



Radiographic horizontal gaze deviation in the setting of acute PICA territory ischemia: A potential mimic of large vessel occlusion

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ABSTRACT

Purpose: Horizontal gaze deviation (HGD) is a predictor of acute large vessel occlusion (LVO) and helps to expedite the triage of patients to CTA and endovascular-capable sites. Patients with acute cerebellar ischemia, particularly involving the PICA territory, can also exhibit HGD.

Materials and methods: We reviewed 2260 CTA stroke assessment cases between January 2016 and May 2020. Forty-six patients with CTA-proven acute PICA occlusions were identified and compared with 114 patients with acute LVO (ICA, M1, and M1/2). Both clinical and radiographic HGD were examined. The degree of radiographic HGD was measured for each patient. Site of ischemia was confirmed on subsequent MRI.

Results: Of the 46 patients with acute PICA occlusions, 20 (43.5%) patients had radiographic (+) HGD with either ipsilateral or contralateral gaze deviation, 6 of whom (13.0%) displayed clinical HGD. Of the 114 patients with LVO (control group), 72 (63.2%) patients had radiographic (+) HGD, all ipsilateral, 49 of whom (68.0%) displayed clinical HGD. The mean degree of HGD between PICA and LVO were 30.0° vs. 22.9°, respectively, $p < 0.001$; AUC = 0.68.

Conclusion: Patients with acute PICA occlusion can exhibit either ipsilateral or contralateral HGD and a higher degree of HGD than LVO occlusion on NECT. In hyperacute stroke, the presence of radiographic HGD $> 30^\circ$ in the absence of ischemic changes in the MCA territory should prompt clinicians to closely evaluate for features of early ischemic changes in the cerebellar hemispheres that suggest acute PICA occlusion.

1. Introduction

Ipsilateral horizontal gaze deviation (HGD), defined as a transient or sustained shift in horizontal gaze toward the same side of ischemia, is among the most common clinical signs of acute ischemic stroke and often suggests ipsilateral frontoparietal ischemia from large vessel occlusion (ICA, M1, M1/2) [1]. On non-enhanced computed tomography (NECT), radiographic HGD can be a useful tool for alerting the stroke team to acute large vessel occlusion (LVO) and thus expediting the transport of patients to endovascular therapy (EVT) capable sites [1,2].

With the expansion of the treatment window for acute ischemic stroke proposed by landmark trials such as DAWN [3] and DEFUSE3 [4], triaging all potential candidates to EVT-capable sites threatens to

overwhelm the system with non-LVO strokes and stroke mimics. Identification of acute LVO mimics on imaging may therefore help to streamline selection of patients for the EVT pathway.

In a prior study, we identified that acute posterior inferior cerebellar artery (PICA) occlusion is a potential mimic of acute LVO on imaging [2]. Acute PICA occlusions do not have as obvious clinical deficits in the hyperacute setting. Differentiating these from stroke syndromes that are mild to moderate in intensity can therefore prove challenging for non-stroke specialists.

Several case reports have suggested that HGD can be seen in acute cerebellar infarction on neurological exam [5,6]. However, the degree of radiographic HGD in acute PICA infarctions has not been systematically examined. To the best of our knowledge, this is the first study to

Abbreviations: IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; HGD, horizontal gaze deviation.

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investigate the severity of HGD in acute PICA territory ischemia and whether measuring the degree of HGD is a useful tool in ruling out this mimic of LVO on imaging.

2. Methods

2.1. Patient characteristics

We reviewed 2004 acute stroke patients admitted for treatment at our regional comprehensive stroke center (Hamilton General Hospital) from January 2016 to May 2020, and identified 50 patients with acute PICA occlusions. For our purposes, PCA, midbrain and pontine territory infarcts, any of which could potentially result in gaze abnormalities, were not included in our analysis.

All patients were assessed by a stroke neurologist upon arrival and underwent NECT head and computed tomography angiography (CTA) from the aortic arch to vertex to confirm presence and location of vessel occlusion, infarct location, and Alberta Stroke Program Early CT Score (ASPECTS). Two patients were excluded from the study due to either the presence of an acute hemorrhagic stroke or the inability to determine the angle of eye deviation on initial scans because of significant motion artifact. Two additional patients with a previous history of strabismus and a previous seizure history were also excluded from the study. The remaining 46 patients were compared with a control group of 114 patients with CTA-proven acute LVO (ICA, M1, and M1/2). Territories of ischemia or infarction were confirmed by subsequent MRI studies. In 5 cases where MRI was not obtained, follow-up CTs were examined.

Patient demographics such as age, sex, and clinical presentation were collected. Stroke severity was classified by the National Institute of Health Stroke Scale (NIHSS) score at time of presentation (NIHSS_{pre}). This study was approved by the local ethics committee.

2.2. Assessment of horizontal gaze deviation

Horizontal gaze deviation (HGD) was determined for both globes from the initial NECT head obtained at the time of initial clinical presentation with the method proposed by Coffman et al. 2015 [5]. Axial images were used to measure angles of gaze deviation by a radiologist (NJ) who, although not blinded to the patient's data, completed all measurements before reviewing the patient chart and CTA for final diagnosis.

An objective and reproducible measurement for HGD was used, mitigating the potential for bias. The first line was drawn antero-posteriorly through the midline nasal structures; the second line was perpendicular to the midline; and the third line was drawn through the horizontal axis of each lens [2]. The angle of deviation was then calculated for each orbit at the intersection of the second and third lines [2]. A representative case of HGD in the PICA group is shown in Fig. 1.

The average HGD for both eyes was obtained for each patient. Radiographic (+) HGD was considered pathological when the average ocular deviation equaled or exceeded 10°, which was greater than 1.96 standard deviation above a reference group mean from our previous study determined by 21 'normal' patients with negative NECT and CTA [2]. Those with no eye deviation (<10°) or non-conjugate eye deviation were considered (−) HGD.

2.3. Statistical analysis

The study population was dichotomized into patients with acute PICA occlusions versus acute LVO. Baseline characteristics and outcome measures were compared between cohorts. Chi-square was used for categorical data, and a univariate ANOVA was used for continuous data to compare differences in the clinical and imaging parameters between the two groups.

A chi-squared test was conducted to determine if the relative frequency of HGD was different between the PICA and the LVO groups. A

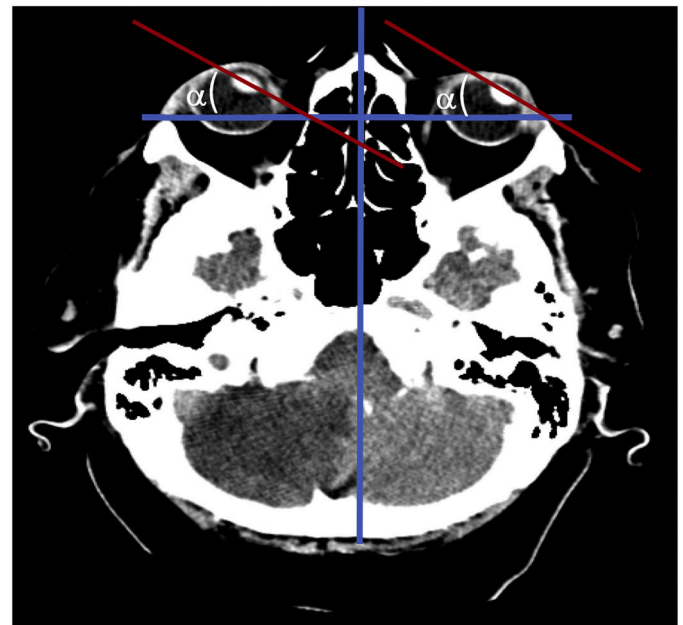


Fig. 1. Measuring gaze deviation (α) on non-contrast CT scan of the head in a stroke code patient presenting to the emergency department.

ROC analysis was conducted to determine if there was an ideal cut-off between the two groups. Individual records that were labelled positive for HGD were selected to compare the average degree of deviation between PICA and LVO patients in our sample. Statistical significance was set at p -value ≤ 0.05 . The statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical features

There were 85 males and 75 females with a median age of 67.4 years old (range: 21–95) included in the study. There was a disproportionately higher number of male patients in the acute PICA occlusion group (33 M, 13F), whereas the male to female ratio was similar in the LVO group (52 M, 62F).

Patients with PICA occlusion had a lower median NIHSS than those with LVO (2 vs.16, $p < 0.001$). A cardioembolic source was more common in the PICA group than in the LVO group (69.6% versus 18.4%, $p < 0.001$). In the PICA group, the median time from symptom onset to NECT was 9.5 h (95% CI: 1.5–72); while in the LVO group the median time from symptom onset was 4.5 h (95% CI, 1.5–6.0), $p = 0.09$. There was no significant difference in the time from symptom onset to NECT between patients with and without HGD in either PICA or LVO group. All HGD resolved on follow-up imaging for PICA group (median, 4 days after admission). The clinical characteristics of the two groups are shown in Table 1.

3.2. Presence of clinical and radiographic gaze deviation in acute PICA occlusion

In the PICA group, 9 out of 46 patients with clinical HGD, 6 out of 9 (66.7%) had radiographic HGD. Conversely, 3 out of 9 (33.3%) with clinical HGD did not have radiographic HGD. Twenty out of the 46 (43.5%) patients demonstrated radiographic (+) HGD (10 ipsilateral and 10 contralateral). Out of the 20 patients, 6 (30.0%) had clinical gaze deviation. In the subgroup with isolated PICA occlusions only, 14 of 25 (56.0%) patients demonstrated radiographic HGD. Whereas, in patients whose lesions were not confined to the PICA territory alone, only 6 of 21

Table 1

Comparison of characteristics between large vessel occlusion and PICA occlusion groups.

| Patient Characteristics | PICA (n = 46) | Large vessel occlusion (n = 114) | p-value |
|---|---------------|----------------------------------|---------|
| Age, median (IQR) | 64.4 (46–94) | 68.32 (21–95) | 0.08 |
| Sex (M:F) | 33:13 | 52:62 | 0.02 |
| NIHSS on admission, median (IQR) | 1–2 (0–21) | 16 (2–30) | <0.001 |
| Stroke etiology (cardioembolic stroke), n (%) | 32 (69.9) | 24 (21) | <0.001 |
| Average degree of HGD, mean (range) | 30.0 (13–50) | 22.9 (8–35) | <0.001 |
| Presence of radiologic HGD, n (%) | 20 (43.5%) | 72 (63%) | 0.03 |
| Ipsilateral vs Contralateral, n (%) | 10:10 (50%) | 72:0 (100%) | <0.001 |

NIHSS, National Institutes of Health Stroke Scale, PICA, posterior inferior cerebellar artery; large vessel (ICA, M1, M1/2); HGD, horizontal gaze deviation.

(28.6%) exhibited radiographic HGD. Thus, the HGD occurrence may be different in these two subgroups. Furthermore, out of the 46 patients with PICA occlusion, 26 (56.5%) patients did not demonstrate radiographic HGD. In this subgroup, 3 (11.5%) out of 26 patients had nystagmus. None of the patients in this subgroup exhibited clinical gaze deviation.

3.3. Presence of clinical and radiographic gaze deviation in acute LVO

In the LVO group, 77/114 patients with clinical HGD, 63.6% (49/77) had radiographic HGD. Conversely, 36.4% (28/77) with clinical HGD did not have radiographic HGD. Seventy-two out of 114 (63.2%) patients demonstrated radiographic (+) HGD, all ipsilateral to the site of vessel occlusion. Out of the 72 patients with radiographic (+) HGD, 49 (68.0%) patients had clinical (+) HGD. Of the 42 (36.8%) patients with LVO but without radiographic HGD, 28 (66.7%) patients had clinical HGD. The rate of clinical HGD in both subgroups regardless of presence or absence of radiographic HGD.

3.4. Degree of gaze deviation between acute PICA and LVO

In patients with (+) HGD, the mean degree of HGD in the PICA group

was 30.0° (95% CI: 26.3°–34.6°) and in the LVO group was 22.9° (95% CI: 21.2°–24.4°), with the difference reaching statistical significance ($p < 0.001$) (Fig. 2). ROC analysis of the sensitivity and 1-specificity of (+) HGD in the prediction of PICA occlusion produced an area under the curve (AUC) = 0.68. The diagnostic performance of a cutoff $>30.0^\circ$ has a moderate sensitivity (41.0%) and better specificity (80.2%) for PICA occlusion.

3.5. Site of infarct in acute PICA stroke

The most frequently involved infarct locations in the PICA occlusion group included the vermis, flocculus, nodule and/or inferomedial aspect of cerebellar hemisphere. Of the 20 patients with radiographic (+) HGD, 5 had infarction in the vermis, 6 in the flocculus, 6 in the nodules and 12 with only cerebellar hemisphere involvement. Ischemia in the lateral medulla was seen in 5 (25%) out of the 20 patients with (+) HGD, in which 3 patients had synchronous ipsilateral vertebral artery occlusion and 2 patients had only ipsilateral PICA occlusion. A summary of characteristics and lesion sites for the 20 patients with acute (+) HGD in the PICA group are shown in Table 2.

4. Discussion

In our series, radiological HGD was observed less often in patients with acute PICA occlusions (43.5%) than in acute LVO (63.2%). In anterior circulation stroke, even a small area of ischemia may result in gaze deviation, if it affects the cortical regions controlling voluntary eye movement, including the frontal eye fields (FEF, Brodmann area), basal ganglia, parietal eye fields, and neighboring temporoparietal cortical regions [7–9]. Gaze deviation in PICA territory strokes may be attributed to ischemia in the flocculonodular lobe, vermis, and lateral medulla [10–16,20].

When radiographic (+) HGD was present, patients with acute PICA occlusion displayed a significantly higher degree of gaze deviation compared to those with large vessel occlusion (30.0° vs. 22.9°, respectively, $p < 0.001$). The mean degree of HGD in our PICA occlusion group is similar to results previously reported by Kattah et al. (2011), where the mean degree of gaze deviation in 9 patients with acute cerebellar infarcts was 27.0° [10].

Clinically, the median NIHSS was much lower in the PICA occlusion group (median NIHSS 1) compared to the LVO group (median NIHSS

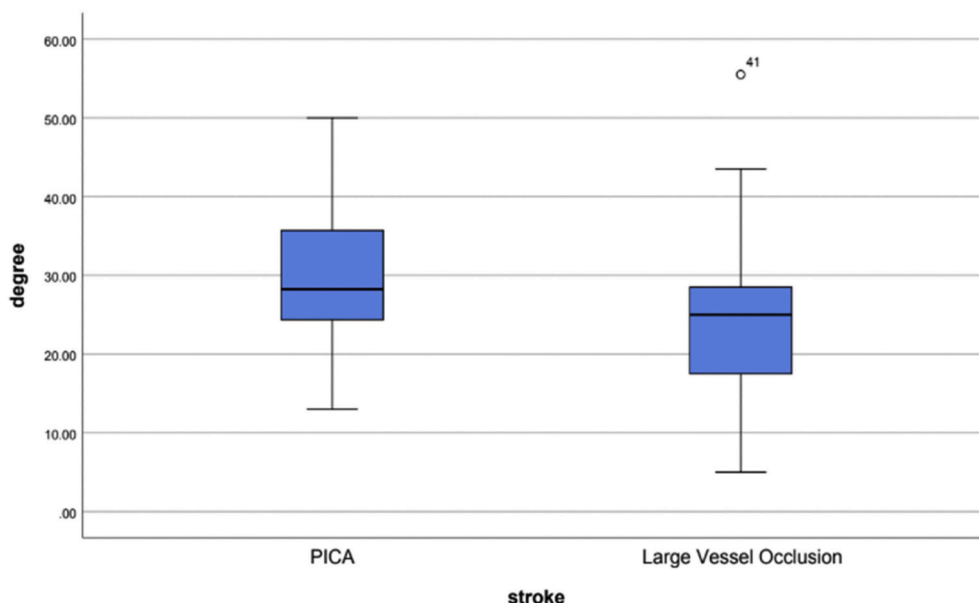


Fig. 2. Boxplot demonstrating distribution of HGD between PICA vs. large vessel occlusion.

Table 2

Summary of the patients with PICA stroke and radiographic (+) HGD.

| Patient # | Sex | Age (y) | Site of occlusion | Lesion site (MR) | NIHSS | Cerebellar limb ataxia | Dysarthria | Vertigo | Nystagmus | Clinical Gaze deviation | Degree of HGD | Direction of HGD relative to occlusion |
|-----------|-----|---------|-------------------|---|-------|------------------------|------------|---------|-----------|-------------------------|---------------|--|
| 1 | M | 46 | PICA + AICA | Vermis flocculus nodule | 1 | + | – | + | + | – | 44.0° | Ipsilateral |
| 2 | M | 66 | PICA | Cerebellar hemisphere | 0 | – | – | + | – | – | 35.4° | Contralateral |
| 3 | F | 79 | PICA + PCA | Cerebellar hemisphere | 7 | – | + | + | + | + | 40.6° | Ipsilateral |
| 4 | M | 61 | PICA + Vertebral | Cerebellar hemisphere | 3 | + | – | + | – | + | 27.5° | Contralateral |
| 5 | M | 56 | Bilateral PICA | Cerebellar hemisphere | 18 | + | + | – | – | + | 50.0° | Ipsilateral |
| 6 | F | 69 | PICA | Flocculus nodule | 2 | – | + | – | – | – | 22.0° | Contralateral |
| 7 | M | 58 | PICA | Cerebellar hemisphere | 4 | + | – | + | – | + | 36.0° | Contralateral |
| 8 | M | 58 | PICA | Nodule | 1 | – | – | + | – | – | 23.0° | Ipsilateral |
| 9 | M | 77 | PICA + Vertebral | Cerebellar hemisphere | 3 | – | – | + | – | – | 15.0° | Ipsilateral |
| 10 | M | 72 | PICA | Flocculus nodule | 1 | – | – | + | – | – | 19.0° | Contralateral |
| 11 | F | 65 | PICA | Vermis | 1 | + | – | + | – | – | 26.5° | Ipsilateral |
| 12 | M | 53 | PICA | Vermis | 2 | + | + | + | + | – | 26.5° | Ipsilateral |
| 13 | M | 66 | PICA + Vertebral | Cerebellar hemisphere | 8 | + | + | + | + | – | 41.6° | Contralateral |
| 14 | F | 72 | PICA + AICA | Flocculus nodule | 4 | + | + | + | – | – | 26.4° | Contralateral |
| 15 | M | 58 | PICA | Cerebellar hemisphere | 3 | – | – | + | – | – | 13° | Contralateral |
| 16 | F | 75 | PICA | Vermis cerebellar hemisphere | 4 | – | + | – | – | – | 35° | Ipsilateral |
| 17 | F | 86 | PICA | Cerebellar hemisphere | 21 | + | + | + | – | + | 25.7° | Ipsilateral |
| 18 | M | 86 | PICA | Flocculus nodule vermis cerebellar hemisphere | 3 | – | + | – | – | + | 33.6° | Ipsilateral |
| 19 | F | 75 | PICA | Flocculus nodule | 4 | – | + | + | – | – | 29.0° | Contralateral |
| 20 | M | 69 | PICA | Cerebellar hemisphere | 4 | + | + | + | – | – | 33.5° | Contralateral |

16), $p < 0.001$. There was also a higher number of male patients in the acute PICA occlusion group (71.7%) than in LVO group (45.6%), $p < 0.02$. Previous studies have shown that patients with LVO and higher NIHSS scores were more likely female patients and were more likely to have radiological deviation [11]. Our study likewise demonstrated a slightly higher number of female patients (55%) in the LVO group with (+) HGD.

We found that radiographic HGD was more commonly identified than clinical HGD in both acute PICA occlusion and LVO groups. For instance, on clinical neurological exam, the rate of clinical gaze deviation in patients with PICA infarction was low, with only 6 out of 46 (13.0%) demonstrating clinical HGD compared to 20 out of 46 (43.5%) demonstrating radiological (+) HGD. Likewise, in patients with LVO, 49 out of 114 (42.9%) demonstrated clinical HGD, compared to 72 out of 114 (63.2%) patients with radiological (+) HGD. Patients often close their eyes during CT scanning, and fixation removal may therefore enhance the manifestation of neurological abnormalities [1,10].

All patients with LVO and radiographic HGD demonstrated ipsilateral HGD, while those with PICA occlusion and radiographic HGD displayed both ipsilateral and contralateral HGD in equal distribution. Prior case reports also described either ipsilateral or contralateral gaze deviation in patients with PICA territory stroke. Fukutake et al (2008) reported two patients with contralateral HGD on neurological examination, in which the vermis was affected [6]. Pierrot-Deseilligny et al (1990) reported 1 patient again with an infarct in left PICA territory, mainly involving posteroinferiorly part of the vermis and left cerebellar hemisphere, demonstrating ipsilateral deviation during eyelid closure [18]. Nishimura et al. (2015) showed that radiographic HGD in 9 (81.8%) out of 11 acute PICA territory infarct patients was directed contralateral to the infarcted side [19].

The mechanisms resulting in either ipsilateral or contralateral HGD in acute PICA occlusion are complex and unclear, but have been postulated by Solomon et al. [12] In ipsilateral gaze deviation, damage to the inferior cerebellar peduncle may interrupt inhibitory climbing fibres projecting from the contralateral inferior olive. Following, there is an increase in the Purkinje cell activity within the flocculus, leading to increased inhibition of the ipsilateral vestibular nucleus and subsequent relative increase in the contralateral vestibular tone. The contralateral vestibular nucleus excites the ipsilateral abducens nucleus and contralateral oculomotor nucleus, and the eyes deviate toward the side of the lesion.

Contralateral gaze deviation is not well understood, but is thought to be a result of disruption in the pathway involving deep cerebellar nuclei. A lesion within the vermis may disrupt vermal Purkinje cells, which normally inhibit the ipsilateral caudal fastigial nucleus. This leads to increased ipsilateral caudal fastigial activity, ultimately resulting in increased activation of the contralateral paramedian pontine reticular formation (PPRF) and medullary reticular formation (MRF) of the brainstem through complex projections passing from the ipsilateral fastigial nucleus across the midline, through the contralateral fastigial nucleus, and around the contralateral superior cerebellar peduncle via fibres of the uncinate fasciculus. The PPRF houses the excitatory burst neurons for the ipsilateral abducens motor neuron while the MRF houses the inhibitory burst neurons for the antagonist muscles (contralateral lateral rectus and ipsilateral medial rectus). Thus increased activity of the contralateral PPRF and MRF may explain gaze deviation away from the lesion and toward the activated PPRF/MRF [12]. Inconsistency in these findings clinically as demonstrated in this work may be attributable to either a combination of variable cerebellar hemispheric contributions to this process and normal variation in vascular territories and

collateralization. By contrast, we noted all vermian infarcts to impart ipsilateral horizontal gaze deviation presumably as there is less redundancy in the small anatomically territory with densely-packed climbing fibres. The majority of flocculonodular infarcts imparted contralateral gaze deviation with or without vermian involvement, and such lesions are thought to invite a relative increase in contralateral vestibular activity.

In our study, 4 out of 9 patients (44.4%) with ischemia in the vermis demonstrated ipsilateral gaze deviation. Two patients with both vermis and flocculonodular lobe ischemia also demonstrated ipsilateral HGD. Furthermore, the presence of ipsilateral HGD may also be explained by ischemia in the lateral medulla (lateral medullary syndrome), which is usually caused by occlusion of the ipsilateral vertebral artery and/or PICA [15–17]. The mechanism proposed includes disruption of the connections from the paravermian region of the cerebellum to the PPRF, where the last supranuclear stage of the lateral gaze pathway occurs [15]. In our study, 5 of the 20 patients with radiological (+) HGD had lateral medullary infarcts: 2 patients displayed ipsilateral HGD, and 3 displayed contralateral HGD, suggesting different ocular outcomes depending on the intricacy of input from multiple neurological networks in balancing vestibular tone.

Interestingly, one patient with bilateral PICA infarctions demonstrated gaze deviation toward the side with larger territory involvement. This finding adds another layer of complexity, suggesting infarct volume also plays a role in determining presence of gaze deviation. Further studies using MRI to qualitatively characterized the volume of infarcted territory in acute PICA occlusions may help elucidate this notion.

Despite the multiple mechanisms proposed, pinpointing the specific neuroanatomy involved in a given patient is challenging, since patients were evaluated while the vascular territory was ischemic, but not yet necessarily infarcted. It is therefore difficult to be certain regarding the exact pathophysiology in the hyperacute setting, in the absence of high-resolution perfusion imaging.

Location of infarct and size of infarction may not be the only factors dictating direction of gaze deviation. Another possible explanation for the direction of gaze deviation may be the periodic alternating gaze deviation (PAGD) phenomenon, resulting in the gaze direction alternating approximately every 1–2 min. This observation may share a common pathophysiological mechanism with periodic alternating nystagmus (PAN), which, in monkeys, is reproduced by removal of the nodulus and ventral uvula, an area supplied by the PICA [21]. In this case, the direction of horizontal gaze may correlate with the slow phase of horizontal nystagmus since the fast phases of nystagmus may have diminished when the patient closes their eyes [22,23]. This mechanism serves as a possible explanation for why 5 of the 20 patients with HGD also displayed concurrent ipsilateral nystagmus on clinical exam. The presence of HGD on axial images in PICA strokes may be only the horizontal component of their rotational nystagmus. It would be interesting to assess whether these patients have a vertical component on coronal imaging to account for rotational nystagmus.

There are two identified limitations in our study. Firstly, the study was a single-centre retrospective analysis with single reviewer design. However, the reviewer was blinded to the final diagnosis based on CTA during initial measurement of HGD, and an objective and reproducible method to determine HGD was used rather than subjective visual determination, mitigating potential bias. Secondly, the sample size for CTA proven acute PICA occlusion cases is relatively small and 21 (45.7%) had PICA occlusion in combination with other site(s) of posterior circulation occlusion. Therefore, the rate of HGD occurrence may be different in these two subgroups. Unfortunately, cases of acute PICA strokes are relatively rare and not all the patients undergo CTA for assessment if clinical presentations suggest cerebellar origin. Therefore, we looked at all code stroke patients over a 4-year period and reviewed subsequent imaging (follow-up CT and MR) to ensure the region of ischemia was predominantly in the PICA territory as preliminary analysis. Larger scale prospective analyses are needed with isolated acute

PICA occlusions to further determine the true impact of location of infarcted territory on ocular motor abnormalities.

5. Conclusion

Regardless of the mechanism behind HGD in the setting of PICA infarction, both the degree and direction of gaze deviation may help differentiate PICA infarction from LVO during the hyperacute stroke setting, especially in cases where the clinical presentation is vague or the NIHSS is low. A greater relative degree of radiological HGD, in the absence of ischemic changes in MCA territory, should prompt radiologists to carefully assess for early ischemic changes in the bilateral cerebellar hemispheres, an area which is usually fraught with artifacts and difficult to assess. Establishing the ability to distinguish LVO from a potential mimic may lead to more efficient utilization of stroke pathway resources.

Declaration of Competing Interest

None.

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