Multiple Strokes in a Newborn

Dear Editor:

Perinatal arterial ischemic stroke (AIS) is an increasingly recognized cause of neurological disability. A heterogeneous variety of diseases and triggers can be synergistically related to pediatric AIS, including congenital heart malformations, sickle cell disorders, vasculopathies, hypertension, dyslipidemia, infections, and inherited prothrombotic predisposition. Herein, we report a case of multiple AIS in a newborn with 2 concomitant thrombophilic gene variants encoding enzymes involved in homocysteine (Hcy) metabolism.

An apparently healthy 7-day-old Caucasian female underwent ophthalmologic examination participating in the vision-screening program for full-term newborns. Eye assessment was bilaterally normal with the exception of a marked pallor of the left optic nerve head (Figure 1; available at http://aaojournal.org). Optic neuropathy was suspected and, thus, additional clinical and laboratory examinations were scheduled. Brain magnetic resonance identified an infarcted area involving the territory of the left middle cerebral artery (Figure 2; available at http://aaojournal.org). Magnetic resonance angiography revealed occlusion of the left internal carotid artery (Figure 3; available at http://aaojournal.org). Laboratory serum analyses showed slight decrease of folate (16.7 nmol/L) and cystathionine (0.41 μmol/L) concentrations, with concomitant increase of methionine (24.2 μmol/L). Plasmatic levels of vitamin B12 and fasting total Hcy were normal, but after oral methionine load an anomalous elevation of Hcy occurred (408%). Urine analyses were unremarkable. DNA genotyping revealed 2 hyperhomocysteinemic heterozygosis predisposing to thrombophilia: c.677C>T in methyltetrahydrofolate reductase (MTHFR) gene, and c.833T>C/c.844-872ins68bp in cystathionine beta-synthase (CBS) gene. The final diagnosis was unilateral occlusion of internal carotid artery, ipsilaterally complicated by ischemic optic neuropathy (Figure 1; available at http://aaojournal.org).

Inherited or acquired clotting abnormalities, associated with unbalanced hemostatic condition, can represent the cause of perinatal AIS. Pediatric hyperhomocysteinemia (HHcy) is frequently related to low nutritional intakes of folate, vitamins B12 and/or B6, but also to several genotypic determinants. Polymorphisms in MTHFR gene, such as the common c.677C>T, result in a reduced function of this enzyme producing thermolabile enzymatic form. The relatively rare c.833T>C/c.844-872ins68bp mutation of CBS gene is not per se an ischemic risk but, when it is combined with an inefficient MTHFR, the thrombotic diathesis markedly increases. Dodelson de Kremer and Grosso have studied the prevalence of hyperhomocysteinemic MTHFR 677 T-allele in newborns with hypoxic-ischemic encephalopathy and in their mothers, concluding that maternal mutated genotypes increase the chance of cerebral occlusive damage in the offspring. These lesions, often characterized by hypoplasia and/or thrombosis of internal carotid artery, poor or absent blood supply of middle and posterior cerebral arteries, and temporal-parietal brain infarction, partially resemble those identified in the present case. On the other hand, Kelly et al. investigating cerebral and retinal infarctions in young hyperhomocysteinemic patients with CBS deficiency, have highlighted the role of carotid intraluminal thrombosis in ischemia pathogenesis.

Elevated plasma level of Hcy, secondary to folate-pathway gene variants, can represent the culprit of an abnormal thrombo-coagulative predisposition. The presence of these peculiar mutations, causing functional defects in MTHFR, CBS, and other enzymes, lead to vascular thrombophilic damage via hyperactivation of endothelial cells and platelets. These hyperhomocysteinemic effects, reliably arising in our newborn affected by an uncommon double heterozygosity (MTHFR c.677C>T plus CBS c.833T>C/c.844-872ins68bp), could play a crucial role in the pathogenesis of multiple AIS. In fact, the HHcy-related oxidant stress in subendothelial spaces may affect the uncoagulable properties of endothelium, giving back basically a more activable surface responsible for these dramatic thromboembolic events.

In this apparently asymptomatic newborn, the early detection of ischemic optic neuropathy allowed us promptly to initiate diagnostic testing and therapy. Although Hcy-lowering treatment did not reliably ameliorate the prognosis of cerebral and ocular damages, no other thromboembolic events have occurred during 9-month follow-up. This case supports the rationale for a routine eye-screening program of full-term newborns, indicating both the crucial role of clinical suspicion to correctly address diagnostic iter and the importance of a proper preventive therapy when it is warranted.

Letters to the Editor

References


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Figure 1. Fundus photography, obtained from the left eye of the baby at the 9th day of life, shows a marked pallor of the optic nerve head without any occlusive sign of the retinal vascular structures.
Figure 2. Brain magnetic resonance imaging, T1-weighted axial sections. The examination, which was performed when the baby was 9 days old, shows a large infarcted area in the left hemisphere, involving the fronto-temporoparietal cortico-subcortical region and the left lenticular nucleus, corresponding to the whole vascular territory supplied by the left middle cerebral artery.

Figure 3. A, Magnetic resonance angiography of the neck vessels shows complete occlusion of the left internal carotid artery (black arrow), with normal appearance of the right carotid bifurcation (white arrow). B, Intracranial magnetic resonance angiography shows absent flow in the left carotid siphon and middle cerebral artery (dotted arrow) and increased flow signal in the left posterior cerebral artery, indicating activation of leptomeningeal collaterals (continuous arrows).
Table 1. Neonatologic Data, Diagnostic Reports, Clinical Management and Follow-up of the Newborn

Neonatologic data
Birth at the 40th week of gestation, after normal pregnancy and uncomplicated vaginal delivery
Normal weight (3040 g), length (49 cm), and cranial circumference (33 cm) at birth
APGAR score = 9 at both the 1st and the 5th minute after birth
Unremarkable perinatal and family histories

Diagnostic reports
Ophthalmologic examination: marked pallor of the left optic nerve head
Cardiological evaluation and echocardiography: normal
Neurological evaluation: normal
Electroencephalography: abnormal tracings generated from the left hemisphere
Brain echography: large area of irregular hyperechogenicity along the middle cerebral artery territory
Cerebral magnetic resonance: wide infarcted area involving the superficial and deep vascular territory of the left middle cerebral artery; no abnormalities within both intraorbital optic nerves
Magnetic resonance angiography: occlusion of the left internal carotid artery, associated with hypertrophy of ipsilateral posterior cerebral artery, due to development of collateral leptomeningeal circulation between terminal branches of the left posterior and middle cerebral arteries
Laboratory serum analyses: folate (16.7 nmol/L) and cystathionine (0.41 μmol/L) decrease; increase of methionine (24.2 μmol/L); normal vitamin B12 (322 pmol/L) and fasting total homocysteine (FHcy – 6.9 μmol/L); abnormal Hcy increase after methionine load test (0.05 g/kg body weight added to maternal milk – absolute increment of FHcy = 35.1 μmol/L; absolute difference between post-load and FHcy = 28.2 μmol/L; percentage difference over FHcy = 408%)
Other hematological examinations: normal (i.e., erythrocyte sedimentation rate, glucose tolerance test, lipoprotein profile, blood cell count, lupus anticoagulant, anti-cardiolipin antibody, prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin, protein S, and protein C levels)
Urine laboratory tests: normal

Genomic DNA was isolated from peripheral blood by using standard proteinase K treatment, followed by phenol-chloroform extraction and ethanol precipitation; samples were polymerase chain reaction genotyped for: factor V G1691A, prothrombin G20210A, methylenetetrahydrofolate reductase C677T, methionine synthase reductase A66G, and cystathionine beta-synthase T833C/844ins68; heterozygous methylenetetrahydrofolate reductase C677T and heterozygous cystathionine beta-synthase T833C/844ins68 mutations were documented
DNA genotyping of baby’s healthy parents: maternal MTHFR C677T heterozygosis and paternal CBS T833C/844ins68 heterozygosis

Clinical management and follow-up
No indication for vascular surgery
Methionine-free milk and supplementations with folate and B vitamins (from the 10th day of life)
Antiepileptic therapy with barbiturates (from the 10th day of life), because of episodes of focal epilepsy
Neurological rehabilitation and cognitive development support (from the 30th day of life), because of the presence of mild right hemiparesis and distal dystonia due to cortical brain damages involving parietal and temporal areas
Ophthalmologic monthly checks (9-month follow-up): no vision in the left eye; persistence of optic disc pallor and absence of foveal reflex (indicating visual perceptive deficit related to optic nerve atrophy)
Possible future treatment with platelet anti-aggregants or anticoagulants to further reduce the risk of thromboembolism recurrence