Clinicoepidemiological profile of cerebral venous thrombosis in Algarve, Portugal: A retrospective observational study

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ABSTRACT

Background: Cerebral venous thrombosis (CVT) is a very uncommon disorder with a wide variety of clinical manifestations. There are few studies describing the clinical and epidemiological profile of CVT in peripheral or rural areas. Over the last decades, the frequency in which this disease is diagnosed has increased due to greater awareness and availability of noninvasive diagnostic techniques. Materials and Methods: A hospital-based retrospective case review of adult (≥15 years) patients with CVT between 2001 and 2012 is described. 31 patients with confirmed imagiological diagnosis of CVT were included. Statistical Analysis Used: Statistical analysis was performed using R version 2.15.2. Incidence rate was computed as number of new cases by time. Confidence interval (CI) was set at 95% and \( P < 0.05 \) was considered significant. Results: The average annual incidence was 0.84 (CI: 0.58–1.18) to 0.73 (CI: 0.5–1.02) per 100,000 cases for adult population. There were 23 (74%) women and 8 (26%) men. Predominant initial manifestations were headache, followed by altered mental status and seizures. Median diagnostic delay from onset of illness was 8 days. All patients were treated with unfractionated heparin or low-molecular heparin followed by warfarin. Complete recovery occurred in the majority of cases 22 (78.6%) but two patients died during hospitalization. Conclusions: Albeit with some particularities, the epidemiology and clinical manifestations we found are comparable to what has been reported in western studies.

Key words: Algarve, cerebral venous thrombosis, epidemiology, peripheral areas

Introduction

Cerebral venous thrombosis (CVT) is a rare cause of stroke with highly variable clinical features, heterogeneous predisposing factors, and unspecific brain imaging findings. Depending on the methodology used, the annual incidence of CVT is between 0.22 and 1.32/100,000/year.[1–5] The outcome of patients with CVT varies from complete recovery to permanent neurological deficits.[6–8] There are few studies characterizing the clinical and epidemiological experience concerning CVT, and most of them are from large centers or university hospitals. We conducted a retrospective cross-sectional review of case series of CVT from relatively peripheral region of Europe, the Algarve. Our aim was to characterize the clinical manifestations, treatment, risk factors, clinical course, and to estimate the incidence of CVT in the region.

Materials and Methods

Study area

Algarve is the southernmost region of mainland Portugal with an area of 4,995.6 km\(^2\). Between the two last censuses in Portugal (2001–2011) the resident population increased from 395,218 to 451,006, and the adult population (≥15 years) increased from 335,935 to 387,865, respectively.[9] Algarve is essentially served
by a net of primary health care units and by three hospitals (Hospital de Faro, Hospital de Portimão and Hospital de Lagos) all belonging to the same functional unit, the “Centro Hospitalar do Algarve.” There are two medico-surgical urgencies services in the region (Hospital de Portimão and Hospital de Faro).

Patients
Medical records of patients older than 15 years with the diagnosis of CVT from June 2001 to June 2012 were identified through International Classification of Diseases-9 (ICD-9) coding system and reviewed retrospectively. In addition, to reduce the risk of missing data, due to miscodification, we manually searched cases of CVT through the institutional clinical pathology database (the “CLINIDATA”) which lists patients treated with oral or intravenous anticoagulation.

All patients at admission or discharge, with proven diagnosis of CVT based on magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV), and/or computed tomography (CT) venography and/or conventional angiography were included. Nonresident patients were excluded from the analysis. Data on clinical and radiological manifestations, time to diagnosis (time interval from symptom onset to the diagnosis of CVT), risk factors, treatment, and clinical outcome were extracted. The outcome was defined by the physician in charge of each patient and classified subsequently by the investigators as follows: Complete recovery (modified Rankin Score or mRS 0–1), partial recovery but independent (mRS 2), partial recovery but dependent (mRS 3–5) and death (mRS 6). To minimize underestimation or overestimation, we used the resident population from the 2001 to 2011 census to estimate the average annual incidence rate CVT. Data are presented in intervals of “minimum and maximum” calculated incidences based on the minimum and maximum (2001 and 2011, respectively) resident population of Algarve.

Statistical analysis
Statistical analysis was performed using (GNU 1991 Free Software Foundation) Incidence rate was computed as number of new cases by time. Linear regression was applied to assess the tendency of total diagnosis time. Confidence interval (CI) was set at 95% and \( P < 0.05 \) was considered significant.

Approval for the study was obtained from our institutional IRB.

Results
Thirty-five patients with CVT were identified using the ICD coding for CVT. Six additional cases were retrieved from the CLINIDATA database. 10 cases were excluded from the analysis (6 patients younger than 15 years, and 4 nonresidents), which left a final number of 31 cases in 11 years. The average annual incidence rate was estimated to be 0.71 (CI: 0.49–0.99) per 100 000 cases for general population, in 2001, and 0.62 (CI: 0.43–0.88) per 100 000 for general population, in 2011. For people older than 15 years the incidence rate was estimated to be 0.84 (CI: 0.58–1.18) per 100 000 cases, in 2001, and 0.73 (CI: 0.5–1.02) per 100 000 cases, in 2011.

There were 23 (74%) women and 8 (26%) men (3:1 ratio). The mean age was 37.4 years (range 16–71 years), with a median of 32 years. The initial clinical manifestations are summarized in Table 1. Predominant initial manifestations were headache 23 (74.1%), followed by altered mental status (AMS) - 10 (32.2%), and seizures 6 (19.6%).

Median diagnostic delay from onset of illness was 6 days (range 0–41 days). There were no significant differences between both genders \( (P = 0.16) \), age was also no significantly associated to greater delay \( (P = 0.899) \).

Although not statistically significant, a tendency for decreasing delay in time to diagnosis was found \( (P = 0.4) \) [Figure 1]. The radiologic features are summarized in Table 1. The first brain TC was considered normal in the majority 19 (61.3%), diagnostic in 7 (22.6%), and gave an alternative diagnosis in four cases (12.9%): Arterial ischemic stroke (2), subarachnoid hemorrhage (1), and cerebritis (1). MRI was performed in all patients. Diagnosis was confirmed by MRV in 27 (87%) patients and by cerebral angiography in four (12.9%). All patients were treated with unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) followed by warfarin. Until 2005 \( (n = 14) \), UFH was used in the majority of patients (13/92.9%), and from 2006 on \( (n = 17) \), most patients were treated with LMWH (11/64.7%).

In one patient, neurosurgical treatment with ventriculoperitoneal shunt was performed in an attempt to avoid visual loss due to severe intracranial hypertension. Regarding risk factors for CVT [Table 1], 25 (80.6%) patients had at least one risk factor, and 12 (38.7%) two risk factors. Oral contraceptives were found in 16 (69.6%) women. 7 (43.7%) of them had an additional predisposing factor. Activated protein C resistance/factor V Leiden (5), prothrombin G20210A (1), and protein S deficiency (1) were the genetic thrombophilias discovered. Isolated cases of systemic disease that could predispose or potentially predispose to
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Patients in the region with potential severe neurological conditions are exclusively referred to one of the two hospitals from which the present data was extracted. This absence of dispersion potentially contributes to greater identification and recognition of cases of CVT. The demographics and clinical presentation in this study are comparable to what has been reported in the majority of recent studies from developed countries. As almost all studies, the most common clinical presentation was headache, followed by AMS and seizures. The overall prevalence of risk factors was 85.7%, with 39.2% having at least two risk factors. Genetic thrombophilias were identified in 21.4% of cases, <34.1 found in the ISCVT study.

Because patients were followed and investigated by different physicians, the possibility of incomplete screening of genetic thrombophilias must be considered. Our study confirms the decrease of infection as a cause of CVT in the western countries, contrasting to findings from low to middle-income countries. Reduction of the frequency of infection and availability of early effective antibiotic treatment justifies this difference.

Early anticoagulation is the mainstay of treatment and reduces morbidity in CVT. LMWH is preferable over UFH. All patients received anticoagulation. From 2006 on, LMWH was preferentially used over UFH. The prognosis of CVT is better than thought in the past. Our rate of death (3.6%) and rate of dependency (mRS ≥3) (10.7%) are among the lowest found in the literature.

The only study to date with a specific objective to address the incidence of CVT, revealed the highest incidence known, 1.32/100,000/year. There are no studies specifically addressing the incidence of CVT in our country. Even so, it is worth to highlight that the annual incidence of CVT we found is superior to that previously described in Portugal (0.22/100,000/year).[2] We believe that modern imaging tools such as MRV introduced in both hospitals in 2002 (Hospital de Portimão) and 2008 (Hospital de Faro) contributed to the increase of diagnosis and reduction of the time to diagnosis. Indeed, CVT was diagnosed by noninvasive imaging – MRV (24/85.7%) in the majority. Our median time to diagnosis (8 days) is comparable to the findings from our county and from the International Study CVT (ISCVT) (7–9 days). The absence of specific clinical manifestations contributes to delayed diagnosis of CVT. Furthermore, as shown in our case series, brain CT can be normal, show subtle abnormalities or even lead to an alternative diagnosis. This emphasizes the need of a high clinical suspicion and actively exclude or confirm the diagnosis using available resources.

Discussion

The frequency in which CVT is recognized is increasing due to greater awareness and availability of noninvasive diagnostic techniques.[6,7] Indeed, the only study to date with a specific objective to address the incidence of CVT, revealed the highest incidence known, 1.32/100,000/year.[3] There are no studies specifically addressing the incidence of CVT in our country. Even so, it is worth to highlight that the annual incidence of CVT we found is superior to that previously described in Portugal (0.22/100,000/year). We believe that modern imaging tools such as MRV introduced in both hospitals in 2002 (Hospital de Portimão) and 2008 (Hospital de Faro) contributed to the increase of diagnosis and reduction of the time to diagnosis. Indeed, CVT was diagnosed by noninvasive imaging – MRV (24/85.7%) in the majority. Our median time to diagnosis (8 days) is comparable to the findings from our county and from the International Study CVT (ISCVT) (7–9 days).[2,10,13] The absence of specific clinical manifestations contributes to delayed diagnosis of CVT. Furthermore, as shown in our case series, brain CT can be normal, show subtle abnormalities or even lead to an alternative diagnosis. This emphasizes the need of a high clinical suspicion and actively exclude or confirm the diagnosis using available resources.

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resources for clinical management. Our study has important limitations. We cannot exclude the possibility of under-representation of cases with poor prognosis, for example, in patients with extensive intracranial hemorrhage, where the possibility or investigation of CVT may not be considered, as also in less severe situations, such as the cases of isolated headache without clinical progression. In addition, because of the retrospective nature of our study, the absence of uniform clinical evaluation, treatment and etiological work-up for CVT in our hospitals, the possibility of recording bias, and undervaluation of clinical pertinent clinical information is considerable. In conclusion, our clinical findings including the prognosis in CVT are comparable to those described in the most recent reports from industrialized countries.

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