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# Cephalometric Features of Moyamoya Disease: a case control study

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## Abstract

**Contribution of authors—**Adnan I Qureshi, Waqas I Gilani MD, Sarwat I. Gilani MD, Malik M. Adil MD . Equally assisted in the synthesis and discussion of ideas, and share equal responsibility for the information written in the manuscript above.

**Conflict of Interest—**No conflict of interests.

**Running title—**Cephalometric Features of Moyamoya Disease

**Background—**Moyamoya disease is highly prevalent among patients with syndromes that have unique cephalometric characteristics such as Down syndrome. We performed a case control study to investigate the relationship between cephalometric parameters and Moyamoya disease.

**Methods—**Patients [aged 16-82 years] with angiographically confirmed Moyamoya disease who underwent cranial CT scan were analyzed. We identified three controls for each patient who were matched for age (±1 year), gender, and race (white or African American). The fronto-occipital diameter, bi-parietal diameter, and distance between bregma and occiput were measured from the head CT scans of cases and controls. The cephalic index was calculated by determining the ratio between bi-parietal diameter and fronto-occipital diameter and multiplying the value by 100.

**Results—**A total of 13 cases of Moyamoya disease and 39 controls were analyzed. The stage of Moyamoya disease in cases was as follows: stage 1 (n=0), stage 2 (n=1), stage 3 (n=4), stage 4 (n=2), stage 5 (n=5) and stage 6 (n=1). There was a significantly greater bi-parietal diameter in Moyamoya disease patients compared with controls (141.5±3.7 mm versus 136.9±5.4 mm, p=0.007). There was a significantly greater fronto-occipital diameter in Moyamoya disease patients compared with controls (186.5±6.5 mm versus 180.2±8.7mm, p=0.02). The distance between bregma and occiput was shorter among cases compared with controls (81.1±6.2 versus 87.5±7.0, p=0.01).

**Conclusions—**We observed an association between cephalometric parameters and Moyamoya disease. Further study of the unique cephalometric characteristics among Moyamoya disease patients may provide additional insight into disease occurrence in white and African American populations.

### Key words

Moyamoya disease; fronto-occipital diameter; cephalic index; cephalometry; race/ethnicity

## Introduction

An association between Moyamoya disease and Down syndrome appears to exist based on reported anecdotal case series. In United States, an estimated 518 patients with co-existing Moyamoya disease and Down syndrome were admitted from 2002 to 2009.[16] There was a 300 fold higher prevalence of Moyamoya disease in patients with co-existing Down syndrome (3760 per 100,000) compared with the prevalence of Moyamoya disease among live births (12 per 100,000). Cephalometric analysis in patients with Down syndrome identifies specific craniofacial features which include reduced anterior and posterior cranial base lengths and reduced anterior and posterior face heights.[2,24,30] Populations with shorter cranial base such as Chinese and Japanese

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populations[8,22] have a higher prevalence of Moyamoya disease.[4] We hypothesized that there is a relationship between cranial base parameters and occurrence of Moyamoya disease. We performed this case control study to further investigate the relationship between cephalometric parameters and Moyamoya disease.

## Methods

We identified all patients discharged with the primary or secondary ICD-9 CM code 437.5 from September 4th 2000 to September 1 9th 2011 at the two university affiliated tertiary care hospitals in Minneapolis, MN. In a previous analysis,[16] we had found that this ICD-9 code had a positive predictive value of 89% for identification of patients with Moyamoya disease. Each patient identified [cases aged 16-82 years] had undergone a non-contrast computed tomographic (CT) scan. Included patients had confirmation of Moyamoya disease by cerebral angiography and had no diagnosis of Down syndrome in the medical records. The severity of Moyamoya disease was classified based on angiographic findings using the previously described method.[32,35] The angiographic findings were used to categorize patients in one of the six stages. These stages range from early carotid narrowing, to the formation of basal Moyamoya vessels, to the disappearance of these collateral vessels and maintenance of the cerebrum by the external carotid and vertebral systems.

We identified three controls for each patient who were matched for age (±1 year), gender, and race (white or African American). Two sources were used to identify controls. First, matched controls were selected from the database of endovascular treated patients with cerebrovascular disease who did not have Moyamoya disease based on angiographic images. In a small proportion of Moyamoya patients, controls were not available through the database. In such a situation, a random list of patients with same age admitted within the same period of time to one of the two hospitals was generated. A quick screening was performed to narrow the list further by matching by gender and race. Subsequently, the diagnostic investigation record was reviewed for patients on the list to identify those who had undergone a head CT scan. We screened patients in an alphabetical order to select those who did not have Down syndrome, craniotomy, or Moyamoya disease. The screening process continued until the required number of controls was identified.

The fronto-occipital diameter, bi-parietal diameter, and distance between bregma and occiput were measured

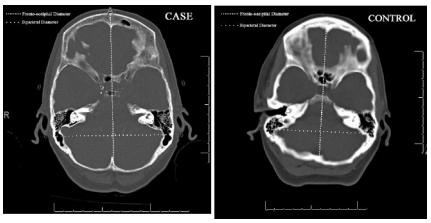
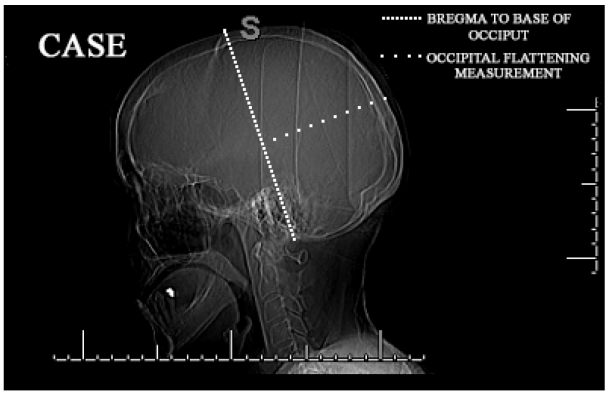



**Figure 1. The axial CT scans of a patient with Moyamoya disease and age/gender/race matched control demonstrating measurement of fronto-occipital and bi-parietal diameters.**

from the head CT scans of cases and controls. The fronto-occipital and bi-parietal diameters were determined using the axial CT scans (see Figure 1). The lateral CT scout radiograph obtained immediately before the axial CT scans was used to determine the distance between bregma and occiput. CT head scan slices were acquired parallel to the orbito-meatal line, defined as passing through the lateral canthus and middle of the external ear canal. The bi-parietal diameter (the scout image with the largest bi-parietal diameter was selected by scrolling through all the axial CT scans) was defined as the maximum measurable bi-parietal diameter (euryon–euryon distance) and the fronto-occipital diameter was defined as the maximum measurable midline anterior–posterior diameter (glabellar–opisthocranium distance)[1]. The distance between bregma and occiput (internal occipital protuberance) were measured from the sagittal scout images acquired as part of head CT scans (see Figure 2).[23] A line was drawn between bregma and posterior aspect of foramen magnum (base of occiput). The distance between the central point of above mentioned line and internal occipital protuberance was measured to determine the distance between bregma and occiput. The images were imported into Imagecast software (Imagecast V10.3.9.91 UP51). Measurements were made using a measurement tool in the software. The cephalic index was calculated by determining the ratio between bi-parietal diameter and fronto-occipital diameter and multiplying the value by 100.

The measured diameters and index were continuous data and descriptively represented as means ± standard deviations. Following determination of normal distribution of data by Anderson-Darling Test, the analysis of variances for fronto-occipital diameter, bi-parietal diameter, and distance between bregma and occiput between the cases and controls was performed using the two sample t-test on SAS 9.3 statistical software (SAS, Cary, North Carolina). The difference of variances was determined by the Folded F method. If the variances were not statistically



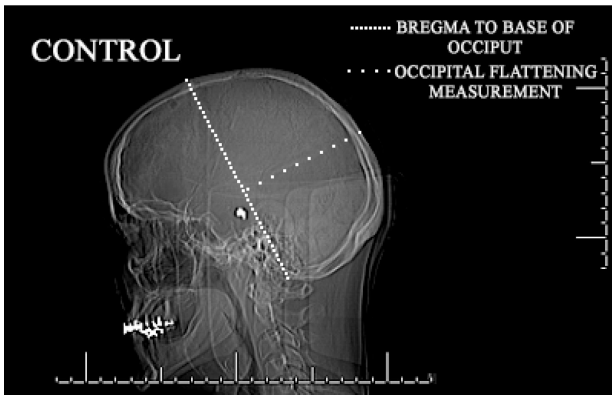
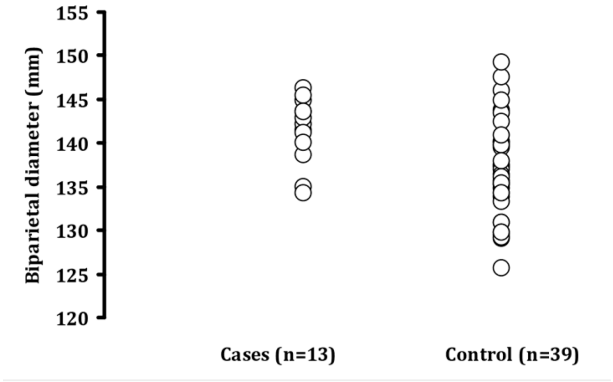




**Figure 2. The sagittal scout images of CT scans of a patient with Moyamoya disease and age/gender/race matched control demonstrating measurement of bregma-occipital diameters.**

different, pooled method of two sample t-test was used. If the variance was statistically different, Satterthwaite method was used. Since cephalic index was not distributed normally, the exact Wilcoxon two-sample test was used to compare the values between cases and controls. A p-value of $< 0.05$ was considered statistically significant.

## Results

A total of 13 cases of Moyamoya disease and 39 controls were analyzed. The mean age (±SD) of cases and controls were 41±17 years and 41±18 years, respectively. A total of 7 of 13 cases and 21 of 39 controls were males. The stage of Moyamoya disease in cases was as follows: stage 1 (n=0), stage 2 (n=1), stage 3 (n=4), stage 4 (n=2), stage 5 (n=5) and stage 6 (n=1).



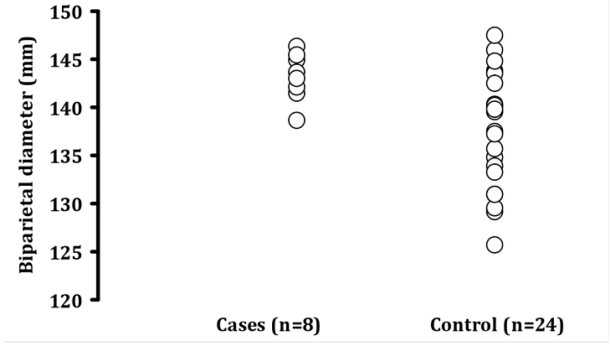




**Figure 3. A scatter plot demonstrating the bi-parietal diameter in patients with Moyamoya disease and age, gender, and race matched controls. a. Includes both white and African patients; B. Includes only white patients.**

There was a significantly greater bi-parietal diameter in Moyamoya disease patients compared with controls (141.5±3.7 mm versus 136.9±5.4 mm, p=0.007). There was a significantly greater fronto-occipital diameter in Moyamoya disease patients compared with controls (186.5±6.5 mm versus 180.2±8.7mm, p=0.02). Figures 1 and 2 provide scatter plots that present the distribution of bi-parietal diameter and fronto-occipital diameter in cases and controls. The cephalic index was not different between cases and controls (75.9±2.8 versus 76.1±5.0, p=0.7). The distance between bregma and occiput was shorter among cases compared with controls (81.1±6.2 versus 87.5±7.0, p=0.01).

In an exploratory analysis limited to only white patients who formed cases (n=8) and controls (n=24), the bi-parietal diameter (Fig 3) (143.2±2.5 mm versus 137.6±5.8 mm, p=0.008) and fronto-occipital diameter (Fig 4) (187.1±7.4 mm versus 179.9±8.6 mm, p=0.04) were significantly greater among Moyamoya cases compared with controls. Other variables were not different

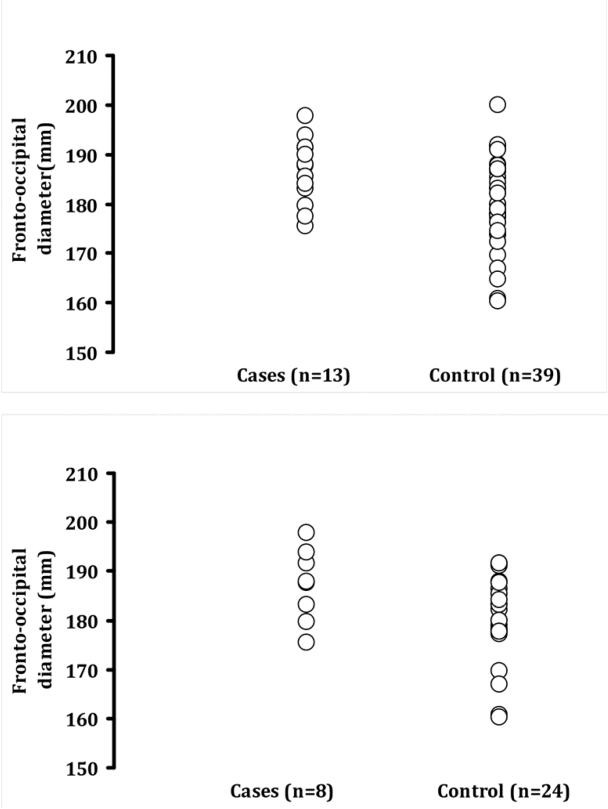



**Figure 4. A scatter plot demonstrating the fronto-occipital diameter in patients with Moyamoya disease and age, gender, and race matched controls. a. Includes both white and African patients; B. Includes only white patients.**

between the two groups. In an exploratory analysis limited to only African American patients who formed cases (n=5) and controls (n=15), the distance between bregma and occiput between the cases and controls was shorter among cases compared with controls (77.8±5.0 mm versus 88.0±7.7mm, p=0.06).

## Discussion

We observed an association between cephalometric parameters and Moyamoya disease. Both the bi-parietal and fronto-occipital diameters were greater in cases of Moyamoya disease. There was also some evidence of occipital flattening in Moyamoya cases by the shorter distance between bregma and occiput. We also noticed in exploratory analysis that there may be some differences unique to whites or African Americans, although the sample size was small. Cephalometric parameters have been used in assessment and surgical planning for dentofacial abnormalities17,21 and obstructive sleep apnea. 14,20 To our knowledge, this is the first report demonstrating unique cephalometric characteristics among Moyamoya disease patients.

An example of association between cephalometric parameters and intracranial vessel changes is seen in patients with cranial synostosis. The premature closure of a coronal, sagittal, metopic, or lambdoid suture lead to compensatory sutures and bone growth.7 Nonsyndromic synostosis results in an age-dependent increased intracranial volume and decreased cephalic index.11,19 Reduced arterial flow velocities and increased pulsitality index has been demonstrated in children with craniosyntosis which may improve after surgical correction. 26,33,34 Regional cerebral hypoperfusion and hypometabolism have been observed in presence of craniosynostoses5,6,29 Reduction in foramen that allow entry or exit of blood vessels intracraniallly has been documented leading to venous outflow obstruction3,25 and proliferation of transosseous venous drainage channels.15 Intracranial arterial tortousity and aneurysms have been seen with craniosyntosis in patients as part of Loeys-Dietz syndrome.27 However, vascular changes in craniosynostosis are attributed to constriction of the brain from the prematurely fused suture or as part of syndromic abnormalities.6 The magnitude of differences in cephalometric parameters in our cases is unlikely to cause major alterations in physiological parameters.

The other possibility is that early development of Moyamoya disease leads to alteration in cephalometric parameters. A prominent influence of underlying dura has been demonstrated on fusion of sutures by regulation of genes involved in paracrine signaling, extracellular matrix, and bone remodeling10,18 Meningeal cellularity and VEGF expression are significantly increased in dura mater of the patients with Moyamoya disease.28 Both transforming growth factor beta-1 and fibro-blast growth factor 2 signaling cascades are involved in the process of cranial suture fusion in experimental models.9 Basic fibroblast growth factor content and enhanced expression of receptors have been demonstrated in meningeal and vascular cells in patients with Moyamoya disease. 13,31 The expression of transforming growth factor beta-1 is significantly higher in cultured smooth-muscle cells derived from the superficial temporal arteries of patients with Moyamoya disease than in those derived from patients with arteriosclerotic cerebrovascular disease.12 The serum level of transforming growth factor beta-1 is also significantly higher in patients with Moyamoya disease than in controls.12 Therefore, the increased expression of various growth factors in patients with Moyamoya disease may influence the development of cephalometric parameters.

The small number of patients with Moyamoya disease results in a higher probability of not detecting small differences between controls and cases. The patient population is limited to white and African American patients and therefore results may not be generalizable to other populations. The underlying pathophysiological basis for variations in cephalometric characteristics and cause effect relationship with Moyamoya disease remains unknown. Therefore, the observations may be considered preliminary and further confirmation is required in larger studies. However, further study of the unique cephalometric characteristics among Moyamoya disease patients may provide additional insight into disease occurrence in white and African American populations.

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The material in the manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract.

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