REVIEW

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Acute limb ischemia in neonates: etiology and morphological findings – short literature review

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Abstract

The acute limb ischemia (ALI) in neonates is a rare phenomenon, but with serious consequences if undiagnosed or untreated. The purpose of this review is to briefly present the etiology of ALI and morphological findings in correlation with specific causes. Etiology can be classified into two main groups: prenatal (*in utero* compression, thrombosis and embolism) and postnatal (iatrogenic, thromboembolism and vascular malformations). The most common cause of ALI is catheter-related thrombosis (almost 90% of thrombosis cases are associated with catheter use), but other rare causes like vascular malformations should not be overlooked. Ultrasound represents a non-invasive, inexpensive and widely available imaging technique, which provides sufficient information to evaluate the situation and establish proper therapeutic strategies. Morphological tests do not represent the standard diagnostic procedure in ALI, but they can provide useful information. The findings depend on the etiology: intraluminal thrombi, vascular changes, placental pathological modifications. Every morphological result must be correlated with the clinical picture and imagistic findings. In conclusion, ALI in neonates is a rare condition, usually associated with catheter use in intensive care unit setting, with multiple risk factors and conditions that increase the risk of occurrence.

Keywords: neonate, acute limb ischemia, morphology, malformations.

Introduction

The acute limb ischemia (ALI) in the newborn is a rare phenomenon that is defined by a sudden loss of limb perfusion that can affect the viability of muscles and nerve fibers if reperfusion is not performed within the first 4–6 hours [1, 2].

The incidence of ALI in neonatal population is low, Schmidt & Andrew reporting that 2.4/1000 newborns admitted to intensive care units will experience a thrombo-embolic event, 89% being associated with catheterization [3].

Clinical signs of ALI include pale or cold extremities, weak or absent pulses, decreased or undetectable blood pressure [4]. Imagistic investigations that can diagnose ALI include Duplex ultrasonography, digital subtraction angiography, computed tomography angiography, magnetic resonance angiography and arteriography. Duplex ultrasound is non-invasive and quick investigation that can both locate the lesion and appreciate the stenosis degree, but it cannot visualize the overall vascular tree. However, it provides sufficient information to establish therapeutic strategies [5].

There are no specific guidelines to treat ALI in pediatric population, only extrapolated treatment strategies from the adult population. However, mortality and amputation rates are lower than in the adult population. Rates of less than 2% amputation and 4% mortality have been described in pediatric population with ALI, with higher mortality rates among infants [6].

Etiology

The etiology for ALI can be classified into two main categories: intrauterine and postnatal causes. Intrauterine causes for ALI include *in utero* compression, prenatal thrombosis and embolism. Postnatal limb ischemia has mostly iatrogenic (umbilical artery catheterization) causes, but also thromboembolism and vascular malformations can also be observed [7].

In utero compression describes the compression *in utero* of a main artery that supplies a limb by an extrinsic process. This condition has been reported in the literature under the name of Volkmann's ischemia and it affects the upper limb and brachial artery. Oligohydramnios and amniotic bands represent risk factors of the occurrence of this condition [7, 8].

Prenatal thrombosis occurs secondary to the interaction of physiological neonatal hypofibrinolitic state (anti-thrombin III, protein S and protein C deficiencies) and certain risk factors: dehydration, sepsis, polycythemia, congenital heart disease, congenital thrombophilia [9]. Other factors that increase the risk of thrombosis can be maternal (primiparity, prothrombotic conditions, cocaine

abuse), *ante-partum* (pre-eclampsia, maternal thyroid disease, diabetes mellitus, gestational diabetes, significant maternal trauma, ovarian stimulation drugs, oligo-hydramnios, decreased fetal movements) or *intra-partum* (chorioamnionitis, prolonged rupture of membranes, fetal distress, cord abnormalities, interventions during delivery) [10].

Prenatal embolism can have maternal origin or fetal origin (the Eustachian valve redirects the blood from the umbilical vein and lower body into the right atrium and through *foramen ovale* into the left atrium and from there into the systemic circulation) [7]. Placental abnormalities that can increase the risk of prenatal embolism are placental infarction, thrombosis, funisitis, chorioamnionitis and chorioangiomas [10].

Catheterization (arterial umbilical catheters or any other arterial catheter) represents the cause in approximately 90% cases of neonatal limb ischemia (arterial thrombosis usually occurs at the site of insertion of catheter) [4, 7]. Incidence of thrombosis in neonates as a complication of catheters use is 9% [11]. Multiple risk factors that can explain the predisposition of a newborn to catheter-related thrombosis are briefly presented in Table 1 [4, 11, 12].

Table 1 – ***Factors that increase the risk of thrombosis in neonates with inserted catheters***

Newborn-related factors	▪ Prematurity; ▪ Small for gestational age; ▪ Macrosomia; ▪ Hypofibrinolitic state (increased levels of plasminogen activator inhibitor + decreased plasma activity of plasminogen); ▪ Reduced plasma activity of vitamin K-dependent coagulation factors (II, VI, IX, X) and factor XI, factor XII, prekallikrein; ▪ Deficiency of protein C, protein S, antithrombin.
Catheter-related factors	▪ Large diameter of the catheter; ▪ Malposition; ▪ Longer than six day stay; ▪ Immobilization; ▪ The addition of blood products transfusions; ▪ Rapid changes in intravascular volumes; ▪ Extensive intravascular instrumentation.
Other factors	▪ Prolonged total parenteral nutrition; ▪ Sepsis (due to increased consumption of coagulation inhibitors); ▪ Dehydration; ▪ Infection; ▪ Asphyxia ▪ Maternal diabetes; ▪ Congenital heart disease; ▪ Polycythemia; ▪ Congenital thrombophilia.

Vascular anomalies that can cause limb ischemia have a low incidence among neonates, most of them being quiescent until adolescence [12]. They can be divided into arterial malformations and arteriovenous malformations (Table 2) [13, 14]. Arteriovenous malformations are formed by afferent arteries, efferent veins and a nidus composed by multiple dysplastic vascular channels, without normal capillaries. Arteriovenous malformations can lead to arterial ischemia by proximal steal through the malformation [15, 16]. Persistent sciatic artery is one of the most frequent arterial anomalies [12].

Coagulation proteins do not cross the placenta into the fetal circulation, but their fetal production occurs early in the fetal life [17]. Therefore, newborns have a particularly increased risk of thrombosis due to the temporary low activity of protein S, protein C, antithrombin III, heparin cofactor II, reduced and dysfunctional concentrations of tissue plasminogen activator and plasminogen, even though neonates have low serum concentrations of coagulation factors XII, XI, vitamin K-dependent factors and prothrombin [18]. Certain congenital conditions also predispose to increased prothrombotic state: protein C resistance, factor V Leiden mutation, G20210A mutation, methylenetetrahydrofolate reductase mutation [17].

Table 2 – ***Vascular malformations that can cause limb ischemia***

Arterial malformations	Positional	▪ Supernumerary; ▪ Absent; ▪ Abnormal course.
	Structural	▪ Hypoplasia; ▪ Aneurysm; ▪ Stenosis; ▪ Arteriectasia.
Arteriovenous malformations	Sporadic	
	Associated with syndromes	▪ Capillary malformations – arteriovenous malformations; ▪ Parkes Weber syndrome (PWS); ▪ Hereditary hemorrhagic telangiectasia (HHT); ▪ *PTEN* hamartoma tumor syndrome (PHTS).

PTEN: Phosphatase and tensin homolog.

Whenever there is right-to-left shunt associated with congenital heart conditions, emboli dislodged from venous system are carried to the right atrium, they pass through *foramen ovale* into the left atrium and into the arterial circulation, being able to cause acute limb ischemia (so-called paradoxical embolism) [19].

Morphological findings

Morphological findings in ALI depend on the etiology. Therefore, morphological results must be correlated with the clinical picture and imagistic findings. Some of the most frequent causes have been histologically investigated and the results will be further presented.

Intraluminal thrombi in arterial thrombosis can be histologically classified as acute or organizing. It has been found that acute thrombi contain fibrin with platelets and entrapped erythrocytes, while the organizing thrombi (also called chronic) contain collagen, inflammatory cells, smooth muscle cells, capillary channels and ingrowth endothelial cells [20].

Biopsy samples from arteries with catheter-related thrombosis show in the early stages fine fibrin-platelet fresh thrombi with intracellular deposits of neutral fat in macrophage-like cells in relation to areas of abrasion of the vascular endothelium. If the catheterization time is prolonged, the thrombus starts to organize. Therefore, there can be observed mitotic activities in the medial smooth muscle cells and edematous, friable and loose intima with lipid deposits and smooth muscle cells passing into the media. The organized thrombi can present the following aspects: polypoid (hemosiderin macrophages, progressive replacement of fibrin with tissue rich in mucopolysaccharides and thickened intima), nodular (predominant smooth muscle cell proliferation and

significantly less fibrin), cylindrical (aspect given by the formation of the thrombus around the catheter) [21].

In cases of prenatal maternal embolism, it is indicated to take biopsy samples from the placenta. Unfortunately, sometimes, the placenta is discarded by the time the limb ischemia becomes clinically evident [10]. In 2011, Elbers *et al.* studied cases of perinatal ischemic stroke caused by placental anomalies (stroke and ALI share pathophysiological mechanisms) and found out that the embolization was determined by decreased placental reserve, thromboinflammatory processes, stressful intrauterine environment or sudden catastrophic event. Placental pathologies that were associated with decreased placental reserve are chronic villitis, distal villous immaturity and placental infarction [22]. Thromboinflammatory processes were accompanied by acute chorioamnionitis, fetal thrombotic vasculopathy (defined by ischemic changes in the fetal capillaries of terminal villi: thrombi in stem and placental vessels and clusters that contain more than five avascular villi), chorionic thrombosis, cord thrombosis, stem thrombosis [22, 23]. Sudden catastrophic events included retroplacental hematoma, umbilical cord entanglements (stasis can promote thrombosis within the umbilical vessels) [22]. Another study divides the placental histological abnormalities that can increase the risk of fetal thrombosis into maternal and fetal abnormalities. Maternal circulation derangements that have been described are: increased syncytial knots (caused by intervillous hypoxia), intervillous fibrin around chorionic plate, stem villi and basal plate (extreme intervillous fibrin increase can be seen in maternal floor infarction), villous infarction (thrombotic occlusion of an uterine spiral artery), thin umbilical cord (caused by fetal hypovolemia) and distal villous hypoplasia and decreased placental weight (caused by chronically reduced maternofetal perfusion) [24]. Proximal fetal circulation anomalies that increase the risk of thrombosis are: distal villous hypoplasia, fetal thrombotic vasculopathy (in the early stages, we can observe hemorrhagic endovasculitis and in the later stages hyalinized avascular villi), chronic stem villitis with fetal obliterative vasculopathy and certain villous capillary lesions (villous chorangiosis and diffuse multifocal chorangiomatosis) [24, 25].

In case of umbilical artery thrombosis (the most frequent location of spontaneous arterial thrombosis), occlusive intraluminal thrombi and necrosis of the inner layer of vascular wall without the villous sclerosis or karyorrhexis can be observed [26].

It is difficult to diagnose an arteriovenous malformation only by biopsy. Light microscopy in arteriovenous malformations reveals thick-walled arteries with variable calibers (tortuous arteries), disruption and fragmentation of the arterial internal elastic lamina (basket-weave-like pattern), intimal and adventitial fibrosis [14]. Veins can be characterized as thin, stiff and fibrotic vessels as a result of hypertrophied smooth muscle being replaced by collagen due to the high pressure flow effects [27]. The small vessel component can be found as: variable number of dispersed small vessels with thick fibrotic walls containing one or two layers of smooth muscle cells/pericytes, or they can mimic pyogenic granuloma (lobules of plump, small, curved capillary vessels with elongated endothelial cells and eosinophilic cytoplasm, collagenous and mucinous matrix and scattered pericytes) or proliferative phase infantile hemangioma (lobules of packed capillaries with plump endothelium and round lumens) [14]. The shunts can be evidenced by elastic staining, but it is a difficult task to do since the connections can be small [27]. The distinction of arteriovenous malformations from capillary malformations can be made by searching four histological criteria: greater thickened vascular walls, vessel density, elongation and disorganized branching of vessels and luminal red blood cells [28].

Conclusions

ALI represents a rare condition among the neonatal population. The etiology is complex, with many risk factors (both fetal and maternal) and pathological conditions that increase the risk of arterial obstruction. The most common cause of ALI represents catheter-related thrombosis, but other rare causes like vascular malformations should not be overlooked. Even though morphological tests are not the gold standard diagnostic procedure in ALI, there are situations when they provide useful information (*e.g.*, differential diagnosis of vascular malformations).

Conflict of interests

The authors declare that they have no conflict of interests.

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