Blood Pressure Elevation and Risk of Moyamoya Syndrome in Patients With Trisomy 21

Jonathan D. Santoro, MD, a Sarah Lee, MD, a,b,c,d Michael Mlynash, MD, MS, a Thuy Nguyen, MD, a Daniel V. Lazzarosci, MD, e Lironn D. Kraler, MD, c,d Elizabeth W. Mayne, MD, PhD, a Gary K. Steinberg, MD, PhD a,b,c,d

OBJECTIVES: Individuals with Down syndrome (DS) are at risk for the development of moyamoya syndrome (MMS); MMS is often recognized only after a resulting stroke has occurred. Our goal with this study was to determine if elevations in blood pressure (BP) precede acute presentation of MMS in individuals with DS.

METHODS: A single-center, retrospective case-control study was performed. Thirty patients with MMS and DS and 116 patients with DS only were identified retrospectively. Three BP recordings were evaluated at set intervals (18–24 months, 12–18 months, and 6–12 months before diagnosis of MMS). These were then compared against control averages from patients with DS only. To assess changes over the time, we used general linear model repeated measures analysis of variance. To identify independent predictors of MMS and DS, we used a multivariable analysis using generalized estimating equations accounting for repeated measures of BP.

RESULTS: BP in patients with MMS and DS rose significantly over the 24-month period preceding presentation (34th, 42nd, and 70th percentiles at the 18–24 month, 12–18 month, and 6–12 month periods, respectively). BPs in the patients with both MMS and DS were significantly higher than in the DS-only controls in the 6 to 12 (P < .001) and 12 to 18 months before presentation (P = .016). Higher Suzuki scores, bilateral disease, and posterior circulation involvement were also predictive of BP elevation before presentation.

CONCLUSIONS: Elevations in BP may foreshadow presentation of MMS in individuals with DS. This simple, low-cost screening measure may lead to early identification of at-risk patients in the medical home and prevent irreversible neurologic injury.
Moyamoya disease is a chronic, progressive cerebrovascular condition that can cause devastating strokes in children and adults. Classically, bilateral stenosis of the proximal intracranial arteries develops over time, leading to the development of abnormal and friable collateral vessels, which creates the characteristic “puff of smoke” pattern seen on cerebral angiography.¹⁻³

There is a well-described association between Down syndrome (DS) and moyamoya syndrome (MMS).⁴⁻⁶ Although the exact pathogenesis is not well understood. Individuals with DS have a threefold increased incidence of MMS,⁹,¹⁰ and there is an ∼26-fold greater prevalence of DS in individuals with MMS.⁷ This association is even more pronounced in those <15 years of age, emphasizing the significance of MMS in the pediatric DS population.⁷,⁸

Hypertension has been described in children and adults with MMS without DS, which is presumed to be a systemic compensatory response against progressive cerebrovascular stenosis.¹¹,¹² In DS, however, blood pressure (BP) is typically low.¹³⁻¹⁶ To date, there have been no studies in which authors evaluate BP in DS patients with MMS.

We hypothesize that rising BP may be an early clinical indicator of MMS in this population. Our objectives with this study were to (1) retrospectively evaluate patients with MMS and DS for hypertension up to 24 months before presentation and (2) compare rates of hypertension in patients with MMS and DS against historical controls with DS only.

METHODS

Patient Selection

All cases were identified retrospectively from a prospectively enrolled, single-center moyamoya disease research database after obtaining institutional review board approval. Included cases fulfilled the following criteria: a previous diagnosis of DS confirmed by karyotype, a diagnosis of MMS based on published angiographic criteria,³ and corrective or prophylactic neurosurgery performed at Stanford University hospitals between 1998 and 2016. Patient demographics, medical comorbidities, and clinical presentation of MMS were collected via chart review. Patients were excluded if they had clinically significant thyroid disease, heart disease, renal artery stenosis, and/or untreated obstructive sleep apnea (OSA). Patients were excluded if these findings were clinically significant, suboptimally treated, or untreated (see Supplemental Information for definitions). Neuroimaging studies were rereviewed to confirm the presence of disease, and Suzuki scores were retrospectively applied to assess disease severity.¹⁷

The control group was identified retrospectively from Stanford University hospitals, Santa Clara Valley Medical Center in San Jose, California, and 1 private practice clinic in San Jose, California by searching electronic medical records for patients with an established International Classification of Diseases, Ninth Revision (ICD-9) code of DS from 1998 to 2015. Exclusion criteria were the following: (1) <3 “well child” visits in which vital signs were measured, (2) an interval of <6 months between each visit, (3) clinic visits occurring exclusively between 2015 and 2018 because this could overlap with the subsequent development of MMS, and (4) clinically significant coexisting conditions (defined above) that predispose to hypertension or may make the interpretation of BP difficult. Patients with well-controlled, comorbid conditions during the data collection period were included in both groups (Supplemental Information).

BP Measurement and Conversion to Percentiles

For patients with MMS and DS, BP measurements were extracted from clinic notes at our institution, outside clinical records, and/or well-child, vaccination-only, or “urgent” visits for conditions not expected to be associated with changes in BP, such as conjunctivitis. BP readings obtained during hospitalizations or emergency department encounters were excluded. All cases had 1 BP measurement during each of the categorical time intervals (18–24 months, 12–18 months, and 6–12 months) before diagnosis of MMS. For the control group, each patient had 3 BP measurements at least 6 months apart during routine health maintenance visits. To allow comparison across ages, BP measurements were converted to percentiles for age and height by using standardized data from the National Heart, Lung, and Blood Institute (NHLBI).¹⁸ Previously published NHLBI normative values were applied to patients >18 years old.¹⁹

Statistical Analysis

We assessed BP percentile differences between groups of patients using the Mann–Whitney U test. Changes over time within the same group of patients were assessed by using the Wilcoxon rank test. Difference between medians was calculated by using Hodges–Lehman estimates with 95% confidence intervals (CIs). To evaluate changes over time in combination with the effects of cofactors, we used general linear model (GLM) repeated measures analysis of variance (ANOVA). To assess the association of BP percentiles at different intervals before presentation with the case versus control groups and to adjust for other variables, we employed
multivariable analysis using generalized estimating equations, taking into account repeated BP measurements in each patient. Using receiver operating characteristic curve analysis, we assessed the ability of BP in patients with DS to predict development of MMS. We identified the optimal discrimination threshold for BP using the maximal value of Youden’s J statistics, and from there, we estimated predictive values of BP. To assess gradual change of the BP in association with the Suzuki grades, we used the Jonckheere–Terpstra test for ordered differences.

All statistical tests were 2 sided, and statistical significance was defined at α < .05. Statistical analysis was done by using IBM SPSS Statistics (IBM SPSS Statistics, IBM Corporation) version 24.

RESULTS

In total, 30 patients with MMS and DS and 116 patients in the control group with DS only were included (Fig 1); baseline characteristics are reported in Table 1. The median age at the time of MMS diagnosis in the MMS and DS group was 13.5 years (interquartile range [IQR]: 7 to 19); the median age of patients in the control group was 12 years (IQR: 9 to 16). Thirty-seven percent (11 of 30) of patients in the MMS and DS group had treated hypothyroidism at presentation, and 17% (5 of 30) had clinically insignificant or previously corrected cardiac disease (typically atrial septal defect or ventricular septal defect). There was no statistically significant difference in the prevalence of comorbid conditions between groups. The majority (77%; 23 of 30) of patients in the MMS and DS group presented with acute arterial ischemic stroke (AIS). Other presentations included subacute hemiparesis in 10% (3 of 30), transient ischemic attack in 7% (2 of 30), and headache and localization-related epilepsy in 3% each (1 of 30). No patients with both MMS and DS presented with hemorrhagic stroke. The patients with progressive hemiparesis and the single patient with headache and localization-related epilepsy did not have neuroimaging findings of acute AIS at the time of presentation and diagnosis. A subset of patients with MMS and DS (6 of 30) reported viral illness within 2 weeks preceding presentation, but the majority (22 of 30) had no provoking factor.

In the MMS and DS group, median BP percentiles rose over the 18 months preceding presentation, from the 34th percentile (IQR: 15 to 52) at 18 to 24 months, to the 42nd percentile (IQR: 28 to 61) at 12 to 18 months, to the 70th percentile (IQR: 39 to 73) at 6 to 12 months before diagnosis. Median BP percentiles at 6 to 12 months before MMS diagnosis were significantly higher than the median BP percentile at the 12 to 18– and 18 to 24–month intervals before diagnosis (P < .001; Fig 2). In contrast, median BP percentiles in the control group did not differ significantly across equivalent time intervals (18–24 months, 12–18 months, and 6–12 months before the index time). When comparing patients with MMS and DS to patients in the control group, there was no difference in the median BP percentile during the 18 to 24–month period before presentation (P = .626). BPs were significantly higher in patients with both MMS and DS than patients in the control group during the 12 to 18–month period (by a median of 10.2 percentile points [P = .016; 95% CI: 1.7 to 18.7]) and the 6 to 12–month period before presentation (a median of 32.0 percentile points [P < .001; 95% CI: 20.0 to 40.3]) (Fig 2). Finally, in patients with both MMS and DS, there were statistically significant changes in BP percentile for each patient throughout each time point (Fig 3). This was driven by increases in BP percentiles at 6 to 12 months compared with the 2 previous time periods (P < .001) in patients with both MMS and DS. There was no significant difference in BP between the 18 to 24– and 12 to 18–month
interval before presentation \((P = .094)\). BP percentiles increased in cases by a median IQR of 4.5 \((-8.0 to 28.0)\) and 12.5 \((3.0 to 31.0)\) between the 18 to 24– and 12 to 18–month period and 12 to 18– and 6 to 12–month period before, respectively. For patients with DS only, there were corresponding changes of 1.0 \((-10.0 to 12.5)\) and 0 \((-8.0 to 10.5)\).

Among patients with both MMS and DS, the median Suzuki grade at the time of diagnostic angiography was 3 \((IQR: 2 to 4; range: 1 to 6)\). Higher Suzuki grades were associated with significantly higher BP recordings at 6 to 12 and 12 to 18 months \((P < .001\) and \(P = .005\), respectively). This association was not observed in the 18 to 24–month group \((P = .085)\). In an additional evaluation of disease severity, 30% \((9 of 30)\) had unilateral disease at presentation, whereas 70% \((21 of 30)\) had bilateral disease at presentation. Twenty-seven percent of patients \((8 of 30)\) had evidence of disease in the posterior circulation. There was no difference in median BP percentiles between cases with bilateral and unilateral disease at earlier time points \((35\% versus 29\% at 18–24 months; P = .428; 45\% versus 30\% at 12–18 months; P = .248)\). However, in the 6 to 12–month interval before presentation, BP was significantly higher in patients with bilateral disease \((71\% versus 31\%; P = .002)\). The repeated measures analysis revealed that both time to presentation \((P < .001)\) as well as bilateral disease \((P = .018)\) affected BP percentiles. Interestingly, there was also interaction between time and bilateral involvement \((P = .023)\), suggesting that time before presentation has a greater impact on BP elevations in individuals with bilateral disease \((Fig 4)\). Presence of bilateral disease was associated with higher Suzuki grades \((P = .014)\).

### TABLE 1 Demographics, Clinical Presentation, and BP Percentiles by Disease Process

<table>
<thead>
<tr>
<th>Demographics</th>
<th>DS</th>
<th>MMS and DS</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>12 (9 to 16)</td>
<td>13.5 (7 to 19)</td>
<td>280</td>
</tr>
<tr>
<td>Sex (female), n (%)</td>
<td>64 (55)</td>
<td>20 (67)</td>
<td>256</td>
</tr>
<tr>
<td>Suzuki grade, n (%)</td>
<td>—</td>
<td>3 (2 to 4)</td>
<td>—</td>
</tr>
<tr>
<td>Comorbid conditions, n (%)</td>
<td>23 (29)</td>
<td>11 (57)(b)</td>
<td>.087</td>
</tr>
<tr>
<td>Hypothyroidy</td>
<td>21 (18)</td>
<td>5 (17)</td>
<td>.981</td>
</tr>
<tr>
<td>Corrected cardiac disease (ASD or VSD)</td>
<td>14 (12)</td>
<td>5 (17)</td>
<td>.548</td>
</tr>
<tr>
<td>None</td>
<td>58 (50)</td>
<td>9 (30)</td>
<td>.084</td>
</tr>
<tr>
<td>Clinical presentation, n (%)</td>
<td>—</td>
<td>23 (17)</td>
<td>—</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>18 (15 to 20)</td>
<td>14 (12)</td>
<td>.248</td>
</tr>
<tr>
<td>Disease severity, n (%)</td>
<td>—</td>
<td>1 (3)</td>
<td>—</td>
</tr>
<tr>
<td>Presence of bilateral disease</td>
<td>—</td>
<td>21 (70)</td>
<td>—</td>
</tr>
<tr>
<td>Posterior circulation involvement</td>
<td>8 (27)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BP percentiles, mo, median percentile (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–24</td>
<td>30 (22 to 43)(d)</td>
<td>34 (15 to 52)</td>
<td>.626</td>
</tr>
<tr>
<td>12–18</td>
<td>42 (28 to 61)(b)</td>
<td>70 (39 to 73)(b)</td>
<td>.016</td>
</tr>
<tr>
<td>6–12</td>
<td>—</td>
<td>30 (21 to 44)</td>
<td>—</td>
</tr>
<tr>
<td>Postsurgery (5–6 mo after)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BP percentiles, mo, median percentile (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>Absent ((n = 9))</td>
<td>Present ((n = 21))</td>
<td>—</td>
</tr>
<tr>
<td>18–24</td>
<td>29 (15 to 40)</td>
<td>35 (22 to 55)</td>
<td>.428</td>
</tr>
<tr>
<td>12–18</td>
<td>30 (23 to 44)</td>
<td>45 (28 to 61)</td>
<td>.248</td>
</tr>
<tr>
<td>6–12</td>
<td>31 (23 to 61)</td>
<td>71 (67 to 77)(e)</td>
<td>.002</td>
</tr>
<tr>
<td>Posterior circulation involvement in patients with bilateral disease</td>
<td>Absent ((n = 13))</td>
<td>Present ((n = 8))</td>
<td>—</td>
</tr>
<tr>
<td>18–24</td>
<td>35 (22 to 55)</td>
<td>39 (21 to 56)</td>
<td>.697</td>
</tr>
<tr>
<td>12–18</td>
<td>31 (23 to 51)</td>
<td>61 (50 to 76)(e)</td>
<td>.008</td>
</tr>
<tr>
<td>6–12</td>
<td>69 (50 to 78)</td>
<td>73 (71 to 90)(e)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(a\) Comorbid conditions were not clinically significant during the time of this study (Supplemental Information).

\(b\) Statistically significant difference compared with DS control.

\(c\) The same patient presented with both headache and localization-related epilepsy.

\(d\) Average of the 3 assessments in the control group.

\(e\) Statistically significant difference compared with absent condition.

\((P < .001)\) as well as bilateral disease \((P = .018)\) affected BP percentiles. Interestingly, there was also interaction between time and bilateral involvement \((P = .023)\), suggesting that time before presentation has a greater impact on BP elevations in individuals with bilateral disease \((Fig 4)\). Presence of bilateral disease was associated with higher Suzuki grades \((P = .014)\). All 8 patients with posterior circulation involvement also had
Evidence of bilateral disease of the anterior circulation as well as presence of collaterals. Median BP percentiles in cases with bilateral disease without posterior involvement (n = 13) compared with bilateral disease with posterior circulation involvement (n = 8) were 33rd percentile versus 39th percentile at 18 to 24 months (P = .697), 31st percentile versus 61st percentile at 12 to 18 months (P = .008), and 69th percentile versus 73rd percentile at 6 to 12 months (P = .045), respectively. Again, both time (P < .001) and posterior circulation involvement (P = .047) affected BP percentiles, but there was no interaction between time and posterior circulation involvement (P = .121) (Fig 5). Presence of posterior circulation involvement was associated with higher Suzuki grades (P = .003).

Adjusted for age, sex, and height, the number of months before MMS presentation was significantly inversely correlated with increasing BP percentiles (P = .001). AIS at initial presentation was a significant predictor of higher BP percentiles at 12 to 18 months and 6 to 12 months (P = .005), and its interaction with the time effect was also significant (P = .001). After revascularization, patients with both MMS and DS demonstrated dramatic normalization of BP with a median value of 30th percentile (IQR: 21 to 44) between 3 and 6 months postoperatively (Table 1). Data for medications that could alter (suppress or increase) BP on follow-up visits were not available for nearly all patients (93%; 28 of 30).

In the multivariable analysis, BP was an independent predictor of development of MMS (P = .002) along with time (P < .001 for time and its interaction with BP), when adjusted for age (P = .098) and sex (P = .520). For each 1-point increase in BP percentile at 18 to 24, 12 to 18, and 6 to 12 months before presentation, the adjusted odds ratio for having MMS was respectively 1.004 (95% CI: 0.98 to 1.02), 1.03 (95% CI: 1.004 to 1.05), and 1.05 (95% CI: 1.03 to 1.08). With each year of age, the odds of developing MMS in individuals with...
DS increased with an adjusted odds ratio of 1.07 (95% CI: 0.99 to 1.17). The BP within 6 to 12 months before presentation was used to classify individuals with DS both with and without MMS with good accuracy (area under the curve [AUC] 0.80 [95% CI: 0.70 to 0.91]). A cutoff of BP percentile >60 was the most optimal cutoff used to predict MMS. BP percentiles ≥60 were found in 20 of 30 (67%) patients with both MMS and DS versus 8 of 116 (7%) patients in the control group. This produced the following prediction performance values with 95% CI: sensitivity of 0.67 (0.47 to 0.82), specificity of 0.93 (0.86 to 0.97), positive predictive value of 0.71 (0.51 to 0.86), and negative predictive value of 0.92 (0.85 to 0.96). However, the BP failed to discriminate 2 groups at 18 to 24 months (AUC = 0.53 [95% CI 0.40 to 0.66]) and performed poorly at 12 to 18 months with AUC = 0.64 (95% CI 0.53 to 0.76).

**DISCUSSION**

We found that significant elevations in BP may occur up to 12 to 18 months before presentation of MMS among individuals with DS. BP is an easily obtainable, cost-efficient, and routinely performed measurement in the pediatric medical home, making it a potentially useful screening measure for early detection of MMS in this at-risk population. The magnitude of increase in BP was driven primarily by patients with radiographic evidence of more advanced disease as defined by higher Suzuki score, bilateral stenosis, and dual anterior and/or posterior involvement. With this finding, we support the hypothesis that more severe vasculopathy leads to dramatic systemic compensatory elevations in BP, which corresponds with the gradual loss of autoregulation in the setting of the increasingly stenotic vessels.³⁻¹⁻²¹ Another explanation is that severe cerebral vasculopathy may co-occur with stenosis of other vessels in the body, such as the renal arteries, which in turn causes secondary hypertension.¹⁵ We also found that BP percentiles decreased after surgical revascularization, which further supports the hypotheses that more severe vasculopathy corresponds with more significant rises in BP.

Definitive diagnosis of MMS requires neuroimaging of the cerebrovasculature, which is both expensive and logistically challenging to obtain, especially in children. Catheter angiography, the gold standard for diagnosis of MMS, is an invasive procedure, requires general anesthesia and experienced interventional radiologists, and may cause harm to patients. Even noninvasive neuroimaging modalities such as magnetic resonance angiography typically requires sedation or general anesthesia to complete, which is not without risk. Furthermore, with any neuroimaging modality, the costs of screening all asymptomatic individuals with DS for MMS are prohibitive. By contrast, BP monitoring is inexpensive, noninvasive, and can be performed in nearly any setting including the pediatric medical home. In addition, automated BP cuffs require virtually no training to use and may be checked routinely by family members, caregivers, or even individuals themselves. With our results, we suggest that...
BP may be a useful early detection tool to help identify a subset of individuals for whom neuroimaging or further neurologic assessment may be warranted. In addition, early identification and implementation of medical or surgical intervention before stroke could reduce long-term morbidity, cost of care, and improve quality of life.\textsuperscript{22,23}

Notably, the BP recordings obtained for nearly all patients in this study are within the “normal” range on the basis of NHLBI standardized data. However, the BP trend over time among cases reveals a progressive rise beginning up to 18 months before presentation of MMS. It is possible that with the transition to electronic medical records over the last decade, wherein abnormal results are typically “flagged” for providers, a decline in manual nomogram charting may contribute to delays in diagnosis of BP changes in this population, although this was not assessed in this study.

One advantage of this study was the comparatively large number of both cases and controls in our cohort. Additionally, with a case-control ratio of 1:3.87 (30 cases; 116 controls), our study was powered to detect true probabilities of exposure among cases as high as 0.609 (assuming a priori probability of exposure to hypertension in controls to be 0.33, the adult rate of hypertension).\textsuperscript{19} Another strength includes the number of BP recordings collected over an extended period of time.

There are several limitations to our study. Firstly, the retrospective design from a surgical database introduces severity bias. Second, this study is not case matched; however, strict inclusion and exclusion criteria were used to minimize the impact of comorbidities conditions on our data, because BP elevations can be attributed to a number of underlying conditions that are not specific for cerebral vasculopathy. Additionally, although excluding patients with these comorbidities helped reduce confounders, how to interpret BP elevations in patients with DS with these conditions is not known. Third, BP percentiles were used to adjust for height and age, which vary greatly in children. However, because this is a nonlinear conversion, it is possible that trends in BP over time were masked in this study. Additionally, all recordings were taken in a clinic or hospital setting, which can notably induce anxiety, agitation, and “white coat hypertension,” although this would be expected to be similar between cases and controls. In addition, although details of medications that could alter BP were obtained for all prepresentation visits, this was not available in 93% of patients in their postsurgical intervention visit, making interpretation of this latter data point difficult. Finally, the strict exclusion of patients with comorbidities when designating the control population resulted in a slightly unbalanced comparison with regard to age and sex, although this was not statistically significant.

With our study, we found that elevated BP in individuals with DS...
may foreshadow symptomatic MMS and could be a simple, cost-effective screening tool for early identification in this at-risk population. The prognosis of patients with MMS is largely dependent on neurologic status at the time of diagnosis. Further prospective investigation is needed to confirm these findings.

ACKNOWLEDGMENTS

We acknowledge Drs Courtney Wusthoff and Maarten Lansberg for their contributions to the editing of this article. We thank Dr Edward Guarino for participating in the collection of these data.

ABBREVIATIONS

AIS: arterial ischemic stroke
ANOVA: analysis of variance
AUC: area under the curve
CI: confidence interval
DS: Down syndrome
GLM: general linear model
ICD-9: International Classification of Diseases, Ninth Revision
IQR: interquartile range
MMS: moyamoya syndrome
NHLBI: National Heart, Lung, and Blood Institute
OSA: obstructive sleep apnea

REFERENCES


Blood Pressure Elevation and Risk of Moyamoya Syndrome in Patients With Trisomy 21
Jonathan D. Santoro, Sarah Lee, Michael Mlynash, Thuy Nguyen, Daniel V. Lazzareschi, Lironn D. Kraler, Elizabeth W. Mayne and Gary K. Steinberg

Pediatrics originally published online September 6, 2018;

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/early/2018/09/04/peds.2018-0840">http://pediatrics.aappublications.org/content/early/2018/09/04/peds.2018-0840</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 26 articles, 6 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/early/2018/09/04/peds.2018-0840#BIBL">http://pediatrics.aappublications.org/content/early/2018/09/04/peds.2018-0840#BIBL</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): Neurology <a href="http://www.aappublications.org/cgi/collection/neurology_sub">http://www.aappublications.org/cgi/collection/neurology_sub</a> Neurological Surgery <a href="http://www.aappublications.org/cgi/collection/neurological_surgery_sub">http://www.aappublications.org/cgi/collection/neurological_surgery_sub</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.aappublications.org/site/misc/Permissions.xhtml">http://www.aappublications.org/site/misc/Permissions.xhtml</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://www.aappublications.org/site/misc/reprints.xhtml">http://www.aappublications.org/site/misc/reprints.xhtml</a></td>
</tr>
</tbody>
</table>
Blood Pressure Elevation and Risk of Moyamoya Syndrome in Patients With Trisomy 21
Jonathan D. Santoro, Sarah Lee, Michael Mlynash, Thuy Nguyen, Daniel V. Lazzareschi, Lironn D. Kraler, Elizabeth W. Mayne and Gary K. Steinberg

Pediatrics originally published online September 6, 2018;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2018/09/04/peds.2018-0840

Data Supplement at:
http://pediatrics.aappublications.org/content/suppl/2018/09/05/peds.2018-0840.DCSupplemental