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Temporal Trends in Incidence, Causes and Associated Factors in Cerebral Venous Thrombosis: A 12-Year Single Center Danish Study

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Abstract

Introduction: We aimed to examine trends in the diagnosis of Cerebral Venous Sinus Thrombosis (CVT) and the differences in symptomatology.

Methods: We retrospectively examined all patients with a diagnosis of CVT discharged from our tertiary referral hospital in the period 2005-2016. We compared an earlier time period (2005-2013) to a later time period (2014-2016). We also compared clinical presentation with respect to age and sex.

Results: We found a total of 64 patients. Thirty patients from the early time period were compared to 34 in the later time period. In the later time period, significantly more men (53%) were seen compared to the earlier period (13%), p = 0.001. Patients were also significantly older in the later time period (median age: 55 years, Interquartile Range (IQR): 27-69) than patients in the earlier period (median age: 32.5 years, IQR 24-49), p = 0.0047.

Discussion: The average age of patients with CVT was higher in the later time period. We suggest that this can be due to either a decreasing incidence of CVT among young women using the oral contraceptive pill (OCP) or due to better diagnostics among elderly. If we disregard the young women using OCP, we achieve a more even distribution in sex and an older population.

Keywords: Cerebral venous thrombosis; Oral contraceptive pill; Age; Clinical presentation

Introduction

Cerebral Venous Sinus Thrombosis (CVT) is a rare cause of stroke, affecting only 1.3/100,000 [1], while the incident of arterial stroke is 100 times higher. Due to the varied symptoms, CVT is easily overlooked despite improved diagnostic methods. Symptoms include headache, focal deficits, seizures and progressive change in mental status [2]. Because of its rarity and the diverse and non-specific symptoms, the diagnosis is often delayed.

A common diagnostic maxim is that CVT should be suspected in the younger population and is more frequent in women, which could be ascribed to the use of the oral contraceptive pill (OCP) [3,4]. Our aim was to examine the incidence of CVT and to look for changes in relation to sex and risk factors. Furthermore, we wanted to describe the typical symptoms of CVT at presentation.

Methods

We identified patients with CVT admitted to a large university hospital through a 12-year period to examine trends in incidence. Data of patients diagnosed with CVT hospitalised between 2005-2016, at a Danish terteriry referral center (population catchment area: 700.000) was collected from records in the electronic patient record system. Data included age, sex, symptoms (headache, seizures and focal neurological deficits) and etiology (unknown, OCP use, mechanical causes, cancer, hereditary causes, generic causes and infection).

Data was dichotomized into two epochs: data from 2005-2013 (30 patients) was compared to 2014-2016 (34 patients), to

analyse if any changes or trends had happened. The reason why these periods were asymmetrically divided was that there were not enough patients admitted in the early years and we wanted the two periods to include approximately the same number of patients. This was only possible by splitting asymmetrically.

Symptoms among males (22 patients) were compared to females (42 patients) and also among patients younger and older than 50 years.

This project was undertaken as a quality improvement project and was thus exempt from ethical clearance by Danish law. The Mann-Whitney test was used to compare continued, non-normally distributed variables, while the chi-square test was used to compare categorical variables. A p-value of <0.05 was deemed significant. For statistical analysis MedCalc v. 18.6 (Ostend, Belgium) was used.

Results

In a 12-year period (2005-2016) 64 patients were diagnosed with CVT. This gives an incidence of 0.8/100,000/year. Patients in the later period (2014-2016) were significantly older with a median age of 55 years (Interquartile Range (IQR): 27-69) than patients in the earlier period (2005-2013) where a median age of 32.5 years (IQR 24-49) was observed, p = 0.0047. Also, a higher proportion of men was seen in later period (18/34 = 53.0 %) than in the earlier period (4/30 = 13.3 %), p = 0.001 (Figure 1).

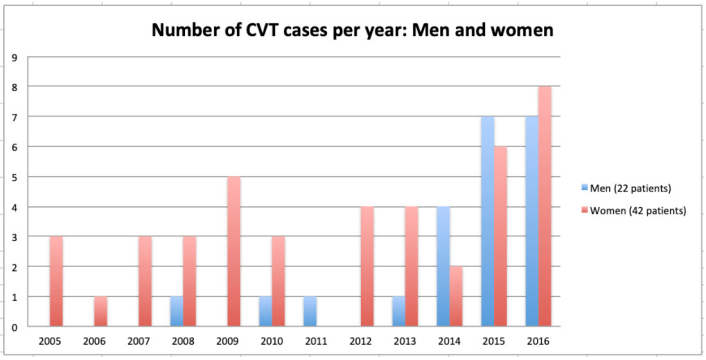

Figure 1: Number of CVT cases per year with shading for male and female.

Regarding etiology, OCP was the identified cause of the CVT in 61.9 % of the women, but removing this source of CVT, the etiology between the two sexes did not differ (Table 1). Patients in the early time-period had significantly more frequent OCP as the etiology compared to patients in the later time period (p-value = 0.014).

	2005-2013 (n=30)	2014-2016 (n=34)	p-value
Incidence	0.5 / 100.000	1.7 / 100.000	
Age (median)	32.5	55	< 0.05
Sex			
Men	4	18	< 0.05
Women	26	16	
Symptomes			
Headache	27 (90 %)	25 (73.5 %)	0.09
FND	21 (70 %)	24 (70.6 %)	0.95
Seizures	9 (30 %)	12 (35.3 %)	0.65
Etiology			
Unknown	9 (30 %)	18 (52.9 %)	0.07
OCP	18 (60 %)	9 (26.5 %)	< 0.05
APS*	2 (6.6 %)	6 (17.6 %)	0.19
GPS**	1 (3.3 %)	1 (2.9 %)	0.91
* Acquired Prothrombotic State; ** Genetic Prothrombotic State.			

Table 1: Descriptive table of the two time periods including incidence, age, sex, symptoms and etiology. Acquired prothrombotic state denotes cancer (3), dehydration (2), infections (2) and post-operative state (1).

Generally, the most frequent presenting symptom was headache, which was seen in 81.3 % of all patients. Comparing presenting symptoms between the sexes, men had less frequent headache (13/22=59.1%) as their first symptom compared to women (35/42=83.3%), p = 0.03, but otherwise presenting symptoms did not differ (Table 2).

	Women (n=42)	Men (n=22)	P-value
Headache (H)	35 (83%)	13 (59%)	0.03
Focal neurological deficits (F)	4 (11%)	5 (23%)	0.15
Seizure (S)	3 (7%)	2 (9%)	0.78
H + F	0	1 (5%)	0.17
F + S	0	1 (5%)	0.17
H + F + S	0	0	1

Table 2: This table describes the first symptom(s) recorded among the patients divided by sex.

Looking at the frequency of headache based on age, patients less than 50 years of age were significantly more likely to have a headache in their course of disease compared to patients above 50 years of age, p = 0.0045 (Table 3).

	Patients less than 50 years of age	Patients above than 50 years of age	p-value
Headache			
Yes	34	17	< 0.05
No	3	10	
FND			
Yes	21	24	< 0.05
No	16	3	
Seizures			
Yes	12	9	0.94
No	25	18	

Table 3: Age specific analysis. Patients less than 50 years compared to patients above 50 years of age.

Patients who were above 50 years of age were significantly more likely to have a Focal Neurological Deficit (FND) in their course of disease compared to patients less than 50 years of age (p = 0.0055). Frequency of seizures based on age was not different between groups (Table 3).

Discussion

Our study finds an incidence of CVT of 0.8/100,000/year. This is comparable to what has been described earlier in the literature. Coutinho, et al. [1], found an incidence of 1.3/100,000 and Bousser, et al. described an incidence of 0.5/100,000 [2]. Interestingly, we have found a change towards patients being older in the recent years and also fewer women were diagnosed in the recent years. This has resulted in an older and more even sex distribution among patients diagnosed with CVT in the later time-period, changing comparative patient demographics. The same trend is observed in a larger Dutch study [5]. But previous studies and reviews on the age change topic are underreported. The patients hospitalized with CVT in 2014-16 were significantly older than the patients hospitalized in 2005-13, with higher proportions of men.

To explain this change, we have looked into the use of OCP. The risk of venous thrombus in women on OCP is higher when using third generation OCP and lower when using second generation OCP. We examined the publicly available Danish Medicines Agency's health data (www.sundhedsdatastyrelse.dk) to investigate the national use of OCP (Figure 2). There is a remarkable shift around 2011, where an increase was seen in the use of the safer second generation OCPs. This national shift in OCP usage may have been a significant driver of the findings in our study. In the literature, it is well known that the thromboembolic risk is related to the dose of ethinyl estradiol, which is lowest in second generation OCPs (20µg) and higher in third and fourth generation OCPs (30-40µg) [6].

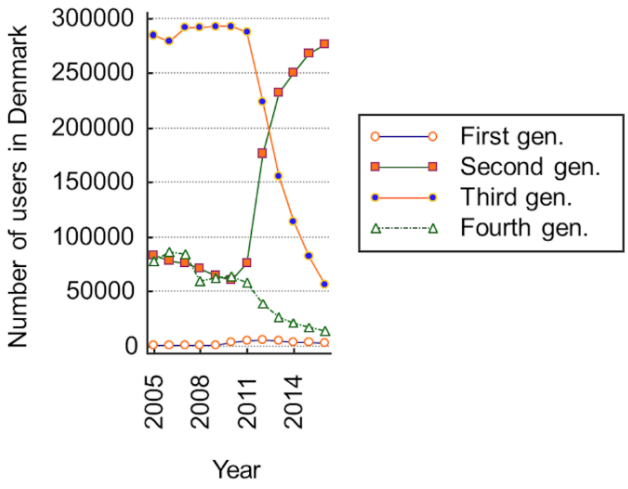

Figure 2: The number of users of the different generations of Oral Contraceptive Pills (OCP) in Denmark is shown on the Y-axis and the year on the X-axis. A shift to the second generation OCPs is seen in 2011.

Generally, we saw no difference in symptomatology, but men seemed to have headache less frequently than women, which also has been reported recently [5,7]. Since headache is the most common symptom in CVT, this could be a contributor to the reduced diagnosis in men.

The incidence of CVT has not decreased, which might be explained by CVT is being diagnosed more often among elderly in the later time epoch. This development can be explained partly by a change in the work up of patients with neurological deficits in our region as of May 2012, where more patients are being evaluated in our tertiary centre [8]. We speculate that these older patients might have been underdiagnosed earlier. In addition, attention to the diagnosis is typically increased in OCP users, and we speculate that women with headache taking OCPs more frequently get a Magnetic Resonance Imaging with venous angiography.

In addition, we found a correlation between age and specific symptoms. While patients older than 50 years had significantly less frequently headache compared to younger patients, the opposite was true for FND. The cause of this has been ascribed to "protection" of intracranial hypertension due to cerebral atrophy and a possible diminished trigeminovascular reactivity [9]. Interestingly, the prevalence of headache in a population with intracerebral haemorrhage was more frequent in women [10]. It is more difficult to explain why the older patients present more frequently with a FND, but it could be speculated that they due to

the lack of headache get diagnosed with a longer delay and develop more severe clinical symptoms. Some studies have reported a higher incidence of intracerebral haemorrhage in the elderly, and therefore also a higher likelihood of a FND [11]. This could have contributed to the worse outcome among elderly patients [12].

Our study is subject to several limitations, beyond the retrospective nature. Symptoms were found in the electronic patient system and not examined systematically. The small sample size limits statistical power, and we view these findings as exploratory. Sample size is often small in series on CVT. However, it is satisfying that our findings are comparable to larger studies as outlined above. Furthermore, the electronic patient system ensures 100% follow up in our cohort.

Conclusion

We saw a decrease in the diagnosis of CVT among young women using OCP, potentially due to a reduced use of the third generation OCP. This produced a more evenly distributed diagnosis among sexes and an older population among the CVT patients. Women had headache more frequently and older patients more frequently had a FND.

Disclosures

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