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Bromocriptine and postpartum cerebral angiopathy: A causal relationship?

Article abstract—We describe a postpartum 30-year-old woman who developed headaches, hypertension, and speech disturbances after bromocriptine treatment to suppress lactation. Brain MRI revealed intraparenchymal hematomas, and an angiographic study showed multiple arterial segmental narrowings compatible with postpartum cerebral angiopathy. We also comment on other cases of postpartum cerebral angiopathy.

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Postpartum cerebral angiopathy (PCA) is a rare entity generally characterized by headaches, vomiting, seizures, and, less often, focal neurologic signs following a normal pregnancy. Angiography shows multiple segmental narrowings in the cerebral arteries, and the clinical outcome is usually good. There are several reports of PCA in relation to the use of ergonovine,¹ sympathomimetic drugs,² bromocriptine,³ and the combination of the latter two⁴ administered during delivery or in the puerperium. Bromocriptine, a semi-synthetic ergot alkaloid, is a direct dopaminergic agonist widely used for suppression of lactation. Rarely, hypertension, myocardial infarction, psychosis, seizures, and strokes have been reported following the use of bromocriptine in the puerperium, but this raises questions about the safety of the drug. Because of these adverse reactions, some of which have been fatal, the indication of bromocriptine for lactation suppression was withdrawn in August 1994 in the United States and Canada.⁵ We describe a patient with PCA after bromocriptine use to suppress lactation. Postpartum intracerebral hemorrhage has already been described after bromocriptine treatment,⁶ but in that case an angiographic study was not performed. To our knowledge, only one other report of demonstrated PCA following bromocriptine treatment has been reported.³

Case report. A 30-year-old woman, gravida 1, para 0, was admitted to another hospital for cesarean section at 39 weeks' gestation. No history of migraine, hypertension, or drug abuse was elicited. She had no clinical signs of preeclampsia during pregnancy. She remained well until the fourth postpartum day, when bromocriptine 2.5 mg twice a day was prescribed to suppress lactation. Over the follow-

ing days she complained of significant headaches that did not respond to analgesic treatment. On day 8 after delivery and day 5 since bromocriptine was started, she was referred to our hospital due to speech disturbances. On arrival, her body temperature was 37.5° C and blood pressure 165/100 mm Hg. On neurologic examination she was agitated and had a global aphasia. There were no motor or sensory deficits and her neck was supple. Babinski sign was positive on the left. Funduscopic examination was normal. Cardiac auscultation showed a systolic murmur. There was no proteinuria or edema. The remainder of the physical examination was normal. Because of the puerperal precedents and neurologic findings, a cerebral venous thrombosis (CVT) was suspected. An emergency brain MRI performed on the day of admission showed acute hemorrhagic lesions located in the head of left caudate nucleus (figure 1A) and in the cortical gray matter of the right frontal lobe.

Over the following days headaches persisted and blood pressure fluctuated between 130/60 and 160/100 mm Hg. The global aphasia improved, and no other focal neurologic signs were seen. Blood analysis showed a serum cholesterol of 369 mg/dL and serum triglycerides of 398 mg/dL. Erythrocyte sedimentation rate was 37 mm/hr. Serologies for HIV, *Borrelia burgdorferi*, and lues were negative. Chest radiograph, ECG, echocardiogram, and blood coagulation tests were normal. Antinuclear and antiphospholipid antibodies were negative. On the fourth hospital day, a second brain MRI demonstrated a new intracerebral hematoma in the cortical gray matter of the left frontal lobe (figure 1B). All cerebral veins and dural sinuses showed normal flow signal. A four-vessel intra-arterial digital angiography performed 5 days after admission revealed widespread segmental irregular narrowing of distal branches of the left middle and anterior cerebral arteries (figure 2A) and of the distal branches of the basilar artery (figure 2B).

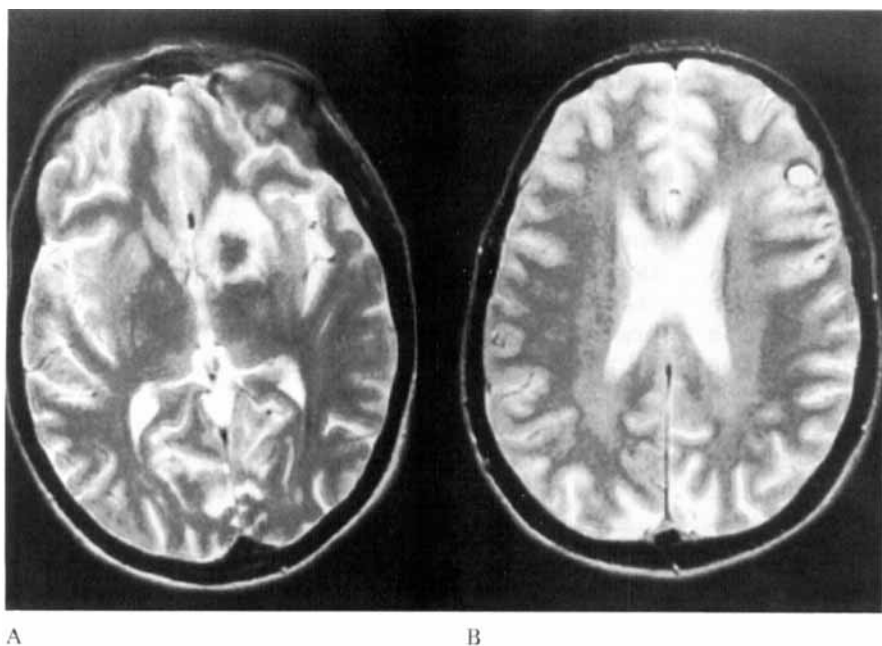


Figure 1. (A) Transverse T₂-weighted MRI (Repetition time 2,200 msec, echo time 80 msec) performed on admission day shows an acute intraparenchymal hematoma located in the head of left caudate nucleus. (B) Four days later a new hematoma was identified on the cortical gray matter of the left frontal lobe.

The venous phase of the angiogram ruled out the presence of CVT. After angiography the patient's aphasia worsened, and a mild right hemiparesis was observed. Blood pressure rose to 150/105 mm Hg. Because of angiographic findings and clinical worsening of the patient, an oral steroid therapy 60 mg/d, and nimodipine three times a day, were started. Over the following days neurologic examination progressively improved. Eighteen days after admission, a follow-up MRI showed a significant improvement of intracerebral hematomas. She was discharged home on the twentieth day after admission, normotensive and with a residual mild nominal aphasia. Because of the good clinical recovery, a second arteriography was not considered necessary.

Discussion. Our patient had clinical and angiographic features similar to that of patients with PCA. The symptoms began soon after bromocriptine treatment was started. There was no radiologic or angiographic evidence of CVT. Another plausible etiologic alternative was a late postpartum eclampsia, defined by the presence of eclamptic signs more than 48 hours after delivery. The incidence of postpartum eclampsia has been reported to range between 14 and 34%. In a study performed by Lubarsky et al.⁷ on 112,500 women delivered, late postpartum eclampsia constituted 56% of total postpartum eclampsia. However, our patient did not have preeclamptic signs,

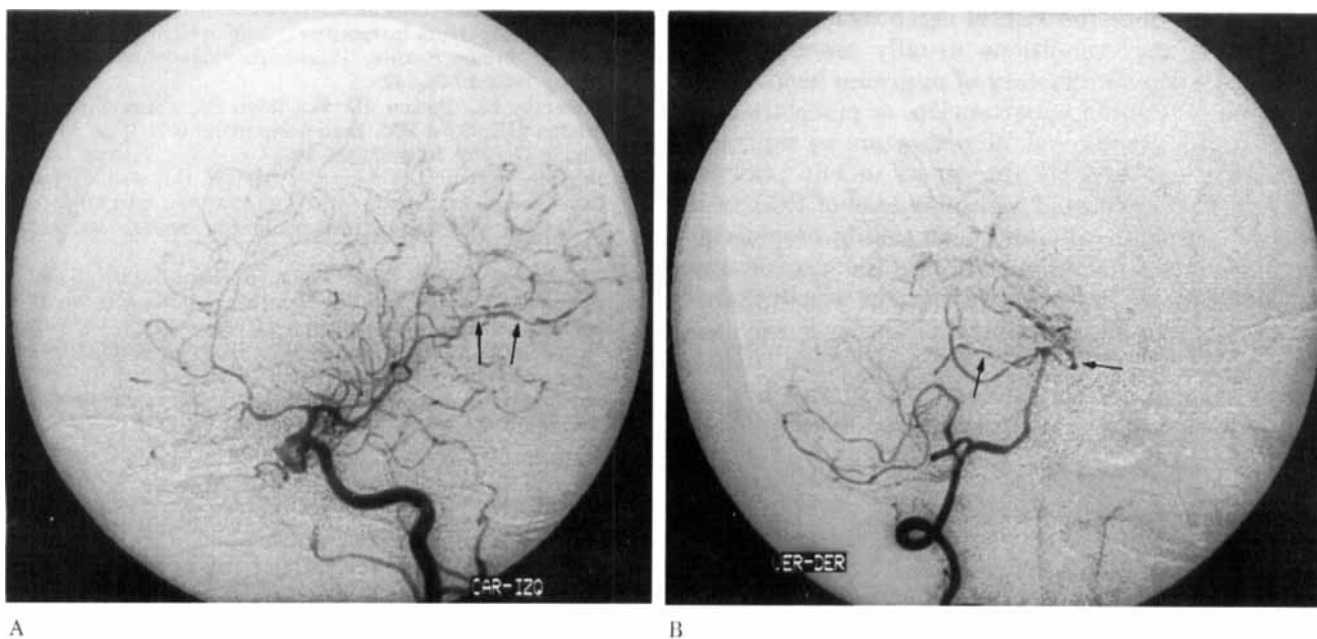


Figure 2. Intra-arterial four-vessel angiography performed on the fifth day after admission. (A) Left internal carotid angiogram (oblique view) shows narrowing of the temporal branches of the middle cerebral artery (arrows). (B) Right vertebral angiogram (oblique view) reveals irregular narrowing of the distal branches of the basilar artery (arrows).

and there were no convulsions or coma, or both, at any time in the intrapartum or postpartum period. PCA is similar to other forms of reversible angiopathy, such as isolated benign cerebral vasculitis, the angiopathy found in pheochromocytoma with intermittent severe hypertension and the angiopathy secondary to ergot derivatives or crack cocaine abuse.⁸

Bromocriptine was perceived initially as an innocuous compound with mild vasodilator propensities, but it may also display vasoconstrictor effects consistent with its ergot alkaloid properties. There is a possible idiosyncratic reaction associated with the use of bromocriptine because it has been widely used to suppress lactation, and side effects are uncommon. Moreover, there is a rather large cohort of women who have used bromocriptine throughout pregnancy for pituitary adenomas in whom side effects such as hypertension, myocardial infarction, psychosis, seizures, and strokes have not been reported. A study including 1,813 postpartum patients⁹ suggested that bromocriptine alone does not contribute significantly to the occurrence of postpartum hypertension, but it has hypertensive propensities in patients with gestationally induced hypertension. In our patient, hemorrhages and cerebral vasospasm may have been the result of hypertension, but direct vasoconstrictive activity could not be ruled out due to the fact that hypertension had not been demonstrated in other reported cases of PCA.^{2,3} In these cases it has been postulated that acute and transient elevations of blood pressure could be missed.⁸ Although PCA without the use of any potentially vasoconstrictive medication has been reported,¹⁰ in most PCA cases ergots (mainly ergonovine) or sympathomimetic drugs, or both, were given during delivery or in the first days of puerperium.^{1-4,8,10} Concomitant use of ergonovine and other drugs with similar actions may increase the risk of cerebrovascular complications.⁴ Other conditions usually associated in PCA cases, such as a history of migraine headaches, gestationally induced hypertension, or preeclampsia, may lead to a greater risk of vasospasm as well, but these situations can be absent, as in our patient. Janssens et al.³ reported a similar case of PCA in a 20-year-old woman who had been taking bromocriptine to suppress lactation without the use of any other medication. However, the patient was migrainous, and that could have acted as a trigger to vasospasm.

The etiology of PCA is unknown. It is clear that in the puerperium there is an increased susceptibility

to arterial vasospasm, and factors related to the hormonal events occurring during pregnancy and the puerperium are probably involved. In this way, the administration of drugs with vasoconstrictor effects in states in which the vasculature is susceptible to vasospasm would explain the clinical and angiographic findings in PCA. In our patient, the clinical worsening seen after angiography may be a reflection of this vascular hypersensitivity in vessels already predisposed by the bromocriptine treatment previously administered. Because of the fact that not all postpartum women develop PCA, in spite of the vasoconstrictive medication administered in some cases, an idiosyncratic factor must be taken into account.

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