Review Article

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Birth Asphyxia

Jayendera R. Gohil*, Heena Hasan**

Author's Affiliation: *Professor & Head, **Resident, Pediatrics Dept., Govt. Medical College & Sir TG Hospital, Bhavnagar - 364002, Gujarat, India.

Reprint Request: Prof. Jayendra R. Gohil, MD, Professor & Head, Pediatrics Dept., Govt. Medical College & Sir TG Hospital, Bhavnagar-364002, Gujarat, India.

E-mail: jayukids@hotmail.com

Abstract

Birth asphyxia is an important cause of acute neurologic injury, occurring in 2 to 3 cases per 1000 term live births in developed countries, with a higher incidence in less developed countries. Birth asphyxia related neonatal mortality and morbidity including long-term neuro-developmental sequele was seen in 25%-60% of survivors. It is estimated that around 23% perinatal deaths are due to birth asphyxia, with a large proportion of stillbirths. Asphyxia should not be confused with hypoxic ischemic encephalopathy (HIE) or cerebral palsy (CP) since not all asphyxiated neonates develop HIE or CP and there are other causes for the same. In this article there is description of definitions, aetiologies, pathophysiology, clinical features, basic and recent investigations, older and newer treatment of birth asphyxia.

Although there is no specific treatment for birth asphyxia only supportive treatment (fluid and electrolytes balance, oxygenation and ventilation etc.) to prevent the complications and primary preventive measures (electronic fetal heart monitoring, training to birth attendants, home based newborn care) are helpful.

In the developed world, for the HIE, hypothermia has been the only treatment that has worked somewhat (8 -18%). The preferred cooling is whole body with a heart-lung bypass or ECMO; since that is rarely available, external whole body or external head cooling is the next best option. Prevention of reperfusion injury by early (within 6 hours) antioxidant therapy seems to hold the promise for future and should be studied.

Key words:Birth Asphyxia; HIE; Hypoxic- Ischemic Encephalopathy; Neonatal Encephalopathy; Neonatal Depression.

Introduction

Birth asphyxia is a major cause of neonatal deaths, especially in rural India and in urban places where birth attendants trained in resuscitation are not available immediately. It also results into severe neurological long term morbidity; hardly any specific treatment is available. Perinataly asphyxiated newborns born in absence of trained manpower results in higher number of stillbirths. Prevention of the primary events and complications seem to be the best strategy at present.

Definition of birth asphyxia designed for use in hospital based settings require evaluation of umbilical cord p^H, Apgar scores, neurologic clinical status, and markers of multisystem organ function[1] and are not feasible for community settings.[2] The majority of neonatal deaths occur in the home without medical supervision; community-based definitions must rely on data gathered from verbal autopsy methods and use more general symptom- and sign-based algorithms. For example, the National Neonatology Forum of India has defined birth asphyxia as "gasping and ineffective breathing or lack of breathing at 1 minute after birth."[3] Such sign-based

definitions are not, however, implemented consistently, and varying study-specific definitions may affect estimation of the proportion of neonatal deaths attributed to birth asphyxia.

Regarding the definition according to American College of Obstetricians and Gynaecologists and the American Academy of Paediatrics, a neonate is labelled to be asphyxiated if the following conditions are fulfilled: (1) Umbilical cord arterial $p^H < 7$; (2) Apgar score of 0 to 3 for longer than 5 minutes; (3) Neurological manifestations (e.g., seizures, coma, or hypotonia); and (4) Multisystem organ dysfunction, e.g., cardiovascular, gastrointestinal, haematological, pulmonary, or renal system.[4]

Outcome of birth asphyxia depends on Apgar score at 5 minutes, heart rate at 90 seconds, time to first breath, duration of resuscitation, arterial blood gases and acid – base status at 10, and 30 minutes of age.[5] It is measured as short term (early) and long-term outcome. The early outcome is either death/or presence of hypoxic ischemic encephalopathy (HIE) grade I, II or III, according to Sarnat staging.[6]

Perinatal asphyxia refers to a condition during the first and second stage of labour in which impaired gas exchange leads to fetal hypoxemia and hypercarbia. It is identified by fetal acidosis as measured in umbilical arterial blood.[7]

Perinatal Hypoxia, Ischemia, and Asphyxia

These pathophyslogical terms describe respectively, lack of oxygen, blood flow, and gas exchanges to the fetus or newborn. These terms should be reserved for circumstances when there are rigorous prenatal, perinatal, and postnatal data to support their use.[7]

Perinatal/Neonatal depression is the preferred clinical descriptive term (over Birth Asphyxia by ACOG, but not in vogue) that pertains to the condition of the infant on physical examination in immediate postnatal period (i.e., in the first hour after birth). The clinical features of infants with these conditions include depressed mental status, muscle hypotonia and possibly disturbance in spontaneous respiration and cardiovascular function. These terms make no association with the prenatal or later postnatal condition (i.e., beyond the first hour) condition, physical exam, laboratory tests, imaging studies or electroencephalograms. After the first hour or so life, neonatal encephalopathy is the preferred descriptive terms for infants with abnormal mental status and associated findings.[7]

Neonatal encephalopathy is a clinical and not an etiologic term that describes an abnormal neurobehavioral state consists of decreased level of consciousness and usually the other signs of brain stem and/or motor dysfunction. It does not imply a specific aetiology, nor does it imply irreversible neurological injury as it may be caused by such reversible conditions as maternal medications or hypoglycemia.[7]

Hypoxic ischemic encephalopathy is a term that encephalopathy as described above with objective data to support a hypoxic ischemic mechanism as the underlying cause for the encephalopathy.[7]

Hypoxic ischemic brain injury refers to neuropathology attributable to hypoxia and/or as ischemia as evidence by biochemical (such as creatine kinase brain bound [CK-BB] ,elecrtophyiologic (EEG), neuoroimaging (head ultrasonography), MRI, CT or pathological (post-mortem) abnormalities.[7]

Neonatal Encephalopathy or Neonatal Neurological Syndrome[8]

- term infant <7 days at onset
- depressed consciousness level
- abdominal tone and power
- feeding difficulty
- seizure

Incidence

Birth asphyxia is an important cause of acute neurologic injury, occurring in 2 to 3 cases per 1000 term live births in developed countries, with a higher incidence in less developed countries. Birth asphyxia related neonatal mortality and morbidity including long-term neuro-developmental disorders was seen in 25%-60% of survivors.[9]

It is estimated that around 23% neonatal deaths are due to birth asphyxia, with a large proportion of stillbirths. Though the improved obstetric care has reduced the incidence of birth asphyxia in developed countries, but in developing countries, still have a higher rate, ranging from 4.6 per 1000.[10]

According to the World Health Organization (WHO), incidence of birth asphyxia is around 3% that is from 130 million newborns each year globally, around four million develop birth asphyxia, and from asphyxiated babies around 1.2 million die and the same number develop severe consequences, such as epilepsy, cerebral palsy, and developmental delay.[11]

Etiology[7]

In the term newborns may be due to impaired gas exchange across the placenta that leads to inadequate oxygen provision and removal of carbon dioxide and hydrogen to fetus. It can also occur due to secondary causes in postpartum period due to pulmonary, cardiovascular and neurological abnormality.

Etiologies of asphyxia may be multiple such as: maternal factors like hypertension, hypotension, chorioamnionitis, hypoxia from pulmonary cardiac disorders, diabetes, vascular disease, cocaine, alcohol abuse. Placental factors, uterine rupture, umbilical cord problems, foetal factors and neonatal factors are also playing an important role.

Pathophysiology[12]

Pathophysiology of hypoxic ischemic encephalopathy includes ischemia superimposed on hypoxia, which is required for injury. The injury then evolves over hours to days after the insult. Enhanced neuronal excitability with clinical seizures, abnormal EEG and encephalopathy are integral component of the cascade. Specific structures and tissues are vulnerable to injury.

Glutamate toxicity is considered to be the most important part of the pathophysiology of HIE. The Fas ligand and mitochondrial involvement are very vital. When there is lack of energy after HIE, glutamate which is generally reabsorbed from the synaptic area does not get absorbed. That in turn leads to stimulation of two glutamate receptors: the NMDA receptor and AMPA receptor. It causes injury to mitochondria. The anti-apoptotic inducing factor is generated which causes DNA fragmentation and apoptosis.

Neurotransmitted excitotoxicity happens through glutamate which in turn stimulates NMDA, AMPA and Kainate receptors. Inflammatory cytokines release like IL-1, IL-6, IL-8, tumour necrosis factor and lipopolysaccharide which can cause direct injury. Oxidative stress causes synthesis of nitric oxide and peroxynitrites. A study found that apoptosis inducing factors are responsible for cell death in men or in male child, caspases are responsible for cell death in female newborns. The cells die but they take different pathways for male and female fetuses.

The thalamus, putamen, globuspallidus, and subthalamic nucleus are vulnerable regions in the brain. These are the phases of cerebral injury over time. Secondary injury occurs between three to ten days because of failure of oxidative mechanisms, seizures, cytotoxins, swelling and excitotoxins which finally causes cell death.

Hypothermia is acting as a broad inhibitory actions on harmful cellular processes induced by HIE. People have postulated that hypothermia decreases lose of organic phosphates, slows the rates of metabolites consumption and lactic acid accumulation and reduces oxygen consumption, Reduction in astrocytosis and TNF-a, IL-6 level leading

to a reduction in neuronal loss.

The Reperfusion Period: The cascade of deleterious events that lead to cell death after insults that result in oxygen deprivation and energy failure occur primarily following termination of the insult. This is initiated by energy depletion, accumulation of extra cellular excitatory amino acids, increase in cytosolic calcium and generation of *free radicals*. This delayed death of neurons following termination of the insult has a bearing on the possibility that intervention, before the reperfusion injury period, would only, be beneficial.

Clinical Features

Neonatal Encephalopathy Grading[13]

Mild

- alternate level of consciousness-periods of lethargy, irritability and hyper alertness, no normal sleep cycle
- The infants are jittery, feed poorly
- Cranial nerves examination – normal
- Muscle tone may be increased and deep tendon reflexes are frequently increased.
- Primitive reflexes are normal exception Moro's which may be increased
- No seizures.
- Autonomic signs (Pupillary dilation and tachycardia)

Moderate - more lethargic, poor feeding, hypotonia, clonus is usually present gag reflex usually depressed, spontaneous myoclonus or extra pyramidal dysfunction. Pupils are constricted, may have bradycardia. Seizures frequently occur in 24 hours.

Severe - infant is comatose and flaccid with absent reflexes. pupils are often fixed or sluggishly reactive doll's eye reflex is absent. May have bradycardia and frequently has apnoea and hypotension.

Following etiologies should be excluded (with corresponding clinical features)

Persistent stiff baby syndrome with encephalopathy due to glycine abnormality or organic acidemia (3-methylchrotonyl CoA carboxylase def.)

- Hepatomegaly suggests tyrosenemia, heamosederosis and occasional mitochondrial disorder.
- Hiccup: Non ketotic hypergylcinemia
- Urine (smell): Maple syrup urine disease,Isovaleric acidemia

Multiorgan Dysfunction:[7]

Kidney: proximal tubule commonly affected leads to acute tubular necrosis with oliguria.

Cardiac: mainly caused by transient myocardial infarction. Absence of sinus arrhythmia (variability in the heart rate with respiration) is a sign of poor prognosis.

Gastrointestinal: increased risk of bowel ischemia and necrotizing enterocolitis.

Haematological: disseminated intravascular coagulation

Liver: inadequate glycogen stores with resultant hypoglycemia, altered metabolism, or elimation of drugs.

Pulmonary: PPHN, haemorrhage, pulmonary oedema.

Investigation[7]

Laboratory evaluation of asphyxia

Cardiac Evaluation

1. Cardiac troponin I and cardiac troponin T may be elevated (normal values are troponin I=0 to 28±0.42 µg/l troponin T=0 to 0.097µg/l).Elevation of CK-MB fraction >5 to 10% may indicate myocardial injury.

Neurological markers CK-BB may be

increased in asphyxiated newborns within 12 hours of the insult but has not been correlated with long term neuro developmental outcome.

Renal evaluation BUN and creatinine may be elevated in perinatal asphyxia. Typically elevation is noted 2-4 days after the insult. Urine levels of β2 micro globulin have been used as indicator of proximal tubular necrosis (although not routinely used), renal sonography abnormality correlate with occurrence of oliguria.

Brain Imaging

Cranial USG: is normal in 50% cases, non specific cerebral oedema, and ventricular lesion best seen.Slit like ventrical is not very specific; is present in normal new born also.Basal ganglia and thalamic echo:If hemorrhagic necrosis persist>7 days there is poor prognosis.

Doppler: anterior cerebral artery blood flow if RI<0.55 (resistive index) than poor prognosis.

If Basal ganglia and thalamus are affected then severe cognitive behaviour

White matter affected then severe cognitive behaviour

If brain stem affected then feeding problem

Cerebral Cortex: mild cognitive disorder

EEG: Spike and Waves

- IBI (inter burst interval) :on day 7 > 20 seconds, low voltage (flat)-poor prognosis .
- Diffuse cortico-thalamic necrosis has discontinuity, birth suppressive low voltage and isoelectric patterns.
- PVL (periventricular leukomalacia) - excessive sharp waves, positive vertex or rolandic.

Amplitude Integrated aEEG: reflects HIE insult. It should be done in first 6 hours (5-10mv reactive) if <5 or >10mv is abnormal. aEEG has been used to evaluate the background pattern particularly when rapid assessment is needed for determination of treatment with therapeutic hypothermia.

Computed Tomography (CT)

May be use to detect cerebral oedema or hemorrhage and eventually HI brain injury. CT is only indicated if imaging urgently needed to determine clinical treatment and neither ultrasound nor MRI is available on an emergency basis.

Magnetic Resonances Imagine (MRI)

Conventional T1, T2 weighted images are the best modality for determining the severity and extent of HI brain injury. These sequences are best for detection of brain injury after 7 – 10days.

1. Diffusion weighted imaging (DWI): can show abnormalities within hours of an HI insult that may be useful in diagnoses of neonatal HIE and an early indicated of possible brain injury.
2. Proton magnetic resonance spectroscopy (MRS): measures the relative concentrations of various metabolites in tissue.
3. Susceptibility weighted imaging may be useful for detection of haemorrhage or hemorrhagic injury.
4. MR angiography or venography may occasionally be useful if there is suspicion of vascular anomalies thromboembolic disease or sinus venous thrombosis resulting in HI brain injury.

Visual evoked potential or somato sensory potential should be done in 6 hours.

Near infrared spectroscopy (NIRS) is a direct measure of cerebral blood flow and it should be done within 48 hour. It is a research tool only.

Neonatal and early Infantile deterioration:- MSUD, Methylmelonic acidemia, Propionic acidemia, Isovolemic acidemia, Multi carboxylase deficiency, Urea cycle disorder, Non ketotic hyperglycenimia.

Many of the procedures are not possible because of critical condition of patient and not availability of bedside instruments.

Prevention of Complication

Neuroprotective strategies for hypoxic ischemic encephalopathy are

- Decreased cerebral metabolic rate caused by hypothermia
- Block NMDA receptor channel caused by magnesium sulphate
- Decreased glutamate release by adenosine
- Inhibition of voltage sensitive calcium channels by calcium channel blockers.
- Decreased free radical reactions by allopurinol, vitamin C, E and superoxide dismutase.
- Prevention of free radical formation-indomethacin, iron chelators, allopurinol, and caspase inhibitors.[12]

Human Error Most Common Cause of Birth Asphyxia: poor fetal monitoring in 50% of cases, Norwegian study shows: "In most compensated cases, poor fetal monitoring led to an inadequate supply of oxygen to the infant," concludes Dr. Andresen. "Training for midwives and obstetricians, along with high-quality audits, could help to reduce claims for compensation after birth asphyxia."[14]

Genetic Abnormalities may Cause Cerebral Palsy, a Study Suggests: "there is a widespread misconception that most cases of cp are caused by difficult delivery leading to birth asphyxia," said andres moreno de luca, M.D., research scientist at the Genomic Medicine Institute, Geisinger Health System, and lead author of the paper. "What we're finding is a growing body of evidence that suggests mutations in multiple genes are responsible for CP. in fact; we suspect these genetic abnormalities may also be the cause of some difficult births to begin with."[15]

Effect of Training Traditional Birth Attendants on Neonatal Mortality (Lufwanyama Neonatal Survival Project): a Randomised Controlled Study. Training traditional birth attendants to manage common perinatal conditions significantly reduced neonatal mortality in a rural African setting. This approach has high potential to be applied to similar settings with dispersed rural populations.[16]

Effect of Home-based Neonatal Care and Management of Sepsis on Neonatal Mortality: Field Trial in Rural India: Abhay Bang and colleagues chose 39 intervention and 47 control villages in the Gadchiroli district in India, collected baseline data for 2 years (1993-95), and then introduced neonatal care in the intervention villages (1995-98). Village health workers trained in neonatal care made home visits and managed birth asphyxia, premature birth or low birth weight, hypothermia, and breast-feeding problems. They diagnosed and treated neonatal sepsis. Assistance by trained traditional birth attendants, health education, and fortnightly supervisory visits were also provided. Other workers recorded all births and deaths in the intervention and the control area (1993-98) to estimate mortality rates.[3]

Findings: Population characteristics in the intervention and control areas, and the baseline mortality rates (1993-95) were similar. Baseline (1993-95) neonatal mortality rate in the intervention and the control areas was 62 and 58 per 1000 live births, respectively. In the third year of intervention 93% of neonates received home-based care. Neonatal, infant, and perinatal mortality rates in the intervention area (net percentage reduction) compared with the control area, were 25.5 (62.2%), 38.8 (45.7%), and 47.8 (71.0%), respectively ($p<0.001$). Case fatality in neonatal sepsis declined from 16.6% (163 cases) before treatment, to 2.8% (71 cases) after treatment by village health workers ($p<0.01$). Home-based neonatal care cost US$5.3 per neonate, and in 1997-98 such care averted one death (fetal or neonatal) per 18 neonates cared for.

Home-based neonatal care, including management of sepsis is acceptable, feasible, and reduced neonatal and infant mortality by nearly 50% among our malnourished, illiterate, rural study population. This approach could

reduce neonatal mortality substantially in developing countries.[3]

Electronic Fetal Heart Rate Monitoring Decreases Neonatal Mortality and Reduces the Event of Birth Asphyxia.[17] The results showed that in 2004, 89% of singleton pregnancies had EFM. EFM was associated with significantly lower infant mortality (adjusted RR 0.75; 95% CI 0.69, 0.81); this was mainly driven by the lower risk of early neonatal mortality (adjusted RR 0.50; 95% CI 0.44, 0.57) associated with EFM. In low-risk pregnancies, EFM was associated with decreased risk for low (< 4) 5 min Apgar scores (RR 0.54; 95% CI 0.49, 0.51), whereas in high risk pregnancies EFM was also associated with decreased risk of neonatal seizures (adjusted RR 0.65; 95% CI 0.46, 0.94).

The study demonstrates that the use of EFM decreased early neonatal mortality by 53%.

Treatment[7]

No specific treatment; only supportive measures:

1. *Ventilation:* CO_2 should be maintaining in normal range. Hypercapnia can cause cerebral acidosis and cerebral vasodilatation. This may lead to more flow to uninjured areas and relative ischemia to injured areas (Steal phenomenon). Excessive hypocapnia leads to low cerebral blood flow.

2. *Oxygenation:* Hypoxemia treated with supplement O_2 and/or ventilation. Hyperoxia may cause decrease CBF or exacerbate free radical damage. Keeping target oxygen to optimum lower levels

3. *Temparature:* Hyperthermia should always be avoided. In full-term babies the warmer may be kept switched off.

4. *Perfusion:* Cardiovascular stability and mean systemic arterial BP are important to maintain cerebral perfusion pressure.

5. *Maintain Physiological Metabolic State:* Hypoglycemia and hypocalcemia should be managed because hypocalcemia can compromise cardiac contractility and may cause seizures.

6. *Judicious Fluid Management*

SIADH (Syndrome of Inappropriate Anti-Diuretic Hormone) is often seen on 3rd or 4th day of life. Fluid restriction may aid in minimizing cerebral oedema found in SIADH, although the effect of fluid restriction on long term outcome in newborns that are not in renal failure is not known.

7. *Seizure control:*

Anticonvulsant

Phenobarbital is drug of choice, loading dose is 20 mg/kg IV. If seizure continues additional loading dose of 5-10 mg/kg may be given.

Maintenance dose is 3-5 mg/kg/day. The side effect of Phenobarbital may lead to respiratory depression and death in non ventilated newborns.

Phenytoin may be added if seizures are not controlled, loading dose of 15 to 20 mg/kg to maintenance dose of 4 to 8 mg/kg/day.

Fosphenytoin is used in place of phenytoin.

Benzodiazepines are used as third line drugs as lorazepam.

Levetiracetam have been recently use due to easy availability, efficacy and safety.

Long term anticonvulsant treatment can be weaned when the clinical exam and EEG indicate that the newborn is no longer having seizure. Other target organ injury is managed accordingly.

8. *Antibiotics:* Birth asphyxia is a risk factor for sepsis therefore antibiotics are used by majority of Indian centres. The evidence for this in full-term babies is not strong enough to justify starting antibiotics when this is the only risk factor present. The deaths and morbidity per se are not caused by sepsis. So changing antibiotics, because patient's condition has worsened, will not improve the outcome. One should strictly follow culture reports for choice of antibiotics. If sepsis prevention protocols are strictly followed then antibiotics are not to be started unless cultures are positive for bacteria. The condition birth asphyxia per se, or patient

on assisted ventilation in itself, should never be an indication. If majority babies of birth asphyxia are found to be culture positive sepsis then aseptic precautions need to be reviewed.

Neuroprotective Strategies

- Agents tested in animals with no data in human newborns include antagonists of excitotoxic neurotransmitter receptors as NMDA receptor blockade, free radical scavengers such as allopurinol, superoxide dismutase, vitamin E, calcium channel blocker ($MgSO_4$), cyclooxygenes inhibitors such as indomethacin, benzodiazepine receptor stimulation such as midazolam, and enhancers of protein synthesis such as dexamethasone.
- Hypothermia and anti-oxidants seem to show some promise.

There are new agents such as xenon and erythropoietin that have undergone preliminary phase 1 trials but there are no data supporting the use of these agents except for therapeutic hypothermia for neuro-protection.

Therapeutic Hypothermia

Decrease the risk of brain injury in newborns exposed to perinatal hypoxia. Both total body and head pulling have been shown to be safe and effective. Criteria (inclusion) for total body cooling to newborns at risk for HIE.

- Gestational age ≥ 36 weeks and birth weight ≥ 2000gm.
- Evidence of fetal distress.
- Evidence of neonatal distress.
- Evidence of neonatal encephalopathy by physical exam.
- Abnormal aEEG (amplitude integrated EEG) with minimum 20 min recording.

Criteria (exclusion) for total body cooling to newborns at risk for HIE.

- Inability to initiate cooling by 6hrs of age.
- Presence of lethal chromosomal anomalies (trisomy 13 or 18).
- Presence of severe congenital anomalies (complex cyanotic CHD, major CNS malformation).
- Symptomatic systemic bacterial or congenital viral infection.
- Bleeding diathesis (platelet < 50000).
- Major Intra cranial haemorrhage.

Cooling should be started before 6hrs of age. The target temperature goal during cooling is 33.5 C (33-34) with acceptable range (32.5-34.5).

Safety monitoring of newborns is must during 72hrs of therapeutic hypothermia and re-warming temperature. At the end of 72hrs of induced hypothermia the newborn is re-warmed at the rate of 0.5C every 2 hrs until reach to 36.5C.

In the developed world hypothermia has been the only treatment that has worked somewhat for HIE. It has been shown by four major studies- NICHD neonatal network study showed 18%, cool cap study showed 11% improvement TOBY which was done in UK and Europe showed 8% improvement and ICE study which was done in Australia mainly showed 15% improvement. This means only one in ten babies would benefit. In addition the high cost of machine (Rs. 20 to 60 lacs) is beyond the reach of many. The preferred cooling is whole body with a heart-lung bypass or ECMO; since that is rarely available, external whole body or external head cooling is the next best option.

Prognosis[7]

Increased risk of death or severe disability-hypoglycaemia, if glucose <2.2mmol/L in the first 30 minutes, or increase by 18-fold for death or disability, increased peripheral neutrophil counts in first 96 hours, high percentage nucleated RBC/WBC, high lactate in cord blood.[18]

The presence of seizures increases the newborn risk of developing CP 40 to 70 times,

if occurring during first 48 hours. Early onset and difficult to control seizure has poor prognosis.

According to Severity of HIE

Mild: good prognosis (98- 100% normal neurological outcomes and <1% mortality).

Moderate: not sure (20 – 37% die or abnormal neuro-developmental outcome).

Severe: poor prognosis (severe neurological outcome or death).

Traditional signs of recovery-eg Apgar scores, early establishment of suck feeds, visual responsiveness, head growth- have low sensitivity/specificity for predicting neurodisability.

If no neurological abnormality in two weeks of birth it suggests normal development.

Follow-up:

All the neonates with the moderate and severe asphyxia, especially those with stage II and III HIE staging should be followed in the High risk clinic; they should have a complete neurological assessment and intervention if needed during the follow up. A formal psychometric assessment at 18 months should be performed in all these babies. Follow-up also should include vision and hearing assessment, for vision, ROP, deafness, and pulmonary assessment and chest physiotherapy when appropriate especially in preterms.

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