Thrombosis of the Abdominal Aorta in a Extremely Low Birth Weight Infant: Treatment with Tissue-Type Plasminogen Activator

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Abstract: Aortic thrombosis during neonatal period is a rare event especially when it is not related to umbilical arterial catheters. A case of a premature infant with a gestational age of 25 weeks who suddenly developed, at the age of 44 days, poor arterial saturation (SaO_2 60%) and legs pale and painful, is reported. In this patient, arterial and venous eco-color Doppler showed a complete aortic thrombosis distal to the renal arteries of unknown etiology. Thrombolytic therapy with tissue-type plasminogen activator (t-PA) was immediately started with a bolus dose of 0.5 mg/kg/h followed by a continuous infusion of 0.2 mg/kg/h. Fresh frozen plasma was also infused in order to increase the concentration of plasminogen. We tried with success to avoid bleeding complications maintaining fibrinogen concentration over 500 mg/L and platelets over $100,000x10^9$/L. Heparinisation with enoxaparin was started after 5 days of t-PA treatment and continued for 85 days. The premature infant recovered but physiotherapy and splints were needed for talipes equinovarus resulted as a consequence of distal thrombosis.

Conclusion: The strategy for treating an acute arterial thrombosis in a neonate may include thrombolytic therapy with t-PA, taking into account that the rate of plasmin generation in newborns and overall activity is decreased compared to adults. The impaired response of newborns may be enhanced not by increasing the dose of t-PA but increasing plasminogen through fresh frozen plasma infusion.

Keywords: Arterial thrombosis, Premature newborn, Aorta, Plasminogen activator, Enoxaparin.

INTRODUCTION

Neonatal arterial thrombosis is a rare event. A paper of 1995 reported that 2.4/1000 newborns admitted in neonatal intensive care units experience a symptomatic thromboembolic event (TE) including venous TE [8]. A study from Germany reported an incidence of 5.1 per 100.000 live births in the period from 1992 to 1994 [5]. In a Medline search of PUBMED, OVID and Cochrane databases Nagel *et al*. reported total number of neonatal patients with aortic thrombosis was 148 and 78% of the aortic thromboses in this review were related to arterial umbilical catheterization [4]. Symptomatic aortic thrombosis represents a potentially devastating subset of these neonates and has an incidence of 0.1–1.1 per 100,000 newborns [3]. Even more rare are thrombotic occlusions of the abdominal aorta in the neonatal period not related to arterial lines. Years ago Emami and coworkers [2] reported a failure of systemic thrombolytic and heparin therapy in the treatment of aortic thrombosis developed following umbilical artery catheterization. Local thrombolytic therapy was not technically feasible in the reported case [2]. Compared to acquired risk factors, congenital prothrombotic disorders are rarely present in infants and children with arterial and venous thrombosis [5].

We report a case of an extremely premature neonate (25 weeks of gestational age), 44 days old, who suddenly presented with poor arterial saturation (SaO_2 60%), and the legs pale and painful when he was already in Neonatal Intermediate Care. The arterial and venous eco-color Doppler showed a complete aortic thrombosis distal to the renal arteries of unknown etiology. Thrombolytic therapy with tissue-type plasminogen activator (t-PA), administered through a central venous line was effective in restoring patency of occluded aorta and bilateral iliac-femoral-popliteal vascular axis.

CASE REPORT

The neonate was a male spontaneously delivered on April 2008 at 25 wk of gestational age by an immigrant (Romanian) mother in her first pregnancy, presenting fever, and her amniotic fluid was foul and swelling. Body weight was 880 g, and Apgar score was 6 and 8 at 1 and 5 min, respectively. Tracheal aspiration was not found productive and neonate was connected to 3100A SensorMedicS™ with a MAP of 10, frequency 11, ΔP 19, FiO_2 of 25%. Surfactant administration (Curosurf®, 200 mg/kg) was provided, and an hour later the neonate was extubated and ventilated by nasal prongs with a FiO_2 of 25%. Umbilical venous catheter was inserted and used for

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parenteral nutrition. A significant PDA was seen at the ecocardiography, but ipobrufen administration was delayed due to the abdominal distention. In fact, during the first few days of life the abdomen was distended but not painful, gastric aspirates contained traces of bile, and the infant was not fed by mouth. Coagulation tests were in the normal range. On day three, an important abdominal distension was observed, and the abdominal roentgenogram showed air in the abdomen. The neonate was in stable condition. However, the umbilical venous catheter was removed and substituted with a peripheral central line and the infant, in prevision of surgery, was intubated. The infant was transferred in pediatric surgery where he was operated for intestinal perforation and PDA was closed surgically. After his return to our Unit, the infant remained in mechanical ventilation with low parameters for 3 days, and then on nCPAP for 10 days. Afterwards, for 25 days he remained in stable conditions, and his weight on day 24 was 1280 g. On day 25 after the readmission to our Unit, the infant, while cared in an incubator with FiO_2 of 23%, suddenly presented with a poor saturation (SaO_2 60%), and the legs appeared to be pale and Painful to the touch. The arterial and venous eco-color Doppler showed a complete aortic thrombosis distal to the renal arteries extending to bilateral iliac-femoral-popliteal vascular axis of unknown etiology (Figure **1**). Thrombolytic therapy with tissue-type plasminogen activator (t-PA) (Actilyse®) was immediately started through a percutaneous catheter inserted in the left harm, with a bolus dose of 0.5 mg/kg/hour followed by a continuous infusion of 0.2 mg/kh/h [3, 4]. Fresh frozen plasma was also infused in order to increase the concentration of plasminogen. We tried with success to avoid bleeding complications trying to maintain fibrinogen concentration over 500 mg/L and platelets over $100{,}000 \times 10^9$/L. The coagulation tests were performed steadily. The infant was intubated and connected with Babylog ventilator with a FiO_2 of 25% in SIPPV. After 3 hours from the starting of thrombolytic therapy, the right leg appeared relatively pink while le left limb was still cyanotic especially at the level of the foot's toes. Gradually also the left leg become less cyanotic but the foot's toes remained cyanotic in spite of the application of nitroglycerine plasters. The echo-color-Doppler examination, carried out after 48 hours from starting thrombolytic treatment, showed that the abdominal aorta was visible up to mesenteric arteries. The aorta bifurcation was not visible while the external iliac arteries were well visible. Twenty four hours later the reperfusion of the entire bilateral aorta-iliac-femoral-popliteal vascular axis was accomplished (Figure **2**). In addition, at the aortic distal level an increased volume of lumbar arteries was observed as sign of compensation. Also, the inferior vena cava and iliac veins, previously not very well visible for a low flow, appeared adequately visible.

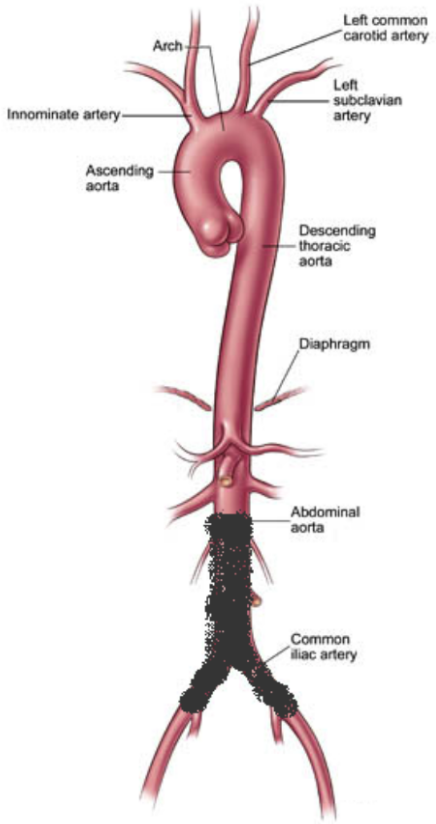
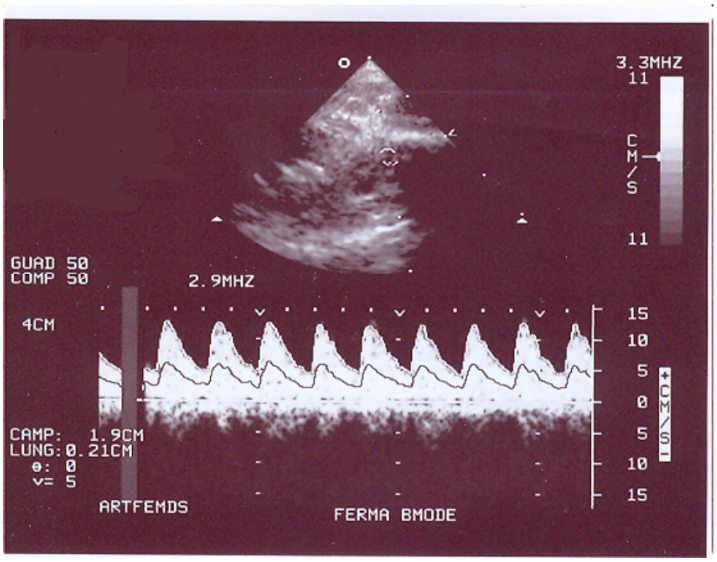


Figure 1: Schematic rappresentation of a complete aortic thrombosis distal to the renal arteries extending to bilateral iliac-femoral-popliteal vascular axis.

In the fifth day after the occurrence of the thromboembolic event, t-PA administration was finished, and low molecular weight, specifically enoxaparin, was started at the dose of 100 UI every 12 hours monitoring antiXa (desired range from 0.5 to 1.0 anti-factor-Xa units). The treatment was continued for 85 days, which was 25 days before the discharge and 60 at home. The dose of enoxaparin was increased according the infant's weight and value of anti-factor-Xa units and antithrombin III [3]. No adverse events were noted either with t-PA or enoxaparin.

The hyperemia and edema of both legs decreased gradually. The apex of fingers 5 and 1 of the left foot required removal of mummified necrosis. Moreover, physiotherapy was needed to mobilize the tibiotarsal articulation of both feet. In addition, splints were prepared for talipes equinovarus. One foot has been already operated, and the infant is able to walk.

(a)



(b)

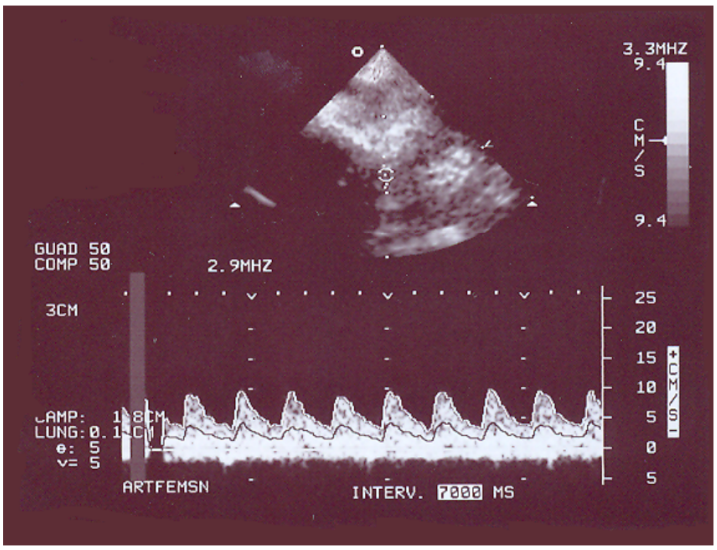


Figure 2: The echo-color-Doppler examination of the right (**a**) and left (**b**) femoral arterials after 72 hours from starting thrombolytic treatment.

Deficiencies in antitrombin (AT), proteins C (PC) and S (PS), and increased lipoprotein (a), and the presence of factor V (FV) G1691A, prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) mutations were investigated and found normal. However, a heterozygous state for deleted allele of plasminogen activator inibitor-1 (PAI-1) gene was found.

DISCUSSION

It is well known that umbilical arterial catheters entail the risk of thrombosis, with an incidence range of 4.5 to 90% [10]. The reported risk factors for thrombosis include the presence of an intravascular catheter, duration of catheterization, infusion of calcium containing fluids and dehydration, sepsis, polycythemia or congenital heart disease [10]. However, in the reported case none of these risk factors.

Moreover, the prevalence of prothrombotic genetic mutations is common in patients of neonatal intensive care units [10]. Aside from the rarity of neonatal arterial thrombosis in newborns without arterial catheters, the present case is interesting because fibrinolytic system in infancy is an age-dependent process with several

important differences to adults [1, 7]. In fact, the rate of plasmin generation in newborns and the overall fibrinolytic activity during infancy and childhood are decreased due to decreased plasma concentration of plasminogen and plasmin inhibitors [10]. The therapy started with t-PA was very effective through the increased concentration of plasminogen obtained with fresh frozen plasma but not by increasing the dose of thrombolytic agent. Even if we have not measured plasminogen in the blood of our little patient, it is possible to conceive that the absence of hemorrhagic events during systemic thrombolysis was due to this prudent approach. In addition, the monitoring of thrombolytic therapy was carried out monitoring coagulation and in particular the production of D-dimers indicating a response to therapy. After thrombolysis an anticoagulant therapy was started with a low molecular weight heparin, specifically enoxaparin, dosed in order to keep anti-factor-Xa (AT) in the range from 0.5 to 1.0. This treatment was pursued monitoring the level of AT, and administering AT in case of values under 40%. In fact, it is known that low molecular weight heparin, enoxaparin, exhibited a procoagulant activity similar to that observed with unfractioned heparin (UFH) in AT-deficient plasma [9].

In conclusion, plasminogen activators stimulating the fibrinolytic pathway to accelerate thrombus resolution can be used safely to treat life-threatening arterial thrombosis in neonates. It must be reminded that the efficacy of this treatment depends on the level of blood plasminogen, and empiric plasminogen supplementation with the infusion of fresh frozen plasma before each course of therapy should be considered [7]. In addition, to avoid bleeding complications, fibrinogen concentration and platelet counts should be constantly monitored. This reported case is of particular interest for the very low gestational age of the neonate and for the sudden appearance of pale legs and increased oxygen requirement. The rapid echo-color-Doppler diagnosis and immediate thrombolytic therapy with t-PA and frozen plasma infusion were very effective saving the life of this infant. It is important that neonatologists become aware of the protocol employed in our setting for the treatment of a this life-threatening emergency.

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