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Frequency of non optico-spinal manifestation in neuromyelitis optica spectrum disorder at tertiary care hospital in Pakistan

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Abstract

Objective: To determine the frequency of non-optico-spinal manifestations in neuromyelitis optica spectrum disorder patients in a tertiary care setting.

Method: The observational study was conducted from February 1 to November 30, 2025, at the Department of Neurology, Dr Ruth K.M. Pfau Civil Hospital, Karachi, and comprised patients aged at least 18 years with confirmed neuromyelitis optica spectrum disorder diagnosis based on the 2015 International Panel for Neuromyelitis Optica Diagnosis criteria. Data included demographics, clinical features, anti-aquaporin-4 antibody status and magnetic resonance imaging findings. Data was analysed using SPSS 25.

Results: Of the 65 patients with mean age 31.17 ± 10.33 years, 47(72.3%) were female, and 32(49.2%) had at least one optico-spinal manifestation. Non-optico-spinal symptoms appeared only alongside core symptoms, with area postrema syndrome being the most common feature 13(20%). Brainstem lesions were observed in 9(13.8%) patients and cerebral lesions in 5(7.7%), with corresponding magnetic

resonance imaging abnormalities observed in these patients. The mean disability score was 3.88 ± 2.98 , indicating moderate disability.

Conclusion: Comprehensive clinical and radiological evaluation in neuromyelitis optica spectrum disorder patients was found to be of critical importance.

Key Words: Demyelinating disorders, Neuromyelitis optica spectrum disorders, Optic neuritis, Transverse myelitis, Acute brainstem syndrome.

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is an autoimmune disorder primarily affecting the optic nerves and spinal cord, with potential involvement of specific brain areas. It is characterised by a relapsing-remitting course in 90% of cases, while the remaining follow a progressive pattern.^[1] The disease is driven by anti-aquaporin-4 (AQP4) antibodies targeting AQP4, a water transporter found in brain-fluid interfaces.^[2-5]

Globally, NMOSD has an estimated prevalence of 0.3-4.4 per 100,000, predominantly affecting females (80%) aged 30-40 years.^[1] The 2015 International Panel for Neuromyelitis Optica Diagnosis (IPND)^[6] criteria include symptoms such as optic neuritis, myelitis, area postrema syndrome, brainstem syndromes, narcolepsy or acute diencephalic syndrome, and cerebral syndrome. While NMOSD primarily affects the optic nerves and spinal cord, non-optico-spinal manifestations (area postrema syndrome, brainstem syndromes, narcolepsy or acute diencephalic syndrome, and cerebral syndrome) are often under-diagnosed.^[2, 7] These atypical presentations can mimic other neurological conditions, leading to misdiagnosis or delayed treatment. To or knowledge, limited data is available on the frequency and presentation of non-optico-spinal manifestations, particularly in Asian populations, including Pakistan. The current study was planned to determine the frequency of non-optico-spinal manifestations in NMOSD patients in a tertiary care setting.

58 **Patients and Methods**

59 The observational, cross-sectional study was conducted from February 1 to November
60 30, 2025, at the Department of Neurology, Dr Ruth K.M. Pfau Civil Hospital, Karachi.
61 After approval from the ethics review board of the Dow University of Health Sciences
62 (DUHS), Karachi, the sample size was calculated using Open Epi, Software Version
63 3.01 based on 4.4% estimated prevalence with 95% confidence level and 5% margin
64 of error.^{[8] [1]} A non-probability consecutive sampling technique was used to recruit all
65 eligible patients presenting to the Neurology outpatient department (OPD) and
66 inpatient wards of Dr Ruth K.M. Pfau Civil Hospital, Karachi, during the study period.
67 All patients fulfilling the inclusion criteria during the study period were included until
68 the calculated sample size sixty-five was reached. Those included were patients aged
69 ≥ 18 years diagnosed with NMOSD based on the 2015 IPND criteria.^[7] The patients
70 were either newly-diagnosed, experiencing a relapse, in remission, or were follow-up
71 patients in the Neurology outpatient department (OPD). Patients in the relapse or
72 follow-up category were identified through the records for the confirmation of
73 NMOSD diagnosis. New diagnoses were established using serum AQP4 testing,
74 magnetic resonance imaging (MRI) brain scans, and contrast-enhanced MRI of the
75 cervical and thoracic spine.^[7]
76 Patients with incomplete medical records or alternative diagnoses that could mimic
77 NMOSD (stroke, systemic autoimmune diseases, multiple sclerosis, acute
78 disseminated encephalomyelitis [ADEM] or malignancies) were excluded.
79 After taking written informed consent from all the participants, data was collected
80 from medical records, including demographic details, clinical presentations, anti-
81 AQP4 antibody status, imaging results, presentation, and core or non-core features.
82 Two independent neurologists reviewed MRI scans. Serum anti-AQP4 antibodies were
83 tested using a cell-based assay. Disability was assessed using the Expanded Disability
84 Status Scale (EDSS) at presentation and again at discharge. For analysis, the EDSS
85 score recorded at discharge was used.^[9]

Data was analysed using SPSS 25. Categorical variables were summarised as frequencies and percentages, while continuous variables were presented using mean $\pm$ standard deviation or median with interquartile range (IQR), as appropriate.

Results

Of the 65 patients with mean age 31.17 ± 10.33 years, 47(72.3%) were female and 18(27.7%) were male. The overall median age was 29 years (IQR: 19-59 years). Regarding residence, 36(55.4%) patients were from rural areas, and 29(44.6%) belonged to urban areas. At the time of presentation, 31(47.7%) patients had their first attack, 29(44.60%) presented with a relapse, and 5(7.70%) were in remission. The majority of patients 56(86.2%) had a relapsing-remitting disease course, while 6(9.2%) had a progressive course. Further, 3(4.6%) patients died during hospital admission. Optico-spinal and non-optico-spinal manifestations were noted separately (Figures 1-2).

Overall, 32(49.2%) patients had at least one non-optico-spinal manifestation. These manifestations were not mutually exclusive, and some patients had more than one non-optico-spinal manifestation. Area postrema syndrome was the most frequent non-optico-spinal manifestation 13(40.5%), followed by acute brainstem syndrome 10(31.5%), acute cerebral syndrome 8(25%) and acute diencephalic syndrome 1(3%) patient (Figure 2). Symptomatic narcolepsy was not observed. Among the individual non-optico-spinal clinical features, nausea and vomiting, intractable hiccups, diplopia, bulbar symptoms, encephalopathy, seizures, hemiparesis, hypotension and hypothermia were observed, whereas sleep disorders, endocrine symptoms, facial palsy, hearing loss and trigeminal neuralgia were not observed (Figure 3).

Among MRI abnormalities detected, longitudinally extensive transverse myelitis (LETM) was the most frequent radiological finding across the whole sample 38(58.5%), followed by optic nerve involvement 17(26.2%), brainstem lesions 9(13.8%), cerebral hemispheric lesions 5(7.7%) and area postrema lesions 4(6.2%). MRI abnormalities in patients presenting with non-optico-spinal manifestations

115 included brainstem lesions in 9(90%) of the 10(31.5%) patients presenting with
116 brainstem symptoms, cerebral lesions in 5(62.5%) of the 8(25%) patients with acute
117 cerebral syndrome, and area postrema lesions in 4(30.8%) of the 13(40.6%) patients
118 with area postrema syndrome. No MRI abnormality was identified in the patient with
119 diencephalic presentation. Patients without non-optico-spinal clinical features
120 33(50.8%) predominantly demonstrated LETM with or without optic nerve
121 involvement (Figure 4).

122 The mean EDSS score at discharge was 3.88 ± 2.98 (median: 3.00; IQR: 0–6.00).
123 When stratified by optico-spinal manifestation, patients with isolated optic neuritis
124 (n=8) had a mean EDSS of 1.00 ± 1.07 , those with isolated transverse myelitis (n=17)
125 had a mean EDSS of 5.06 ± 3.15 , and patients with combined optic neuritis and
126 transverse myelitis (n=39) had a mean EDSS of 3.95 ± 2.74 . Patients with isolated
127 optic neuritis tended to have lower EDSS scores compared to those with transverse
128 myelitis, either alone or in combination.

130 Discussion

131 In the current NMOSD cohort, the most common presentation was relapsing and
132 remitting. Also, there was female predominance and seropositivity for AQP4
133 antibodies, which was in line with literature.^[10-12] Among the patients, optico-spinal
134 involvement was the predominant manifestation of NMOSD,^[13] with non-optico-
135 spinal features occurring only alongside core optico-spinal symptoms. None of the
136 current patients presented with isolated non-optico-spinal manifestations. This finding
137 is inconsistent with previous reports^[7, 14]. Given the smaller sample size in the current
138 study, it is likely that isolated non-optico-spinal presentations were not identified.

139 Among non-optico-spinal features, area postrema syndrome was the most common,
140 presenting as intractable hiccups and nausea/vomiting.^[15, 16] Brainstem and cerebral
141 involvement, including diplopia, bulbar symptoms, encephalopathy and seizures, were
142 also observed,^[17-19] whereas diencephalic involvement and symptomatic narcolepsy
143 were rare, which was similar earlier studies.^[20, 21] Many non-optico-spinal symptoms

are nonspecific and initially managed symptomatically at primary care centres, which may delay recognition until optico-spinal manifestations appear. This reflects limited awareness of NMOSD among physicians and the public.

Radiologically, LETM was the most frequent finding in the current study, followed by optic nerve lesions. Brainstem, cerebral and area postrema lesions were less common^[19, 22]. Comprehensive MRI of the brain and spine with contrast was performed to detect subtle non-optico-spinal lesions and correlate them with clinical symptoms. Despite this, some symptomatic patients lacked corresponding MRI findings, consistent with the known clinic-radiological dissociation in NMOSD.^[23-27]

Patients presenting exclusively with core clinical features mainly demonstrated LETM with or without optic nerve involvement, emphasising the central role of optico-spinal pathology. The heterogeneity of clinical and radiological presentations underscores the importance of maintaining a high index of suspicion, particularly for patients with atypical or multisystem symptoms.

The current study has limitations because of its single-centre design, relatively small sample size, and variability in MRI timing which may have affected lesion detection.

Future studies should involve multicentre collaboration and larger populations to improve generalisability of the findings. Further research is needed to characterise patients as per updated criteria, and to follow them longitudinally for clinical and radiological outcomes.

Conclusion

Opticospinal involvement was the main feature of NMOSD, while non-optico-spinal manifestations usually occurred together with core symptoms. Area postrema syndrome was the most common non-optico-spinal symptom, and LETM was the predominant MRI finding. The clinic-radiological findings highlighted the need for careful clinical and imaging assessment in NMOSD patients.

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177 10% solely for language refinement, including grammar correction and sentence
178 restructuring. AI was not used for study design, data collection, data analysis,
179 interpretation of results, or generation of scientific content. All authors reviewed and
180 verified the final content and take full responsibility for the integrity of the work.

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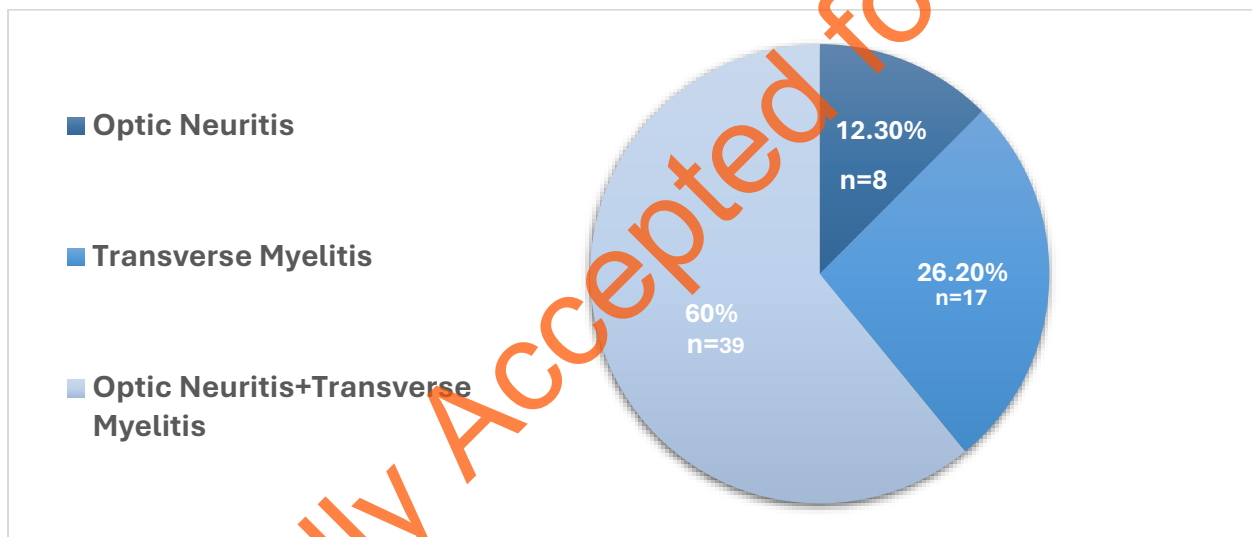
182 **References**

- 183 1. Shumway CL, Patel BC, Tripathy K, De Jesus O. Neuromyelitis Optica
184 Spectrum Disorder (NMOSD). StatPearls. Treasure Island (FL): StatPearls
185 Publishing; 2025.
- 186 2. Rosales D, Kister I. Common and Rare Manifestations of Neuromyelitis Optica
187 Spectrum Disorder. Curr Allergy Asthma Rep. 2016;16(6):42.
- 188 3. Pandit L. Neuromyelitis optica spectrum disorders: An update. Ann Indian Acad
189 Neurol. 2015;18(Suppl 1):S11-5.
- 190 4. Cazzaniga J, Jara Silva CE, Quinonez J, Ruxmohan S, Leyva MM, Fahs A.
191 Neuromyelitis Optica Spectrum Disorder. Cureus. 2023;15(11):e48168.
- 192 5. Chu FA-O, Shi M, Liu C, Zhu J. Discrepancy in clinical and laboratory profiles
193 of NMOSD patients between AQP4 antibody positive and negative: can
194 NMOSD be diagnosed without AQP4 antibody? (1365-2249 (Electronic)).
- 195 6. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al.
196 International consensus diagnostic criteria for neuromyelitis optica spectrum
197 disorders. Neurology. 2015;85(2):177-89.
- 198 7. Li Z, Yang M, Pan Y, Fang Q. Neuromyelitis optica spectrum disorder with acute
199 brainstem manifestations as initial symptoms. Heliyon. 2024;10(12).

- 200 8. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic
201 Statistics for Public Health, Version: 3.01. [Online] 2013 [Cited 2026 September
202 28]. Available from URL: https://www.openepi.com/Menu/OE_Menu.htm
- 203 9. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded
204 disability status scale (EDSS). *Neurology*. 1983;33(11):1444-52.
- 205 10. Cakan M, Demirel E, Cimen B, Özen NPA, Çolpak İ, Karabudak R, Tuncer A.
206 Comparison of clinical features of aquaporin-4 positive neuromyelitis optica
207 spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein associated
208 disorder (MOGAD), and double seronegative NMOSD - A single center
209 experience. *J Neuroimmunol*. 2025;403:578591.
- 210 11. Siriratnam P, Huda S, Van Der Walt A, Sanfilippo PG, Sharmin S, Foong YC, et
211 al. Prevalence of Progression Independent of Relapse Activity and Relapse-
212 Associated Worsening in Patients With AQP4-IgG-Positive NMOSD. *Neurology*.
213 2024;103(12):e209940.
- 214 12. Rajput HM, Hassan M, Badshah M. Clinical and radiological profile of
215 neuromyelitis optica spectrum disorders in a Pakistani cohort. *Mult Scler Relat*
216 *Disord*. 2023;74:104656.
- 217 13. Gupta S, Rehani V, Acharya R, Purohit P, Anadure R, Ahmad F, et al.
218 Multicentric clinical and epidemiological comparison of neuromyelitis optica
219 spectrum disorder with multiple sclerosis from India. *Mult Scler Relat Disord*.
220 2021;47:102616.
- 221 14. Li R, Lu D, Li H, Wang Y, Shu Y, Chang Y, et al. Neuromyelitis optica spectrum
222 disorders with non opticospinal manifestations as initial symptoms: a long-term
223 observational study. *BMC neurology*. 2021;21(1):35.
- 224 15. Popescu BF, Lennon VA, Parisi JE, Howe CL, Weigand SD, Cabrera-Gomez JA,
225 et al. Neuromyelitis optica unique area postrema lesions: nausea, vomiting, and
226 pathogenic implications. *Neurology*. 2011;76(14):1229-37.

- 227 16. Apiwattanakul M, Popescu BF, Matiello M, Weinshenker BG, Lucchinetti CF,
228 Lennon VA, et al. Intractable vomiting as the initial presentation of neuromyelitis
229 optica. *Ann Neurol*. 2010;68(5):757-61.
- 230 17. Wang KC, Lee CL, Chen SY, Lin KH, Tsai CP. Prominent brainstem
231 symptoms/signs in patients with neuromyelitis optica in a Taiwanese population.
232 *J Clin Neurosci*. 2011;18(9):1197-200.
- 233 18. Kremer L, Mealy M, Jacob A, Nakashima I, Cabre P, Bigi S, et al. Brainstem
234 manifestations in neuromyelitis optica: a multicenter study of 258 patients. *Mult*
235 *Scler*. 2014;20(7):843-7.
- 236 19. Kim W, Kim SH, Huh SY, Kim HJ. Brain abnormalities in neuromyelitis optica
237 spectrum disorder. *Mult Scler Int*. 2012;2012(1):735486.
- 238 20. Etemadifar M, Nouri H, Khorvash R, Salari M, Ghafari K, Aghababae A.
239 Frequency of diencephalic syndrome in NMOSD. *Acta Neurol Belg*.
240 2022;122(4):961-7.
- 241 21. Etemadifar M, Nouri H, Khorvash RA-O, Salari M, Ghafari K, Aghababae A.
242 Frequency of diencephalic syndrome in NMOSD. (2240-2993 (Electronic)).
- 243 22. Cabrera-Gomez JA, Quevedo-Sotolongo L, Gonzalez-Quevedo A, Lima S, Real-
244 Gonzalez Y, Cristofol-Corominas M, et al. Brain magnetic resonance imaging
245 findings in relapsing neuromyelitis optica. *Mult Scler*. 2007;13(2):186-92.
- 246 23. Dutra BG, da Rocha AJ, Nunes RH, Maia ACM. Neuromyelitis optica spectrum
247 disorders: spectrum of MR imaging findings and their differential diagnosis.
248 *Radiographics*. 2018;38(1):169-93.
- 249 24. Nagireddy RBR, Kumar A, Singh VK, Prasad R, Pathak A, Chaurasia RN, et al.
250 Clinico-radiological comparative study of Aquaporin-4-IgG seropositive
251 neuromyelitis optica spectrum disorder (NMOSD) and MOG antibody associated
252 disease (MOGAD): A prospective observational study and review of literature. *J*
253 *Neuroimmunol*. 2021;361:577742.

- 254 25. Kim W, Park MS, Lee SH, Kim SH, Jung IJ, Takahashi T, et al. Characteristic
255 brain magnetic resonance imaging abnormalities in central nervous system
256 aquaporin-4 autoimmunity. Mult Scler. 2010;16(10):1229-36.
- 257 26. Zhang Z, Zhou H, Liu X, Liu L, Shu S, Fang F. Identification of the clinical and
258 neuroimaging characteristics in children with neuromyelitis optica spectrum
259 disorders: a case series. Transl Pediatr. 2021;10(10):2459-66.
- 260 27. Clarke L, Arnett S, Lilley K, Liao J, Bhuta S, Broadley SA-O. Magnetic
261 resonance imaging in neuromyelitis optica spectrum disorder. (1365-2249
262 (Electronic)).



266 **Figure 1: Optico-spinal manifestation in neuromyelitis optica spectrum disorder**
267 **(NMOSD) (n=64).**

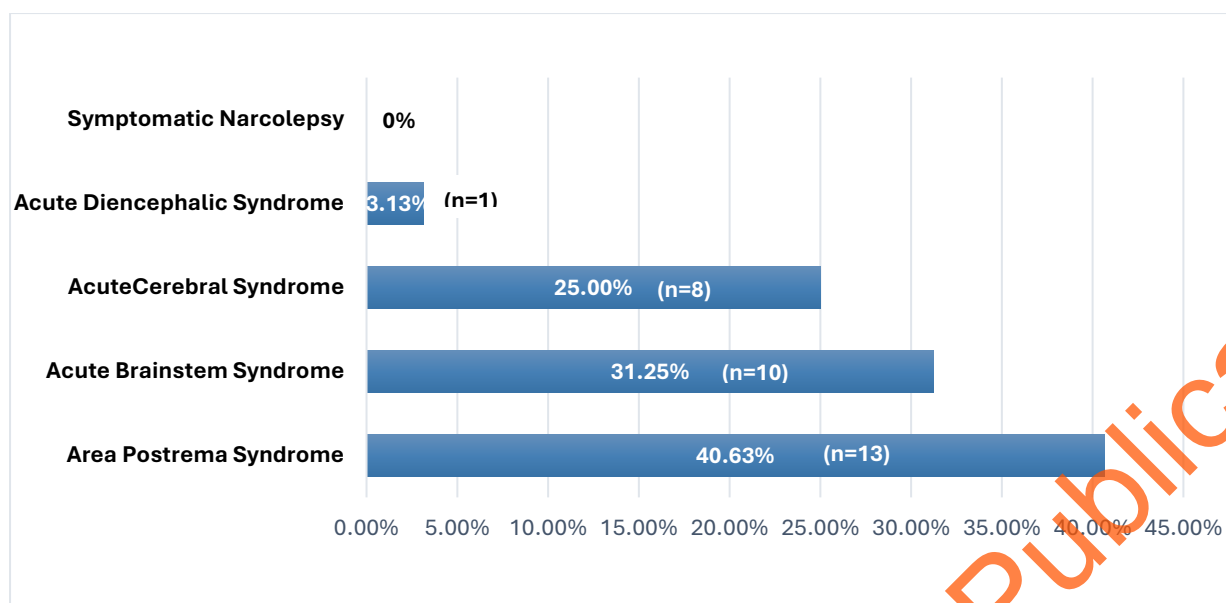


Figure 2: Non-optico-spinal manifestations in neuromyelitis optica spectrum disorder (NMOSD) (n=32).

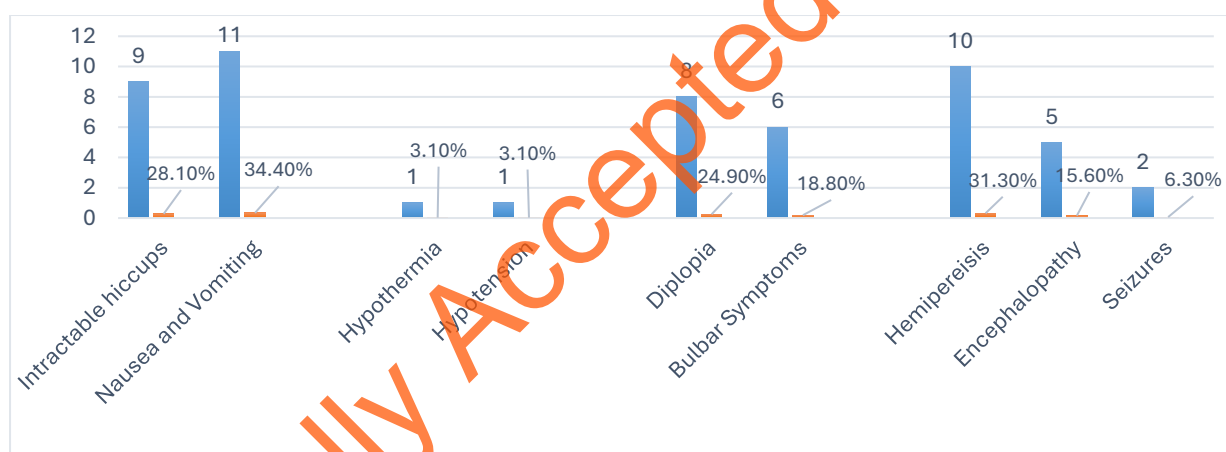


Figure 3: Non-optico-spinal presenting features.

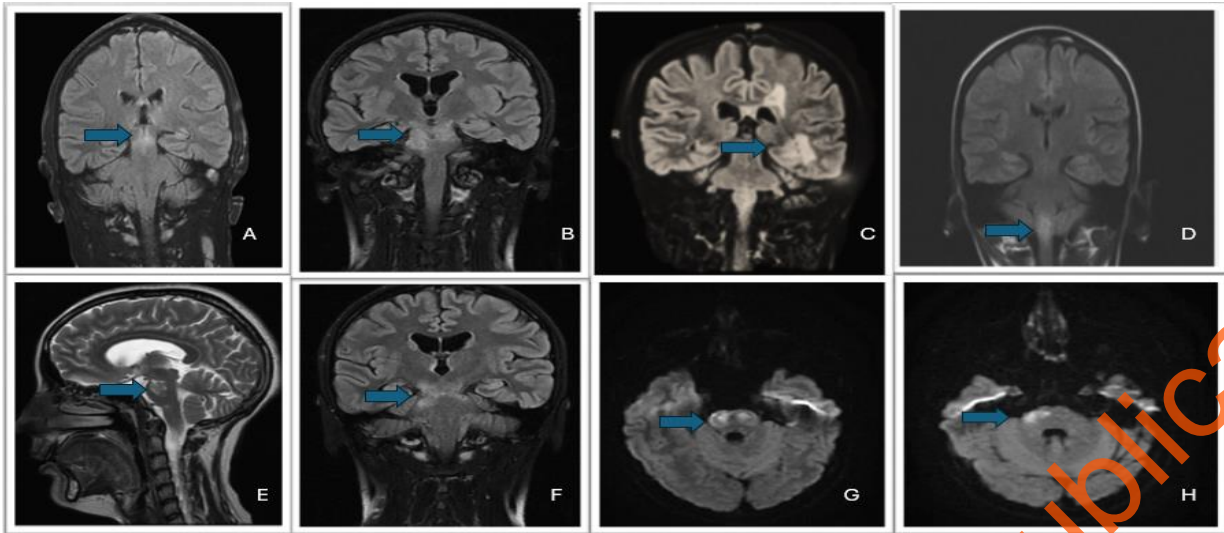


Figure 4: Magnetic resonance imaging (MRI) brain scan T2/FLAIR images showing hyperintense signals in different anatomical regions in a patient presenting with non-optico-spinal symptoms. (A) FLAIR image demonstrating a hyperintense lesion in the midbrain (arrow). (B) Hyperintense lesion in the pons (arrow). (C) Cortical and subcortical white matter lesions (arrow). (D) Hyperintense signal at the cervicomedullary junction (arrow). (E) Sagittal T2-weighted image showing a hyperintense signal in the area postrema (arrow). (F) Midbrain involvement. (G&H) Hyperintense lesions in the medulla oblongata. FLAIR: Fluid-Attenuated Inversion Recovery

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RN: Concept, design, data collection, analysis and writing.

SRU & QUN: Design, data analysis and revisions.

WJ: Concept, data analysis and revisions.

TS: Data analysis, interpretation and writing.

MA: Data collection, analysis and writing.