Brain Abscess and Stroke in Children and Adults With Hereditary Hemorrhagic Telangiectasia: Analysis of a Large National Claims Database

Author(s):
Andrew J White, MD¹; Itay Marmor, MD²; Kate M Peacock³; Katelin B Nickel¹; Jessica Zavadil, MD, PhD³; Margaret A Olsen, PhD, MPH³

Corresponding Author:
Andrew J White, andrew.white.1@health.slu.edu

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
Affiliation Information for All Authors: 1. Department of Pediatrics, Saint Louis University School of Medicine, St. Louis, Missouri, USA; 2. Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA; 3. Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA.

Equal Author Contribution:

Contributions:
Andrew J White: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Itay Marmor: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Kate M Peacock: Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Katelin B Nickel: Major role in the acquisition of data; Analysis or interpretation of data
Jessica Zavadil: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Margaret A Olsen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
0

Table Count:
5
Search Terms:

Acknowledgment:

Study Funding:
This study was supported in part by Center for Administrative Data Research via the Washington University Institute of Clinical and Translational Sciences (grant no UL1 TR002345) from the National Center for Advancing Translational Sciences of the NIH

Disclosures:
The authors report no relevant disclosures.

Preprint DOI:

Received Date:
2022-10-10

Accepted Date:
2023-02-22

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.
**Objective:** Hereditary hemorrhagic telangiectasia (HHT) is an inherited disease associated with pathogenic variants in TGF-β signaling pathway-related genes, resulting in abnormal vascular development in various organs. Brain arteriovenous malformations (AVMs) may lead to intracranial hemorrhage, and brain abscess or ischemic stroke may result from right to left shunting via pulmonary AVMs. We aimed to investigate the risk for these severe complications in both adult and children HHT patients.

**Methods:** We conducted a case-control study among participants aged 1-64 years in the MarketScan® Commercial (2006-2019) and Multistate Medicaid Databases (2011-2019). We identified cases with HHT using International Classification of Diseases diagnosis codes (ICD-9-CM 448.0, ICD-10-CM I78.0). Control patients without HHT coding were frequency matched 10:1 to HHT patients by age, duration of insurance enrollment, sex, and Medicaid status. Outcomes of interest (brain abscess, stroke and intracranial/subarachnoid hemorrhage) were identified using the appropriate ICD-9/10 diagnosis codes. We calculated incidence and standardized rates of the various outcomes and compared rate ratios (RR) between HHT cases and controls.

**Results:** 5796 patients with HHT, of which 588 were children (age <16 years) were matched with 57,960 controls. There was increased incidence of brain abscesses in HHT cases compared with controls, with an RR of 35.6 (95% CI 15.4 – 82.5). No brain abscesses were recorded in children aged 15 years or less. Hemorrhagic strokes/subarachnoid hemorrhages were more common in HHT cases, with an RR of 4.01 (95% CI 2.8 to 5.7) in adults and 60.2 (95% CI 7.2 –
500.4) in children. Ischemic strokes were also more common in cases, with an RR of 3.7 (95% CI 3.0 – 4.5) in adults and 70.4 (95% CI 8.7– 572.3) in children.

**Conclusion:** We observed much higher incidence of severe CNS vascular complications in HHT patients, particularly in children. Though higher incidence of brain abscesses was noted in adult HHT patients, no brain abscesses were recorded in children, a result that may be considered when surveillance recommendations for this population are revisited.

**Introduction**

Hereditary hemorrhagic telangiectasia (HHT) is an under-recognized genetic disorder of vasculature that is caused by pathogenic mutations in the TGF-B signaling pathway\(^1\-\(^3\). These mutations include *endoglin*, *activin A receptor like kinase*, *SMAD4* and others, which are transmitted in an autosomal dominant fashion with variable penetrance. Mutations lead to a disruption in the balance between pro- and anti-angiogenic signals that are necessary for normal vascular development.

The diagnostic criteria reflect the common clinical symptoms, which include recurrent spontaneous epistaxis, mucocutaneous telangiectasia, solid organ arteriovenous malformations typically in the lung\(^4\), brain\(^5\), spinal cord or liver, and a first degree relative with HHT\(^6\). Epistaxis may occur daily and can lead to anemia and chronic blood transfusion dependence. Mucocutaneous telangiectasia is generally only of cosmetic concern, although telangiectasias throughout the GI tract may also contribute to iron deficiency anemia and transfusion dependence. Arteriovenous malformations (AVMs) may result in intracranial hemorrhage when
present in the brain, pulmonary hemorrhage when present in the lung, and high output heart failure when present in the liver. Brain abscess or ischemic stroke may also occur, due to right to left shunting through pulmonary AVMs. While the overall prevalence of HHT is estimated to be between 1:5000 to 1:8000 in various populations, precise estimates of the risk of complications from HHT have been difficult to ascertain due to both the rarity of HHT and to the observation that most people with HHT have not yet been diagnosed. This has been particularly true for children with HHT.

Claims databases have been used to describe the epidemiology of less common diseases. One such study of HHT included the population of Alberta, Canada with approximately 4 million people, in which the incidence of stroke in patients with HHT was examined. These authors found a significantly higher incidence rate of stroke in patients with HHT but did not assess the occurrence of brain abscess and did not specifically assess the risk in children.

Using administrative claims data, we compared the risk of stroke and brain abscess in both adult and pediatric patients with HHT compared to control populations in the databases.

Methods

Identification of the HHT and Control Populations

We identified persons aged 1-64 years in the IBM® MarketScan® Commercial Database from 1/1/2006-12/31/2019 and from 1/1/2011-12/31/2019 in the MarketScan® Medicaid Database with an HHT diagnosis using International Classification of Diseases diagnosis codes (ICD-9-CM 448.0, ICD-10-CM I78.0). To establish the diagnosis of HHT coding was required on at
least 1 inpatient facility claim and/or 2 or more outpatient/provider claims spaced at least 30 days apart. Diagnostic claims (e.g., laboratory, diagnostic radiology) were not used to identify HHT to avoid identification of rule-out conditions\textsuperscript{10}.

Control persons aged 1-64 years without HHT were identified based on no coding for HHT during the time period of health insurance enrollment. For the purpose of comparison to the HHT population, controls were frequency matched 10:1 to individuals with HHT by age (in 5-year categories), duration of health insurance enrollment (per completed year), insurance enrollment start year, sex, and Medicaid status.

\textit{Identification of Underlying Conditions}

Comorbidities were defined using the classification of Elixhauser\textsuperscript{11} and the pediatric chronic conditions classification of Feudtner\textsuperscript{12}, including conditions coded at any time during the medical insurance enrollment dates. Comorbidities, which included various malignancies and anemia, were defined as above for HHT, requiring coding on at least 1 inpatient facility claim and/or 2 or more outpatient/provider non-diagnostic claims spaced at least 30 days apart. In addition, the mean number of clinic visits per year was determined per person using CPT-4 codes 99201-99215, 99241-99245, 99381-99386 and 99391-99396 as a measure of overall healthcare utilization.

\textit{Identification of Outcomes}

Outcomes were identified at any time during health care enrollment using 1 or more diagnosis codes on non-diagnostic claims, including: brain or CNS abscess, hemorrhagic stroke, ischemic
stroke (includes embolic/thromboembolic stroke) and subarachnoid hemorrhage. The specific diagnostic codes for these outcomes are listed in Table 1.

For acute ischemic and hemorrhagic stroke, brain/CNS abscess, and subarachnoid hemorrhage, coding was required during an inpatient admission of at least 2 days or in an inpatient admission with shorter length of stay with a discharge status of died. Hemorrhagic stroke data included cases in which there was either a hemorrhagic or a subarachnoid stroke, or both in the same patient, as some cases were entered as having both a subarachnoid and hemorrhagic stroke. In order to avoid double counting any single patient, hemorrhagic stroke and subarachnoid hemorrhage were combined into one outcome variable for analysis.

Statistical Analyses

Descriptive statistics were performed for the HHT case and control populations for underlying comorbidities and number of office visits per year. The prevalence rate of HHT was calculated based on person time of observation (per 100,000 person years of observation (PYO)), using the medical insurance enrollment start and end dates for the entire population of persons aged 1-64 years in the MarketScan Commercial and Medicaid databases.

Incidence and prevalence rates per 100,000 PYO were calculated overall and for subgroups of children, defined as age 1-15 years and adults 16-64, for the individual outcomes of interest in the HHT case and control populations, respectively. The age of 16 years was used to define adulthood for consistency with other HHT studies\textsuperscript{13, 23, 25}. In addition, rates were calculated for various age subgroups. Comparisons of the standardized rates per 100,000 PYO between the HHT and frequency matched control groups were performed using PROC STDRATE, with calculation of rate ratios. P < 0.05 was considered statistically significant in comparison of
incidence and prevalence ratios. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). Data acquisition and analysis was carried out through the Center for Administrative Data Research, which is supported in part by the Washington University Institute of Clinical and Translation Sciences from the National Center for Advancing Translation Science of the National Institutes of Health.

**Standard Protocol Approvals, Registrations and Patient Consents**

This study was declared a non-human study by the WU Human Research Protection Office, due to the use of a limited dataset with no identifiable information.

**Data Availability**

The data underlying this article were provided by IBM® MarketScan® Commercial Database under license. Data will be shared on reasonable request to the corresponding author with permission from IBM® MarketScan® Commercial Database.

**Results**

5796 patients with HHT were identified from the MarketScan Commercial and Multistate Medicaid Databases, which included 588 children under the age of 16 years.

The control group of frequency matched patients who were not coded for HHT during their insurance enrollment observation time included 57,960 total patients, of which 5880 were children under the age of 16 years. Approximately 9% of the HHT and the control patients were
on Medicaid and 91% were not enrolled in Medicaid. 64% of patients were female, 36% were male in both the case and in the control groups.

**Comorbidities and medical office visits**

HHT cases had increased risk for various types of malignancies and chronic anemias (*eTable 1*), compared to matched controls - a matter worthy of a discussion which extends beyond the scope of this paper. In addition, HHT patients were much more likely to be seen 21 or more times a year, compared to controls (*eTable 2*).

**Brain Abscess**

A significantly higher incidence of brain abscess was found in patients with HHT compared with the control patients (Table 2). Brain abscess was identified in 25 adult patients with HHT, a rate of 94.6 cases per 100,000 PYO, compared with 7 cases of brain abscess in the control group (2.4 cases per 100,000 PYO), resulting in a rate ratio of 35.6 (95% CI 15.4 – 82.5). In children 15 years and younger, there were no cases of brain or CNS abscess recorded in the control group, nor were there any cases in those with HHT.

Grouped by decade, an examination of the data by age at onset of brain abscess was performed. No clear peak age of onset of brain abscess was apparent, and the risk ratios were significantly elevated in each age bracket (Table 3).
Stroke

Stroke was found more commonly in adult patients with HHT compared to the control population (Table 2). Hemorrhagic stroke or subarachnoid hemorrhage occurred in 43 adults with HHT (162.9 cases per 100,000 PYO) compared with controls (40.6 cases per 100,000 PYO) in which there were a total of 107 cases total. The calculated incidence rate ratio of hemorrhagic stroke in HHT cases was 4.01 (95% CI 2.8 to 5.7).

The rate ratio for ischemic stroke in adults with HHT compared to control cases was 3.7 (95% CI 3.0 – 4.5) occurring in 120 adult patients with HHT compared with 329 control patients (458.1 vs 125.3 cases per 100,000 PYO).

In comparing children with HHT to frequency matched controls, both hemorrhagic and ischemic strokes were more common. The rate ratio for hemorrhagic stroke/subarachnoid hemorrhage in children was 60.2 (95% CI 7.2 – 500.4). There were 6 cases of hemorrhagic stroke/subarachnoid hemorrhage (189.7 cases per 100,000 PYO) in children with HHT versus 1 case in matched control patients (3.2 cases per 100,000 PYO).

The rate ratio for ischemic stroke in children with HHT was 70.4 (95% CI 8.7– 572.3). There were 7 cases of ischemic stroke in children with HHT (221.7 cases per 100,000 PYO) versus 1 case in controls (3.2 cases per 100,000 PYO).

When broken down into 10-year interval age groups (Tables 4 and 5), incidence rates for both hemorrhagic and ischemic (embolic/thromboembolic) stroke demonstrate increases with age in frequency matched controls. This increase, however, was not witnessed as clearly in stroke rates among HHT cases, particularly involving hemorrhagic stroke rates, which seemed to be non-age related in this population. The rate ratios for both types of strokes, however, were consistently
higher in HHT cases compared to controls, across all age groups. The highest rate ratio for hemorrhagic strokes was 89.6 (95% CI 11.3-707.5) and was seen in the 16-25 years age group, and the highest rate ratio for ischemic stroke was 69.8 (8.6-567.7), in the 1-15 years age group.

Discussion

Complications from HHT such as stroke and brain abscess, while rare, are potentially serious and may be life-threatening. Estimates of the risk of these complications have been difficult to quantify due to the relative rarity of HHT as well as its diagnostic under-recognition and under-representation in some databases. In addition, the low frequency of events such as stroke and abscess necessitate examination of large datasets. The data included in the MarketScan database allow for capture of these occurrences and allows for the calculation of such risks.

Brain abscess was found to be more common in patients with HHT compared with controls. The rate ratio of 35.6 confirms the clinical experience of many physicians caring for these patients, as well as the community of those with HHT and their families. This rate is similar to the adjusted odds ratio reported by Donaldson of 30 in their analysis of 675 patients with HHT from an UK primary care database of 3.5 million individuals.

Interestingly, no cases of brain abscess were present in children with HHT, nor in the controls. Scattered case reports of brain abscess in HHT do exist in the literature, but are rare in children. Roberts reported a single case of a 3 yo male and Press reported an 11 year old child, in a cohort of 31 cases, of which 30 were adults. In addition to the presence of a pulmonary AVMs, some of the risk factors for developing abscesses in patients with HHT include dental infections, (both treated and untreated), and hypoxemia, both of which may be less common in
children and which therefore may contribute to the lower rates. These data suggest that recommendations for the prevention of brain abscess, which include both the treatment of pulmonary AVMs and use of antibiotic prophylaxis for invasive dental procedures, eg, remain important in adult patients with HHT, but may not be as necessary in children. More data are needed to before recommendations can be made with confidence.

The relative proportion of stroke type (ischemic versus hemorrhagic) was roughly 1:1 in children, whereas there were approximately 3 times as many ischemic (versus hemorrhagic) strokes in adults in both the control group and those with HHT.

The rate ratio for hemorrhagic stroke/subarachnoid hemorrhage was 60.2 and for ischemic (embolic/thromboembolic) stroke was 70.4, both indicating an increased risk for children with HHT compared with the frequency matched controls. It is known that adults with HHT are at risk for stroke, but this dramatic increase in the incidence risk rates for children demonstrated here is not as well recognized. One possible reason for the lower rate ratios in adult patients may be the observation that adults, with or without HHT, suffer from strokes that are unrelated to HHT, at much higher rates than children. Lehman et al. calculated a pediatric stroke rate of 4.4 per 100,000 children, which is but a small fraction compared to the estimated 150 cases per 100,000 of people of all ages with stroke world-wide. Indeed, hemorrhagic or ischemic stroke in children are rare in the general population, and HHT patients are at much higher risk for these severe manifestations with often grim consequences.

13 cases of stroke occurred in children with HHT, but only 2 cases in the controls, even though there were 10 times as many patients included in the control group. Further analysis using stratification of adult patients into 10-year interval age groups showed astronomical rate ratio for
ischemic and hemorrhagic strokes in young adult HHT patients, compared to controls. Consequently, when stroke occurs in those under the age of 25 years, an evaluation for possible underlying HHT may be considered.

Since HHT patients with a relatively mild phenotype can remain undiagnosed for years, the high complication rates demonstrated in this study may be somewhat exaggerated since undiagnosed patients without complications were not included in the denominator of our incidence rate calculation. On the other hand, it is possible that some of the controls in this study diagnosed with a CNS complication were in fact undiagnosed HHT patients, especially in fatal cases which may not undergo a complete evaluation. Larsen et al\textsuperscript{15} showed that 2.5\% of patients evaluated for a brain abscess were subsequently diagnosed with HHT, a much higher fraction than the prevalence of HHT in the population (less than 0.02\%). The female: male ratio of almost 2:1 in our cohort has been reported by others\textsuperscript{13,24}. It has been suggested that women tend to seek medical evaluation more commonly than men and may therefore be diagnosed more quickly. The same concept of increased exposure to medical care is also demonstrated in our data showing a higher number of annual medical office visits in HHT patients compared to controls (eTable 2). It is possible that diagnosed HHT patients have an overall better medical surveillance compared to the general population, and that they may also be diagnosed more often with hematologic and oncologic conditions (eTable 1), as well as the CNS complications discussed in this paper.

\textit{Strengths and Limitations}

The strength of this study is the population-based design allowing examination of a large proportion of the privately insured non-elderly US population. There are some potential
limitations of this study, however. Firstly, the inability to link the claims data to direct clinical information precludes the verification of the HHT diagnoses. Secondly, assignment of specific diagnostic codes is variable in administrative datasets and therefore these results likely underestimate the true prevalence of these complications. Finally, this data is limited to privately and Medicaid insured patients and the results may not be representative of patients without health insurance coverage.

Conclusions

In summary, the MarketScan database was used to assess complications and associations in patients with HHT. Over 5000 adults and nearly 600 children were identified with this uncommon disease. Rate ratios for complications were significantly higher for hemorrhagic stroke and ischemic stroke in adults with HHT compared to controls. Rate ratios were also higher in children with HHT for hemorrhagic and ischemic stroke. Brain abscess rate ratios were significantly higher in adults with HHT compared with controls. However, no cases of brain abscess in children with HHT were present in the database, nor in the controls. Taken together, these findings confirm clinical observations that adults with HHT are at higher risk for neurologic complications such as brain abscess, hemorrhage, and stroke. The absence of brain abscesses in children suggests that this complication is rare.

WNL-2023-000149_etab1 ---http://links.lww.com/WNL/C763

WNL-2023-000149_etab2 ---http://links.lww.com/WNL/C764
References:


Tables

Table 1: ICD-CM-9 and 10 codes used for outcome variables

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD-CM-9</th>
<th>ICD-CM-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain/CNS abscess</td>
<td>324.0, 324.9</td>
<td>G06.0, G06.2</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>431, 432</td>
<td>I61, I62.00, I62.01 I62.1 I62.9</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>433, 434</td>
<td>I63</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>430</td>
<td>I60</td>
</tr>
</tbody>
</table>

AV, arteriovenous; CNS, central nervous system; TIA, Transient ischemic attack
Table 2: Outcomes in HHT cases vs. controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Rate Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Freq. (%)</td>
<td>Rate**</td>
<td>Freq. (%)</td>
<td>Rate</td>
</tr>
<tr>
<td>All patients</td>
<td>5796 cases, 57960 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain/CNS abscess</td>
<td>25 (0.43)</td>
<td>84.4</td>
<td>7 (0.01)</td>
<td>2.4</td>
</tr>
<tr>
<td>Hemorrhagic stroke or subarachnoid hemorrhage</td>
<td>49 (0.85)</td>
<td>165.8</td>
<td>108 (0.19)</td>
<td>36.6</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>127 (2.19)</td>
<td>432.6</td>
<td>330 (0.57)</td>
<td>112.1</td>
</tr>
<tr>
<td>Age &lt; 15 y</td>
<td>588 cases, 5880 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain/CNS abscess</td>
<td>0 (0.00)</td>
<td>0.0</td>
<td>0 (0.00)</td>
<td>0.0</td>
</tr>
<tr>
<td>Hemorrhagic stroke or subarachnoid hemorrhage</td>
<td>6 (1.02)</td>
<td>189.7</td>
<td>1 (0.02)</td>
<td>3.2</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>7 (1.19)</td>
<td>221.7</td>
<td>1 (0.02)</td>
<td>3.2</td>
</tr>
<tr>
<td>Age &gt; 15 y</td>
<td>5208 cases, 52080 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain/CNS abscess</td>
<td>25 (0.48)</td>
<td>94.6</td>
<td>7 (0.01)</td>
<td>2.7</td>
</tr>
<tr>
<td>Hemorrhagic stroke or subarachnoid hemorrhage</td>
<td>43 (0.83)</td>
<td>162.9</td>
<td>107 (0.21)</td>
<td>40.6</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>120 (2.30)</td>
<td>458.1</td>
<td>329 (0.63)</td>
<td>125.3</td>
</tr>
</tbody>
</table>

Freq., frequency; CNS, central nervous system
* Frequency is presented as number of persons with an observed event
** Rates are presented as number of events per 100,000-person years of observation

Table 3: Brain/CNS Abscess in adult HHT cases vs. controls, by age

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Cases</th>
<th>Controls</th>
<th>Rate Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>PYO</td>
<td>Rate*</td>
<td></td>
</tr>
<tr>
<td>16-25</td>
<td>457</td>
<td>2214</td>
<td>2 (0.51)</td>
<td>90.3</td>
</tr>
<tr>
<td>26-35</td>
<td>607</td>
<td>2639</td>
<td>2 (0.33)</td>
<td>75.8</td>
</tr>
<tr>
<td>36-45</td>
<td>981</td>
<td>5077</td>
<td>2 (0.2)</td>
<td>39.4</td>
</tr>
<tr>
<td>46-55</td>
<td>1625</td>
<td>9172</td>
<td>10 (0.62)</td>
<td>109.0</td>
</tr>
<tr>
<td>56-64</td>
<td>1538</td>
<td>7394</td>
<td>9 (0.59)</td>
<td>121.7</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>PYO</td>
<td>Rate</td>
<td>458.1</td>
</tr>
<tr>
<td>16-25</td>
<td>457</td>
<td>22051</td>
<td>0 (0.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>26-35</td>
<td>607</td>
<td>26138</td>
<td>1 (0.02)</td>
<td>3.8</td>
</tr>
<tr>
<td>36-45</td>
<td>981</td>
<td>50456</td>
<td>0 (0.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>46-55</td>
<td>1625</td>
<td>91350</td>
<td>2 (0.01)</td>
<td>2.2</td>
</tr>
<tr>
<td>56-64</td>
<td>1538</td>
<td>73504</td>
<td>4 (0.03)</td>
<td>5.4</td>
</tr>
</tbody>
</table>
| CNS, central nervous system; Freq, frequency; PYO, person years of observation; CI, confidence interval
* Frequency is presented as number of persons with an observed event
** Rates are presented as number of events per 100,000 PYO
Table 4: Hemorrhagic strokes in adult HHT cases vs controls, by age

| Age group (yrs) | Cases | | Controls | | | Rate Ratio | p |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                | N   | PYO | Freq. (%) | Rate | N   | PYO | Freq. (%) | Rate | (95% CI) | p                |
| 16-25          | 457 | 2214 | 9 (1.97) | 406.5 | 4570 | 22051 | 1 (0.02) | 4.5 | 89.6 (11.3, 707.5) | <.0001 |
| 26-35          | 607 | 2639 | 6 (0.99) | 227.4 | 6070 | 26138 | 3 (0.05) | 11.5 | 19.8 (4.9, 79.2) | <.0001 |
| 36-45          | 981 | 5077 | 3 (0.3) | 59.1 | 9810 | 50456 | 12 (0.12) | 23.8 | 2.48 (0.7, 8.8) | 0.159 |
| 46-55          | 1625 | 9172 | 12 (0.74) | 130.8 | 16250 | 91350 | 43 (0.26) | 47.1 | 2.78 (1.5, 5.3) | 0.0017 |
| 56-64          | 1538 | 7394 | 13 (0.8) | 175.8 | 15380 | 73504 | 48 (0.31) | 65.3 | 2.69 (1.5, 5) | 0.0015 |

CNS, central nervous system; Freq, frequency; PYO, person years of observation; CI, confidence interval
* Frequency is presented as number of persons with an observed event
** Rates are presented as number of events per 100,000 PYO

Table 5: Ischemic strokes in adult HHT cases vs controls, by age

| Age group (yrs) | Cases | | Controls | | | Rate Ratio | p |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                | N   | PYO | Freq. (%) | Rate | N   | PYO | Freq. (%) | Rate | (95% CI) | p                |
| 16-25          | 457 | 2214 | 5 (1.1) | 225.8 | 4570 | 22051 | 1 (0.02) | 4.5 | 49.8 (5.8, 426.2) | 0.0004 |
| 26-35          | 607 | 2639 | 4 (0.66) | 151.6 | 6070 | 26138 | 7 (0.12) | 26.8 | 5.6 (1.7, 19.3) | 0.0057 |
| 36-45          | 981 | 5077 | 14 (1.4) | 275.7 | 9810 | 50456 | 27 (0.28) | 53.5 | 5.1 (2.7, 9.8) | <.0001 |
| 46-55          | 1625 | 9172 | 38 (2.3) | 414.3 | 16250 | 91350 | 117 (0.72) | 128.1 | 3.2 (2.2, 4.6) | <.0001 |
| 56-64          | 1538 | 7394 | 59 (3.8) | 797.9 | 15380 | 73504 | 177 (1.15) | 240.8 | 3.3 (2.5, 4.4) | <.0001 |

CNS, central nervous system; Freq, frequency; PYO, person years of observation; CI, confidence interval
* Frequency is presented as number of persons with an observed event
** Rates are presented as number of events per 100,000 PYO