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Editorial

Recurrent venous thromboembolism after cerebral venous thrombosis: which lower-risk survivors are at risk for recurrence?☆

When speaking to young, high-functioning survivors of cerebral venous thrombosis (CVT) and other causes of stroke in the young, one common theme that emerges in follow-up is fear of recurrence. CVT is known to have an excellent functional prognosis in most, with 85–90% achieving functional independence with the ability to carry out all previous activities [1,2]. However, as a rare cause of stroke in the young, an already rare event, CVT can be a traumatic and isolating experience, compounded by the aggravations of anticoagulation, and made worse by residual "invisible" deficits such as headache, fatigue, and neuropsychiatric symptoms, which may affect up to 60% of survivors [3,4]. The possibility of VTE recurrence remains an ongoing worry for those young women and men keen to resume their lives after stroke.

There is limited available literature to reassure our patients regarding the overall risk of recurrent VTE after first-ever CVT. An excellent recent review of the existing literature suggests that recurrence rates for all comers are similar to those for more common sites of VTE - approximately 2–4% per year, with an annual recurrence risk of 1–2% for CVT specifically [5]. In this issue of the journal, Dr. Pires and colleagues [14] add to the state of knowledge by examining rates of recurrence of CVT and associated risk factors in a large Brazilian cohort.

The authors prospectively followed 203 consecutive patients presenting to 4 centres over 14 years. To be included in the cohort, the index CVT was their first-ever VTE, and there was no indication for lifelong anticoagulation. Participants with radiologically-confirmed CVT were assessed at onset and in follow-up with a standardized questionnaire administered by trained hematologists, with follow-up beginning at the time of discontinuation of anticoagulation and spanning a minimum of six months. Follow-up spanned a median of 36 months (IQR 14.5–67.8). Those with a recurrent VTE or suspected recurrence were reassessed in person and recurrent events were confirmed with clinical and diagnostic means. Seven percent were lost to follow-up. Of the remaining 189 participants, 13 (6.8%) developed a recurrent VTE, with 23% occurring within the first year of follow-up.

One major strength of this study in adding to our understanding of the natural history of the disease is that it prospectively follows a large, low-risk cohort. Again, many of the commonest clinical risk factors for recurrence from previous studies do not apply here: participants did not have a history of previous VTE or malignancy, and only those who are heterozygotes for genetic thrombophilias were included (although presence of other thrombophilias, such as antithrombin deficiency, protein C and S deficiency, antiphospholipid antibodies, and JAK2 was not systematically investigated). Of the 86% of participants who were female, 93% were of childbearing age and three-quarters had their event while on oral contraceptives (65%) or during the puerperium (8%). So what can this tell us about risk of recurrence in low-risk patients, and how should this inform our antithrombotic strategy after CVT?

First, as with other forms of VTE, males were at highest risk for recurrence [6,7]. Next, heterozygosity for Factor V Leiden was an independent risk factor for recurrence. (Similarly, prothrombin gene mutation heterozygosity was also associated with recurrence, though not in the multivariable analysis, which may have been underpowered to detect a significant difference). In other cohorts including higher-risk individuals, male sex has frequently, but not consistently, been identified as a risk factor for recurrence [5]. Heterozygosity for genetic thrombophilias has not been specifically examined in previous studies of VTE recurrence after CVT. As with other forms of VTE, these risk factors may contribute to the case-by-case decision-making process regarding extended anticoagulation in CVT.

There was no difference in recurrence risk between "provoked" (73%) and "unprovoked" index events. However, most (10/13) recurrences were characterized as being provoked. Of those with provoked recurrence, 9/13 were women, 6 of whom had a provoked index event. Unfortunately, the authors do not provide further details about the specific provoking incidents associated with recurrences, such as whether these may have mainly occurred, for example, in association with pregnancy/puerperium in a participant who had her first event while on the oral contraceptive. More information regarding the "provoking" factor for recurrence (and its timing in relation to the event) may help to inform future research about targeted thromboprophylaxis and its duration in lower-risk patients during times of illness, immobility, or other higher-risk situations for VTE.

Median duration of anticoagulation in the entire cohort was 9.9 months (IQR 6.9–14.4). This is slightly longer than typical duration of treatment in recent clinician surveys [8,9], but generally within the guideline-recommended duration of 3–12 months [10,11]. While it would be helpful to know if those with recurrence had a shorter duration of anticoagulation than those without, it is notable that three-quarters of those with recurrences experienced them *after* their first year off anticoagulation. That individuals with recurrence were not clustered early after their index event again raises the question as to

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what the optimal antithrombotic strategy, if any, might be after the first year following CVT. Other studies also suggest that the risk of recurrent VTE after CVT increases somewhat linearly, and is not front-loaded within the first year after the event [5].

Extended antithrombotic therapy is of benefit for preventing recurrent DVT/PE [12]. However, the question is largely undiscussed in CVT, where individuals with the condition are likely to be younger (thus exposing them to a longer lifetime risk of bleeding if on antithrombotics), female, and more likely to have a provoked event (mainly oral contraception or the puerperium, as in this study's cohort). For those lower-risk individuals after CVT, targeted prophylaxis at times of higher risk may be appropriate, but this is not described in current guidelines and we are in need of research to inform this approach.

In context, and to address the front-of-mind question for many CVT survivors, these results provide further reassurance that recurrence rates for VTE in this context are low. Recurrence rates in this lower-risk cohort were lower than rates that are typically reported of ~1–2% annually for CVT and ~2–4% annually for all VTE [5], though 7% of participants were lost to follow-up. Overall incidence of VTE recurrence in this study was 1.6/100 patient-years, with recurrent CVT comprising 0.2/100 patient-years.

Other strengths of the study include its prospective, multicentre design, its inclusion of only individuals without a history of prior VTE, neuroimaging confirmation of the index event and diagnostic confirmation of the recurrent event, and follow-up for six months or more after cessation of anticoagulation. In comparison to other studies examining risk of VTE recurrence after CVT, this study gives helpful information as to what happens in a *low-risk* cohort after cessation of anticoagulation. The information in this study is helpful for informing clinical practice: the majority of CVT patients will be lower-risk women, with their event occurring in the context of exogenous hormones or the puerperium, and they may have questions around the risks of stopping anticoagulation. Most cohorts examining recurrence include higher-risk thrombophilias, and follow-up periods variably include the time from onset of the index event, and not time after cessation of anticoagulation [5].

Another added benefit of this study is that it adds to the international body of CVT literature, and thus, the international network of CVT researchers. The majority of the observational literature in CVT from Latin America is from Mexico, and greater representation in the CVT literature from this part of the world is needed. Questions regarding variations by geography and by genetics [13] in the incidence and risk factors will best be answered by global participation in research efforts. Central to survivors' concerns, the natural history of this rare disease and how to prevent recurrence will be best answered by large cooperative efforts.

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