Neonatal Aortic Arch Thrombosis as a Result of Congenital Cytomegalovirus Infection

Marcello Lanari, MD, PhD*; Tiziana Lazzarotto, MB‡; Irene Papa, MD*; Valentina Venturi, MD*; Gabriele Bronzetti, MD§; Brunella Guerra, MD¶; Giacomo Faldella, MD*; Luigi Corvaglia, MD*; Fernando Maria Picchio, MD, FESC§; Maria Paola Landini, MD¶; and Gian Paolo Salvioi, MD*

ABSTRACT. Thrombotic disease is rare in neonates. The main risk factors at this age are perinatal asphyxia, maternal diabetes, sepsis, polycythemia, dehydration, a low cardiac output, and in primis the catheterization of central lines. Another important risk factor is inherited thrombophilia. Arterial thrombosis is even more rare than venous thrombosis and less related to most of the risk factors listed above; it occurs more frequently in the iliac, femoral, and cerebral arteries but very rarely in the aorta. Most of the described cases of aortic thrombosis are associated with the catheterization of an umbilical artery and involve the descending tract and the renal arteries; very few relate to the ascending tract and the aortic arch. The possible role of virus-induced primary vascular endothelium damage in the etiopathogenesis of neonatal arterial thrombosis has been previously hypothesized. Herpesviruses, particularly human cytomegalovirus (HCMV), can infect endothelial cells and directly damage intact vascular endothelium, altering its thromboresistant surface as a result of procoagulant activity mediated by specific viral surface phospholipids, necessary for the coagulation enzyme complex assembly that leads to thrombin generation. We describe a case of congenital aortic arch thrombosis. The clinical, laboratory, and virologic pictures; the anatomopathologic findings (fully compatible with viral infection); the detection of HCMV in various tissues (including the aorta); and the absence of other causes of aortic thrombosis make it possible to attribute the case to a severe congenital HCMV infection with multiple organ involvement, after the primary infection of the mother. The hemostatic system disorders and hemodynamic disturbances related to viral cardiac damage explain the clinical features of the case and indicate that congenital HCMV infection should be included among the causes of neonatal aortic thrombosis.

CASE REPORT

A female infant was delivered by cesarean section after 37 weeks of gestation because ultrasonography revealed fetal cardiomegaly, cardiac hypertrophy, and pericardial effusion, and it was difficult to image the aorta and aortic flow. Moreover, the pregnancy was complicated by intrauterine growth retardation (IUGR) and oligohydramnios. Genetic amniocentesis performed during the 18th week of gestation revealed a fetal 46XX karyotype. Maternal serologic tests for transmissible infections were performed only during the first trimester of pregnancy; the mother was immune to toxoplasmosis and rubella and negative for HCMV, hepatitis C, hepatitis B, and human immunodeficiency virus; the presence of herpes simplex viruses was not investigated. The pregnancy was uncomplicated until the 30th week, when fetal echography first revealed IUGR; there were no signs of altered fetal morphology at the time, and the Doppler velocimeter values were within the norm.

The neonate was born live (birth weight: 2050 g [<10th percentile]) and transferred to our neonatal intensive care unit (NICU). She was pale, her pulse was 140 beats per minute, and she had a grade 2 Levine systolic murmur. Her respiration was 55 breaths per minute, with slight dyspnea and transcutaneous oxygen saturation in ambient air of 90%; she had hypophyseal femoral pulses, her liver was palpable 1.5 cm from the costal arch with no spleen enlargement, and a left arm arterial pressure of 97/76 mm Hg (her mean arterial pressure was 80 mm Hg). A chest radiograph revealed a volumetric increase in the whole cardiac shadow, with a cardiothoracic ratio of 0.8 (normal values ≤0.60). To sustain respiratory pressure, nasal continuous positive airway pressure was started immediately, and E2 prostaglandins were infused at a rate of 0.05 μg/kg/min because of suspected duct-dependent heart disease. During the first hours of life, electronic

ABBREVIATIONS. HCMV, human cytomegalovirus; IUGR, intrauterine growth retardation; NICU, neonatal intensive care unit; qPCR, quantitative polymerase chain reaction.

From the Departments of *Preventive Pediatrics and Neonatology, ‡Clinical and Experimental Medicine (Section of Microbiology), §Pediatric Cardiology, and ¶Obstetrics and Gynecology, University of Bologna, Bologna, Italy. Received for publication May 14, 2001; accepted Jul 30, 2001. Reprint requests to (M.L.) Istituto di Pediatria Preventiva e Neonatologia, Via Massarenti 11, 40138 Bologna, Italy. E-mail: lanari@med.unibo.it

PEDIATRICS (ISSN 0031-4005). Copyright © 2001 by the American Academy of Pediatrics.
The laboratory tests revealed metabolic acidosis (pH 7.29) and an increase in creatininemia (from 0.7 to 1.1 mg/dL) and bilirubinemia (from 3.43 to 8.68 mg/dL), without direct hyperbilirubinemia. The patient presented ABO incompatibility but was negative to Coombs’ direct test. Hemochromocytometry revealed mild anemia and leukopenia (white blood cells: 7990/mm³; neutrophils: 2724/mm³; hemoglobin: 14.1 mg/dL; hematocrit: 42%; platelets: 316 000/mm³), whereas glycemia, aspartate aminotransferase, alanine aminotransferase, serum electrolytes, activated partial thromboplastin time, and prothrombin activity were within the normal range for her age. Systemic bacterial septicemia was excluded on the basis of a negative blood culture, persistently normal C-reactive protein values, and the repeated absence of neutrophilic leukocytosis.

Brain echography showed cystic cavities within the context of diffuse white-matter hyperechogenicity, with intensely hyperechogenic periventricular foci compatible with calcifications in the right frontoparietal region and at the level of the basal nuclei. Computed tomography was not possible because of the patient’s clinical condition.

An electrocardiogram showed ischemic-type repolarization alterations. The echocardiogram excluded cardiac anomalies; left ventricular systolic function was severely reduced, with a 20% ejection fraction; the interventricular septum was thickened and more hypokinetic than the other cardiac segments. There was severe mitral regurgitation; the aortic valve was normal, but the ascending aorta was completely obstructed by a large thrombus extending to the origin of the left subclavian artery, and aortic flow was almost entirely provided by the patent ductus arteriosus. Moderate pericardial effusion was also confirmed (Figs 1 and 2).

Heparin therapy was begun at a dose of 2000 U/24 hours and adjusted to maintain an activated partial thromboplastin time ratio of between 2 and 2.5; the major cerebral lesions contraindicated the use of systemic fibrinolytic therapy.

The patient’s general condition improved slightly during the second day, with a progressive reduction in dyspnea and the need for oxygen. The systolic murmur was louder, the peripheral pulses were symmetrical with normal blood pressure, and diuresis was restored. An echocardiogram showed a reduction in the thrombotic mass, particularly the distal portion. At the end of the third day, her general condition worsened toward intractable hemodynamic shock despite the continuous infusion of maximum inotro-
targets of the virus and clarified the differences in viral replication and cytolytic potential, depending on the stage of infection and the involved vascular district. The virus replicates with a potent cytopathic effect in various organs and tissues, presumably as a result of initial endothelial damage.

Herpesviruses can alter the normal thromboresistance of endothelial surfaces by means of 3 potential mechanisms:

1. Inhibiting the anticoagulant/antithrombotic properties of vascular endothelium and consequently reducing the synthesis and endothelial surface expression of heparan sulfate, a molecule that binds antithrombin to the surface and activates many coagulation factors (thrombin and activated factors IX, X, XI, and XII)

2. Inducing the procoagulant/prothrombotic properties mediated by changes in endothelial membrane phospholipids, thus increasing the production of thrombin and reducing the synthesis of prostaglandin I₂, and therefore increasing platelet aggregation and adhesion

3. Increasing the number of endothelial cell binding sites, thus increasing the adhesion of inflammatory cells and platelets.

Furthermore, HCMV can directly induce procoagulant activity, as its surface contains the procoagulant phospholipid necessary for the coagulation enzyme complex assembly that leads to thrombin generation.

Thrombotic disease is rare in neonates. A German study reported a prevalence of 5.1 per 100,000 live births, and a multicenter study coordinated by a Canadian group reported a prevalence of 2.4 per 1000 NICU admissions. In both studies, the thrombotic manifestations mainly involved large venous vessels as central line complications. The different prevalences are attributable to the fact that the Canadian study was based on a sample of NICU neonates who therefore already had conditions that favored thromboembolism. The main risk factors at this age are perinatal asphyxia, maternal diabetes, sepsis, polycythemia, dehydration, a low cardiac output, and in primis the catheterization of central lines.

Another important risk factor is inherited thrombophilia as a result of a deficit in antithrombin or proteins C or S, the presence of factor V Leiden, or antiphospholipid syndrome. Inherited thrombotic disorders become manifest in <5% of affected children.

Arterial thrombosis is more rare than venous thrombosis and less related to most of the risk factors listed above; it occurs more frequently in the iliac, femoral, and cerebral arteries but very rarely in the aorta. Most of the described cases of aortic thrombosis are associated with the catheterization of an umbilical artery and involve the descending tract and the renal arteries; very few relate to the ascending tract and the aortic arch.

The abnormal aortic features of our patient, associated with the cardiomegaly and pericardial effusion revealed by fetal echography, could have been attributable to severe coarctation or an interruption of the aortic arch. In fact, the early neonatal echographic study excluded any structural anomaly but revealed pericardial effusion, severe cardiac hypokinesia, and aortic thrombosis, suggesting the diagnosis of perimyocarditis with secondary thrombosis as a result of a low cardiac output. However, it was unlikely that such an extended arterial thrombosis was attributable to this alone. However, our patient did not have any perinatal or neonatal thrombogenic
risk factors, such as perinatal asphyxia, maternal diabetes, polycythemia, or central vessel catheterization. Furthermore, her family history was negative for thrombotic diseases, and the results of parental laboratory tests (proteins C and S, antithrombin, antiphospholipid antibodies, and factor V Leiden) made it possible to rule out inherited thrombophilia. A more plausible hypothesis was the presence of an agent capable of independently sustaining both the perimyocarditis and aortic thrombosis, such as HCMV.

CONCLUSION

Although the qPCR detection of HCMV in the aortic vessel wall cannot be considered direct evidence of HCMV-induced endotheliitis, the histologic findings of aortitis with necrotic aspects in our case, together with the presence of arterial thrombosis, whose extension was unlikely to have been attributable to low output alone, and the absence of other causes of aortic thrombosis, allow us to sustain the hypothesis that HCMV should be sought as a cause of neonatal thrombosis.

ACKNOWLEDGMENT

We thank Kevin Smart (LINK, Milan, Italy) for help in preparing the manuscript.

REFERENCES

Neonatal Aortic Arch Thrombosis as a Result of Congenital Cytomegalovirus Infection

Marcello Lanari, Tiziana Lazzarotto, Irene Papa, Valentina Venturi, Gabriele Bronzetti, Brunella Guerra, Giacomo Faldella, Luigi Corvaglia, Fernando Maria Picchio, Maria Paola Landini and Gian Paolo Salvioli

Pediatrics 2001;108:e114
DOI: 10.1542/peds.108.6.e114
Neonatal Aortic Arch Thrombosis as a Result of Congenital Cytomegalovirus Infection

Marcello Lanari, Tiziana Lazzarotto, Irene Papa, Valentina Venturi, Gabriele Bronzetti, Brunella Guerra, Giacomo Faldella, Luigi Corvaglia, Fernando Maria Picchio, Maria Paola Landini and Gian Paolo Salvioli

*Pediatrics* 2001;108:e114
DOI: 10.1542/peds.108.6.e114

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/108/6/e114.full.html