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Birth-associated neonatal encephalopathy: post-resuscitation care in West African newborns

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Education and Practice gap

Clinicians caring for newborns in low-resource settings need to recognize that:

- Several local and complex dynamics influence the burden of perinatal asphyxia in West Africa
- Appropriate use of clinical tools may improve diagnostic accuracy of birth-associated neonatal encephalopathy
- Therapeutic hypothermia without an effective package of intensive monitoring and care may not be safe
- Prevention, early diagnosis and management of secondary causes of brain injury is critical for improving health outcome

Objectives

After completing this article, readers should be able to:

- Describe the burden and causes of birth-associated neonatal encephalopathy in West Africa
- Recognize limitations in diagnosis and appropriate management of affected newborns
- Review feasible community and facility-based interventions to reduce death and disability

Abstract

The West African sub-region has the highest burden of neonatal mortality globally and the neonatal mortality rate indices is reducing very slowly. A high proportion of newborn deaths are preventable and improved quality of care can reduce long-term morbidity in survivors. Perinatal asphyxia is the major cause of death and disability in term babies in the sub-region. Neonatal resuscitation training programs have reduced stillbirths and early neonatal mortality but the overall effect on survival to discharge, population-based perinatal mortality and long term impairment is uncertain. Gaps in the health system and quality of post-resuscitation care for affected newborns may defeat gains from global efforts to improve care around the time of birth. The aim of this review is to discuss the current situation of post-resuscitation care of term babies with presumed birth-associated neonatal encephalopathy in West Africa. Limitations in diagnosing and treating affected babies and feasible interventions to improve acute and post-discharge care are discussed.

Introduction

The West Africa sub-region is comprised of 17 low and low-middle income countries with an estimated 350 million population of great diversity in culture, language, religion, and colonial legacy [Figure 1). It has the highest burden of neonatal mortality globally. (1) (2) Available data on major causes of neonatal deaths and disability in the sub-region are estimates; many births still occur at home without skilled providers, vital registration systems are relatively weak, and health systems face many challenges. (1) (3) (4) Efforts by countries to improve maternal-newborn health outcomes has resulted in significant increase in facility-based

antenatal and delivery services. (4) However, there are still major gaps in the quality of services provided around the time of birth and preventable birth complications especially perinatal asphyxia (PA) remain a major cause of death and disability. (5) (6)

PA occurs when there is interruption of blood flow and gas exchange to the foetus around the time of birth. Significant interruption results in hypoxic brain injury and neonatal encephalopathy (NE). The "golden minute" – the first minute after birth, provides a crucial window of opportunity for skilled essential care to reduce death and disability. (7) Standardized neonatal resuscitation training (NRT) programs such as Helping Babies Breathe (HBB) have significantly improved resuscitation skills of frontline providers and reduced deaths on the first day of life. (8) (9) (10) Although HBB may reduce intrapartum-related neonatal mortality by 30% in low-resource settings, the overall effect of neonatal resuscitation training on survival to discharge, population-based perinatal mortality and long term impairment is uncertain. (7) (11) (12) Improving the quality of care beyond the time around birth may save more lives and reduce severe disability.

In West Africa, many births still occur at community and primary health facility level, often without a skilled provider or one skilled provider attending both mother and newborn. (4) Newborns who require help to breathe or have weak or no cry at birth may not receive effective intrapartum resuscitative care. However, with government investments in community-based health services, HBB program is making inroads into intrapartum care at all levels of health service delivery. (13) Consequently, increasing number of successfully resuscitated newborns are being referred to higher level facilities for post-resuscitation care. This paper describes the situation in West Africa and suggests options that may reduce the burden of birth-associated NE and improve hospital-based post-resuscitation care for affected term newborns.

The burden of perinatal asphyxia

The burden of PA reflects the quality of maternal-newborn health services; underlying factors for inadequate services in the sub-region has been described. (3) In Africa, the West Africa sub-region has the poorest indices for facility-based maternal care; about 50% of births still occur at home with 20% occurring with no person present and only 35% attended by a doctor or nurse/midwife. (14) Inequalities in access to health and wealth significantly contribute to giving birth with no one present and Nigeria accounts for a significant proportion of the global burden. (15) Facility-based skilled delivery is inversely correlated to early neonatal deaths and varies widely between and within countries, from 5% in north western Nigeria and 7.2% in rural Burkina Faso to 78% in Senegal. (16) (17)

Access to emergency obstetric care is limited especially in rural communities where transportation is a major constraint. (18) (19) Overall, inadequate linkages and standards, health workforce numbers and competencies and other health system gaps undermine emergency obstetric care. Ambulance services, where they exist, are not equipped for transportation of sick newborns and may not be accessible for rural communities. Newborns who require post-resuscitation care may not receive respiratory support during transportation in regular vehicles.

Published country data on the burden of PA in the sub-region are mostly estimates due to inadequate health information systems. In 2010, modelled estimates of population level data on rates of adverse outcome related to intrapartum events showed an estimated 198,000 intrapartum stillbirths, 129,000 intrapartum-related neonatal deaths, and 173,000 incident cases of NE (Table 1). Unpublished 2017 data from 16 neonatal referral centres in Republic of Benin, Ghana and Nigeria show that PA accounted for 30% (range 14% – 58%) of term newborn admissions and 20% (range 11% – 36%) of all neonatal admissions. According to World Health

Statistics 2015, intrapartum-related complications among live-born caused 8 – 13% of deaths in young children under 5 years in West African countries. (20)

Little is known about long-term morbidity among survivors of PA in low-resource settings, but high risks of impaired neurodevelopmental outcome has been reported from high-income countries. (21) (22) Although most hospitals in the sub-region lack requisite human resource and infrastructure for intensive post-resuscitation care efficient use of available resources may improve the quality of care and reduce severity of long-term morbidity. (23) (24)

Diagnosis of birth-associated neonatal encephalopathy

NE has been described as "clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes." (25) Maternal, placental and foetal risk factors may predispose newborns to NE but intrapartum-related acute hypoxic ischaemia is the underlying cause of NE in 50-80% of cases in high-income countries; this proportion may be higher in low-resource settings. (26)

The criteria for attributing birth-associated hypoxic-ischemic event as underlying cause of NE has evolved since 1996 but the cornerstone criteria remain the presence of severe metabolic acidosis (pH < 7.0 and base deficit ≥ 12 mmol/L) with early signs of moderate or severe encephalopathy. Other minor criteria include sentinel obstetric hypoxic-ischaemic event, abnormal foetal heart rate patterns, Apgar score, neuroimaging, and multisystem organ complications. NE is an evolving disorder and no single test or clinical tool is diagnostic. (27) Acid-base measurements and neuroimaging are not available at the point of care in West Africa, but effective application of clinical criteria could improve the diagnostic accuracy of birth-associated NE.

There are multiple challenges to accurate diagnosis of birth-associated NE in the sub-region. Many mothers arrive at hospital in the second stage of labour. The partograph for intrapartum monitoring and Apgar scoring system, are often not used appropriately or interpreted accurately. (24) (28) Human resource is very limited, integrated perinatal care is rare, paediatric teams attend relatively few complicated births and often arrive after the 'golden minute'. Newborns referred for post-resuscitation care arrive with inadequate information about perinatal events and unaccompanied by the mother or a health worker who attended the delivery. Routine clinical observation for seizures is standard practice. Clinical encephalopathy assessment tools are infrequently used.

The Thompson score, first described in a South African population, is a sensitive early predictor of abnormal amplitude-integrated electroencephalogram and moderate-severe encephalopathy. (29) (30) The modified Sarnat and Sarnat score has been used to diagnose cases of intrapartum-related NE among newborns referred as PA in Senegal. (31) It is feasible to diagnose other causes of perinatal asphyxia without expensive technology. These clinical encephalopathy assessment tools are easy to use and can be applied as early effective screening tools for birth-associated NE in low-resource settings.

Currently, in West Africa, birth-associated NE is diagnosed when a newborn who required resuscitative care at birth presents with abnormal neurological examination especially clinical seizure. Perinatal or birth asphyxia is still the most commonly used terminology. Almost all cases are presumed to be intrapartum-related and other causes of encephalopathy that present at birth are largely undiagnosed.

Accurate diagnosis of intrapartum-related NE is an essential before application of specific therapies that improve health outcomes in high-income settings. The prevailing circumstances in West Africa undermines application of therapeutic hypothermia. Training and supervision of front-line clinicians on appropriate use of partograph, Apgar score, encephalopathy assessment tools, and use of checklists (Table 2) to capture intrapartum events and other clinical data may improve the diagnostic accuracy of birth-associated NE.

Management of birth-associated neonatal encephalopathy: current practice

There is no specific treatment for birth-associated NE although therapeutic hypothermia reduces death and disability when given as part of a package of neonatal intensive care. (32) The safety and efficacy of therapeutic hypothermia in low-resource settings is uncertain especially where the package of neonatal intensive care is largely rudimentary. (33) In the sub-region, neonatal intensive care package is limited to tertiary centres and few non-tertiary hospitals and consist of essential care, oxygen therapy, intravenous infusions including blood products, gavage feeding and non-invasive respiratory support. Very few centres provide mechanical ventilation. Human resource is severely limited and certified neonatal nurses are rare. Laboratory and radiological services may not be accessible at the point of care and basic monitoring devices such as pulse oximeters are limited.

Effective care of affected newborns requires a well-organized health service that provides timely and appropriate supportive care. None of the countries have specific national guidelines for referral of babies for post-resuscitation care. In the few countries with national guidelines for clinical care the information is scanty and not updated, and some institutional guidelines are not evidence-based. (34) In rural settings, affected babies may not receive skilled post-resuscitation assessment before discharge; it is not uncommon for cases to be referred on the second or third day of life because of poor feeding or seizures.

Generally, standard care consists frequent monitoring of vital signs and blood glucose, oxygen therapy and respiratory support if indicated, no enteral feeding on day 1, intravenous dextrose and electrolytes infusion, observation for seizures, antibiotics if presumed risk of sepsis. The general recommendation not to provide extra warmth is described as passive cooling in some countries. Few centres use improvised cooling with towels and icepacks but the practice has not been evaluated. Feeding with breastmilk is commenced when the baby is stable. Phenobarbital is the first-line anticonvulsant and second line is phenytoin, where available. Some tertiary centres use midazolam infusion for intractable seizures. Concerns about respiratory depression from anticonvulsants limits appropriate treatment of clinically diagnosed seizures. All centres that provide intensive care package provide post-discharge follow-up care for about 6 – 24 months but the content and quality of the service is variable as there are no national standards. It is not uncommon for families to seek rehabilitation care from spiritual and traditional healers post-discharge and only return for hospital care when there is severe disability.

Evidence-based guidelines and clinical pathways may reduce variability in practice and improve quality of services during the acute and rehabilitation stages of care. (35) (36) Limited capacity to continuously monitor body temperature and oxygen therapy is a major constraint. Babies undergoing facilitated endogenous cooling, so-called passive cooling, are at risk of severe hypothermia, hypoxia or hyperoxia; this may worsen brain injury. Clinical observation, the only method available for diagnosing seizures, is known to be highly inaccurate; underdiagnosis increases the risk of brain damage while overdiagnosis may lead to unnecessary and toxic treatments. (37)

Recommendations to improve health outcomes

Reductions in stillbirths and early neonatal death from improved intrapartum care and HBB may lead to increasing population of children and adults with severe disability and this has socioeconomic implications for society. (21) (38) Effective implementation of low-cost approaches could prevent some cases of NE, improve the quality of resuscitative and post-resuscitation care and enhance post-discharge rehabilitation services. (24) (39) This section provides general recommendations that can be adapted to local circumstances.

Community engagement:

Of the 3 major causes of neonatal death, PA is the least understood by communities in West Africa. Cultural beliefs and myths about pregnancy and birth-associated injuries affect health-seeking behaviour for facility-based delivery services and post-discharge rehabilitative care. Improving the health literacy of mothers and families about PA and the socioeconomic consequences of acute and rehabilitative care is critical to reducing the burden of disease. (24) (39) The increasing number of antenatal care attendance in the sub-region provides an opportunity to educate mothers and families about the risk factors and consequences of PA and the value of rehabilitation care.

Engaging traditional, political and religious leaders as well as social groups of women and men in rural communities as advocates for reducing PA and its complications will reduce cultural barriers to care-seeking. The tradition of restricting pregnancy-related information to women only needs to change. Community health services should create opportunities to educate men about PA, the 'School of Husbands' in Niger is a program worth emulating. (40) In communities where there is limited access or cultural resistance to facility-based care integrating traditional birth attendants into the health system should be considered as it has been shown to improve maternal-newborn outcome in Sierra Leone and other African countries. (41). Effective community engagement has the potential to significantly reduce demand-side barriers to facility-based care. (42)

Improve referral systems and integrate care

No single referral system can meet the needs of all communities; lessons can be learned from diverse approaches to improve referral systems for emergency maternal-newborn care. (43) Rural community efforts and social media platforms are bridging some gaps in maternal services. These approaches can be extended to newborns when intrauterine transfer is not possible. Adequate oxygen therapy and respiratory support should be provided throughout the journey from the labour room to the neonatal unit. Every place where birth occurs should have a newborn transport kit (Table 3) containing appropriate sizes of bag and mask and other supplies. Where ambulance or other form of vehicular transport service exist, efforts should be made to equip them with an oxygen source and a safe flat surface for the newborn who may require respiratory support in transit.

There is little formal communication between obstetric and paediatric services except during perinatal mortality meetings and providers of neonatal care know little about rehabilitation services available in the health system. Effective communication and collaboration between departments is essential. An integrated approach to perinatal care may improve diagnostic capacity and management of affected babies. (36) (44) Hospitals that offer comprehensive obstetric care should have a paediatric team responsible for the newborn around the time of birth. Limited human resource is a major handicap as district hospitals, where most births occur, may have one medical officer or paediatrician responsible for all neonatal and paediatric cases. However, a team of skilled paediatric

nurses equipped with guidelines and checklist (Table 2) could provide this service under supervision of the single doctor.

Quality clinical care

Like other low-resource settings, many facility-based birth attendants in the sub-region have not received NRT and basic resuscitation equipment are not available at the point of care. (45) With central government support, national paediatric/neonatal societies have the pivotal role of formulating national guidelines, training birth attendants, possibly instituting a national NRT program, and advocating for essential equipment and supplies for newborn services. Other approaches to improving essential care and resuscitation around the time of birth has been described. (46)

Recognized causes of secondary brain injury in babies with birth-associated NE include: secondary hypoxia and hyperoxia, hypocapnia and hypercapnia, untreated and prolonged seizures, sepsis, hyperthermia and excessive (< 33 Centigrade) and prolonged cooling (>72 hours). In high income settings over the last decade, neonatal neurocritical care has emerged as a culture change towards a "brain focused" approach to mitigate secondary brain injury, rapid recognition of complications and seizures, consistent use of protocols and use of experienced teams. There is urgent need for culture change in the practice of neonatology in West Africa; a culture of teamwork and continuous quality improvement in the organization and practice of neonatal care.

Culture change will require basic training in measures to prevent secondary brain injury and use of affordable and durable diagnostics including simple amplitude integrated electroencephalography device to improve the diagnosis of seizures especially in tertiary centres. Affordable and durable pulse oximeters and acid-base measurement equipment may improve the quality of care and health outcomes. Anticonvulsant therapy needs review; phenobarbital and phenytoin may cause neuronal apoptosis, have variable pharmacokinetics and may not effectively treat neonatal seizures. (47) Phenobarbital, the most commonly used anticonvulsant suppresses respiration and increase the risk of hypoxia and hypercapnia; this has implications for secondary brain.

Facilitated endogenous cooling, so-called passive cooling is currently standard practice in most West African countries. The endogenous physiological response to asphyxia, central cooling, was observed in babies in 1958 by Bernard and Cross and recently in a pilot randomised trial in Uganda. (48) (49) The cooling response may be exaggerated and prolonged in babies with severe NE. It is unclear whether this endogenous cooling response is as neuroprotective as therapeutic hypothermia. Currently, there is no convincing evidence on the safety and efficacy of therapeutic hypothermia in low-resource settings. (32) (33) Antenatal inflammation, which may be relatively more prevalent in low-resource settings, increases the risk of NE and therapeutic hypothermia may not be protective. (50) Inappropriate application of therapeutic hypothermia may cause harm. Concerted efforts should focus on reducing secondary brain injury until local randomized trials provide evidence for other therapies.

Future interventions and research

Countries should consider setting up a national centre of excellence on neonatal neurocritical care to scale up national training. Tertiary institutions or countries should consider joining established neonatal networks. Collaborative networks provide opportunity for improving standards, learning, research collaboration, data-driven quality improvement and more. Ethiopia has recently joined the Vermont Oxford Network and other countries can learn from

Ethiopia's experience. West African Health Organization should recognize the burden of birth-associated NE as a sub-regional priority, advocate for improved neonatal services and facilitate a regional collaborative neonatal network.

Parenteral levetiracetam, commonly used for neonatal seizures in high-income countries is expensive and not available in the sub-region. Safer, effective and affordable drugs for neonatal seizures will reduce morbidity. Feasibility of conducting randomised clinical trials on newer anticonvulsants for newborns in the sub-region should be explored.

Accurate diagnosis of antenatal inflammation in the sub-region is a challenge. Research on rapid diagnostic tests are needed. The benefits or otherwise of endogenous physiological cooling should be investigated in a randomized controlled trial in a setting with high burden of disease.

Summary

- There are major gaps in the health system of West African countries that inevitably result in high burden of neonatal deaths and disability from perinatal asphyxia.
- Expensive technologies are not required to reduce the high burden of death and disability; engaging communities and improving timely access to maternal-newborn services is essential
- New technologies and therapies will improve the diagnosis and management of newborns with birth-associated NE but the primary goal should focus on prevention.
- Quality improvement interventions should address the organization and culture of clinical care
- More research on safer anticonvulsants and endogenous and therapeutic cooling are needed

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