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NEWBORN ASPHYXIA AND ITS ASSESSMENT, MEDICAL CARE

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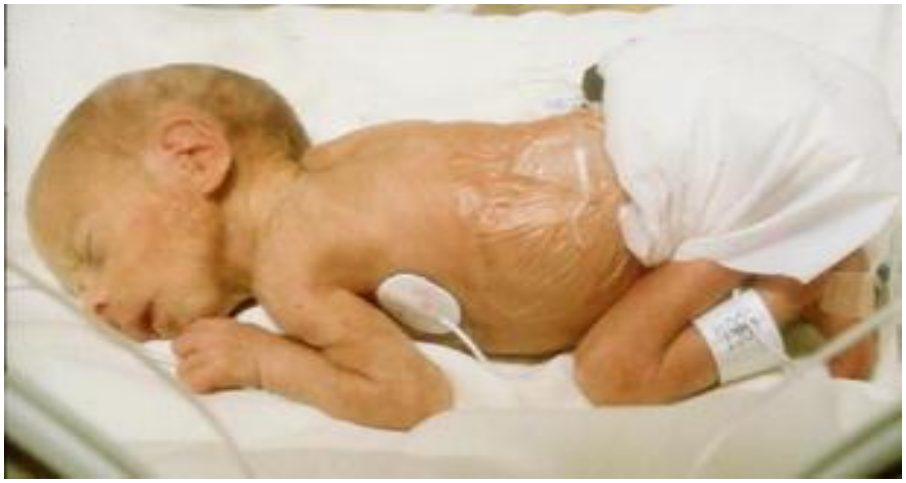
Annotation: *asphyxia (as-FIX-ee-uh) means lack of oxygen and blood flow to the brain. Birth asphyxia happens when a baby's brain and other organs do not get enough oxygen and nutrients before, during or right after birth. This can happen without anyone knowing. Without oxygen and nutrients, cells cannot work properly.*

Key words: *Paediatrics, CNS injury, Neurodegeneration, Diabetes, Cancer, Personalised medicine.*

INTRODUCTION

Perinatal Asphyxia—oxygen deficit at delivery—can lead to severe hypoxic ischaemic organ damage in newborns followed by a fatal outcome or severe life-long pathologies. The severe insults often cause neurodegenerative diseases, mental retardation and epilepsies. The mild insults lead to so-called “minimal brain-damage disorders” such as attention deficits and hyperactivity, but can also be associated with the development of schizophrenia and life-long functional psychotic syndromes. Asphyxia followed by re-oxygenation can potentially lead to development of several neurodegenerative pathologies, diabetes type 2 and cancer. The task of individual prediction, targeted prevention and personalised treatments before a manifestation of the life-long chronic pathologies usually developed by newborns with asphyxic deficits, should be given the extraordinary priority in neonatology and paediatrics. Socio-economical impacts of educational measures and advanced strategies in development of robust diagnostic approaches targeted at effected molecular pathways, biomarker-candidates and potential drug-targets for tailored treatments are reviewed in the paper. Asphyxia—insufficient oxygen supply—can lead to severe hypoxic ischaemic organ damage in newborns followed by a fatal outcome or severe life-long pathologies. Although birth asphyxia is not always distinguishable as the cause of perinatal and postnatal death, its pronounced impact for the mortality in newborns is well-documented, representing profound deficits in current healthcare systems worldwide. Secondary to

birth asphyxia, a postnatal manifestation of hypoxic-ischaemic encephalopathy (HIE) is frequently observed being associated with either mild or severe organ damage in asphyxiated newborns, both leading to the development of chronic pathologies. The severe insults often cause neurodegenerative diseases, mental retardation and epilepsies. The mild insults lead to so-called “minimal brain-damage disorders” such as attention deficits and hyperactivity, but can also be associated with the development of schizophrenia and life-long functional psychotic syndromes. In some particular cases it is difficult to discriminate between mild and severe asphyxia: advanced methodology to improved diagnosis of birth asphyxia and prediction of individual short- and long-term outcomes obligatory needs to be developed. The task of individual prediction (Fig 1), targeted prevention and personalised treatments before a manifestation of life-long chronic pathologies usually developed by asphyxiated newborns, should be given the extraordinary priority in paediatrics.



Newborn with asphyxic deficits. For timely protection against severe outcomes, a predictive diagnostics should be performed to detect individual pathology predisposition followed by targeted preventive measures and creation of personalised treatment algorithms.

According to the statistical data collected in years 2000–2002 by the Global Burden of Disease Study, worldwide 56 million deaths occur every year, from that 10.5 million, i.e. 20% represent children aged below 5 years. In this group, the leading cause of death is perinatal complications. Current statistical data considering epidemiology of prenatal, perinatal and postnatal pathologies are worldwide have not been systematically analysed; sometimes these data are even controversial as provided for single countries. Here we overview the most systematic studies as published to the issue. One the most reliable issue-related studies performed in the USA has demonstrated the perinatal morbidity comprising 60% of the child death cases giving a general idea of the biggest impact of perinatal complications in childhood and reflecting extensive issue-related problems in corresponding healthcare system as well as massive deficits in knowledge about and/or practical application of targeted prevention and effective treatment of neonatal, perinatal and postnatal pathologies.

Among different countries, a prevalence of birth asphyxia varies dramatically depending on corresponding geographic localisation and socio-economical level of development. Hypoxic ischaemic organ damage can occur at antepartum—prenatal asphyxia, at intrapartum—perinatal (birth) asphyxia, or after delivery as postpartum asphyxia. Acute maternal infections, pre-maturity of a newborn and multiple births are the most frequent natural risk factors leading to hypoxic conditions in a fetus or newborn. However, specifically perinatal asphyxia (PA) occurring at the parturition process of delivery is the leading cause of the overall mortality due to hypoxic-ischaemic damage to newborns. Consequently, the quality of a medical care at birth is crucial for the overall newborn mortality and long-term outcomes. The impact of a density of healthcare units is even more pronounced in prevalence of PA-related mortality compared to this of general mortality in newborns.

Grading of perinatal asphyxia

Depending on the grade of oxygen deficiency that a newborn suffered at delivery and individual reactions developed under asphyxic event, the corresponding perinatal asphyxia is graduated either as mild or severe one. The latter is the most frequent cause of perinatal and neonatal death as well as of severe injury of central nervous system (CNS) and damage to other organs resulting in hypoxic-ischaemic encephalopathy, nephropathy, and cardiomyopathy as the most usual long-term outcomes. The APGAR score is named by the author, Dr. Virginia Apgar, who has developed the system in the middle of 20th century. Since that time, it is still the worldwide practised grading of the severity of perinatal asphyxia, as summarised in Fig 2.

A brief description of the APGAR system for the severity grading of perinatal asphyxia (PA) in newborns: PA severity ranges between 0 and 10, whereby 10 (healthy) corresponds to the best score 2 for all five parameters evaluated; *acrocyanosis occurs due to altered parameters of blood flow resulting in a gradually changing skin colour:

Component of Acronym	Score of 0	Score of 1	Score of 2 (the best score, healthy)
1. Skin color / **A**ppearance	Overal blue / pale	Acrocyanosis*, trunk and head are pink, but the arms and legs are blue	No blue cyanosis, the skin is pink all over
2. Hearth rate beats per minute / **P**ulse	Absent	< 100 bmp	> 100 bmp
3. Reflex irritability / **G**rimace	No response to stimulation	Grimace / slight cry when stimulated	Vigorous cry in response to stimuli (like nasal suctioning); sneeze / cough / pulls away when stimulated
4. Muscle tone / **A**ctivity	No movement, limpness	Some flexion	Vigorous, active movement of arms and legs
5. Breathing / **R**espiration	Absent, apnoea	Slow, Weak or irregular	Strong, visible breathing and crying

The Apgar score uses five criteria: Appearance, Pulse, Grimace, Activity, and Respiration, shortly APGAR**.** Ranging from zero to ten, the scores below 3 are considered as critically low for cases of the highest emergency, 4 to 6—as fairly low, and the scores equal to or above 7 correspond to generally normal states of the newborn's health. In regions with a traditionally high neonatal mortality, the Apgar score is frequently calculated as less than seven. Hence, in Saudi Arabia, the Apgar scores below 7 were registered for 22% of newborns; 7.6% of them represented cases of neonatal morbidity. In Tanzania, Apgar scores below 7 for registered for 79% of the neonatal deaths. These are clear indications for perinatal asphyxia as the major cause of neonatal morbidity.

The APGAR grading of a severity of perinatal asphyxia is relevant for the most probable short-term outcomes, such as generalised survival potential and an immediate risk of severe damage to CNS after asphyxic event. However, this diagnostic system has not been designed for prognostic purposes, evaluation of long-term risks and individual outcomes. Adequate diagnostic systems are currently missing and obligatory must be created to predict and prognose long-term risks and individual outcomes for asphyxiated newborns. In particular, a reliable diagnostic and prognostic system should be further created for newborns suffered from mild asphyxia graded as fairly to slightly low APGAR

scores. Long-term affects of mild asphyxia are completely underestimated, due to less dramatic short-term outcome compared to severe asphyxia. Although mild insults do not cause perinatal death, the most frequent long-term outcomes include functional psychotic syndromes, attention deficit disorder, hyperactivity, epilepsies, schizophrenia and plenty of other chronic/life-long pathologies, which are assumed to be potentially caused by a sub-optimal delivery. The reaction towards mild insults is highly individual and should be subjected to extensive pre/clinical studies, in order to promote optimal protective measures and possibly full recovery.

Supportive and protective therapeutic approaches for newborns with asphyxic deficits:

Re-oxygenation of newborns with asphyxic deficits triggers a cascade of compensatory biochemical events to restore function, which may be accompanied by improper homeostasis and oxidative stress. In the clinical scenario, no specific treatments have yet been established to protect asphyxic newborns against hypoxic/re-oxygenation stress. In the clinical setting, after resuscitation of an infant with birth asphyxia, the emphasis is on supportive therapy. Several interventions have been proposed to attenuate secondary neuronal injuries elicited by asphyxia, including hypothermia. Hypothermia has been pointed out to be an effective intervention against the secondary neuronal injury, elicited by the birth asphyxia. Applied immediately after birth asphyxia, hypothermia generally lowers metabolic rates, and diminishes the glutamate levels in brain . Although promising, the clinical efficacy of hypothermia has not been fully demonstrated. It is evident that new approaches are warranted. In the context of neuroprotection, several sentinel proteins have been described to protect the integrity of the genome (e.g. PARP-1, XRCC1, DNA ligase IIIα, DNA polymerase β, ERCC2, DNA-dependent protein kinases). They act by eliciting metabolic cascades leading to (i) activation of cell survival and neurotrophic pathways; (ii) early and delayed programmed cell death, and (iii) promotion of cell proliferation, differentiation, neuritogenesis and synaptogenesis. It is proposed that sentinel proteins can be used as markers for characterising long-term effects of perinatal asphyxia, and as targets for novel therapeutic development and innovative strategies for neonatal care . Nicotinic acid and nicotinamide have been proposed to protect against oxidative stress , ischaemic injury and inflammation by replacing the depletion of the NADH/NAD^+-pair produced by PARP-1, which is over-activated under severe hypoxic conditions. Therapeutic application of nicotinamide has been reported to prevent several of the changes induced by perinatal asphyxia on monoamines, even if the treatment is delayed for 24 h, suggesting a clinically relevant therapeutic window. Therefore, this approach is currently considered as the therapeutic strategy against the long-term deleterious consequences of birth asphyxia as well as for several pathophysiologic conditions such as myocardial reperfusion injury, stroke, neurotrauma, arthritis, multiple sclerosis and severe complications secondary to Diabetes mellitus. The

application of low concentrations of NO-inhibitors is beneficial against extensive ischaemic lesions in brain. Pre- and post-hypoxic treatment with NMDA-receptor antagonists appears to reduce cerebral tissue injury. Calcium-channel blockers have also been demonstrated to have beneficial effects by reducing post-asphyxic lesions in brain. Pretreatment with barbiturates may improve survival and reduce the severity of brain injury. It reduces cerebral metabolism and decreases oxygen consumption. By lowering the oxygen consumption, it prevents free-radical destruction of the cell membranes. The barbiturate pretreatment reduces the intra- and extra-cellular accumulation of water and, in this way, prevents convulsions. Postnatal treatments with free-radical scavengers such as dimethylthiourea, xanthine-oxidase, and allopurind-inhibitor improve clinical outcomes after perinatal asphyxic insults.

In conclusion, infants with mild-to-moderate birth asphyxia who receive prompt treatment may make a full recovery. However, in some cases, birth asphyxia can be fatal. In infants with birth asphyxia, the death rate is 30% or moreTrusted Source within the first few days following birth. Birth asphyxia can also cause long-term complications and may cause mild-to-severe neurological disorders, such as seizures, cerebral palsy, or developmental delays. Proper care and monitoring before and after the birth may help reduce the risk of birth asphyxia in some cases.

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