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

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**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[7].

While the overall prevalence of HHT is estimated to be between 1:5000 to 1:8000 in various populations[8], 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[9] 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[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.

*Identification of Underlying Conditions*

Comorbidities were defined using the classification of Elixhauser[11] and the pediatric chronic conditions classification of Feudtner[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.

*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[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[13]. 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[14-17] 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[18] 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[19] reported a single case of a 3 yo male and Press[20] 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[21], (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.[22] 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[23]. 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[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[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.

*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.

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

**References:**


1. Shovlin CL. Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment. *Blood Rev.* 2010;24(6):203-219.
2. Sabbà C, Pasculli G, Cirulli A, et al. Hereditary hemorrhagic teleangiectasia (Rendu-Osler-Weber disease). *Minerva Cardioangiol.* 2002;50(3):221-238.
3. Marchuk DA. Genetic abnormalities in hereditary hemorrhagic telangiectasia. *Curr Opin Hematol.* 1998;5(5):332-338.
4. Vase P, Holm M, Arendrup H. Pulmonary arteriovenous fistulas in hereditary hemorrhagic telangiectasia. *Acta Med Scand.* 1985;218(1):105-109.
5. Román G, Fisher M, Perl DP, Poser CM. Neurological manifestations of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease): report of 2 cases and review of the literature. *Ann Neurol.* 1978;4(2):130-144.
6. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet.* 2000;91(1):66-67.
7. Agarwal J, LaBranche J, Dhillon S, Allison WT, Jeerakathil T, Vethanayagam D. Neurologic Complications in Hereditary Hemorrhagic Telangiectasia with Pulmonary Arteriovenous Malformations: A Systematic Review. *Can J Neurol Sci.* 2022:1-12.
8. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *European Journal of Human Genetics.* 2009;17(7):860-871.
9. Chowdhury FN, Chandrarathne GS, Masilamani KD, et al. Links Between Strokes and Hereditary Hemorrhagic Telangiectasia: A Population-Based Study. *Can J Neurol Sci.* 2019;46(1):44-50.
10. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol.* 2000;53(12):1258-1267.
11. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care.* 1998;36(1):8-27.
12. Feudtner C, Hays RM, Haynes G, Geyer JR, Neff JM, Koepsell TD. Deaths attributed to pediatric complex chronic conditions: national trends and implications for supportive care services. *Pediatrics.* 2001;107(6):E99.
13. Pahl KS, Choudhury A, Wusik K, Hammill A, White AJ, Henderson K, Pollak J, Kasthuri RS. Applicability of the Curaçao Criteria for the Diagnosis of Hereditary Hemorrhagic Telangiectasia in the Pediatric Population. *J Pediatr*. 2018
14. Grosse SD, Boulet SL, Grant AM, Hulihan MM, Faughnan ME. The use of US health insurance data for surveillance of rare disorders: hereditary hemorrhagic telangiectasia. *Genetics in Medicine.* 2014;16(1):33-39.
15. Boother EJ, Brownlow S, Tighe HC, Bamford KB, Jackson JE, Shovlin CL. Cerebral Abscess Associated With Odontogenic Bacteremias, Hypoxemia, and Iron Loading in Immunocompetent Patients With Right-to-Left Shunting Through Pulmonary Arteriovenous Malformations. *Clin Infect Dis.* 2017;65(4):595-603.
16. Larsen L, Marker CR, Kjeldsen AD, Poulsen FR. Prevalence of hereditary hemorrhagic telangiectasia in patients operated for cerebral abscess: a retrospective cohort analysis. *Eur J Clin Microbiol Infect Dis.* 2017;36(10):1975-1980.
17. Themistocleous M, Giakoumettis D, Mitsios A, Anagnostopoulos C, Kalyvas A, Koutsarnakis C. Hereditary hemorrhagic telangiectasia patient presenting with brain

abscess due to silent pulmonary arteriovenous malformation. *Pan Afr Med J.* 2016;25:145.
18. Dong SL, Reynolds SF, Steiner IP. Brain abscess in patients with hereditary hemorrhagic telangiectasia: case report and literature review. *J Emerg Med.* 2001;20(3):247-251.
19. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. Complications and mortality in hereditary hemorrhagic telangiectasia: A population-based study. *Neurology.* 2015;84(18):1886-1893.
20. Roberts JI, Woodward K, Kirton A, Esser MJ. Pearls & Oy-sters: Cerebral Abscess Secondary to Pulmonary Arteriovenous Malformation in Hereditary Hemorrhagic Telangiectasia. *Neurology.* 2022;98(7):292-295.
21. Press OW, Ramsey PG. Central nervous system infections associated with hereditary hemorrhagic telangiectasia. *Am J Med.* 1984;77(1):86-92.
22. Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Risk Factors for Brain Abscess: A Nationwide, Population-Based, Nested Case-Control Study. *Clin Infect Dis.* 2020;71(4):1040-1046.
23. Lehman LL, Khoury JC, Taylor JM, et al. Pediatric Stroke Rates Over 17 Years: Report From a Population-Based Study. *J Child Neurol.* 2018;33(7):463-467.
24. Ding C, Wu Y, Chen X, et al. Global, regional, and national burden and attributable risk factors of neurological disorders: The Global Burden of Disease study 1990-2019. *Front Public Health.* 2022;10:952161.
25. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: a population-based study. *Thorax.* 2014;69(2):161-167.



Tables

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

| Condition | ICD-CM-9 | ICD-CM-10 |
|---|---|---|
| Brain/CNS abscess | 324.0, 324.9 | G06.0, G06.2 |
| Hemorrhagic stroke | 431, 432 | I61, I62.00, I62.01 I62.1 I62.9 |
| Ischemic stroke | 433, 434 | I63 |
| Subarachnoid hemorrhage | 430 | I60 |

AV, arteriovenous; CNS, central nervous system; TIA, Transient ischemic attack

**Table 2: Outcomes in HHT cases vs. controls**

| | Cases | | Controls | | Rate Ratio (95% CI) | *p* |
|---|---|---|---|---|---|---|
| | Freq. (%) | Rate** | Freq. (%) | Rate | | |
| All patients (5796 cases, 57960 controls) | | | | | | |
| Brain/CNS abscess | 25 (0.43) | 84.4 | 7 (0.01) | 2.4 | 35.6 (15.4-82.3) | <0.0001 |
| Hemorrhagic stroke or subarachnoid hemorrhage | 49 (0.85) | 165.8 | 108 (0.19) | 36.6 | 4.53 (3.23-6.35) | <0.0001 |
| Ischemic Stroke | 127 (2.19) | 432.6 | 330 (0.57) | 112.1 | 3.86 (3.14-4.74) | <0.0001 |
| Age < 15 y (588 cases, 5880 controls) | | | | | | |
| Brain/CNS abscess | 0 (0.00) | 0.0 | 0 (0.00) | 0.0 | n/a | |
| Hemorrhagic stroke or subarachnoid hemorrhage | 6 (1.02) | 189.7 | 1 (0.02) | 3.2 | 60.2 (7.2-500.4) | <0.0001 |
| Ischemic Stroke | 7 (1.19) | 221.7 | 1 (0.02) | 3.2 | 70.4 (8.7-572.3) | <0.0001 |
| Age > 15 y (5208 cases, 52080 controls) | | | | | | |
| Brain/CNS abscess | 25 (0.48) | 94.6 | 7 (0.01) | 2.7 | 35.6 (15.4-82.5) | <0.0001 |
| Hemorrhagic stroke or subarachnoid hemorrhage | 43 (0.83) | 162.9 | 107 (0.21) | 40.6 | 4.0 (2.8-5.7) | <0.0001 |
| Ischemic Stroke | 120 (2.30) | 458.1 | 329 (0.63) | 125.3 | 3.7 (3.0-4.5) | <0.0001 |

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**

| | Cases | | | | Controls | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group (yrs) | N | PYO | Freq. (%) | Rate* | N | PYO | Freq. (%) | Rate | Rate Ratio (95% CI) | *p* |
| 16-25 | 457 | 2214 | 2 (0.51) | 90.3 | 4570 | 22051 | 0 (0) | 0.0 | | |
| 26-35 | 607 | 2639 | 2 (0.33) | 75.8 | 6070 | 26138 | 1 (0.02) | 3.8 | 19.81 (1.8, 218.5) | 0.015 |
| 36-45 | 981 | 5077 | 2 (0.2) | 39.4 | 9810 | 50456 | 0 (0) | 0.0 | | |
| 46-55 | 1625 | 9172 | 10 (0.62) | 109.0 | 16250 | 91350 | 2 (0.01) | 2.2 | 49.8 (10.9, 227.3) | <.0001 |
| 56-64 | 1538 | 7394 | 9 (0.59) | 121.7 | 15380 | 73504 | 4 (0.03) | 5.4 | 22.4 (6.9, 72.6) | <.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

## Table 4: Hemorrhagic strokes in adult HHT cases vs controls, by age

| | Cases | | | | Controls | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age group (yrs)** | **N** | **PYO** | **Freq. (%)** | **Rate** | **N** | **PYO** | **Freq. (%)** | **Rate** | **Rate Ratio (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

| | Cases | | | | Controls | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age group (yrs)** | **N** | **PYO** | **Freq. (%)** | **Rate** | **N** | **PYO** | **Freq. (%)** | **Rate** | **Rate Ratio (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

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

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