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ORIGINAL RESEARCH

Incidence, Clinician Misdiagnosis Rate, Radiologist Missed Diagnosis Rate, and Lesion Distribution of Isolated Medial Longitudinal Fasciculus Infarction: A Retrospective Study

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Purpose: This study aimed to determine the incidence, clinician misdiagnosis rate, radiologist missed-diagnosis rate, and lesion distribution of isolated medial longitudinal fasciculus infarction (IMLFI).

Patients and Methods: A retrospective analysis was conducted on 14,385 patients hospitalized with ischemic stroke at the General Hospital of Ningxia Medical University between 2020 and 2023. The objectives were to estimate the incidence of IMLFI, assess clinician misdiagnosis and radiologist missed-diagnosis rates based on initial clinical and imaging reports, and characterize the anatomical distribution of lesions.

Results: IMLFI accounted for 0.17% (24/14,385) of all ischemic stroke cases. Among these patients, 70.83% (17/24) were male, with a mean age of 60.88 ± 10.25 years. Nineteen patients presented with internuclear ophthalmoplegia (INO). Most cases (75.00%, 18/24) were initially evaluated in the Emergency Department by neurologists, while the remaining 25.00% (6/24) were first assessed in the Department of Ophthalmology. The overall initial clinical misdiagnosis rate was 41.67% (10/24), with the most frequent misdiagnoses being oculomotor nerve palsy (50.00%) and peripheral vertigo (40.00%). On initial radiological evaluation, diffusion-weighted imaging (DWI) lesions were missed in 37.50% (9/24) of cases. Anatomically, lesions were distributed in the caudal midbrain (20.83%, 5/24), the midbrain–pontine junction (4.17%, 1/24), and the rostral pons (45.83%, 11/24).

Conclusion: IMLFI is a rare clinical entity with a high risk of both clinical misdiagnosis and radiological oversight. Lesions are predominantly located from the caudal midbrain to the rostral pons, highlighting the need for increased clinical and radiological awareness of this condition.

Keywords: medial longitudinal fasciculus, internuclear ophthalmoplegia, misdiagnosis, missed-diagnosis, imaging

Introduction

The medial longitudinal fasciculus (MLF) is a paired white matter tract in the brainstem, located ventrolateral to the cerebral aqueduct and ventral to the fourth ventricle. It contains ascending, descending, and decussating fibers that interconnect key ocular motor nuclei, including the ipsilateral oculomotor nucleus and the contralateral abducens nucleus.[1] The MLF is essential for coordinating conjugate eye movements in the horizontal, vertical, and torsional planes.[1] Lesions of the MLF most commonly result from cerebrovascular disease, multiple sclerosis, or trauma.[2] The classic clinical manifestation is internuclear ophthalmoplegia (INO), characterized by impaired adduction of the ipsilateral eye with dissociative nystagmus of the contralateral abducting eye. More extensive involvement may lead to INO-plus syndromes, such as one-and-a-half syndrome, or additional motor and sensory deficits,[1] which are generally more readily identified on clinical examination.

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Isolated medial longitudinal fasciculus infarction (IMLFI) is a distinct and rare subtype of cerebral infarction, defined by lesions confined strictly to the MLF without involvement of adjacent brainstem structures. Owing to its rarity, dedicated epidemiological studies are lacking. One study reported that cerebral infarctions presenting with INO as the sole or primary symptom accounted for 0.47% of all brainstem infarctions, indirectly suggesting the incidence of IMLFI.[3] Because IMLFI is not associated with typical stroke manifestations such as hemiplegia, aphasia, or sensory deficits, mild INO is easily overlooked in clinical practice.[4] Consequently, reliance on isolated internuclear ophthalmoplegia (IINO) alone may lead to underestimation of the true incidence of IMLFI. The lesions are typically very small and difficult to detect on computed tomography (CT).[5] Diffusion-weighted imaging (DWI) is therefore a key diagnostic modality for IMLFI,[5] although its sensitivity in detecting all such lesions remains uncertain. Most existing clinical evidence is derived from case reports,[6–16] which have described its characteristic clinical and imaging features and provide indirect diagnostic guidance. As a subtype of acute ischemic stroke, timely and accurate early diagnosis of IMLFI is crucial for improving recovery from diplopia and functional impairment.[7,17] At present, clinicians' understanding of IMLFI is largely extrapolated from studies on INO, with few investigations focusing directly on IMLFI. By retrospectively analyzing clinical and imaging data from a large cohort of ischemic stroke patients, this study is the first to report the incidence, misdiagnosis rate, and missed diagnosis rate of IMLFI, as well as to characterize its lesion distribution on DWI, thereby increasing awareness among clinicians and radiologists.

Methods

This single-center retrospective study was jointly conducted by two neuroradiologists and four neurologists. We retrospectively reviewed the electronic medical records of patients with cerebral infarction admitted to the General Hospital of Ningxia Medical University between January 1, 2020, and December 31, 2023. From this cohort, cases of IMLFI were identified to determine its incidence among hospitalized patients with cerebral infarction. By analyzing clinical diagnoses and DWI reports at initial presentation, we calculated the misdiagnosis rate by clinicians and the missed diagnosis rate of IMLFI lesions by radiologists. In addition, neuroradiologists re-evaluated all imaging data to characterize the anatomical distribution of IMLFI lesions.

The diagnosis of IMLFI was established based on predefined inclusion and exclusion criteria. Inclusion criteria were: (1) anatomical localization of the MLF according to established MRI criteria,[18,19] with suspected lesions identified as lacunar infarctions in the paramedian pontine tegmentum or ventrolateral region adjacent to the midbrain aqueduct; and (2) neurological findings consistent with internuclear ophthalmoplegia (IINO), as assessed by neurologists. Exclusion criteria included: (1) evidence of infarction outside the MLF on cranial CT or MRI; and (2) the presence of focal neurological deficits other than IINO, such as facial paralysis, ptosis, dysarthria, dysphagia, sensory impairment, limb motor dysfunction, or other ocular movement disorders (eg, oculomotor or abducens nerve palsy, or gaze palsy).

Given that mild IINO may be difficult to detect clinically, its presence was not mandated for diagnosis. Accordingly, IMLFI cases were classified into two categories: definite IMLFI, fulfilling all inclusion and exclusion criteria, and probable IMLFI, fulfilling Inclusion Criterion (1) and all exclusion criteria only. Two neuroradiologists independently screened potential IMLFI cases, while four neurologists independently evaluated patients for IINO. Inter-rater reliability within each group (radiologists and clinicians) was assessed separately using Cohen's kappa statistic. The misdiagnosis rate was defined as the proportion of IMLFI cases not diagnosed as cerebral infarction at the initial clinical encounter and was calculated as: (number of misdiagnosed IMLFI cases / total number of IMLFI cases) × 100%. The missed diagnosis rate referred to the proportion of IMLFI cases in which lesions were not detected on the initial DWI examination by radiologists and was calculated as: (number of cases with missed lesions on initial DWI / total number of IMLFI cases) × 100%.

Data Collection

Clinical data collected from confirmed IMLFI patients included demographic variables (age and sex), presenting symptoms, medical history, and neurological examination findings. Particular attention was given to details of the first clinical encounter, including the time of presentation, the initial diagnosis and management by clinicians, the timing of MRI, and the radiological interpretation of lesion location. Neuroradiologists further reassessed the diagnostic performance of head CT, DWI, and T2-weighted imaging/fluid-attenuated inversion recovery (T2/FLAIR) sequences for IMLFI, along with the spatial distribution characteristics of the lesions.

Statistical Analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Data normality was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median (interquartile range, IQR). Categorical variables were summarized as frequencies and percentages. Data completeness checks confirmed the absence of missing values, and therefore complete-case analysis was performed. Between-group comparisons for continuous variables were conducted using the independent-samples *t* test for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. For categorical variables, the chi-square test was applied for large samples, while Fisher's exact test was used when expected cell counts were small. All statistical tests were two-tailed, and a *P* value < 0.05 was considered statistically significant.

Results

General Characteristics of the Baseline Population

From January 2020 to December 2023, a total of 14,385 consecutive patients with acute cerebral infarction were admitted to the Department of Neurology at the General Hospital of Ningxia Medical University. The cohort comprised 9,834 males (68.4%) and 4,551 females (31.6%), with ages ranging from 14 to 98 years (mean 63.88 ± 12.08 years). Among these patients, 1,538 (10.53%) had isolated brainstem infarction. Specifically, 78 cases (5.07%) involved isolated midbrain infarction, 951 (61.83%) involved isolated pontine infarction, 280 (18.21%) involved isolated medulla oblongata infarction, and 40 (2.60%) involved infarctions in multiple regions of the brainstem. Additionally, 189 cases (12.29%) were documented as having brainstem infarction but lacked definitive imaging examination.

General Characteristics of IMLFI Patients

The general characteristics of IMLFI patients are shown in Figure 1. Among the 14,385 hospitalized ischemic stroke patients, 24 cases of IMLFI were identified, including 19 definite and 5 probable cases. Based on the Landis and Koch criteria, interobserver agreement was high for radiologist-based screening (κ = 0.76, *P* < 0.001) and nearly perfect for

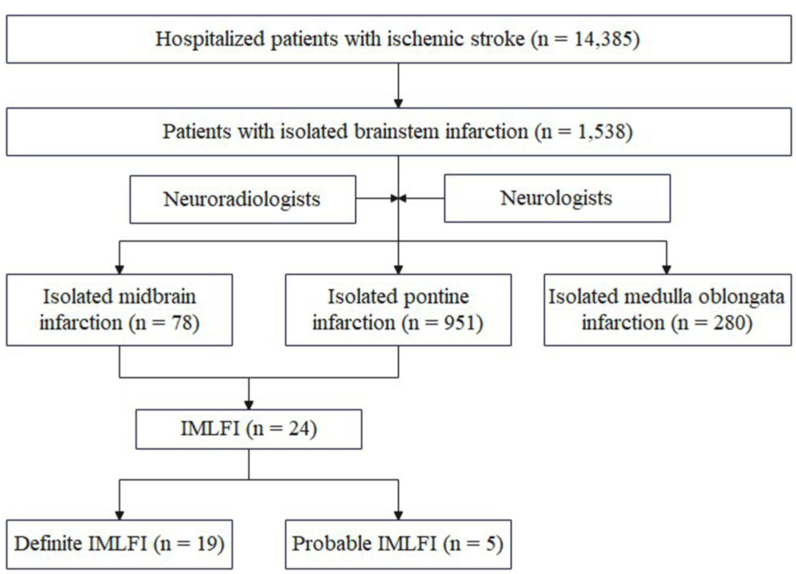

Figure 1 Flowchart of patient screening for isolated medial longitudinal fasciculus infarction (IMLFI).
Abbreviation: IMLFI, isolated medial longitudinal fasciculus infarction.

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neurologist-based assessment of IINO (κ = 0.81, $P < 0.001$). IMLFI accounted for 0.17% (24/14,385) of all ischemic strokes and 1.56% (24/1,538) of isolated brainstem infarctions. The IMLFI cohort comprised 17 males (70.83%) and 7 females (29.17%), with a mean age of 60.88 ± 10.25 years (range: 42–79 years). No significant differences in age or sex distribution were observed between patients with and without IMLFI (Table 1). The median time from symptom onset to hospital admission was 16.39 hours (IQR: 7.53–43.43 hours). Only four patients (16.67%) presented within the 4.5-hour thrombolysis window, and none received reperfusion therapy.

Misdiagnosis Rate at the Initial Visit Among Patients with IMLFI

Among 24 patients, 18 (75%) initially presented to the emergency department and were evaluated by neurologists. Of these, 13 cases (72.22%) were correctly suspected to have acute cerebral infarction, whereas 5 cases (27.78%) were misdiagnosed—four as peripheral vertigo and one as brainstem encephalitis. The remaining six patients (25%) first attended ophthalmology clinics, where only one case (16.67%) was suspected to be cerebral infarction and the other five (83.33%) were misdiagnosed as oculomotor nerve palsy. Overall, the misdiagnosis rate was 41.67% (10/24), with the most frequent incorrect diagnoses being oculomotor nerve palsy (50.00%) and peripheral vertigo (40.00%). The misdiagnosis rate was significantly higher among ophthalmologists than neurologists (Fisher's exact test, 95% CI: 0.007–0.833, $P = 0.050$). No significant differences were observed between the correctly diagnosed and misdiagnosed groups with respect to age, sex, infarct location, radiological diagnosis, IMLFI classification, or time from symptom onset to admission (all $P > 0.05$; Table 2).

Missed Diagnosis Rate of Lesions by Radiologists in Patients with IMLFI at the Initial Visit

All 24 IMLFI cases were confirmed through retrospective reassessment of DWI by neuroradiologists, which demonstrated abnormal signal changes within the MLF territory (Figure 2a–c). No lesions were detected on CT in any patient. Among the 19 patients who underwent additional T2/FLAIR imaging, MLF hyperintensity was observed in only 68.42% (13/19; Figure 3a), whereas the remaining six cases (31.58%) showed no detectable abnormalities (Figure 3b and c). The median interval from symptom onset to MRI acquisition was 48.26 hours (IQR: 23.78–73.71 hours; range: 14.07–196.82 hours). On initial review, radiologists correctly identified IMLFI lesions in 62.50% (15/24) of cases, resulting in a missed diagnosis rate of 37.50% (9/24). Among the missed cases, 88.89% (8/9) involved pontine lesions. However, no statistically significant differences were found between the lesion-detected and lesion-missed groups in terms of age, sex, lesion location, first-contact physician, or time to MRI completion (all $P > 0.05$; Table 3).

Distribution Characteristics of IMLFI Lesions

Regarding lesion distribution, 20.83% (5/24) of cases involved the caudal midbrain, 4.17% (1/24) the midbrain–pontine junction, and 75.00% (18/24) the pontine region. Among pontine lesions, 11 were located in the rostral pons, six in the mid-pons, and one involved both rostral and mid-pons regions. Left-sided lesions accounted for 62.50% (15/24), right-sided lesions for 33.33% (8/24), and bilateral involvement was observed in 4.17% (1/24) of cases. No lesions were identified in the rostral midbrain or caudal pons. Overall, 70.83% (17/24) of IMLFI lesions were concentrated between the caudal midbrain and

Table 1 Comparison of the Demographic Characteristics Between the IMLFI and Non-IMLFI Groups

	IMLFI Group n = 24	Non-IMLFI Group n = 14,361	Statistical Value	95% CI	*p*-value
Age, years	60.88 ± 10.26	63.88 ± 12.09	t =1.218†	−0.152 to 0.649	0.223
Gender, n(%)			χ^2 = 0.069	0.369 to 2.147	0.795
Male	17 (70.83%)	9817(68.39)			
Female	7 (29.17%)	4544(31.64)			

Note: †Degrees of freedom = 14,383.
Abbreviations: CI, confidence interval; IMLFI, isolated medial longitudinal fasciculus infarction.

Table 2 Comparison of Demographics and Clinical Characteristics Between the Clinically Diagnosed and Misdiagnosed Groups of Isolated Medial Longitudinal Fasciculus Infarction

Characteristic	Diagnosed Groups (n = 14)	Misdiagnosed Groups (n = 10)	Statistical Value	95% CI	*p*-value
Age, years	58.70 ± 11.26	62.43 ± 9.60	Independent-samples *t*-test, t = −0.608†	−11.91 to 6.53	0.550
Gender, n (%)					
Male	9 (64.29)	8 (80.00)	Fisher's exact test	0.29 to 11.16	0.647
Female	5 (35.71)	2 (20.00)			
Lesion location, n (%)*					
Midbrain	3 (21.43)	2 (22.22)	Fisher's exact test	0.009 to 0.964	1.000
Pons	11 (78.57)	7 (77.78)			
First-visit physician, n (%)					
Ophthalmologists	1 (7.14)	5 (50.00)	Fisher's exact test	0.007 to 0.833	0.050
Neurologists	13 (92.86)	5 (50.00)			
Missed by radiology, n (%)					
Yes	7 (50.00)	8 (80.00)	Fisher's exact test	0.039 to 1.623	0.210
No	7 (50.00)	2(20.00)			
IMLFI diagnosis, n (%)					
Confirmed	11 (78.57)	8 (80.00)	Fisher's exact test	0.147 to 8.123	1.000
Probable	3 (21.43)	2 (20.00)			
Time to visit, hours	12.00 (6.19–23.75)	29.86 (7.68–50.19)	Mann–Whitney *U*-test, U = 50.000	–	0.259

Notes: †Degrees of freedom = 21.*One IMLFI case with a lesion located at the midbrain-pontine junction could not be definitively classified as either midbrain or pontine infarction. Given the small sample size, this case was excluded from the lesion distribution analysis.
Abbreviations: CI, confidence interval; IMLFI, isolated medial longitudinal fasciculus infarction.

rostral pons. Notably, the incidence of IMLFI was significantly higher in patients with midbrain infarction than in those with pontine infarction (6.41% [5/78] vs 1.89% [18/951]; χ^2 = 4.824, OR = 3.55, 95% CI: 1.28–9.84, *P* = 0.028; Table 4).

Discussion

To date, direct epidemiological studies of IMLFI remain unavailable, and most published data consist of case reports.[6–16] Kim et al[3] reported that brainstem infarctions presenting with INO as the sole or major symptom accounted for 0.47% (25/5,315) of all hospitalized ischemic stroke patients; however, some of these patients also had additional focal neurological deficits. Yun Zhang et al[20] found that midbrain IINO cases accounted for 20% (5/25) of isolated midbrain infarctions, but their study excluded patients with pontine IINO, preventing an accurate estimation of the overall incidence of IMLFI among ischemic stroke patients. In contrast, the present study is the first to screen for IMLFI

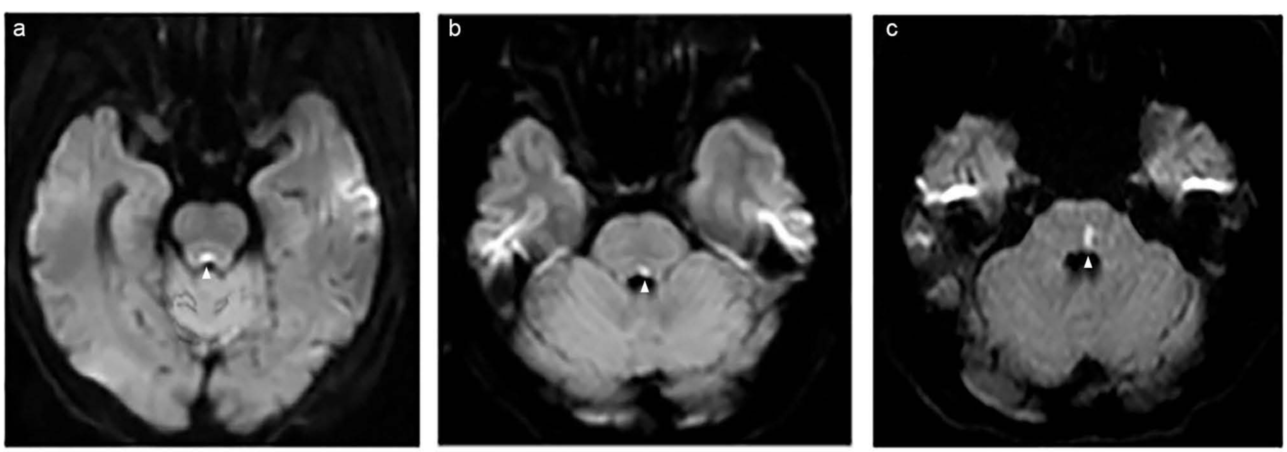

Figure 2 Manifestations of isolated medial longitudinal fasciculus infarction (IMLFI) in different locations on diffusion-weighted imaging (DWI): Hyperintensities are shown in the bilateral caudal dorsal midbrain (**a**) (white arrow), the left rostral dorsal pons (**b**) (white arrow), and the left mid-dorsal pons (**c**) (white arrow).

Figure 3 Identification of isolated medial longitudinal fasciculus infarction (IMLFI) lesions on T2-weighted imaging/fluid-attenuated inversion recovery (T2/FLAIR): Despite the visibility of lesions in all patients on diffusion-weighted imaging (DWI), variability has been detected in their detection on T2/FLAIR imaging: lesions can be identified in certain cases (**a**) (white arrow), while they remain undetectable in others (**b** and **c**) (white arrows).

based on imaging findings confirmed by neurologists, a methodology not previously reported. Our results demonstrated that IMLFI accounted for 0.17% (24/14,385) of all hospitalized ischemic stroke patients and 1.56% (24/1,538) of those with isolated brainstem infarction, confirming its extreme rarity. No significant differences in age or sex distribution were observed between IMLFI and non-IMLFI patients.

The misdiagnosis rate of IMLFI at initial presentation was as high as 41.67%, underscoring the diagnostic challenges associated with this condition. IINO represents the hallmark clinical sign of IMLFI, and accurate recognition of this sign is critical for correct diagnosis. Among the 10 misdiagnosed cases, 5 (50%) were misdiagnosed by ophthalmologists as oculomotor nerve palsy, whereas 4 (40%) were misdiagnosed by neurologists as peripheral vertigo. These findings indicate that insufficient recognition of IINO is the primary cause of misdiagnosis. In addition, mild IINO manifestations are easily overlooked, further contributing to diagnostic errors. Previous studies have shown that 71% of physicians fail

Table 3 Comparison of Demographics and Clinical Characteristics Between the Lesion-Detected and Lesion-Missed Groups of Isolated Medial Longitudinal Fasciculus Infarction

Characteristic	Lesions-Detected Groups (n = 15)	Lesions-Missed Groups (n = 9)	Statistical Value	95% CI	*p*-value
Age, years	58.67 ± 10.86	64.56 ± 8.46	t = 1.389†	−2.65 to 14.24	0.179
Gender, n (%)			Fisher's exact test	0.017 to 0.897	0.061
Male	13 (86.67)	4 (44.44)			
Female	2 (13.33)	5 (55.56)			
Lesion Location, n (%)*	(n=14)	(n=9)	Fisher's exact test	0.30 to 34.59	0.611
Midbrain	4 (28.57)	1 (11.11)			
Pons	10 (71.43)	8 (88.89)			
IMLFI Diagnosis, n (%)			Fisher's exact test	0.344 to 0.806	0.118
Confirmed	10 (66.67)	9 (100.00)			
Probable	5 (33.33)	0 (0.00)			
T2-FLAIR Hyperintensity, n (%)**			Fisher's exact test	0.427 to 26.039	0.320
Yes	10 (76.92)	3 (50.00)			
No	3(23.08)	3 (50.00)			
Time to Visit, hours	18.77 (8.35–46.00)	12.00 (2.50–40.00)	U = 79.000	–	0.519
Time to MRI, hours	47.40 (20.45–77.70)	49.12 (33.03–73.55)	U = 60.000	–	0.682

Notes: † Degrees of freedom = 22.*One IMLFI case with a lesion located at the midbrain-pontine junction could not be definitively classified as either midbrain or pontine infarction. Given the small sample size, this case was excluded from the lesion distribution analysis.**T2-FLAIR sequences was assessed in 19 patients, with lesions visible in 13 and absent in the remaining 6.

Abbreviations: CI, confidence interval; IMLFI, isolated medial longitudinal fasciculus infarction; T2-FLAIR,T2-weighted imaging/fluid-attenuated inversion recovery.

Table 4 Comparison of Midbrain and Pontine Involvement Between the Isolated Medial Longitudinal Fasciculus Infarction (IMLFI) and Non-IMLFI Groups

Lesion Distribution*	IMLFI Group (n=24)	Non-IMLFI Group (n=1006)	Statistical Value	95% CI	p-value
Midbrain	5 (21.74)	73(7.56)	χ^2 = 4.824	1.28~9.84	0.028
Pons	18 (78.26)	933(92.74)			

Notes: *Since IMLFI lesions are exclusively confined to the midbrain and pons, the analysis of lesion distribution differences in IMLFI was performed only in patients with isolated midbrain infarction or isolated pontine infarction (n = 1029). One IMLFI case with a lesion located at the midbrain-pontine junction could not be definitively classified as either midbrain or pontine infarction. Given the small sample size, this case was excluded from the lesion distribution analysis.
Abbreviations: CI, confidence interval; IMLFI, isolated medial longitudinal fasciculus infarction.

to identify mild adduction slowing, and 25% miss moderate conjugate gaze palsy in patients with INO.[4] The diagnostic accuracy of INO varies by specialty and clinical experience, with neuro-ophthalmologists demonstrating the highest recognition rate.[4] Our study similarly found that ophthalmologists had a lower recognition rate of INO than neurologists and experienced difficulty in distinguishing incomplete oculomotor nerve palsy from IMLFI. Advanced techniques such as quantitative infrared eye movement scanning,[4] electrooculography,[21] and eye movement-tracking systems[22] can objectively detect INO features, including slowed adducting saccades, abducting nystagmus, and reduced adducting saccade amplitude, thereby significantly improving diagnostic accuracy. However, these methods are not routinely available in neurology departments and are impractical for early-stage IMLFI screening. Therefore, IMLFI should be actively considered in the differential diagnosis of patients presenting with suspected oculomotor nerve palsy or peripheral vertigo, which may help reduce its misdiagnosis rate in clinical practice.

Although IMLFI is primarily diagnosed through imaging, radiologists are highly susceptible to missing these lesions in the absence of IINO as a clinical warning sign. In our cohort, DWI detected IMLFI lesions in all patients (100%); however, 37.5% of these lesions were not recognized by radiologists during initial interpretation. While T2/FLAIR sequences can assist in lesion identification, their sensitivity is inferior to that of DWI because of cerebrospinal fluid (CSF) flow artifacts and vascular pulsation.[23] Comparative analyses revealed no significant differences between the lesion-detected and lesion-missed groups with respect to age, sex, infarct location, initial department of presentation, or time to MRI completion. No clinical or demographic predictors of radiological detection were identified. The medial longitudinal fasciculus (MLF), however, has a diameter of only 2.0–2.5 mm[24] and lies adjacent to the floor of the fourth ventricle. The minute size of IMLFI lesions likely constitutes the primary reason for missed diagnoses. Improved communication by clinicians—specifically emphasizing the presence of IINO as a key warning sign—may enhance detection rates, although this strategy requires prospective validation.

Our study demonstrated that IMLFI lesions were more frequently located in the pons (18 cases, 78.26%) than in the midbrain (5 cases, 21.74%), consistent with findings reported by Chuang et al,[5] who observed pontine involvement in all eight of their IMLFI cases. Kim et al[3] defined the midbrain–pontine junction as the isthmus and reported lesion distribution among 12 patients with IINO as follows: rostral pons in 5 cases (41.67%), isthmus in 6 cases (50%), and combined involvement of the rostral pons and isthmus in 1 case (8.33%). Although most IMLFI lesions occurred in the pons, this reflects the higher incidence of pontine infarctions compared with midbrain infarctions (92.42% vs 7.58%). Interestingly, the relative prevalence of IMLFI among patients with midbrain infarction was higher (6.41% vs 1.89%). This may be attributable to the heightened vulnerability of the anteromedial midbrain to ischemia. The oculomotor nucleus and the rostral segment of the MLF are located in the anteromedial midbrain adjacent to the cerebral aqueduct. Ischemic damage to either structure can produce impaired eye adduction. Clinically, such presentations are often misattributed to oculomotor nerve palsy, leading to underestimation of midbrain IMLFI incidence. Although Yun Zhang et al[20] reported that 20.0% of patients with isolated midbrain infarction presented with IINO, their cohort may have included cases of oculomotor nerve palsy. Therefore, in patients presenting with isolated adduction deficits, pontine or midbrain IMLFI should always be considered.

In most published case reports, MLFI lesions are broadly described as being located in “the midbrain or pons.” However, given the close anatomical relationship between the MLF and adjacent nuclei and fiber tracts, more precise lesion localization may significantly enhance neuroanatomical correlation during clinical examination. Following the pontine segmentation proposed by Tatjana et al,[25] we divided the pons into rostral (superior cerebellar peduncle level), middle (trigeminal nerve level), and caudal (facial nerve level) regions. The midbrain was subdivided into rostral (superior colliculus level) and caudal (inferior colliculus level) portions. Our findings showed that midbrain IMLFI was confined exclusively to the caudal midbrain, whereas pontine lesions were predominantly located in the rostral and middle pons. No cases were observed in the rostral midbrain or caudal pons. Notably, 70.83% of lesions were clustered at the caudal midbrain–rostral pontine junction. Neuroanatomical studies indicate that at the superior colliculus level, the MLF lies in close proximity to the oculomotor nucleus, a region where IMLFI is rarely observed.[24] Similarly, MLFI in the caudal pons is more likely to involve the genu of the facial nerve, resulting in facial colliculus syndrome.[26] Furthermore, 95.83% (23/24) of IMLFI lesions in our cohort were unilateral, consistent with the typical presentation of ischemic INO. In contrast, bilateral INO is more commonly associated with multiple sclerosis.[27]

IMLFI represents a distinct ischemic stroke subtype characterized predominantly by vertigo and diplopia rather than classic motor deficits such as hemiparesis. Commonly used stroke recognition tools, including "Stroke 1-2-0" and "FAST," demonstrate limited sensitivity for posterior circulation stroke.[28] In our cohort, the median time from symptom onset to hospital presentation was 16.39 hours (interquartile range [IQR]: 7.53–43.43 hours). By comparison, a large survey of ischemic stroke patients in China reported a median presentation time of 4 hours (IQR: 1.50–14.05 hours).[29] The delayed presentation observed in IMLFI patients likely reflects both atypical symptomatology and insufficient recognition. Notably, 25% (6/24) of patients initially sought care in ophthalmology clinics due to diplopia. As a subtype of ischemic stroke, IMLFI may benefit significantly from early reperfusion therapy. Case reports have demonstrated complete resolution of IINO within 1.5 hours following thrombolysis,[6] whereas spontaneous recovery is much slower, with a mean duration of 2.25 months, and over 21.2% of patients requiring more than 6 months for full recovery.[17] In our study, only 22.22% (4/18) of patients presented within the 4.5-hour therapeutic window, and none received reperfusion therapy due to diagnostic delays. These findings highlight the critical importance of improving early recognition to optimize clinical outcomes in IMLFI.

Conclusion

This study is the first to integrate neuroimaging screening with clinical examination to determine the incidence of IMLFI (0.17%) in an ischemic stroke population and to quantify both the clinician misdiagnosis rate and radiologist lesion oversight rate. Our findings highlight the need for clinicians to prioritize IMLFI as a critical differential diagnosis when evaluating patients presenting with suspected oculomotor nerve palsy or peripheral vertigo. Radiologists should likewise maintain heightened vigilance for subtle lesions within the caudal midbrain and rostral pons on DWI. It should be emphasized that, as this was a single-center retrospective study, the diagnosis of IINO relied primarily on descriptive neurological examination findings rather than objective quantitative measures, which may have contributed to under-detection of IMLFI cases. In addition, the relatively small number of confirmed IMLFI cases limited the statistical power of subgroup analyses. Future multicenter, prospective cohort studies are therefore warranted to develop rapid and reliable diagnostic strategies for IMLFI, enabling earlier intervention and potentially improving clinical outcomes.

Abbreviations

CT, Computed tomography; DWI, Diffusion-weighted imaging; IINO, Isolated internuclear ophthalmoplegia; IMLFI, Isolated medial longitudinal fasciculus infarction; INO, Internuclear ophthalmoplegia; IQR, interquartile range; MLF, Medial longitudinal fasciculus; MLFI, Medial longitudinal fasciculus infarction; MRI, Magnetic resonance imaging; SD, Standard deviation; T2/FLAIR, T2-weighted imaging/ fluid-attenuated inversion recovery.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author, Professor Qing Zhang. The data are not publicly available due to privacy limitations.

Ethical Approval

The Ethics Committee of the General Hospital of Ningxia Medical University approved this study (Ethics Committee Approval Number: KYLL - 2024 - 1585). The study was performed in line with the principles of the Declaration of Helsinki. All the patients under follow-up gave written informed consent.

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Disclosure

Conflict of interest All authors declare no conflicts of interest.

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