J MEDICINE 2025; 26: 94-100

Original Article

HANS – A Novel Solution to Distinguish Monomelic Amyotrophy from Amyotrophic Lateral Sclerosis

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Abstract

Introduction: *Although similar in the initial presentation, monomelic amyotrophy (MMA) and amyotrophic lateral sclerosis (ALS) have different courses, management protocols, and outcomes. Correct diagnosis of MMA and ALS is crucial in the management aspect. This study aimed to assess the utility of nerve conduction study (NCS) to differentiate MMA from ALS and also to develop an NCS-based scoring system for this purpose.*

Methods: *This diagnostic accuracy study included 17 patients with MMA and 37 patients with ALS. Motor NCS parameters of the median and ulnar nerves were compared between the two groups. An NCS-based scoring system, 'HANS', was developed from the parameters with significant differences between the two groups, and its diagnostic validity to differentiate MMA from ALS was assessed.*

Results: *Both MMA and ALS showed a male predominance. The median age was lower in MMA, 24(18-34) years than in ALS, 37(25-55) years. HANS (Hirayama ALS NCS Score) showed 77% sensitivity and 78% specificity, with a good overall diagnostic accuracy of 78%.*

Conclusion: *The use of HANS may facilitate the differentiation of MMA from ALS and aid in directing appropriate treatment.*

Key words: *Monomelic amyotrophy, amyotrophic lateral sclerosis, nerve conduction study, HANS.*

DOI: *https://doi.org/10.3329/jom.v26i2.84354*

Received: *21.03.2025;* ***Accepted:*** *04.06.2025*

Introduction

Monomelic amyotrophy (MMA) and amyotrophic lateral sclerosis (ALS) are rare neurodegenerative disorders affecting the motor neurons. The prevalence of these two diseases varies widely across the world. The prevalence of MMA and ALS is 3.3 and 8.0 per 100,000 in Japan, respectively.[1-2]

MMA and ALS begin with focal muscle weakness and wasting. Despite similar initial presentation, MMA and ALS differ widely in the context of age of onset, gender ratio, course, outcome, and pharmacological intervention.

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MMA, also known as Hirayama disease, accounts for 11.3% of diseases affecting motor neurons. The majority of cases occur within the 15-25 age range, with a strong male predominance. MMA affects a single limb. It progresses very slowly over 2-5 years, followed by a period of stabilization. The life expectancy of MMA patients is similar to that of the general population. There is no approved pharmacotherapy to alter the course of MMA, and using a neck collar and cervical spine surgery are the mainstay of treatment.[5]

ALS typically begins in the sixth or seventh decade, with a slight male predominance. ALS progresses relentlessly to involve the other parts of the body, resulting in death within 10 years in the majority of patients. Median survival in ALS is 3 years.[8] Drugs approved to improve the median survival of ALS are Riluzole, Edaravone, and Sodium phenylbutyrate-Taurursodiol (PB-TURSO).[9-10]

MMA and ALS are diagnosed after the exclusion of other causes of muscle wasting, such as neuropathy, plexopathy,

and radiculopathy, using MRI spine and nerve conduction study (NCS), followed by demonstration of chronic denervation in needle electromyography (EMG).[11] ALS is diagnosed with widespread EMG evidence of denervation and fulfillment of El Escorial criteria.[12] MMA is diagnosed when EMG evidence of denervation is limited to a single limb.[11]

Similarities in the initial presentation of ALS and MMA make it difficult to differentiate these two diseases, particularly in the early stages. ALS has a predilection for the abductor pollicis brevis (APB) and first dorsal interossei (FDI) muscles, clinically manifested as thenar wasting and dorsal guttering, known as 'split-hand syndrome' (SHS).[13-14] MMA, on the other hand, preferentially involves abductor digiti minimi (ADM), leading to hypothenar wasting, described as 'reverse split-hand syndrome' (R-SHS).[15]

These distinguished clinical signs were demonstrated in nerve conduction studies (NCS) by different researchers. Most of the studies performed a motor study of the median and ulnar nerves on the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles, respectively. The motor NCS parameters assessed were median and ulnar motor amplitude or compound muscle action potential (APB-CMAP and ADM-CMAP, respectively) and distal latency (APB-DL and ADM-DL, respectively), APB-ADM CMAP ratio, and APB-ADM DL ratio.[15-17] ADM-CMAP and APB-CMAP were lower in MMA and ALS, respectively.[15] APB-ADM CMAP ratio was found to be higher in MMA than in ALS.[15,17] NCS can be a helpful tool in differentiating MMA from ALS.

Objective

The objectives of this research were to explore the motor NCS parameters between MMA and ALS and formulate an NCS-based scoring system to differentiate between MMA and ALS.

Methods

This diagnostic accuracy study was conducted on 17 cases of MMA and 37 cases of ALS who were undergoing regular follow-up in the Medicine outpatient department of a tertiary-level teaching hospital from 2022 to 2024. ALS was diagnosed with the fulfillment of El Escorial criteria, with the aid of needle EMG.[16] MMA was diagnosed in patients with upper limb wasting, who did not have a positive family history, and did not progress to affect the other limbs over three years of follow-up, and showed needle EMG evidence of denervation limited to one limb.[16] All the study participants underwent an MRI of the cervical spine and NCS, ruling out radiculopathy, plexopathy, and neuropathy.

Data on the motor NCS of the median and ulnar nerves were collected in all 54 study participants. Abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles were used for motor studies of the median and ulnar nerves, respectively. Median and ulnar CMAP amplitudes and distal motor latencies (APB-CMAP, APB-DL, ADM-CMAP, and ADM-DL) were recorded. APB-ADM CMAP ratio and APB-ADM DL ratio were calculated. All these parameters were compared between the MMA and ALS groups. The Mann-Whitney U test was used to compare all these right-skewed quantitative data. P-value <0.05 was regarded as statistically significant.

An NCS-based scoring system, 'Hirayama ALS NCS Score' (HANS), was developed based on the parameters that showed significant differences between MMA and ALS. Suitable cut-off values for these parameters were derived from the actual positive rate versus false positive rate (TPR/FPR) curves. HANS was evaluated for diagnostic power with the ROC curve. The area under the ROC curve (AUROC) ≥ 0.7 was considered acceptable. A suitable cut-off value of the total score of HANS was determined from the TPR/FPR versus threshold curve. Finally, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and overall accuracy were calculated for HANS.

Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS) 26.0 were employed for the final analyses.

Ethical consideration

The investigation was granted formal authorization by the Institutional Ethical Review Board (IERB) of Shaheed Monsur Ali Medical College Hospital [Ref: SMAMC/IERB/2024/3(11), dated: 24/03/2024]. All procedures adhered to ethical standards and the principles outlined in the Declaration of Helsinki, with informed consent obtained from participants aged 18 and older and assent from a parent or guardian for minors.

Results

All the quantitative data showed high right skewness and were expressed in terms of median and inter-quartile range (IQR). The median age of the ALS group was higher than that of the MMA group, 37(25-55) years and 24(18-34) years, respectively, which was statistically significant (p-value 0.01). Both MMA and ALS groups showed a male predominance. The ALS group had a higher male-female ratio (5.2 versus 2.4), but this difference was not significant. (Table 1).

Basic motor NCS parameters (APB-CMAP, ADM-CMAP, APB-DL, and ADM-DL) were abnormal in a total of 15(27%) participants, 5(29%) and 10(27%) belonging to the MMA and ALS groups, respectively.

In MMA group, APB-CMAP was 5.6(2.7-9.2) mV and ADM-CMAP was 2.8(1.3-6.1) mV. APB-CMAP and ADM-CMAP in the ALS group were 3.6(3.2-4.0) mV and 5.7(3.2-7.1) mV, respectively. ADM-CMAP was significantly lower in the MMA group (p-value 0.03) (Table I).

APB-DL and ADM-DL were 3.3(3.1-3.8) mSec and 2.7(2.6-3.4) mSec, respectively in MMA group, and 3.6(3.2-4.0) mSec and 2.5(2.2-3.1) mSec, respectively in ALS group. There was no statistically significant difference in distal latencies between the MMA and ALS groups (Table I).

APB-ADM CAMP ratio in the ALS group was 0.8(0.6-1.4). The MMA group had a higher APB-ADM CMAP ratio of 1.3 (0.8-3.6), which was statistically significant (p-value = 0.03) (Table I).

APB-ADM DL ratio was significantly lower in the MMA group at 1.2 (1.1-1.3) than in the ALS group, which had a ratio of 1.4 (1.2-1.6). This difference reached statistical significance (p-value 0.02) (Table I).

Table-1. Age, gender and motor NCS parameters in study participants

Parameters	MMA(n1=17)	ALS(n2=37)	p-value
Age (Years)[1]	24(18-34)	37(25-55)	0.01[2]
Gender (M:F)	12:5	31:6	0.29[3]
APB-CMAP (mV)[1]	5.6(2.7-9.2)	4.2(3.2-4.0)	0.51[2]
APB-DL (mSec)[1]	3.3(3.1-3.8)	3.6(3.2-4.0)	0.22[2]
ADM-CMAP (mV)[1]	2.8(1.3-6.1)	5.7(3.2-7.1)	0.03[2]
ADM-DL (mSec)[1]	2.7(2.6-3.4)	2.5(2.2-3.1)	0.15[2]
APB-ADM CMAP ratio[1]	1.3(0.8-3.6)	0.8(0.6-1.4)	0.03[2]
APB-ADM DL ratio[1]	1.2(1.1-1.3)	1.4(1.2-1.6)	0.02[2]
1-Median(IQR)	2-Mann-Whitney *U* test	3-Fisher's exact test	

An NCS-based scoring system, named the Hirayama ALS NCS Score (HANS), was developed based on NCS parameters that have significantly different values between MMA and ALS: ADM-CMAP, APB-ADM CMAP ratio, and APB-ADM DL ratio (Table II).

TPR/FPR versus threshold curves showed that ADM-CMAP ≤3.5 mV (Figure 1), an APB-ADM CMAP ratio ≥3 (Figure 2), and an APB-ADM DL ratio ≤1.3 (Figure 3) were suitable cut-off values for diagnosing MMA over ALS. Each component was assigned a score of 0 or 1, based on the cut-off values. The minimum and maximum total scores were 0 and 3, respectively (Table II). The ROC curve indicated that HANS was a satisfactory model, achieving an AUROC of 0.78 (Figure 4).

Table-2. Hirayama ALS NCS Score (HANS)

NCS Parameters	Value	Score
ADM-CMAP (mV)	>3.5	0
	≤3.5	1
APB-ADM CMAP ratio	<3.0	0
	≥3.0	1
APB-ADM DL ratio	>1.3	0
	≤1.3	1
Total Score		0-3
2-3 : **MMA**	0-1: **ALS**	

A HANS score ≥2 was designated as the cut-off point for the diagnosis of MMA over ALS as indicated by the TPR/FTR versus threshold curve (Figure 5). A HANS score of 0-1 was indicative of ALS, whereas a score of 2-3 would point to MMA (Table II). HANS exhibited 76.5% sensitivity, 78.4% specificity, 61.9% positive predictive value, and 87.9% negative predictive value, achieving an overall accuracy of 77.8% (Table III).

Table-3. Diagnostic validity of HANS

Parameters	Estimate	95% Confidence interval
Sensitivity	76.5%	50.1-93.2
Specificity	78.4%	81.8-75.3
Positive predictive value	61.9%	45.5-76.1
Negative predictive value	87.9%	75.2-94.6
Positive likelihood ratio	3.5	1.8-6.9
Negative likelihood ratio	0.3	0.1-0.7
Accuracy	77.8%	54.5-89.0

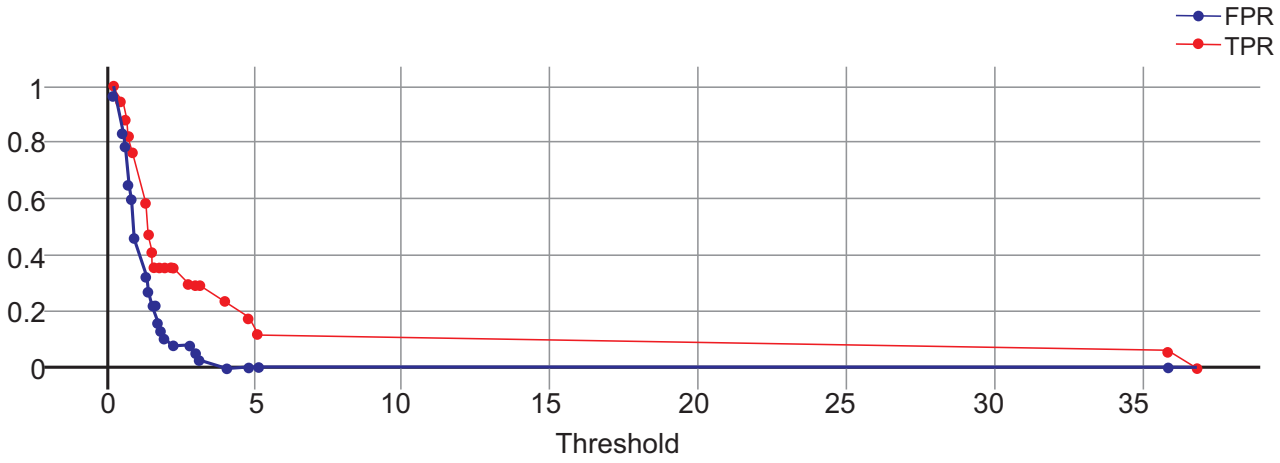

Figure-1: TPR/FPR versus threshold curve for ADM-CMAP

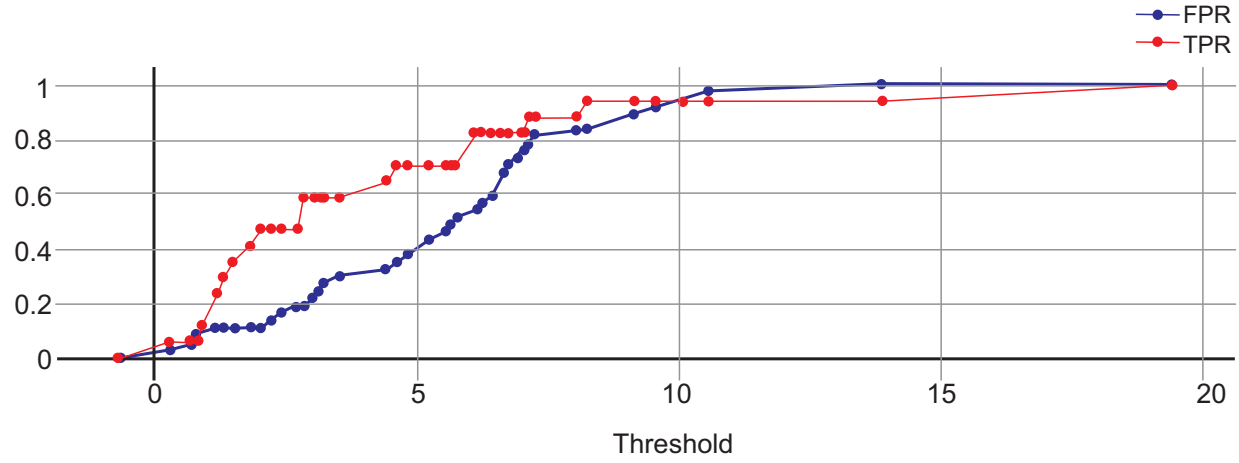

Figure-2: TPR/FPR versus threshold curve for APB-ADM CMAP-ratio

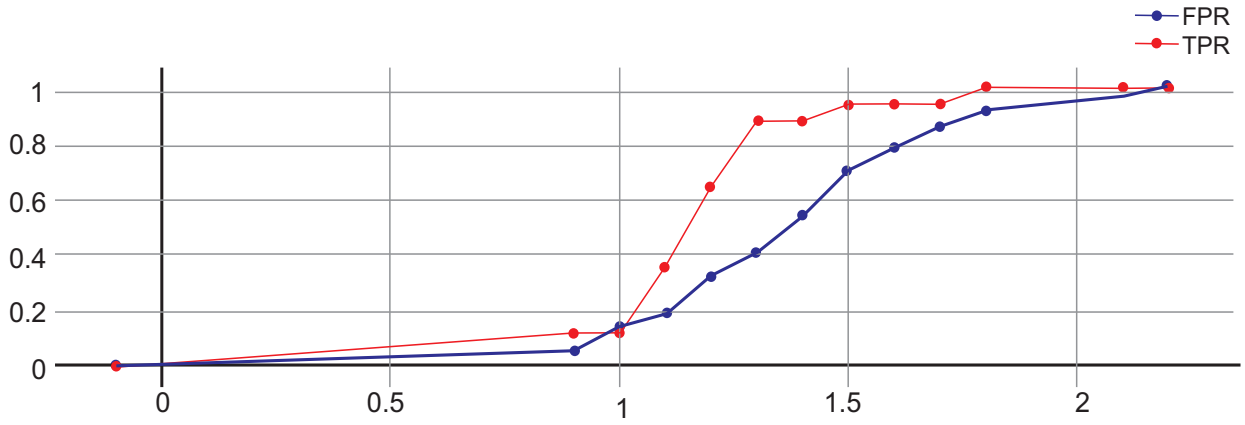

Figure-3: TPR/FPR versus threshold curve for APB-ADM DL-ratio

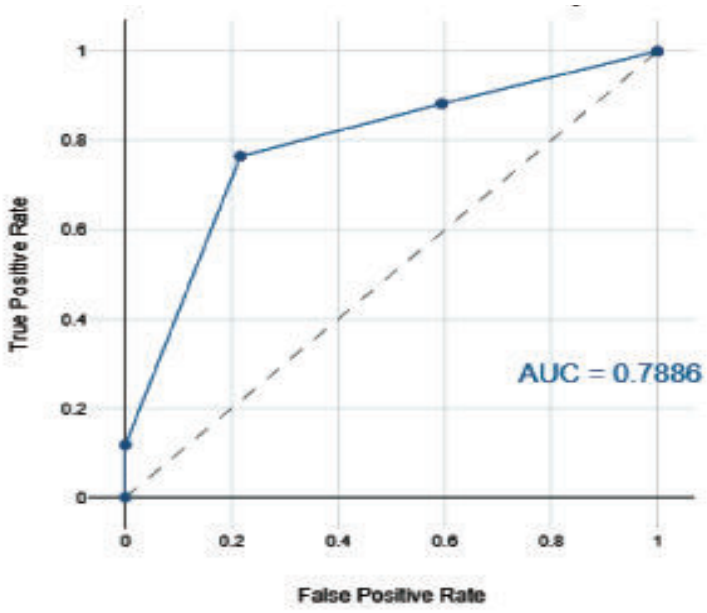

Figure-4: ROC curve for HANS

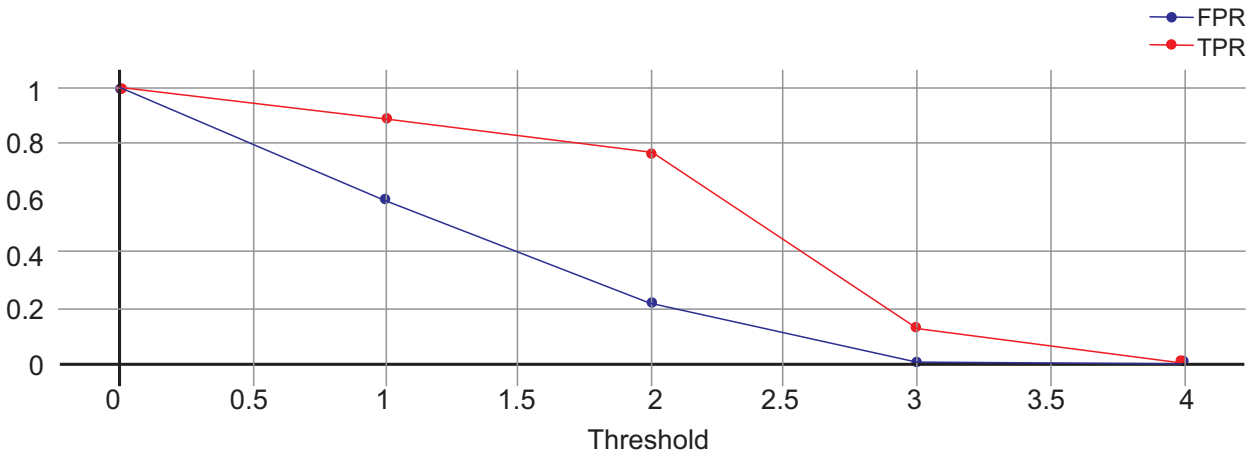

Figure-5: TPR/FPR versus threshold curve for HANS

Discussion

The median age of the MMA and ALS groups was 28 and 40 years, respectively, which is similar to a few recent Asian studies[3-4,18]. The male dominance evident in both groups corresponds with the gender distributions identified in a majority of earlier research.[19-21]

ADM-CMAP was lower in the MMA group than in the ALS group. A study from India reported similar findings.[15]

In the MMA group, the APB-ADM CMAP ratio was considerably higher. A recent study from India indicated that 80% of MMA patients had an APB-ADM CMAP ratio greater than 1.4, contrasting with a ratio of less than 0.8 observed in all ALS patients.[15] Additionally, research conducted in China found mean APB-ADM CMAP ratios of 1.8 in MMA patients and 0.4 in ALS patients.[17]

The APB-ADM DL ratio was significantly lower in individuals with MMA. This finding diverges from a recent Chinese study that reported no significant differences in the APB-ADM DL ratio between MMA patients and those with ALS.[17]

The application of NCS in the context of MMA and ALS primarily serves to rule out neuropathy and plexopathy. The diagnostic capabilities of NCS were investigated for ALS, with MUNIX and MScanFit-MUNE demonstrating encouraging outcomes as diagnostic instruments for ALS. The latter has shown potential in distinguishing ALS from MMA.[22-24]

The NCS-based scoring system, HANS, is less technically demanding and has demonstrated remarkable diagnostic precision in distinguishing between MMA and ALS.

Timely diagnosis of MMA is crucial in the management aspect because the use of cervical collars and spine surgery results in excellent functional outcomes.[5] Avoidance of redundant drug therapies for ALS is possible once the diagnosis of ALS is ruled out. HANS can assist in distinguishing between MMA and ALS, and thereby inform suitable management strategies.

Limitations

Due to the rarity of the diseases, the research was conducted with a limited sample size. Participants were sourced from a single center. The quantitative data could not be analyzed using more rigorous tests, such as the t-test, due to its skewed distribution.

Conclusion

The exceptional diagnostic performance of HANS highlights its potential for accurately distinguishing between MMA and ALS. There is a need for further prospective, multi-site investigations of HANS utilizing larger cohorts.

References:

1. Brown CA, Lally C, Kupelian V, Flanders WD. Estimated prevalence and incidence of amyotrophic lateral sclerosis and SOD1 and C9orf72 genetic variants. Neuroepidemiol. 2021;55(5):342-53.
2. Sharma DN, Yerramneni VK, Yerragunta T, Gaikwad GB, Rangan VS, Akurati S. Venous pathology targeted surgical management in Hirayama disease: a comprehensive case series of nine cases exploring this potential etiology. J Craniovertebr Junction Spine. 2024;15(1):37-44.
3. Nalini A, Thennarasu K, Gourie-Devi M, Shenoy S, Kulshreshtha D. Clinical characteristics and survival pattern of 1,153 patients with amyotrophic lateral sclerosis: experience over 30 years from India. J Neurol Sci. 2008;15(272):60-70.
4. Huang YC, Ro LS, Chang HS, Chen CM, Wu YR, Lee JD, et al. A clinical study of Hirayama disease in Taiwan. Musc Nerv. 2008;37(5):576-82.
5. Wang H, Tian Y, Wu J, Luo S, Zheng C, Sun C, et al. Update on the pathogenesis, clinical diagnosis, and treatment of Hirayama Disease. Front Neurol. 2022;12:811943. doi: 10.3389/fneur.2021.811943.
6. Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. Curr Opin Neurol. 2019;32(5):771-6.
7. Manjaly ZR, Scott KM, Abhinav K, Wijesekera L, Ganesalingam J, Goldstein LH, et al. The sex ratio in amyotrophic lateral sclerosis: a population based study. Amyotroph Lateral Scler. 2010;11:439–42.
8. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;27(10):1918-29.
9. Tzeplaeff L, Wilfling S, Requardt MV, Herdick M. Current state and future directions in the therapy of ALS. Cells. 2023;12(11):1523. doi: 10.3390/cells12111523.
10. Hoxhaj P, Hastings N, Kachhadia MP, Gupta R, Sindhu U, Durve SA, et al. Exploring advancements in the treatment of amyotrophic lateral sclerosis: a comprehensive review of current modalities and future prospects. Cureus. 2023;15(9):e45489. doi: 10.7759/cureus.45489.
11. Talbot K. Monmelic amyotrophy Hirayama's disease. Pract Neurol. 2004;4(6):362-5.
12. De-Jongh AD, Braun N, Weber M, van Es MA, Masrori P, Veldink JH, et al. Characterising ALS disease progression according to El Escorial and Gold Coast criteria. J Neurol Neurosurg Psychiatry. 2022;93(8):865-70.
13. Corcia P, Bede P, Pradat PF, Couratier P, Vucic S, de Carvalho M. Split-hand and split-limb phenomena in amyotrophic lateral sclerosis: pathophysiology, electrophysiology and clinical manifestations. J Neurol Neurosurg Psychiatry. 2021;92(10):1126-30.
14. Benny R, Shetty K. The split hand sign. Ann Indian Acad Neurol. 2012;15(3):175-6.
15. Singh RJ, Preethish-Kumar V, Polavarapu K, Vengalil S, Prasad C, Nalini A. Reverse split hand syndrome: Dissociated intrinsic hand muscle atrophy pattern in Hirayama disease/ brachial monomelic amyotrophy. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(1-2):10-6.
16. Fang J, Liu MS, Guan YZ, Du H, Li BH, Cui B, et al. Pattern differences of small hand muscle atrophy in amyotrophic lateral sclerosis and mimic disorders. Chinese Med J. 2016;129(07):792-8.
17. Jin X, Jiang JY, Lu FZ, Xia XL, Wang LX, Zheng CJ. Electrophysiological differences between Hirayama disease, amyotrophic lateral sclerosis and cervical spondylotic amyotrophy. BMC Musculoskelet Disord. 2014;15:349. doi: 10.1186/1471-2474-15-349.
18. Rai N, Shukla G, Goyal V, Shrivastava A, Behari M. Clinical profile of Indian patients with amyotrophic lateral sclerosis (ALS): A retrospective hospital based study. Neurology. 2012;80(7 Suppl):77. Doi: 10.1212/WNL.80.7_supplement. P07.077.
19. Raknuzzaman M, Habib MA, Jannaty T, Masum ASMHA, Shahidullah M, Dey SK. Demographic pattern of amyotrophic lateral sclerosis in Bangladesh among patients admitted in a tertiary level hospital. IOSR J Dental Medi Sci. 2020;19(8):24-9.

20. Gourie-Devi M, Nalini A. Long-term follow-up of 44 patients with brachial monomelic amyotrophy. Acta Neurol Scand. 2003;107(3):215-20.

21. Garg N, Park SB, Vucic S, Yiannikas C, Spies J, Howells J, et al. Differentiating lower motor neuron syndromes. J Neurol Neurosurg Psychiatry. 2017;88(6):474-83.

22. Donaghy R, Pioro EP. Neurophysiologic Innovations in ALS: enhancing diagnosis, monitoring, and treatment evaluation. Brain Sci. 2024;14(12):1251. https://doi.org/10.3390/brainsci14121251

23. Gunes T, Sirin NG, Sahin S, Kose E, Isak B. Use of CMAP, MScan fit-MUNE, and MUNIX in understanding neurodegeneration pattern of ALS and detection of early motor neuron loss in daily practice. Neurosci Lett. 2021;741:135488. doi: 10.1016/j.neulet.2020.135488.

24. Jacobsen AB, Bostock H, Fuglsang-Frederiksen A, Duez L, Beniczky S, Møller AT, et al. Reproducibility and sensitivity to motor unit loss in amyotrophic lateral sclerosis of a novel MUNE method: MScanFit MUNE. Clin Neurophysiol. 2017;128(7):1380-8.