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Case Report

Cerebral venous sinus thrombosis due to oral contraceptive use: Postmortem 3 T-MRI and autopsy findings

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Abstract Cerebral venous sinus thrombosis (CVST) is an uncommon form of stroke, and mortality of the acute phase is high. We report the clinical, postmortem 3 T-MRI, and autopsy features of a patient, 20-year-old Japanese woman, with CVST who died shortly after starting to use low-dose estrogen combined hormonal contraceptives (CHCs). A postmortem 3 T-MRI study with our originally developed system revealed abnormal intensities suggestive of thrombi extending throughout the straight sinus and left sigmoid sinus. At autopsy, in accordance with the images, we performed careful preparations of the sinuses. Histological examination revealed an organizing white thrombus occupying the lumen of the left sigmoid sinus, and an acute, red thrombus in the lumen of the left transverse, straight, and tentorial sinuses, and vein of Galen, indicating that the thrombus had developed first in the left sigmoid sinus, then extended retrogradely to the more proximal portion of the sinus system, reaching the vein of Galen. The features of the present CVST patient appear to be informative, when encountering CHC users with neurological symptoms, even in those who begun to use low-dose estrogen CHCs only recently.

1. Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon form of stroke, accounting for 0.5%–1.0% of all strokes [1]. The clinical manifestations of CVST depend on the

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location of the thrombus, and may include headache, seizure, focal neurological symptoms, and consciousness disturbance. CSVT is often associated with hemorrhagic infarction in the thalamus and basal ganglia. Thereupon, mortality in the acute phase is high, and ranging from 3% to 15%. CSVT mostly affects young women of childbearing age because they sometimes have several risk factors, including pregnancy and use of oral contraceptives [2]. Recent cohort studies have provided evidence that the relative risk of thrombotic events associated with newly developed, low-dose estrogen combined hormonal contraceptives (CHCs) may be lower than that with conventional CHCs [3,4]. In Japan, low-dose estrogen CHCs were recently approved for use. Therefore, for precise assessment of the risk or safety of this drug for Japanese women, both a large-scale cohort study and information on extraordinarily unexpected cases in this population would be useful.

Recently, we encountered a patient with CVST who died shortly after starting to use low-dose estrogen CHCs. Here we report the clinical, postmortem 3 T-MRI, and autopsy features of this patient.

2. Case report

A 20-year-old Japanese woman with no significant medical history was prescribed an oral CHC tablet, drospirenone (3 mg)/ethinyl estradiol (20 μg) (YAZ®), for dysmenorrhea. In a few days after starting to take the CHC, she developed a headache. On the 9th day of CHC use, her headache worsened and she experienced nausea, appetite loss, and difficulty in walking: therefore she discontinued taking the CHC. In the afternoon of the following day, she was confined to bed, and next early morning, on the 11th day after starting to take the CHC, she was found unconscious and rushed to a hospital. A brain CT and MRI study revealed infarcts with edema in the bilateral thalami and left cerebellar hemisphere (Fig. 1A and B). Then, under a tentative diagnosis of CVST, she was transferred immediately to Niigata University Hospital. On admission, the patient was suffering from generalized convulsions and was administered diazepam. She then became comatose and quadriplegic. A CT scan disclosed a large thrombus in the vein of Galen and straight sinus (Fig. 1C), and CT venography clearly demonstrated absence of flow in the vein of Galen, straight sinus, and left transverse and sigmoid sinus (Fig. 1D), leading to a diagnosis of CSVT. A serological examination demonstrated a low level of hemoglobin (7.3 g/dL), and an elevated D-dimer level (6.8 μg/mL), but the titers of several autoantibodies, including antinuclear, anti-cardiolipin, and anti-β2-glycoprotein I were normal. Despite administration of anticoagulants shortly after admission, on the second day she developed respiratory failure and required artificial respirator support thereafter. She died on the third day.

Written informed consent for postmortem imaging and autopsy, and subsequent use of the images and tissue samples for research purposes was obtained from her parents. We performed a postmortem MRI study with our originally developed system. Briefly, the body was packed in a sealable polyethylene bag, and placed supine in a polycarbonate coffin, which was maintained at 7.5–8.5 °C with circulating cooled dry air. The whole body within the coffin was imaged with a SIGNA 3 T MRI (GE Healthcare, Waukesha, WI, USA) using a body coil. Acquisition of the head was performed using a T1-weighted (T1W) image (axial—TSE, TE 3.2 ms, TR 7.5 ms, 1.5-mm thickness) and a T2W image (axial—TSE, TE 81.0 ms, TR 4000 ms, 4.0-mm thickness), followed by T2W imaging of the neck, abdomen, thighs, and legs. The total acquisition time was about 7 h. Consistent with the antemortem images (Fig. 1), hemorrhagic or anemic infarcts and edema in the bilateral thalami and left cerebellar hemisphere (Fig. 2A and B), and abnormal intensities suggestive of thrombi extending throughout the straight sinus (Fig. 2H and I) and left sigmoid sinus (Fig. 2N and O) were evident. No thrombus was observed in the right sigmoid sinus (Fig. 2T and U), body or extremities.

A general autopsy was performed. The fresh brain was severely swollen and soft. Fresh hemorrhagic or anemic infarcts involving the bilateral thalami, midbrain tegmentum and base on the left side, and the left cerebellar hemisphere, were confirmed. In accordance with the postmortem images, we performed careful preparation of the sinuses and found that a continuous thrombotic substance occupied the lumen of the vein of Galen, and straight, tentorial, left transverse, and left sigmoid sinuses (Fig. 2C-E). Histological examination revealed an organizing white thrombus occupying the lumen and involving the wall of the left sigmoid sinus (Fig. 2P and Q), and an acute, red thrombus in the lumen of the left transverse, straight, and tentorial sinuses, and vein of Galen (Fig. 2J and K), indicating that the thrombus had developed first in the left sigmoid sinus, then extended retrogradely to the more proximal portion of the sinus system, reaching the vein of Galen. No thrombus was evident in the right transverse sinus.

Comparative images of the antemortem 1.5 T-MRI and postmortem 3.0 T-MRI, histopathologic pictures of the corresponding sinuses, and a schematic representation of the sinus thrombosis are shown in Fig. 2F–V.

3. Discussion

In the present study, we demonstrated the features of the sinus thrombosis in detail using our originally developed postmortem 3 T-MRI system, and then investigated the corresponding lesions in histopathologic preparations (Fig. 2).

The patient had acute symptoms possibly associated with the development of thrombus shortly after starting to take the CHC. In general, venous thrombosis tends to develop in women who have used oral contraceptives for a prolonged period [4]. However, a population-based, case–control study