Thrombosis Research 130 (2012) S19–S22

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Cerebral venous thrombosis, pregnancy and oral contraceptives

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ARTICLE INFO

Keywords:
Cerebral venous thrombosis
Stroke
Oral contraceptives
Pregnancy
Puerperium
Ovarian hyperstimulation syndrome

ABSTRACT

Cerebral venous thrombosis (CVT) is a rare variety of cerebro-vascular disease accounting for 0.5% of all stroke. It can occur at any age. It has a 3/1 female preponderance with a peak in young women due to gender specific risk factors, especially oral contraceptives and to lesser extent pregnancy, post-partum, and in vitro fertilization. Despite a wide variety of clinical presentations, early diagnosis, mostly based on MRI/MRA, is crucial but often difficult particularly during post-partum because of the numerous causes of headache that may occur after delivery. Antitrombotic treatment based on low molecular weight heparin and symptomatic treatment should be started as rapidly as possible. The overall prognosis of CVT is much better than that of arterial stroke and it is even better in women with gender specific risk factors, with a complete recovery in 80% of patients. Future pregnancy is not contra-indicated, but contraception with oestro-progestogens is definitely contra-indicated.

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Introduction

Cerebral venous thrombosis (CVT) is a rare variety of venous thromboembolism (VTE) that involves cerebral veins and dural sinuses which drain the blood towards the internal jugular veins. The reason why it is so rare is unknown but CVT shares many characteristics (red clot, prothrombotic risk factors, anticoagulant treatment…) with other VTE so that many of the recommendations which are evidenced-based for VTE are also applied by neurologists to CVT. CVT affects about 5 people per million and accounts for 0.5% of all stroke. It may occur at any age and in both sexes, but it has a 3 to 1 female preponderance, mostly due to oral contraceptive use and, to a lesser extent, pregnancy, post partum, hormone replacement therapy, and in vitro fertilization [1,2]. CVT is typically a multifactorial condition and gender specific causes are often associated with any of the numerous disorders that can cause – or predispose to – CVT. These include all the usual medical and surgical causes of VTE as well as number of local causes such as brain tumors, head trauma, central nervous system infections, intracranial hypotension, and any local (ear, sinus, face, mouth…) infection [1]. By far the most frequently associated factor is congenital thrombophilia [1]. Although a few differences have been identified between men and women in the clinical presentation of CVT, these differences are minor and the diagnostic work up and treatment strategies are roughly similar in both sexes. The prognosis is overall much better in CVT than in arterial stroke and it is particularly good in women with a gender specific risk factor [2].

Pregnancy and puerperium

The association of CVT with pregnancy and puerperium has been known for about 200 years [3] and regularly emphasized since then [1–6]. The incidence is around 10/100 000 deliveries in high-income countries, accounting for 5–20% of all CVT, but the incidence is as much as 10 times higher in countries like India or Mexico where it accounts for up to 60% of all CVT [5] In the International study of cerebral venous thrombosis (ISCVT), 17% of the 465 women had CVT related to pregnancy or puerperium, and it was 12% in our own prospective (unpublished) series of 286 CVT in women aged under 50 years.

As other VTE, most pregnancy related CVT occur during the third trimester, but the risk is much greater during puerperium, reaching 13 times more in the Mexican series [5]. The risk is maximal during the first month after delivery [6–8] and increases with maternal age, multiparity, increasing hospital size, home deliveries, cesarean delivery, hypertension, infection, dehydration, excessive vomiting and anemia [5–8]. By contrast in our series, post partum CVT was not significantly more frequent during post-partum than during pregnancy (6.5% versus 5%), possibly reflecting an improved post-natal care, and the most frequently associated factor was cerebro-spinal fluid hypotension after epidural anesthesia.

Besides these temporary factors related to the conditions of delivery or to characteristics of post-natal care, other factors are often associated with the prothrombotic changes that occur during pregnancy and puerperium. Approximately half of the patients in ISCVT [2] and two-thirds in our series had at least another cause or prothrombotic risk factor, most frequently congenital thrombophilia., such as Factor V Leiden or prothrombin 20210A mutation. Among other factors, hyperhomocysteinemia in pregnant women was associated

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http://dx.doi.org/10.1016/j.thromres.2012.08.264

with a ten times risk of puerperal CVT [9], possibly adding to the low folate concentration that exists during pregnancy.

In summary, although relatively rare nowadays in high income countries, pregnancy and puerperium related CVT still accounts for 10–15% of causes of CVT in women of childbearing age. In over half the cases, there is at least one associated prothrombotic risk factor or cause that should thus be systematically looked for. These data are in accordance with those concerning other VTE for which the risk is also increased predominantly during the 3rd trimester of pregnancy, 10 times more during the first 6 weeks after delivery and furthermore with congenital thrombophilia [10].

Oral contraceptives

That oral contraceptives may cause CVT has been known since the 1960s, but for many years there were controversies about the reality of the association, the size of the risk, the role of hormonal type and dosage, and the implication of associated prothrombotic risk factors. There is nowadays no doubt about the reality of the association : in all series of CVT, oral contraceptives use is the most frequent risk factor in women : it was present in 47% in ISCVT, and 96% in an Italian study [11]. Other case control studies [12] and meta-analysis [13] have confirmed that estrogens increase the risk of CVT (OR 5.59, 95% CI 3.95 to 7.91 ; $p<0.001$) [13]. There is no doubt either that the risk is dramatically increased by congenital thrombophilia such as factor V leiden with an odds ratio of 30 and prothrombin G20210A mutation with an odds ratio of 79.3 [11].

The risk of CVT with estroprogestogens increases with age and high dose estrogen content. There are not enough data in CVTto compare the risks associated with all the varieties of hormonal contraception but cases have been reported with transdermal patches and vaginal rings [14] in accordance with VTE data [15]. The magnitude of the risk for VTE seems to be the same with third generation oral contraceptives as with older ones [10]. There are so far no case–control data of CVT in women using oral contraceptives containing drospirenone which has recently shown to double the risk of VTE compare to oral contraceptives containing levonorgestrel [16,17].

Clinical presentation and diagnosis

The clinical presentation of CVT is remarkably diverse, according to the location of the thrombosis, the presence of parenchymal brain lesions, the age of patients, and the time between onset of symptoms and admission to hospital [1]. There are no major differences of CVT presentations between sexes, although in ISCVT, a less often chronic onset of symptoms and a higher frequency of headache have been found in women with a gender specific risk factors, mostly oral contraceptive and pregnancy/puerperium.

The most common symptoms and signs are headache, seizures, focal neurological deficits, altered consciousness, and papilledema which can be present in isolation or in association. According to the grouping of symptoms and signs, four main patterns have been identified : isolated intracranial hypertension, focal syndrome, - usually related to hemorrhagic or ischaemic stroke -, cavernous sinus syndrome, and subacute encephalopathy [1]. However, there are many other more unusual presentations such as isolated headache, transient ischaemic attacks, attacks of migraine with aura, isolated psychiatric disturbances, subarachnoid hemorrhage etc…. Headache is by far the most frequent symptom, present at any time in 90-95% of cases and atonset in 80%. It has no specific pattern but it is a recent , persisting, usually severe headache that worsens rapidly. Such headache in young women using oral contraceptives or during pregnancy or puerperium should urgently prompt appropriate neuroimaging investigations. The diagnosis of CVT may be particularly difficult during puerperium because of the many other causes of headache and eventually of stroke occurring after delivery such as migraine recurrence, cerebro-spinal fluid hypotension, reversible cerebral vasoconstriction syndrome (RCVS), cervical artery dissection. It is even more difficult in the rare cases in which several of these conditions are associated such as the association of CVT with RCVS and dissections [18].

The clue to the diagnosis of CVT is the demonstration of the thrombotic occlusion of cerebral veins or sinuses. This may be seen, but only in less than 20% of cases, on plain CT scan, as vessels spontaneously hyperdense. On plain MRI thrombosis appears as an increased signal on T1T2-WI and as a decreased signal on T2 gradient echo (T2*) [1,19,20]. The T2* sequence has the highest sensitivity, particularly in the very first few days when the hypersignal on T1 may still be missing [20]. The changes over time of the signal of the clot on various sequences thus allow not only to visualize but also to date the thrombus and follow its evolution. On the widely used angiographic techniques (MR angiography, CT angiography or -rarely nowadays- conventional angiography), the thrombosed vessels appear missing but, firstly, these techniques do not differenciate between thrombosis and hypoplasia, which is frequent in the cerebral venous system, and secondly, injections and X-rays should better be avoided in pregnant women.

The imaging of the brain itself has less diagnostic value because it usually shows non specific lesions such as hemorrhages, infarctions, oedema in isolation or in combination, and it can be normal in up to 25% of patients. It has however an important prognostic value and it is also crucial for the diagnosis of the many other conditions that CVT can mimic, such as arterial stroke, encephalitis, abscess, eclampsia etc …

Other investigations are of little diagnostic value. In febrile patients, provided that there is no contra-indication, lumbar puncture is necessary to rule out meningitis, a rare cause of CVT. D-dimer measurement may be useful, but it does not have the same high negative predictive value as for deep venous thrombosis in the legs [21]. In patients with a recent CVT and encephalic signs, such as seizures, focal deficits or disorders of consciousness, D-Dimer are normal in only 4% of cases, but in those presenting with isolated headache, they are normal in one fourth of the patients [21]. A negative D-Dimer assay cannot thus rule out CVT in the setting of a recent isolated headache, a very frequent practical situation in which the decision to perform MRI is the most debated.

In summary, although CT and MR angiographies are useful, plain MRI including T2* sequences is the gold standard for the diagnosis of CVT particularly during pregnancy and should therefore be performed as rapidly as possible, whenever there is a reasonable degree of clinical suspicion.

Treatment

Patients with CVT should be admitted to stroke unit, where, as soon as the diagnosis is firmly established, a triple treatment will be initiated : anti-thrombotic, symptomatic and, whenever appropriate, etiologic. The principles of these treatments are the same in young women with gender specific risk factors as in all other CVT patients [19,22]. Once recognized, CVT should, on an emergency basis and in even in the presence of intra cerebral or subarachnoid hemorrhage, be anti-coagulated with body weight-adjusted low molecular weight subcutaneous heparin (LMWH). On the basis of non randomized data, LMWH seems to have a better efficacy and safety profile that unfractionated heparin (UFH) [23]. Furthermore, during pregnancy, LMWH is definitely recommended over UFH whether in CVT [19] or in other VTE [24] patients. Intravenous or local thrombolysis and mechanical thrombectomy are feasible but not proven superior to LMWH.In the few patients who deteriorate despite anti-coagulation, the reasons for this deterioration should be evaluated and treatment adapted accordingly : insufficient anticoagulation ? uncontrolled seizures ? heparin-induced thrombocytopenia ? thrombosis extension ? Pulmonary embolism ? Brain herniation ?

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