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Additional benefit of ultrasonography to evaluate nerve root condition of degenerative cervical spine disease

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STUDY DESIGN: A cross-sectional explanatory study.

OBJECTIVES: To clarify the nerve root condition and the association between nerve root cross-sectional area (CA) on ultrasonography (US) and other examinations such as MRI or compound muscle action potentials (CMAPs) in degenerative cervical spine diseases.

SETTING: A university hospital in Japan.

METHODS: Fifty-one patients diagnosed with proximal cervical spondylotic amyotrophy (CSA) (13 patients), cervical radiculopathy of C5 or C6 nerve root (CR) (26 patients), or cervical spondylotic myelopathy (CSM) (12 patients), and twenty-nine healthy volunteers were included in this study. Neurological findings, US findings and CMAPs of deltoid and biceps muscles of all participants were evaluated. In addition, CSA, CR, and CSM patients underwent MRI.

RESULTS: A significant correlation was not observed between CA and CMAP amplitude or foraminal diameter on MRI (P > 0.05). In the US examination, the C6 CA of the affected side of the CR group was significantly larger than that of both the normal side and the other groups (P < 0.001). The C5 CA of the affected side of the CSA group clearly showed a bimodal distribution: enlarged and small CA groups. In the CMAP findings, CSA cases respectively showed the lower amplitude of deltoid and bicep CMAPs on both the normal and the affected side ($P \le 0.01$). CSM and healthy volunteers were nearly identical in CA and CMAPs.

CONCLUSION: Utilizing US in addition to NCS and MRI can contribute towards an evaluation of the nerve root condition of degenerative cervical spine disease.

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INTRODUCTION

Degenerative change of the cervical spine develops with age and results in both spinal canal and foraminal stenosis. These changes are responsible for a variety of neurological deficits such as myelopathy, radiculopathy, and radiculomyelopathy. Assessment of these pathologies is usually based on image and neurological findings. Because both the spinal cord compression and the nerve root encroachment on MRI are frequently observed findings in either symptomatic or asymptomatic patients, the neurological physical findings associated with the imaging findings are important for clinical diagnosis [1]. Nevertheless, neurological differentiation of the spinal cord and nerve root involvement is sometimes difficult. And MRI is less efficient for evaluating the nerve root itself when foraminal stenosis is present [2]. Recently, ultrasonographic (US) evaluation, which directly shows the nerve root, is being utilized in cervical nerve root disease [3–5]. However, nerve root ultrasonographic findings in other degenerative cervical conditions and the association between US and MRI or nerve conduction study (NCS) remains unclear. To establish the significance of cervical nerve root US examination in degenerative cervical disease, the aim of this study is to clarify the nerve root ultrasonographic findings of cervical degenerative conditions: amyotrophy featuring muscle weakness with no or minimal sensory deficit, radiculopathy with disabling arm pain and numbness, and myelopathy presenting the sensorimotor disturbance in extremities.

MATERIAL AND METHODS

We conducted this study between April 2019 and June 2021 on patients diagnosed with proximal cervical spondylotic amyotrophy (CSA), cervical radiculopathy affecting unilateral C5 or C6 nerve root (CR), cervical spondylotic myelopathy (CSM) and healthy volunteers in our institution. CSA is generally divided into two types; proximal and distal [6]. Proximal CSA exhibits deltoid and biceps weakness. As deltoid and biceps muscles have a relatively limited contribution from the C5 and C6 nerve root/spinal cord segment [7-9], C5 and C6 radiculopathy patients were adopted for cervical radiculopathy (CR), corresponding to the lesion level of CSA. And unilateral symptomatic patients of CSA and CR were used to compare sideto-side differences. All CSA patients had unilateral weakness of deltoid and/or biceps (MMT < 3) with no or minimal sensory deficit. CR patients had radicular arm pain with dermatomal sensory disturbance and a varying degree of deltoid and bicep weakness. CSM patients showed sensorimotor disturbance with C3/4 and/or C4/5 cord compression. To distinguish CSM from CSA, CSM patients who had muscle weakness in the deltoid and/or biceps were excluded from this study. Healthy volunteers were conveniently recruited from patients who scheduled hip or knee joint replacement surgery in our department. Those with a history of stroke, peripheral neuropathy and history of cervical trauma were excluded.

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Table 1. Patients characteristics.

	CSA	CR	CSM	Healthy volunteers	P value
Number of patients	13	26	12	28	
Male/ female	8/5	14/12	7/5	15/14	
Age	72.5(67.6–77.4)	50.7(46.1–55.3)	66.9(60.3–73.5)	72.8(69.2–76.4)	< 0.001 ^a
Number of cases	13	3	0	0	

With MMT <3 in deltoid or biceps muscle

Kruskal-Wallis test with Bonferroni correction for post-hoc is used for statistical analysis.

CSA cervical spondylotic amyotrophy, CR cervical radiculopathy, CSM cervival spondylotic myelopathy.

P < 0.05 was considered to be significant.

^aCR group vs three other groups.

Because they underwent elective orthopaedic surgery, their general condition was good and were classified as ASA class 1 or 2. Their age and gender distribution were identical to those of other groups except for the age of the CR group. Neurological examination including manual muscle testing (MMT) and ultrasonography examination of the cervical nerve root

were conducted on all subjects. The imaging findings using MRI were evaluated in three cervical disease groups. Furthermore, a nerve conduction study to record compound muscle action potentials (CMAPs) was used to support the diagnosis and to evaluate the motor function in all four groups. Informed consent from all participants of this study and institutional review board approval for this study were obtained (IRB:30–156).

Ultrasonography

Ultrasonographic examination was performed according to the previously reported method [5–11] by a single orthopedic surgeon with more than five years' experience using 13-5 MHz linear probe (SONIMAGE HS1, Konica Minolta, Tokyo, Japan). Participants were placed in a supine position with their heads turned toward the contralateral side. After confirming a longitudinal image of the nerve root, we obtained its true axial image by turning the probe perpendicularly. Firstly, we identified C7 nerve root because its anterior transverse process is rudimentary compared to that of C6. Then, moving the probe cranially, the C6 and C5 nerve roots were identified. In some cases, it was difficult to identify the C7 nerve root because of the patient's body habitus. In such cases, we started by searching the upper trunk of the brachial plexus in the supraclavicular fossa where it is located in the most superficial among the three trunks, and then traced it cranially to the level of the process where it becomes "C5 nerve root". We measured the cross-sectional area (CA) of the C5,6 nerve root between the anterior and posterior tubercle of the transverse process. CA (mm²) of the C5 and C6 nerve root were measured by tracing the outer rim of the nerve [11]. The mean value of at least two measurements was used for the analysis. We tested the intraobserver and test-retest reliabilities. Intraclass correlation coefficient (ICC) estimates and their 95% confident intervals were evaluated based on a mean-rating (k = 2), absolute agreement, 2-way mixed-effects model [12]. These data were analyzed using statistical software (SPSS for Windows version 12, IBM, Chicago, Illinois, USA). The ICC was 0.95 (95% CI; 0.85-0.98). Values <0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability. The results of the ICC were evaluated as "good" to "excellent."

MRI

All patients underwent surface coil MR examination of cervical spine with the superconducting system (Siemens Healthineers AG MAGNETOM Area1.5 T; Erlangen, Germany). The spin echo pulse sequences were 350–600/9–12 (TR ms/TE ms) for T1-weighted images and 2600–4000/90–110 for T2-weighted images. C5 and C6 spinal cord segments are respectively located at the C3/4 and C4/5 spinal level [13]. The C5 and C6 nerve root run through the C4/5 and C5/6 foramen. To evaluate cord compression and foraminal stenosis, we checked MRI of CSA, CR, and CSM patients. With the axial images, we measured the area of the spinal cord at the level of C3/4, 4/5 and the foraminal anterior-posterior diameter (FD) at the level of C4/5, 5/6.

Nerve conduction study

Electrophysiological examination was performed using a standard EMG machine (NeuroPak S1, Nihon Koden, Tokyo, Japan). Participants lay in the

supine position with their heads turned toward the contralateral side. Compound muscle action potentials (CMAPs) of the deltoid and biceps muscles elicited from Erb point stimulation were recorded. The recording and reference electrodes were placed on the middle of the deltoid and biceps muscles and the acromion and lateral epicondyle, respectively. Electrical stimulation which consisted of a square wave of 0.1msec in duration, was given at a rate of 1/sec. The stimulus intensity was increased gradually until the size of CMAP no longer increased. The baseline-tonegative peak amplitude of CMAP was measured.

Statistical analysis

The correlation between CA and CMAPs amplitude or foraminal diameter on MRI in each group was evaluated by the Spearman's rank correlation coefficient.

To reveal the differences in CA of the nerve root among the four groups and between affected and normal sides in CR and CSA patients, we compared the affected and the normal side of these groups with values assessed from the bilateral sides of CSM and healthy volunteers. CMAP amplitude was also evaluated in the same way as CA. We used the Kruskal-Wallis test with Bonferroni correction for group comparison and the Wilcoxon signed rank test for making a side-to-side comparison of CA and CMAP amplitude. All data were analyzed with statistical software (SPSS for Windows version 12, IBM, Chicago, Illinois, USA). The difference was considered statistically significant when p < 0.05.

RESULTS

This study included 13 CSA patients (72.5 \pm 9.0 y.o), 26 CR patients (50.7 \pm 12.0 y.o) including 4 in C5 and 22 in C6, 12 CSM patients (66.9 \pm 11.7 y.o), and 28 healthy volunteers (72.8 \pm 9.6 y.o). CR patients were significantly younger than other groups (p < 0.001). Muscle weakness of either deltoid and biceps muscles with MMT <3 was found in all of the CSA cases and 3 of the C6CR cases (Table 1).

The correlation between US findings and foraminal stenosis on MRI or CMAP amplitude among three degenerative cervical diseases

There was no significant correlation between the foraminal diameter on MRI and CA among the three disease groups: CSA; C4/5 FD and C5 CA, r = 0.22, p = 0.27, C5/6 FD and C6 CA, r = 0.31, *p* = 0.12, CR; C4/5 FD and C5 CA, *r* = 0.23, *p* = 0.1, C5/6 FD and C6 CA, r = -0.22, p = 0.11, CSM; C4/5 FD and C5 CA, r = 0.37, p = 0.078, C5/6 FD and C6 CA, r = -0.029, p = 0.89. Neither was there any significant correlation between CA and CMAPs among all four groups: CSA; deltoid CMAP and C5 CA, r = -0.12, p = 0.56, biceps CMAP and C6 CA, r = -0.05, p = 0.82, CR; deltoid CMAP and C5 CA, r = -0.07, p = 0.68, biceps CMAP and C6 CA, r = -0.004, p = 0.98, CSM; deltoid CMAP and C5 CA; r = -0.17, p = 0.46, biceps CMAP and C6 CA; r = 0.24, p = 0.5, Healthy Volunteers; deltoid CMAP and C5 CA, r = 0.14, p = 0.3, biceps CMAP and C6 CA, r = 0.13, p = 0.41. (See supplementary appendix Figs. 1-4 for the scatter plot of C5,6 CA and C4/5, C5/6 FD or deltoid and biceps CMAP amplitude.)



Fig. 1 Cross sectional area of C5 and C6 nerve root of each groups. A C5 nerve root. B C6 nerve root.

Ultrasonographic examination (Fig. 1, Table 2)

The C5 CA of the affected side in CSA showed a bimodal distribution with enlarged and small CAs (Fig. 1A). When comparing C5 and C6 CA among all groups, the affected side C6 CA in CR was significantly larger than that of the three other groups (P < 0.001). The affected side C6 CA in CR was also significantly larger than that of the normal side (P = 0.003). The normal C5 and C6 CAs in CR were also significantly larger than those of healthy volunteers (P < 0.05). In contrast, those of CSM did not show any significant difference compared with healthy volunteers (P > 0.05).

Nerve conduction study (Table 2)

The affected side deltoid CMAPs in CSA showed a significantly smaller amplitude than that of the three other groups (P < 0.001).

The normal side deltoid CMAPs in CSA also showed a significantly smaller amplitude compared to that of CR and healthy volunteers. The side-to-side difference was also remarkable in CSA (P = 0.002).

The affected side biceps CMAPs in CSA showed a smaller amplitude compared to that of CR (P = 0.01). The normal side biceps CMAPs in CR showed a larger amplitude than that of the healthy group (P = 0.04). Those of CSM did not show any significant difference compared with those of healthy volunteers (P > 0.05).

MRI (Table 3)

The CSM group showed a significantly smaller spinal cord area at C3/4 (P = 0.02) compared with the CR group. As to foraminal stenosis, CSA and CSM patients had significantly severe C4/5 foraminal stenosis on the affected side compared with CR patients

Table 2. US and NCS findings.			
	CSA	CR	CSM
n	13	26	24
US findings			
Cross Sectional Area (cm ²)			
C5; normal side	0.065(0.053-0.077)	0.066(0.056-0.076)	0.058

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	CSA	СК	CSIVI	nealthy volunteers	P value
n	13	26	24	56	
US findings					
Cross Sectional Area (cm ²)					
C5; normal side	0.065(0.053–0.077)	0.066(0.056-0.076)	0.058(0.048–0.068)	0.050(0.046–0.054)	0.04 ^c
C5; affected side	0.070(0.052-0.088)	0.067(0.055–0.079)			0.82
P value ^b	0.57	0.152			
C6; normal side	0.081(0.065–0.097)	0.090(0.082-0.098)	0.080(0.070–0.090) 0.0	0.072(0.066-0.078)	0.014 ^c
C6; affected side	0.073(0.057–0.089)	0.12(0.11-0.13)			<0.001 ^d
P value ^b	0.07	0.003			
NCS findings					
CMAP amplitude (mV)					
Deltoid; normal side	5.9(5.1–6.7)	8.25(7.4–9.1)	7.4(6.7–8.1)	7.5(6.9–8.1)	0.009 ^e
Deltoid; affected side	1.2(1.0–1.7)	7.9(7.1–8.7)			< 0.001 ^f
P value ^b	0.002	0.38			
Biceps; normal side	5.3(4.4–6.2)	7.2(6.3-8.1)	5.7(4.4–7.0)	5.6(4.8–6.4)	0.04 ^c
Biceps; affected side	2.9(1.7-4.1)	6.4(5.4–7.4)			0.01 ^g
P value ^b	0.052	0.13			

Data were expressed as mean and 95% confidence interval(CI).

US ultrasonographic study, NCS nerve conduction study, CSA cervical spondylotic amyotrophy, CR cervical radiculopathy, CSM cervival spondylotic myelopathy. P < 0.05 was considered to be significant.

^aKruskal–Wallis test with Bonferroni correction for post-hoc is used for statistical analysis.

^bWilcoxon singled rank test is used for statistical analysis.

^cStatistical significance between CR group and healthy volunteers.

^dStatistical significance in CR group compared to three other groups.

^eStatistical significance in CSA group compared with CR, herthy volunteers.

^fStatistical significance in CSA group compared with other three groups.

⁹Statistical significance between CSA group and CR group.

Table 3. MRI findings in each disease group.					
	CSA	CR	CSM		
Cross sectional area of spinal cord(mm ²)				P value ^a	
C3/4	71.8(65.4–78.1)	77.1(74.2-80.0)	65.2(58.1–72.2)	0.02 ^c	
C4/5	73.3(63.3–83.2)	77.4(73.6-81.2)	66.3(58.1–74.5)	0.55	
Foraminal anterior-posterior diameter(mm)					
C4/5; normal side	1.50(0.82–2.18)	2.41(1.93–2.89)	0.91(5.89–1.23)	<0.001 ^c	
C4/5; affected side	0.89(0.07-1.70)	1.92(1.45–2.38)		0.002 ^d	
P value ^b	0.23	0.04			
C5/6; normal side	1.12(0.61–1.63)	1.64(1.20-2.08)	1.11(0.75–1.47)	0.13	
C5/6; affected side	0.61(0.14-1.08)	1.04(0.62-1.46)		0.12	
P value ^b	0.43	0.11			

Data were expressed as mean and 95% confidence interval(CI).

CSA cervical spondylotic amyotrophy, CR cervical radiculopathy, CSM cervival spondylotic myelopathy.

P < 0.05 was considered to be significant.

^aKruskal-Wallis test with Bonferroni correction for post-hoc is used for statistical analysis.

^bWilcoxon singled rank test is used for statistical analysis.

^cStatistical signifficance between CR group and CSM group.

^dStatistical signifficance in CR group compared with CSM and CSA groups.

(P = 0.002). CSM patients also showed significance on the normal side C4/5 foramen compared to CR patients (P < 0.001). C4/5 foraminal stenosis in the CR group was more severe on the affected side (P = 0.04). On the other hand, there was no significant difference among the three groups at C5/6 foramen (P > 0.05).

Case presentation

A C6CR case; a 47-year-old-female patient presenting with radicular pain in the upper arm and finger numbness on the left side was referred to our institution. US examination demonstrated swelling of the left C6 root (Fig. 2A). NCS showed a slightly lower amplitude only on the left side (Fig. 2A). An axial MRI image

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Fig. 2 A C6CR case. A US images and deltoid CMAP of left C6CR patient. (A) An axial image of the bilateral C5 nerve roots showed that they were almost the same size. (B) An axial image of the C6 nerve root showed swelling of the left C6 root. (C) Deltoid CMAPs showed slightly lower amplitude only on the left side. (D) Biceps CMAPs showed almost the same amplitude on both sides. B MRI of the left C6CR patient. (A) A sagittal image of cervical spine showed C5/6 disc hernia (arrowhead). (B) An axial image of C5/6 level showed severe foraminal stenosis (arrowhead) on the left side.

showed disc herniation causing foraminal stenosis at the left C5/6 level (Fig. 2B).

A CSA case; a 67-year-old male patient presenting with weakness of deltoid and bicep muscles on the right side was referred. While US did not show any swelling on the affected side nerve root, NCS demonstrated an absence of deltoid CMAPs on the right side with a slightly lower amplitude of that on the normal side. (Fig. 3A) Axial images of cervical MRI showed cord compression and foraminal stenosis at the C3/4, 4/5, 5/6 levels (Fig. 3B).

DISCUSSION

To the best of our knowledge, this is the first study to compare US findings among CSA, CR, CSM patients and healthy volunteers. The CA did not correlate with the foraminal stenosis on MRI or CMAP amplitude. Although MRI is the standard method to evaluate spinal cord compression and its associated intramedullary damage, nerve root dysfunction is not associated with foraminal stenosis on MRI. The specific MRI section such as the sagittal oblique view [2, 14] is an optional method to evaluate nerve root morphology. However, this mainly demonstrates the foraminal stenosis, the extra-nerve root condition while US directly focuses on the nerve root. The nerve root US findings from this study could support its usefulness to assess nerve root conditions in degenerative cervical disease.

The CA enlargement, nerve root swelling, was a characteristic feature of CR [4, 5] for distinguishing properly between symptomatic and asymptomatic foraminal stenosis on MRI. In accordance with the previous reports [4, 5], CA enlargement was associated with cervical radiculopathy. It was suggested that the nerve root compression caused the breakdown of the blood nerve barrier and increased vascular permeability, which resulted in intraradicular edema and an increase of macrophage and mast cells in an

animal study [15]. Since the foraminal stenosis due to degenerative process is observed with aging [16], nerve root ultrasonography is useful to detect the symptomatic lesion in cervical radiculopathy.

The responsible lesions of CSA, the nerve root, spinal cord or both of them, still remain a controversial matter [17–20]. Although C5 and C6 CA of CSA patients showed no statistical difference as continuous variables in this study, the scatter plot of C5 CA clearly showed a bimodal distribution. Six out of 26 arms (23.1%) showed an enlarged C5 CA compared to the reported value, i.e., more than 0.1 cm² [3]. The enlarged C5 CA was most frequently observed in the CSA group (23.1%) among four groups (17.4% in CR, 8.3% in CSM, 0% in healthy volunteer group) (P = 0.0006, Fisher's exact test). The enlarged C5 CA was also observed more often on the affected side (five out of thirteen (38.5%)), while there was only one case of C5 CA with more than 0.1 cm² on the normal side. The nerve root enlargement might represent the nerve root lesion in CSA, which was similar to radiculopathy and/or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [21]. Meanwhile, neural degeneration or axonal loss is theoretically considered to be a consequence of spinal cord or nerve root compression. Nerve root thinning, reflecting neural degeneration, was reported in amyotrophic lateral sclerosis, which is a neurodegenerative disorder and an important differential diagnosis of CSA. However, the percentage of the CA reduction was not high even in ALS; C6 CA reduction was 26% in ALS [22]. In this study, the reduced C6 CA, which was less than 0.04cm² (i.e., the minimum value for healthy controls in this study) was observed in three out of 26 hands (11.5%) in the CSA group. Because the enlarged CA was easy to detect compared to the small CA, the enlarged CA might become a useful surrogate marker of nerve root condition.

On the other hand, CMAP amplitude reduction was remarkable in CSA patients. The bilateral deltoid CMAP reduction in CSA,



Fig. 3 A CSA case. A US images and deltoid CMAPs of right CSA patient. (A) An axial image of the bilateral C5 nerve roots showed that they were almost the same size. (B) An axial image of the bilateral C6 nerve roots showed that they were almost the same size, too. (C) Deltoid CMAPs showed slightly lower amplitude on the left side and severely lower amplitude on the right side. (D) Biceps CMAPs showed lower amplitude on the left side compared to the right side. B MRI of right CSA patient. (A) A sagittal image of the cervical spine showed cord compression at the C3/4,4/5,5/6 levels (arrowhead). (B)–(D) Axial images of C3/4(B), C4/5(C), and C5/6(D) level showed canal and foraminal stenosis (arrowhead).

despite unilateral weakness, supports the hypothesis that the spinal cord anterior horn damage, bilaterally, would be the responsible lesion [23]. In fact, spinal cord compression, albeit mild, was observed in CSA. As mentioned above, we could not confirm a significant CA reduction in CSA compared to other groups including healthy volunteers. Thus, CMAP amplitude reduction in CSA plays an important role in assessing the degree of the neural damage: the damage severity and the intramedullary transverse extent. The seemingly conflicting findings such as the enlarged C5 CA and the reduced CMAP amplitude could support the combined usefulness of US and CMAPs for the pathophysiologic evaluation of CSA to elucidate the nerve root involvement in the presence of spinal cord involvement.

Although CSM is a heterogenous pathologic condition with sensorimotor dysfunction, CSM included in this study was restricted to patients mainly exhibiting sensory and motor long tract symptoms without clear segmental signs, muscle weakness, or sensory disturbance associated with radicular symptoms. US and CMAPs findings were not significant between the CSM and the healthy volunteer group. Accordingly, clinical characteristics such as radicular pain and muscle weakness are probably associated with the abnormal findings in US and CMAP amplitude.

Our study has several limitations. First, the wide range of US normal values has been reported previously [10, 11]. In fact, C6 CA of CSA, CR and CSM showed some overlap with that in healthy controls. Second, this study included C5 and C6 radiculopathy cases as the representatives of cervical radiculopathy because we aimed to clarify the differences between C5 and C6 nerve root and C5 and C6 spinal segmental cord lesions. However, just four out of 26 cases (15.4%) were included in this study because of the rarity of C5CR [24]. And because C5 CA is small even in normal volunteers, C5 CA in CR had no significant swelling. Third, the sample size of the CSA group is relatively small, preventing us from making a detailed analysis of clinical data such as duration of symptoms. Further studies with a large sample size are necessary to clarify the associations among physical findings, US findings

and CMAP findings. In addition, CSM is a heterogenous condition as mentioned above. Although the CSM adopted for this study consisted of a relatively homogenous cohort, the difference in US findings and CMAP findings between the heterogenous CSM group and the healthy control group is unclear. Thus, US and CMAP changes among CSM with muscle weakness and radicular pain should confirm the heterogeneity of CSM. Fourth, the age of CR patient groups was younger than other groups including the healthy control group. Although the age was reported to have no significant effect on the cross-sectional area on the adult subjects with mean ages of forty-two [25], the effect of aging can also concern the elderly population.

CONCLUSION

The nerve root ultrasound could demonstrate different nerve root morphological changes compared to MRI. CR patients showed swelling of the nerve root without CMAP reduction. Proximal CSA patients showed both enlarged and small CAs, though a significant difference was not observed, with significantly lower amplitude of deltoid and biceps CMAPs. CSM patients without deltoid and biceps weakness and healthy volunteers were nearly identical on the US and CMAP findings. Utilizing US in addition to MRI and NCS can contribute towards an evaluation of the nerve root condition in degenerative cervical spine disease.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

HK and NT were responsible for designing the study protocols, conducting the research, analyzing data, interpreting results, and writing the manuscript. NT, KK, NA, and RT were involved in recruiting patients and editing the manuscript. NT, KK, NA, RT, and MI reviewed the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

We obtained written informed consent from all participants and institutional review board approval for this study (IRB:30-156).

ADDITIONAL INFORMATION

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