

Cardiotocography, Hypoxia, and Feto-Neonatal Neurological Damage

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Abstract

Complications occurring at any level of fetal oxygen supply can result in hypoxemia, which may ultimately lead to hypoxia/acidosis and neurological damage. Hypoxic-ischemic encephalopathy (HIE) is the short-term neurological dysfunction caused by intrapartum hypoxia/acidosis. This diagnosis requires the presence of several findings, including confirmation of newborn metabolic acidosis, low Apgar scores, early imaging evidence of cerebral edema, and the appearance of clinical signs of neurological dysfunction in the first 48 hours of life. Cerebral palsy (CP) comprises a heterogeneous group of nonprogressive movement and posture disorders, often accompanied by cognitive and sensory impairments, epilepsy, nutritional deficiencies, and secondary musculoskeletal lesions. Although CP is the most common long-term neurological complication associated with intrapartum hypoxia/acidosis, over 80% of cases are caused by other factors. Data on minor long-term neurological deficits are limited, but they suggest that less severe intellectual and motor impairments may result from intrapartum hypoxia/acidosis.

Birth asphyxia is a broad term referring to intrapartum asphyxia severe enough to cause neurological damage in some newborns and, rarely, intrapartum or neonatal death. Cerebral palsy and long-term neurological complications such as learning difficulties and motor impairments may have causes other than birth asphyxia. Several intrapartum events can lead to asphyxia (i.e., hypoxia and metabolic acidosis), increasing the likelihood of neurological injury. The cardiotocograph (CTG) is a screening tool used to assess fetal well-being during labor and to identify the possibility of asphyxia. An abnormal CTG, sometimes severe enough to be described as a pathological trace, is commonly referred to as "fetal distress", although many fetuses with such traces may not have hypoxia and metabolic acidosis. In current practice, these events are appropriately termed "pathological CTG trace" or "acidotic pH" rather than "fetal distress". Accurate interpretation of the CTG is essential, and it is important to recognize a fetus displaying a pathological CTG in labor, which may imply possible hypoxia and birth asphyxia. Considering the broader clinical context when interpreting the CTG and taking timely and appropriate action based on the findings may help prevent birth asphyxia.

Keywords: Cerebral Palsy, Fetal Hypoxia/Acidosis, Hypoxic-Ischemic Encephalopathy, Neonatal Acidosis.

Introduction

A constant supply of oxygen is essential for energy production and the maintenance of cellular integrity. Oxygen supply is therefore crucial for the life of cells and the entire individual. For its oxygenation, the fetus is dependent on the placenta; transient or permanent interruptions of placental blood flow can result in varying degrees of oxygen deprivation to the baby, ranging from hypoxemia to fetal anoxia. It should be noted that the fetal brain has significant anaerobic tolerance compared to the adult brain, allowing the fetus to tolerate longer periods of oxygen deprivation without injury compared to adults. The fetal cardiovascular system is programmed to rapidly detect, assess, correct, and tolerate temporary oxygen deprivations. The purpose of this fetal

sensory capacity is to centralize circulation to maintain perfusion and oxygenation of essential organs such as the brain, heart, and adrenal glands, at the expense of non-essential organs like the lungs, liver, kidneys, intestines, skeleton, muscles, and skin. The fetal response to oxygen deficiency is rapidly supported by the chemoreflex response, which acts in the immediate and short term; subsequently, slower endocrine actions and fetal endothelial and behavioral responses occur in the medium and long term [1].

Labor during childbirth is one of the moments in intrauterine life that is particularly predisposed to changes in fetal oxygenation. During labor, rhythmic contractions represent a physiological stressor. Uterine contractile activity causes a reduction in maternal

blood flow to the placenta due to compression of maternal vessels within the myometrium, resulting in a rhythmic and temporally brief reduction in fetal oxygenation. A fetus in good oxygenation conditions can optimally tolerate oxygenation changes dependent on contractions. However, these physiological changes in fetal oxygenation can sometimes be associated with events that are not entirely physiological. In some cases, uterine contractions can be too close together and may not allow enough time for the fetus to reoxygenate. In other instances, contractions can lead to compression of vessels within the umbilical cord, as can occur in cases of severe oligohydramnios. More rarely, severe maternal and/or fetal complications during labor can drastically reduce or entirely interrupt the supply of blood to the baby. These complications may include severe alterations in maternal oxygenation (severe and sudden maternal hypotension, maternal cardiorespiratory arrest), or severe and sudden alterations in fetal oxygenation related to mechanical complications (umbilical cord prolapse, shoulder dystocia) or hemorrhagic complications (massive placental abruption, rupture of previous vessel injuries). The consequences of these different events on the fetus will be more severe the more severe and persistent the insult was and the more precarious the fetal starting conditions were.

Classification of Hypoxic Damage

As previously mentioned, the quantity and duration of oxygen deprivation are directly related to the type of response and fetal-neonatal outcomes. We will now discuss fetal responses to different conditions of oxygen deprivation.

Slowly Progressive Hypoxia

The presence of slowly progressing hypoxic insults allows the fetus to implement homeostatic adaptations, including metabolic adjustments. Experimental studies conducted on sheep fetuses have shown that during prolonged hypoxemia (in the absence of metabolic acidosis), the fetus can sustain protective adaptations of the cardiovascular system for an extended period without damage [2-4]. The regional redistribution of blood flow in the fetal brain redirects blood from the cortex to deep nuclei and structures of

the brainstem, thereby safeguarding vital centers and the baby's well-being. However, these protective adaptations begin to fail when acidemia develops. At a pH lower than 7.0, cerebral oxygen consumption substantially decreases, and acidemia progressively leads to cellular damage. If persistent, it can result in loss of vascular tone, depression of myocardial function, hypotension, and, ultimately, ischemic brain injury [5,6]. If acidemia does not develop, the fetus can support its protective circulatory adaptations almost indefinitely. At birth, a baby exposed to slowly progressive hypoxia is likely to show signs of acquired hypoxic insult in utero. These signs may include high levels of nucleated red blood cells [7,8] and clinical manifestations of hypoxic injury, such as multi-organ dysfunction [9] (including abnormal liver and kidney function, consistent with prolonged circulatory redistribution in response to hypoxia), pulmonary hypertension [10], seizures [11], and brain injuries [12].

Acute Hypoxia

During an acute episode of complete oxygen deprivation (such as in cases of massive placental abruption or total umbilical cord occlusion, as in the case of umbilical cord prolapse), the lack of oxygen and substrates rapidly leads to energy failure. Fetal pO₂ (oxygen pressure) decreases so quickly in a matter of minutes that it initiates an initial rapid generalized vasospasm mediated by chemoreflexes (aimed at centralizing blood flow to maintain central perfusion). This is followed by hypoxic decompensation and, ultimately, marked systemic hypotension, leading to cerebral infarction. The sequence of events is so rapid that the regional redistribution of blood within the brain, typical in cases of slowly progressive hypoxia, cannot occur temporally in these sudden circumstances. As a result, the fetus is unable to protect deep structures. In the most severe cases, reduced cardiac output and hypotension result in such profound and prolonged bradycardia that it causes damage to vulnerable regions of the brain even before other systemic organs are affected. Thus, high metabolic rate areas like deep nuclei and cortical areas of the brain are affected (Figure 1).

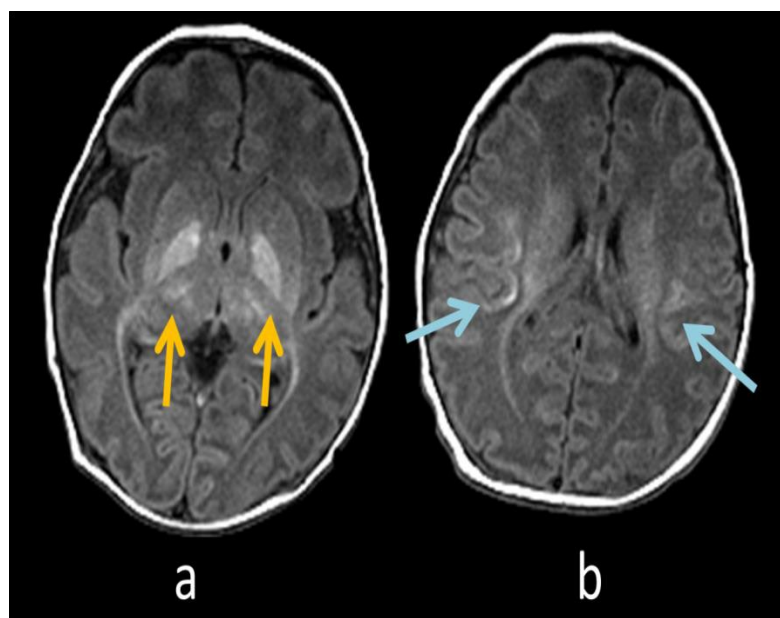


Figure 1: Brain Lesions from Acute Hypoxia Axial T1-weighted magnetic resonance imaging frames in a term neonate with neonatal encephalopathy from hypoxic-ischemic injury: bilateral lesions in the basal ganglia (orange arrows) and insular cortex (blue arrows).

Hypoxic Insult Associated with Fetal Infections and Inflammations

Although the fetal response to inflammatory insults is less well understood than the response to hypoxia, it now appears certain that inflammation can sensitize the fetal brain to hypoxic injury [13] by lowering the threshold at which hypoxia triggers the process of neuronal apoptosis [14]. This can lead the fetus to exhibit damage much earlier than fetuses not exposed to inflammatory insults. In the case of infection, maternal chorioamnionitis (even subclinical) can progress to fetal inflammation, known as fetal inflammatory response syndrome [15], which is mediated by inflammatory cytokines and widespread endothelial damage [16]. Fetuses exposed to infectious/inflammatory insults may not be able to tolerate even modest levels of hypoxia (such as the physiological hypoxia during labor), resulting in neurological damage even in the absence of acidosis. Inflammation itself seems capable of causing damage by disrupting hemodynamic stability: cytokines and inflammatory mediators increase permeability at the blood-brain barrier, leading to an increase in leukocyte infiltration. This sets off a vicious cycle in which leukocytes stimulate the fetal brain's inflammatory response through cerebral chemokines, and microglia and astrocytes are stimulated to produce cytokines. This leads to brain damage. Infection can thus cause neurological injury either directly or through an alternative non-hypoxic pathway [17]. From a clinical perspective, fetal systemic inflammatory response syndrome is associated with symptoms at birth such as hypotension, seizures, the need for intubation, and multiorgan dysfunction, just like in the case of hypoxic insult.

Types of Fetal Insult

Although there may be situations of overlap, cerebral damage can be fundamentally divided into four distinct types, which will be discussed below. These four types result from various combinations

of three factors: the level of brain maturity at the time of the insult, the severity of the hypoperfusion event, and the duration of the insult [18]. The configuration of cerebral vasculature depends on the degree of brain maturity: in the immature brain, arteries extend ventriculopetally, from the surface of the brain inward, to supply the periventricular region; as the brain matures, vessels arrange themselves in a ventriculofugal pattern, from the lateral ventricles toward the parasagittal zone [18] (Figure 2). The gestational week also makes a difference in the fetus's ability to tolerate hypoxic insult, not only due to anatomical differences in vascularization but also because the brain of a healthy preterm fetus exhibits much greater tolerance than that of a full-term fetus. The differing tolerance capacity is likely related to the baseline oxidative metabolism, which increases with fetal maturation [19]. The degree of hypoperfusion determines the type of fetal response and, consequently, the clinical outcome of the hypoperfusion itself. In cases of mild to moderate hypoperfusion, blood flow to the brain is redistributed to ensure perfusion of the metabolically more active areas of gray matter, so lesions predominantly occur at the intervascular level. In cases of severe hypoperfusion, redistribution of circulation is generally not achievable, and therefore, areas that are typically more vascularized are the first to be affected by the insult, such as deep gray matter and myelinated fibers with high concentrations of neurotransmitter receptors [18]. Thus, the level of brain maturity at the time of the insult and the severity-duration of hypoperfusion determine the four types of cerebral damage: hypoperfusion with mild to moderate hypotension in the preterm fetus, hypoperfusion with severe hypotension in the preterm fetus, hypoperfusion with mild to moderate hypotension in the full-term fetus, and hypoperfusion with severe hypotension in the full-term fetus.

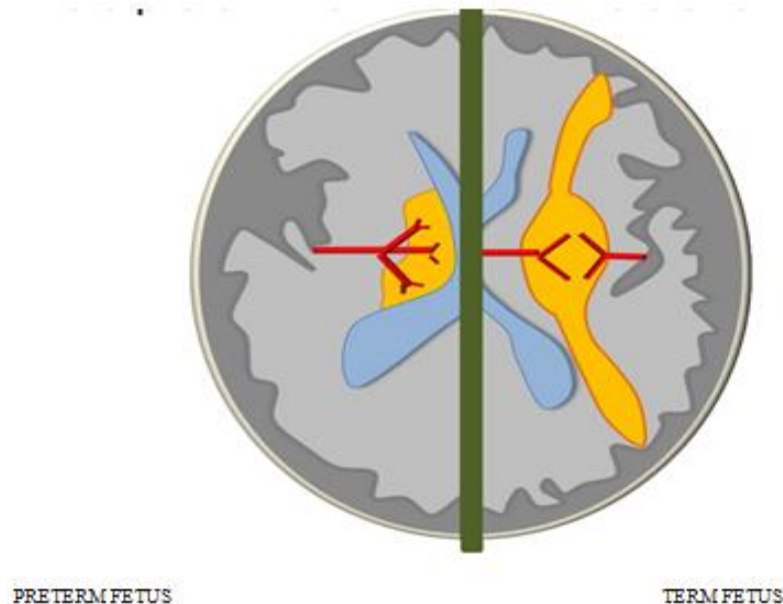


Figure 2: Cerebral Vasculature in the Preterm and Term Fetus. In the immature brain (on the left), arteries extend ventriculopetally from the brain's surface towards the interior to provide blood supply to the periventricular region; hypoperfusive damage during this stage of pregnancy will result in lesions in the periventricular area (orange zone on the left) and periventricular white matter. As the brain matures (on the right), vessels instead follow a ventriculofugal course, from the lateral ventricles towards the parasagittal area (orange zone on the right); hypoperfusive damage during this stage of pregnancy will thus lead to more peripheral lesions with subcortical white matter injury and parasagittal lesions. Adapted from Chao CP. *RadioGraphics*. 2006; 26: S159–S172.

Mild-Moderate Hypotension in the Preterm Fetus

The most common location of hypoperfusion damage in preterm neonates is the periventricular white matter, especially between 24 and 32 weeks of gestation when the white matter is mainly populated by oligodendrocyte precursors and immature oligodendrocytes [18]. The spectrum of imaging findings can indicate the ischemic evolution of brain parenchymal damage: initially, ultrasound reveals hyperechogenicity in the periventricular regions. Subsequently, approximately 2-6 weeks after the insult, the characteristic periventricular leukomalacia cysts and cavities become evident (Figure 3). The distribution of damage may vary from focal periventricular necrosis to diffuse white matter injury. Progressive periventricular necrosis with ventricular dilatation is, in fact, the final stage of periventricular leukomalacia. Brain vascularization includes long penetrating arteries (that dive deep and terminate in the periventricular white matter), basal arteries (that directly supply the periventricular area), and short penetrating arteries (that supply the subcortical white matter). Focal white matter necrosis most commonly occurs in the border zones of penetrating arteries, anteriorly and posteriorly, due to the immaturity of these vessels, involving the trigone of the lateral ventricle and areas around the foramen of Monro [20]. These lesions typically progress to coagulative necrosis and the formation of cysts or focal glial fibrosis [20]. Diffuse white matter injury can occur due to the immaturity of vessels in the immature brain (especially between 24 and 28 weeks of gestation), where there are few anastomoses between long and short penetrating arteries. Damage then occurs at the vascular border zone, with

greater diffusion into the subcortical and periventricular regions. Non-myelinated oligodendrocytes are involved with a global loss of these cells and an increase in hypertrophic astrocytes [20]. Loss of oligodendrocytes leads to a reduction in white matter volume and ventriculomegaly. The subsequent reperfusion of ischemic tissue in the context of weakened capillaries and increased venous pressure can result in germinal matrix hemorrhage with varying degrees of severity (Figure 4), ranging from subependymal hemorrhage (Grade 1) to intraventricular hemorrhage without ventricular dilation (Grade 2), intraventricular hemorrhage with ventricular dilation (Grade 3), to intraparenchymal extension with concomitant periventricular venous infarction (Grade 4). Underlying both intraventricular hemorrhages are anatomical and physiological predisposing factors: the coagulation system of the preterm neonate is still immature, and the germinal matrix consists of fragile vessels characterized by thin walls without supporting tissue. These fragile vessels tend to rupture spontaneously or in response to insults such as hypoxia, ischemia, blood pressure changes, and alterations in cerebral perfusion. Preterm fetuses also have an immature cerebral autoregulation system known as "passive pressure circulation" in response to systemic hypotension [20], making preterm neonates more susceptible to hemorrhages. Identical patterns of intraventricular hemorrhage, white matter damage, and periventricular leukomalacia can be due to fetal inflammatory response syndrome (Figure 5), rather than primarily hypoperfusion-hypoxic injury, for the reasons previously discussed in section 2.3. From a clinical perspective, the most common long-term sequela of periventricular leukomalacia is spastic diplegia,

where the lower limbs are more affected than the upper limbs. This is because the descending fibers from the motor cortex (which

regulate lower limb functions) pass through the periventricular area and are therefore more at risk of damage.

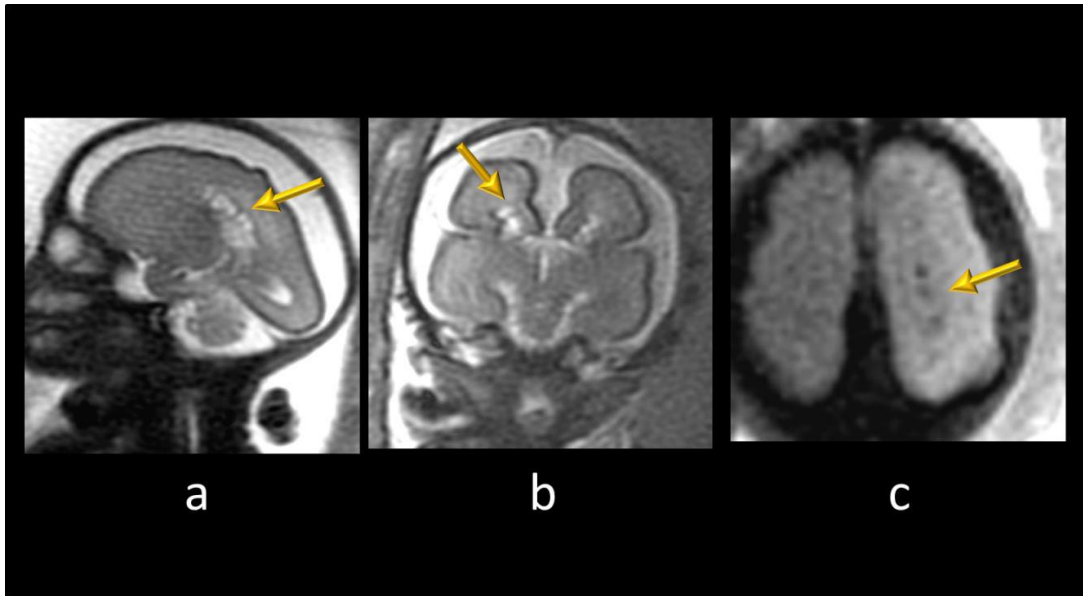


Figure 3: Periventricular Leukomalacia. Sagittal (a) and coronal (b) T2-weighted sections of a 26-week-old fetus with periventricular leukomalacia (arrows) due to hypoxic-ischemic injury following the death of the co-twin that occurred 4 weeks before this magnetic resonance imaging. Panel c (FLARE) also displays the periventricular leukomalacia area.

Severe Hypotension in the Preterm Fetus

Because the thalamus, brainstem, and cerebellum are the most metabolically active areas in the preterm brain, they are also the most susceptible to severe hypotension. This condition can also be associated with the typical lesions of moderate hypoperfusion, such as periventricular white matter lesions and germinal matrix hemorrhage [18].

Mild-Moderate Hypotension in the Full-Term Fetus

In the full-term fetal brain, damage primarily affects the gray matter. The main location of hypoperfusion damage in the full-term fetus has a parasagittal extension and involves the intervascular zone referred to as the "watershed" (between the anterior and middle cerebral arteries and between the middle cerebral and

posterior cerebral arteries) (Figure 4). Imaging diagnostics can show alterations in the cortex and subcortical white matter in the parasagittal region [18] (Figure 6). Clinically, when oxygen deficiency develops gradually, there will be signs of circulatory redistribution (alterations in renal and hepatic functions) associated with chronic brain damage. The dominant picture is symmetric infarction of central cortical areas (two oblong areas parallel on both sides of the interhemispheric fissure), often associated with basal ganglia lesions (especially the putamen) [21]. In these cases, neonates generally exhibit typical signs of severe brain injury characterized by severe spastic paralysis of all four limbs (spastic quadriplegia) [21]. Over time, children may also experience poor growth in head circumference, leading to microcephaly [21].

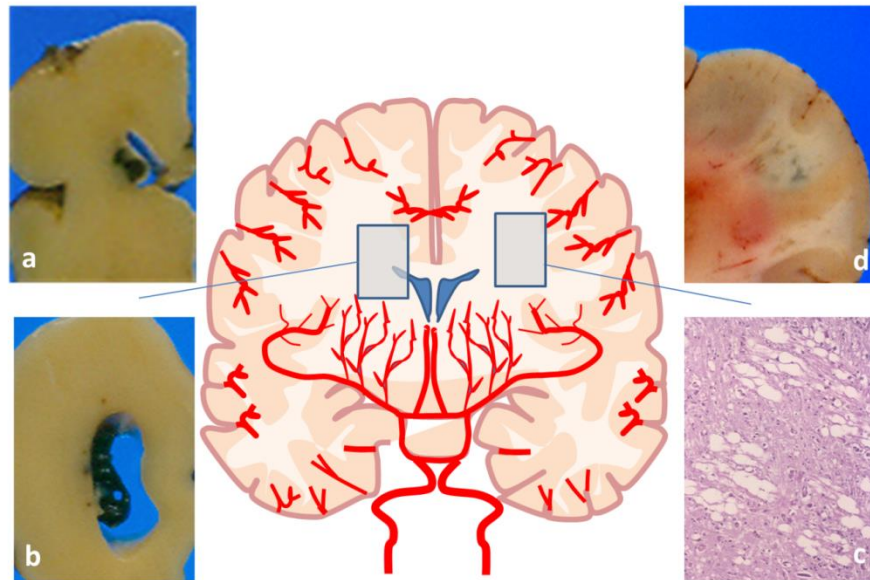


Figure 4: Examples of Brain Damage. In (a), there is a picture of hemorrhage in the germinal matrix, in the subependymal area. In (b), there are subependymal hemorrhages with extension of the hemorrhage into the ventricular space with ventricular dilation. In (c), recent parenchymal infarction is visible. In (d), areas of periventricular leukomalacia are shown.

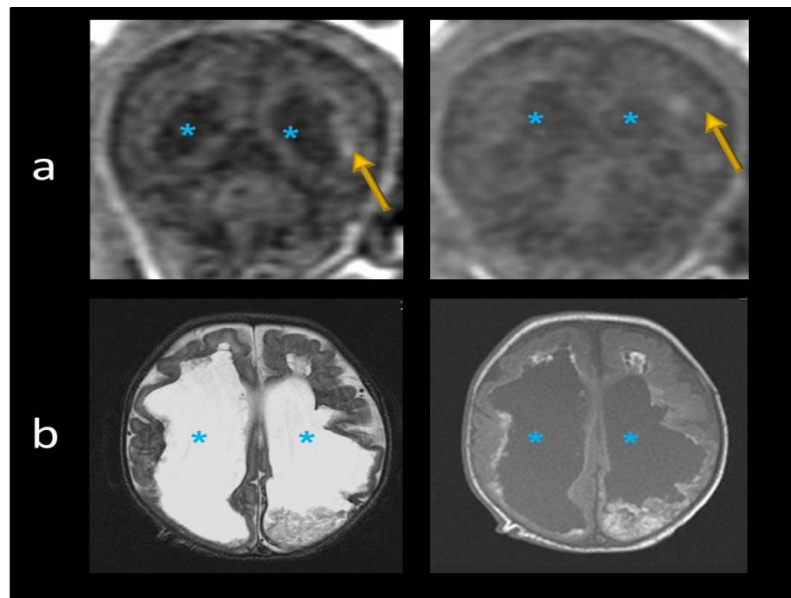


Figure 5: Periventricular Leukomalacia on an Infectious-Inflammatory Basis. In utero picture (a, T1-weighted images in a 32-week fetus) and postnatal picture (b, T1-weighted image on the left, T2 on the right) of periventricular leukomalacia associated with bilateral ventriculomegaly (asterisk) on an infectious-inflammatory basis.

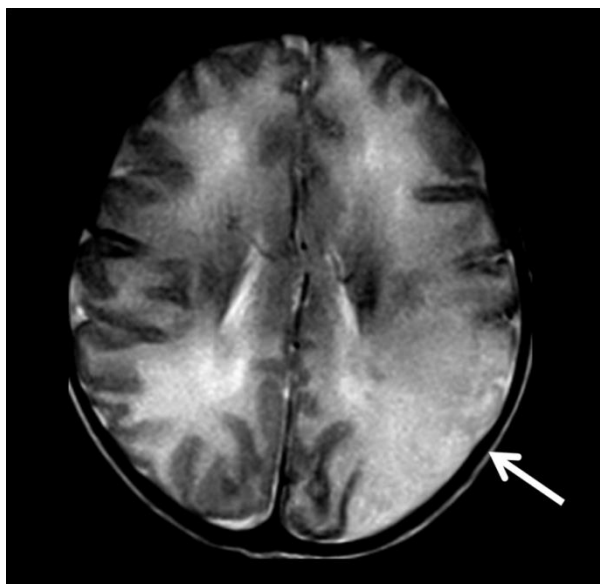


Figure 6: Hypoxic-Ischemic Brain Damage at Term Pregnancy. Axial T2-weighted section in a term neonate with a large area of hyperintensity and loss of distinction between cortex and white matter in the left parietal area, as seen in recent ischemic injury in the territory of the left middle cerebral artery (arrow).

Severe Hypotension in the Full-Term Fetus

In the full-term fetal brain, damage from severe hypoperfusion primarily occurs in areas with high metabolic rates, high blood supply, high carbohydrate metabolism, and a high number of excitatory glutaminergic neurons. These areas correspond to the ventro-lateral thalamic nuclei, brainstem, hippocampus, corticospinal tract, and sensorimotor cortex [18]. A severe acute insult that causes a complete lack of blood supply or oxygen often results in the death of the affected infants; surviving neonates often exhibit difficulties with sucking, swallowing, oculomotor paresis, and frequently respiratory and thermoregulatory problems [22]. From a motor standpoint, as evidence that the basal ganglia are the areas with the highest oxygen demand (greater even than the cortex), the typical clinical picture in these cases is a child with a normal head circumference but severe impairment in motor coordination and balance; the picture is therefore that of athetosis [21].

While the preterm brain is generally more affected in the white matter and the full-term brain is more affected in the gray matter, there can be overlapping situations: sometimes, in full-term neonates, the white matter may also be involved (corona radiata, optic radiations, and occasionally periventricular leukomalacia), while in preterm neonates, damage may extend to the gray matter [23]. A prolonged period of moderate or mild hypotension with damage to the parasagittal zone can be characterized by cortical and adjacent white matter necrosis and may involve both anterior and parieto-occipital regions. Hypoperfusion of the gyri leads to necrosis of the deep parts of the convolutions with atrophy of the gray and white matter around it (ulegyria), a damage pattern specific to the full-term or near-term fetal brain [23].

Clinical Manifestations and Neonatal Outcomes

Neonates subjected to insults in utero or during labor that compromise their oxygenation can exhibit signs of short-term and/or long-term neurological impairment. The clinical presentations encompass various manifestations, which are described below.

Neonatal Encephalopathy

Neonatal encephalopathy occurs in approximately 3 out of 1000 full-term live births [24] and is characterized by alterations in consciousness, seizures, respiratory difficulties, and depression of tone and reflexes [25]. Hypoxic-ischemic encephalopathy is a type of neonatal encephalopathy in which short-term neurological dysfunction is caused by a hypoxic event associated with acidosis. It has an incidence of approximately 1.5 out of 1000 live births [24]. Since neonatal encephalopathy also encompasses non-hypoxic causes, the diagnosis of hypoxic-ischemic encephalopathy requires confirmation of metabolic acidosis in the umbilical cord blood or neonatal circulation during the first few minutes of life [26], along with low Apgar scores at the 5th and 10th minutes, associated with an early imaging diagnosis showing evidence of cerebral edema at birth [25] (Figure 7). Multi-organ damage may also coexist, involving the renal, hepatic, gastrointestinal, and cardiac systems; however, the severity of neurological injuries does not necessarily correlate with the degree of multi-organ involvement [27]. It is important to note that metabolic acidosis at birth is not indicative of neonatal encephalopathy or adverse long-term neurological outcomes. Metabolic acidosis at birth is estimated to occur in about 0.3-2% of births; of these cases, more than 60% of neonates do not experience any difficulties in the delivery room, do not require intensive care admission, and will have an uncomplicated neonatal course. The remaining cases may require intensive care admission, mainly due to the need for respiratory support. Nevertheless, 90% of this group of children will

have a benign neurological course [28]. The severity of hypoxic-ischemic encephalopathy is classified into three forms, according to the criteria described by Sarnat [29]: severe (Sarnat grade 3, characterized by coma, flaccidity, absent reflexes, decerebrate rigidity, and depression of both parasympathetic and sympathetic systems; a condition generally associated with death or severe neurological sequelae); moderate (Sarnat grade 2, characterized by lethargy, hypotonia, strong tonic neck reflex, parasympathetic

dominance, and seizures with occasional multifocal crises; a condition at risk of death or long-term sequelae in approximately 30% of cases); and mild (Sarnat grade 1, characterized by hyperactivity, irritability, sympathetic dominance, absence of seizures, and a normal electroencephalogram with generally good prognosis). The severity levels of neonatal encephalopathy are summarized in Table 2.

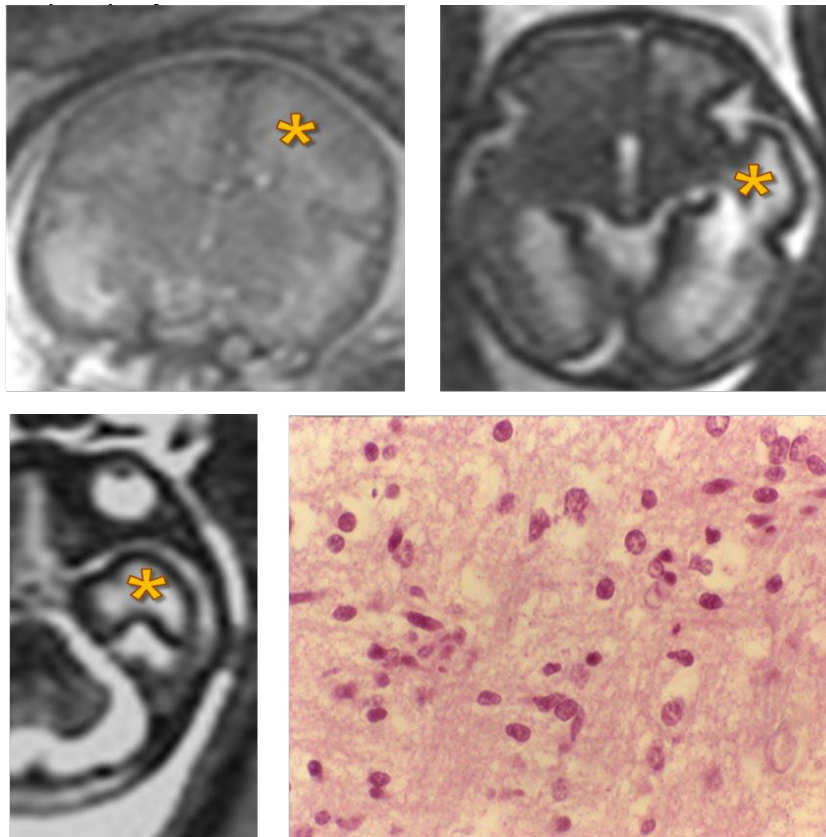


Figure 7: Radiological (MRI) and Histological Picture of Brain Edema. Images of brain edema (asterisk) visible on magnetic resonance imaging (courtesy of Dr. A. Righini, Vittore Buzzi Children's Hospital, Milan). Bottom right shows histological picture of brain edema in a term newborn who died in the early hours of life following severe neonatal acidosis and multiorgan damage.

Cerebral Palsy

Cerebral palsy is the most common physical disability in childhood and comprises a heterogeneous group of non-progressive movement and posture disorders, often accompanied by cognitive and sensory impairments, epilepsy, and secondary musculoskeletal injuries. Despite advancements in obstetric care during pregnancy and labor, the worldwide prevalence of cerebral palsy has remained stable over the past 50 years, affecting 2-3 children per 1000 live births [30].

The causes of cerebral palsy are diverse (e.g., genetic, metabolic, infectious), and hypoxia during pregnancy or childbirth represents only one of the possible etiologies. The necessary criteria to consider a correlation between birth hypoxia and neurological damage are summarized in Table 1. Many children with cerebral palsy do not have identifiable causes related to the pre- or perinatal

period. Furthermore, most children with cerebral palsy do not exhibit signs of encephalopathy at birth.

Cerebral palsy is classified based on muscle tone characteristics and limb involvement. When muscle tone is increased, cerebral palsy may be classified as spastic, further divided into unilateral (hemiplegia) or bilateral based on limb involvement. Involvement of all four limbs is termed spastic quadriplegia, while involvement of only the lower limbs is termed spastic diplegia.

If muscle tone is variable, cerebral palsy is classified as dyskinetic. Dyskinetic cerebral palsy is further subdivided based on activity and tone. If there is reduced activity associated with increased tone, it is called dystonic cerebral palsy. If there is increased activity with reduced tone, it is termed choreoathetoid cerebral palsy. If there is generalized hypotonia, it is classified as ataxic cerebral

palsy, and if there is reduced tone without ataxia, it is labeled as non-classifiable.

Spastic hemiplegic cerebral palsy is generally not associated with perinatal hypoxia but rather with infarctions of the cerebral artery or stroke, a condition that will be discussed in a dedicated section. Spastic diplegic cerebral palsy is typically associated with preterm infants and is often related to periventricular leukomalacia.

Spastic quadriplegic cerebral palsy is generally typical of full-term or near-term neonates and is associated with chronic or intermittent (lasting at least 1 hour) parasagittal cerebral injury due to acute and severe fetal hypoxia (such as in cases of acute insults like umbilical cord prolapse, massive placental abruption, maternal cardiovascular collapse, or uterine rupture). This disorder results from the selective neuronal necrosis of the hippocampus, thalami, basal ganglia, reticular formation, and cerebellar Purkinje cells, leading to lesions visible on imaging (magnetic resonance imaging) termed "status marmoratus" due to their marble-like appearance [31].

Children with cerebral palsy, especially in its more severe forms, often have other associated neurological abnormalities, such as intellectual disabilities (approximately 50% of cases), epilepsy (25-45% of cases), language disorders (40% of cases), visual deficits (40% of cases), and hearing impairments (10-20% of cases) [32].

Other organs and systems may also be affected in the child's overall clinical condition, including the somatosensory system (with stereognostic and proprioceptive impairment), genitourinary system (urinary dysfunction with a high rate of urinary tract infections), gastrointestinal system (dysphagia, esophageal and intestinal dysmotility), endocrine system (growth insufficiency

and osteopenia), and musculoskeletal system (hip subluxation and progressive hip dysplasia, scoliosis, foot deformities). Chronic lung disease is a frequent cause of death in these children due to recurrent aspiration pneumonias caused by gastroesophageal reflux and restrictive chronic lung diseases related to scoliosis [27].

A definitive diagnosis of cerebral palsy usually requires repeated observations over time and should be deferred to early childhood (from 36 months of age), especially in preterm infants. Isolated abnormalities may resolve progressively after 9 months of age, while others may become evident only over time. Spasticity may not be apparent until 6 months of age, and dyskinesia may become noticeable after 18 months [33].

Perinatal Stroke

Perinatal stroke refers to an arterial ischemic cerebrovascular event that occurs around the time of birth and manifests with clinical evidence and imaging findings of focal infarction in the cerebral arteries. It frequently occurs in the distribution territory of the middle cerebral artery and affects approximately 1 in 4000 live births. Children typically present with seizures without other signs of neonatal encephalopathy. Risk factors include congenital or acquired coagulation disorders (including antiphospholipid antibody syndrome and endothelial damage from infection), cardiac issues, placental disorders, trauma, and drug use. Although not all children affected by perinatal stroke experience long-term outcomes, 50-75% of those affected have chronic seizures or neurological deficits. Perinatal ischemic stroke is, in fact, the most common cause of spastic hemiplegic cerebral palsy.

Table 3 summarizes the clinical characteristics of different types of brain damage according to the timing of insult and the fetal response.

1. Metabolic acidosis in umbilical artery blood or in neonatal circulation during the first minutes of life (pH <7.00, BD ≥12 mmol/l, lactate ≥10 mmol/l)
2. Low Apgar score at 1st and 5th minute of life.
3. Early onset of neonatal encephalopathy of grade 2 or 3.
4. Early imaging indicating an acute and non-focal brain abnormality.
5. Types of spastic quadriplegic or dyskinetic cerebral palsy.
6. Exclusion of other identifiable causes such as birth trauma, coagulation disorders, infections, and genetic disorders.

Table 1: Criteria for Considering Hypoxia/Acidosis at Birth as a Possible Cause of Neurological Damage.

MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999;319(7216):1054-9; American College of, O. and Gynecologists. Neonatal encephalopathy and cerebral palsy:

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Parameters	Mild Encephalopathy	Moderate Encephalopathy	Severe Encephalopathy
Consciousness state*	Hyperalert	Lethargic	Stupor/coma
Motor- Muscular tone	Normal/tremors	Hypotonia	Absent
Posture	Normal	Distal flexion/ complete	Decerebrate §
Axial tone	Normal	Hypotonia	Flaccidity
Primitive reflexes (sucking or Moro)	Normal/Exaggerated	Weak/incomplete	Absent
Autonomic dysfunction of the pupils	Absent	Miosis	Mydriasis/deviation or absent reactivity

Table 2: Severity Levels of Encephalopathy.

*Hyperalert or hyperawake means the state of a neonate who is fully awake and having difficulty sleeping, with wide-open eyes that appear to be staring and reduced blinking. In the case of lethargy, the response to stimuli is complete but delayed, with an increased threshold, and there is also a reduction in spontaneous movements. In the case of stupor/coma, there is a response only to vigorous stimuli, and the response consists of limb withdrawal or assuming a decerebrate posture; corneal reflexes are absent,

and respiratory assistance is often required; # Distal flexion/ complete extension refers to an arm posture with flexion at the wrists and extension at the elbows, which is generally increased by stimulation; § Decerebrate posture refers to a rigid posture with wrist flexion, arm extension, and inward rotation of the arms, leg extension, and forced plantar flexion of the feet, extending to opisthotonos. Shalak LF et al. Paediatrics. 2003; 111:351-7 e Shankaran S et al. N Engl J Med. 2005; 353:1574-84.

Gestational Age	Cerebral Sites Most Involved	Neuropathology	Type of Neurological Damage
Preterm Fetus	Immature White Matter	Periventricular Leukomalacia and White Matter Damage	Spastic Diplegic Cerebral Palsy.
Preterm or Term Fetus (Slowly Progressive Insult)	Subcortical White Matter	Severe White Matter Damage (with symmetric infarction of central cortical areas on both sides of the interhemispheric fissure) ± deep gray matter nuclei involvement	Quadriplegic Spastic Cerebral Palsy Learning Disabilities. Reduced head size (microcephaly)
Term Fetus (Acute Insult)	Deep Gray Matter Nuclei	Lesions in Ventro-lateral Thalamic Nuclei, Brainstem, Hippocampus	Choreoathetoid Dyskinetic Cerebral Palsy Sucking, Oromotor, Oculomotor Disorders Normal head size
Term Fetus	Arterial Vascular Territory (Middle Cerebral Artery)	Focal Cerebrovascular Accident	Hemiplegic Spastic Cerebral Palsy Epilepsy

Table 3: Characteristics of Neurological Damage Based on Gestational Age.

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