Management Options In Neonatal Encephalopathy

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Abstract

Neonatal encephalopathy is important for its association with significant morbidity and mortality in the newborn period as well as chronic handicapping conditions later in life. It most commonly occurs following perinatal asphyxia and causes significant brain damage. Although, it is characterized by specific clinical and neuroimaging features, the management of the condition is largely supportive. Recent advances in the pathophysiology of neonatal encephalopathy include the role of increased cytosolic influx of calcium ions, excitatory amino acid neurotransmitters and mediators of inflammation like nitric oxide and free radicals in the disruption of neuronal metabolism thus, resulting in widespread neuronal deaths. The role and clinical applicability of these pathophysiological proposals in selecting management options for neonatal encephalopathy are discussed.

INTRODUCTION

Neonatal encephalopathy (NE), formerly known as Hypoxic - ischaemic encephalopathy (HIE) is a major challenge in newborn care worldwide. Literatures suggest that it is a major cause of perinatal morbidity and mortality as well as a cause of post-neonatal neurologic deficits.[1] There are many confounding issues surrounding the definition, aetiologies and scope of NE which have often made it a matter for litigations in the developed world.[2] While the developed world is pre-occupied with defining the precise basis of NE, the developing world still gropes with the occurrence of perinatal asphyxia which is widely believed to be a major cause of NE. Perinatal asphyxia remains a topical issue in health circles in the developing world.[3,4,5] No doubt, there may be other yet undefined mechanisms behind NE.

Although, hypoxaemia and circulatory changes remain central to the pathogenesis of NE, the precise mechanism by which these hypoxic and ischaemic situations result in NE is still largely unknown.[2] However, there are new ideas of the pathophysiology of NE and these have yielded new management options which are aimed at preventing further brain damage after NE. This paper aims to highlight the clinical applicability of some of these new developments about the pathophysiology and management of NE.

NEONATAL ENCEPHALOPATHY

This is a state of acute neurologic dysfunctions resulting from the effects of perinatal asphyxia on the brain tissue. The constellation of cerebral hypoxic and ischaemic changes which follows perinatal asphyxia results in increased cerebral blood flow, cerebral oedema and massive cellular necrosis involving the cortex, basal ganglia and brain stem. Intraventricular or intracerebral haemorrhages may also occur.

Depending on the extent of cerebral involvement, NE presents in different shades of severity described by Sarnat and Sarnat.[6] However, the major clinical presentations include severe central nervous system depression and abnormalities of respiration, muscle tone and deep tendon reflexes.

Neuroimaging features of NE include cerebral oedema and haemorrhages within the first one week of asphyxial insult while cerebral necrosis and atrophy occur subsequently. The resuscitation of the asphyxiated infant is followed by a therapeutic window where the infant may appear grossly normal despite an on-going brain damage. Therefore, steps need to be taken to prevent secondary brain damage that occurs in the therapeutic window. The handling of this therapeutic window determines the outcome of NE. The outcome includes mortality in about 20% and neurologic sequelae in another 45%. These neurologic sequelae include handicapping motor and sensorial dysfunctions like cerebral palsy, seizure disorders, mental retardation, deafness and speech defect.

PATHOPHYSIOLOGY

Compromise in the cerebral blood flow is the basis of NE; this is usually accompanied by poor tissue oxygenation and

perfusion resulting in ischaemic tissue damage. Although knowledge is limited in terms of defining with precision, the point at which a foetus or newborn baby suffers the hypoxic – ischaemic insult causing the NE,[2] the mechanism of neuronal damage in NE have been elucidated to be due to either or all of dysregulation of cerebral blood flow, increased anaerobic metabolism, decreased energy stores, increased excitatory amino acid neurotransmitters, calcium binding abnormalities, nitric oxide formation and generation of free radicals.

Hypoxaemia : This may occur in - utero following placental insufficiency or postnatally from either respiratory or cardiac insufficiency. The brain has a high metabolic rate despite a relatively poor energy reserve. When oxygen supply is low, the brain Adenosine Triphosphate (ATP) falls severely and energy dependent processes like neuronal activities cease too. In addition, hypoxaemia causes reduced glucose uptake, increased glycolysis, increased lactate production and reduced ATP. Initially, lactic acidosis leads to cerebral vasodilatation and increased supply of substrate but later on, increasing tissue acidosis leads to reduced glycolysis, loss of vascular autoregulation and reduced substrate supplies.

Ischaemia Bradycardia and hypotension occur following systemic hypoxia and this is meant to maintain the cardiac output. This initial circulatory response also results in shunting of blood flow away from apparently less-important organ-systems like the kidneys, liver, intestine, lungs and skeletal muscles to the heart, brain and adrenal glands. When this hypoxic – ischaemic state persists, the cardiac output falls, systemic acidosis increases and the cerebral autoregulation mechanism is lost. Thus, cerebral perfusion reduces or increases in consonance with the systemic circulation and this predisposes parts of the brain to infarction.

Cyto-toxic cascade: Central to the pathogenesis of NE is the formation of cerebral swelling which also reduces cerebral perfusion leading to infarctive damage to the neurones. Loss of cerebral autoregulation may explain the cerebral oedema. It is also likely that the involvement of inflammatory reaction mediators may cause increased capillary permeability and oedema.

When the hypoxic – ischaemic situation persists, the ATP stores are depleted and this results in excessive neuronal membrane depolarization. Thus, excitatory amino acid neurotransmitters like glutamate are released excessively at the synaptic clefts. The latter leads to increased calcium influx into the cells under the mediation of membrane receptors like N-methyl D aspartate (NMDA) and - amino 3- hydroxyl-5 methyl - 4 isoxazole propionate (-AMPA). The intracellular calcium influx activates lipases, nucleases and proteases resulting in cellular injury.[7] It may also be responsible for increased nitric oxide production and increased generation of free radicals. Ischaemic injuries are also known to cause the release of xanthine oxidase and formation of xanthine.[8] The latter is known to play a role in the formation of free radicals which damage neuronal membranes and disrupts cytocellular structure and functions resulting in cell deaths.[9]

MANAGEMENT

Prevention remains the best tool in the management of NE. Health education to influence the utilization of quality prenatal and obstetric services may improve the outcome of high-risk pregnancies and reduce the occurrence of perinatal asphyxia. Health workers must be trained to properly identify features of abnormal labour particularly, foetal distress and arrange prompt materno-foetal referral. Every delivery must be attended by people skilled in the resuscitation of newborn babies to assist with the establishment of spontaneous respiration as soon after birth as possible.[10] Immediate post-delivery newborn care must also be optimal to prevent metabolic derangements particularly hypoglycaemia and acidosis.

The management of NE is largely supportive. Oxygen therapy and assisted ventilation (if necessary) may be required to maintain tissue oxygenation and perfusion. The arterial blood gases must be monitored since the partial pressure of carbon dioxide (PCO_2) influences the tone of cerebral vessels and so determines the risk of cerebral tissue infarction or haemorrhage. The arterial blood pressure must also be closely monitored in the face of lost auto regulation of the cerebral circulation. It is also important to monitor the serum electrolytes and urea profile since poor renal perfusion may result in pre-renal type of renal insufficiency. The random blood glucose should also be frequently monitored to detect hypoglycaemia. Hypoglycaemia should be corrected with 4 to 5mL/ kg of 10% Dextrose-in-water intravenously followed with 10% Dextrose-in-water maintenance infusion at 5 to 8mg/ kg/ minute. The correction of metabolic acidosis is controversial. However, correction may be effected with 2mL/ kg of 8.4% Sodium Bicarbonate solution administered slowly intravenously.

Normal tissue perfusion is important during NE hence,

shock should be adequately treated. Fluid restriction is not necessary within the first 24 hours of life because cerebral oedema does not start until after 24 hours in full term babies. Fluid restriction to between 75% and 80% of normal maintenance requirement is adequate to manage cerebral oedema. Mannitol and dexamethazone have no proven efficacy in reducing cerebral oedema in NE. The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) may complicate NE, hence fluid restriction must be instituted when features of SIADH like hyponatraemia, plasma hyposmolality and elevated urinary electrolytes are present.[11]

Seizures increase oxygen consumption. Phenobarbitone aborts and prevents seizures; it also reduces cerebral metabolism and oxygen consumption.[12] Given in high doses (40mg/ kg intravenously), phenobarbitone had been shown to reduce the incidence of seizures in NE and also improved neurologic outcome at 3 – year follow up.[12] Phenytoin is equally useful in this wise. Hypocalcaemia may complicate perinatal asphyxia and may also cause seizures even in the absence of NE. Thus, efforts should be made to correct it with 2mL/ kg of intravenous 10% Calcium gluconate given with electrocardiographic monitoring.

The mainstay in the treatment of NE is the prevention of subsequent brain damage. Magnesium sulphate has been shown to be neuroprotective because magnesium antagonises excitatory amino acids and NMDA receptors.[13] It is known to improve the outcome of babies with perinatal asphyxia if administered soon after birth. In the presence of radiological evidences of antepartum occurrence of NE, it is unlikely that magnesium sulphate can still be effective because these glutamate antagonists only benefit babies with fresh ischaemic insults.[14] Therefore, radiological screening of high-risk pregnancies for evidences of antepartum NE may be incorporated into routine labour management.

Calcium channel blockers inhibit calcium influx during ischaemic episodes thus preventing the activation of enzymes which destroy cellular membranes and the generation of free radicals.[15] The blockage of calcium influx is of great research interest since asphyxial injury is also known to cause hypocalcaemia via calcitonin release and calcium supplementation is traditionally required in the management of asphyxia. Flunarizine has been shown to be effective in preventing cerebral damage if administered before ischaemic insults in rats but trials in human adults have been disappointing.[16] Allopurinol, the inhibitor of the enzyme xanthine oxidase, prevents the production of xanthine and free radical superoxide. Allopurinol has been shown to decrease mortality among asphyxiated babies probably via the prevention of free radicals generation and increased cerebral blood flow.[17] No significant adverse effects had been reported. The anti-oxidants, ascorbic acid (Vitamin C) and - tocopherol (Vitamin E) are also neuroprotectors. While the latter prevents the destructive actions of free radicals, the former acts as a neuromodulator, preventing the activation of NMDA by neurotransmitters.[8] Lately, cerebral cooling or selective cerebral hypothermia was found to be neuroprotective.[18] It reduces oxygen consumption, metabolic rate, the accumulation of excitatory amino acids, nitric oxide synthase activity production of cytotoxic cytokines and delayed cell death by apoptosis. Moderate cerebral cooling (core temperature reduced by 4 to 6°C), when applied within 3 hours of ischaemic insult, was found to be effective in preventing secondary cerebral tissue damage and hence, improving the outcome. This is an improvement over the initial trials of whole body hypothermia (body temperature 32 to 34 °C) for up to 72 hours.[19] The procedure was also reported to be safe.

Though, still at the experimental stage, the monosialogangliosides, [8] the nerve growth factors, [20] anti-NMDA receptor immunization [21] and gene therapy with specific proto-oncogenes [22] have also been identified to be neuroprotective. The clinical suitability is yet to be convincingly determined.

CONCLUSION

The pathophysiology of NE appears to be dependent on multiple factors although the final pathway is the same – cell death by apoptosis. It is attractive to consider a combination of the options outlined for the prevention of cerebral damage after NE. This appears a heinous task since the management options involve many diverse agents. Further clinico-laboratory studies are desired to address the appropriate handling of the therapeutic window in NE.

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