Neurologic symptoms are common during gestation and puerperium in CADASIL

Abstract—Based on a structured questionnaire and medical records, the authors found that 12 of 25 mothers with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with the R133C *NOTCH3* mutation had had neurologic symptoms in 17 of their 43 pregnancies, most commonly hemiparesthesia (76%), hemiparesis (36%), aphasia (65%), and visual disorders (47%). In 82% of the patients, the symptoms were the first manifestation of CADASIL. The symptoms were most common during puerperium and in patients older than age 30.

NEUROLOGY 2005;64:1441–1443

S. Roine, MD; M. Pöyhönen, MD, PhD; S. Timonen, MD, PhD; S. Tuisku, MD; R. Marttila, MD, PhD; R. Sulkava, MD, PhD; H. Kalimo MD, PhD; and M. Viitanen, MD, PhD

Ischemic cerebrovascular complications during gestation and puerperium are rare, with an estimated incidence of 8.1 per 100,000 pregnancies.¹ In particular, the postpartum state is associated with an increased risk of stroke.^{2–4} Stroke is often (in 25 to 50% of cases) associated with preeclampsia,^{2,5} which occurs in 3 to 5% of pregnancies.⁶

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a microangiopathy caused by mutations in the *NOTCH3* gene.⁷ One-third of CADASIL patients have migraine, often with severe, long-lasting aura (visual, sensory, or motor disturbances) and onset around 25 years. The first-ever stroke in CADASIL usually occurs at age 30 to 50.⁸ Recurrent ischemic strokes due to lacunar infarcts lead to cognitive decline and finally to subcortical vascular dementia. CADASIL is diagnosed by demonstrating *NOTCH3* mutation or by the presence of specific granular osmiophilic material in dermal arteries.

We have analyzed the frequency of neurologic symptoms and signs during pregnancy in CADASIL patients.

Methods. In Finland (population about 5 million), we have identified 19 families and 46 female patients with CADASIL carrying the genetically verified R133C *NOTCH3* mutation. From these 46 female patients, 39 have had pregnancies (see figure E-1 on the

Neurology Web site at www.neurology.org). In 25 of 39 patients, we were able to assess the clinical course of pregnancy (both obstetric and neurologic) in 21 based on a structured questionnaire and medical records and in 4 based on medical records only. The pregnancies of the remaining 14 patients could not be analyzed because the cases were either deceased ($n = 3$) or demented ($n = 4$) with no medical records available or they did not consent to take part in this study ($n = 7$). The questionnaire comprised details of pregnancies, deliveries, and puerperium and possible neurologic symptoms or diagnosis of preeclampsia as well as questions about migraine, hormonal medications, and smoking. The Ethical Committee of Varsinais-Suomi Hospital District approved the study.

Our criteria for preeclampsia were elevated blood pressure ($>140/90$ mm Hg) with no previous history of hypertension, peripheral edema, proteinuria, headache, or neurologic deficits. Severe placental insufficiency ($n = 1$) was also regarded as preeclampsia. Neurologic symptoms included migrainous headache, vertigo, confusion, and focal neurologic deficits such as hemiparesis, hemiparesthesia, aphasia, dysarthria, and visual disorders. The patients with neurologic complications or preeclampsia formed the manifesting and those with normal pregnancies the nonmanifesting group. Pregnancy refers to both gestation and puerperium.

The differences between the manifesting and nonmanifesting groups were calculated with paired t test or two-sample t test using SAS software (Cary, NC).

Results. The 25 examined female patients with CADASIL had a total of 78 pregnancies. Twelve of them (48%, manifesting group, 11 living) had experienced neurologic symptoms or preeclampsia during gestation or puerperium in 19 (44%) of their 43 pregnancies. These 19 complicated pregnancies constituted 24% of the 78 pregnancies. The symptoms were the first clinical manifestation of CADASIL in 9 (82%) of the 11 living patients. The 13 patients with 35 uncomplicated pregnancies composed the nonmanifesting group (figure; see also figure E-1).

All patients taken together, the mean age at the complicated pregnancies was 31.6 years, which differed from the age at the uncomplicated pregnancies (24.7 years [$p < 0.0001$, linear mixed model]). In the 10 manifesting patients who experienced both complicated and uncomplicated pregnancies, the first complicated pregnancy occurred at a higher age (29.9 years, range 25 to 38 years) than their first uncomplicated pregnancy (23.8 years, range 20 to 37 years; $p = 0.051$, paired t test). Similarly, the mean age at the first complicated pregnancy (28.8 years, range 19 to 38 years) in the manifesting group was higher than the age at the first pregnancy in the nonmanifesting group (22.2 years, range 18 to 28 years; $p = 0.001$, two-sample t test).

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the April 26 issue to find the title link for this article.

From the Departments of Neurology (Drs. Roine and Marttila), Obstetrics and Gynaecology (Dr. Timonen), and Pathology (Dr. Kalimo), University and University Hospital of Turku, and Department of Geriatric Medicine (Dr. Viitanen), University of Turku, Department of Medical Genetics (Dr. Pöyhönen), Family Federation of Finland, Helsinki, Department of Neurology (Dr. Tuisku), Keski-Pohjanmaa Central Hospital, Kokkola, Department of Public Health and General Practice (Dr. Sulkava), University of Kuopio, and Department of Pathology (Dr. Kalimo), University and University Hospital of Helsinki, Finland; and Division of Clinical Geriatrics (Dr. Viitanen), Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

Received March 29, 2004. Accepted in final form December 27, 2004.

Address correspondence and reprint requests to Dr. H. Kalimo, Department of Pathology, University and University Hospital of Helsinki, FI-00014 Helsinki, Finland; e-mail: hannu.kalimo@helsinki.fi

Figure. The occurrence and duration of neurologic symptoms (excluding the two pregnancies in which headache associated with preeclampsia was the only neurologic symptom) during pregnancy and puerperium in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. The triangles indicate the neurologic symptoms, and the dotted lines link the symptoms of the same pregnancy.

In 17 of the 19 complicated pregnancies with neurologic symptoms, the most common manifestations were hemiparesthesia (in 13/17, or 76% of pregnancies), aphasia (11/17, or 65%), hemiparesis (6/17, or 36%), and visual disorders (8/17, or 47%). In addition, confusion or vertigo was present in two and dysarthria in one. For one of the patients, MRI was performed during the neurologic symptoms; it revealed remarkable hyperintensities in periventricular white matter and in the anterior temporal lobes (see figure E-2). Severe migrainous headache with aura was associated with other neurologic symptoms in 9 (82%) of the 11 living patients, but only 3 of these had previous history of migraine with aura. Migrainous headaches lasted from hours to many days. In the nonmanifesting group, 4 of the 13 patients had experienced migraine with aura; in 3 of them, migraine began after age 30.

A total of 8 (42%) of the 19 complicated pregnancies were associated with preeclampsia-like symptoms, 2 of them without neurologic signs. Only two of these eight preeclampsias occurred in the first pregnancy.

In 15 of the 19 complicated pregnancies, the symptoms appeared during puerperium, 4 manifesting also before delivery (see figure). In only two pregnancies, the symptoms occurred exclusively prepartum. The symptoms resolved within a few to 30 minutes in 53% of pregnancies, but one patient had problems for 1 to several days in all three pregnancies. Three women had symptoms in two pregnancies and eight so far in one pregnancy. The single fatal case was from the late 1940s, when pregnancy-related mortality was much higher.

There was no difference in the miscarriage rate, gestational age at delivery, or mode of the delivery in the manifesting vs nonmanifesting groups, except for the patients with preeclampsia, which led to cesarean section at earlier gestational weeks (weeks 34 to 39). Smoking did not influence the symptoms. The patients in the manifesting group used only diuretics for preeclampsia; in addition, one patient was treated with propranolol for migraine prophylaxis and acetylsalicylic acid 50 mg/day. Maternal

CADASIL did not influence the infant birth weights, neonatal periods, or Apgar points.

Discussion. CADASIL is a previously unrecognized disease to be considered when searching for the cause of transient or permanent stroke-like symptoms during pregnancy, especially puerperium. Complicated course of pregnancy occurred in almost every other CADASIL mother and in every fourth assessed pregnancy. Furthermore, neurologic symptoms and preeclampsia during pregnancy were frequently (in 82% of the manifesting group) the first clinical manifestation of CADASIL.

In preeclampsia, multiorgan vasospasm is considered an important pathophysiologic mechanism, and preexisting microvascular disease predisposes a woman to preeclampsia.⁹ This is concordant with the fact that preeclampsia was more frequent (10.3%) in our CADASIL patients than in the normal population (3 to 5%).⁶ Furthermore, the preeclampsia in our patients most often (6/8) occurred in later pregnancies, whereas preeclampsia in general is two times more common in primigravid females,¹⁰ suggesting that CADASIL is a risk factor for preeclampsia.

This is necessarily a retrospective cohort study of a female CADASIL population. In all except one obligate carrier, the R133C *NOTCH3* mutation was genetically verified. The majority of these pregnancies were carefully followed, and occurrence of complications was entered in the medical records. This reduces the risk for recall bias; furthermore, any potential for misreporting is likely to apply equally to both the manifesting and the nonmanifesting group. Even if the 14 nonconsenting CADASIL patients had had only uncomplicated pregnancies, the frequency of patients with complicated pregnancies remains high (12/39, or 31%).

Transient neurologic symptoms and preeclampsia appear to be common in CADASIL patients in all age groups but particularly in women older than age 30. The first manifestation of CADASIL may occur during pregnancy, especially during puerperium. Thus, CADASIL should be taken into consideration as a possible cause of a neurologically complicated pregnancy. The pregnancies of mothers with established or suspected diagnosis of CADASIL should be carefully followed.

Acknowledgment

The authors thank Tero Wahlberg, MSci, for performing the statistical analyses.

References

1. Grosset DG, Ebrahim S, Bone I, Warlow C. Stroke in pregnancy and the puerperium: what magnitude of risk? *J Neurol Neurosurg Psychiatry* 1995;58:129–131.
2. Kittner SJ, Stern BJ, Feaser BR, et al. Pregnancy and the risk of stroke. *N Engl J Med* 1996;335:768–774.
3. Wilterdink JL, Easton JD. Cerebral ischemia in pregnancy. *Adv Neurol* 2002;90:51–62.
4. Boussier M-G. Migraine, female hormones, and stroke. *Cephalalgia* 1999;19:75–79.

5. Sharshar T, Lamy C, Mas JL. Stroke in pregnancy study group. Incidence and causes of strokes associated with pregnancy and puerperium. *Stroke* 1995;26:930–936.
6. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. *Am J Obstet Gynecol* 1989;161:1200–1204.
7. Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;383:707–710.
8. Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol* 1998;44:731–739.
9. Kaplan PW. Neurologic aspects of eclampsia. *Adv Neurol* 2002;90:41–49.
10. Trupin LS, Simon LP, Eskenazi B. Change in paternity: a risk factor for pre-eclampsia in multiparas. *Epidemiology* 1996;7:240–244.

NeuroImages

Figure. (A) Postcontrast, T1-weighted MRI study shows a diffusely enlarged and enhancing right optic nerve. (B) External photograph demonstrating proptosis of the right eye. (C) Preoperative fundus photograph of the right optic nerve showing the optociliary shunt vessels (arrows). (D) Left optic nerve is normal. (E) Three months after surgery there is complete regression of the optociliary shunt vessels as a result of the progressive optic atrophy. Note the development of diffuse optic nerve pallor and attenuation of the blood vessels.

Optociliary shunt vessels

Christine Nichols, AB; David W. Pincus, MD, PhD; and
M. Tariq Bhatti, MD, Gainesville, FL

A 16-year-old boy underwent surgery with complete excision of a right optic nerve sheath meningioma for progressive disfiguring proptosis (figure, A, B). Preoperatively, the patient had no light

perception and optociliary shunt vessels were noted on the right optic nerve (figure, C, D). There was complete regression of the optociliary shunt vessels with optic nerve pallor and continued lack of light perception 3 months after surgery (figure, E).

Optic nerve sheath meningiomas are classically associated with the triad of vision loss, optic nerve pallor, and optociliary shunt vessels. These vessels represent a preexisting collateral vascular system spanning across the optic disk, shunting venous blood from the retinal circulation to the choroidal circulation.¹

Copyright © 2005 by AAN Enterprises, Inc.

Supported in part by an unrestricted departmental grant from Research to Prevent Blindness, Inc. (New York).

Address correspondence and reprint requests to Dr. M. Tariq Bhatti, University of Florida College of Medicine, Department of Ophthalmology, Box 100284 JHMHS, Gainesville, FL; e-mail: tbhatti@eye.ufl.edu

1. Schatz H, Green WR, Talamo JH, Hoyt WF, Johnson RN, McDonald HR. Clinicopathologic correlation of retinal to choroidal venous collaterals of the optic nerve head. *Ophthalmology* 1991;98:1287–1293.

Neurology®

Optociliary shunt vessels

Christine Nichols, David W. Pincus and M. Tariq Bhatti

Neurology 2005;64;1443

DOI 10.1212/01.WNL.0000147465.63518.F9

This information is current as of April 25, 2005

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/64/8/1443.full>

References

This article cites 1 articles, 0 of which you can access for free at:
<http://n.neurology.org/content/64/8/1443.full#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.