

# Asphyxia from the eyes of the neonatologist

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## Proceedings

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*The last ten years, the next ten years in Neonatology*

Guest Editors: Vassilios Fanos, Michele Mussap, Gavino Faa, Apostolos Papageorgiou

## Abstract

The perinatal asphyxia occurs at a frequency of 4-6‰ in developed countries. The hypoxic-ischemic encephalopathy (HIE) has an incidence of 0.5-2‰, and is a frequent cause of death and severe disability.

Cerebral hypothermia is a well-established therapy of HIE, and its benefits have been described by systematic reviews and meta-analyses of numerous controlled clinical trials.

Authors describe their experience in implementation of cerebral hypothermia in a Neonatal Intensive Care Unit, the creation of a network to perform neurophysiologic study of asphyxiated infants  $\geq 35$  weeks gestation, potential hypothermia candidates. Neurodevelopmental prognosis of HIE infants is of paramount importance for parents. To improve the quality of prognosis and communication with the parents, two studies have been undertaken. First, EEG and magnetic resonance imaging (MRI) relationships analysis showed that the severity of the background EEG is associated with the severity and location of MRI lesion patterns in infants treated with hypothermia because of HIE. The second study aims to elucidate the relationships between MRI patterns and neurodevelopmental assessment by Griffiths scales. We found that neuroimaging findings correlate significantly with overall neurodevelopmental assessment at 12 and 24 months of life; in particular, this correlation is significant for the loco-motor and psycho-social sides.

These instrumental data, with the EEG evaluation and clinical data, allow the neonatologist to predict quite precisely the neurological outcome of an infant.

## Keywords

Perinatal asphyxia, hypoxic-ischemic encephalopathy, brain cooling, amplitude integrated EEG monitoring, neonatal emergency transport service, magnetic resonance imaging patterns.

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## Introduction

The perinatal asphyxia is an event that occurs at a frequency of 4-6‰ in countries with high levels of socio-economic development. The hypoxic-ischemic encephalopathy (HIE) has an incidence of 0.5-2‰, and is a frequent cause of death and severe disability in survivors.

Much progress has been made in preventing anoxic event through careful monitoring of pregnancies, the centralization of high-risk pregnancies in level III centers and application by trained personnel of the modern techniques of neonatal resuscitation, leading to a more specialized approach to the problem of asphyxia as a whole. In the absence of a causal therapy, the treatment of HIE has been symptomatic for years, aimed at the control of the signs and symptoms secondary to multiorgan anoxic damage. In fact, besides brain damage, there are always involvement of muscle, liver, kidney, heart that can lead to death even in 50% of cases.

Recently cerebral hypothermia (a brain cooling technique maintained for 72 hours after the hypoxic-ischemic event) has gained consensus.

Systematic reviews and meta-analyses of numerous controlled clinical trials demonstrate the benefits of brain hypothermia, especially in the less severe HIE [1]. The hypothermic treatment is safe, the incidence of side effects is low and its implementation is relatively simple from the technical point of view.

Brain damage and neuronal death depends on an evolving process that begins during the hypoxic-ischemic insult and, in severe and/or prolonged cases, continues into the next phase of reperfusion.

In the acute phase of the hypoxic-ischemic insult, cellular hypoxia causes a depletion of cellular energy metabolism (primary energy failure) with direct neuronal necrosis. The lack of oxygen prevents oxidative phosphorylation and causes the switch to anaerobic metabolism

(glycolysis) with a lower production of adenosine triphosphate (ATP). The lack of energy substrates leads to a rapid consumption of ATP reserve, the accumulation of lactic acid and an inability of the cell to maintain its functions.

However, many neurons do not die during the first phase of the insult, but after reoxygenation of the newborn, during reperfusion of the ischemic brain tissue which begins after a latency period of at least 6 hours (from 6 to 100 hours after the hypoxic-ischemic insult). In this phase neuronal death mostly occurs by apoptosis, a mechanism that may last for several days.

The hypothermic treatment should therefore be initiated within the first 6 hours of life, before the onset of the delayed neuronal damage. The decision to submit a HIE newborn to hypothermic treatment requires three consecutive steps to ascertain his clinical, neurological and electrophysiological status, that have been clearly defined by national guidelines of the Italian Society of Neonatology [2].

## Starting hypothermia in a Neonatal Intensive Care Unit

The therapy of HIE by moderate cerebral hypothermia, which in Italy was restricted to a few centers, has spread rapidly after the publication of the meta-analysis of randomized controlled trials and guidelines issued by the Italian Society of Neonatology (SIN). We consider, however, interesting to report our experience since 2001, the year of initial application of brain hypothermia at the Neonatal Intensive Care Unit (NICU) of “ASO S. Croce e Carle” of Cuneo, after thorough discussion about the risks and benefits of treatment. Based on early pilot studies, brain cooling was reserved only to newborns with severe asphyxia, with particular attention to safety. Only inborn infants were enrolled, after informed consent of the parents.

In 2005-2006 it begins the participation in the randomized trial neo.nEuro.Network [3]. We experienced ethical difficulties because on the basis of our experience we felt the difference between treated infants and historical controls. In 2006, enrollment was interrupted by the steering committee of the study after the publication of the first trials, and we continued to treat our patients with HIE following the protocol approved by the local Ethics Committee. At this time, it emerged the need to extend the hypothermic treatment even to infants in the reference area. Because of the

narrow therapeutic window, the whole process that begins with the birth of an asphyxiated infant and ends with the start of brain hypothermia needs to be clearly defined.

This requires careful preparation in all peripheral centers, coordinated by the level III NICU.

### **Towards neuroprotection: organisation of the network**

Some studies have described the problems associated with the implementation of hypothermia from the technical point of view, and have focused on organizational relationships either locally or between the NICU and area hospitals [4, 5].

We have faced and solved these problems due to the preexistence of an efficient high risk pregnancies centralization network and a neonatal emergency transport service. In a first phase starting in 2006 educational meetings were organized with the area hospitals, focused on knowledge updating and dissemination of our guidelines, drawn from the study protocol neo.nEuro.Network.

The main obstacles that emerged during these meetings were resistance to (fear of) change, lack of information on the usefulness of the treatment and experience already available in the literature, doubts about the quality of evidence and the safety of hypothermia. Previous negative experiences in the treatment of HIE (death, severe disability) and even adverse experiences in the treatment of patients in accidental hypothermia were reported.

The main objectives of these meetings were therefore the correction of fatalistic attitude toward HIE and its development, and a change of habits in the neonatal management: avoidance of hyperthermia in potential candidates, study of blood gas analysis, rational use of oxygen (start resuscitation in room air and adjust the fraction of inspired oxygen on the basis of pulse oximetry), compliance with the criteria of recruitment and observance of the 6 hours limit. An underrated aspect is the negation or non-recognition of a neonatal depression and/or encephalopathy. Sometimes, the assessment of encephalopathy and the possible indication for cooling can be neglected because of other critical situations, such as hypotension, bleeding, meconium aspiration syndrome and persistent pulmonary hypertension. It was emphasized during the meetings that the execution of cord blood or neonatal blood gas analysis (arterial or arterialized capillary samples)

is essential to identify an infant potential candidate for the brain cooling, or to suggest a no-HIE condition as a cause of neonatal depression.

Although not all babies with umbilical pH < 7 have to undergo hypothermia, all should be investigated for signs of encephalopathy.

It was therefore emphasized that not all infants  $\geq 35$  weeks gestation with pH < 7 are hypothermia candidates, but all should be studied, trying to spread in the area hospitals the concept of studying whether the patient is “encephalopathic enough to benefit from cooling” [6]. This preparatory work has generated a protocol shared by Departmental Obstetrics, NICU and Child Neuropsychiatry of “ASO S. Croce e Carle” and Pediatrics-Neonatology Units of the reference area.

### **Therapeutic hypothermia in the reference area**

Our NICU serves an area of 8,299 square kilometers with approximately 700,000 inhabitants: the surface is 50% occupied by the mountains. Local hospitals with units of Obstetrics/Neonatology are 4, for a total of over 5,600 deliveries/year.

Our area network integrates the risk pregnancies centralization network, using the network of emergency

On analyzing neonatal transport, the average travel time to reach the peripheral hospitals is approximately 1 hour.

We enroll patients with mild-to-moderate and severe HIE, and an instrumental assessment of brain function is always performed.

The SIN guidelines set the duties of local Neonatology unit as follows:

- evaluation of clinical criteria;
- emogasanalysis (cord blood, ideally paired samples, newborn arterial or capillary arterialized samples) by 1 hour of life;
- verification of inclusion criteria ( $\geq 35$  weeks gestation, birth weight  $\geq 1,800$  g);
- turn off resuscitation bed (passive hypothermia);
- measure of rectal temperature;
- communication with the NICU;
- stabilization of the newborn awaiting transport.

The team transport continues or completes stabilization of the newborn and passive hypothermia.

The passive cooling with appropriate monitoring is a simple and effective technique to start therapeutic hypothermia during transport

to the III level. It is not easy to predict the rate of temperature decrease in the newborn passive hypothermia. It has been shown that a healthy newborn, dried and wrapped passes from a rectal temperature of 37.5°C to 36.0°C within 30 minutes after birth. In case of moderate depression, if the baby breathes spontaneously, the temperature can drop to 34.5°C in 30 minutes. Therefore, an “active” cooling is rarely indicated, because the reduction of metabolism and heat production in the newborn asphyxia lowers the core temperature. Furthermore, an active cooling can inadvertently lead to overcooling. This demonstrates the importance of controlling the rectal temperature, and the fact that skin temperature does not reflect reliably the internal temperature [7, 8].

Upon arrival at the NICU it is started amplitude integrated EEG monitoring (CFM) or VideoEEG to determine the actual need of hypothermia. If treatment is not necessary, in the absence of conditions that require intensive care, the baby is transferred back to the local hospital within 24 hours, to minimize the separation of the newborn from the mother. Since the beginning of the project (period 2005-2013), 15 infants/year (median value) were studied with CFM and transferred back. During the same period, the percentage of back transport in treated outborn infants was 35%. The most common causes of back transport failure include prolonged hospitalization (intensive care, mother already discharged from Obstetrics Unit), organizational difficulties, and refusal of parents, depending on obstetrical history.

### Prognosis of hypoxic-ischemic encephalopathy

The most important question addressed by the parents to the neonatologist in the early hours of the infant's life, is the formulation of a prognosis both in terms of survival and in terms of permanent neurologic sequelae. To date there is no single unique prognostic marker, but it is the sum of the information coming from some instrumental examinations and clinical neurological assessment that allows to comment on the future of the child.

EEG and magnetic resonance imaging (MRI) are useful tools to assess the severity of brain injury and to provide prognostic information in asphyxiated newborns. We analyzed the relationship between neonatal serial EEG, severity and location of brain lesions on MRI in infants undergoing hypothermia, following a hypoxic-ischemic injury.

#### *A first study: 48 term newborns treated with hypothermia*

Forty-eight term newborns treated with hypothermia were studied. VideoEEG serial recordings were taken at 6, 24, 48 and 72 hours and during the second week of life. Brain MRI was performed at the end of the second week of life and correlated with EEG. Results showed that EEG improved during the first few days. At the first registration 25 children showed a severe or very low EEG amplitude pattern, while at the 2<sup>nd</sup> week only 7 showed these patterns.

MRI in 21 children showed a predominant damage to basal ganglia and thalami, 4 infants showed a predominant focal thalamic lesion and 23 had normal imaging or only mild white matter abnormalities. The severity of the EEG pattern has been associated with the odds to have MRI lesions in the basal ganglia, thalami, white matter, internal capsule, but not at cortex. Infants who showed only minor EEG abnormalities in the first two days had no basal ganglia and thalami MRI lesion.

The persistence of a discontinuous EEG recording at the 2<sup>nd</sup> week is always associated with damage to the basal ganglia and thalami. The severity of the background EEG is associated with the severity and location of MRI lesion patterns in infants treated with hypothermia because of hypoxic-ischemic encephalopathy [9].

The EEG can give much information, especially after the end of hypothermia and after the first week of life.

#### *A second study: 68 asphyxiated term infants undergoing hypothermic treatment*

In a subsequent study, we investigated the most interesting and less known topic, that is the prognostic value of brain imaging performed in the second week of life.

Morphological patterns were recognized and classified into 5 categories, which would be extremely reliable outcome predictors [10]:

- pattern I: lesions of the basal ganglia and thalami associated with severe white matter damage;
- pattern II: lesions of the basal ganglia and thalami with mild or moderate alterations of the white matter;
- pattern III: isolate thalamic lesion;
- pattern IV: moderate white matter damage;
- pattern V: slight damage of the white matter or normal findings.

Preliminary data suggest that the determination of the resonance pattern is highly prognostic with respect to outcome death or severe cerebral palsy [11].

The integration of data from neuroimaging and neurodevelopmental assessment thus provides a useful tool to guide clinical choices and the information to be transmitted to the parents. According to the study of Okerefor et al., in fact, no infant with mild or moderate alterations in cortical or white matter undergoes death. Those who have cerebral palsy (CP) typically show an imaging framework compatible with pattern I or II; the severity of the lesions in the basal ganglia correlates with the severity and nature of the CP [10].

Approximately 50% of infants with lesions of the basal ganglia shows associated injuries of white matter; the severity of this involvement is reflected in the severity of cognitive outcome [12].

In addition, changes in the signal level of the posterior arm of the internal capsule associated with lesions of the basal ganglia and thalamus are an important predictor of motor outcome abnormalities [13].

We studied 68 asphyxiated term infants undergoing hypothermic treatment at our NICU during the period between 2001 and 2010.

The neurological outcome was classified as normal (outcome 0 – no neurological sign) or as cerebral palsy or death event (outcome 1). The evaluation was performed by Griffiths neuromotor scale, divided into quotient of total development, and subscales A (loco-motor), B (personal-social), C (language-communication), D (eye-hand coordination), E (performance).

The neurological outcome was assessed as related to the individual MRI patterns described above, which were in turn grouped into two groups: severe damage (patterns I and II) and moderate damage (patterns III, IV and V).

At 12 months of age, 20% of patients had outcome 1 (death or paralysis) and 80% of patients outcome 0 (no neurological signs). At 12 months overall assessment with the Griffiths neuromotor scale was significantly lower in patients with severe MRI injury compared to patients with moderate impairment; the lowest scores are found in the subscales A and B. There was a statistically significant correlation for subscales A, B, C, D; on the contrary there was no statistically significant correlation for the subscale E.

Among patients with pattern I, 82% had an event death or paralysis at one year. This percentage

becomes 25% for patients with pattern II and zero for patients with pattern III, IV or V.

Even at 24 months of life overall neuromotor assessment with the Griffiths scale was significantly lower in patients with severe MRI injury compared to patients with moderate impairment. There was a statistically significant correlation for subscales A and B; on the contrary there is no statistically significant correlation for subscales C, D and E. At 24 months assessment, 28% of patients had outcome 1 and 72% of patients outcome 0. Among patients with pattern I, 83% had at 2 years an event death or paralysis. This percentage becomes 33% for patients with pattern II, 50% for pattern III (2 patients only), 14% for the pattern IV, and 4% for the pattern V.

Grouping the patients with pattern I and II on one side (severe impairment) and those with patterns III, IV and V on the other (moderate damage), 91% of patients with moderate impairment has a normal outcome versus 33 % of patients with severe impairment ( $p = 0.00002$ ).

Neuroimaging findings correlate significantly with overall neurodevelopmental assessment at 12 and 24 months of life; in particular, this correlation is significant for the loco-motor and psycho-social sides.

These instrumental data, with the EEG evaluation and clinical data allow the neonatologist to predict quite precisely the neurological outcome of an infant, thus allowing a more accurate communication to parents [14].

## Conclusions

The neonatal HIE is an uncommon condition.

Infants with HIE should be evaluated (with neurological examination and CFM) by regional centers with sufficient experience of therapeutic hypothermia and management of associated clinical problems. For this reason it is important the creation of an area network to transfer outborn asphyxiated infants to the NICU.

It is appropriate to minimize the separation of the newborn from the mother, so it is crucial to strengthen the network of back transport already operative for other categories of hospitalized infants.

Good communication throughout the process and the back-transport strengthens the relationship between NICU local teams, improves the perception of teamwork by the parents and avoids inappropriate admissions to the NICU. Formulation

of the neurodevelopmental prognosis requires the integration of clinical and instrumental data and a thorough interdisciplinary follow-up.

### Declaration of interest

The Authors declare that there is no conflict of interest.

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