Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought
A Retrospective Population-Based Study

Sharon Devasagayam, MBBS; Ben Wyatt, MBBS; James Leyden, MBBS; Timothy Kleinig, PhD, MBBS

Background and Purpose—The incidence of cerebral venous thrombosis (CVT) varies between studies, but it is estimated to be between 2 and 5 per million per year. A recent study in the Netherlands with comprehensive ascertainment suggested a much higher incidence. It is uncertain whether these differing estimates reflect the quality of ascertainment or true variation. The purpose of this study was to determine the incidence of CVT in Adelaide, using a novel clinical and radiological methodology.

Methods—We retrospectively identified CVT International Classification of Diseases-coded cases from all Adelaide public hospitals from 2005 to 2011. We also searched all neuroimaging studies (259101) from these hospitals for text variations containing venous thromb. All potential cases were reviewed, and cases of incident CVT ascertained. Associations and outcomes were determined.

Results—Of 169 possible cases, 105 cases of CVT were confirmed (59 cases by both coding and neuroimaging, 40 from neuroimaging alone, and 6 from coding alone). In our population of 953,390 adults, this represented an incidence of 15.7 million per year (95% confidence interval, 12.9–19.0), the highest incidence reported. Of these cases, a possible procoagulant predisposition was identified in 48%. Fifty-five of 105 cases occurred in females. Relative risk of CVT in females of reproductive age was insignificantly higher than in males (1.18 [95% confidence interval, 0.94–1.48]).

Conclusions—Cerebral venous sinus thrombosis in our study was more common than previously reported, perhaps because of more complete ascertainment. Future CVT incidence studies should include comprehensive capture and review of neuroimaging.

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Key Words: cerebral veins • incidence • neuroimaging • stroke • venous thrombosis

See related article, p 2169.

Cerebral venous thrombosis (CVT) is a rare neurovascular disorder with a highly variable presentation and clinical course.1–11 The low incidence and incongruous presentation of CVT often lead to late diagnosis.1–8,11 The incidence of CVT has been reported as being between 2 and 5 million per year.1–5,7–11 A recent report suggested a much higher incidence (13 million person-years1). Incidence may have been previously underestimated for several reasons, primarily inaccurate coding and lack of sophisticated neuroimaging. The purpose of this study was to accurately determine the incidence of CVT in Adelaide, South Australia by using a novel ascertainment methodology. We hypothesized that incidence would be higher than previously reported.

Methods
We conducted a retrospective population-based study of all public hospital-admitted adults in the greater Adelaide Metropolitan Area, an adult population of 953,390 (2011 Australian Census) between January 1, 2005 and December 31, 2011.

Cases were identified using 2 reproducible searches. International Statistical Classification of Diseases and Related Health Problems (ICD) codes are recorded on discharge from all hospitals in Australia. These ICD discharge codes were searched to identify all patients with a potential diagnosis of CVT. The following ICD codes were searched: ICD Ninth Revision, 671.5; 325; 437.6 and ICD-10, I676. Seven cases with an ICD code for CVT were admitted to private hospitals in this period but were not covered by the ethics approval for this study.

All neuroimaging performed in public hospitals is entered into a central searchable data repository. We additionally searched all 259101 neuroimaging studies performed between 2005 and 2011. The reports of these studies were searched for text variations containing venous thromb. Before performing this search, we tested various search strategies in 20 known cases of CVT to determine which phrase had the best sensitivity with reasonable specificity. All full reports containing this phrase were reviewed independently by 2 individuals to determine whether CVST was possible. Acceptable neuroimaging was computed tomographic venography.
or magnetic resonance imaging venography (either time-of-flight or contrast enhanced). No cases were diagnosed with catheter angiography.

A database of all cases identified by the 2 searches was created. All nonincident cases, duplicates, and patients <18 years of age were removed, as were patients not residing in metropolitan Adelaide (country transfers or visitors). Then electronic and written medical records of every identified patient were searched to confirm that a diagnosis of CVT had been made. Only clinically compatible cases confirmed by neurovascular imaging were included. If there was uncertainty about the diagnosis, then full medical records were retrieved and reviewed. Ambiguous cases were assessed by an independent experienced vascular neurologist (T.K.) who reviewed the images and medical records together, as a final arbiter of case validity. Cases with inadequate documentation to confirm the diagnosis of CVT were excluded, as were any duplicates. Death at discharge and recurrences were recorded.

The study was approved by the ethics committees of all Adelaide public hospitals. Graphpad for Prism was used for statistical calculations. Attack rates were calculated million/yr with confidence intervals calculated from the Poisson distribution.

Results

A total of 168 cases were identified by the combined ICD and neuroradiology database searches. Table 1 shows the reasons for exclusion. Of these 105 cases of confirmed CVT, 59 (56%) were identified with both ICD and radiology database searches, 40 (38%) by radiology alone, and 6 (6%) by ICD coding alone. Therefore, the radiology database search correctly ascertained 94% of all cases.

Of the 6 coding cases not detected by text variations containing venous thrombus search term, 1 had private imaging only which was not accessible by our search, 1 was missed through human error, and 4 were initially reported as showing no evidence of venous sinus thrombosis (and were, therefore, not included). Subsequent neuroimaging or imaging review showed the initial report in these 4 cases to be a false-negative.

One hundred five cases were, therefore, confirmed. In our population of 953,390 adults, this equates to an incidence of 15.7 million per year (95% confidence interval, 12.9–19.0). The clinical and radiological manifestations are highlighted below in Table 2.

### Table 1. Reasons for Exclusion

<table>
<thead>
<tr>
<th>Exclusion Criteria*</th>
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<tbody>
<tr>
<td>Inadequate documentation</td>
<td>10</td>
</tr>
<tr>
<td>Radiological CVT only</td>
<td>11</td>
</tr>
<tr>
<td>Radiological artifact</td>
<td>12</td>
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<tr>
<td>Incorrect Coding</td>
<td>20</td>
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<tr>
<td>Chronic CVT</td>
<td>7</td>
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<tr>
<td>Duplicates</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
</tr>
</tbody>
</table>

*Exclusion Criteria: inadequate documentation, insufficient documentation or work-up to determine whether cerebral venous sinus thrombosis (CVT) was likely; radiological CVT only, neuroimaging and clinical presentation did not correlate; radiological artifacts, venous sinuses abnormalities determined artifactual on review or further imaging; incorrect coding, cases proven not CVT after medical record review; chronic, onset of CVT before 2005.

The median age was 49 years (range, 19–84; interquartile range, 40–61). There was an insignificant female preponderance (52%). Although a seemingly high proportion (31%) of females were on some sort of estrogen therapy (contraceptive or hormone replacement), the relative risk of CVT in females of reproductive age (18–50 years) was insignificantly higher than in males of the same age, 1.18 (95% confidence interval, 0.94–1.48). Mortality at discharge was 9%, and cumulative mortality at February 2016 was 12%.

### Discussion

In our population, using a novel ascertainment methodology, we found CVT to have an incidence of 15.7 million per year. Incidence was higher than others have found previously published.1–5,7–11 Including the recent study of Coutinho et al,1 that demonstrated an incidence of 13 million person-years, which was also substantially higher than expected from previous research. They studied a 3-year period in an organization with comparable access to neuroimaging; however, they identified cases solely using clinical coding. To broaden ascertainment beyond a CVT primary diagnosis, the authors included ischemic stroke and hemorrhagic stroke in patients aged <65 years, assuming CVT would be rare in this group.1 Our study was inclusive of all individuals during the age of 18 years.

Our higher incidence rate more likely represents more complete ascertainment, rather than a higher incidence in our population. Using coding alone would have led to an incidence ~40% lower than our final figure. Due to differing methodologies, it is not possible for us to compare directly with Coutinho et al’s study the proportion ascertained via CVT coding versus those ascertained by other means.

Previous studies have found an association with CVT and oral contraceptive pill use, an unexpected finding was that...
CVT incidence was not significantly higher in females of reproductive age. This may be because in Australia, low-estrogen oral contraceptive pills with levonorgestrel (which has a lower thrombosis risk) have been first line for several years, although this may also have been a chance of finding. The fact that Coutinho et al found an increased incidence only in women aged 31 to 50 years, rather than for women of reproductive age (18–50 years), suggests that they found a weak or absent association in the whole cohort of reproductive age.

Our study has limitations. First, only public hospitals were included. However, only 7 patients were coded as having CVT in a private hospital in this period (versus 65 in public hospital), so this would have had a minimal impact on our conclusions. Second, ours was a retrospective study and is not, therefore, a gold standard epidemiological prospective incidence study. Third, 10 patients had inadequate medical documentation to determine whether CVT was a likely diagnosis. Finally, as radiology reports were reviewed rather than the scans themselves, it is possible that some cases were missed by the initial radiologist. However, all these limitations would lead to an underestimate of the true incidence.

Conclusions

Using a novel ascertainment methodology, we have confirmed that CVT incidence is historically underestimated. Contrary to previous studies, the sex ratio was evenly distributed. We propose that future incidence studies include comprehensive capture and review of neuroimaging to maximize ascertainment.

Disclosures

None.

References

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