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Clinical features, course and outcomes of a UK cohort of paediatric moyamoya

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- Shakti Agrawal ran the study at their centre (including governance permissions, patient identification and data collection) and critically reviewed and provided feedback on the manuscript
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• The members of the British Paediatric Neurology Association Moyamoya Study group listed above individually ran the study at their centres (including governance permissions, patient identification and data collection) and critically reviewed and provided feedback on the manuscript

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Abstract

Objectives
To describe characteristics and course of a large United Kingdom cohort of children with moyamoya from multiple centres, and examine prognostic predictors.

Methods
Retrospective review of case notes/radiology, with use of logistic regression to explore predictors of outcome.

Results
Eighty-eight children (median presentation age 5.1 years) were included. Thirty-six presented with arterial ischaemic stroke (AIS) and 29 with transient ischaemic attack (TIA). Eighty had bilateral and eight unilateral carotid circulation disease; 29 patients had posterior circulation involvement. Acute infarction was present in 36/176 hemispheres and chronic infarction in 86/176 hemispheres at the index presentation. Sixty-two of 82 with symptomatic presentation had at least one clinical recurrence.

Fifty-five patients were treated surgically with 37 experiencing fewer recurrences after surgery. Outcome was categorised as good using the Recovery and Recurrence Questionnaire in 39/85 patients. On multivariable analysis presentation with TIA (OR= 0.09, 95% CI= 0.02-0.35), headache (OR= 0.10, 95% CI= 0.02-0.58) or no symptoms (OR= 0.08, 95% CI= 0.01-0.68) was less likely to predict poor outcome than AIS presentation. Posterior circulation involvement predicted poor
outcome (OR = 4.22, 95% CI = 1.23-15.53). Surgical revascularisation was not a significant predictor of outcome.

**Conclusions**

MM is associated with multiple recurrences, progressive arteriopathy and poor outcome in half, especially with AIS presentation and posterior circulation involvement. Recurrent AIS is rare after surgery. Surgery was not a determinant of overall outcome, likely reflecting surgical case selection and presentation clinical status.
**Introduction**

Moyamoya (MM) is a cerebrovascular condition characterised angiographically by occlusive disease of the terminal internal carotid, anterior or middle cerebral arteries (ICA/ACA/MCA) and a network of basal collaterals\(^1\). In Japan and East Asia, where MM is most prevalent\(^2\), reported natural history has been of high rates of progressive disease, recurrent events and cognitive decline, with major functional effects\(^3–5\). However, a recent population screening study in Japan identified many asymptomatic cases, suggesting that natural history may be more variable\(^6\). As MM is rare outside East Asia\(^7,8\) the disease phenotype has not been well characterised elsewhere. Available data suggests a more benign disease course and a lower rate of cerebral haemorrhage\(^9,10\). Most non-Eastern series are subject to significant ascertainment bias, with potential over-reporting of severe presentations. The diagnostic label of MM is applied variably to cases of bilateral cerebral occlusive arteriopathy but specific radiological features are likely to be important in defining clinically important subgroups\(^11\).

Surgical revascularisation is widely offered in MM to prevent ischaemic symptoms. Although symptom reduction and good functional outcomes are reported both in Eastern patients\(^12,13\) and others\(^14–16\), uncertainty regarding natural history and prognostic predictors makes it difficult to identify optimal surgical candidates and to objectively evaluate the efficacy of surgery.

Here, we describe the clinical and radiological features, course, outcomes, and their predictors in an eleven-year cohort of UK paediatric moyamoya patients.
Methods

Children (aged up to 18 years) with a new diagnosis of MM (whether symptomatic or incidentally identified, and whether idiopathic (MM disease) or secondary to a recognised association (MM syndrome)) between 1 January 2004 and 31 December 2014 were eligible for inclusion. All cases were considered as a single group, with separate consideration of the influence of a recognised risk factor for MM. MM was defined as stenosis or occlusion of the TICA and/or MCA and/or ACA with basal collaterals (CASCADE category 3A (bilateral) & 2A (unilateral))\(^{17}\). Intracranial occlusive arteriopathy without basal collaterals (unilateral (CASCADE 2B,C,D) or bilateral (CASCADE 3B,C) were excluded – to enable comparison with published series. Angiographic features were confirmed by review of imaging (VG/DS) in all cases.

Patients were identified from two sources:

(i) the multidisciplinary MM clinic at Great Ormond Street Hospital for Children (GOSH) that accepts UK-wide referrals for diagnostic opinions or evaluation for revascularisation surgery. Patients were evaluated uniformly with clinical assessment, brain magnetic resonance imaging and angiography (MRI/A) and catheter angiography (CA). Surgery was considered in patients with a demonstrable tendency to recurrence - i.e. more than one clinical or radiological event - although ultimately surgical decisions were made on a case-by-case basis. The hospital audit department confirmed that ethical approval was not required for review of existing
clinical and radiological material that was obtained as part of standard clinical care in these patients.

(ii) the British Paediatric Moyamoya Study group. A local investigator (LI) was identified at each paediatric regional neuroscience centre in the UK. Cases were notified by them and additional cases sought via the British Paediatric Neurology Surveillance group (BPNSU), a national collaboration of UK paediatric neurologists who receive a monthly e-mail requesting notification of rare conditions under study. The study was reviewed and approved by the London and Bloomsbury research ethics committee (ref 14/LO/0323) and opened in 17 sites, with local governance approval at each site. Two regional centres did not open as study sites as it was anticipated (and confirmed at study closure) that cases were unlikely to be seen. The LIs sought assent from patients; the GOSH team obtained informed consent. Clinical data was obtained from parental interview by telephone. Relevant imaging studies were electronically transferred (with consent) to GOSH and centrally reviewed.

Data on patient demographics, co-morbidities, family history, clinical presentation, recurrent events, treatment and outcomes was obtained from clinic letters, case notes or parent interview.

Demographic data included age, sex, family history, comorbidities and other diagnoses. Presentation was categorised as transient ischaemic attack (TIA), arterial ischaemic stroke (AIS), cerebral haemorrhage, seizures, headache, chorea or other (including silent infarcts). All medical and surgical interventions were noted.
Recurrent events were categorised as for presenting symptoms and also in terms of temporal relationship to any surgical intervention.

Scans were reviewed to confirm study eligibility. Brain MRI findings were summarized according to infarct distribution (unilateral/bilateral) and infarct timing (acute/established). For serial imaging studies, the first and most recent scans were compared to ascertain identify new changes. Cerebrovascular findings were summarized from MRA or CA. Initial findings were categorised according to whether the disease was unilateral or bilateral, and for posterior circulation involvement. First and most recent cerebrovascular imaging was compared to ascertain progression of arteriopathy (defined as more extensive abnormality of previously abnormal artery or involvement of a new artery).

Clinical outcome was evaluated from case notes or parent interview using a combination of the modified Rankin Scale (mRS) and the type of school attended (mainstream or needing educational support). This has been previously validated for evaluation of outcome after childhood AIS\textsuperscript{(18)} and confirmed to have good concordance with the Paediatric Stroke Outcome Measure (PSOM), a commonly used childhood stroke outcome scale. Good outcome was defined as a mRS ≤ 2 and attendance at mainstream school without additional support; poor outcome was defined as a mRS ≥ 3 and/or attendance at special school or mainstream school with additional support\textsuperscript{(18)}.

Statistical analysis was undertaken using SPSS Statistics v22. Univariable logistic regression was used to explore the relationship between clinical/radiological
variables and outcome. Significant and clinically important variables were then entered into a multivariable model. Predictors which did not significantly alter the odds ratios were removed to create the final model.

**Results**

**Patient demographics**

Figure 1 summarises the identification pathway for the patients whose data is reported here. Eighty-eight children were included (56 female). Ethnicity was White (57%), Black (19%) and South Asian (15%); no patients were East Asian. Thirty-one (35%) had a risk factor known to be associated with MM (MM syndrome, table 1). Eight had a family history of MM, including sibling pairs from two families, without an identified genetic or syndromic diagnosis.

**Initial clinical and radiological findings**

Median age at initial presentation was 5.1 years (range= 0.3-16.4 years), with most children presenting during primary school years. Patients presented predominantly with ischaemic symptoms, 36 (40.9%) with AIS and 29 (33.0%) with TIA. Other presentations included cerebral haemorrhage in one case, seizures in four cases, headache in ten cases and hemi-chorea in two cases. Six children were asymptomatic at diagnosis and had MRI scans for other indications such as sickle cell disease and microcephalic osteodysplastic primordial dwarfism type II.

**Initial radiological findings**

All patients had brain MRI at presentation that showed acute focal infarction in 36/176 hemispheres in the 88 children. Eighty-six hemispheres additionally had
evidence of chronic ischaemic injury on the index MRI, indicating previous, clinically silent, ischaemic damage. Magnetic resonance angiography of the circle of Willis showed bilateral arteriopathy in 80 cases (CASCADE 3A) and unilateral disease in the remaining 8 (CASCADE 2A). The findings from the initial brain MRI and MRA are schematically summarised in figure 2.

**Subsequent course**

The patients’ clinico-radiological course is summarised in table 2, divided into those that had had surgical revascularisation and those that did not. Surgical revascularisation was undertaken in 55 children (unilateral surgery= 19, bilateral surgery= 36), 44 with recurrent clinical symptoms and a further seven who had had further cerebral infarction on re-imaging. The specific surgical indication was not available in the remaining four as this was not apparent from parental interview. The median age at first surgery was 6.3 years (range= 1.3-17.6 years), a median of 1.1 years (range= 0.1-7.4 years) from initial presentation. The 45 patients surgically treated at GOSH had pial synangiosis; procedural details in the others could not be obtained from parental interview. One patient with bilateral disease treated surgically with pial synangiosis went on to have multiple burr holes due to refractory ischaemic symptoms, with some clinical improvement.

Ten patients (18%) had a neurological event within one week of surgery; seven had a TIA (of which five related to the surgical hemisphere), one had a cerebral haemorrhage (whilst anticoagulated) and two had AIS. The latter three patients experienced new neurological deficits related to these events.
Seventy-three (83.0%) patients were on antiplatelet therapy (73 on aspirin; one also on clopidogrel and one also on dipyridamole). Six (6.8%) patients were on anticoagulants.

Median duration of follow-up was 43 months (0.3-135 months): 47 months in the surgical group (2-145 months) and 36 months in the non-surgical group (0.3-109 months). In total, 62 of the 82 patients with symptomatic presentation had at least one recurrent event (40 TIA, 28 AIS (not mutually exclusive)). Of the six who had been asymptomatic at the time of initial diagnosis two went on to have TIAs. Of the 36 patients with initial AIS, 17 went on to have recurrent AIS (of whom 3 also had recurrent TIA) and 7 had subsequent TIA; 12 children in this group did not have further recurrences after the index AIS. Fifty-two patients had more than one recurrent event.

Thirty-three patients of the 55 in the surgical group had clinical recurrence of cerebral ischaemia (29 TIA, four AIS) after surgical revascularisation (including the post-operative events described above). However, 37/55 of the surgical group had an absolute reduction in the frequency or severity of recurrences compared with pre-operative levels.

Fifty-seven patients (18 non-surgical and 39 surgical group) had repeat brain imaging, undertaken 0.2-10.2 years from initial diagnosis. Comparing initial and final MRI and MRA, 18 patients had evidence of new ischaemic damage on MRI, a median of 3.6 years from presentation, including new brain injury identified after surgical revascularisation in 7 cases. This was usually in deep grey structures or
white matter – i.e. relatively deep in the brain. Five of the seven who developed new infarcts after surgery had had a corresponding clinical event. Twenty-one patients had further transient clinical events without new infarcts on re-imaging.

Twenty-seven patients had evidence of progressive arteriopathy (including 23 who had had surgery); however, the timing of arteriopathy progression could not be precisely evaluated in relation to surgery due to variable imaging time points. It is of note that surgery patients were significantly more likely to have progressive arteriopathy (23/39 compared with 4/18, p = 0.01) – suggesting patients with potentially more aggressive disease are being selected for surgery. It is difficult to meaningfully comment on the rates of new infarcts in the patients imaged serially, either pre- or post-operatively as these represent a subset, without any systematic imaging schedule.

Outcomes

One child died secondary to cerebral haemorrhage. Outcome data was available for 85 survivors; the remaining three were pre-schoolers who could not be assigned a mRS score. Outcome was categorised as good in 39 (44.3%) patients. Interestingly of patients who had been managed in centres other than GOSH, outcome was classed as good in two patients and poor in 14 patients (compared with 37 good and 32 poor in the GOSH cohort; Fisher’s exact text p<0.01) – as will be discussed, the reasons for this are likely to be complex. A breakdown of the mRS, type of school attended and overall outcomes in the surgical and non-surgical patients is shown in table e-1.

Prognostic predictors
Predictors of poor outcome are shown in tables e-2 (univariable) and 3 (multivariable). In univariable analysis children with non-AIS presentation were significantly less likely to have a poor outcome; presence of a risk factor associated with MM was also a predictor of poor outcome (OR= 6.00, 95% CI= 2.11-17.06).

Multivariable analysis confirmed that presentation with TIA, headache or no symptoms was significantly associated with a lower chance of poor outcome than AIS presentation. Having controlled for other variables, posterior cerebral circulation involvement was also a predictor of poor outcome; however, having a MM risk factor (MM syndrome) was no longer significant.

**Discussion**

Here we present data from a recent multi-centre UK cohort of childhood MM confirming frequent ischaemic presentations. Approximately half of patients had a good neurological outcome – although it is difficult to dissect the contribution of surgical revascularisation as surgical cases were selected on the basis of their presumed higher risk for progression. Adverse prognostic features were AIS presentation and posterior circulation involvement.

In order to enable comparison to other, particularly East Asian, series our cohort was selected according to strict radiological criteria. We may have inadvertently excluded early cases of bilateral MM (prior collateral development, CASCADE 3B) but we felt radiological homogeneity was important as, in a previous study of young children with bilateral cerebral arteriopathies, disease trajectory was different in those with
and without collaterals. There may also be cases of unilateral cerebral arteriopathy without collaterals (CASCADE 2B) that represent early cases of unilateral MM. Without a robust disease biomarker for MM, there is risk of both under- and over-ascertainment but, by applying consistent and transparent radiological criteria, we aimed to identify a relatively uniform group.

The lack of serial imaging in a proportion of patients reflects the long ascertainment period (with variations in practice), differences in approach between centres and short follow-up in a small number of cases. We may have under-ascertained clinically silent progression of brain injury and arteriopathy as this was apparent in some re-imaged patients. However, the clinical significance of asymptomatic disease progression is unclear, especially since arteriopathy progression appeared to continue even after surgery. We have not used progressive radiological change as an outcome parameter and therefore this issue should not alter our conclusions.

While it would be incorrect to present this as an epidemiological study, we have attempted to reduce ascertainment bias by involving a national network of paediatric neurologists. Paediatric neuroscience centres in the UK generally work in a multidisciplinary model and it would be extremely unusual for patients to present to other professionals (e.g. neurosurgeons) without paediatric neurology involvement. Thus, it is likely that the vast majority of UK paediatric cases UK between 2004 and 2014 were identified. We had a high rate of enrolment but recognise that ascertainment was likely incomplete. For example, many children with sickle cell disease and cerebrovascular disease are managed by paediatric haematologists not neurologists. There appear to be differences in clinical outcomes between children
seen in GOSH, with a higher proportion of these with good outcomes. The reasons for this are likely to be diverse and impossible to tease out – but this observation suggests that the potential referral centre bias for more severe presentations did not hold true in this cohort. Comparing the groups, this difference seems more likely to be due to clinical state at diagnosis, rather than any difference in management approach. Thus, with the reservations discussed we feel this study presents useful data on a large non-Eastern paediatric cohort.

The majority of patients in our study presented with ischaemic events, consistent with findings from both East Asian and Western studies\(^{(16,19–21)}\). Posterior cerebral circulation involvement is common in MM\(^{(22,23)}\) and, unsurprisingly an adverse prognostic feature – presumably due to impairment of an alternate source of collateral circulation. Also unsurprising is the relationship between AIS and poor outcome as these children have irreversible brain injury at presentation. Whilst the apparent adverse effect of co-morbidities on outcome appeared to be accounted for by presentation and posterior circulation involvement, the high rate of these in MM pose an additional challenge to dissecting out the relative effects of the disease, its treatment, and additional factors.

Whilst the mRS/school type assessment has been shown to relate well to the Paediatric Stroke Outcome Measure\(^{(24)}\) we acknowledge that it is really only a crude assessment of function, with a major motor bias. Young age and co-morbidities are also expose the limitation of this outcome assessment. These limitations mean that there is a likely underestimate of “good” outcomes. Naturally prospective studies should aim to be more comprehensive and to use standardised measures, ideally
within the International Classification of Functioning, Disability and Health (ICF) framework.

The main aim of surgical revascularization in MM is to prevent AIS, and only four of the fifty-five surgical patients experienced post-surgery AIS and three quarters of patients with recurrent events prior to surgery experienced a reduction in the frequency or severity of these, consistent with previous UK, US and Japanese studies\textsuperscript{(12,14,15)}. It is difficult compare studies as many only report reductions in TIA symptoms, while our study reports reductions in all types of recurrences. In addition, MRI identified new infarcts in seven patients after surgery, suggesting that, while surgery appears successful in preventing clinical recurrence, it may not prevent radiological disease progression, as was also evident by the rates of arteriopathy progression observed.

We were interested to observe that outcome was categorised as poor in over half of patients who underwent surgical revascularization, in contrast to the higher proportions of favourable outcomes (using different measures) reported in previous studies\textsuperscript{(16,25)}. The possible reasons behind this are complex and we emphasise that the surgery and non-surgery groups are not inherently comparable, nor randomly allocated. Potential explanations are that surgery does not influence the natural history of MM, thus its effects on outcome are limited. Alternatively, patients who underwent surgery might have had poor pre-operative functional and cognitive abilities due to established brain injury, such that post-operative outcome would continue to be categorised as poor. Given that many patients presented with AIS this is an important consideration but unfortunately in our retrospective study we were
not able to ascertain pre-operative functional status and naturally accept this as a limitation. A further reason might be that all non-surgical patients were accurately predicted to have a good outcome – which was why they were not offered surgery. It is difficult to draw any wider conclusions from these data but they do challenge the concept that surgery is mandatory in all MM patients. From an ethical and logistic perspective, it seems very unlikely that there will ever be a trial of surgical revascularization in MM, and unclear on what basis one would randomise patients. However, data such as those presented here could form the basis of expert consensus, to standardise management and enable prospective critical appraisal of practice.
References


Tables and figures

BPNSU notifications n = 31

Potentially eligible* n = 23

Consented and interviewed n = 17  GOSH MM clinic n = 71

Total cohort n = 88

Source of patient identification

Figure 1: Source of patient identification; *8 patients were ineligible as they did not meet age/study time period criteria
Summary of the distribution of arterial disease and brain infarcts

Figure 2: A schematic of the Circle of Willis showing the major cerebral arteries, summarising the distribution of arterial disease and of brain infarcts. The number of hemispheres that went on to be treated by surgical revascularisation is also indicated.
<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>14</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>11</td>
</tr>
<tr>
<td>Neurofibromatosis type I</td>
<td>3</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>17</td>
</tr>
<tr>
<td>Renal/renovascular disease</td>
<td>5</td>
</tr>
<tr>
<td>Cranial radiotherapy/proton beam therapy</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 1**: Risk factors and co-morbidities of the patient cohort.
<table>
<thead>
<tr>
<th>Clinico-radiological feature</th>
<th>Number of surgical patients (n=55)</th>
<th>Number of non-surgical patients (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td>Recurrent events</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Vascular disease progression</td>
<td>Total= 23/39 re-imaged patients</td>
<td>4/18 re-imaged patients</td>
</tr>
<tr>
<td>New infarcts</td>
<td>8/39 re-imaged patients</td>
<td>7/39 re-imaged patients</td>
</tr>
</tbody>
</table>

**Table 2:** Table of the clinico-radiological features of the cohort.
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Initial presentation</td>
<td></td>
<td></td>
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<tr>
<td><em>AIS (reference category)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>0.09 (0.02-0.35)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>0.10 (0.02-0.58)</td>
<td>0.010</td>
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<td><strong>Chorea</strong></td>
<td>Undefined (n = 2)</td>
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<tr>
<td><strong>Cerebral haemorrhage</strong></td>
<td>Undefined (n = 1)</td>
<td>NA</td>
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<tr>
<td><strong>Seizure</strong></td>
<td>0.50 (0.04-6.56)</td>
<td>0.593</td>
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<tr>
<td><strong>Asymptomatic</strong></td>
<td>0.08 (0.01-0.68)</td>
<td>0.021</td>
</tr>
<tr>
<td>Posterior cerebral circulation involvement</td>
<td>4.22 (1.23-15.53)</td>
<td>0.022</td>
</tr>
<tr>
<td>Moyamoya risk factor*</td>
<td>2.45 (0.64-9.36)</td>
<td>0.189</td>
</tr>
</tbody>
</table>

*risk factors include Down syndrome, neurofibromatosis type I, sickle cell disease and cranial radiotherapy/proton beam therapy

**Table 3:** Multivariable analysis of clinical and radiological predictors of poor outcome. Significant findings are shown in bold.