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Thin Section Magnetic Resonance Diffusion Weighted Imaging in the Detection of Acute Infratentorial Stroke.

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Abstract

Introduction: Magnetic resonance diffusion-weighted imaging (DWI) is the most accurate technique available for demonstrating acute infarction; however, false negative DWI is higher in the infratentorium due to the limited spatial resolution with conventional 5 mm DWI. The aim of this study was to compare 5 mm DWI with 3 mm DWI in the detection of acute infratentorial infarction.

Method: A 3 mm DWI sequence of the infratentorium was incorporated into the conventional MRI stroke protocol for the evaluation of patients with vertebrobasilar stroke-like deficits. The 5 mm and 3 mm DWI sequences were assessed by two neuroradiologists who were blinded to the clinical findings. Sensitivity and specificity analysis was then performed against the final clinical diagnosis.

Results: The sensitivity for detection of infratentorial infarction was 81.1% for 5 mm DWI and 94.6% for 3 mm DWI and the specificity was 100% for 5 mm DWI and 97.7% for 3 mm DWI. The false negative rate in detection of infratentorial infarcts was 5.6% for the 5 mm sequence and 1.6% for the 3 mm sequence. The six 5 mm DWI false negative cases (4.8%) were less than 9 mm in diameter (3 - 8 mm, average 4.67 mm) and located in the brainstem. This supports the hypothesis that small lesions may not be detected on 5 mm DWI due to partial volume averaging.

Conclusion: Where there is clinical suspicion of infratentorial infarction, 3 mm DWI of the infratentorium adds sensitivity compared to 5 mm DWI with only a small reduction in specificity.

Key words: infratentorial infarction, diffusion-weighted magnetic resonance imaging

Introduction

Small infarcts in the infratentorium, particularly the brainstem, can cause greater morbidity compared to the supratentorium because of the high density of cranial nerve nuclei and white matter tracts. Early and accurate detection of acute infarction has important therapeutic, prognostic and secondary prevention implications.

Although magnetic resonance diffusion-weighted imaging (DWI) is the most sensitive and specific technique available for demonstrating acute infarction [(1)], there have been multiple studies demonstrating the limitations of the technique [(2-11)]. Negative DWI has been reported between 0 - 21% in acute stroke [(3)] and between 18 - 100% in transient ischaemic attack (TIA) [(12)]. The DWI false negative rate in acute stroke is higher in the vertebrobasilar circulation than in the anterior circulation with reported rates ranging from 0 - 42.9% [(3)]. This has been attributed to a number of factors including small lesion size, scanning within the first 24 hours, TIA, non ischaemic pathologies; and the technical limitations of DWI, particularly slice thickness, isolated axial plane imaging and increased susceptibility from the skull base and adjacent air cells [(2-11, 13-17)]. Negative DWI in TIA is not uncommon and is thought to be due to small lesion size, and that reversible ischaemia can result in absent or faint DWI signal abnormality [(17-24)].

Our institution incorporated 3 mm axial DWI, apparent diffusion coefficient (ADC) and T2 fat saturation sequences of the infratentorium into the conventional whole brain MRI stroke protocol for the evaluation of patients presenting with symptoms and signs of vertebrobasilar ischaemia. The aim of this study was to compare the conventional 5 mm DWI sequence with 3 mm DWI in the detection of infratentorial infarction and to determine whether incorporating 3 mm DWI of the infratentorium into the standard stroke protocol was justified.

Methodology

Ethics approval was obtained from our institution's research and ethics committee prior to the commencement of the study. Over a period of 17 months from February 2013 to June 2014, all patients undergoing an MRI for evaluation of vertebrobasilar stroke-like deficits were included in the study. Presenting clinical features included cranial nerve palsies, vertigo, ataxia, upper and lower limb sensorimotor deficits localising to the brainstem or cerebellum, and reduced conscious

state. All patients were evaluated by the Emergency Department and Stroke Unit at presentation and underwent immediate CT to exclude haemorrhage, major territory infarction and other non ischaemic pathologies. Stroke-directed MRI, including thin slice imaging directed to the posterior fossa, was subsequently performed.

Patient demographics, clinical presentation data, time to MRI from symptom onset and the final clinical diagnosis were obtained from Ambulance Victoria, the Stroke Unit records and from the patient's medical history.

MRI examinations were performed in either the inpatient or outpatient setting as determined clinically by the Stroke Unit. Although high DWI signal in brain ischaemia is maximal within the first 10 days, it can remain hyperintense for 57 days on average, with normalisation occurring between 34 - 138 days from stroke onset [(25)]. Patients were excluded from the study if the time from clinical onset to MRI was greater than 60 days.

All imaging was performed at 1.5T (Avanto, Siemens Healthcare) with a 12 or 32 channel Head Matrix coil. Our institution's standard MRI stroke protocol includes sagittal T1, slice matched axial 5mm thick T2, FLAIR, T1 and DWI, as well as axial susceptibility weighted imaging (SWI) and a Time of Flight (TOF) 3D Multislab MR angiography. Both the 5 mm and 3 mm DWI sequences employed an echo planar imaging (EPI) sequence with b-values of 0 and 1000s/ mm^2 for diffusion weighting. Parallel imaging with an acceleration factor of 2 was employed for each sequence. Conventional 5 mm DWI parameters were: TR/TE 3000/89ms, slice thickness/interspacing 5/2.0mm, FOV 230 x 230mm^2, phase/frequency resolution 192 x192, voxel size 1.2 x 1.2 x 5.0 mm^3, bandwidth 1240 Hz/Px, echo spacing 0.9 ms, EPI factor 192. Whole brain coverage was achieved in 19 slices with an acquisition time of 59 seconds. The 3 mm DWI parameters were: TR/TE 2500/80ms, slice thickness/interspacing 3/0.3mm, FOV 200x200mm, base resolution 144 x144, voxel size 1.4 x 1.4 x 3.0 mm^3, bandwidth 1388 Hz/Px, echo spacing 0.8 ms, EPI factor 144. Posterior fossa coverage was achieved in 19 slices with an acquisition time of 1 minute 49 seconds. The 3 mm axial T2 FS sequence was performed with the same slice thickness, spacing and positioning.

Two neuroradiologists blinded to the clinical presentation independently examined the de-identified MRI examinations, assessing the 5mm DWI and 3mm DWI sequences in two separate sittings. The sittings were separated by 4 weeks to minimise recall bias.

The presence of DWI signal abnormality was initially recorded using a five point scale of definitely negative (1), probably negative (2), equivocal (3), probably positive (4) or definitely positive (5). Equivocal or positive DWI abnormality was correlated with the ADC, T2, FLAIR and SWI sequences, which were similarly assessed using a five point scale. The datasets were subsequently dichotomised: positive (consisting of probably and definitely positive subgroups) and negative (consisting of probably and definitely negative subgroups). Equivocal and discordant results were resolved by consensus. Information on lesion location and size, multifocality, and vascular territory involvement was also recorded.

Image quality and parenchymal artefact were assessed using five point scales. Image quality was rated as follows: non diagnostic (1), poor (2), average (3), good (4) and excellent (5); and then dichotomised as non diagnostic (which consisted of the non diagnostic and poor subgroups) and diagnostic (which consists of the average, good and excellent subgroups). Parenchymal artefact was rated as follows: definitely none (1), minor (2), mild (3), moderate (4) and severe (5); and then dichotomised to no significant artefact (which consisted of the none, minor and mild subgroups) and significant artefact (which consisted of the moderate and severe subgroups). High DWI signal, typical of artefact, at the pial-CSF interface and near the skull base was commented on but classified as artefact.

The final clinical diagnosis was used as the best available reference standard for statistical analysis and was determined by the Stroke Unit based on clinical features as well as CT, MRI, cardiac, vascular, cerebrospinal fluid (CSF) and blood investigations. The final clinical diagnosis was categorised as either acute infratentorial infarction or other, which included TIA, chronic infarction and non-ischaemic pathology. Cases demonstrating isolated acute supratentorial infarction or non-ischaemic pathology such as haemorrhage (acute or chronic), demyelination or tumour, were excluded from analysis.

Sensitivity, specificity and receiver operator characteristic (ROC) area under the curve statistical analysis was performed on the consensus ratings for both the 5 mm DWI and 3 mm DWI sequences against the final clinical diagnosis and compared using the chi-square test and Fisher exact test. Results were considered statistically significant when $p < 0.05$. Kappa statistic was used to assess inter-observer agreement between the DWI, image quality and artefact readings.

Results

Between February 2013 and June 2014, 181 patients underwent an MRI examination for investigation of clinical features of vertebrobasilar stroke (78 females, 103 males). The average patient age was 66.4 years (23 - 89 years old).

Twenty-three patients were excluded because MRI was performed more than 60 days after clinical onset, five patients were excluded due to non-ischaemic infratentorial pathology (four haemorrhage and one demyelination) and 28 patients were excluded due to isolated acute supratentorial infarction.

For the remaining 125 patients, the average time to MRI after symptom onset was 8 days (7 hours - 60 days, median 4 days, IQR 2.25 - 8), with 96 (76.8%) examinations performed within 10 days of symptom onset.

There was almost perfect inter-observer agreement between the two readers for the DWI readings with Kappa scores of 0.898 for the 5 mm DWI sequence and 0.925 for the 3 mm sequence.

Thirty eight out of 125 (30.4%) patients demonstrated positive DWI signal (3mm and/or 5mm) in the infratentorium and 87 patients (69.6%) had negative DWI following consensus (Table 1). Of the 38 positive DWI cases, there were 29 true positive cases (76.3%) where DWI abnormalities were identified by both readers in the clinically appropriate region on both the 5 mm and 3 mm sequences.

Nine out of the 125 cases were discordant, of which six were false negative on 5 mm DWI, two were false positive on 3 mm DWI and one was false negative on 3 mm DWI (Table 1 and 2). There was a solitary 5 mm and 3 mm DWI false negative case that was diagnosed as an acute stroke clinically. In this instance, both readers rated image quality as good with no or minor artefact on the two sequences.

The sensitivity for detection of infratentorial infarction was 81.1% and 94.6% for 5 mm DWI and 3 mm DWI respectively. The specificity for detection of infratentorial infarction was 100% for the 5 mm sequence and 97.7% for the 3 mm sequence.

There were 26 cases (20.8%) with a diagnosis of TIA but none of these demonstrated positive DWI signal on either the 5 mm or 3 mm sequences. The average time to MRI for these cases was 8.3 days, with 79.2% (19 cases) performed within 10 days of symptom onset.

Despite the extra scan time (1 minute 49 seconds for the 3 mm sequence vs 59 seconds for the 5 mm sequence), there was no significant difference in image quality (p=0.008 and p=0.048 respectively). Inter-observer agreement was almost perfect for the 5mm DWI images (Kappa 1.0) and substantial for the 3mm DWI images (Kappa 0.66). Image quality was assessed as non-diagnostic in 3.2% of the 5 mm DWI cases and 2.4% of the 3mm DWI cases.

A higher proportion of the 3 mm DWI cases (5.6%) were classified as significant artefact by one reader compared to 3.2 % of the 5 mm cases (p=0.015). There was no significant difference in artefact between the two sequences for the second reader (p=1.000), with 2.4% demonstrating significant artefact.

Discussion

Our results demonstrate that 3 mm DWI provides a higher sensitivity than 5 mm DWI in the detection of infratentorial infarction with only a small reduction in specificity. These results are in keeping with reports in the literature [10, 11].

Sorimachi et al [11] reported a 6 mm DWI false negative rate of 8.1% in infratentorial infarction with 3 mm DWI subsequently detecting 85.7% of these cases (12 of 14). All of the scans were performed within 24 hours of symptom onset and a follow up MRI was performed at 10 days if no obvious ischaemic lesion was identified. This differed from our study where the time to MRI was variable and a follow up MRI could not be performed due to resource allocation.

Nakamura et al [10] demonstrated improved accuracy in the diagnosis of stroke subtype using the TOAST classification [26] with 3 mm DWI. They used contrast to noise ratio measurements to demonstrate higher lesion conspicuity with 3 mm DWI, which differed from our study. However, the standard deviation in these measurements was large due to high background noise which limited their significance.

False negatives with conventional DWI are more frequently demonstrated with small infratentorial infarcts in the first 24 hours where lower resolution fails to detect the lower signal-noise ratio lesions [27]. Our false negative rate in detection of acute infarcts in the infratentorium was 5.6% for the 5 mm sequence and 1.6% for the 3 mm sequence. This compared favourably with Sorimachi et

al (8.1% for 6 mm DWI and 1.2% with 3 mm DWI) and with other reports in the literature ranging from 0 - 21% [28].

The sensitivities in our study compared favourably with those reported by Nakamura et al of 78% for 5 mm DWI and 100% for 3 mm DWI, which suggests added diagnostic value of 3 mm DWI in the detection of posterior fossa acute ischaemic stroke.

The six 5 mm DWI false negative cases (4.8%) detected on 3 mm DWI were less than 9 mm (3 - 8 mm, average 4.67 mm) and located in the brainstem (Table 3, Figure 1-3). This suggests that smaller sized DWI lesions may not be detected on 5 mm DWI due to partial volume averaging.

The solitary 3 mm DWI false negative case had a small focus of high DWI signal in the appropriate clinical region on the 5 mm DWI sequence. The 3 mm DWI sequence was considered probably negative as the high signal was faint and ill-defined and there was no corresponding signal abnormality on the other sequences (Figure 4). In this instance, each reader rated image quality as diagnostic and artefact mild on both sequences.

When assessing the trade off between sensitivity and specificity with ROC statistics, the 3 mm sequence had a higher ROC value indicating an overall improved performance compared to the 5 mm sequence (0.96 vs 0.92 respectively) but this was not statistically significant (p=0.1998). In this study, the reduction in specificity of 3 mm DWI (97.7%) compared to 5 mm DWI (100%) was only minimal. This is a common and not unexpected outcome from a statistical point of view when sensitivity is increased. The reduction in specificity was due to two 3 mm DWI false positive / 5 mm DWI true negative cases (1.6%).

The first patient with a 3 mm DWI false positive lesion presented with two weeks of intermittent dizziness and left limb weakness. MRI 14 days after symptom onset demonstrated a subtle 4 mm high DWI lesion in the right pons which could explain the patient's symptoms. Despite this, the final clinical diagnosis at discharge was vestibular migraine. The accuracy of the clinical diagnosis in this case could be questioned.

The second patient with a false positive 3 mm DWI lesion presented with ataxia and encephalopathy due to an acute decompensation of previously undiagnosed alcoholic cirrhosis. The patient developed sepsis, profound metabolic derangement, multiple organ failure and subsequently died. A diagnosis of stroke could not be confirmed clinically.

Our negative rate for both the 5 mm and 3 mm DWI sequences in TIA of 100% is at the highest end of those reported in the literature (18 - 100%) [12]. This in part could be explained by the variable time to MRI from symptom onset.

There were four 5 mm DWI cases that demonstrated bilateral, symmetric high DWI signal regions measuring 4 - 5 mm in the paramedian midbrain adjacent to the interpeduncular cistern (Figure 5). These were all scanned within 10 days of symptom onset. On consensus review, this was considered artefact given the bilateral symmetric distribution, location at the pial surface, faint intensity and lack of corresponding signal abnormality on the 3 mm DWI and other sequences. Furthermore, the location of the lesions did not correlate with any of the four patient's clinical presentation. Being able to recognise this as artefact on the 5 mm sequence, and a possible source of future false positives, may be important.

In one case, the 3mm DWI sequence demonstrated a 10mm high signal lesion in the left pons. The same lesion on the 5mm DWI sequence was much less conspicuous and significantly smaller, measuring 4 mm (Figure 6). There were no instances where the improved resolution of 3 mm DWI revealed a cluster of multiple small infarcts that appeared as a single lesion on 5 mm DWI.

Even when there is strong clinical suspicion of infratentorial infarction, whole brain coverage with DWI is critical given there were 28 cases in our study (22.4%) that demonstrated isolated acute supratentorial infarcts. Whole brain coverage with 3 mm DWI would require a significantly longer scan time (4 minutes 15 seconds on our magnet) which would likely result in an increase in movement artefact and thus may not add clinical benefit.

There were several limitations of this study. Firstly, the time to MRI from symptom onset was not uniform, with significant delay (>10 days) between the time to MRI and symptom onset in 23.2% of patients scanned. During this period, high DWI signal in ischaemia begins to fade and the false negative DWI rate may increase. This could not be avoided at our institution due to limited resource allocation in the public health system. Secondly, follow up MRI in false negative cases was not performed to assess whether a DWI or T2 / FLAIR lesion subsequently became apparent in the clinically appropriate region. Thirdly, with no gold standard for the diagnosis of acute stroke, the final clinical diagnosis was the best available reference standard which was not determined independent of the diagnostic test being evaluated. Finally, the indications for imaging were not standardised and may have varied between referring clinicians.

Conclusion

Where there is clinical suspicion of infratentorial infarction, 3 mm DWI of the infratentorium adds sensitivity compared to conventional 5 mm DWI with only a small reduction in specificity. This justifies the extra-scan time and could be incorporated into routine diagnostic algorithms where there is a clinical suspicion of acute infratentorial stroke.

Tables

Table 1. Classification of cases with a final diagnosis of acute infratentorial infarction.

	3 mm DWI True Positive	3 mm DWI False Negative
5 mm DWI True Positive	29	1
5 mm DWI False Negative	6	1

Table 2. Classification of cases without a final clinical diagnosis of acute infratentorial infarct.

	3 mm DWI False Positive	3 mm DWI True Negative
5 mm DWI False Positive	0	0
5 mm DWI True Negative	2	60

Table 3. Characteristics of six patients with acute infratentorial infarction with false negative 5mm DWI identified on the 3 mm DWI (true positive). The persisting, severe disability † in patient 3 was mainly attributed to a chronic right middle cerebral artery infarct.

Case Number	Age	Sex	Time to MRI from Symptom Onset (days)	Lesion Site	Size (mm)	Symptoms at Follow Up
1	62	F	3	Right midbrain	3	Complete resolution
2	87	M	5	Left midbrain	4	Complete resolution

3	86	M	6	Left midbrain	3	Persistent, severe disability †
4	81	M	8	Left pons	6	Persistent, non-disabling
5	49	M	2	Right medulla	4	Complete resolution
6	51	F	3	Right medulla	8	Persistent, moderate disability

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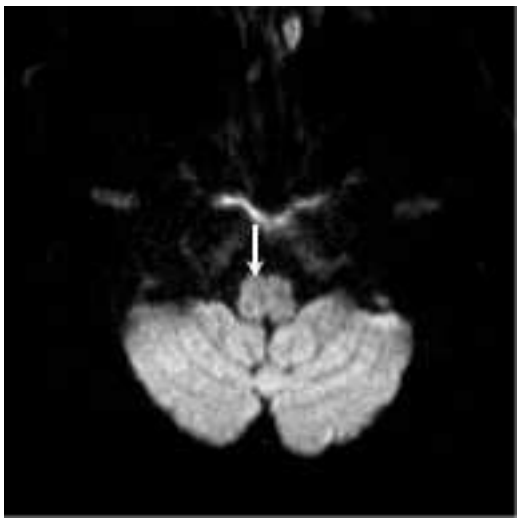
300 **Bibliography**



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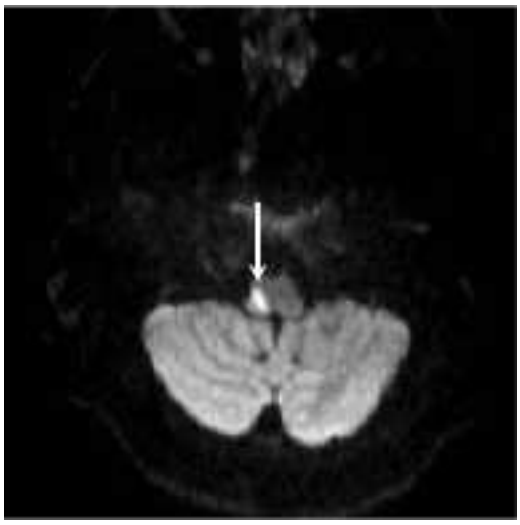

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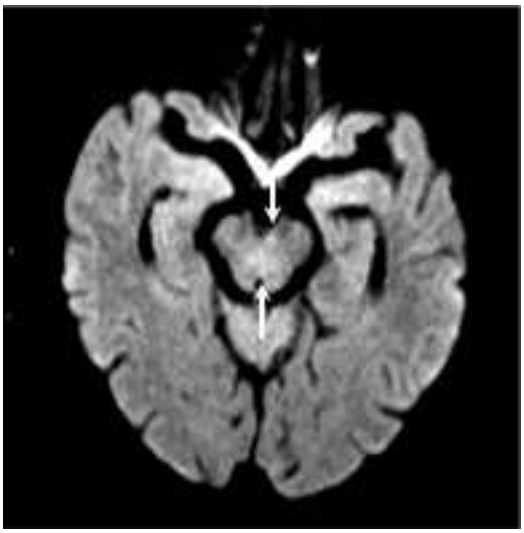

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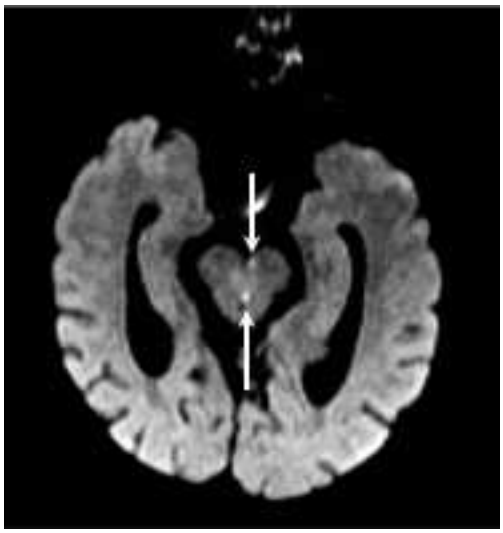

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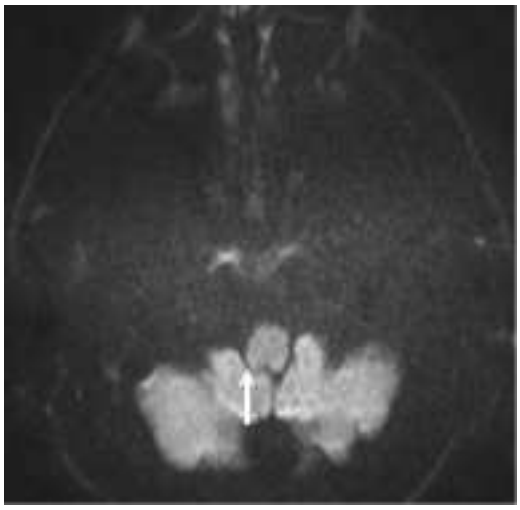

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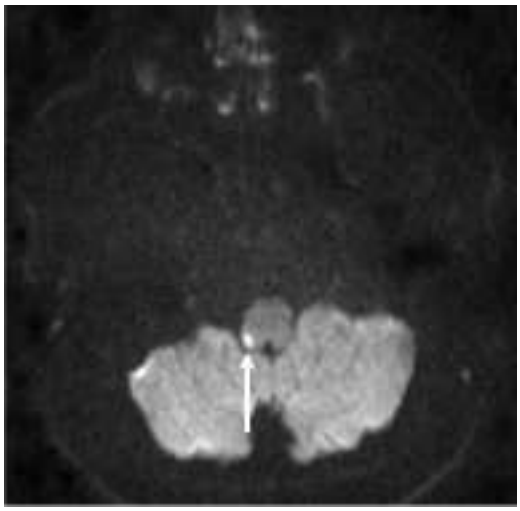

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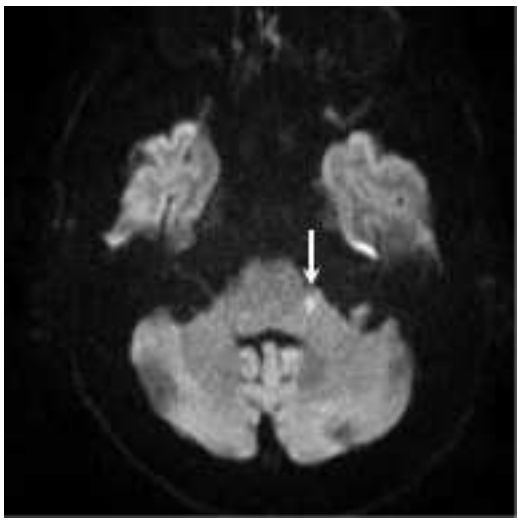

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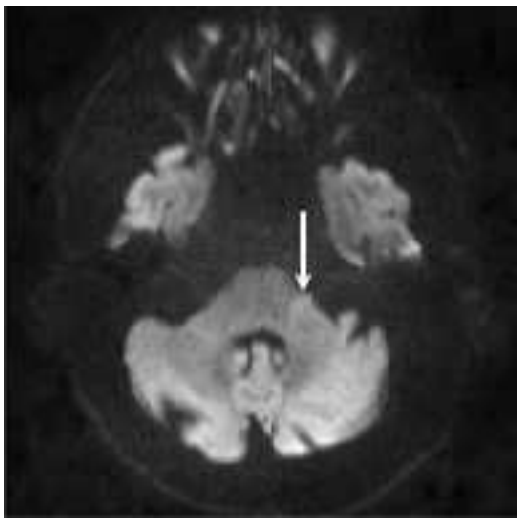

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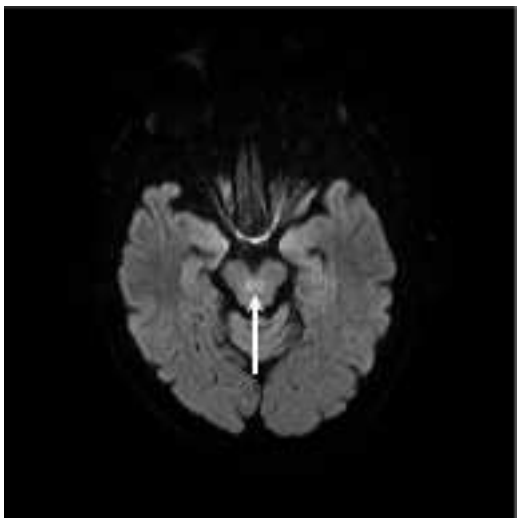

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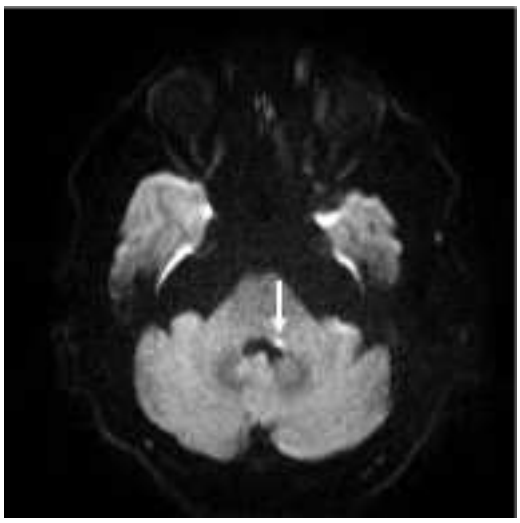

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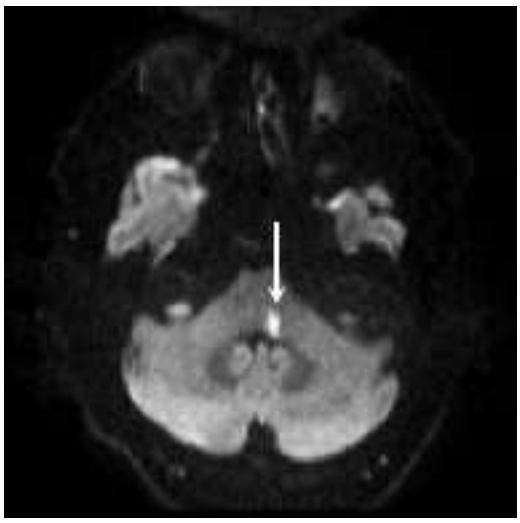

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