The role for surgical revascularization for symptomatic moyamoya in children has been well established, with multiple studies demonstrating a clear benefit to patients, with reduced rates of ischemic injury when compared with the natural history. Less clear, however, is the natural history and appropriate course of action to take in the case of children found to have the arteriopathy of moyamoya who are asymptomatic. Whereas a sound rationale has been proposed for revascularization in patients with symptomatic moyamoya based on the premise that long-term outcome is largely dependent on neurological status at the time of surgery, there are few data on the natural history of incidentally discovered moyamoya, with almost no data specific to children.

One of the major limitations to the study of asymptomatic moyamoya in children is the rarity of incidentally discovered cases. The majority of pediatric moyamoya is idiopathic moyamoya disease (bilateral, presumably genetic, arteriopathy), which is found only after presentation with ischemic symptoms. However, there are populations of pediatric patients who have medical conditions known to be associated with moyamoya (moyamoya syndrome) who undergo periodic screening studies of the brain and cerebral vasculature and are thus more likely to have an incidental diagnosis. In particular, if one excludes idiopathic moyamoya disease, children with NF1 and SCD comprise the most common subgroups of syndromic moyamoya. Patients with NF1 may receive surveillance MR images to monitor tumor status, and patients with SCD routinely undergo TCD studies to ascertain the need for exchange transfusions, which are frequently corroborated with MR images. In addition, patients with unilateral...
moyamoya syndrome are frequently followed with serial imaging, because approximately one-third of unaffected hemispheres will ultimately progress to develop moyamoya.\textsuperscript{3,4,23}

This study exploits the availability of serial imaging studies in select populations of pediatric patients—those with NF1, SCD, or the unaffected hemisphere in children with unilateral moyamoya—to characterize the radiographic and clinical progression of incidentally found, asymptomatic moyamoya syndrome. The objectives of this work are to document the incidence of radiographic and clinical progression in previously asymptomatic children found to have moyamoya. A clear demonstration that asymptomatic, incidentally discovered moyamoya can progress—both radiographically and clinically—along with data identifying general rates of progression and at-risk populations would aid clinicians involved with the care of these children.

Methods

We performed a review of the clinical database from the Boston Pediatric Neurosurgical Foundation to identify all patients referred to either of the senior authors (R.M.S. and E.R.S.) for the diagnosis of moyamoya and who had the coexisting diagnosis of either NF1 or SCD. This series thus included both surgically and nonsurgically treated patients, with the surgically treated cases obtained from clinical records of a consecutive series of 418 patients with moyamoya syndrome who underwent surgical revascularization performed by the senior authors at the Children’s Hospital, Boston, between 1988 and 2010. All patients ultimately received a diagnosis of moyamoya arteriopathy as defined by the ICD and outlined in the guidelines from the Japanese Ministry of Health.\textsuperscript{4} All patients also had a concomitant diagnosis of NF1, SCD, or unilateral moyamoya. A total of 83 patients met these criteria.

We determined patient age, sex, length of follow-up, radiographic findings, and clinical symptoms. All patients had undergone multiple MR imaging sessions, including at least 1 individual with no evident arteriopathy. Radiographic progression was defined as the following: 1) worsening of arteriopathy, with development of collateral vessels and/or greater narrowing of the anterior cerebral, middle cerebral, or internal carotid arteries on MR imaging or catheter angiogram (per the cited guidelines); 2) development of FLAIR hyperintensity in the sulci on MR imaging—the “ivy sign”—as a marker of slow cerebral blood flow; and 3) evidence of radiographic infarction, as determined by MR imaging and reported by neuroradiologists.\textsuperscript{3,4,23}

Although all patients were by definition asymptomatic at the time of the initial radiographic diagnosis of moyamoya, we collected data on the number of patients in whom clinical symptoms occurred after development of the arteriopathy. Clinical progression was defined as the new onset of any of the following symptoms: TIA, stroke, headache, seizure, or symptomatic hemorrhage.\textsuperscript{16} In addition, the number of patients who ultimately underwent surgical revascularization was analyzed, along with the time interval between diagnosis of the arteriopathy and the revascularization procedure.

Special note should be made of the patients with unilateral moyamoya. Although these individuals had radiographic evidence of moyamoya in the initial, ipsilateral, affected hemisphere (with or without symptoms), the patients selected for this study had no evident disease—radiographically or clinically—on the contralateral, unaffected hemisphere. They are included here as a population that had no disease contralaterally at the time of diagnosis of the ipsilateral hemisphere, but who are known to be at risk for potential involvement of the contralateral hemisphere, and are thus followed carefully with serial imaging and office visits in the practice of the senior authors.

This work was performed with approval of the Children’s Hospital Boston’s institutional review board.

Results

Demographic Information and Clinical Characteristics at Diagnosis

A total of 83 patients were included in this study, with demographic and summary data reviewed in Table 1. The majority of the children were female (49 patients, 59%), and the mean age was 9.1 years (range 1–21 years). Of the 83 patients, 34 had NF1, 20 had SCD, and 29 had unilateral disease. Differences in age and sex were noted between these groups (see Table 1), but all had comparable overall lengths of follow-up (5.4 ± 3.8 years; mean ± SD).

Radiographic Progression

Radiographic data are summarized in Table 2. Overall, 45 patients (54%) had evidence of radiographic progression within a mean of 5.4 years of follow-up. Differences in the incidence of progression were present, with the SCD subgroup having the greatest number of patients who worsened (75%), followed by NF1 (59%) and patients with unilateral moyamoya (35%). Radiographic data collected included the following: 1) the interval between the date of the first diagnosis of the clinical syndrome (NF1, SCD, or the first affected hemisphere in unilateral moyamoya) and the date of the first radiographic study (MR imaging or angiogram) in which the diagnosis of moyamoya was recognized; 2) the interval between the last MR imaging study with no reported moyamoya (that is, the last “normal” scan) and the first radiographic study

| TABLE 1: Demographic information and clinical characteristics on admission in 83 patients with asymptomatic moyamoya* |
|--------------------------------------------------|----------------|-------------|----------------|----------------|
| Characteristic | NF1 | SCD | Unilat Moyamoya | All Pts |
| no. of pts | 34 | 20 | 29 | 83 |
| mean age in yrs | 7.3 ± 3.9 | 9.0 ± 4.9 | 11.7 ± 7.4 | 9.1 ± 5.7 |
| sex (%) | | | | |
| F | 22 (65) | 13 (65) | 14 (48) | 49 (59) |
| M | 12 (35) | 7 (35) | 15 (52) | 34 (41) |
| mean FU in yrs | 5.5 ± 4.3 | 5.3 ± 3.9 | 5.5 ± 2.7 | 5.4 ± 3.8 |

* Unless otherwise indicated, values are expressed as the mean ± SD. Abbreviations: FU = follow-up; pts = patients.
Asymptomatic moyamoya in children

TABLE 2: Radiographic progression in 83 patients with asymptomatic moyamoya*

<table>
<thead>
<tr>
<th>Feature</th>
<th>NF1</th>
<th>SCD</th>
<th>Unilat Moyamoya</th>
<th>All Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of pts</td>
<td>34</td>
<td>20</td>
<td>29</td>
<td>83</td>
</tr>
<tr>
<td>any radiographic progression (%)</td>
<td>20 (59)</td>
<td>15 (75)</td>
<td>10 (35)</td>
<td>45 (54)</td>
</tr>
<tr>
<td>mean FU in yrs</td>
<td>5.5 ± 4.3</td>
<td>5.3 ± 3.9</td>
<td>5.5 ± 2.7</td>
<td>5.4 ± 3.8</td>
</tr>
<tr>
<td>time interval measurements in yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interval btw diagnosis of syndromic disease &amp; arteriopathy</td>
<td>5.9 ± 3.7</td>
<td>8.3 ± 5.1</td>
<td>1.8 ± 2.4</td>
<td>5.8 ± 4.7</td>
</tr>
<tr>
<td>interval btw last normal scan &amp; arteriopathy</td>
<td>1.5 ± 0.9</td>
<td>2.4 ± 2.4</td>
<td>2.0 ± 1.6</td>
<td>1.9 ± 1.6</td>
</tr>
<tr>
<td>interval btw arteriopathy &amp; slow cortical blood flow (&quot;ivy sign&quot;)</td>
<td>0.4 ± 0.4</td>
<td>1.1 ± 1.4</td>
<td>NA</td>
<td>0.7 ± 1.1</td>
</tr>
<tr>
<td>interval btw arteriopathy &amp; stroke</td>
<td>0.5 ± 0.4</td>
<td>1.3 ± 1.9</td>
<td>0.5 ± 0.7</td>
<td>1.0 ± 1.6</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated, values are expressed as the mean ± SD. Abbreviation: NA = not available.

(MR imaging or angiogram) in which the diagnosis of moyamoya was recognized; and, for the subset of patients in whom the findings developed, 3) the interval between the first scan in which the diagnosis of moyamoya was identified and the first scan that demonstrated “ivy sign” on FLAIR imaging; and 4) the interval between the first scan in which the moyamoya was diagnosed and the presence of a stroke on MR imaging.

Clinical Progression

Clinical progression is defined as the new onset of any of the following symptoms: TIA, stroke, headache, seizure, or symptomatic hemorrhage. It is important to note that individual patients could experience more than 1 symptom, making the total number of reported findings greater than the total number of patients. Results are reported in Table 3, with 37 patients (45%) developing at least 1 new symptom following the diagnosis of moyamoya. Overall, any ischemic symptoms including TIA or stroke (clinically persistent neurological deficit) were the most common, followed by headache, then seizure, with no symptomatic hemorrhages. These relative frequencies were conserved across all 3 subgroups.

Discussion

This study seeks to better inform the clinician faced with the scenario of a child presenting with asymptomatic, incidentally discovered moyamoya. Although the natural history of the symptomatic patient generally supports the use of surgical revascularization, there are few data to guide decision-making in the asymptomatic pediatric population. However, reports from the literature on adult patients, coupled with isolated pediatric papers (or individual patients within larger series), lend support to the hypothesis that asymptomatic moyamoya is not a benign entity, and—although variable in rate and severity—often progresses to affect individuals adversely.

Patient Population

The overall demographic composition of the patient population in this report was reflective of larger series reported by us and others. Female sex predominated in a roughly 2:1 ratio overall, although the percentages for unilateral cases were nearly evenly split between the sexes, at 48:52. The composite mean age was 9.1 years, slightly older than in other reported series (including the previously reported series from our institution, in which the mean age was 6.5 years). The older age at diagnosis may correlate with the absence of symptoms or with referral patterns from subspecialists who may think it unnecessary to send outwardly healthy patients for neurosurgical evaluation.

There was a clear age division by subgroup: the patients with NF1 were the youngest, at 7.3 years; those with SCD were in between, at 9 years; and the patients with unilat...
lateral moyamoya were the oldest, at 11.7 years. Although difficult to assess from the relatively small numbers, it is interesting to note that the group with the youngest age is also the one that most commonly starts screening with MR imaging soonest, with the attendant risk of tumors in children with NF1. It is tempting to speculate that the younger age of detection in this study might be related to the earlier use of imaging, although subsequent studies will need to address this question more formally.

**Radiographic Progression**

More than half of all patients (45 [54%]) demonstrated radiographic progression after being diagnosed with moyamoya within the mean 5.4 years of follow-up, suggesting that this is a dynamic process that is particularly likely to have an impact on pediatric patients, given their expected long life spans. When children are born or first diagnosed with genetic conditions, such as NF1 or SCD, it can take a long time (5.9–8.3 years) for moyamoya arteriopathy to first develop, but once started, the disease often moves quickly. Following the first-ever development of asymptomatic evidence of radiographically confirmed arteriopathy, the mean time to then develop radiographic evidence of ischemia (as manifested by the “ivy” sign) is 0.4 and 1.1 years for NF1 and SCD patients, respectively. It is then only 1–3 months longer, on average, until the first radiographic evidence of infarction appears for the one-third of patients who develop strokes. These data suggest that any evidence of progression of the arteriopathy on serial scans in asymptomatic patients may herald precipitous changes in cerebral perfusion, with a continually increased risk of ischemic injury. Although further study of this interesting finding is warranted, it provides additional justification to consider revascularization in this asymptomatic population.

**Clinical Progression**

Of the 83 patients in whom incidentally discovered, asymptomatic moyamoya was found in this series, 37 (45%) went on to develop clinical symptoms referable to the arteriopathy within the mean 5.4 years of follow-up. As outlined in Table 3, the most common symptoms in the 37 patients with clinical progression were directly related to cerebral ischemia, including TIA (29 patients, 78%) and stroke (10 patients, 27% [manifesting clinically as fixed neurological deficits]). These symptoms were followed in frequency by headache (10 patients, 27%) and seizure (3 patients, 8%). No patient had clinically evident hemorrhage. Interestingly, these symptomatic presentations were essentially unchanged in order of frequency, regardless of whether the patient had NF1, SCD, or unilateral moyamoya. The overwhelming preponderance of ischemic symptoms is concordant with many other series of pediatric patients with moyamoya and suggests that the natural history of these children—once they become symptomatic—will probably become indistinguishable from patients with symptomatic moyamoya in any population.7,16

Comparisons With Previous Reports, Including Adult Series, With Rationale for Surgical Intervention

Similar to what we have reported here, there is evidence in the adult literature that substantial numbers of patients with asymptomatic moyamoya can experience radiographic and clinical progression. One group reported that 24% of 63 adults with idiopathic moyamoya exhibited radiographic progression within a 6-year period, with more than 50% of these patients manifesting ischemic or hemorrhagic infarction during this time.13 In a more recent series from Japan, a group of asymptomatic adults and children who were followed without undergoing surgery demonstrated a 7% mortality rate from cerebral infarction/hemorrhage over a mean of 3.7 years.24 Other adult case reports reveal that untreated, asymptomatic moyamoya can present with catastrophic stroke or death, adding further support to the premise that this disorder can be rapidly progressive, and that preemptive treatment in asymptomatic patients may be warranted.1,2,7

The findings in these reports, coupled with our data in this series, are important because the practice of performing surgical revascularization in asymptomatic patients—including populations of syndromic children (those with Down syndrome, SCD, NF1, unilateral cases, and brain tumor survivors postirradiation)—demonstrates minimal operative morbidity and, in contrast to the natural history reported above, durable protection from ischemic symptoms in long-term outcomes.6,8–10,16–19,22 Surgery has been successfully used in adults who were found to have asymptomatic progression of their moyamoya, with evidence of improved perfusion and absence of ischemic symptoms postoperatively, despite the radiographic progression.9 The protective effect of surgery against stroke in this population was further highlighted in another study of 34 asymptomatic adults, in which 20% of untreated patients became symptomatic within approximately 3.5 years, with an overall 3.2% annual stroke rate; this contrasts with a 0% stroke rate in surgically treated patients.11

In the series described here, 49 (59%) of the 83 patients elected to undergo surgical treatment with pial synangiosis, a technique of indirect revascularization developed by one of the senior authors (R.M.S.).17,20 With the exception of the SCD patients (in whom had a mean of 1.9 years elapsed between the development of radiographic arteriopathy and surgical intervention), most patients were treated within 7 months of the scan on which radiographic progression of the moyamoya was seen. As with other series, the surgical treatment was offered to provide protection from stroke but did not halt the ongoing radiographic progression of the arteriopathy.14,18,19

**Operative Indications and Technique, Follow-Up**

It is the practice in our institution to offer surgical revascularization with pial synangiosis to patients in whom moyamoya is diagnosed, including asymptomatic patients. Although individual review occurs with each case, we will generally proceed with surgery in children with radiographically documented moyamoya (Suzuki Stage 2 or greater), barring medical contraindications to craniotomy or a recent stroke (<6 weeks). In patients with bilateral disease, we have routinely performed surgery on both sides during a single anesthetic session; we have used this method for nearly a decade. For greater detail on the operative technique, along with specific protocols
for subpopulations of syndromic patients (such as children with SCD), readers are referred to other reports from our group.\textsuperscript{7,18,20,21}

For those patients who are observed (unclear diagnosis, Suzuki Stage 1, medically unstable—or patients with unilateral disease undergoing monitoring of the unaffected hemisphere), we will commonly perform surveillance imaging with MR imaging/MR angiography on an annual basis. In cases with the onset of new symptoms or in infants (<3 years of age), we will consider more frequent studies and offer surgical treatment if moyamoya is confirmed. In surgically treated patients we typically obtain an MR imaging/angiography study at 6 months and then imaging at 1 year postoperatively, with annual MR imaging/angiography for at least 5 years thereafter.

\textbf{Study Limitations}

There are obvious limitations to this type of study, including its retrospective nature, limited number of patients, and the inherent variability in defining many of the measures used in the evaluations (progression of arteriopathy, "ivy" sign, clinical manifestations of cerebral ischemia). The selection of specific subgroups of patients with syndromic moyamoya was based on availability of data and relatively homogeneous patient populations. It would be beneficial to expand this work to include other groups, such as patients with brain tumor postirradiation and children with Down syndrome, among others.

It is also important to note that the population in this study is derived from a center that has a high volume of moyamoya referrals. This may introduce a bias, because it is likely that asymptomatic patients in other locations may not be referred for evaluation and treatment. Our center has a bias toward offering treatment—even to asymptomatic patients—and it would be potentially useful to understand the natural history better in untreated individuals. However, data from Japan and the US suggest that the natural history in moyamoya is highly likely to be progressive, with a substantial risk of stroke, as reviewed previously in the discussion. Therefore, although we acknowledge that a bias probably exists at our institution and appreciate that further study would certainly be of interest, we would contend that our aggressive approach to offering treatment can be justified.

Although we acknowledge that further study is certainly warranted, we hope that this work will provide some preliminary observational data to assist in the clinical practice of physicians involved in the care of children with these syndromes and with moyamoya.

\textbf{Conclusions}

Incidentally discovered asymptomatic moyamoya in children has the potential to progress, both radiographically and clinically. Once started, development of signs and symptoms referable to cerebral ischemia can present in rapid fashion, sometimes within months, with the potential for permanent deficits. These data support the practice of continued monitoring in at-risk syndromic populations and early referral to neurosurgeons once evidence of arteriopathy develops, and they provide additional justification to consider revascularization in asymptomatic patients with moyamoya.

\textbf{Disclosure}

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Smith, Ullrich, Scott. Acquisition of data: Lin, Koss, Kopecky, Gone. Analysis and interpretation of data: Smith, Lin. Drafting the article: Smith. Critical revising the article: Smith, Baird. Reviewed submitted version of manuscript: Smith, Baird. Study supervision: Smith.

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