

HYPOXIC ISCHEMIC ENCEPHALOPATHY IN THE NEONATAL PERIOD, EVALUATION WITH MAGNETIC RESONANCE

Encefalopatía hipóxico-isquémica en el periodo perinatal, evaluación por resonancia magnética

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Summary

Hypoxic ischemic encephalopathy has an incidence between two and four in a thousand newborns. The main causes are related to prenatal factors. Evaluation by MRI has a fundamental role to determine the type and degree of injury. In the following study we reviewed the most concise available radiologic literature and then we made a retrospective evaluation of different cases in our institution to illustrate with examples of our daily practice the different presentations of this entity according to the age of the patient, the timing of the injury and its severity. The value of MRI to characterize the different presentation of these lesions in the perinatal period was confirmed.

Resumen

La hipoxia perinatal es una condición médica que tiene una incidencia de dos a cuatro casos por cada mil nacidos vivos. Las principales causas están relacionadas con condiciones que se dan en el anteparto. La evaluación por resonancia magnética (RM) es un método fundamental para determinar el tipo y extensión del compromiso. Se realizó una revisión de la literatura radiológica disponible y posteriormente una evaluación retrospectiva de los pacientes de nuestra institución con el fin de ilustrar, con ejemplos de la práctica diaria, las diferentes presentaciones de dicha entidad, según la edad del paciente al momento de la lesión y el grado de la misma. Se confirmó la utilidad de la RM para caracterizar las diferentes lesiones secundarias a la hipoxia en el periodo perinatal.

1. Introduction

Perinatal hypoxia is a condition that occurs when the supply of glucose and oxygen to different tissues of the body is deprived, causing an energy failure, triggering a cascade of biochemical events that lead to

dysfunction and cell death. The intensity of the initial lesion will determine the mode of cell death, with severe damage resulting from necrosis and moderate lesions resulting from apoptosis (1, 2).

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These events may occur in utero or during birth, also known as intrapartum asphyxia. Up to 23% of deaths in the neonatal period are directly related to hypoxic-ischaemic injury (3).

This article will describe the most significant magnetic resonance imaging (MRI) findings in term or preterm newborn patients, and the extent and duration of hypoxic lesion - sustained and mild to moderate, or short and deep - illustrated by examples from studies conducted at the Instituto de Alta Tecnología Médica (IATM) (4).

2. Epidemiology

The 2005 Lancet Neonatal Survival study, which included data from 147 countries, showed that the majority of neonatal deaths occur in low- and middle-income countries (about 99% of all deaths). However, research efforts have been conducted in high-income countries. Up to 23% of neonatal deaths are associated with brain injuries directly related to hypoxic-ischaemic damage (3).

The incidence of hypoxic-ischemic encephalopathy (HIE) has decreased in recent years. Studies up to 2005 reported values of between two and four cases per 1000 live births (5), while more recent studies estimated an incidence of 1.5 cases per 1000 live births; however, there are differences between high- and low-income countries: higher-income countries show greater survival. Treatments such as controlled hypothermia (6) have been shown to be more effective in reducing mortality in high-income countries (7), compared to those with low-middle income. Less access to technologies and a lower quality of the health system could be some of the causes of this phenomenon (8).

The main causes of hypoxia have to do with antepartum conditions that vary considerably in different populations, as they are directly related to sociodemographic factors, including the socioeconomic stratum (9) and the pathologies of the mother's base. Also included are factors such as twin pregnancy, antepartum bleeding, placental factors, infertility treatments, arterial hypertension (10) and peripartum infection, which includes prolonged rupture of the membrane and maternal hyperpyrexia at the time of delivery; while only 10% of cases are due to post-natal factors, such as sepsis or respiratory distress syndrome (10-12).

3. Physiopathology and treatment

Clinical signs are evident during the days following injury; however, there are immediate signs that provide reliable information, such as intrapartum heart rate abnormalities, neonatal depression by a low APGAR scale, the need for cardiopulmonary resuscitation, acidemia, an altered electroencephalogram, and abnormalities at the initial neurological exam (11, 13).

If the damage was severe, the patient will suffer from depression of consciousness, bradycardia and apneas; if there is a cortical lesion, the patient will manifest hypotonia. If the patient survives the severe hypoxic injury, the sequelae may be quadriplegia, choreoathetosis, spastic diplegia, and quadriplegia. If the injury was mild, the patient may suffer only a slight delay in neurodevelopment (5, 11).

Patients born before term have less myelinated structures than those born at term, and the greater the myelin the greater the metabolic requirements; this aspect is important given that there are specific periods of gestation in which key structures are myelinated that are affected by the hypoxic lesion: thalamus and

globus pallidum between weeks 24 and 25 of gestation, caudate nuclei and putamens between weeks 35 and 36 (14).

The physiology of the hypoxic-ischemic lesion is complex and is still under study. The poor supply of oxygen increases the concentration of carbon dioxide (15, 16), which generates acidosis and a decrease in blood pressure, as well as the loss of normal vascular self-regulation, and results in a decrease in cerebral perfusion in patients born at term.

In preterm born patients, the mechanisms of cerebral blood flow regulation are immature so they suffer a failure in self-regulation and a flow called passive pressure flow (17).

The duration of hypoperfusion is a critical factor, as short episodes of hypotension (less than 8-10 minutes) have no major side effects. On the other hand, hypoxia can alter capillary permeability, and the reperfusion of these capillaries can break blood vessels, which generates intracranial or intraventricular hemorrhage in preterm patients. In addition, when the cell membrane is damaged, excitatory neurotransmitters are released, mainly glutamate. For this reason, places with higher concentrations of glutamate and higher energy demand, such as grey matter structures, are more susceptible to hypoxia. Some cells with programmed death may take longer to die, so the lesion will persist even though the hypoxia state has been reversed (5, 11, 18-20).

The brain of newborns is resistant to hypoxia and can use other substrates, such as ketone bodies, which minimizes or prevents brain damage, provided there is normal brain flow, so that hypoxic injury in newborns is more related to hypoperfusion than hypoxia.

In the spectroscopy sequences, a lactate peak can be observed that reflects energy failure and a decrease in ATP. These findings begin to normalize 6 to 18 hours after the lesion and return to abnormal values within 24 hours, due to secondary energy failure resulting from damage to intracellular molecular structures, resulting in a deterioration of cellular metabolism.

Treatment for perinatal hypoxia is supportive, including controlled hypothermia (6, 21), as HIE leads to high proapoptotic oxidative stress resulting in permanent neuronal damage. In the last decade hypothermia has been implemented to modulate the inflammatory response, increase antioxidants and decrease apoptosis and autophagia.

The aim is to achieve a total body temperature of less than 33.5°C or a selective head temperature of 34.5°C within the first 6 hours of life, for three days, in order to reduce brain damage and improve the prognosis of term newborns and late preterm patients born at 35 weeks or older (15, 21, 22).

Such treatment has better evidence in patients with moderate or severe HIE, defined by the presence of lethargy, stupor, coma, abnormal tone or convulsions, evidence of peripartum HIE, with APGAR score less than or equal to 5 at 10 minutes, the need for mechanical ventilation after 10 minutes, and metabolic acidosis in arterial or cord gases at 60 minutes after birth. This evidence has been described in multiple studies and systematic reviews, as concluded by Jacobs and collaborators, who conducted a systematic review of 11 studies, with $n = 1505$ newborns (7).

Recent studies have shown that treatment with systemic hypothermia has reduced the combined rate of death or disability at 2 years by 15%, which is statistically significant and of clinical importance (23, 24).

Other strategies under study include erythropoietin as an anti-inflammatory and antioxidant molecule expressing antiapoptotic genes, neuroserpine, melatonin, N-acetyl serotonin, magnesium sulfate and nitric oxide.

Studies have shown that hypothermia has an impact on diffusion values, and it has been found that the course of reduction of mean diffusion values is delayed, with slower recovery to normal values, compared with normothermic patients. Pseudonormalization in normothermic patients is at 6-8 days versus 11-12 days for patients treated with hypothermia (25).

In this review patients are classified according to lesion severity and gestational age, focused on magnetic resonance imaging (MRI) findings.

4. Hypoxic-ischaemic lesions in term newborns

4.1 Term newborn with severe injury

A pattern of central affection predominates. The main structures affected are putamen, thalamus, hippocampus, dorsal stem and lateral geniculated nuclei. If the lesion is prolonged, the remaining cortex is affected. The main differential diagnosis is mitochondrial disease (14, 26). The diagnostic methods of choice are MRI and ultrasound, the latter with low sensitivity (27).

In MRI, diffusion sequences are sensitive during the first 24 hours with a peak of sensitivity 2 to 3 days after injury (11-14). On the other hand, sequences with T1 and T2 information may be normal in this initial period. The findings in the diffusion sequences will be restriction to diffusion in the basal ganglia, posterior putamen, ventrolateral thalamus, pre-rolandic cortex and spinal cortical tracts (5, 28).

Two days after the lesion, findings will be found in sequences with T1 information with high signal and in sequences with T2 information with low signal. Subsequently, high signal will be found in sequences with T2 information (10, 27).

The diffusion sequences will have a pseudonormalization at the end of the first week, in which the sequences with T1 and T2 information will be more useful (5, 10, 28) (figure 1).

4.2 Term newborn with prolonged moderate lesion

The affected structures will be the bark and the white substance in the bordering territories. This is explained by the system short-circuiting vital structures, such as the stem, thalamus, basal nuclei, hippocampus and cerebellum, at the expense of the cortex and white matter (28-30). On physical examination, patients will have weakness, spasticity and convulsions (30).

MRI findings will be initially evident in diffusion sequences in which restriction will be observed in the cortex and sometimes in the white substance in bordering territories (13, 18, 28, 31).

48 hours after the lesion, the findings will be evident in sequences with T2 information, with bark edema and loss of cortical-subcortical differentiation. Follow-up studies will show loss of volume: thinning of the bark and white substance (18, 28, 31) (figure 2).

5. Hypoxic-ischaemic lesions in those born before term

5 % of patients born before 32 weeks and up to 19 % of those born before 28 weeks suffer from cerebral palsy. This is because they are exposed to more events associated with hypoperfusion, such as persistent ductus arteriosus, sepsis, respiratory distress and poor self-regulation. Diagnosis is difficult, since the signs can be confused with neurodevelopmental immaturity. Additionally, these patients have poor self-regulation (32).

5.1 Deep hypoxic injury, from a severe episode of short duration in preterm infants

The lesions are mainly found in the deep grey substance (base nuclei and thalami) and on the stem. The affected regions are similar to that described in those born at term, but with more severe thalamus involvement, especially if the patients are extreme preterm (14, 29).

In MRI, cavitation may be observed initially and then loss of volume, rarely associated with gliosis in these regions; the perirondic cortex tends to be less affected. These lesions may also be associated with haemorrhages of the germinal matrix. The diagnostic aids of choice are ultrasound and MRI (10, 14, 19).

Transfontanellar ultrasound shows hyperecogenicity in the affected structures; MRI is the most sensitive and specific method in these cases. In the diffusion sequences, restriction can be observed in the first 24 hours, although the findings are more evident after 3-5 days. Then, an extension of T2 in thalami and basal nuclei will be given 48 hours after the lesion; after three days the shortening of T1 is evident (high signal in sequences with T1 information) and later the shortening of T2 to seven days (5, 10, 28) (figure 3).

5.2 Mild to moderate hypoxia lesions in preterm infants

Mild to moderate perinatal hypoxia in preterm infants is divided into two types of lesions that may occur alone or together.

5.2.1 Germinal matrix hemorrhage (GMH) and intraventricular matrix hemorrhage (IVH)

Its incidence is inversely proportional to weight and gestational age, reaching values of up to 25% in patients weighing less than 2 kg (33, 34).

Most IVH is associated with GMH. The cells that give rise to the neurons and glia are located in the ventricular walls, and are much more active during the first and second semesters. They then involute, almost completely by 34 weeks of gestation (5, 34).

The last region to involute is the caudotalamic cleft; it is currently believed that this is due to a greater vasculature in this region. The capillaries are larger and with a simple epithelium, without layers of collagen or muscle. Additionally, they have more mitochondria, i.e. high energy requirements. Hypoxia damages these capillaries and then, with reperfusion, hemorrhage appears (5, 33, 35).

GMH are divided into 4 types. The greater the degree, the greater the mortality (Table 1) (Figure 4).

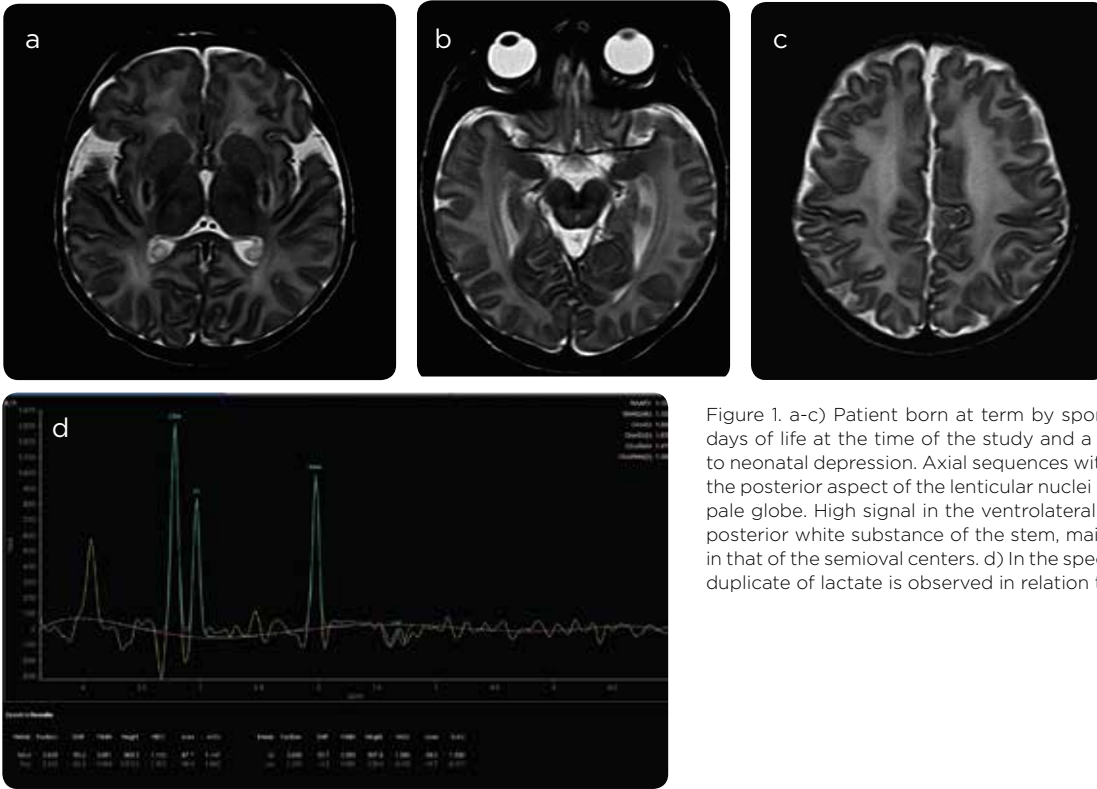
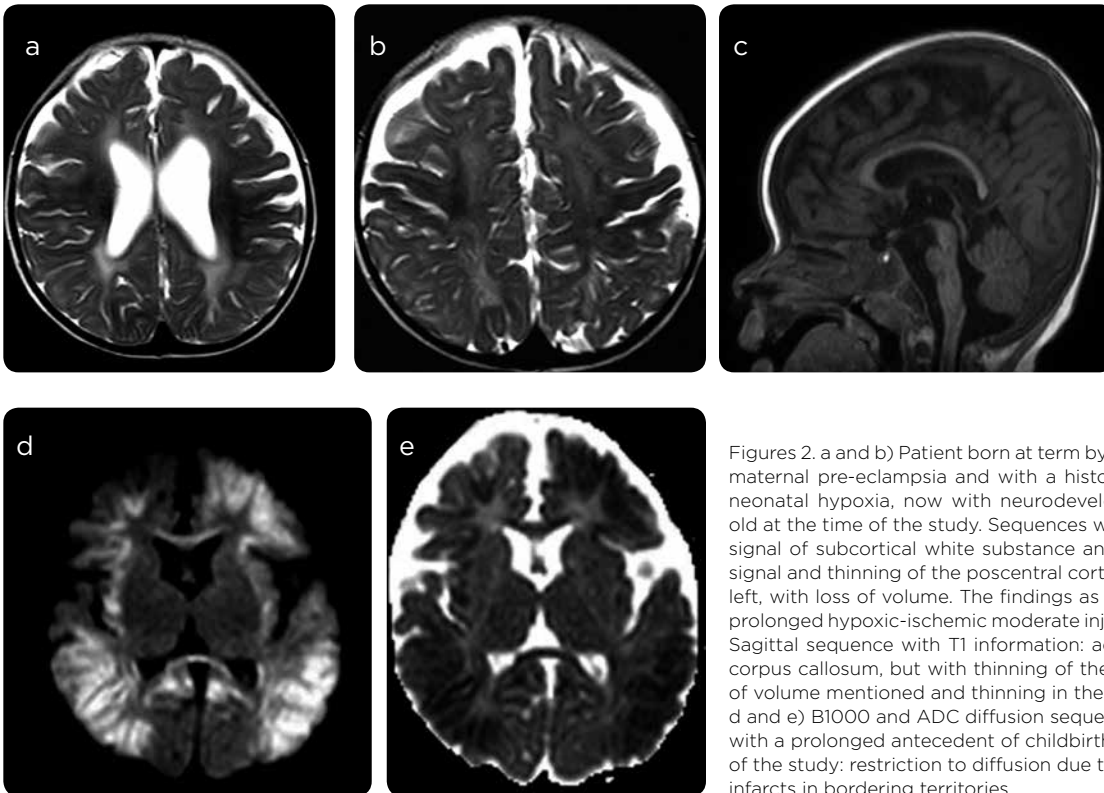


Figure 1. a-c) Patient born at term by spontaneous vertex birth, with 19 days of life at the time of the study and a history of severe hypoxia due to neonatal depression. Axial sequences with T2 information: low signal in the posterior aspect of the lenticular nuclei involving the putamen and the pale globe. High signal in the ventrolateral nuclei of the thalamus, in the posterior white substance of the stem, mainly in the periaqueductal, and in that of the semioval centers. d) In the spectroscopy sequences, inverted duplicate of lactate is observed in relation to severe hypoxia.



Figures 2. a and b) Patient born at term by caesarean section, by severe maternal pre-eclampsia and with a history of moderately prolonged neonatal hypoxia, now with neurodevelopmental delay, ten months old at the time of the study. Sequences with axial T2 information: high signal of subcortical white substance and semioval centers and high signal and thinning of the poscentral cortex and upper parietal, mainly left, with loss of volume. The findings as a whole indicate sequelae of prolonged hypoxic-ischemic moderate injury in bordering territories. c) Sagittal sequence with T1 information: adequate myelination of the corpus callosum, but with thinning of the same secondary to the loss of volume mentioned and thinning in the ventral aspect of the bridge. d and e) B1000 and ADC diffusion sequences in another term patient, with a prolonged antecedent of childbirth, of 3 days of life at the time of the study: restriction to diffusion due to ischemic commitment with infarcts in bordering territories.

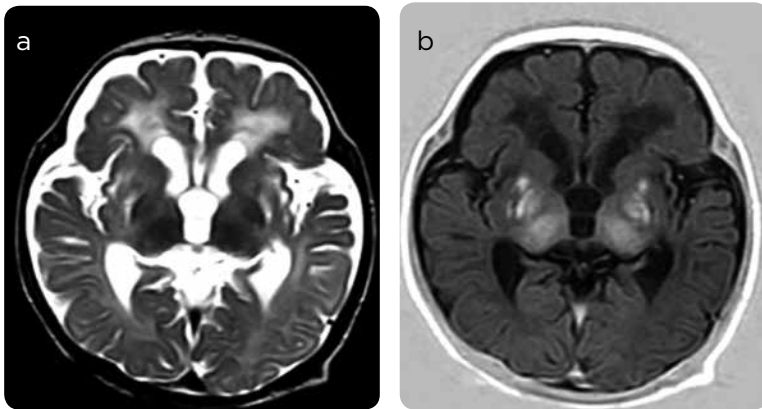


Figure 3. a) Patient born late preterm of 35 weeks by spontaneous vertex delivery, with one month of life at the time of the study and history of severe hypoxia by episode of short duration of neonatal depression requiring cardiopulmonary resuscitation. Sequence with axial T2 information: decrease in volume and increase in signal intensity of both thalami, globus pallidum and putamens. There is also loss of volume and compensatory dilation of the ventricular system. b) IR sequence with axial T1 information: the affected regions are of high signal.



Figure 4. a-c) Patient 21 days old at the time of the study, with a history of extreme prematurity by 27 weeks preterm birth. Mother with a history of diabetes and ETS and poor metabolic control. Axial sequence with T2 information, axial sequence gradient echo and sagittal BFFE: germinal matrix hemorrhage grade III with low signal within the lateral ventricles, third and fourth ventricles and secondary dilation of the ventricular system including the fourth ventricle, as observed in c. Additionally, in the infratentorial region, there is a germinal matrix zone so we can find in up to 25% of cases cerebellar hemorrhages (36).

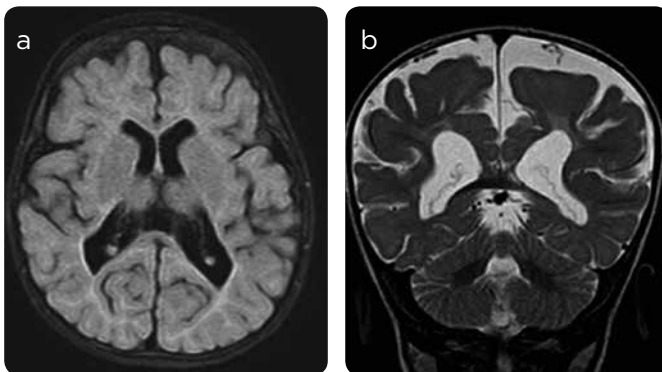


Figure 5. a and b) Patient with ten months of life at the time of the study, born preterm at 32 weeks, due to mother-induced abortion, fetal distress and neonatal depression, requires continuous positive airway pressure (CPAP). Now with neurodevelopmental delay and sequelae of periventricular leukomalacia. Axial FLAIR sequences and with coronal T2 information: high signal of the white periventricular substance that contacts the ependymal surface and loss of secondary peritrigonal volume due to sequels of periventricular leukomalacia. Additionally, there is generalized volume loss with greater prominence of brain furrows according to age.

Table 1. Classification of germinal matrix haemorrhages

Grade	Findings
I	Subependymal, caudothalamic
II	Extension to ventricles without secondary dilation of the ventricles
III	Extension to ventricles and with secondary dilation of the ventricles
IV	Hemorrhage in the parenchyma

5.2.2 Periventricular leukomalacia

Also called prematurity white matter injury; its prevalence is inversely proportional to the age of the patient.

Previously there was a theory of a circulation during fetal life from the periphery to the ventricles (ventriculopetal) and after birth, a reversal of this circulation, to be predominantly from the ependy-

mal surface to the periphery (ventriculofugal), which would explain the greater involvement by cortex hypoxia in adults (35, 37, 38).

Currently, it has been shown that preoligodendrocyte cells, precursors of oligodendrocytes, are more susceptible to oxidative damage, as are the neurons of the subplate. These cells are located mainly adjacent to the trigons and the foramen of Monro. Due to the location of the respective tracts, the sequels are visual and motor deficit with spastic diplegia, with greater involvement of lower limbs (39-41).

In the evolution of these lesions, high signal foci are initially observed in sequences with T1 information (shortening of T1) and at 3-4 days the prolongation of T2 becomes evident; then, there is a period of slight shortening of T2 at 6-7 days due to astrogliosis and focal mineralization, so the signal is not as low as in hemorrhagic lesions.

In the chronic stage there is loss of volume of periventricular white matter and semioval centres associated with irregularity of the ventricular contour that contacts the ependymal surface, mainly in the peritrigonal region. It is associated with thinning due to loss of volume of the corpus callosum, mainly with involvement of the splenium and body (26, 42-44) (figure 5).

6. Conclusions

Hypoxic-ischaemic lesions in the perinatal period depend on several factors, the most important of which are the duration of the lesion, gestational age and the risk factors antepartum, peripartum and immediate postpartum.

The role of MRI is fundamental for confirming the diagnosis and for follow-up imaging, as it is the most sensitive and specific method for identifying both the initial findings and the sequelae of hypoxic-ischemic lesion. The radiologist should be familiar with the different lesion patterns. These patterns are directly influenced by the maturation of the cerebral parenchyma.

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