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Review

Histological markers of neonatal asphyxia: the relevant role of vascular changes

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Proceedings

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The role of the clinical pathological dialogue in problem solving
Guest Editors: Gavino Faa, Vassilios Fanos, Peter Van Eyken

Abstract

Perinatal asphyxia is one of the leading causes of morbidity and mortality in the perinatal period, with 4 million neonates suffering annually from birth asphyxia. Tissue hypoxia can cause several pathological changes in multiple organs, hypoxic-ischemic encephalopathy (HIE) representing one of the most severe consequences in the newborn, occasionally leading to the insurgence of the multi-organ dysfunction syndrome. The pathological diagnosis of neonatal asphyxia is complex, histological markers of tissue hypoxia often overlapping with pathological changes due to other etiologies. This work is aimed at summarizing the most important pathological markers of asphyxia occurring in a newborn in the different organs. The endothelial lesions (swelling, apoptosis, detachment and loss of the endothelial barrier) in our experience, represent the most relevant pathological changes induced by hypoxia in all the organs. The finding of increased hepatic hemopoiesis represents one of the most important markers of chronic tissue hypoxia. In conclusion, the accurate histological study of all the organs in every case of perinatal asphyxia may allow, in expert hands, perinatal pathologists to give important data to neonatologists for reaching, together, a complex clinical/pathological diagnosis, able to explain the clinical course in the majority of asphyxiated newborns undergoing multiple organ dysfunction.

Keywords

Neonatal asphyxia, endothelial dysfunction, MOF, newborn, tissue hypoxia.

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Introduction

Tissue hypoxia represents a clinical problem frequently observed in newborns admitted to neonatal intensive care unit (NICU), in the clinical setting of placental, pulmonary and cardiac diseases. Perinatal asphyxia is one of the leading causes of morbidity and mortality in the perinatal period, with 4 million neonates suffering annually from birth asphyxia [1]. Hypoxia can cause several pathological changes in multiple organs, hypoxic-ischemic encephalopathy (HIE) representing one of the most severe consequences in the newborn, occasionally leading to the insurgence of the multi-organ dysfunction syndrome [2]. The clinical diagnosis of perinatal asphyxia is mainly based on the evidence of neurological and cardiorespiratory depression associated with acidemia. Recently, the analysis of the urinary metabolomic profile has been proposed as a new tool for a more in depth diagnosis and for a better prognosis in asphyxiated neonates [1]. The pathological diagnosis of neonatal asphyxia is much more complex, histological markers of asphyxia often overlapping with pathological changes due to other etiologies.

This work is aimed at summarizing the most important pathological markers of asphyxia occurring in a newborn in the different organs, helping pathologists involved in autopsy of an asphyxiated neonate to find their way for an in-depth clinical-pathological diagnosis. Moreover, we will try to correlate the most important data on the molecular pathways involved during neonatal hypoxia with the histological data, trying to remove the gap actually existing between our knowledge of molecular events taking place during asphyxia and their histological counterpart.

Molecular mechanisms of hypoxia-induced tissue damage

The most important mediators in cellular oxygen homeostasis are represented by hypoxia-inducible factor-1 (HIF-1) and -2 (HIF-2), two hydroxilases that facilitate oxygen delivery in physiology and adaptation to oxygen deprivation in the clinical setting of asphyxia [3]. HIF-1 and HIF-2 are both transcriptional factors (TF) that increase transcription of multiple specific hypoxia-responsive genes [4]. Differential roles have been described regarding the target genes regulated by HIF-1 and HIF-2, only occasionally the action of both TFs overlapping [5]. HIF-1 regulates glycolytic genes and in particular insulin-like growth factor 2 [6], and it is also involved in the regulation of adipogenesis, through the transcriptional regulation of the DEC1/Stra13 gene [7]. HIF-2 is involved in the regulation of angiogenesis, being the main regulator of vascular endothelial growth factor (VEGF). HIF-2 also regulates hemopoyesis through the transcriptional regulation of the erythropoietin (EPO) gene, and iron metabolism through the transcriptional activation of the transferring receptor gene [8], whereas HIF-1 regulates the expression of the transferring gene [9]. In conditions of tissue hypoxia, HIF-2 also interferes on iron metabolism by suppressing the hepatocytic production of hepcidin, resulting in increased iron uptake and transport in the intestinal epithelium [10]. A specific HIF-2 target is Oct4: through its activation, HIF-2 regulates stem cell function and embryonic development [11]. In addiction to acting as TFs, HIF-1 and HIF-2 regulate important intracellular pathways and modulate fundamental biological processes through direct protein-protein interaction. HIF-1 induces cell cycle arrest by functionally counteracting the proto-oncogene Myc [12]. By interacting with the protein product of the NOTCH gene, HIF-1 modulates NOTCH signaling, maintaining the undifferentiated state in stem cells during development [13].

Histological markers of hypoxia

Vascular changes

Blood vessels, and in particular endothelial cells, probably represent the most important target of neonatal asphyxia. From a practical point of view, arterial and venous changes should represent the focus of the histological examination of all the organs in every case of perinatal asphyxia. The

main histological changes detectable in every organ are here reported.

Arteriolar vasodilatation

Vasodilatation of arterioles represents one of the most important changes induced by hypercapnia. This effect, easily recognized at histology by the presence of enlarged arterioles containing red blood cells within their lumen, is mainly due to the disactivation of mitochondrial ATP-sensitive K+ channels, which results in arteriolar vasodilatation [14].

Endothelial cells

Major changes are constantly observed in endothelial cells when tissue hypoxia occurs (**Fig. 1**). The molecular pathway leading to hypoxia-induced endothelial damage is probably related to the increase in HIFs production. One of the most important consequences of HIF hyper-secretion in neonates affected by asphyxia is the increase in VEGF expression [15]. At morphological level, the consequences of VEGF hyperexpression could be summarized as follows: i) endothelial swelling, probably representing the first physiological response of endothelial cells to VEGF hyper-secretion; ii) endothelial exhaustion, consequent to a persistent and pathological hyper-stimulation by VEGF, followed by endothelial cell death by apoptosis; iii) enlargement of the inter-endothelial tight junctions, followed by endothelial detachment; iiii) loss of the endothelial barrier. These histological changes are all easily recognized at histology, and may be observed both in arteries and in veins (**Fig. 2**). The consequences of the loss of the endothelial barrier are multiple and, taken together, may explain the vast majority of lesions in multiple organs observed in the clinical setting of perinatal asphyxia, occasionally leading to multiple organ failure [16]. At histology, the loss of the endothelial barrier is generally associated with the following lesions.

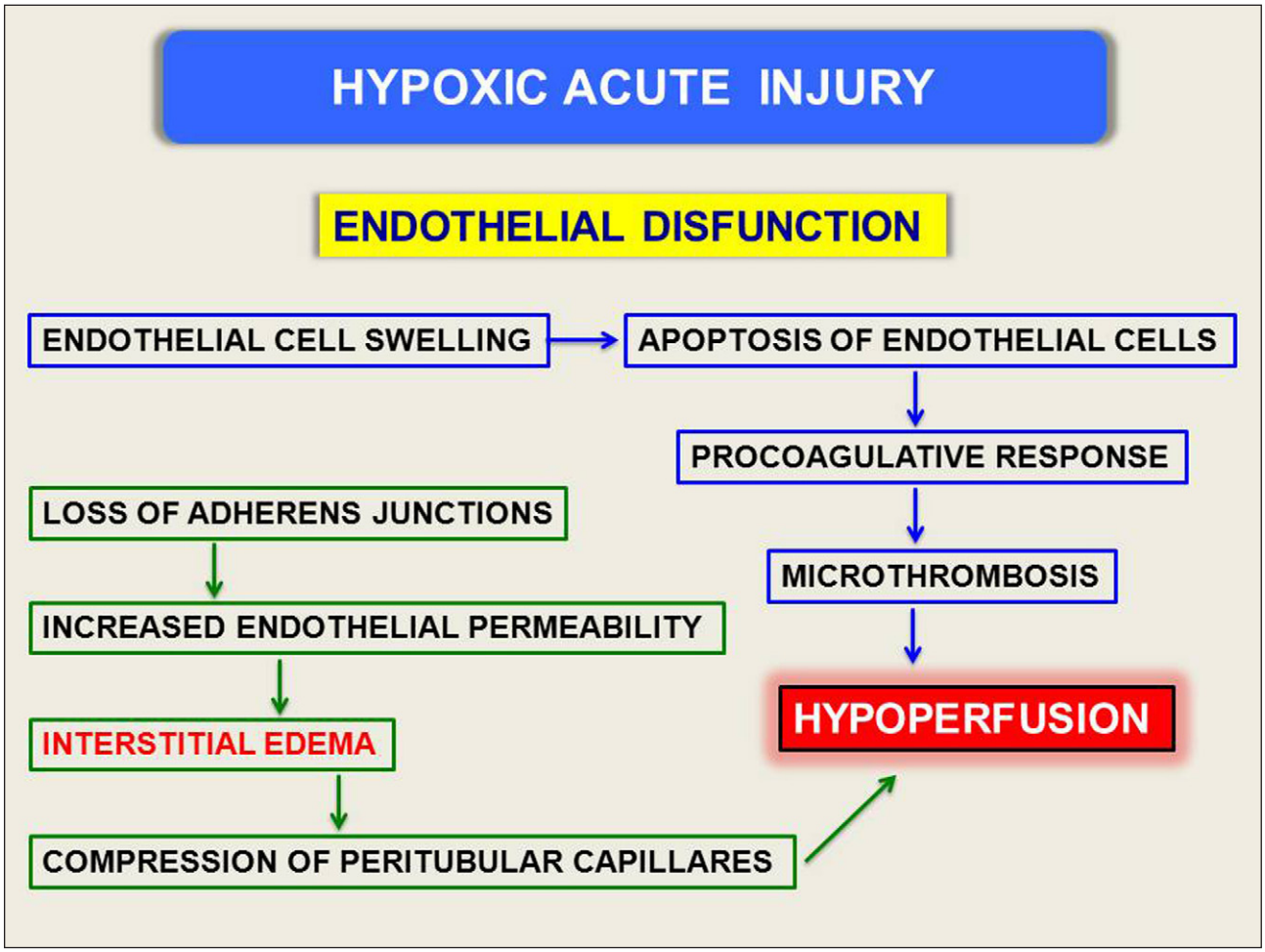

Figure 1. Endothelial disfunction in hypoxic acute injury.

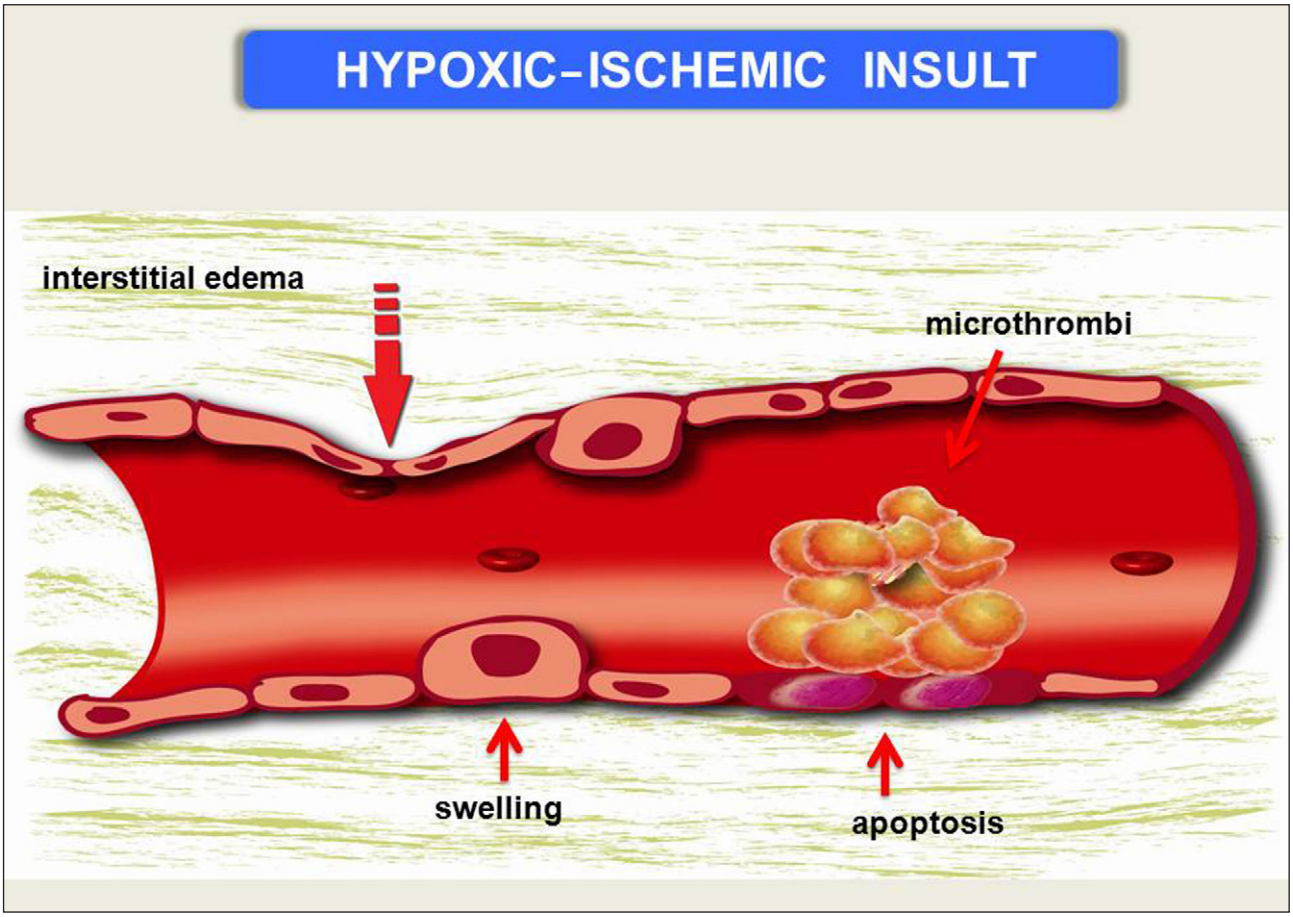

Figure 2. Summary of histological changes in arteries and in veins.

a. Diffuse intravascular coagulation (DIC), characterized by the presence of thrombi in the lumen of blood vessels, mainly affecting arteries and veins in which endothelium is absent (**Fig. 3**).
b. Edema of the perivascular tissues, due to the leakage of liquid and proteins related to the loss of the physiological selective barrier represented by the endothelial cells (**Fig. 4**).
c. Loss of the microvascular reactivity, in part related to the endothelial cells, leading to persistent dilatation of the affected vessels.
d. Perivascular hemorrhages, due to a severe disruption of the vascular wall.
e. Dysfunction of the neurovascular brain unit, followed by dysfunction of the brain blood barrier, leading to perivascular edema and neuronal cell death [17] (**Fig. 5**). Recently, the use of immunohistochemistry for albumin has been suggested as a useful tool for detecting the pathological changes of the blood brain barrier in neonates affected by perinatal asphyxia [18].

Liver

The finding of increased hepatic hemopoiesis represents one of the most important markers of chronic tissue hypoxia.

Erythropoiesis is a dynamic process regulated through complex interplay of cytokines, nutrient availability, and the cellular environment of erythroid precursors [19] (**Fig. 6**). Critical factors governing red cell formation include oxygen and iron sensing, which act through the transcription factor hypoxia-inducible factor-2α (HIF-2α) [20]. Intestinal HIF-2s have been shown to be essential for iron absorption, HIF-2α promoting duodenal iron absorption following iron deficiency [21]. Moreover, HIF-2α plays a central role in erythropoiesis and hematopoietic development by regulating EPO expression [22]. In preterm babies with birth weight < 1.0 kg (commonly designated as extremely low birth weight, or ELBW, infants) affected by anemia, the hemoglobin levels are lower than in term infants, due to diminished plasma EPO levels in response to anemia. Erythroid progenitor

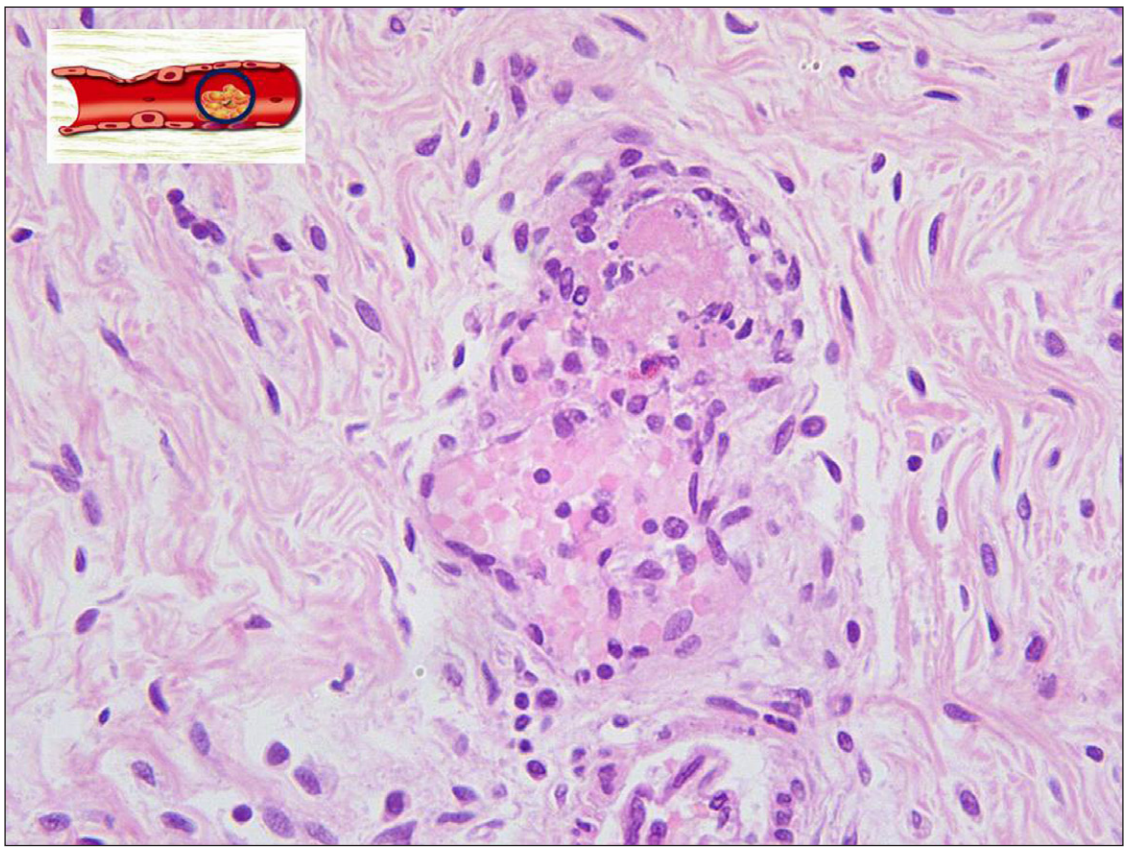

Figure 3. Thrombosis.

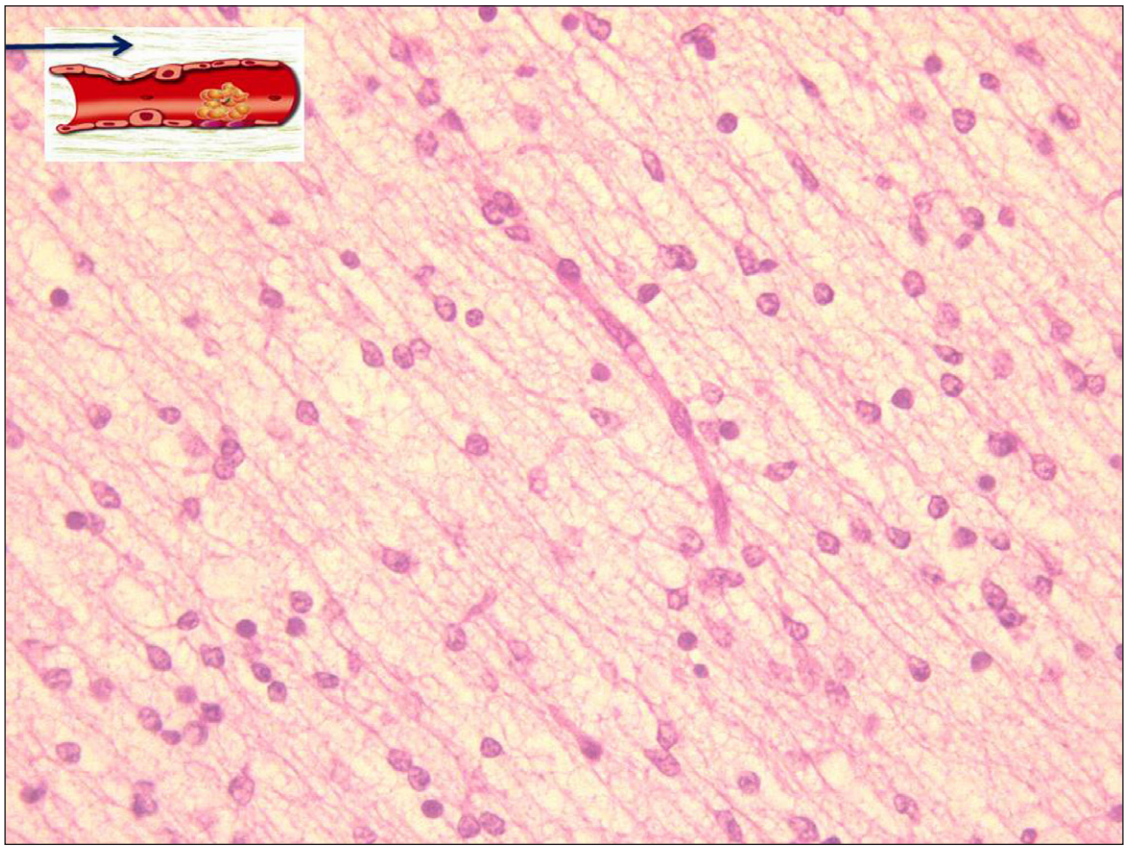

Figure 4. Edema.

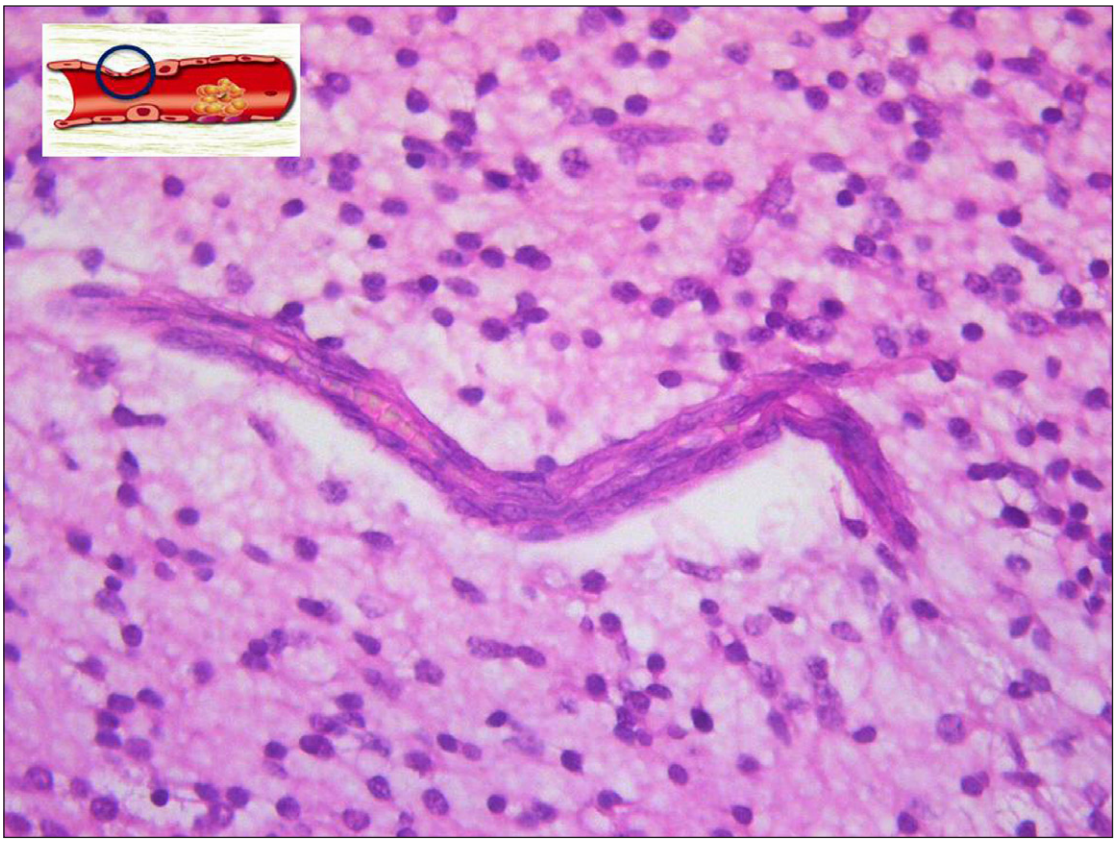

Figure 5. Perivascular edema.

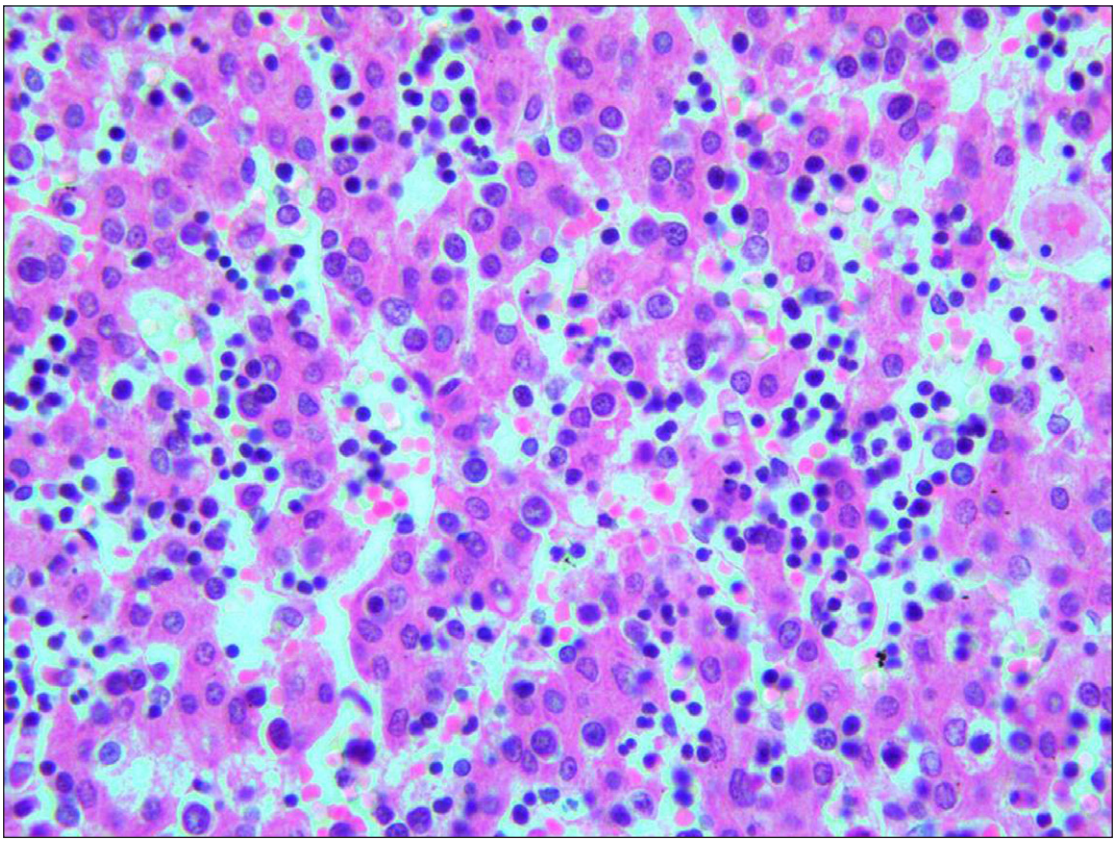

Figure 6. Hepatic hemopoiesis.

cells of newborn infants are quite responsive to EPO *in vitro* – a finding suggesting that inadequate production of EPO is one major cause of neonatal anemia, and not marrow unresponsiveness [23]. The iron regulatory protein 1 (IRP1) has been recently shown to play a role in the control of hemopoiesis, by inhibiting mRNA translation of HIF-2α, with which it forms a regulatory axis that coordinates iron and oxygen sensing with erythropoiesis [24] (**Fig. 2**). During gestation, hematopoietic stem cells develop from the mesodermal germ layer and successfully localize to two independent anatomical sites, the yolk sac and the dorsal aorta. Subsequently, hematopoietic cell populate the fetal liver, that represent the principal source of blood cells during the intrauterine life [25, 26]. Recent studies indicate that EPO is a critical regulator of multiple aspects of erythroid precursors during primitive and definitive erythropoiesis, including cell survival, proliferation and the rate of terminal maturation [27].

All these data, summarized in **Fig. 7**, clearly indicate the utility of a deep analysis of the degree of liver hemopoiesis in the pathological evaluation of perinatal asphyxia. Higher the degree of hemopoiesis, higher the level of tissue hypoxia. In case of absence of morphological evidences of hepatic hemopoiesis, particularly in preterm infants, caution should be taken in performing a certain pathological diagnosis of perinatal asphyxia, and other etiologies other than hypoxia should be considered.

Since HIFs have been shown to interfere on the expression of hepcidin in liver cells, by decreasing its production [28], immunohistochemistry for hepcidin should be mandatory in all cases of perinatal asphyxia, in order to better correlate the clinical picture with the consequences of hypoxia at molecular level.

Lungs

Vascular changes probably represent the most frequent lesions observed at histological level in newborns affected by asphyxia. Congestion, i.e. dilatation of alveolar capillaries, arteries and veins, is the most frequent change observed at histological level in lung specimens of asphyxiated neonates, capillary and arteriolar dilatation representing the loss of vascular reactivity due to hypercapnia [14]. Pulmonary

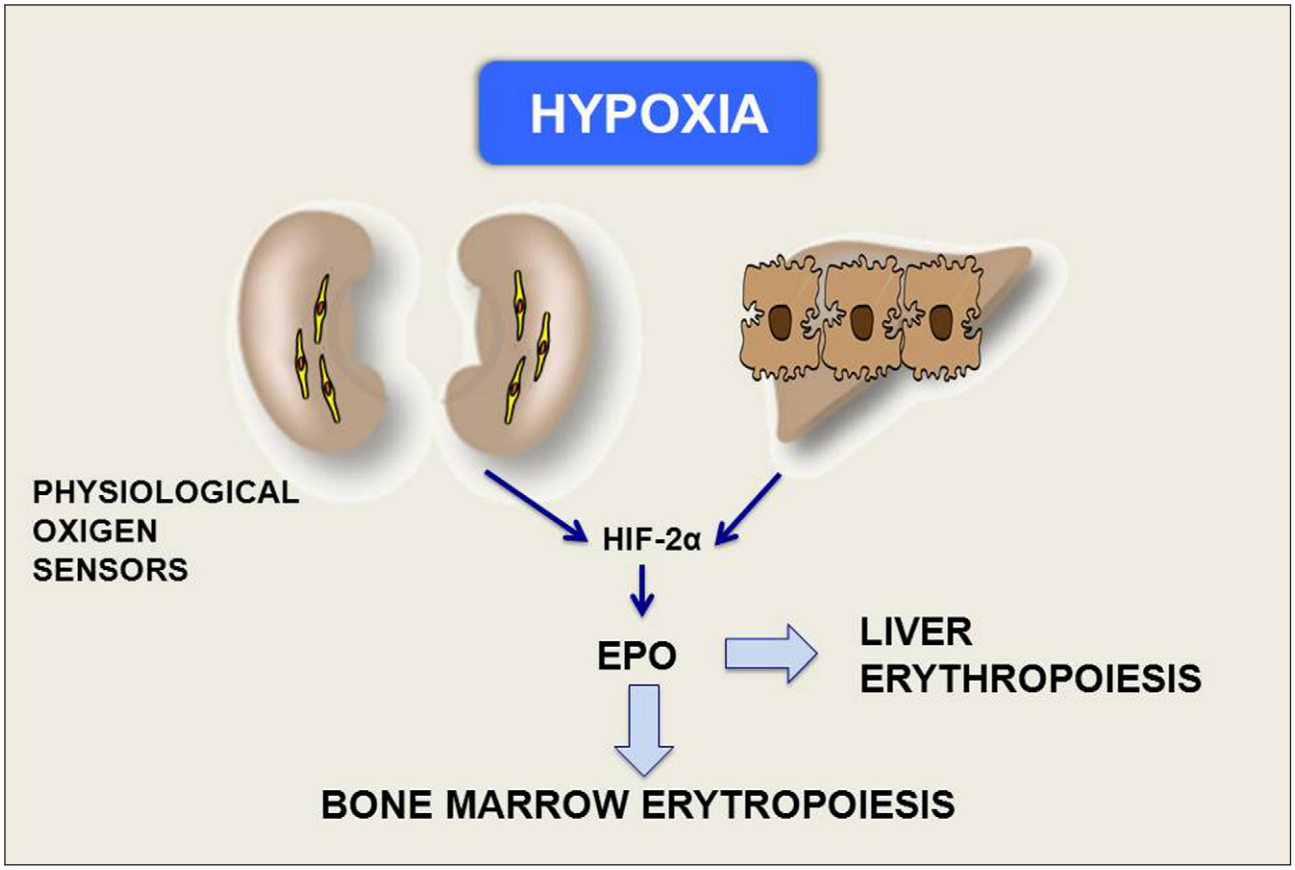

Figure 7. Erytropoiesis in hypoxia. EPO: erythropoietin; HIF-2α: hypoxia-inducible factor-2α.

hemorrhage is the other histological change often observed in the setting of asphyxia, following a more severe disruption of the vascular unit [29]. Birth asphyxia has been shown to be associated with increased pulmonary vascular resistance (PVR), due to the absence of the physiological increase of oxygen tension at birth that represents an important factor in decreasing PVR after delivery [30]. As a consequence, the presence of pulmonary arterioles with the typical "fetal appearance", characterized by a thick muscular wall and a narrow lumen, should be always verified, in order to verify if pulmonary hypertension has been caused by the persistence of fetal arteries or by other factors.

Brain

Assuming that HIE represents the most important clinical consequence of perinatal asphyxia [31], brain lesions have been reported in many studies. The most important histological changes are summarized in **Fig. 8**.

a. Pial arteriolar vasodilatation is a constant finding in the brain of asphyxiated newborns. It is simply evidenced at panoramic view, and it is mainly related to the loss of microvascular reactivity in cerebral vessels [14].
b. Endothelial damage represents probably the most important change in the brain of asphyxiated newborns. All the endothelial lesions previously reported may be encountered at the histological examination of brain samples. Endothelial swelling represents a peculiar feature in the small intracerebral vessels. Given the narrow lumen of the intravascular capillaries, endothelial swelling may lead to the occlusion of the vascular lumen, leading to the block of the intracerebral circulation, aggravating brain hypoxia.
c. The endothelial damage is followed by the dysfunction of the neurovascular unit that contributes to subsequent neuronal cell death [17].
d. Neuronal cell death represents a major pathological finding in the interpretation of the severity of the hypoxic encephalopathy. Apoptosis is the most frequent type of cell death occurring in the brain of asphyxiated newborns. At histology, affected neurons show shrinkage, increased eosinophylia of the cytoplasm, nuclear piknosis and kariorexis, ending with the formation of roundish eosinophilic globules that appear intermingled with preserved neurons.

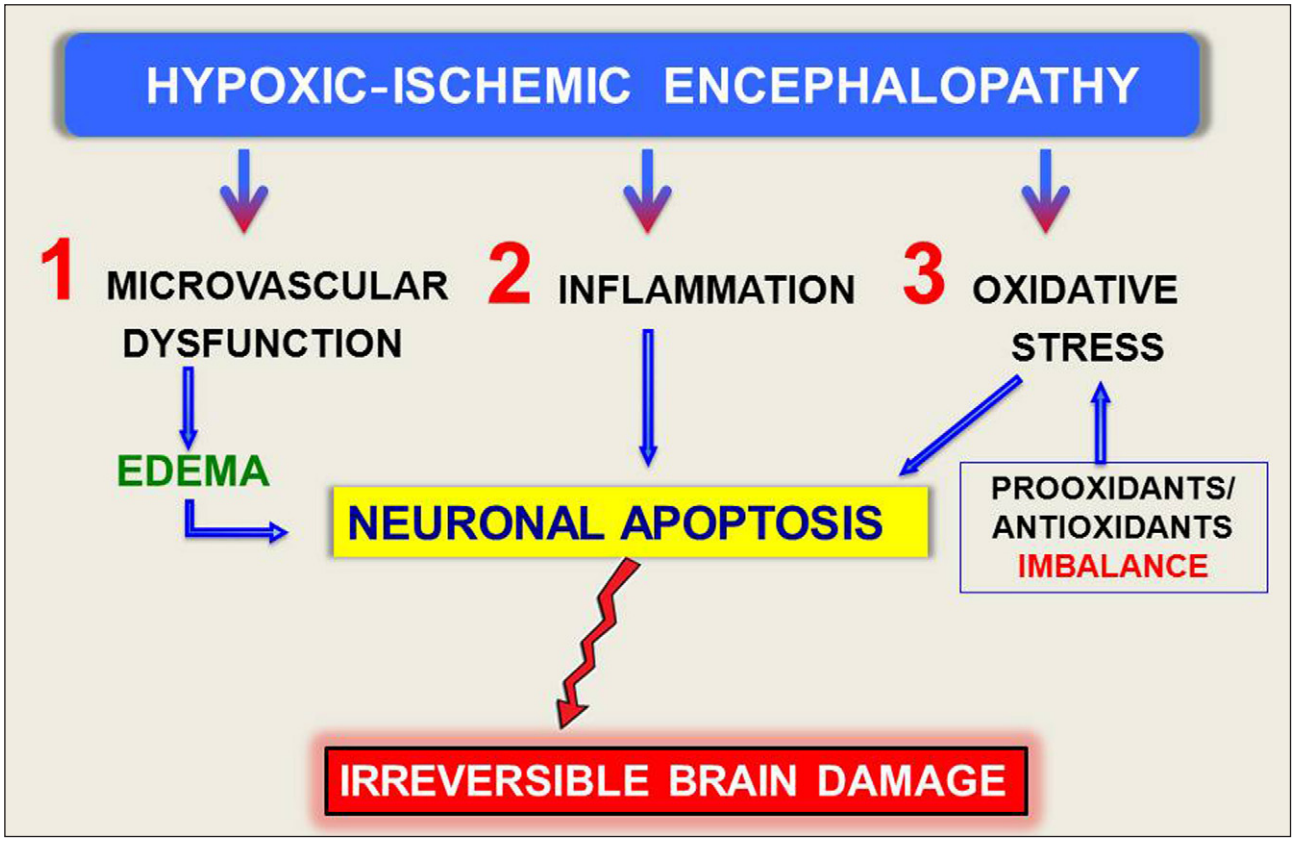

Figure 8. Brain damage in hypoxic-ischemic encephalopathy.

Neuronal apoptosis may be encountered, in the clinical setting of asphyxia, in all the cerebral regions. In our experience, neurons of the brain stem, basal nuclei and cerebellum appear as the most frequently affected by apoptosis, often in association with apoptosis of the cerebral cortical neurons. Recently, the increased expression of pro-apoptotic proteins – including BAX, cytoplasmic cytochrome C and caspase-3 – has been reported in the cortex and thalamus of the brain of mice affected by birth hypoxia [32], suggesting the use of these antibodies in cases in which histology could not clearly evidence the typical features of neuronal cell death. The hippocampus should be always sampled for histological studies, given the frequent functional compromise of this brain region in newborns affected by asphyxia, particularly in female infants [33]. In a recent study, all 16 full-term asphyxiated infants displayed neuronal cell damage and glial reactivity in the hippocampus. In the same study, a strong immunreactivity for acquaporin was detected on hippocampal astrocytes in 50% of patients [18], suggesting the use of this immunohistochemical reaction in all newborns with a clinical history of perinatal asphyxia.

Kidneys

Acute kidney injury (AKI) has been reported in variable percentages, up to 56%, of newborns affected by perinatal asphyxia [34]. The prevalence of AKI is about three fold higher in neonates with birth weight lower than 1,500 g [35]. At histology, AKI is characterized by prevalent changes in tubular epithelial cells, proximal tubular cells representing the main target of hypoxia [36] (**Fig. 9**). At histology, proximal tubular cells show all the morphological markers of apoptosis: detachment from neighboring cells; increased eosinophilia of their cytoplasm; condensation of the chromatin; fragmentation of the nucleus; detachment from the basal lamina; aggregation into the tubular lumen, giving rise to cellular casts.

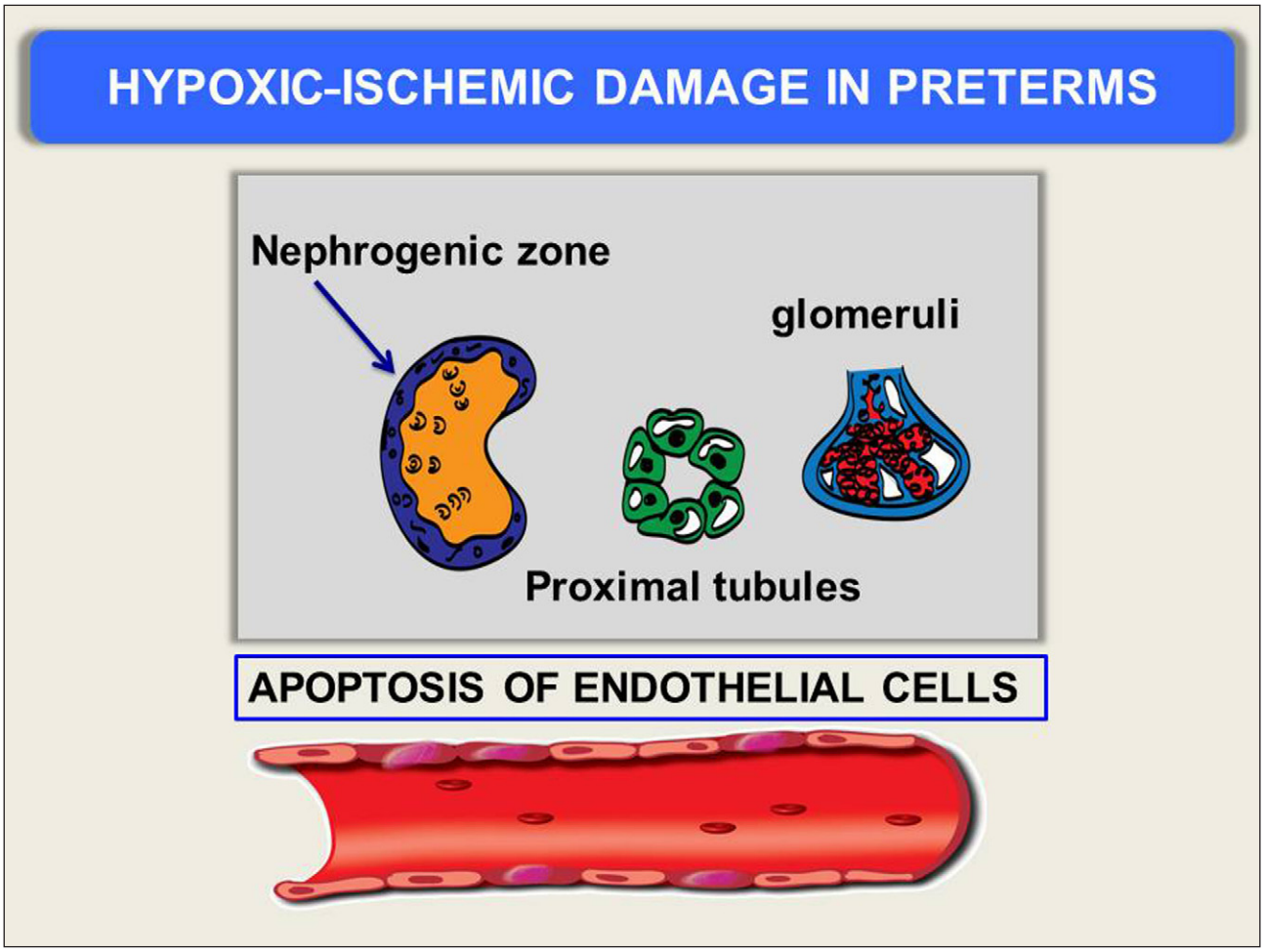

Figure 9. Hypoxic-ischemic damage in preterms.

Thyroid gland

Alterations in thyroid metabolism in newborns have been first described about 30 years ago, asphyxiated neonates being characterized by the absence of the increase of FT4 and FT3 serum levels in the perinatal period [37]. Further studies evidenced the occurrence of hypothyroidism in newborns with HIE, the involvement of the thyroid gland representing a greater risk of death in these patients [38]. Even though, at the best of our knowledge, no histological study has been carried out on thyroid histology in asphyxiated newborns, these data taken together induce to suggest a careful histological examination of the thyroid gland in every case of perinatal asphyxia.

Discussion

Given the practical aim of this work, mainly focused on giving a simple check list of the histological lesions pathologists should look for in the autopsy of a newborn affected by asphyxia, the last part of our work is dedicated to this aim. In **Tab. 1** all the most relevant histological lesions here described are reported.

Table 1. Main histological changes related to perinatal hypoxia.

1. **Blood vessels**
   - Endothelial swelling
   - Endothelial detachment
   - Loss of the endothelial barrier
   - Perivascular edema
   - Intravascular coagulation
2. **Brain**
   - Pial vessel dilatation
   - Intracerebral capillary endothelial swelling
   - Perivascular edema
   - Neuronal apoptosis
3. **Lungs**
   - Interstitial edema
   - Interstitial hemorrhage
   - Alveolar capillary dilatation and congestion
4. **Heart**
   - Coronary vessel congestion
   - Coronary vessel thrombosis
   - Interstitial edema
5. **Kidneys**
   - Apoptosis of proximal tubular cells
6. **Liver**
   - Increased hepatic hemopoiesis

Among them, we want to lay stress on the endothelial lesions that, in our opinion, represent the most relevant pathological changes induced by hypoxia in all the organs. The progressive morphological changes representing endothelial dysfunctions related to tissue hypoxia are, probably, at the basis of the most relevant consequences in the different tissues: edema and thrombosis. The former dissociates the multiple cell types of different organs, with complex and severe consequences of their function; the latter aggravates hypoxia in affected tissues, mainly in cases in which disseminated intravascular coagulation occurs. All these data taken together, induce to a better analysis of blood vessels and, in particular, of endothelial cells, looking for the morphological markers of endothelial dysfunction. Starting with endothelial swelling that, particularly in the small capillaries of the brain, due to their narrow lumen, may represent a mechanical block to red blood cell circulation, leading to the aggravation of the hypoxic state, ending with neuronal cell death.

In conclusion, the accurate histological study of all the organs in every case of perinatal asphyxia may allow perinatal pathologists to give important data to neonatologists for reaching, together, a complex clinical/pathological diagnosis, able to explain the clinical course in the majority of asphyxiated newborns undergoing multiple organ dysfunction.

Declaration of interest

The Authors declare that there is no conflict of interest.

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