EPMA Journal (2011) 2:197–210
DOI 10.1007/s13167-011-0087-9

REVIEW ARTICLE

Birth asphyxia as the major complication in newborns: moving towards improved individual outcomes by prediction, targeted prevention and tailored medical care

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Received: 13 April 2011 / Accepted: 19 May 2011 / Published online: 9 June 2011
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Abstract 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.

Keywords Paediatrics · CNS injury · Neurodegeneration · Diabetes · Cancer · Personalised medicine

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Introduction

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.

Global burden in newborn healthcare and the role of perinatal complications

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 [2]. 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 [3] 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.

Particularly alarming statistical data are currently delivered by developing countries with large populations. Currently one-third part of all neonatal deaths registered worldwide occurs in India [4, 5]. The most frequent prenatal, perinatal and neonatal complications leading to death are summarised in Fig. 2 for Tamil Nadu—one of the Indian regions.

It is obvious that the number of deaths during the first week of life comprises the highest overall mortality in newborns. Consequently, in Tamil Nadu, 81.5% of deaths were monitored during the first week of life, compared to more than 4-

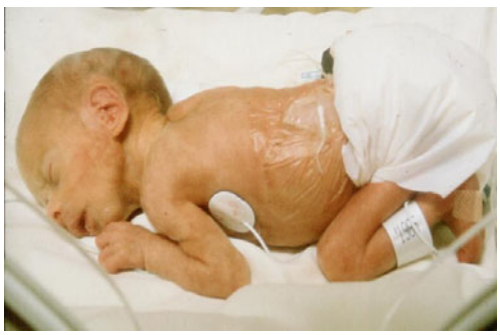

Fig. 1 Newborn with asphyxic deficits. For timely protection against severe outcomes, a predictive diagnostics should be performed to detect individual pathology predisposition followed by targeted preventive measures and creation of personalised treatment algorithms. Data taken from [1]

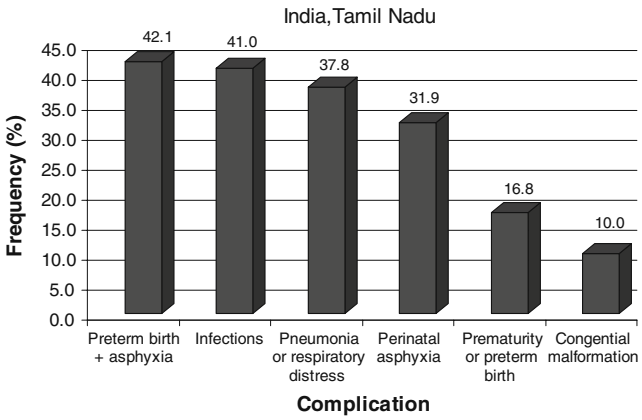

Fig. 2 Frequent complications leading to neonatal deaths with the highest contributions by birth asphyxia as monitored Tamil Nadu, India. Data taken from [1, 6]

times (18.5%) and 10-times (8.2%) lower mortality during the second week and after the sixth month of life, respectively [6].

Further studies performed in South Africa have demonstrated clear area-dependent preferences in distribution of neonatal death rates (Fig. 3). There is an obvious inverse relationship between a decreased density of healthcare units and an increased mortality in newborns.

Intensity of medical care has great impacts on neonatal death rates even in countries, where a healthcare is generally well established. Hence, despite of the overall low mortality of newborns in Canada, an increased risk of stillbirth and neonatal death during weekends is well documented indicating significant fluctuations in the intensity, i.e. quality of healthcare, the level of which, therefore, depends of the day of a week [8].

Currently a categorisation of perinatal complications is still not well classified. Worldwide there are three actively used diagnostic systems, namely Nordic-Baltic, Aberdeen and Wigglesworth one [9]. Among perinatal complications, 40% of all cases are defined as "unknown", when diagnosed according to the parameters of the Aberdeen classification system alone. The Wigglesworth system

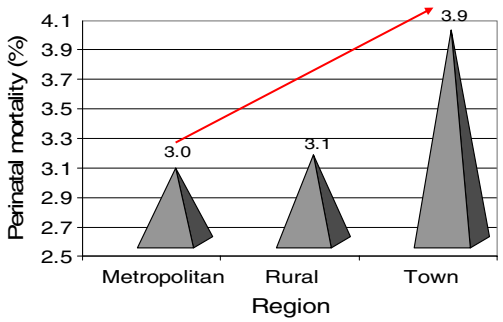

Fig. 3 Prevalence of neonatal mortality represented in percentages with respect to a delivery area as monitored in South Africa [7]

provides satisfactory diagnosis for less then 60% of cases. Although in average 85% of the cases can be reliably diagnosed by a combination of all three diagnostic systems, still 15% of the cases remain undiagnosed [9]. Therefore, we conclude the absolute necessity to optimise currently used diagnostic systems by utilising innovative non-invasive technologies and creating reliable approaches capable to provide information for follow-up personalised treatments.

Prevalence and risk factors of birth asphyxia

Among different countries, a prevalence of birth asphyxia varies dramatically depending on corresponding geographic localisation and socio-economical level of development (Fig. 4).

The data are well in agreement with the above given conclusions about a direct influence of the healthcare quality on delivery outcomes.

Hypoxic ischaemic organ damage can occur at ante-partum—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 [8]. 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 (Fig. 5) compared to this of general mortality in newborns (Fig. 3).

Ethical and socio-economical impacts of educational measures in prevention of birth asphyxia

Current limited perinatal and postnatal diagnostics cause long-term consequences in a society, which can include a spectrum of negative aspects. From a social and ethical point of view, innovative technologies for an early/predictive diagnostics and individualised treatment should be applied in all routine medical services. From an economic point of view, emphasis should be put into the costs effectiveness to promote advanced healthcare with appropriate budgets for targeted prevention applied before pathologies manifest.

What are the potential measures that can be applied already now? One example of the high impact of educational measures to improve the healthcare system is given in Figs. 6 and 7.

The prevalence of birth asphyxia registered for children born to educated mothers is several times lower compared with those born to uneducated/illiterate mothers. It is evident that strong restrictions in the amount of education lead to dramatic deficits and costs that are essentially then felt in other branches of the system, including a consequently chaotic healthcare in the society. When the whole spectrum of asphyxia-related pathologies is considered such as type 2 diabetes, neurodegenerative diseases and cancer, the consequent costs increase dramatically for treatment of manifesting pathologies. Therefore, new guidelines are

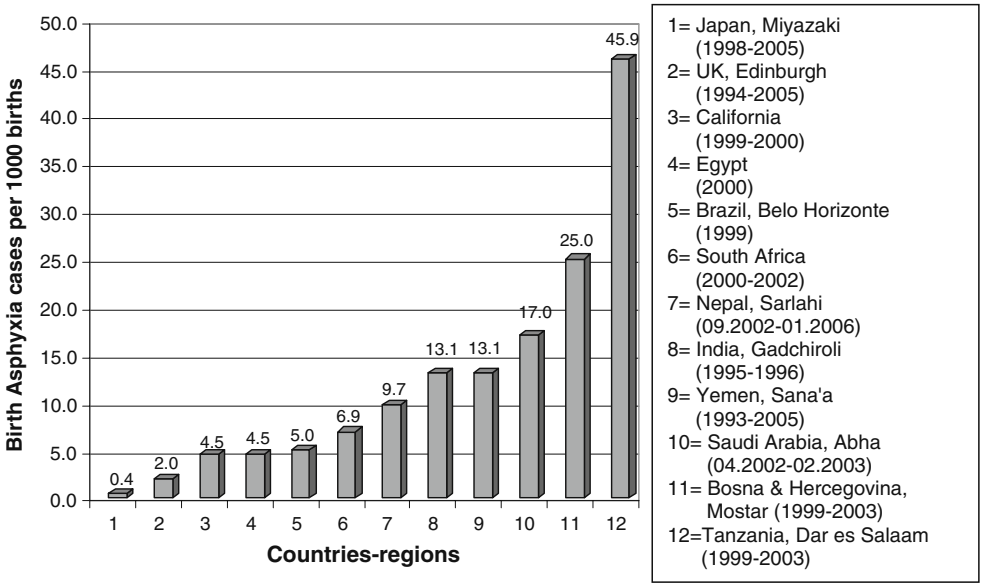

Fig. 4 The prevalence of birth asphyxia as documented by a series of population studies: a corresponding number of cases has been calculated per 1,000 life births. Data taken from [10–21]

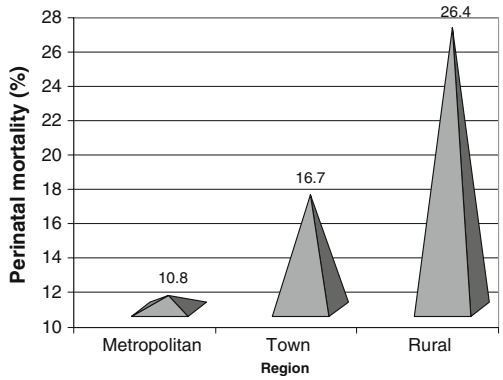

Fig. 5 Significant regional preferences in PA-related mortality depending on the density of healthcare units (maximal and minimal density in metropolitan and rural area, respectively) as documented for South Africa. Data taken from [1, 7]

essential to regulate the field in favour of educational measures, personalised treatment approaches before manifesting pathologies, particular emphases on primary prevention, innovative reimbursement programmes introduced by policy-makers [22].

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 [24]. Since that time, it is still the worldwide practised grading of the severity of perinatal asphyxia, as summarised in Fig. 8.

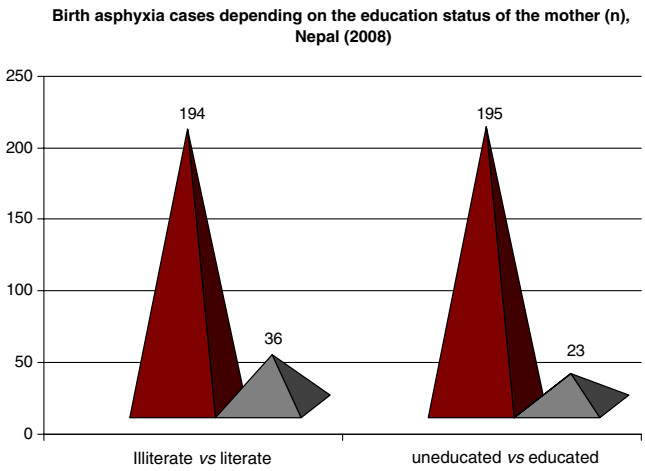

Fig. 6 Ratio of newborns with asphyxic deficits born to uneducated versus educated mothers. Data taken from [22]

The Apgar score uses five criteria: **A**ppearance, **P**ulse, **G**rimace, **A**ctivity, and **R**espiration, 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 [19]. In Tanzania, Apgar scores below 7 for registered for 79% of the neonatal deaths [21]. 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.

Moving from basic research to clinical implementation: essential steps in creating the robust diagnostic platform for personalised treatment of newborns with asphyxic deficits

The overall concept foresees advanced strategies as summarised in Fig. 9. An optimal set-up of stakeholders and a high quality of the performance of single operating steps (subprojects) guarantee for a discovery and qualification of

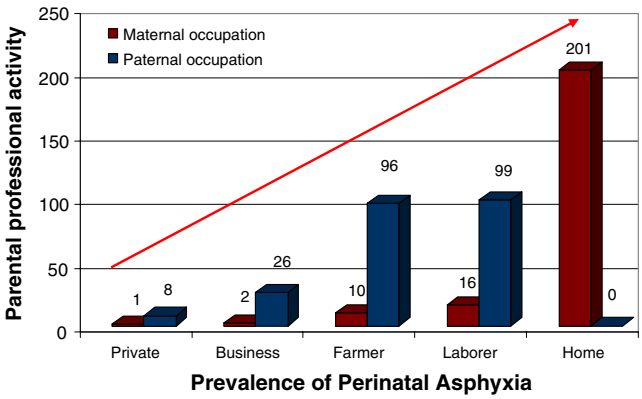

Fig. 7 Influence of maternal and paternal professional activity on prevalence of birth asphyxia in sub-grouped families as monitored in Nepal [16, 23]

innovative diagnostic approaches and valid drug targets to be successfully implemented in clinical practice. The crucial step in the overall experimental scheme is a well-established animal model to simulate clinical conditions. In the case of perinatal asphyxia, these are robust experimental conditions for totally-reproducible birth asphyxia and reliable (neuro) physiological tests characterising the specific features of the pathology. The animal model that has been created to simulate the perinatal asphyxia with characteristic asphyxia-related long-term outcomes in humans is described below. Optimal experimental conditions and general regulations including ethical aspects for a successful bio-preservation and bio-banking will be separately discussed in current and follow-up journal-issues.

In vivo simulation of human birth asphyxia

A reliable animal model of perinatal asphyxia has been established by M. Herrera-Marschitz et al. [25]. This model provides highly reproducible results and is well-acknowledged worldwide. The most important steps are illustrated in Fig. 10.

Pregnant Wistar rats at the last day of gestation are neck-dislocated and quickly hysterectomised. The uterus horns containing fetuses are placed in a water-bath at 37°C for time-periods ranging 0–20 min, in order to simulate the in vivo mild (below 10 min) and severe (above 15 min) birth

Fig. 8 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. Data taken from [1, 24]

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

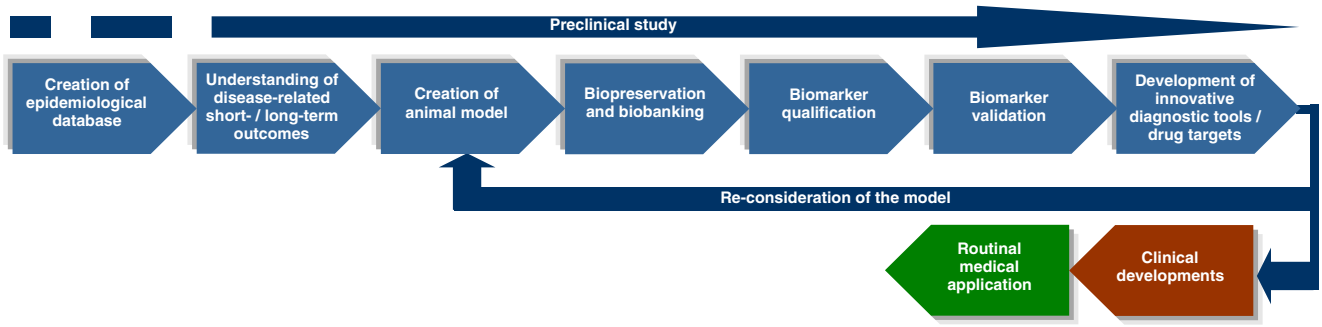

Fig. 9 Advanced strategies in the development of a robust diagnostic platform and novel drug targets with high potential for their clinical implementation

asphyxia. Following asphyxiation, the uterus horns are rapidly opened, and the pups are removed and stimulated for breathing (re-oxygenation period). In vivo and in vitro neurophysiological evaluations are performed in order to characterise the severity grade of asphyxia and brain injury [26]. The long-term CNS effects of the simulated asphyxia are examined by behavioural evaluations. Ex vivo and in vitro analyses characterise the consequent damage to several organ, pathology-specific alterations in (sub)cellular structures and condition specific molecular patterns.

Behavioural tests applied to confirm clinically relevant alterations in asphyxiated rats

Adult rats subjected to perinatal asphyxia as described above, are tested for long-term modifications in non-spatial and spatial memory, and in motor tasks. They display impaired novel object recognition in accordance with the rodent model used to assess non-spatial working memory deficits [27, 28]. In contrast, the Y maze or Barnes, maze tests validated for spatial memory deficits, do not demonstrate any effects by the asphyxiation episodes, at delivery [28–30]. An evident impairment in motor coordination is monitored by rotarod performance; however, no significant difference in intensity of non-finalised motor behaviour and time-course of gross motor activity can be observed between the asphyxiated and control rats [28]. Taken together, the experimental rates exposed to the birth asphyxia, evidently, demonstrate altered fine movement functions, reflecting deficits in motor coordination and balance, whereas the locomotion and general motor activity remained non-affected. The cognitive and motor deficits observed in rats indicate the

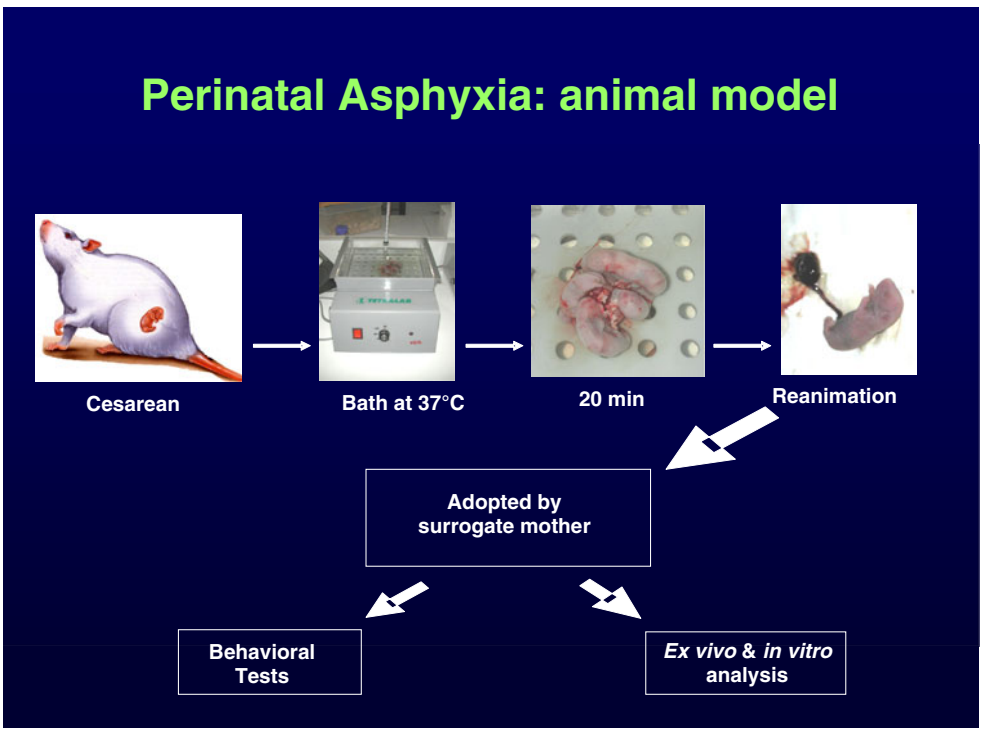

Fig. 10 The sequence of steps resulting in a set-up of clinically relevant perinatal asphyxia conditions and well reproducible asphyxiated newborn rats [25]. The uterus horns containing foetuses are placed in a water-bath at 37°C for 20 min to simulate severe birth asphyxia. Without re-oxygenation, the asphyxiated pups die after 22 min. By using this model, mild insults can be observed by 5–10 min simulation of perinatal asphyxia followed by immediate re-oxygenation

deleterious effects of birth asphyxia similar to those observed in human newborns suffered from perinatal asphyxia. The above described experimental model allows for monitoring of the deficits in cognitive performance, specific asphyxia-induced changes in motoric and stress-mediated behaviour [31, 32].

Expression profiling by "Gene Hunting"- technology discovered functional groups of genes involved in the pathophysiology of perinatal asphyxia

The principles underlie the "gene hunting"-technology of "subtractive hybridisation", applied to profile differentially expressed gene-transcripts, has been described in several publications [33–35].

This strategy has been chosen to identify functional groups of genes, differentially regulated in the brain under the severe birth asphyxia versus normoxia [36–38]. The transcription profiling revealed the following functional groups of genes affected by the asphyxia [36]:

- synthesis of signalling molecules (such as nitric-oxide) and heat-shock proteins
- nuclear and DNA-binding factors
- transcription and translation regulation
- energy metabolism
- membrane transport
- ion-handling
- several metabolic pathways (e.g. nucleic acid, lipid metabolism)
- redox-control and free-radical production
- proto-oncogenes.

These functional groups comprise the genes, the transcriptional rates of which are significantly altered in brain of asphyxiated rats. Concomitantly, the same functional groups have been reported as resulting from research projects dedicated to the translational alterations identified by differential protein profiling [39]. These extensive alterations in the central molecular pathways can be potentially implicated in the development of potential asphyxia-related chronic complications, such as several sorts of degenerative processes in organs and onset of pre/cancerous lesions in the affected organs as summarised in Fig. 11.

Central biological processes affected by perinatal asphyxia

Asphyxia is characterised by hypoxia (mild or severe oxygen deficiency) and the pH-values reduced below 7. Depending on the grade of oxygen deficits (see previous subchapters in the manuscript) perinatal asphyxia causes either severe brain injury or subtle perturbations affecting further development of the central nervous system (CNS) [40–42]. Under global hypoxia, "up-stream" CNS damage is followed by ischaemic lesions in kidney [43] and heart [44]. Global hypoxia impairs the general availability of oxygen [45, 46], affecting the electron transport pathways [47], increasing calcium influx and triggering fragmentation of both chrDNA and mtDNA [48]. The consequently triggered cascade of biochemical events creates a significant imbalance in central oxygen-dependent molecular pathways. Even more damaging is the reversion to normal oxygen levels during the post-asphyxic re-oxygenation associated with an extensive production of highly reactive oxygen species. Respectively, suppression and over-activation of the affected molecular pathways occur during both periods: hypoxia and re-oxygenation [36, 38]. Established chronic deficits underlie severe pathologies developed as individual long-term outcomes of perinatal asphyxia. Among them is the synthesis of compounds critical for postnatal CNS-development, nerve growth and "synaptogenesis" which are impaired by and depend on the asphyxia severity and damaging effects by the post-asphyxic re-oxygenation [26, 49–54]. Metabolic particularities of the asphyxia/re-oxygenation pathology are summarised in Fig. 11. Hypoxic-ischaemic encephalopathy [55–57], CNS damage [58, 59], epilepsy [60, 61], nephropathy [43], cardiomyopathy [62, 63], vascular pathologies [64], senescence [32, 65], diabetes mellitus [66, 67], cancer [68], neurodegenerative diseases [58], morbidity and mortality [69] and tissue remodelling [70] all belong to individual short- and long-term outcomes of birth asphyxia. Specialised issue of *The EPMA Journal*, further treat the major related topics, namely "PPPM in Diabetes", "PPPM in Neurodegenerative Diseases", "PPPM in Cancer", "PPPM in Cardiovascular Diseases", "PPPM in Body Culture and Sport Medicine", "Healthcare Overview", where the articles overview the innovative technologies of predictive diagnostics, targeted prevention measures and desirable personalisation of medical care [71–80].

Biomarker-candidates in blood specific for asphyxia and related complications

Blood tests is a highly attractive approach for performing non-invasive examinations to accurately diagnose a severity grade of birth asphyxia and to predict/prognose individual predispositions to or a progression of secondary complications in asphyxia affected newborns. Furthermore, the discovered blood-brain barrier permeability in hypoxic-

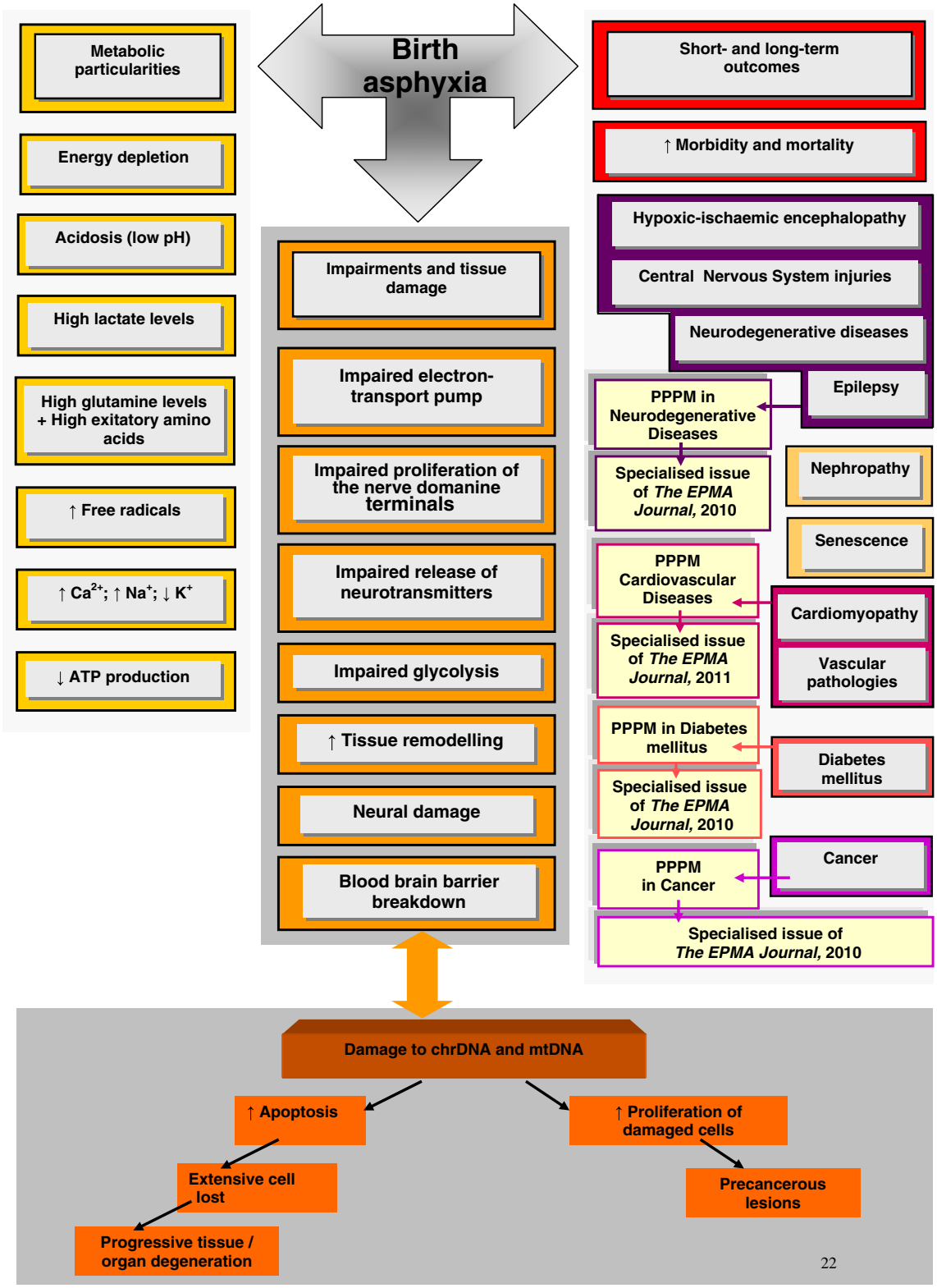

Fig. 11 Metabolic particularities, impairments and individual outcomes by perinatal asphyxia. Abbreviations: mtDNA = mitochondrial DNA; chrDNA = chromosomal DNA; ATP = adenosine three-phosphate; PPPM = predictive, preventive and personalised medicine

ischaemic encephalopathy well explains potential correlations in pathology specific molecular profiles between brain and blood, justifying the high prognostic value of non-invasive blood examinations [81].

In newborn term infants with intra-partum signs of foetal distress, the blood-plasma levels of lactate-dehydrogenase are considered as a good predictor of hypoxic-ischaemic encephalopathy during the first 12 h after birth. This result is of clinical interest offering a potential inexpensive and safe prognostic marker in newborn infants with perinatal asphyxia [82].

The oxidative stress markers as measured in blood, are well recognised as the good predictors of poor outcomes in newborns with asphyxic deficits [83].

Acute kidney injury is a common consequence of perinatal asphyxia, occurring in up to 56% of these infants. Therefore, the pathology specific biomarkers are of great clinical value being currently under extensive consideration by researchers [84].

S100B is considered as one of the most potent blood-markers, significantly increased in blood serum 24 h after severe birth asphyxia insult in newborns [85–89].

Our recent studies demonstrated highly increased S100B expression rates, specifically, in the mesencephalon of the experimental rats, even 1 month after severe birth asphyxia. Potentially the brain tissue of the mesencephalon area overproducing S100B can be also the source of the increased S100B levels in the blood-serum, due to the blood-brain-barrier breakdown that is characteristic for hypoxic-ischalmic encephalopathy. However, the proteins of S100-family cannot be considered as asphyxia specific biomarkers, since significantly increased expression levels of them have been detected in blood of several patient cohorts, who suffer from different types of pathologies—neurodegenerative and vascular disorders [90–92], cardio-myopathy [93], several cancer types [94, 95].

The diagnostic approaches, which utilise pathology-specific biomarkers, are more promising in predicting an individual predisposition to pathologies, monitoring a disease progression and serving as the selective targets for tailored therapeutic measures. Here we provide some examples for potential biomarker-candidates discovered in our recent studies. Hence, a significant elevation of TAU-protein transcriptional rates has been demonstrated in the blood of experimental rats with expression peaks specific for the brain-regions in certain time-frame: 48-h—in mesencephalon and hypothalamus and 1-week—in telencephalon, as monitored after the severe asphyxic insult (see Fig. 12).

Moreover, there is an evident correlation between the expression peaks in individual brain-regions and appearance of the TAU-transcripts in blood of asphyxiated pups. The up-regulation of the TAU-levels is characteristic for Alzheimer's disease and has been implicated in the pathology-specific molecular mechanisms [97].

Further, the measurements of the HER-2 transcripts in brain and full blood revealed sufficient differences between the groups of asphyxiated and normoxic animals as demonstrated in Fig. 13.

According to the above given results, both TAU-protein and HER-2 can be considered as biomarker-candidates for further validating tests in clinical studies.

Outlook: 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 [98]. Applied immediately after birth asphyxia, hypothermia generally lowers metabolic rates, and diminishes the glutamate levels in brain [98–100]. 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 [101].

Nicotinic acid and nicotinamide have been proposed to protect against oxidative stress [102, 103], ischaemic injury [104] and inflammation [105] by replacing the depletion of the $NADH/NAD^+$-pair produced by PARP-1, which is over-activated under severe hypoxic conditions [106]. 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 [107]. Therefore, this approach is currently considered as the therapeutic strategy against the long-term deleterious consequences of birth asphyxia as well as

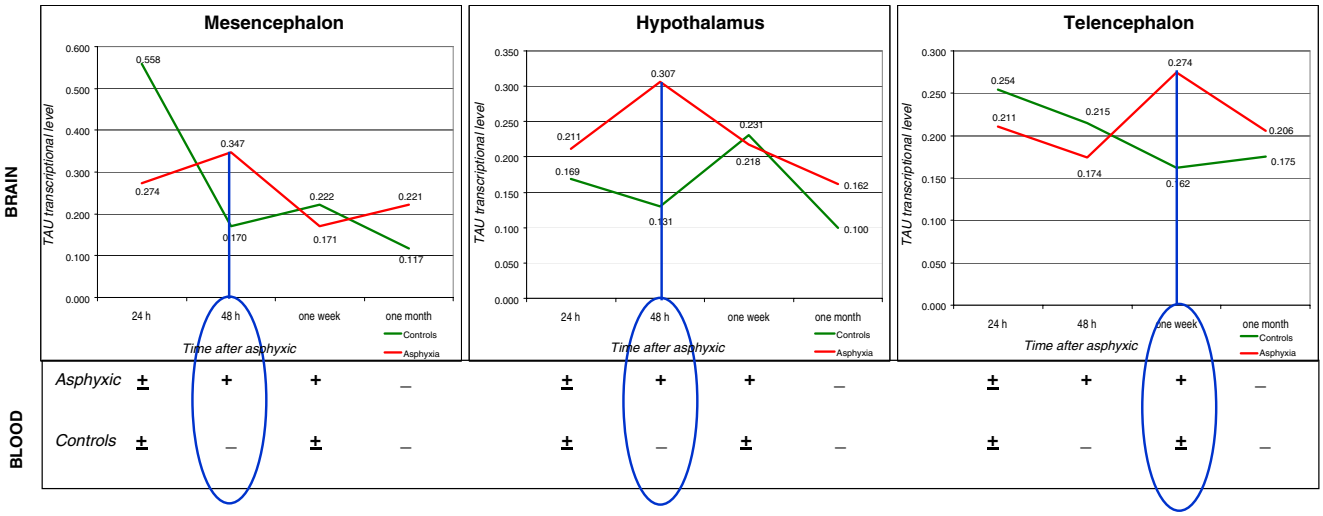

Fig. 12 Transcription levels of the TAU-protein as measured in experimental rats exposed to birth asphyxia versus control animals (normoxia). The transcriptome-profies are specific for the brain-regions – Mesencephalon, Hypothalamus and Telencephalon. The brain-region/time specific peaks correlate with the appearance of TAU-transcripts in full blood of all asphyxiated animals tested. Data taken from [96]

for several pathophysiologic conditions such as myocardial reperfusion injury, stroke, neurotrauma, arthritis, multiple sclerosis and severe complications secondary to *Diabetes mellitus* [105].

The application of low concentrations of NO-inhibitors is beneficial against extensive ischaemic lesions in brain [108]. Pre- and post-hypoxic treatment with NMDA-receptor antagonists appears to reduce cerebral tissue injury [109, 110]. Calcium-channel blockers have also been demonstrated to have beneficial effects [109] by reducing post-asphyxic lesions in brain.

Pretreatment with barbiturates may improve survival and reduce the severity of brain injury [109]. It reduces cerebral metabolism [111] and decreases oxygen consumption [112]. By lowering the oxygen consumption, it prevents free-radical destruction of the cell membranes [113]. The barbiturate pretreatment reduces the intra- and extra-cellular accumulation of water and, in this way, prevents convulsions [114].

Postnatal treatments with free-radical scavengers such as dimethylthiourea, xanthine-oxidase, and allopurind-inhibitor improve clinical outcomes after perinatal asphyxic insults [115, 116].

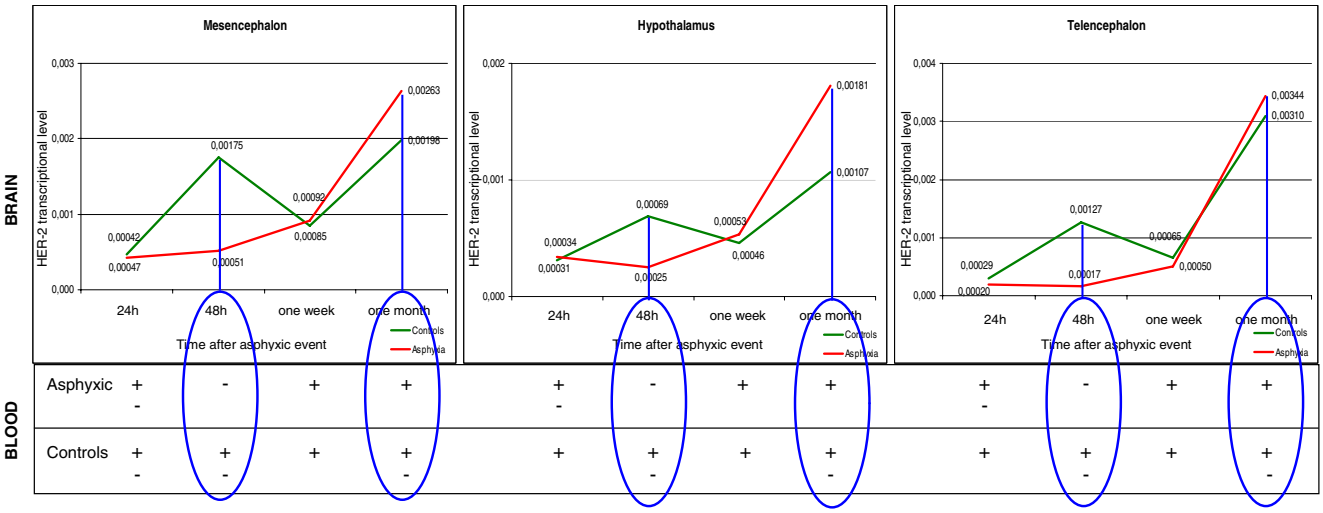

Fig. 13 Transcription levels of the HER-2 protein as measured in experimental rats exposed to birth asphyxia versus control animals (normoxia). The transcriptome-profies are specific for the brain-regions – Mesencephalon, Hypothalamus and Telencephalon. The brain-region specific up-regulation (1 month after asphyxia) and down-regulation (48 h) correlates well with the respective appearance/disappearance of HER-transcripts in full blood asphyxiated animals. Data taken from [96]

Acknowledgements The Authors—Olga Golubnitschaja and Mario Herrera-Marschitz—have been granted for the bilateral collaboration by *The German Agency for Academic Exchange* (DAAD); the international project numbered D/06/33975 (2006–2010) was dedicated to "Perinatal Asphyxia". The authors thank to DAAD for the support. Also, the authors would like to thank M.Sc. Viktoriya Peeva for the literature search to the topic performed in 2008–2009.

References

1. Peeva V, Golubnitschaja O. Birth asphyxia as the most frequent perinatal complication. In: Golubnitschaja O, editor. Predictive diagnostics and personalized treatment: dream or reality? New York: Nova Science Publishers; 2009. p. 499–507.
2. Lopez AD, Mathers CD. Measuring the global burden of disease and epidemiological transitions: 2002–2030. Ann Trop Med Parasitol. 2006;100:481–99.
3. Tomashek KM, Crouse CJ, Iyasu S, Johnson CH, Flowers LM. A comparison of morbidity rates attributable to conditions originating in the perinatal period among newborns discharged from United States hospitals, 1989–90 and 1999–2000. Paediatr Perinat Epidemiol. 2006;20:24–34.
4. Baqui AH, Darmstadt GL, Williams EK, Kumar V, Kiran TU, Panwar D, et al. Rates, timing and causes of neonatal deaths in rural India: implications for neonatal health programmes. Bull World Health Organ. 2006;84:706–13.
5. Shantharam Baliga B, Vivekananda Prabhu B, Shenoy R, Rajeev A. Scaling up of facility-based neonatal care: a district health system experience. J Trop Pediatr. 2007;53:107–12.
6. Vaid A, Mammen A, Primrose B, Kang G. Infant mortality in an urban slum. Indian J Pediatr. 2007;74:449–53.
7. Buchmann EJ, Pattinson RC, Nyathikazi N. Intrapartum-related birth asphyxia in South Africa-lessons from the first national perinatal care survey. S Afr Med J. 2002;92:897–901.
8. Luo ZC, Liu S, Wilkins R, Kramer MS; Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. Risks of stillbirth and early neonatal death by day of week. CMAJ. 2004;170:337–41.
9. Elamin S, Langhoff-Roos J, Boedker B, Ibrahim SA, Ashmeig AL, Lindmark G. Classification of perinatal death in a developing country. Int J Gynaecol Obstet. 2003;80:327–33.
10. Sameshima H, Ikenoue T; Miyazaki Perinatal Data Group. Risk factors for perinatal deaths in Southern Japan: population-based analysis from 1998 to 2005. Early Hum Dev. 2008;84:319–23.
11. Becher JC, Stenson BJ, Lyon AJ. Is intrapartum asphyxia preventable? BJOG. 2007;114:1442–4.
12. Wu YW, Backstrand KH, Zhao S, Fullerton HJ, Johnston SC. Declining diagnosis of birth asphyxia in California: 1991–2000. Pediatrics. 2004;114:1584–90.
13. Campbell O, Gipson R, el-Mohandes A, Issa AH, Matta N, Mansour E, et al. The Egypt National Perinatal/Neonatal Mortality Study 2000. J Perinatol. 2004;24:284–9.
14. Lansky S, Franca E, Leal Mdo C. Avoidable perinatal deaths in Belo Horizonte, Minas Gerais, Brazil, 1999. Cad Saúde Pública. 2002;18:1389–400.
15. Pattinson RC. Why babies die - a perinatal care survey of South Africa, 2000–2002. S Afr Med J. 2003;93:445–50.
16. Lee AC, Mullany LC, Tielsch JM, Katz J, Khatry SK, LeClerq SC, et al. Risk factors for neonatal mortality due to birth asphyxia in southern Nepal: a prospective, community-based cohort study. Pediatrics. 2008;121:e1381–90.
17. Bang AT, Reddy HM, Bang RA, Deshmukh MD. Why do neonates die in rural Gadchiroli, India? (Part II): estimating population attributable risks and contribution of multiple morbidities for identifying a strategy to prevent deaths. J Perinatol. 2005;25:S35–43.
18. Banajeh SM, Al-Rabee AM, AI-Arashi IH. Burden of perinatal conditions in Yemen: a 12-year hospital-based study. East Mediterr Health J. 2005;11:680–9.
19. Arafa MA, Alshehri MA. Predictors of neonatal mortality in the intensive care unit in Abha, Saudi Arabia. Saudi Med J. 2003;24:1374–6.
20. Tomić V, Galić M. Perinatal mortality at University Hospital Mostar for five years. Med Arh. 2005;59:354–7.
21. Kidanto HL, Massawe SN, Nystrom L, Lindmark G. Analysis of perinatal mortality at a teaching hospital in Dar es Salaam, Tanzania, 1999–2003. Afr J Reprod Health. 2006;10:72–80.
22. Golubnitschaja O, Costigliola V. Common origin but individual outcomes: Time for new guidelines in personalised healthcare. Per Med. 2010;7:561–8.
23. Lee AC, Mullany LC, Tielsch JM, Katz J, Khatry SK, LeClerq SC, et al. Verbal autopsy methods to ascertain birth asphyxia deaths in a community-based setting in southern Nepal. Pediatrics. 2008;121:e1372–80.
24. Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg. 1953;32:260–7.
25. Herrera-Marschitz M, Loidl CF, You Z-B, Andersson K, Silveira R, O'Connor WT, et al. Neurocircuitry of the basal ganglia studied by monitoring neurotransmitter release. Effects of intracerebral and perinatal asphyctic lesions. Mol Neurobiol. 1994;9:171–82.
26. Morales P, Reyes P, Klawitter V, Huaiquin P, Bustamante D, Fiedler J, et al. Effects of perinatal asphyxia on cell proliferation and neuronal phenotype evaluated with organotypic hippocampal cultures. Neuroscience. 2005;135:421–31.
27. Dix SL, Aggleton JP. Extending the spontaneous preference test of recognition: evidence of object-location and object-context recognition. Behav Brain Res. 1999;99:191–200.
28. Simola N, Bustamante D, Pinna A, Pontis S, Morales P, Morelli M, et al. Acute perinatal asphyxia impairs non-spatial memory and alters motor coordination in adult male rats. Exp Brain Res. 2008;185:595–601.
29. McLay RN, Freeman SM, Zadina JE. Chronic corticosterone impairs memory performance in the Barnes maze. Physiol Behav. 1998;63:933–7.
30. Morrow BA, Elsworth JD, Roth RH. Prenatal cocaine exposure disrupts non-spatial, short-term memory in adolescent and adult male rats. Behav Brain Res. 2002;129:217–23.
31. Venerosi A, Valanzano A, Cirulli F, Alleva E, Calamandrei G. Acute global anoxia during C-section birth affects dopamine-mediated behavioural responses and reactivity to stress. Behav Brain Res. 2004;154:155–64.
32. Caputa M, Rogalska J, Wentowska K, Nowakowska A. Perinatal asphyxia, hyperthermia and hyperferremia as factors inducing behavioural disturbances in adulthood: a rat model. Behav Brain Res. 2005;163:246–56.
33. Labudova O, Kitzmüller E, Rink H, Cairns N, Lubec G. Gene Expression in fetal Down Syndrome brain as revealed by subtractive hybridization. In: Lubec G, editor. The molecular biology of down syndrome. Wien: Springer; 1999. p. 125–36.
34. Golubnitschaja-Labudova O, Liu R, Decker C, Zhu P, Haefliger IO, Flammer J. Altered gene expression in lymphocytes of patients with normal-tension glaucoma. Curr Eye Res. 2000;21:867–76.
35. Golubnitschaja O, Fountoulakis M. Gene hunting by substractive hybridisation in down syndrome. Correlation with proteomics analysis. In: Lajtha A, editor. Handbook of neurochemistry and molecular neurobiology. New York: Springer Science+Business Media, LLC; 2007. p. 345–58.

36. Labudova O, Schuller E, Yeghiazaryan K, Kitzmueller E, Hoeger H, Lubec G, et al. Genes involved in the pathophysiology of perinatal asphyxia. Life Sci. 1999;64:1831–8.
37. Mosgoeller W, Kastner P, Fang-Kircher S, Kitzmueller E, Hoeger H, Seither P, et al. Brain RNA polymerase and nucleolar structure in perinatal asphyxia of the rat. Exp Neurol. 2000;161:174–82.
38. Lubec B, Labudova O, Hoeger H, Kirchner L, Lubec G. Expression of transcription factors in the brain of rats with perinatal asphyxia. Biol Neonate. 2002;81:266–78.
39. Weitzdörfer R, Höger H, Burda G, Pollak A, Lubec G. Differences in hippocampal protein expression at 3 days, 3 weeks, and 3 months following induction of perinatal asphyxia in the rat. J Proteome Res. 2008;7:1945–52.
40. Thompson DG. Consequences of perinatal asphyxia. AACN Clin Issues Crit Care Nurs. 1994;5:242–5.
41. Simon NP. Long-term neurodevelopmental outcome of asphyxiated newborns. Clin Perinatol. 1999;26:767–78.
42. Maneru C, Junque C, Botet F, Tallada M, Guardia J. Neuropsychological long-term sequelae of perinatal asphyxia. Brain Inj. 2001;15:1029–39.
43. Nouri S, Mahdhaoui N, Beizig S, Zakhama R, Salem N, Ben Dhafer S, et al. Acute renal failure in full term neonates with perinatal asphyxia. Prospective study of 87 cases. Arch Pediatr. 2008;15:229–35.
44. Børke WB, Munkeby BH, Mørkrid L, Thaulow E, Saugstad OD. Resuscitation with 100% O(2) does not protect the myocardium in hypoxic newborn piglets. Arch Dis Child Fetal Neonatal Ed. 2004;89:F156–60.
45. Lubec B, Chiappe-Gutierrez M, Hoeger H, Kitzmueller E, Lubec G. Glucose transporters, hexokinases and phosphofructokinase in brain or rats with perinatal asphyxia. Pediatr Res. 2000;47:84–8.
46. Seidl R, Stockler-Ipsiroglu S, Rolinski B, Kohlhauser C, Herkner KR, Lubec B, et al. Energy metabolism in graded perinatal asphyxia of the rat. Life Sci. 2000;67:421–35.
47. Numagami Y, Zubrow AB, Mishra OP, Delivoria-Papadopoulos M. Lipid free radical generation and brain cell membrane alteration following nitric oxide synthase inhibition during cerebral hypoxia in the newborn piglet. J Neurochem. 1997;69:1542–7.
48. Akhter W, Ashraf QM, Zanelli SA, Mishra OP, Delivoria-Papadopoulos M. Effect of graded hypoxia on cerebral cortical genomic DNA fragmentation in newborn piglets. Biol Neonate. 2001;79:187–93.
49. Andersson K, Blum M, Chen Y, Eneroth P, Gross J, Herrera-Marschitz M, et al. Perinatal asphyxia increases bFGF mRNA levels and DA cell body number in the mesencephalon of rats. Neuroreport. 1995;6:375–8.
50. Cheng Y, Gidday JM, Yan Q, Shah AR, Holtzman DM. Marked age-dependent neuroprotection by brain-derived neurotrophic factor against neonatal hypoxic-ischemic brain injury. Ann Neurol. 1997;41:521–9.
51. Gluckman PD, Guan J, Williams C, Scheepens A, Zhang R, Bennet L, et al. Asphyxial brain injury- the role of the IGF system. Mol Cell Endocrinol. 1998;140:95–9.
52. Gustafson K, Hagberg H, Bengtsson BA, Brantsing C, Isgaard J. Possible protective role of growth hormone in hypoxia-ischemia in neonatal rats. Pediatr Res. 1999;45:318–23.
53. Morales P, Klawitter V, Johansson S, Huaiquin P, Barros VG, Avalos AM, et al. Perinatal asphyxia impairs connectivity and dopamine neurite branching in organotypic triple culture from rat substantia nigra. Neurosci Lett. 2003;348:175–9.
54. Klawitter V, Morales P, Johansson S, Bustamante D, Goiny M, Gross J, et al. Effect of perinatal asphyxia on cell survival, neuronal phenotype and neurite growth evaluated with organotypic triple cultures. Amino Acids. 2005;28:149–55.
55. Lukaskova J, Tomsikova Z, Kokstein Z. Cerebral function monitoring in neonates with perinatal asphyxia - preliminary results. Neuro Endocrinol Lett. 2008;29:522–8.
56. Shiraishi M, Takizawa Y, Ide S, Obonai T, Goto Y, Itoh M. Brainstem monoamine pathology of neonatal hypoxic-ischemic brain damage: a model of acute stage of neonatal asphyxia. Brain Res. 2008;1213:120–6.
57. Nabieva TN. Physical and neurological state of the newborn. Usp Fiziol Nauk. 2007;38:73–9.
58. Dell'Anna E, Chen Y, Engidawork E, Andersson K, Lubec G, Luthman J, et al. Delayed neuronal death following perinatal asphyxia in rat. Exp Brain Res. 1997;115:105–15.
59. Loidl CF, Herrera-Marschitz M, Andersson K, You ZB, Goiny M, O'Connor WT, et al. Long-term effects of perinatal asphyxia on basal ganglia neurotransmitter systems studied with microdialysis in rat. Neurosci Lett. 1994;175:9–12.
60. Oguni H, Sugama M, Osawa M. Symptomatic parieto-occipital epilepsy as sequela of perinatal asphyxia. Pediatr Neurol. 2008;38:345–52.
61. Nunes ML, Martins MP, Barea BM, Wainberg RC, Costa JC. Neurological outcome of newborns with neonatal seizures: a cohort study in a tertiary university hospital. Arq Neuropsiquiatr. 2008;66:168–74.
62. Trevisanuto D, Picco G, Golin R, Doglioni N, Altinier S, Zaninotto M, et al. Cardiac troponin I in asphyxiated neonates. Biol Neonate. 2006;89:190–3.
63. Matter M, Abdel-Hady H, Attia G, Hafez M, Seliem W, Al-Arman M. Myocardial performance in asphyxiated full-term infants assessed by Doppler tissue imaging. Pediatr Cardiol. 2010;31:634–42.
64. Nako Y, Tomomasa T, Morikawa A. Plasma thrombomodulin level in newborn infants with and without perinatal asphyxia. Acta Paediatr. 1997;86:91–5.
65. Jiang ZD, Liu XY, Shi BP, Lin L, Bu CF, Wilkinson AR. Brainstem auditory outcomes and correlation with neurodevelopment after perinatal asphyxia. Pediatr Neurol. 2008;39:189–95.
66. Yap F, Högler W, Vora A, Halliday R, Ambler G. Severe transient hyperinsulinaemic hypoglycaemia: two neonates without predisposing factors and a review of the literature. Eur J Pediatr. 2004;163:38–41.
67. Dinleyici EC, Tekin N, Colak O, Aksit MA. Cord blood IGF-1 and IGFBP-3 levels in asphyxiated term newborns. Neuro Endocrinol Lett. 2006;27:745–7.
68. McKinney PA, Juszczak E, Findlay E, Smith K, Thomson CS. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. Br J Cancer. 1999;80:1844–51.
69. Yu VY. Global, regional and national perinatal and neonatal mortality. J Perinat Med. 2003;31:376–9.
70. Morales P, Fiedler JL, Andrés S, Berrios C, Huaiquín P, Bustamante D, et al. Plasticity of hippocampus following perinatal asphyxia: effects on postnatal apoptosis and neurogenesis. J Neurosci Res. 2008;86:2650–62.
71. Sena CM, Bento CF, Pereira P, Seiça R. Diabetes mellitus: new challenges and innovative therapies. EPMA J. 2010;1:138–63.
72. George B, Cebioglu M, Yeghiazaryan K. Inadequate diabetic care: global figures cry for preventive measures and personalized treatment. EPMA J. 2010;1:13–8.
73. Li Calzi S, Neu MB, Shaw LC, Grant MB. Endothelial progenitor dysfunction in the pathogenesis of diabetic retinopathy: treatment concept to correct diabetes-associated deficits. EPMA J. 2010;1:88–100.

74. Cebioglu M, Schild HH, Golubnitschaja O. Cancer predisposition in diabetics: risk factors considered for predictive diagnostics and targeted preventive measures. EPMA J. 2010;1:130–7.
75. Coelho JF, Ferreira PC, Alves P, Cordeiro R, Fonseca AC, Góis JR, et al. Drug delivery systems: advanced technologies potentially applicable in personalized treatments. EPMA J. 2010;1:164–209.
76. Golubnitschaja O. Neurodegeneration: accelerated ageing or inadequate healthcare? EPMA J. 2010;1:211–6.
77. Characiejus D, Hodzic J, Jacobs JJL. "First do no harm" and the importance of prediction in oncology. EPMA J. 2010;1:369–76.
78. Mallmann MR, Staratschek-Jox A, Rudlowski C, Braun M, Gaarz A, Wolfgarten M, et al. Prediction and prognosis: impact of gene expression profiling in personalized treatment of breast cancer patients. EPMA J. 2010;1:421–38.
79. Zhan X, Desiderio DM. The use of variations in proteomes to predict, prevent, and personalize treatment for clinically nonfunctional pituitary adenomas. EPMA J. 2010;1:439–60.
80. Costigliola V. Healthcare overview: global process of personalisation in medicine. EPMA J. 2010;1:525–8.
81. Kumar A, Mittal R, Khanna HD, Basu S. Free radical injury and blood-brain barrier permeability in hypoxic-ischemic encephalopathy. Pediatrics. 2008;122:722–7.
82. Karlsson M, Wiberg-Itzel E, Chakkarapani E, Blennow M, Winbladh B, Thoresen M. Lactate dehydrogenase predicts hypoxic ischaemic encephalopathy in newborn infants: a preliminary study. Acta Paediatr. 2010;99:1139–44.
83. Mondal N, Bhat BV, Banupriya C, Koner BC. Oxidative stress in perinatal asphyxia in relation to outcome. Indian J Pediatr. 2010;77:515–7.
84. Durkan AM, Alexander RT. Acute kidney injury post neonatal asphyxia. J Pediatr. 2011;158:e29–33.
85. Murabayashi M, Minato M, Okuhata Y, Makimoto M, Hosono S, Masaoka N, et al. Kinetics of serum S100B in newborns with intracranial lesions. Pediatr Int. 2008;50:17–22.
86. Giuseppe D, Sergio C, Pasqua B, Giovanni LV, Salvatore C, Frigiola A, et al. Perinatal asphyxia in preterm neonates leads to serum changes in protein S-100 and neuron specific enolase. Curr Neurovasc Res. 2009;6:110–6.
87. Gazzolo D, Abella R, Marinoni E, Di Iorio R, Li Volti G, Galvano F, et al. Circulating biochemical markers of brain damage in infants complicated by ischemia reperfusion injury. Cardiovasc Hematol Agents Med Chem. 2009;7:108–26.
88. Gazzolo D, Abella R, Marinoni E, di Iorio R, Li Volti G, Galvano F, et al. New markers of neonatal neurology. J Matern Fetal Neonatal Med. 2009;22:57–61.
89. Florio P, Abella R, Marinoni E, Di Iorio R, Li Volti G, Galvano F, et al. Biochemical markers of perinatal brain damage. Front Biosci (Schol Ed). 2010;1:47–72.
90. Shepherd CE, Goyette J, Utter V, Rahimi F, Yang Z, Geczy CL, et al. Inflammatory S100A9 and S100A12 proteins in Alzheimer's disease. Neurobiol Aging. 2006;27:1554–63.
91. Geroldi D, Falcone C, Emanuele E. Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. Curr Med Chem. 2006;13:1971–8.
92. Wilhelm KR, Yanamandra K, Gruden MA, Zamotin V, Malisauskas M, Casaite V, et al. Immune reactivity towards insulin, its amyloid and protein S100B in blood sera of Parkinson's disease patients. Eur J Neurol. 2007;14:327–34.
93. Mazzini GS, Schaf DV, Vinadé ER, Horowitz E, Bruch RS, Brunm LM, et al. Increased S100B serum levels in dilated cardiomyopathy patients. J Card Fail. 2007;13:850–4.
94. Arai K, Takano S, Teratani T, Ito Y, Yamada T, Nozawa R. S100A8 and S100A9 overexpression is associated with poor pathological parameters in invasive ductal carcinoma of the breast. Curr Cancer Drug Targets. 2008;8:243–52.
95. Egberts F, Pollex A, Egberts JH, Kaehler KC, Weichenthal M, Hauschild A. Long-term survival analysis in metastatic melanoma: serum S100B is an independent prognostic marker and superior to LDH. Onkologie. 2008;31:380–4.
96. Yeghiazaryan K, Peeva V, Morelli M, Herrera-Marschitz M, Golubnitschaja O. Potential targets for early diagnosis and neuroprotection in asphyxiated newborns. In: Golubnitschaja O, editor. Predictive diagnostics and personalized treatment: dream or reality? New York: Nova Science Publishers; 2009. p. 509–25.
97. Hampel H, Bürger K, Teipel SJ, Bokde AL, Zetterberg H, Blennow K. Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. Alzheimers Dement. 2008;4:38–48.
98. Engidawork E, Loidl F, Chen Y, Kohlhauser C, Stoeckler S, Dell'Anna E, et al. Comparison between hypothermia and glutamate antagonism treatments on the immediate outcome of perinatal asphyxia. Exp Brain Res. 2001;138:375–83.
99. Edwards AD, Wyatt JS, Thoresen M. Treatment of hypoxic-ischaemic brain damage by moderate hypothermia. Arch Dis Child Fetal Neonatal. 1998;78:F85–8.
100. Berger R, Garnier Y. Perinatal brain injury. J Perinat Med. 2000;28:261–85.
101. Herrera-Marschitz M, Morales P, Leyton L, Bustamante D, Klawitter V, Espina-Marchant P, et al. Perinatal asphyxia: current status and approaches towards neuroprotective strategies, with focus on sentinel proteins. Neurotox Res. 2011;19:603–27.
102. Yan Q, Briehl M, Crowley CL, Payne CM, Bernstein H, Bernstein C. The NAD + precursors, nicotinic acid and nicotinamide upregulate glyceraldehyde-3-phosphate dehydrogenase and glucose-6-phosphate dehydrogenase mRNA in Jurkat cells. Biochem Biophys Res Commun. 1999;255:133–6.
103. Wan FJ, Lin HC, Kang BH, Tseng CJ, Tung CS. D-amphetamine-induced depletion of energy and dopamine in the rat striatum is attenuated by nicotinamide pretreatment. Brain Res Bull. 1999;50:167–71.
104. Mokudai T, Ayoub IA, Sakakibara Y, Lee EJ, Ogilvy CS, Maynard KI. Delayed treatment with nicotinamide (Vitamin B (3)) improves neurological outcome and reduces infarct volume after transient focal cerebral ischemia in Wistar rats. Stroke. 2000;31:679–85.
105. Virág L, Szabó C. The therapeutic potential of poly (ADP-ribose) polymerase inhibitors. Pharmacol Rev. 2002;54:375–429.
106. Martínez-Romero R, Martínez-Lara E, Aguilar-Quesada R, Peralta A, Oliver FJ, Siles E. PARP-1 modulates deferoxamine-induced HIF-1alpha accumulation through the regulation of nitric oxide and oxidative stress. J Cell Biochem. 2008;104:2248–60.
107. Bustamante D, Goiny M, Aström G, Gross J, Andersson K, Herrera-Marschitz M. Nicotinamide prevents the long-term effects of perinatal asphyxia on basal ganglia monoamine systems in the rat. Exp Brain Res. 2003;148:227–32.
108. Hamada Y, Hayakawa T, Hattori H, Mikawa H. Inhibitor of nitric oxide synthesis reduces hypoxic–ischemic brain damage in the neonatal rat. Pediatr Res. 1994;35:10–4.
109. Vannucci RC, Perlman JM. Interventions for perinatal hypoxic-ischemic encephalopathy. Pediatrics. 1997;100:1004–14.
110. Gilland E, Hagberg H. NMDA Receptor-dependent increase of cerebral glucose utilization after hypoxia-ischemia in the immature rat. J Cereb Blood Flow Metab. 1996;16:1005–13.
111. Belopavlovic M, Buchthal A. Barbiturate therapy in cerebral ischaemia. Anaesthesia. 1980;35:235–45.

112. Steen PA, Michenfelder JD. Cerebral protection with barbiturates: relation to anesthetic effect. Stroke. 1978;9:140–2.
113. Demopoulos HB, Flamm ES, Seligman ML, Jorgensen E, Ransohoff J. Antioxidant effects of barbiturates in model membranes undergoing free radical damage. Acta Neurol Scand Suppl. 1997;64:152–3.
114. Smith AL, Marque JJ. Anesthetics and cerebral edema. Anesthesiology. 1976;45:64–72.
115. Martz D, Rayos G, Schielke GP, Betz AL. Allopurinol and dimethylthiourea reduce brain infarction following middle cerebral artery occlusion in rats. Stroke. 1989;20:488–94.
116. Kaandorp JJ, Benders MJ, Rademaker CM, Torrance HL, Oudijk MA, de Haan TR, et al. Antenatal allopurinol for reduction of birth asphyxia induced brain damage (ALLO-Trial); a randomized double blind placebo controlled multicenter study. BMC Pregnancy Childbirth. 2010;10:8.