Cerebral venous sinus thromboses are one CNS manifestation of an adverse effect directly related to sex hormone therapy. Other causes may include hypercoagulable states such as pregnancy, carcinomatous syndrome, and protein S deficiency. According to Lidegaard and Kreiner, cerebral thrombosis in users of oral contraceptives is directly associated with the estrogenic component and its dose. Severe headache was the most common symptom, followed by motor focal deficits and comatose state. Deep infarcts were located in the thalamic and basal ganglia region in 11 cases. Seven women had associated intracerebral hemorrhage, and 3 had ventricular dilation. Angiographic MR imaging was done in 10 patients, and conventional angiography was done in 7. Genetic analysis of chromosomal abnormalities associated with stroke was done in 5 cases.

Results. The intracranial pressure (ICP) was monitored in all cases. Three patients underwent external ventricular drainage, and 1 had a decompressive craniotomy. All had absence of signal in the cerebral sinus rectus, with associated thrombosis of the transverse sinus in 7 cases. Angiograms were negative for additional vascular malformation. Medical treatment included sodium heparin and mannitol in 9 cases, and enoxaparin in the other 6 patients. Genetic analysis was positive for prothrombin mutation G20210A (factor II variant) in 2 cases. The mean follow-up duration of 53 months demonstrated no neurological deficit in 10 patients, hemiparesis in 3, and severe hemiparesis with aphasia in 1 case. One woman died 5 days after a decompressive craniotomy.

Conclusions. Cerebral venous sinus thrombosis secondary to oral contraception in young women, including lesions in critical and deep regions, can be treated medically with acceptable morbidity. In spite of this, a subgroup of patients needed basic neurosurgical management of the lesions, including surgical measures for controlling raised ICP.

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Key Words • cerebral sinus thrombosis • oral contraceptive • craniotomy • intracranial pressure • cerebral angiography

Cerebral venous sinus thromboses are one CNS manifestation of an adverse effect directly related to sex hormone therapy. Other causes may include hypercoagulable states such as pregnancy, carcinomatous syndrome, and protein S deficiency. According to Lidegaard and Kreiner, cerebral thrombosis in users of oral contraceptives is directly associated with the estrogenic component and its dose. These complications are usually sporadic and solitary, whereas cases with a genetic component are characterized by multiple lesions. Martinelli et al. reported a high risk of cerebral vein thrombosis in users of oral contraceptives who were carriers of a prothrombin gene mutation. The dominant autosomal transmission of high penetrance is associated with the 20210 chromosome mutation.

Cerebral venous drainage is characterized by many collateral vessels, so if occlusion occurs gradually, it changes collateral drainage, hence avoiding cerebral edema and elevated ICP. Thrombosis of the cerebral venous outflow is an uncommon and difficult problem to manage, particularly when complicated by venous infarction, which may be disabling or even life-threatening.

There is bias and confounding factors among studies regarding the overall morbidity rate of general series. Controversies exist regarding the best surgical management, control of hemorrhagic risk, and treatment of associated adjacent or distal developmental vascular anomalies. Given the lack of neurosurgical series of young women with overt cerebral thrombosis secondary to hormone replacement therapy, we decided to conduct a retrospective analysis of our treated cases during the last 15 years.

The objective of this study was to determine a straightforward management protocol according to clinical presentation, lesion location, and radiological characteristics.
Patient Population

Fifteen female patients with overt cerebral venous thrombosis received neurosurgical treatment between 1990 and 2007. The patient ages ranged from 23 to 45 years (mean 31 years). The women were relatively healthy, and all had a history of use of oral contraceptives of ~ 1 year before onset of neurological symptoms. Oral contraceptive agents included combinations of the following: norgestrel; l-norgestrel; norethindrone; and norethindrone acetate, either with mestranol or ethinyl estradiol, in all cases. The main clinical presentation included acute severe headaches (7 patients), with vomiting (3), papilledema (3), and chronic headaches (5), focal neurological deficits such as monoparesis or motor or sensory aphasia (4), hemiparesis (5), and generalized seizures (2). The initial level of consciousness ranged from fully awake with subsequent deterioration (7 patients) to a stuporous (4) or comatose state (4). The clinical history ranged from a few hours to > 6 months in a patient with chronic headaches and papilledema.

Neuroimaging Findings

Initial head CT scanning showed that 11 patients had a single hypodense lesion, whereas the other 4 had multiple lesions. Hypodense lesions were located in the basal ganglia and thalamus in 11 cases, and 4 had bilateral lesions. Seven patients had lesions in the paraventricular regions or cortico-subcortical area. Lobar lesions (7) included the cortico-subcortical temporoparoccipital area located on the right side in 4 cases, with 2 other lesions located in eloquent areas. Hemorrhage, which was present in 7 patients, was deeply located in 4 cases, cortico-subcortical in 2, and both in 1 case. In 2 patients, rim SAH was observed in the basal cisterns. Three cases had ventricular enlargement and the other 2 had diffuse brain swelling. The “empty delta” sign on enhanced CT scanning was seen in 3 of 5 patients who underwent contrast head CT.

In 10 patients an MR angiography study was performed using phase-sensitive gradient echo imaging, and lesions were classified according to location of the involved sinus, whereas a conventional cerebral angiogram (obtained in patients treated in the early 1990s) or DS angiography was performed in 7 patients or cases with either associated hemorrhage or bilateral deep lesions, for identification of the related vascular anomalies.

Genetic studies for identification of chromosomal abnormalities associated with stroke were done in 5 patients.

Intracranial monitoring was instituted in all patients. Surgery was done within 12 hours in patients presenting in a comatose state or after neurological deterioration. Three patients underwent insertion of an external ventricular device, and 1 had a decompressive craniotomy.

Results

Clinical and Imaging Results

The anatomical location of the lesion was correlated with the patient’s clinical condition. On MR angiographic studies and conventional angiograms, we identified thrombosed veins and hypoplastic or thrombosed sinus, which were present in all cases. There was absence of signal in the deep venous system and sinus rectus in all studies. The transverse sinus was compromised on the right side in 4 cases and on the left in another 3 (Fig. 1). Developmental venous anomalies were identified in 5 patients, and were categorized as venous angioma and “venous-like” angioma (the latter was present in 3 patients, with 2 of the anomalies adjacent to and 1 distant to the thrombosis). Other adjacent findings included hypertrophic veins in 4 cases, and capillary blush in another 3 cases. There were no other vascular lesions such as arteriovenous malformations and aneurysms.

Antithrombolytic therapy included sodium heparin IV (24,000 IU/24 hours), along with courses of mannitol and dexamethasone in 9 cases. Oral anticoagulant therapy was started between Days 8 and 15 with warfarin and continued for 6–12 months. In 6 cases we instituted enoxaparin (200 IU/kg/24 hours), starting between Days 10 and 16 with warfarin and continuing the therapy for 6–12 months.
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Fig. 2. Left: Cerebral CT scan showing bilateral hemorrhagic infarcts of the thalamic area, with diffuse cerebral swelling and hemorrhagic small ventricles with basal ganglia infarcts. Right: Phase-sensitive gradient echo MR angiography study showing overt thrombosis of sinus rectus and left transverse sinus, with venous stagnation in the basal cisterns and posterior fossa. The patient received ICP monitoring, and due to uncontrollable raised pressures, she underwent a right frontoparietal decompressive craniotomy. Her condition remained critical and she died a few days later.

Two patients with lobar hemorrhagic lesions who presented with generalized seizures were treated with intravenous phenobarbital. Oral anticonvulsant therapy was continued in all patients with cortico-subcortical lesions and hemorrhage for up to 12 months.

Neurosurgical Management

Intracranial pressure monitoring disclosed initial high ICP (levels > 20 cm H2O) in 4 patients; initial normal ICP, with raised ICP after 24–48 hours in 5 cases; and normal ICP in 6 cases. Except in 1 case, the ICP was easily controlled with sedation, mannitol, and intermittent steroid courses. An external ventricular drain was inserted in 3 patients with moderate ventricular enlargement, and ICP was controlled in all 3 after that.

One patient initially presented with headaches, which rapidly evolved to a comatose state, presenting with a deep hemorrhage and diffuse cerebral swelling along with small ventricles on head CT scans (Fig. 2). She underwent screening for vascular malformations, along with raised ICP that medical treatment failed to control. She subsequently underwent a decompressive craniotomy 18 hours after admission to the critical care unit. Her clinical condition remained unchanged after surgery, and she died 3 days later.

The clinical condition remained stable in all other patients after monitoring ICP, and none had further complications such as pulmonary embolism or deep venous thrombosis. Overall, patients remained in the intensive care unit for 2–7 days after surgery; the mean hospital stay was 12 days.

The mean follow-up duration was 53 months (range 12–132 months), and no neurological deficit was demonstrated in 7 patients, moderate neurological deficit was found in 5, and there were severe deficits in 2 cases. Patients with moderate and severe disability had lesions in eloquent and deep cerebral areas. No patient had residual epilepsy. The last imaging follow-up study disclosed no de novo vascular lesions.

Results of genetic studies disclosed the chromosome mutation G20210A of prothrombin (factor II variant) in 2 cases.

Discussion

Our experience confirms that cerebral venous thrombosis secondary to oral contraception in young women, including those lesions in critical and deep regions, can be treated medically in the majority of cases. Mild symptoms of venous thrombosis, such as headaches, can be treated with supportive measures. Despite these findings, there was a subgroup of patients with deep infarcts secondary to deep venous sinus thrombosis in whom basic neurosurgical management included medical and surgical measures for controlling raised ICP.

Headache is a major initial symptom of occlusion of a venous sinus. Focal deficits may follow, depending on the location of the thrombosis. Papilledema and altered sensorium may be noted as the condition advances. In fact, most of our patients presented with headaches, some of a chronic type. As well, venous infarction has a greater tendency for hemorrhage than ischemic infarction of arterial occlusion. Intracerebral hemorrhage and SAH happened in 7 of our patients, and most of them presented at first with altered consciousness.

Multiple findings of edema and hemorrhage on the unenhanced and contrast-enhanced CT scans give strong indications of dural sinus thrombosis. Whether the “empty delta” sign on enhanced CT, indicating venous engorgement around a thrombosed superior sagittal sinus, is the most specific finding on CT scanning and carries an ominous prognosis, is controversial. Conventional cerebral angiography and DS arterial angiography have been the definitive diagnostic procedures for this condition. However, MR angiography using phase-sensitive gradient echo imaging is an accurate, noninvasive method that can measure flow velocities within the dural sinuses, and it may replace contrast injection angiography as the preferred method for evaluating the cerebral venous system. We used initial head CT scanning and we were able to approximate, in the majority of cases, initial diagnosis of sinus thrombosis. We confirmed our results either with conventional angiography during the early 1990s, and with MR angiography or DS angiography more recently. Angiography was used basically in 7 patients in whom additional vascular disease was suspected, even though we couldn’t find any other overt vascular lesion.

General supportive care with intensive care monitoring, parenteral fluids, and systemic anticoagulation with heparin and warfarin are the usual procedures for patients with acute venous sinus thrombosis. Whether anticoagulation will aggravate the hemorrhagic infarction that characteristically accompanies acute sinus occlusion is a dilemma. Direct intervention by surgical clot removal has met with only limited success, and series include few patients. Further success in reestablishing venous sinus patency has been reported using direct sinus perfusion of thrombolytic enzymes; that is, urokinase or streptokinase. Also, activated tissue plasminogen may have some advantage in local treatment of sinus thrombosis, but a definitive conclusion awaits further trials.
Although many patients recover with supportive measures, it is the patient who continues to decline in spite of these measures who may be salvaged by local thrombolytic manipulation of the sinus. Yet, these patients may have a grim prognosis.\textsuperscript{13,16,18}

Our cases were initially treated with general supportive care, although as the thrombosis advanced, monitoring of ICP was necessary in all patients. Subsequent treatment of ICP, which included sedation, mannitol, and steroids, was done in 9 cases. Four patients required surgical maneuvers to control ICP (namely ventricular drainage), and a decompressive craniotomy was also performed in a young woman who later died. Direct approach to the thrombosed sinus was not followed in any case, basically because we did not believe it to be strictly necessary, given the favorable evolution the patients experienced during and after medical management. In the patient who underwent a decompressive craniotomy, her condition evolved to critical and it was not possible to implement further aggressive measures, such as direct revascularization of the sinus.\textsuperscript{2,3} Eventually she might have had some benefit with direct sinus perfusion of thrombolytic agents.

### Oral Contraception and Cerebral Sinus Thrombosis

The early study of Longstreth and Swanson\textsuperscript{10} clearly

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
Case No. & Age (yrs) & Main Initial Sx & Level of Consciousness on Admission & Location of Lesion & Venous System Compromised & Hemorrhage & ICP Management & Tx & Neuro Deficit on Clinical FU\textsuperscript{†} \\
\hline
1 & 37 & headache & FAD & BG/Th & deep & no & sedation, mannitol, steroids & ICP mon & moderate \\
2 & 31 & headache & stuporous & BG/Th, cortico-subcortical & deep & yes & sedation, mannitol, steroids & ICP mon & moderate \\
3 & 29 & chronic headache & FAD & BG/Th & deep & no & none & ICP mon & none \\
4 & 23 & hemiparesis & stuporous & BG/Th & deep, rt transverse sinus & yes & sedation, mannitol, steroids & ICP mon & moderate \\
5 & 25 & headache & stuporous & cortico-subcortical & deep & yes & mannitol, steroids & ICP mon & moderate \\
6 & 36 & vomiting & comatose & BG/Th (bilat) & deep & yes & sedation, mannitol, steroids & ICP mon, EVD & severe \\
7 & 34 & headache & comatose & BG/Th (bilat) & deep, rt transverse sinus & yes & sedation, mannitol, steroids & ICP mon, EVD, craniotomy & death \\
8 & 28 & vomiting & FAD & BG/Th & deep & no & none & ICP mon & none \\
9 & 42 & chronic headache & FAD & cortico-subcortical & deep, rt transverse sinus & no & sedation, mannitol, steroids & ICP mon & none \\
10 & 30 & headache & comatose & BG/Th (bilat) & deep, lt transverse sinus & no & sedation, mannitol, steroids & ICP mon & moderate \\
11 & 45 & chronic headache & stuporous & cortico-subcortical & deep, rt transverse sinus & yes & none & ICP mon & none \\
12 & 25 & cronic headache & FAD & BG/Th & deep & no & sedation, mannitol, steroids & ICP mon & none \\
13 & 28 & headache & comatose & BG/Th (bilat) & deep, lt transverse sinus & yes & sedation, mannitol, steroids & ICP mon, EVD & severe \\
14 & 42 & aphasia & FAD & cortico-subcortical & deep, lt transverse sinus & no & steroids & ICP mon & none \\
15 & 30 & headache & FAD & BG/Th & deep & no & steroids & ICP mon & none \\
\hline
\end{tabular}
\caption{Clinical summary of 15 young women with cerebral venous sinus thrombosis due to oral contraceptives*}
\end{table}

\textsuperscript{*} BG/Th = basal ganglia/thalamus; EVD = external ventricular drainage; FAD = fully awake with subsequent deterioration; FU = follow-up; mon = monitoring; neuro = neurological.

\textsuperscript{†} After a mean follow-up of 53 months.
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indicated that women who take oral contraceptives in the childbearing years, particularly if they are older than 35 years of age, are at increased risk of cerebral infarction and SAH. Indeed, cerebral and noncerebral venous thromboses are other known complications. These observations, coupled with evidence that estrogen alters the coagulability of the blood,\textsuperscript{6,9,15} suggest that a state of hypercoagulability is an important factor in the genesis of contraceptive-associated infarction. The vascular lesions underlying cerebral thrombosis in women taking oral contraceptives has been studied by Irey et al.\textsuperscript{8} It consists of nodular intimal hyperplasia of eccentric distribution, with increased acid mucopolysaccharides and replication of the internal elastic lamina. Whether these promote in situ thrombosis is not known.\textsuperscript{6} At increased risk of stroke are mainly women taking high-dose (0.5-mg) estrogen pills; lowering the estrogen content has substantially reduced this risk.\textsuperscript{9} The use of progestin-only pills or of subcutaneously implanted capsules of progesin alone has not been associated with an increased risk of stroke.\textsuperscript{12} It has also become clear that mutations of the prothrombin gene are far more frequent in patients who have cerebral venous thrombosis while on oral contraceptive pills. These genetic abnormalities are thought by Martinelli et al.\textsuperscript{11} to account for 35\% of idiopathic cases of cerebral venous thrombosis; this dominant autosomal genetic inheritance makes the use of contraceptives increase the risk of thrombosis 20-fold.

Whether familial genetic studies can help the physician manage patient risk is controversial. Genetic factors have been identified in 20–30\% of patients with thrombosis\textsuperscript{2} and 20-fold. Genetic studies have also been performed in 20–30\% of patients with thrombotic abnormalities.\textsuperscript{6,15} In our experience, genetic studies were positive in 2 of 5 of the cases studied.

One caveat of our study is that patients were preselected, so it remains uncertain how frequent and necessary neurological management is in young women with cerebral sinus thrombosis. Our quest was directed toward a surgical series, to categorize a different kind of cerebral sinus thrombosis. Our quest was directed toward a surgical series, to categorize a different kind of cerebral sinus thrombosis. Our quest was directed toward a surgical series, to categorize a different kind of cerebral sinus thrombosis. Our quest was directed toward a surgical series, to categorize a different kind of cerebral sinus thrombosis.

Conclusions

Cerebral sinus thrombosis associated with oral contraception in young women is a serious complication. Neurosurgical management should follow normally accepted indications. Surgical goals included control of ICP, which was indicated in deep and eloquent lesions with progressive neurological deterioration, evident hemorrhage, and noncontrolled cerebral swelling. Still unresolved are questions about the need for long-term imaging follow-up in these patients; for conventional cerebral angiography, even in preselected cases; and for genetic screening studies.

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