European Neurology

Clinical Neurology: Brief Report

Eur Neurol
DOI: 10.1159/000512269

Received: June 19, 2020
Accepted: October 8, 2020
Published online: December 9, 2020

Comorbidity of Cervical Spondylogenic Myelopathy and Amyotrophic Lateral Sclerosis: When Electromyography Makes the Difference in Diagnosis

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Keywords
Cervical spondylogenic myelopathy · Amyotrophic lateral sclerosis · Electromyography · Awaji criteria

Abstract
Cervical spondylogenic myelopathy (CSM) represents a common differential diagnosis for spinal onset Amyotrophic Lateral Sclerosis (ALS). Identifying occurrence of ALS in patients with CSM may be challenging. We evaluated the accuracy of Awaji criteria in the diagnosis of ALS in a cohort of patients with CSM. We screened all patients attending Turin ALS Center during the 2006–2018 period. We selected only patients for whom cervical cord MRI showed radiological signs of CSM. All patients underwent electromyography (EMG), and Awaji criteria were used for diagnosis of clinically probable ALS. All patients were followed up clinically for at least 6 months, and ALS diagnosis was eventually confirmed according to El-Escorial revised criteria, based on disease progression. Of 2,059 patients screened, in 42 cases, MRI showed signs of CSM; CSM incidence and prevalence risks were 0.16 and 2.04%, respectively. Based on clinical progression, 72.7% of patients were diagnosed as CSM and 27.3% as CSM + ALS. At EMG 6 (18.2%) patients fulfilled the criteria for ALS, 5 of them (83.3%) during clinical follow-up were diagnosed as clinical definite ALS + CSM. Accuracy of Awaji criteria in diagnosing ALS was good (AUC = 0.757, $p = 0.03$). Sensitivity and specificity of Awaji criteria were, respectively, 55.6 and 95.8%. Positive predictive value was 83.3%, while negative predictive value was 85.2%. CSM-ALS comorbidity is a relatively common problem in clinical practice. To better choose patients who could benefit from surgery, EMG should be performed in CSM patients, due to its good accuracy in recognizing ALS.

Introduction

Cervical spondylogenic myelopathy (CSM) is a common Amyotrophic Lateral Sclerosis (ALS) mimic syndrome, because both diseases occur at a higher frequency in elderly people and there is a possible overlap when ALS patients lack bulbar signs [1]. Identifying the occurrence

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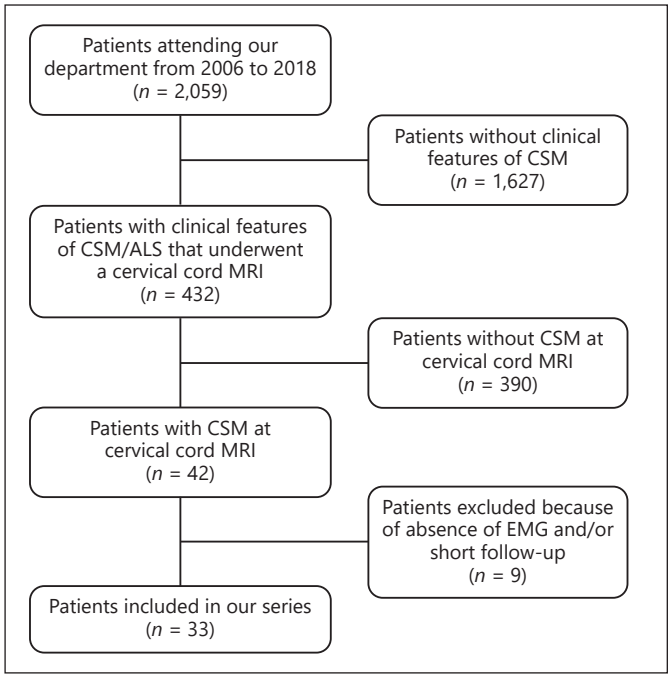

Fig. 1. Flowchart: patients included in our series.

of ALS in patients with a clinical and radiological diagnosis of CSM could be challenging. Here, we studied the prevalence of CSM-ALS comorbidity and evaluated the accuracy of the Awaji criteria in the diagnosis of ALS in a cohort of CSM.

Materials and Methods

Case Ascertainment

This is a retrospective cohort study. We included all patients attending the ALS Center of Turin during the 2006–2018 period, who showed clinical features (lack of bulbar signs and at least 1 of the following: hyposthenia/hypotropia/hyporeflexia in upper limbs; hypereflexia/spasticity/Babinski sign caudal to the cervical level; sensory disorders; gait disturbance; and sphincter disorders) and radiological signs of CSM at cervical spine MRI (cervical myelopathy due to spondylosis/cervical disc herniation/ossification of the posterior longitudinal ligament) [2].

All patients underwent electromyography (EMG) to detect the presence of chronic and acute neurogenic changes, as defined elsewhere [3]. According to Awaji criteria, EMG was performed in at least 1 muscle for the bulbar region and at least 2 muscles, innervated by different roots/nerves for the cervical and lumbosacral regions [3].

All patients included in this study were followed up for at least 6 months. Diagnosis of clinically definite ALS in patients with CSM was confirmed, based on disease progression, according to the revised El-Escorial criteria [4]. All subjects gave their written informed consent, and this study protocol was approved by Ethical Committee of the Azienda Ospedaliero-Universitaria Città della Salute (Prot. No. 0036344).

Statistical Analysis

Comparison between means and proportions was evaluated using the t test and χ^2 or Fisher's exact test, respectively. AUC-ROC curve was used to show the diagnostic performance of Awaji criteria in the differential diagnosis between CSM and CSM + ALS. Sensitivity, specificity, positive, and negative predictive values were consequently calculated. All hypotheses were two-tailed with a significance level of 0.05. Data were analyzed using IBM SPSS Statistics 25.0.

Results

432 patients had symptoms suggestive for CSM and underwent a cervical cord MRI. In 42 (9.7%) patients, MRI showed radiological signs of CSM. Prevalence and incidence rates of CSM in our cohort were 2.04 and 0.16%, respectively. Nine patients were lost at follow-up, and 33 were included in our study (Fig. 1). At the end of follow-up, 24 (72.7%) patients were diagnosed as CSM and 9 (27.3%) as CSM + ALS. Age at onset (60.4 years, SD 12.7 for CSM; 61.6 years, SD 10.4 for CSM + ALS; $p = 0.80$) and sex (19 men, 79.2% for CSM vs. 6 men, 66.7% for CSM + ALS; $p = 0.65$) did not differ between the 2 groups. All CSM + ALS patients showed a disease spinal onset.

Based on the Awaji criteria, 6 (18.2%) patients were fitting the criteria for clinically probable ALS (Table 1): 5 of them (83.3%) during the clinical follow-up received the diagnosis of clinical definite ALS. Awaji criteria identified ALS comorbidity in 55.6% of CSM + ALS patients confirmed clinically at follow-up. Chronic neurogenic changes (CNCs) were recorded in the cervical and lumbar regions in both categories (Table 1); all CSM patients, who showed these alterations in the lumbar region, had lumbar spondylosis at MRI.

Fasciculation potentials in the context of CNCs were recorded more frequently in CSM + ALS patients (8 CSM + ALS, 88.9% vs. 10 CSM, 41.7%; $p = 0.02$; Table 1), in both cervical and lumbar regions (Table 1), and showed a good correlation with CSM + ALS diagnosis ($R = 0.42$, $p = 0.01$). The accuracy of Awaji criteria in distinguishing between CSM and CSM + ALS patients was good (AUC = 0.757, $p = 0.03$). Sensitivity of Awaji criteria was 55.6%, while specificity was 95.8%. Positive predictive value and negative predictive value were 83.3 and 85.2%, respectively. For 28 patients, information about surgical intervention was available (19 CSM, 9 ALS): 11 (57.9%) patients diagnosed as CSM underwent surgery, and only 1

Table 1. CNCs and SA frequencies at EMG in CSM and CSM + ALS

	CSM, $n = 24$	CSM + ALS, $n = 9$	p value*
CNC in the bulbar region, *n* (%)	3 (12.5)	0 (0.0)	0.55
CNC in the cervical region, *n* (%)	23 (98.5)	9 (100.0)	1.00
CNC in the lumbar region, *n* (%)	17 (70.8)	8 (88.9)	0.39
SA in the bulbar region, *n* (%)	0 (0.0)	0 (0.0)	–
SA in the cervical region, *n* (%)	12 (50.0)	9 (100.0)	**0.01**
SW/fibrillation potentials, *n* (%)	8 (33.3)	5 (55.6)	0.22
Fasciculation potentials, *n* (%)	8 (33.3)	8 (88.9)	**0.01**
SA in the lumbar region, *n* (%)	6 (25.0)	7 (77.8)	**0.01**
SW/fibrillation potentials, *n* (%)	3 (12.5)	4 (44.4)	0.07
Fasciculation potentials, *n* (%)	5 (20.8)	6 (66.7)	**0.03**
SWs/fibrillation potentials, *n* (%)	8 (33.3)	6 (66.7)	0.12
Fasciculation potentials, *n* (%)	10 (41.7)	8 (88.9)	**0.02**
Clinically probable ALS diagnosis (Awaji criteria)	1 (4.2)	5 (55.6)	**0.01**

Significant differences are reported in bold. CNC, chronic neurogenic changes; SA, spontaneous activity; SWs, sharp waves. * *T*-test and χ^2/Fisher's exact test were performed for continuous and discrete variables, respectively.

(9.1%) experienced a progression of the symptoms despite surgery; the remaining 8 (42.1%) CSM patients, who did not undergo surgery, did not show a worsening of the clinical conditions. Among CSM + ALS patients only 1 (11.1%) underwent surgery and showed a progression of disease at follow-up.

Discussion

Our study shows that incidence and prevalence risks for CSM are higher among ALS patients attending a tertiary Center (0.16 and 2.04%, respectively), when compared to general population: indeed in North America, its incidence and prevalence risks in the general population are, respectively, 0.004 and 0.061% [5]. ALS is frequently complicated by cervical spondylosis: indeed, it can be detected in almost half of ALS patients [6]. We showed that even the comorbidity of ALS and CSM is not so rare and was found in about a quarter of cases. The overlap in age and sex between CSM and ALS makes the differential diagnosis harder. Recognizing ALS in CSM patients is extremely important to prevent the patient suffering from CSM + ALS being subjected to invasive treatments: indeed, ALS patients are at high risk for intraoperative and postoperative complications, and general anesthesia may exacerbate respiratory failure [7]. Moreover, no improvement has been shown for decompressive spinal surgery in ALS patients in 86% of cases [8], and there is evidence that surgical interventions could even accelerate progression of ALS, probably due to surgical stress and anesthesia [9]. In our study, the only ALS patient who underwent surgery did not show any improvement of the clinical conditions.

An early diagnosis of ALS is beneficial also to properly plan the multidisciplinary care and to include patients in randomized clinical trials earlier. The role of EMG is well established for ALS diagnosis, but electrophysiological changes are not specific to ALS. In our study, Awaji criteria showed good accuracy in detecting CSM patients with ALS overlap. Their sensitivity was not so good and a little bit lower than described previously (around 63% for ALS with spinal onset [10]), probably due to the fact that we did not include the thoracic region in the electrophysiological study. Specificity instead reached high values, suggesting that surgeon should avoid proposing surgery in patients with wide denervation at EMG, due to the high probability of ALS comorbidity. The only CSM patient who fulfilled Awaji criteria for ALS showed lumbar spondylosis at MRI, justifying the presence of spontaneous activity at EMG in the lumbar region; anyway, it has been highlighted that CSM patients can surprisingly have fasciculations even in the lower limbs [11].

High values of positive predictive value and negative predictive value of Awaji criteria can reassure the clinician about the matching between the result of the electrophysiological test and the diagnosis, being reasonably sure of excluding ALS in a patient with CSM when Awaji criteria are not fitted. This could help to better choose patients that could really benefit from surgery. Fascicula-

tion potentials showed the highest accuracy for ALS, confirming their diagnostic value, when found in the context of CNCs, as stated by the latest ALS diagnostic criteria [4, 12].

Despite the small number of patients included and the presence of a selection bias due to the screening of patients attending a tertiary center, we showed that CSM + ALS comorbidity is not so rare and should be considered. Awaji criteria turned out to be accurate to detect ALS overlap, and we suggest that EMG should be performed even when CSM diagnosis could justify the symptoms, due to its widespread availability, low costs, good tolerability, and high specificity.

Acknowledgements

This study was performed under the Department of Excellence grant of the Italian Ministry of Education, University and Research to the "Rita Levi Montalcini" Department of Neuroscience, and University of Turin, Italy.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All subjects (or their parents or guardians) have given their written informed consent, and the study protocol was approved by Ethical Committee of the Azienda Ospedaliero-Universitaria Città della Salute (Prot. No. 0036344).

Conflict of Interest Statement

Dr. Torrieri, Dr. Monticelli, Dr. Vasta, Dr. Cofano, Dr. Ajello, Dr. Canosa, Dr. Penner, Dr. Marengo, Dr. Manera, Dr. Garbossa, and Dr. Moglia report no conflicts of interest.

Funding Sources

Prof Calvo has received research grant from Cytokinetics. Prof Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, and Cytokinetics. The sponsor organizations had no role in the data collection and did not participate in writing and approving the manuscript. The information reported in the manuscript has never been reported elsewhere.

Author Contributions

M.C.T. and M.M. conceptualized the study, collected the data, conducted the statistical analysis, interpreted the data, and prepared the initial manuscript. R.V., F.C., A.M., A.Can., F.P., N.M., U.M., A.Cal., A.Chi., D.G., and C.M. interpreted the data and critically revised the manuscript for important intellectual content. All authors contributed equally to the revision and approval of the final manuscript.

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