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Posterior Circulation Stroke in Manitoba Children: A Population Based Longitudinal Study of Clinical Presentation and Outcome

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Summary:

This study is a retrospective review of a population-based cohort of children with diagnosis of posterior circulation arterial ischemic stroke (PAIS) in Manitoba. Children were consecutively enrolled in the Canadian Pediatric Ischemic Stroke Registry and the Manitoba Pediatric Stroke Database. We examined demographics, clinical and radiological presentation, treatment and outcome of children with PAIS. We also examined the clinical and radiological predictors of outcome in our study cohort using the Pediatric Stroke Outcome Measure (PSOM).

Between 1992 and 2010, 24 patients met inclusion criteria, 54.2% male, and average age 4.9 years. Follow-up data at 24 months was available for 20 patients. For pediatric PAIS in Manitoba, an incidence rate of 1 person per 10,000 if followed for 18 years was estimated. Our reported ratio of PAIS to AIS is 20%, which corresponds with previous data of PAIS comprising 15-20% of AIS with incidence of all AIS being 2.5 - 3/100,000 per year[3-9]. Warning symptoms were present in one-third, and identifiable risk factors found in two thirds of the cohort. We found poor outcomes in aboriginal patients (45.8%, $p=0.003$), high PedsNIHSS score ($p=0.02$), patients with vasculopathy (25%, $p=0.05$), bilateral infarcts (42%, $p=0.003$), large caliber artery infarcts (53%, $p=0.02$) and occipital lobe infarcts (42%, $p=0.04$). Abnormalities found on vascular imaging (performed in 62.5%) trended towards recurrence ($p=0.07$). Outcome at 3, 12 and 24 months was correlated ($p<0.001$).

The incidence rate, as well as predictors of outcome and recurrence, is valuable clinical information that will help direct treatment and prognostication of children with PAIS.

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I) Background:

Ischemic stroke is an increasingly recognized event in the pediatric population[1-3]. Arterial ischemic stroke (AIS) in children has a reported incidence of about 2.5 - 3 /100,000 children per year[3-9]. Previously it was thought that posterior AIS (PAIS) accounts for 15-20% of all pediatric AIS[3]. Recently, Mackay *et al* reported PAIS frequency of 37%[4]. Despite limited literature regarding PAIS, it is believed to differ from anterior circulation strokes in etiology, presentation and outcome[3,5]. PAIS presents non-specifically, with ataxia, vertigo, vomiting and alteration in consciousness, which can delay diagnosis[2,3,6-14].

Head CT, the most common initial imaging modality, is inferior to MRI brain in determining posterior fossa involvement, which can result in missed or delayed diagnosis[1-4,6-13,15]. Cerebral CT and MR angiography (CTA/MRA) are comparable in identifying vascular involvement in PAIS, but have limitations[1-3,4,15]. Conventional catheter cerebral angiogram remains the gold standard for vascular imaging of both circulations[1,15,20].

Risk factors for PAIS are known in adults, but common risk factors in adults such as hypertension and atherosclerosis do not apply to children[4,14]. Risk factors for both populations include coagulopathies, vasculopathies, raised intracranial pressure, cardiac disease, and vasculitis[4]. Dissection of posterior cerebral vasculature, including traumatic vertebral artery dissection, is a frequently reported cause in young adults and children compared to older age groups[3,4].

Little is known about outcome of pediatric PAIS. DeVeber *et al.* identified predictors of outcome in a Canadian cohort of children using the already validated Pediatric Stroke Outcome Measure (PSOM)[19]. AIS and venous thrombosis were separated, but outcomes specific to posterior and anterior circulation were not. In a PAIS specific study by Ganesan *et al.*, 55% of patients were left with no residual impairment at follow up (length of follow up ranged from 6 months-11 years)[3]. The Mackay study followed their cohort for at least 12 months after the initial event, and found recurrence in half of PAIS patients[4]. Mackay *et al.* reported radiographic data, finding normal MRA in 36% of patients after 3 months, and stable MRA findings in 76%, but did not correlate this to clinical outcome[4]. This highlights the need to study PAIS clinical outcomes both in relation to radiographic features, and separately from AIS[3-6,9]. In adults with PAIS, lower scores on the National Institute of Health Stroke Severity Scale (NIHSS) have been linked to better outcomes at 3 months[5]. The pediatric equivalent (pedsNIHSS), has not yet been shown to predict outcome in PAIS specifically[21, 22]. A recent study in adults with PAIS found better outcomes with isolated PCA territory involvement[14].

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Treatment of pediatric AIS has its own challenges. Current approaches are based on small population case-based studies[7,20]. No randomized controlled trials have been completed to date, and at present there is no standard accepted approach to treatment[5-7,10,11]. Severity of neurological sequelae has been clearly outlined and therefore further investigation into more aggressive and targeted treatment is warranted [12,20]. While it has not yet been shown in children that use of anticoagulants such as heparin have prognostic benefit for posterior circulation strokes, current practice is to use these agents in some instances of PAIS, such as older children and adolescents[5,20]. It is not uncommon for PAIS patients, even with moderate infarct size, to manifest increased intracranial pressure often limited to the posterior fossa because of the already crowded nature of this region. It is therefore imperative to monitor patients with PAIS carefully[12]. In addition to watching for clinical signs of elevated intracranial pressure, PAIS is known to recur frequently in the acute period making clinical and radiologic monitoring for stroke recurrence imperative[3].

II) Hypothesis:

We hypothesize the existence of prognostic factors and improved outcomes unique to pediatric PAIS compared to anterior AIS and adult PAIS.

III) Methods:

A retrospective chart review of a population based consecutively enrolled cohort of children, birth to 18 years, from January 1992- December 2010, was completed. To improve case ascertainment, PAIS patients were identified from several sources (ICD 9 and 10 medical record searches, ischemic stroke database at the Winnipeg Children's Hospital (2003 -2010), and the Canadian Pediatric Ischemic Stroke Study Registry database (CPISR) for Winnipeg site which includes Manitoba Health record search (1992 -2002)). Children with a confirmed PAIS diagnosis (by neurologist/radiologist) who received care in Winnipeg met the inclusion criteria**.** Patients with unavailable medical charts or unclear PAIS diagnosis were excluded.

PedsNIHSS, which is already validated for retrospective scoring, was used to retrospectively score presentation severity. Outcome was determined from the 2 year and most recent follow-up clinic visits by the already collected PSOM scores obtained either from the chart or the afore mentioned databases. Patients without available PSOMs were retrospectively scored by reviewing their neurology clinic visit information. For patients without 2-year follow-up (either lost to follow-up or index event less than 2 years before analysis) the most recent follow-up PSOM was used. PSOM is also validated for retrospective scoring[21-23]. Outcomes were categorized as: *good* (PSOM $\leq$3) and *poor* (PSOM $>$3 or death).

For categorical and nominal variables, the Chi-square or Fisher's exact test (for cell count less than 5) was used (significance $\leq$0.05). For continuous variables

we performed Mann Whitney non-parametric test. Following univariate analysis, multivariate models of association using binary logistic regression between significant predictors ($p<0.06$) and outcome were created.

IV) Results:

Twenty-four patients met inclusion criteria, and 54.2% were male. Almost sixty percent (58.3%) of patients were less than 5 years old at index event (average 4.9 years). Based on the 2006 Manitoba population census, for PAIS, an incidence rate of 1 person per 10,000 (or 0.1 per 100,000) if followed for 18 years was estimated for the Manitoba pediatric population. Aboriginal patients comprised 45.8%, and caucasians 37.5% of the study cohort; 12.5% had unknown ethnicities *(Figure 1)*.

Warning symptoms before stroke onset, including vomiting, headache, and dizziness were present in 33% of patients. Seventy-one percent of patients presented with at least one sensorimotor deficit, 75% with impaired level of consciousness and 29% with seizures and or abnormal posturing *(Table 1)*.

In our cohort, 71% of patients had identifiable risk factors. The most common risk factor present was an identifiable vasculopathy, found in 25% of patients. Infection was noted in 21% of patients and trauma and congenital heart disease were each present in 12.5% patients.

All patients had an initial head CT, and 58% were diagnosed by the first CT scan. Those with non-diagnostic initial imaging went onto further studies (either MRI or second CT). MRI brain was subsequently diagnostic in 21%, and second CT diagnosed the remaining 21% of all study patients. The most commonly involved structure was the thalamus followed by the brainstem and other structures *(Figure 2)*. Vascular imaging was performed in 62.5% of patients with 60% abnormal. Fifty-three percent of all infarcts involved large artery territory either alone, or both large and small vessel territories. Basilar tip thrombosis was observed in 3 patients *(Table 2, Figure 4, Figure 5)*.

Average PedsNIHSS was 11 out of 42 at presentation. Eight patients (33%) fell into the “severe” category with PedsNIHSS greater than 15. Average PSOM at 3 months was 1.35 out of 10, which remained relatively stable at 1.2/10 at 12 and 24 months. Twenty of the enrolled patients had follow up at 24 months. Of the four patients without 24-month follow-up, two had index events less than 24 months ago, one patient was a non-Manitoba resident and was followed in his or her hometown, and one patient’s family declined further follow-up after ten months of care. Recurrence was observed in 25% and death in 25% (four deaths in the acute period, and one death due to aspiration pneumonia 15 months after the index event).

Fourteen of twenty-four patients (58.3%) received antithrombotic treatment; 37.5% were anticoagulated with either heparin or coumadin, 33% received antiplatelet therapy, 12.5% received both anticoagulation and antiplatelet therapy.

In univariate analysis, significant clinical predictors of poor outcome at 24 months included aboriginal ethnicity (p=0.003), high initial PedsNIHSS score (p=0.02), bilateral infarction (p=0.003), large caliber artery territory infarctions (p=0.02), presence of vasculopathy (p=0.05), and occipital lobe infarction (p=0.04) *(Figure 2, Table 3)*. Outcome at 3 months and at 12 months correlated with outcome at 24 months with p<0.001. Trends towards poor outcome at 24 months included cerebellar involvement (p=0.06), diagnosis by first CT scan (p=0.08), and lack of treatment with antithrombotic therapy (p=0.08). At 12 months, predictors of poor outcome were largely consistent with those at 24 months *(Table 3 and Figure 3)*.

In multivariate analysis, although trends were observed, none of the predictors reached statistical significance. Multivariate analysis of the most significant predictors - ethnicity, vasculopathy and PedsNIHSS - was undertaken. The Cox and Snell R-square values reported for ethnicity alone was 0.48, for ethnicity and PedsNIHSS was 0.51 and for ethnicity, PedsNIHSS and vasculopathy was 0.65.

Predictors of recurrence included abnormality on vascular imaging (p=0.07) and lack of antithrombotic treatment (p=0.04), with anticoagulation treatment alone approaching significance (p=0.06).

Factors that may have contributed to death included absence of warning symptoms at presentation (p=0.09), diagnosis made by the first CT scan (p=0.04) and bilateral strokes (p=0.09).

V) Discussion:

Our study is the first to report a population-based incidence of ischemic stroke involving the posterior circulation in children. Our data represents the best-estimated incidence rate since patients were ascertained and identified from multiple sources. We found the incidence of PAIS in children is in keeping with the reported incidence of AIS in general. The reported incidence of AIS (both anterior and posterior circulation AIS) is up to 2.5 - 3/100,000 people per year. We found similar proportion of PAIS in our pediatric cohort. PAIS comprised 20% of all AIS as found in our cohort and reported in other studies. This is consistent with reported rates in recent adult literature, with PAIS overall rates of 28.2%[14]. This is interesting considering the different risk factors in each group, but corresponds with the literature[3-6]. However, recently published data from Australia, reported somewhat higher PAIS frequency of 37%[3,4] likely related to the fact that the Australian centre is a tertiary hospital based patient population,

and a primary centre for cardiothoracic patients, leading to increased numbers of patients with AIS in general and specifically cardioembolic AIS[4,27].

Contrary to published literature in both childhood and adult AIS, our cohort identified only a slight male preponderance. Mackay *et al.*, Ganesan *et al.*, and adult studies report around 70% of their population as male, compared to about half in the Manitoba cohort[3-5,14]. Increased male representation is reported to be due to presence of head and neck risk factors, such as trauma, dissection and cervical spine abnormalities in boys[3,4]. The low frequency of these abnormalities (less than 25%) in our study may explain a low male to female ratio in our cohort.

With regards to ethnicity, aboriginal patients were overrepresented in our cohort. In the 2006 census, aboriginal individuals comprised 33.2% of the under 15 population in Manitoba, but made up 41% of our patient cohort *(Figure 1)*. This finding is similar to previously reported data from our centre in children with cardioembolic AIS[27]. The risk factors for PAIS identified in our study correspond to the previously reported data[3].

The majority of our patients had 2-year outcome data available, allowing us to analyze predictors of outcome exclusive to children with PAIS. However, because of the small population size, a characteristic not unique to this pediatric AIS study, significant predictors of outcome identified on the univariate analysis did not reach statistical significance in multivariate analysis. However, a consistent trend towards certain predictors for poor outcome was observed on multivariate analysis. Aboriginal status predicted poor outcome in our cohort, which also trended towards significance in multivariate model. This is new finding for the Manitoba cohort. Previously black ethnic subjects and male gender with AIS have been correlated to poor outcome in an American study indicating that ethnic and gender disparities do exist in pediatric AIS[28]. One plausible explanation for poor outcome in our aboriginal individuals may be related to community distance from tertiary medical services. Many live in the underserviced remote communities with limited available resources, and hence may experience delays in accessing appropriate and adequate acute and long-term stroke specific medical care. In addition, risk factors such as diabetes and hyperlipidemia, unique to this pediatric population, may be contributing to this difference. Although these risk factors were not observed in the present report, the retrospective nature of this study may be one limiting factor. Further studies focused on aboriginal AIS patients are warranted to determine if distance of home community from hospital or other undetermined risk factors can be identified. Neither age nor sex was found to be predicative of outcome in children with PAIS.

In univariate analysis, a PedsNIHSS score of more than 15 (“severe”)[21, 22] predicted poor outcome at 24 months and trends towards significance in the multivariate model *(Table 3)*. Although we had suspected that both the pediatric and the adult NIHSS scoring systems are biased towards anterior circulation

stroke presentation symptoms, (such as language defecits, neglect, motor and sensory symptoms), the study findings indicate utility in predicting outcomes in patients with PAIS as well.

Another predictor of poor outcome was the presence of an identified vasculopathy *(Table 3)*. One proposed explanation is that there is increased risk of recurrence in patients with an underlying vasculopathy[3,24,] However, in our cohort, recurrence on its own did not predict poor outcome, which is contrary to the other published data for AIS [3,4]. All patients in our study with recurrent events had good outcomes at 24 months. This could be a result of the low rate of recurrence observed in our population compared to the recent Australian data (25% vs. 52%)[4]. However, an earlier study on PAIS recurrence by Ganesan *et al* reported lower risk of recurrent stroke (18%) which is similar both to the reported recurrence risk for all AIS (10-30%), and the recurrence observed in our cohort[3,24]. By the same logic as previously described, the reasons for discrepancy between the Manitoba cohort and the Australian data are multiple.

In our cohort, bilateral and large artery infarctions were predictive of poor outcome. This is likely associated to the size of infarct. As already reported with AIS in general, infarcts with large volumes leads to significant residual deficits and hence worse long-term outcomes[19,24]. By the same token, if the patients had the PAIS diagnosis confirmed by the first CT scan, they fared poorly. As CT is an inferior imaging modality compared to MRI for the posterior fossa visualization, we anticipate that to be identified by CT scan at presentation, a larger volume of brain must be infarcted. Similarly, occipital lobe and cerebellar infarcts also correlated with poor outcome. We question the authenticity of this finding since two occipital lobe infarcts in our cohort were secondary to the increased intracranial pressure (caused by another intracranial primary pathology) and were not primary outcomes for PAIS. Further reason to question these findings arise from a recent paper in adults with PAIS which found that isolated PCA territory infarcts had better outcomes in regards to disability and mortality compared to strokes involving multiple territories including PCA[14]. Another adult study found that 74% of occipital lobe primary infarctions had good outcomes[25]. Further investigation and separation of patients based on raised intracranial pressure could delineate whether this finding is unique to pediatrics, or if raised intracranial pressure due to other intracranial pathology, as we believe, may have contaminated this finding. With regards to the cerebellar infarcts, interestingly, all but one of our patients with cerebellar infarcts had another posterior fossa structure infarcted, again suggesting that burden of infarct is likely the confounding factor. In addition, research has emphasized the importance of the cerebellum in short-term memory and cognitive function of pediatric stroke patients thereby causing poor outcome in these patients[26].

Intriguingly, lack of antithrombotic treatment, mainly anticoagulation treatment, was also loosely correlated to poor outcome at 24 months (p=0.08).

This probably relates to the lack of treatable causative factors, such as an underlying vasculopathy or cardioembolic risk factors in these patients.

As expected, outcome (measured by PSOM) at 3 months and 12 months correlated with outcome at 24 months ($p<0.001$). Contrary to adult data and popular belief that patients with PAIS fare worse than anterior circulation stroke, we found that 60% of PAIS patients had a good outcome at 24 months, which corresponds to other reported overall AIS data, with 61% having good outcome[19]. In addition, good correlation was found for factors predictive of outcome at 12 and 24 months. Our research adds valuable information on outcome stability and extrapolation to PAIS specifically. These findings are clinically useful since it will allow physicians to prognosticate as early as 12 months with similar accuracy.

We also investigated predictors for recurrence in addition to outcome, since recurrence did not correlate to poor outcome in our study. Lack of antithrombotic treatment ($p=0.04$) and abnormality on vascular imaging trended towards recurrent events ($p=0.07$). Patients not treated with antithrombotic therapy who had recurrent events may have had initially undiagnosed risk factors such as congenital heart disease, vasculopathy or coagulopathy[3,4]. An untreated risk factor is likely to recur. Pediatric PAIS studies report vascular abnormalities to be a major cause of recurrence [3,4]. In our cohort, none of the children with normal vascular imaging had a recurrent event. Previously reported literature exclusive to children with PAIS has also revealed similar association[3]. However, it should be noted that the rate of recurrent stroke was significantly higher in the Ganesan study compared to our patients with vascular abnormalities (50% versus 21%)[3]. This indicates that aggressive and prompt antithrombotic treatment in children with vascular abnormalities favorably alters recurrent stroke risk in children with PAIS and hence may positively affect their outcome. For physicians caring for these complex stroke patients, this is an important finding and calls for early vascular imaging for prompt management and treatment and prevention of future strokes in these patients.

Finally, for factors specifically related to death, in our cohort of patients, presence of warning symptoms, unilateral stroke, and failure to diagnose PAIS on initial head CT had a trend towards decreased number of deaths ($p=0.09$). Warning symptoms are likely a sign of a more insidious event with slowly increasing burden of infarct. Since warning symptoms may also encourage patients to present earlier for treatment with the possibility of saving ischemic penumbra, we believe that their existence had a positive effect on outcome of our PAIS patients, but this finding may not be unique to PAIS alone. Similarly, unilateral stroke and failure to diagnose PAIS on initial head CT indicates either less burden of infarct with or without early intervention and hence better outcome.

VI) Implications, Limitations and Future Directions:

Our study carries a high impact since it is the first population based incidence study of ischemic stroke involving the posterior circulation in children. It has identified several meaningful predictors of outcome for children with PAIS, which are clinically relevant and affect clinical practice. This and a previous study[27] in Manitoba children with stroke has identified an increased occurrence of AIS subtypes (cardioembolic and PAIS) in the aboriginal population which requires urgent studies for all AIS children, especially their underlying risk factors and co-morbidities. The current study also suggests poor outcome in these ethnic individuals which also needs to be tested either in a prospective or multicentre study. Theories including distance to treatment and lack of adequate long term therapies have been speculated, but further evaluation is necessary before conclusions can be drawn.

The retrospective design of this project has resulted in several limitations and afore mentioned uncertainties. Some important limitations to this study include lack of follow up in some patients, inherent bias to the retrospective scoring of PedsNIHSS and some PSOM scores, lack of consistent imaging data to assess infarct volume as a predictor of outcome (several predictors identified in our study indicate this association) and failure to assess effect of rehabilitative intervention on outcome, (a measure well known to affect outcome)[18,19]. In our cohort, almost all patients with available follow-up, according to their medical charts, received organized rehabilitative treatment after their stroke, a service available to all patients with stroke in Manitoba, but the extent of these services and patient compliance to such therapies could be not be assessed because of the retrospective nature of the study.

Considering the limitations of our study, we would like to expand the study to an international and multicentre study, allowing us to determine if the predictors identified in our study would carry more weight in a large multi centre cohort and show similar weight in multivariate analytical models.

VII) Conclusion

In conclusion, this study has successfully calculated PAIS incidence and frequency in a population based cohort and has shown unique features and meaningful predictors of PAIS in children. Our data calls for both prompt and appropriate parenchymal and vascular imaging of children with suspected PAIS and close observation and management of these patients, in particular aboriginal patients, patients with bilateral and large infarcts and with abnormal vascular imaging, as there is increased risk of recurrence and poor outcomes in these patients.

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Table 1: Clinical Presentation of Children with PAIS

	Number of Patients	Percentage
Sensorimotor Deficits	17	71
Hemiparesis	14	58
Monoparesis	1	4
Quadriparesis	1	4
Ataxia	3	13
Cranial Nerve Deficits	4	17
Visual Deficits	7	29
Speech *Deficits*	7	29
Seizures/ Abnormal Posturing	7	29
Focal	2	8
Generalized	5	21
Impaired Consciousness	18	75

Table 2: Radiological Characteristics of Children with PAIS

	Number of Patients	Percentage
Initial Neuroimaging for Diagnosis		
CT Brain	14	58
MRI Brain	5	21
Posterior Circulation Only	14	58
Vascularity Involved		
Vertebral-Basilar	9	38
Posterior Cerebral Artery	8	33
Circle of Willis	7	29
Infarct Characteristics		
Multiple	18	75
Bilateral	10	42
Infarct Location		
Thalamus	17	71
Brainstem	12	50
Occipital Lobe	10	42
Cerebellum	7	29

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Table 3: Predictors of Poor Outcome for PAIS at 12 and 24-Month Follow-up

	12 months (p-value)	24 months (p-value)
Aboriginal Ethnicity	0.002	0.003
PedsNIHSS Score	0.08	0.06
First CT Diagnosis	0.06	0.08
Bilateral Infarct	0.002	0.003
Large Caliber Artery	0.02	0.02
Cerebellar Infarction	0.03	0.07
Vasculopathy	0.04	0.05
Occipital Infarction	0.07	0.04

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Figure 1: Ethnic Distribution of PAIS patients

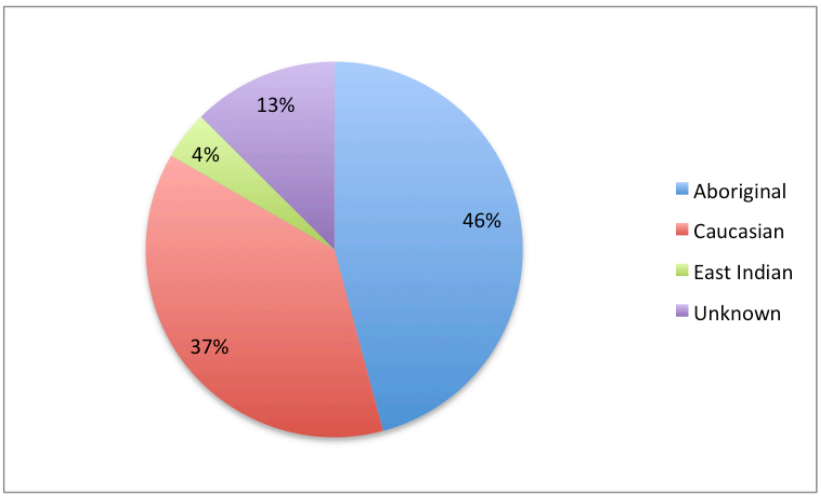

Figure 2: Structures Infarcted in PAIS Patients

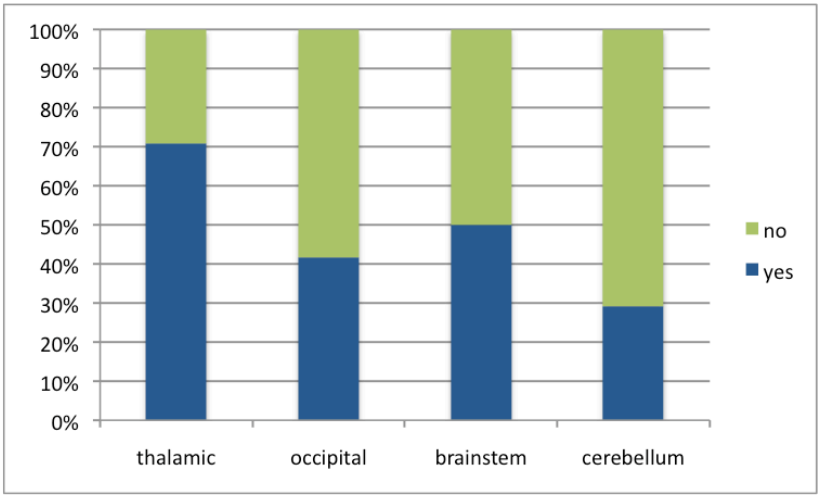

Figure 3: Outcome at 12 months Correlated to Outcome at 24 months

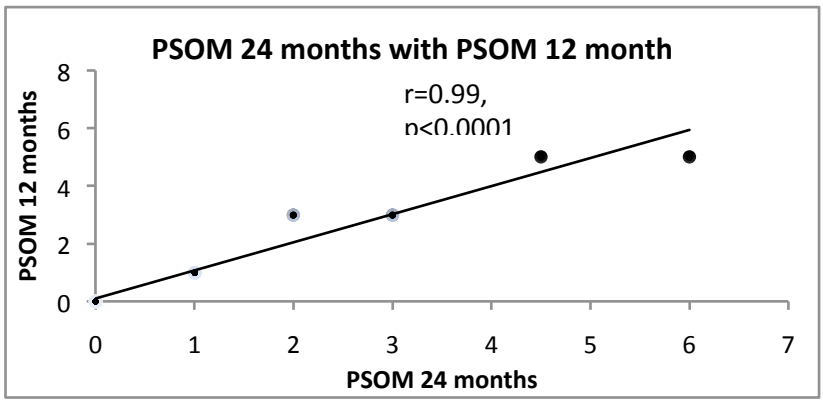

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Figure 4A): CT Imaging of A Study Subject With Bilateral Cerebellar Infarction

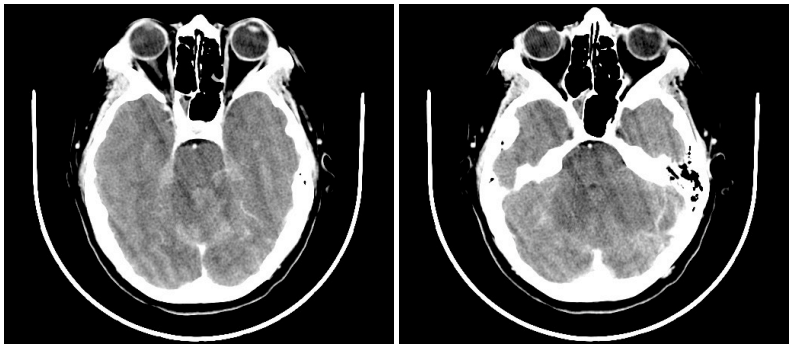


Figure 4B): MR Imaging of Bilateral Cerebellar and Brain Stem Infarction

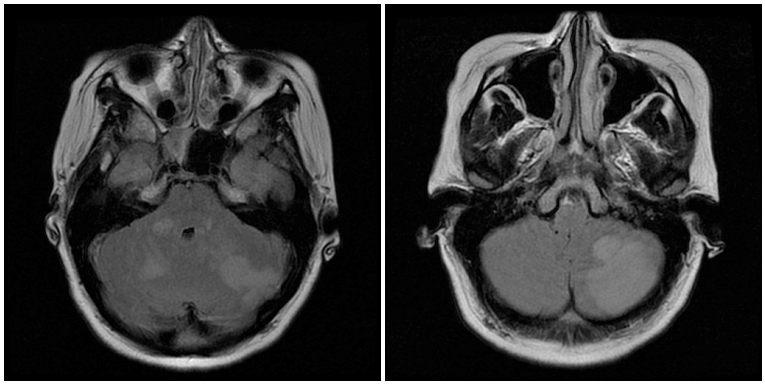
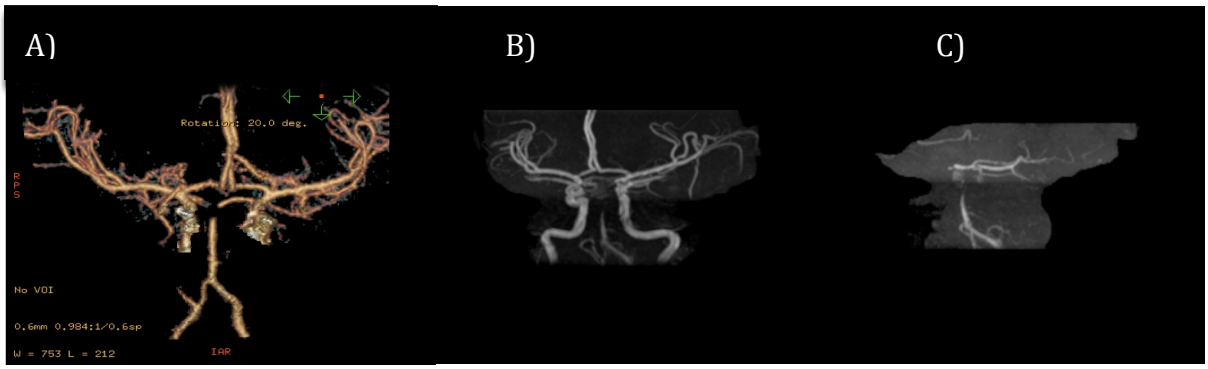


Figure 5: A) CT Angigram, B) Anterior View MRA, and C) Lateral View MRA Showing Basilar Tip Occlusion



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