STROKE

Vol 3|Issue 17|2024

Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Stroke Newsletter" which contains latest and interesting news in the field of Neuropsychiatry.

This issue contains:

1. **Identification of serum biomarkers at stroke onset on the risk of developing post-stroke epilepsy**
2. **Association between Glycated albumin levels with poststroke outcomes in patients with acute ischemic stroke or transient ischemic attack**
3. **Clinical features, response to treatment, and prognostic factors of Vascular Vertigo and Dizziness due to Vertebrobasilar Transient Ischemic Attacks**
4. **Case report on Horizontal direction changing Nystagmus in Patients with Left Cerebellar-Medullary Stroke**

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Looking forward to your valuable feedback
Best Regards,
Medical Team, Micro Labs Ltd

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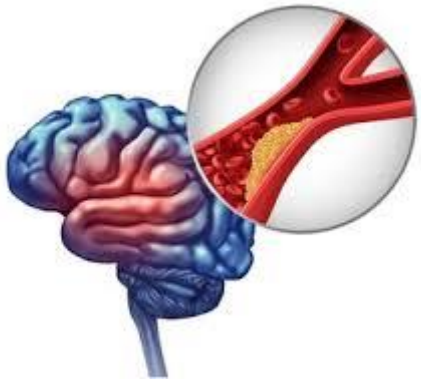
Identification of serum biomarkers at stroke onset on the risk of developing post-stroke epilepsy

Introduction –

Low levels of TNFSF-14 may predict post-stroke epilepsy risk, indicating its potential as a biomarker for epileptogenesis.

Stroke is a significant precursor to newly diagnosed epilepsy in the elderly, with post-stroke epilepsy (PSE) accounting for 30–50% of newer epilepsy cases in individuals aged 60 and older. Furthermore, PSE is associated with higher mortality rates following stroke.[1] According to the International League Against Epilepsy (ILAE) guidelines, the occurrence of a late-onset seizure qualifies as epilepsy due to the heightened risk of recurrence. Recent studies have identified various clinical risk factors for PSE, including stroke severity, hemorrhagic stroke, and younger age, and predictive models like SELECT score. However, there remains a need for additional biomarkers to accurately identify patients at risk of developing epilepsy post-stroke. Blood-based biomarkers, alongside clinical factors, could provide valuable insights into the risk of PSE. Further, studies on the role and function of specific biomarkers in the epileptogenesis process are limited.[2] So, this study aimed to identify serum biomarkers present at stroke onset that may help predict which patients are at higher risk for developing PSE.



Ischemic stroke

Methods –

This longitudinal study utilized data from a previous cohort of 895 acute stroke patients, followed over five years, of whom 51 developed post-stroke epilepsy (PSE). For the current analysis, 15 PSE patients were randomly selected and matched with 15 controls (stroke patients without epilepsy). A two-step biomarker analysis was performed; Initially, serum levels of 480 proteins were assessed in the 15 PSE patients and 15 controls using Olink Proteomics' proximity extension assay. After that, significant proteins were then validated using enzyme-

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linked immunosorbent assay (ELISA) in a larger cohort of 100 patients (50 PSE and 50 controls), matched for age, sex, and stroke characteristics. A ROC curve analysis was used to assess the predictive ability of significant biomarkers to develop PSE.

Results–

In the discovery analysis, 15 PSE patients had a mean age of 61.7 ± 13.3 years, with 86.7% male and 73% experiencing ischemic strokes. The median NIHSS score was 9 [2–15], and the median time from stroke to seizure onset was 286 [133–1405] days. In the validation cohort of 50 PSE patients, the mean age was 68.56 ± 15.1 years, with 90% having ischemic strokes and a median NIHSS score of 12 [1–25]. Protein expression analysis showed nine proteins with significantly lower expression in PSE patients ($p < 0.01$), including Caspase-8 and TNFSF-14. EDA2R and CLEC1B were identified as the only neurology panel biomarkers, while TCN2 and c-KIT were overexpressed (Figure 1). STRING-Cytoscape analysis revealed significant interactions for VEGFa, CD40, and CCL4 in PSE patients. ELISA validation confirmed that TNFSF-14 was significantly downregulated ($p = 0.006$) and correlated strongly with Olink results ($r = 0.837$; $p<0.001$). ROC curve analysis indicated TNFSF-14 has good predictive capability for developing PSE, with an AUC of 0.733 (95% CI 0. 601–0.865) (Figure 2).

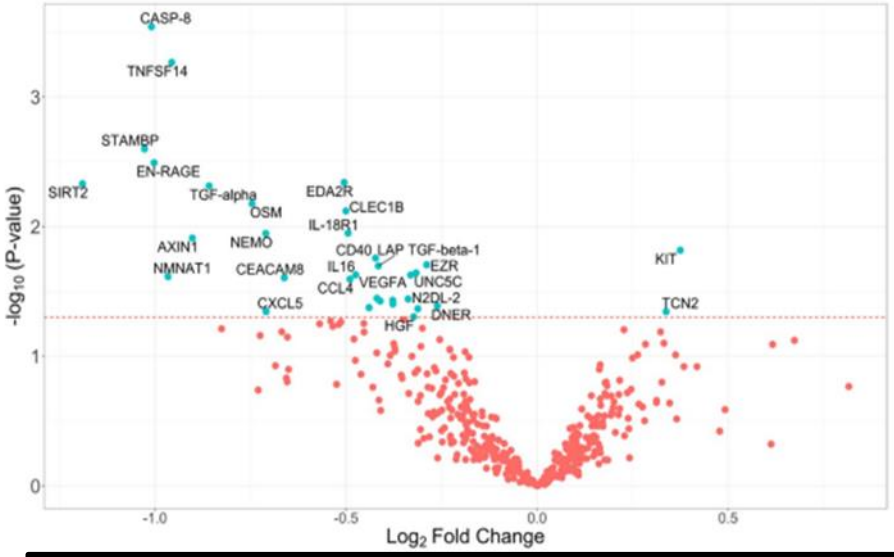

Figure 1. Volcano plot illustrating differentially expressed proteins between PSE patients and controls, as determined by the Olink Proteomics assay. Proteins on the left side are downregulated, while those on the right are upregulated. The dashed line represents the level of significance of 0.05.

Discussion –

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This study highlights TNFSF-14 as a key biomarker for post-stroke epilepsy (PSE), showing significantly lower expression levels in affected patients compared to controls. This finding supported the existing studies that link dysregulated inflammatory proteins to altered seizure thresholds, indicating that low TNFSF-14 may increase the risk of epilepsy post-stroke.[3] While ENRAGE and oncostatin M (OSM) also demonstrated relevant findings, they did not reach statistical significance. Notably, previous studies reported elevated ENRAGE levels in stroke patients compared to those with transient ischemic attack (TIA) or controls at 1- and 3- hours post-event, contrasting with this study's findings.[4]

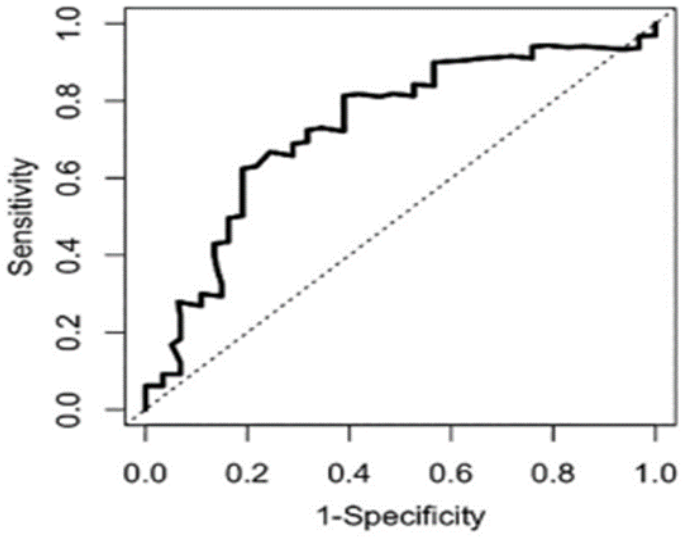

Figure 2. Time-dependent ROC curve (5-year follow-up) revealing TNFSF-14's predictive ability for PSE development

Conclusion –

TNFSF-14 was the only biomarker significantly different between PSE patients and controls, suggesting that low levels may predict the development of PSE alongside clinical risk factors. Its analysis is straightforward using various laboratory techniques. The differences in protein expression indicate a potential dysregulation contributing to post-stroke epileptogenesis

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Association between Glycated albumin levels with poststroke outcomes in patients with acute ischemic stroke or transient ischemic attack

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Introduction-

Elevated GA levels in serum were associated with stroke adverse outcomes.

Stroke represents a significant cerebrovascular condition marked by high rates of incidence, disability, and mortality.[1] Studies indicate that 15%–30% of individuals with ischemic stroke face poor functional outcomes, and around 20% may experience recurrent strokes, which can further impair recovery and elevate mortality risk.[2] Thus, precise prediction of recurrence and unfavorable outcomes is essential for effective stroke management. Blood biomarkers offer objective measures that can improve the accuracy of risk assessments. While glycated hemoglobin (HbA1c) is widely recognized as the standard for assessing long-term glycemic control, it does not adequately reflect short-term glycemic changes before a stroke, raising concerns about its predictive utility. Glycated albumin (GA) provides insight into glycemic levels over a shorter period of 2–4 weeks before stroke onset and was closely linked to diabetes progression. However, studies examining the relationship between GA and adverse stroke outcomes remain limited.[3] So, this study aimed to evaluate GA as a predictive biomarker for post-stroke prognosis, specifically regarding stroke recurrence, poor functional outcomes, and combined vascular events at 3 months and 1 year in patients with acute ischemic stroke or transient ischemic attack (TIA).

Methods –

This Third China National Stroke Registry (CNSR-III) included patients with acute ischemic cerebrovascular events over 3 years. Participants were aged 18 or older and diagnosed with ischemic stroke or transient ischemic attack (TIA) confirmed by MRI or CT within 7 days of symptom onset. Exclusion criteria included missing serum GA data, loss to follow-up, or incomplete admission timing. Data collection involved trained neurologists who gathered baseline characteristics (age, sex, lifestyle factors) and medical histories (previous strokes, hypertension, cardiovascular issues, etc.). The modified Rankin Scale (mRS) score before stroke and the NIHSS score were also recorded, along with details about intravenous thrombolysis therapy and the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.

Fasting blood samples were collected from 171 sites within 24 hours of admission and stored at -80°C. Primary outcomes assessed included stroke recurrence, poor functional outcomes (defined as an mRS score >2), and combined vascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke). Outcomes were evaluated through face-to-face interviews at 3 months and via telephone at 1-year post-stroke.

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Results-

This study analyzed baseline characteristics and clinical outcomes associated with GA levels in a cohort of 3,861 participants. Higher GA levels were linked to being predominantly male, older, and having a history of diabetes, stroke, hypertension, dyslipidemia, and cardiovascular disease. At the three-month follow-up, 6.17% experienced stroke recurrence, 10.93% had poor functional outcomes, and 6.01% faced combined vascular events, rising to 8.99%, 8.75%, and 9.17%, respectively, by one year. Continuous GA values were associated with functional deterioration, with crude odds ratios (OR) of 1.02 at three months and 1.03 at one year. Participants in the highest GA quartile had a 49% increased risk of poor outcomes at three months (crude OR 1.49) and a 99% increase at one year (crude OR 1.99).

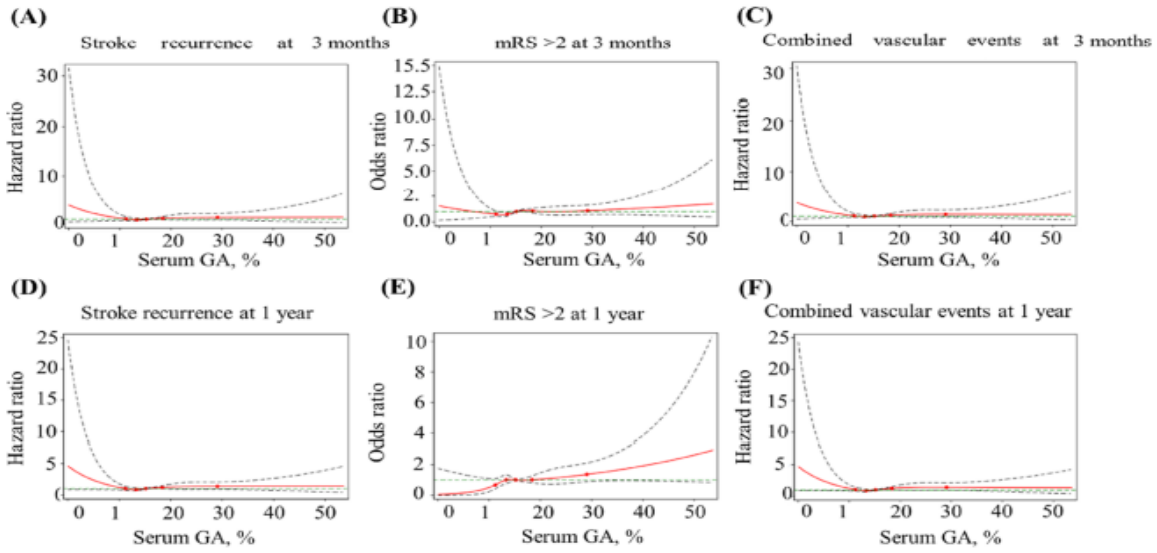

Figure 1: Spline models depicting the association between glycated albumin (GA) levels and adverse stroke outcomes. The first row shows the relationship between GA and (A) stroke recurrence, (B) modified Rankin Scale (mRS) score >2, and (C) combined vascular events at three months. The second row presents the association at one year for (D) stroke recurrence, (E) mRS score >2, and (F) combined vascular events. Red lines indicate adjusted hazard ratios, while green lines represent 95% confidence intervals.

Multivariable-adjusted analyses showed a trend toward higher adverse outcomes with increasing glycosylated albumin (GA) levels, although this was not statistically significant (Figure 1). Subgroup analyses revealed that in nondiabetic patients, higher GA levels correlated with increased risks of stroke recurrence and poor functional outcomes, particularly in those under 65. Incorporating GA into predictive models improved risk stratification, achieving net reclassification improvements of 18.67% at 3 months and 12.30% at 1 year. Elevated HbA1c

levels were also linked to increased risks of adverse outcomes, highlighting GA's significance as a predictor following stroke

Discussion –

The present study demonstrated the predictive value of GA levels in assessing functional outcomes in stroke patients. By incorporating GA into predictive models, the author achieved an 18.67% net reclassification improvement at 3 months and 12.3% at 1 year, consistent with findings from the CHANCE trial.[4] Notably, higher GA levels were particularly associated with adverse outcomes in nondiabetic patients, a critical distinction supported by previous research, including a Korean cohort study, which identified GA as an independent factor linked to unfavourable short-term outcomes in this population.[5]

Conclusion –

This study found that elevated serum glycosylated albumin (GA) levels were associated with adverse outcomes in ischemic stroke and TIA patients, including recurrence and poor functional outcomes. This association was particularly strong in non-diabetic patients, highlighting the need for careful monitoring and targeted interventions in this group.

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Clinical features, response to treatment, and prognostic factors of Vascular Vertigo and Dizziness due to Vertebrobasilar Transient Ischemic Attacks

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Introduction – Vertebrobasilar (VB) stroke accounts for approximately 20% of all strokes and transient ischemic attacks (TIAs), with nearly one-fourth of all TIAs and strokes occurring in the vertebrobasilar region.[1] TIAs and minor ischemic strokes result from localized brain dysfunction due to reduced blood flow (ischemia), leading to transient or subtle clinical symptoms. Recognizing ischemia is crucial, as about 20% of patients with ischemic strokes reported having experienced a TIA in the hours to days prior to the stroke.[2]

VBTIA is marked by weekly imbalance attacks, and effective secondary prevention with antiplatelet therapy led to a 93.2% recurrence-free rate.

Diagnosing a TIA can be challenging, as it largely relies on the patient's reported symptoms, the clinician's interpretation, and the exclusion of alternative diagnoses. Many studies still utilize the National Institute of Neurological Disorders and Stroke (NINDS) criteria for diagnosis; however, these criteria often overlook symptoms such as vertigo and dizziness, which can be indicative of a TIA. Consequently, studies on vertigo and dizziness associated with vertebrobasilar TIAs have been limited.[3] So, this study aimed to characterize the clinical features, treatment responses, and prognostic factors related to vestibular vertigo due to vertebrobasilar TIAs, as these factors may significantly influence treatment outcomes.

Methods – This cohort study included patients evaluated in emergency or outpatient settings. Exclusion criteria involved acute ischemia on cranial MRI, other neurotological disorders, chronic antiplatelet or anticoagulant use, prior vertebrobasilar strokes, multiple strokes, additional symptomatic causes, incomplete evaluations, or lack of consent. Participants underwent comprehensive otolaryngological and neurological assessments, cardiovascular evaluations, and advanced imaging studies. Stroke classification was based on imaging findings and vertigo history, with specific criteria leading to exclusion. First-line treatment for vestibular vertigo disease (VVD) was subsequently administered based on the evaluations. The Mantel–Haenszel test was a key statistical tool used to evaluate treatment outcomes and prognostic factors while controlling for confounding variables.

Results –

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Out of 1,957 patients screened, 103 were included in the study, with a mean age of 70.9 years. During the follow-up period, 96 patients (93.2%) reported no further episodes of dizziness or vertigo, indicating a significant therapeutic effect. The presence of vertebrobasilar (VB) large artery disease emerged as the only significant prognostic factor associated with recurrence, showing a 37.5% increased risk of events in these patients as shown in Table 1. The treatment regimen yielded a number needed to treat (NNT) of 1, suggesting that nearly every patient benefited from the intervention.

Recurrences were predominantly observed within the first year, with only seven patients (6.8%) experiencing a single recurrence. The Kaplan–Meier survival curve illustrated a decreasing probability of recurrence over the 36-month follow-up. This data underscores the effectiveness of the treatment in reducing vertigo-related episodes, particularly in patients without VB large artery disease.

Prognostic factor analyzed	Statistical test		
	Risk ratio	Risk difference	P-value
Sex (female vs. male)	1.0 (0.2, 4.4)	0.2 (−9.5, 10.0)	0.48
Age group (younger vs. older)	2.3 (0.5, 11.2)	5.2 (−4.3, 14.7)	0.15
Attack duration (short vs. high)	1.2 (0.2, 6.0)	1.4 (−8.6, 11.4)	0.40
Attack frequency (less vs. more)	2.1 (0.3, 16.9)	4.2 (−5.2, 13.5)	0.23
Comorbidities (≥3 vs. ≤2)	2.5 (0.5, 9.3)	6.6 (−4.8, 18.0)	0.10
Comorbidities (≥2 vs. ≤1)	2.8 (0.3, 22.5)	5.5 (−3.2, 14.3)	0.15
Arterial hypertension (presence vs. absence)	1.1 (0.2, 5.2)	0.5 (−10.6, 11.6)	0.47
Time from onset (short vs. high)	1.2 (0.3, 5.0)	1.1% (−6.0, 11.3)	0.41
VB large artery disease (yes vs. no)	0.0 (0.0, ?)	−37.5 (−27.8, −47.1)	0.04

Table 1. Prognostic Factors in Vertebrobasilar Transient Ischemic Attack

Discussion –

The current study indicated that secondary prevention strategies, including antithrombotic therapy, were highly effective, with 93.2% of patients experiencing no recurrence. This finding aligns with AHA/ASA guidelines and supports the notion that proactive management significantly reduces the risk of stroke after TIA, consistent with the results of Tuna and Rothwell.[4] Additionally, the study found that 39 patients (37.8%) had vertebrobasilar artery abnormalities, predominantly vertebral artery stenosis and severe hypoplasia. This observation was consistent with existing research that identifies vertebral artery hypoplasia as a significant risk factor for posterior circulation ischemia, particularly in the presence of other vascular risk factors.[5,6,7]

Conclusion –

VBTIA demonstrated a diverse clinical presentation, primarily characterized by weekly imbalance attacks lasting up to 10 minutes, often accompanied by transient visual disturbances, syncope, diplopia, and falls. Following AHA/ASA guidelines, secondary prevention with aspirin, clopidogrel, or dual antiplatelet therapy (DAPT) was effective, as 93.2% of patients experienced no recurrences during follow-up.

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Case report on Horizontal direction changing Nystagmus in Patients with Left Cerebellar-Medullary Stroke

Early treatment of nystagmus after stroke, related to the NPH and medial vestibular nucleus, enhances outcomes.

Introduction – Horizontal nystagmus is an involuntary eye movement characterized by rhythmic oscillations in a horizontal plane. In the context of left cerebellar-medullary strokes, particularly lateral medullary syndrome, it can result from damage to the vestibular nuclei or their connections to the cerebellum. This type of nystagmus typically beats away from the lesion, with the drift velocity directed toward the affected side, and its intensity can vary with eye position and fixation.[1] These patterns are critical for diagnosing and managing vestibular dysfunction following a stroke. This study details a patient with a posterior inferior cerebellar artery (PICA) stroke who exhibited horizontal direction-changing nystagmus alongside a complex clinical phenotype.

Case presentation – A 78-year-old man with a history of hypertension presented with acute vertigo and gait imbalance. Neurological examination revealed dysphagia, left-sided ataxia, and left lateropulsion. He exhibited fast right-beating nystagmus in the primary and right gaze, with slower left-beating nystagmus in the left gaze. No significant changes were noted after fixation removal or the head-shaking test, and the head impulse test was unremarkable.

Initial CT and CT angiography showed no acute changes, but leftward conjugate eye deviation was observed. The patient received intravenous Alteplase (0.9 mg/kg) approximately four hours after symptom onset. Subsequent cardiovascular evaluations were unremarkable, and Aspirin was started at 300 mg daily, later reduced to 100 mg. MRI confirmed an acute stroke in the left posterior inferior cerebellar artery (PICA) territory, involving the dorsal medulla and cerebellum (Figure 1). Spontaneous nystagmus improved by the fifth day and nearly resolved by two weeks. The patient was discharged to rehabilitation, with long-term EKG monitoring for atrial arrhythmia. At the six-month follow-up, a barely noticeable nystagmus remained in left gaze.

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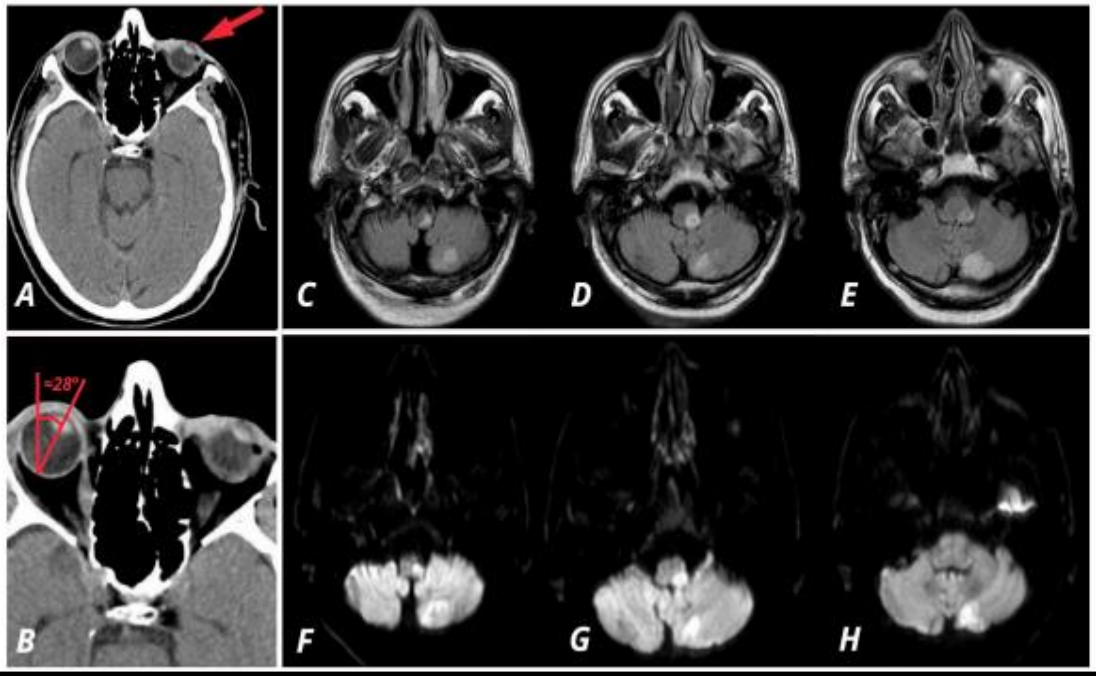

Figure 1. Brain CT and MRI. A: Admission CT shows leftward ocular deviation (arrow); B: Deviation angle; C-E: MRI FLAIR images; F-H: MRI DWI reveals ischemic stroke in the left retro-olivary medulla, extending to the upper medulla and ipsilateral cerebellar hemisphere, affecting the inferior semilunar lobe and the nucleus prepositus hypoglossi, within the left posterior-inferior cerebellar artery.

Discussion –In this study, it was observed that horizontal direction-changing nystagmus (DCN) was attributed to central lesions resulting from a stroke, consistent with existing literature indicating that such nystagmus can be either spontaneous or gaze-evoked and remains unchanged after fixation removal.[2] The lesions in the patient extended into the midline and upper medulla, implicating the nucleus prepositus hypoglossi (NPH). Damage to the NPH, alongside the medial vestibular nucleus, was known to be associated with ipsilateral gaze-evoked nystagmus (GEN). This finding aligns with previous studies that demonstrate a correlation between NPH lesions and GEN, highlighting the critical role of the NPH in horizontal gaze integration.[3,4]

Conclusion –

This study emphasized the crucial roles of the nucleus prepositus hypoglossi (NPH) and medial vestibular nucleus in horizontal direction-changing nystagmus (DCN) following

stroke. The favorable outcomes after treatment highlight the importance of early recognition and intervention.

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