Author/s:
Mackay, MT;Lee, M;Yock-Corrales, A;Churilov, L;Donnan, GA;Monagle, P;Babl, FE

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DR MARK THOMAS MACKAY (Orcid ID : 0000-0002-3787-1112)

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Differentiating arterial ischaemic stroke from migraine in the paediatric emergency department

MARK T MACKAY[1,2,3,4]

MICHELLE LEE[5]

ADRIANA YOCK-CORRALES[6]

LEONID CHURILOV[3,4]

GEOFFREY A DONNAN[3,4]

PAUL MONAGLE[2,3,7]

FRANZ E BABL[2,3,5]

1 Department of Neurology, Royal Children's Hospital, Parkville, Victoria; **2** Murdoch Children's Research Institute, Parkville, Victoria; **3** University of Melbourne, Parkville, Victoria; **4** Florey Institute of Neurosciences and Mental Health, Parkville, Victoria; **5** Emergency Department, Royal Children's Hospital Melbourne, Parkville, Victoria, Australia. **6** Hospital Nacional de Ninos, San Jose, Costa Rica. **7** Department of Haematology, Royal Children's Hospital, Parkville, Victoria, Australia.

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Correspondence to Mark Mackay, Department of Neurology, Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville, VIC 3052, Australia. E-mail: mark.mackay@rch.org.au

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ABBREVIATIONS

AIS	Arterial ischaemic stroke
FAST	Face Arm Speech Time

AIM To estimate the strengths of association between clinical features and migraine or arterial ischaemic stroke (AIS) in children presenting to the emergency department.

METHOD Eighty-four children with migraine, prospectively recruited from 2009 to 2010, were compared with 55 children with AIS, prospectively/retrospectively recruited from 2003 to 2010. Odds ratios were calculated via logistic regression to measure associations between clinical features and process-of-care factors, and migraine and AIS.

RESULTS Median age was 13 years 5 months (interquartile range 12y 11mo–13y 10mo) for migraine and 5 years (interquartile range 3y 7mo–8y) for patients with AIS. All cases of AIS and 30% of migraine cases underwent neuroimaging. Over 40% of children with migraine had vomiting, numbness, or visual disturbance; other symptoms were uncommon. Fifty-five per cent had no signs on physician assessment. Weakness or speech disturbance were common in patients with AIS. Significant clinical features associated with increased odds of AIS included sudden symptom onset, weakness, seizures, speech disturbance, and ataxia, and signs of face, arm, or leg weakness, inability to walk, dysarthria, dysphasia, and altered consciousness ($p<0.05$). Significant features associated with decreased odds of AIS included

older age, vomiting, visual, sensory, other symptoms, and absent focal signs on assessment (p<0.05).

INTERPRETATION Presenting features can discriminate childhood AIS from migraine. These differences inform decisions about urgency and type of neuroimaging in children presenting to the emergency department with brain attack symptoms.

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What this paper adds

- Weakness, seizures, ataxia, speech, or walking difficulties are more frequent in arterial ischaemic stroke (AIS).
- Vomiting, visual, or sensory disturbance and absent focal signs are more frequent in migraine.
- Identifying features of AIS and migraine guides neuroimaging in children with brain attack symptoms.

[Main text]

Migraine is the most common chronic paediatric neurological condition,[1] with an overall prevalence of 10.6% in the childhood population. Auras, which occur in up to 30% of children with migraine,[2] are more common in females,[2] children over 6 years of age,[3] and

those with a positive family history of migraine. In contrast, childhood arterial ischaemic stroke (AIS) is an uncommon occurrence, with an estimated incidence of 1.6 per 100 000 children per year in a recent population-based study.[4]

Headaches were the third leading neurological cause of referral to paediatric emergency departments,[5] accounting for more than 340 000 visits per year, in a USA national survey.[6] In a French study of 79 433 children, non-febrile, non-traumatic headache accounted for 2.6% of all emergency department presentations, and headache associated with at least one neurological deficit for 102 (0.13%) presentations.[7] In the subset of children with headache with focal symptoms, migraine with aura was the most common diagnosis, in 62% of all cases, followed by epilepsy-associated headache, in 26% of cases.[7] In contrast, cerebrovascular disorders accounted for 6% of cases, which is similar to a larger cohort of children with brain attacks from our institution (which included all children with migraine and some stroke patients in the current study).[8]

Migraine is also the most common cause of brain attack (stroke-like) symptoms in children presenting to the emergency department, accounting for 11% to 29% of cases.[8,9] A challenge for emergency department physicians, in children presenting with headache and focal neurological symptoms or signs, is to differentiate migraine, a common and benign condition in children, from far less common but serious neurological disorders such as stroke, which require urgent diagnostic imaging to confirm diagnosis and treatment to minimize the extent of brain injury.

We have previously reported the key clinical features that differentiate childhood stroke from mimics in children presenting to the paediatric emergency department with brain attack symptoms.[10] Preliminary analyses suggested that factors that discriminated AIS from mimics were different to those that discriminated haemorrhagic stroke from mimics. Understanding the clinical differences between migraine and AIS is important to assist emergency department physicians with clinical decision-making, and for the development of paediatric emergency department Code Stroke protocols,[9] to enable targeted utilization of urgent magnetic resonance imaging to confirm diagnosis, while avoiding overuse of a limited resource for benign conditions such as migraine.

The purpose of this study was therefore to estimate strengths of association between presenting clinical features, demographics, and process-of-care factors, and migraine or AIS,

and to describe parental concerns leading to visits to the paediatric emergency department in children with migraine.

METHOD

Ethical approval and patient consent

Our institutional ethics committee did not require investigators to obtain informed consent from study participants because data collected consisted of presenting symptoms and signs of stroke and non-stroke brain attacks, documented by the emergency department physician assessing the patient. Informed consent was however obtained for the subset of patients with migraine who were contacted for the follow up phone calls.

Participants

Children with migraine consisted of consecutive patients presenting to a tertiary paediatric emergency department between June 2009 and December 2010. Migraine was defined according to the International Classification of Headache Disorders criteria.[11] Children with migraine needed to have associated neurological symptoms or signs before presentation (weakness, sensory, speech, or visual disturbance; altered mental state; vertigo or unsteadiness), and persistent headache on arrival to the emergency department, to be eligible for inclusion. Performance of neuroimaging was at the discretion of the emergency department physician. Children with AIS consisted of a mixed prospective and retrospective group of patients with radiologically confirmed acute infarction on magnetic resonance imaging, presenting to the same emergency department between January 2003 and December 2010. Children with AIS who were directly admitted to the ward or with incomplete medical records, and children with headache not meeting International Classification of Headache Disorders criteria, were excluded.

Measures and procedures

Information collected included patient demographics, process-of-care factors, and neurological symptoms and signs (Tables I and II). Final diagnosis of migraine or AIS was determined by the study neurologist (MTM) after review of clinical data, neuroimaging, and other investigations. Children were triaged using the Australian triage scale; patients assigned

a category of 1, 2, 3, 4, and 5 are to be seen immediately, within 10, 30, 60, and 120 minutes respectively.[12] During the prospective study from 2009 to 2010, the triage nurse used a brain attack screening tool to identify eligible children with at least one neurological symptom relevant for stroke or stroke mimics (brain attacks),[8] including focal weakness, focal sensory disturbance, dysarthria or dysphasia, visual disturbance, altered conscious state, unexplained collapse, first febrile or afebrile seizure, headache with other neurological symptoms, dizziness, or unsteadiness. The triage nurse notified the research assistant of eligible children, between 9 a.m. and 6 p.m. on weekdays, who were then followed by a research assistant during their emergency department stay, and data were directly entered to the case report form. The patient discharge list in the emergency department triage system was reviewed daily for children who presented on the previous day outside recruitment hours, and data were retrospectively entered to the case report form.

Parents of children with a discharge diagnosis of migraine were contacted by phone approximately 6 weeks after their child's visit to the emergency department, to ensure there was no change of diagnosis, anticipating low rates of admission and neuroimaging. Parents were asked to answer questions about (1) past history of migraine, and, if so, how the current episode differed from previous attacks; (2) the reasons for their child's visit; (3) specifically whether they were concerned about a brain tumour or stroke; and (4) familiarity with the Face Arm Speech Time (FAST) to call emergency medical services public education message (Appendix S1, online supporting information).[13] The study was approved by the Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC30194A).

Statistics

Categorical variables are described as *n* (%), and age as median and interquartile range. Univariate logistic regression modelling was used to investigate associations between independent variables and final diagnosis of migraine or stroke. Odds ratios and corresponding 95% confidence intervals (CIs) were estimated; CIs not including 1 were indicative of statistical significance at a two-tailed *p*-value of 0.05. Multivariable regression analyses were not performed because of the low numbers of individuals with positive signs, compared with the potential number of combinations of independent variables ratios, resulting in numerically unstable models and poorly estimated associations. Statistical analyses were performed with STATA 13 (Stata Corp., College Station, TX, USA).

RESULTS

The study population consisted of a prospective group of 83 children with 84 migraine presentations to the emergency department, seen from July 2009 until December 2010, and a prospective/retrospective group of 55 children with AIS. Twelve children with headache not meeting International Classification of Headache Disorders criteria for migraine and 10 children with AIS, who were direct admissions to the inpatient unit, or who had incomplete medical records, were excluded from the analysis. Median age was 13 years 5 months (interquartile range 12y 11mo–13y 10mo) for migraine, and 5 years (interquartile range 3y 7mo–8y) for AIS (Table I). Neuroimaging was performed in 25 (30%) patients with migraine and all children with AIS. Only one child with migraine had an abnormal scan, with computed tomography showing incidental left ethmoidal sinus disease. Twenty-seven (33%) patients with migraine and all patients with AIS were admitted to the ward. Process-of-care factors significantly associated with increased odds of stroke diagnosis included health care professional referral, ambulance transport, and high triage category (Table I).

More than 40% of children with migraine had vomiting, focal numbness, or visual symptoms, but other symptoms were uncommon. Focal weakness or speech disturbance were the most common symptoms in patients with AIS (Table I). Sudden symptom onset, focal weakness, speech disturbance, seizures, and ataxia were significantly associated with increased odds of stroke. Older age (all but three children with migraine were aged over 5y), vomiting, focal numbness, visual disturbance, and other symptoms were significantly associated with decreased odds of stroke (Table I).

Fifty-five per cent of children with migraine had no signs at the time of emergency department physician assessment, and individual signs were infrequent; altered arm sensation, while most common, occurred in only 14% of children (Table II). Signs significantly associated with increased odds of stroke included face, arm and leg weakness, dysarthria, dysphasia, abnormal Glasgow Coma Scale score, and inability to walk. In contrast, resolution of neurological deficits before emergency department physician assessment was significantly associated with decreased odds of stroke diagnosis (Table II). However, odds ratios for most signs were poorly estimated with wide CIs, because few children with migraine had positive neurological findings (in the order of 1–2% for weakness and speech disturbance).

Follow-up data were available for 60 (72%) of 83 children with migraine. There was no change in final diagnosis for the 60 (72%) children who could be contacted. Two contacted parents could not remember visiting the emergency department, nine families could not be contacted because an incorrect number was entered to their medical record, and the remainder failed to return calls despite four attempts to contact them. Reasons for presentation to the emergency department are presented in Table III. Thirty per cent of parents stated they were concerned about a possible stroke, 28% were concerned about a brain tumour, and 15% thought their child's symptoms could be another serious neurological condition. Thirty-seven (62%) parents were familiar with the FAST to call emergency medical services public awareness acronym.

DISCUSSION

We found several important differences in the presenting features of migraine associated with focal deficits and AIS in children presenting to the paediatric emergency department. Children with AIS were younger than those with migraine. Migraine with aura is less common in children under 8 years of age, with a prevalence of 3% to 4% in children aged 3 to 7 years, versus 23% to 31% of teenagers.[3,7] By comparison, previous research suggests that approximately half of childhood AIS occurs in children aged less than 5 years at symptom onset.[4] Sudden symptom onset was significantly more common in children with AIS. The more gradual onset of neurological symptoms in migraine, which typically develop over more than 5 minutes,[14] is explained by cortical spreading depression of Leao, consisting of depolarization followed by hyperpolarization, at a rate of 3 to 5 millimetres per minute across contiguous brain regions.[15]

Visual and sensory disturbance occurred less frequently in children with AIS than migraine, consistent with clinical observations that visual symptoms and sensory symptoms are the most common migraine aura symptoms in children, occurring in up to 87% and 12% to 39% of cases respectively.[2,16] These findings are also explained by electrophysiological and functional neuroimaging studies of cortical spreading depression, which moves in a wave from posteriorly to anteriorly without conforming to neurovascular boundaries.[15]

Symptoms or signs of focal weakness, speech disturbance or ataxia, seizures, inability to walk, and abnormal conscious state were significantly more frequent in childhood AIS. Multicentre prospective case series have reported hemiparesis in 72% to 79%, altered

consciousness in 42% to 52%, speech disturbance in 33% to 55%, and seizures in 29% to 31% of AIS cases.[4,17] In contrast, hemiparesis is an uncommon form of migraine aura, occurring in less than 10% of cases,[2,16] and very rarely in the absence of other symptoms.[2] In sporadic hemiplegic migraine motor symptoms gradually develop over minutes, are more likely to affect the arm than the leg (while sparing the face), can be bilateral, and are almost always accompanied by headache.[14] Acute confusional state is also very uncommon in childhood migraine, reported in only 3% of children in one study,[18] and no cases were observed in another study.[16]

Seizures are a relatively common occurrence in childhood AIS, reported in up to 58% of children.[19] Some studies report seizures after migraine in up to 10% of adults,[20] but we observed seizures in only 4% of children with migraine. Finally, vomiting is a common migrainous symptom, particularly in younger children,[3] but it is uncommon in AIS. Absence of symptoms and signs at the time of emergency department physician assessment was significantly more common in migraine, consistent with clinical observations that migraine auras are usually fully reversible within 60 minutes, and often within even shorter time periods in children. The higher likelihood of signs resolving before emergency department physician assessment in migraine is important because it negates the need for urgent imaging in children presenting within the time window for reperfusion therapies, because a Pediatric National Institutes of Health Stroke Score of less than 4 is considered an exclusion criterion for off-label use of thrombolysis.[21] Conversely, given the uncommon occurrence of aura in younger children with migraine, the study findings suggest a low threshold for neuroimaging in children aged less than 8 years with headache and focal neurological deficits.

The increased odds of ambulance transport and higher triage categorization on arrival at the emergency department suggest the time course or constellation of AIS symptoms were more concerning to parents and triage nurses than those associated with migraine. Unfortunately, the small numbers of patients limited our ability to determine the relationship between particular symptoms and parental concerns, or their relationship to care-seeking behaviour such as calling an ambulance.

To date, there have only been two paediatric studies investigating expectations and reasons for seeking medical assistance for headaches.[22,23] Concerns about frequency and severity of pain were the two most common reasons for consultation, according to parents and the treating paediatrician, in an Italian study of 100 children attending an outpatient clinic. To the best of our knowledge, this study is the first to focus on parental concerns in

children presenting to the paediatric emergency department with headache and focal neurological symptoms. On open-ended questions, more severe attacks or the presence of focal symptoms, both in approximately one-third of cases, were the main parental reasons provided for presenting to the emergency department. In total, almost three-quarters of parents of children with migraine also reported concerns about serious neurological conditions, with one-third considering the possibility of stroke. This contrasts with only 2% of parents being concerned about tumours in the Italian study.[23] The same study explored families' expectations from the medical consultation and found that parents and children were seeking reassurance that headaches were not caused by a serious illness, and answers about the underlying cause of the headaches. Another USA study, which focused on the child's expectations, found that their most important priorities were understanding the cause of their headache, what would make it better, and gaining reassurance that they did not have a life threatening illness.[22]

The FAST to call emergency medical services message, developed in the UK, has been adopted as the main stroke public education message by stroke advocacy organizations in several countries, including the USA, Australia, and the UK. Sixty-two per cent of parents were familiar with the FAST to call emergency medical services acronym for the symptoms of stroke, at similar rates to a recent UK study, suggesting that public education programmes are reasonably effective, even in younger adults.[24]

The study has several limitations. The different methods of patient selection for the AIS and migraine groups, and the retrospective data entry for patients with AIS presenting after hours, are sources of study bias. It is possible there were additional cases of migraine in the 12 children with headache where International Headache Society diagnostic criteria were not met. The fact that only three children with migraine were younger than five highlights the challenges in diagnosing migraine in preschool children owing to their limited ability to describe pain or associated neurological symptoms. Because this was an observational study, less than one-third of children with migraine underwent imaging at the clinician's discretion (only one had an incidental abnormality), and it was not possible to compare imaging characteristics between the AIS and migraine groups. It is possible that some had more serious underlying conditions or their symptoms were caused by transient ischaemic attacks, but there was no change in final diagnosis in 72% of children whose families were contacted 6 weeks after diagnosis. Performance of diffusion-weighted magnetic resonance imaging and magnetic resonance angiography within a week of presentation, in children with a discharge

diagnosis of migraine would have been required to exclude underlying cerebrovascular disorders.

We did not explore differences in positive versus negative symptoms, the coexistence of hemiplegia with other symptoms, or the presence of common associated migrainous symptoms such as photophobia or phonophobia, between patients with AIS and migraine. We were unable to identify factors independently associated with AIS or migraine diagnosis, nor could we assess the effect of potential confounding factors (e.g. past history of migraine) on reasons for parental care-seeking behaviour or emergency department presentation, because the small patient numbers prevented multivariable analyses. Children who were referred by health care providers or transported by ambulance were likely preselected as having more severe neurological symptoms and therefore are not directly comparable to those who were not. The follow-up telephone calls relied on parental recall, potentially introducing study bias, and it is possible there were differences in reasons for presentation, or change in diagnosis in the non-respondent migraine group. The mixed prospective and retrospective design may have influenced the quality and completeness of the AIS data collected, and the study was conducted at a single tertiary hospital so the findings may not be applicable to a broader paediatric population.

In conclusion, migraine and AIS have different presenting clinical features in children presenting to the emergency department with brain attack symptoms, which may inform the development of paediatric Code Stroke protocols, to assist emergency department physicians with decision-making about the urgency and type of diagnostic brain imaging.

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Supporting information

The following additional material may be found online:

Appendix S1: Follow-up form – migraines.

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Table I: Demographics, process factors, and symptoms associated with arterial ischaemic stroke (AIS) and migraine diagnoses

Demographics process factors	AIS (*n*=55)	Migraine (*n*=84)	OR[a]	95% CI	*p*
Median (IQR) age (y)	5.0 (3.6–8.0)	13.4 (12.9–13.8)	0.74[b]	0.67–0.82	<0.001
Median (IQR) lag time (h)	10 (7–25)[c]	4 (4–9)[d]	1.003[e]	0.99–1.10	0.236
Male sex	25 (45)	34/83 (41)	1.20	0.60–2.39	0.602
Past medical history	25 (45)	46/83 (55)	0.67	0.34–1.33	0.252
Well in the previous week	44 (80)	69/83 (83)	0.81	0.34–1.95	0.640
Referred to emergency department	27 (49)	12/83 (15)	5.71	2.54–12.81	<0.001
Ambulance transport	33 (60)	28/83 (34)	2.95	1.45–5.97	0.003
High triage category	17 (31)	13/83 (16)	2.41	1.06–5.49	0.036
Symptom					
Sudden symptom onset	46 (84)	54/83 (65)	2.74	1.18–6.39	0.019
Headache	26/53 (49)	83/83 (100)	1.00	0	
Vomiting	9/53 (17)	39/83 (47)	0.23	0.10–0.53	0.001
Focal weakness	40 (73)	23/83 (28)	6.96	3.24–14.93	<0.001
Focal numbness	9 (16)	37/83 (45)	0.24	0.11–0.56	0.001
Visual disturbance	8/53 (15)	35/82 (43)	0.24	0.10–0.57	0.001
Seizure	12 (22)	3/83 (4)	7.44	1.99–27.81	0.003
Altered mental	11 (20)	11/83 (13)	1.64	0.65–4.09	0.292

state					
Dizziness	7/52 (13)	19/83 (23)	0.52	0.20–1.35	0.181
Speech disturbance	28 (51)	21/83 (25)	3.06	1.48–6.32	0.002
Ataxia	13/54 (24)	5/82 (6)	4.88	1.63–14.65	0.005
Loss of consciousness	0 (0)	4/83 (5)	1.00	0	
Vertigo	2/50 (4)	2/83 (2)	1.69	0.23–12.37	0.607
Other symptoms	1 (2)	19/83 (23)	0.06	0.01–0.48	0.008

Data are *n* (%) unless otherwise indicated. [a]Odds of the factor or symptom among those with AIS divided by odds among those with migraine. [c]Odds if AIS per extra year of age. [d]*n*=54. [e]*n*=76. [f]Odds of AIS per extra hour of lag time. OR, unadjusted odds ratios; CI, confidence interval; IQR, interquartile range.

Table II: Signs associated with arterial ischaemic stroke (AIS) and migraine diagnoses

	AIS (*n*=55)	Migraine (*n*=84)	OR[a]	95% CI	*p*
Sign					
Face weakness	36 (65)	1/83 (1)	155.37	20.03–1205.33	<0.001
Arm weakness	36 (65)	9/83 (11)	15.58	6.41–37.84	<0.001
Leg weakness	30 (55)	6/83 (7)	15.40	5.75–41.27	<0.001
Dysarthria	19/52 (37)	1/83 (1)	47.21	6.07–367.13	<0.001
Dysphasia	7/52 (13)	1/83 (1)	12.76	1.52–106.97	0.019
Ataxia	6 (11)	0/83 (0)	1.00	Infinity	
Inability to walk	14/54 (26)	2/83 (2)	14.18	3.07–65.41	0.001
Abnormal eye movement	3 (5)	4/82 (5)	1.13	0.24–5.23	0.881
Visual defects	4/45 (9)	9/82 (11)	0.79	0.23–2.73	0.711
Face altered sensation	5 (9)	5/83 (6)	1.56	0.43–5.66	0.499
Arm altered sensation	9 (16)	12/83 (14)	1.16	0.45–2.96	0.760
Leg altered sensation	7 (13)	8/83 (10)	1.37	0.47–4.01	0.569
GCS abnormal (<15)	15 (27)	11/83 (13)	2.45	1.03–5.85	0.043
Pupillary abnormalities	1/54 (2)	1/79 (1)	1.47	0.09–24.05	0.786
Sensory neglect	2 (4)	0/83 (0)	1.00	Infinity	
Other signs[b]	7 (13)	9/83 (11)	1.20	0.42–3.43	0.735
No focal signs	3 (5)	45/83 (54)	0.05	0.01–0.17	<0.001

Data are *n* (%) unless otherwise indicated. [a]Odds of the factor or symptom among those with AIS divided by odds among those with migraine. [b]Other signs included abnormal deep tendon reflexes (DTRs), confusion, altered consciousness or slowed mentation, involuntary

movements, papilloedema. OR, unadjusted odds ratios; CI, confidence interval; GCS, Glasgow Coma score. **Table III**: Parental interviews of children with migraine

Differences between this and previous attacks in children with past history of headache	*n*=40
More severe headache	13 (33)
Focal symptoms or signs	12 (30)
More severe and more frequent headaches	5 (13)
More severe and focal symptoms or signs	4 (10)
No reason provided	4 (10)
Parental concerns on open ended questioning	*n*=60
Stroke	18 (30)
Brain tumour	17 (28)
Other serious brain condition	9 (15)
Parental concerns on direct questioning	*n*=60
Stroke	29 (48)
Brain tumour	22 (37)
Both	6 (10)
Neither	3 (5)
Awareness of FAST public awareness acronym	37 (62)

Data are *n* (%). FAST, Face Arm Speech Time to call emergency medical services.