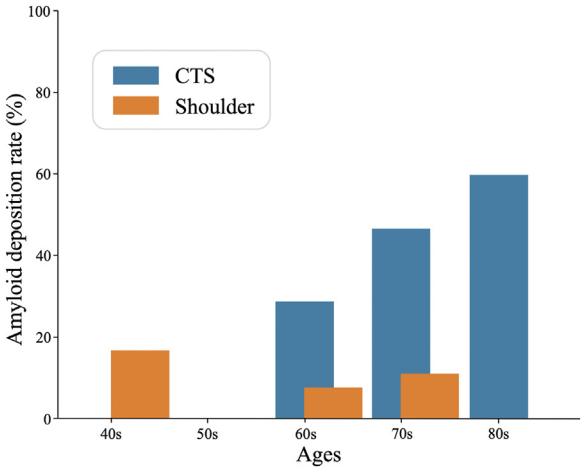

Figure 3 Amyloid deposition rate by age group for the CTS and shoulder surgery groups. *CTS*, carpal tunnel syndrome.

Previously, Hallie et al[14] reported that 33.3% of ATTRwt cardiac amyloidosis patients had a history of biceps brachii tendon rupture, suggesting a relationship between cardiac amyloidosis and biceps brachii tendon rupture. In the present study, there were three cases of deposition in the LHB tendon; however, only one of these had deposition in the synovium. Regarding the types of harvested samples, the amyloid positivity rate of the LHB tendon was higher than that of the synovium. Accordingly, this may suggest that anatomical structures have differing affinities for amyloid; however, further studies are required to analyze the tissue distribution of amyloid.

Bilateral CTS is frequently observed in patients with cardiac amyloidosis.[8,10,11,27] In this study, while bilateral CTS was notably prevalent within the CTS cohort, both cases diagnosed with cardiac amyloidosis displayed bilateral CTS. However, with regard to shoulder disease, there are no reports suggesting that shoulder disease associated with cardiac amyloidosis is frequently bilateral. In this study, all shoulder cases had unilateral disease, and cardiac amyloidosis was not identified within the shoulder cohort. Therefore, it remains unclear whether bilateral shoulder disease is commonly associated with cardiac amyloidosis.

The results of this study emphasize a clinical implication; specifically, the screening of intraoperative specimens in CTS surgery can lead to the early detection of cardiac amyloidosis, which is similar to previous reports. However, it remains unclear whether assessing amyloid deposition in specimens of the shoulder can predict cardiac amyloidosis at an early stage. Nevertheless, it is possible that patients with deposits may develop cardiac amyloidosis in the future. Therefore, long-term studies are required to investigate patients with amyloid deposits in shoulder surgery specimens.

This study had some limitations. First, the number of shoulder surgery patients was small; therefore, a larger number of cases are required to determine the prevalence of cardiac amyloidosis and the tendencies of deposition sites more accurately. Second, because arthroscopic surgery is predominantly performed at our institution, this single-institution study was limited to arthroscopic surgery for the shoulder surgery cohort. Additionally, there were no cases of shoulder instability during the research period, which is more common in young individuals. This could have changed the age of the cohort from the general population, which could have affected the amyloidosis prevalence. It would be desirable to include open surgeries such as arthroplasty and shoulder instability in the survey

Table III
Details of the amyloid deposition cases in each group.

	CTS surgery (n = 12)	Shoulder surgery (n = 3)
Age, mean ± SD (range), years	75.5 ± 5.6 (63–83)	64.7 ± 14.6 (49–78)
Sex (male:female)	3:9	2:1
Amyloid subtype (TTR:AL)	12:0	3:0
Cardiac evaluation	7	3
Diagnosis of cardiac amyloidosis	2	0

AL, amyloid light-chain; *CTS*, carpal tunnel syndrome; *SD*, standard deviation; *TTR*, transthyretin.

Table IV
Amyloid deposition rates according to the specimen location.

	Total sample	Age, mean ± SD, years	Amyloid deposition-positive, n (%)
CTS (TCL)	33	69.8 ± 10.5	12 (36.4%)
Shoulder (synovium)	41	62.0 ± 9.4	1 (2.4%)
Shoulder (LHB)	20	66.4 ± 7.6	3 (15%)

CTS, carpal tunnel syndrome; *LHB*, long head of biceps brachii; *SD*, standard deviation; *TCL*, transverse carpal ligament.

for overall shoulder disease, in which case the results may be different. Third, not all patients with amyloid deposits in the CTS group underwent cardiac evaluation. Consequently, the exact prevalence of cardiac amyloidosis remains unknown, and the results may affect the understanding of the relationship between CTS, amyloid deposition, and cardiac amyloidosis. Therefore, the prevalence in the CTS group could not be strictly compared to that in the shoulder group. Finally, participants negative for amyloid in both groups did not undergo cardiac evaluation. Thus, the exact prevalence of cardiac amyloidosis in the study cohort is unknown. To elucidate the exact prevalence of cardiac amyloidosis, we are planning further studies comprising cardiac evaluation for all participants.

Conclusions

Our findings regarding the rate of amyloid deposition in intraoperative specimens and the prevalence of cardiac amyloidosis in CTS surgery patients were consistent with those of previous studies; however, the rate of amyloid deposition in the synovium or LHB tendon in shoulder surgery patients was much lower, and no cases had cardiac amyloidosis. Therefore, while our findings may not conclusively support the routine investigation of amyloid deposition in the synovium or LHB tendon specimens obtained from shoulder surgery, a multicenter study involving a larger number of cases and assessment of cost-effectiveness will provide clearer insights into whether routine examination is recommended.

Disclaimers:

Funding: This work was supported by the JSPS KAKENHI Grant Number JP22K09418.
Conflicts of interest: Koji Fujita's institution received the grant JSPS KAKENHI Grant Number JP22K09418. The other authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

Acknowledgments

The authors would like to thank Dr. Tomohiko Waki for the patient recruitment and their critical reading of the manuscript, and Editage (www.editage.com) for English language editing.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jseint.2023.11.009

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