

ORIGINAL ARTICLE

LONG TERM OUTCOME OF NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY

S raphin Nguetack^{1,2}, Fleurine Lekeulem Tebon³, Daniel Armand Kago Tague^{1,2}, Francklin Djifack Tetinou³, Nadia Adjifack Tetinou³, F licit e Nguetack^{1,2}, Evelyn Mah^{1,2}, Andreas Chiabi^{1,2}.

¹Department of Pediatrics, Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Cameroon;

²Gynaeco-Obstetrics and Pediatric Hospital, Yaounde, Cameroon;

³Faculty of Medicine, Higher Institute of Health Sciences, Universit  des Montagnes, Bangangt , Cameroon.

ABSTRACT

Aim: To determine the long-term outcome of neonates with hypoxic-ischemic encephalopathy (HIE).

Materials and Methods: This was a descriptive cross-sectional study carried over a period of 4 months from February 20 to May 22, 2018. We recruited consecutively 60 children aged 6 to 72 months who had survived HIE and had followed up in the outpatient department. Children born at term (≥ 37 weeks of amenorrhea) and who got an Apgar score < 7 at the 5th minute of birth and/or mild, moderate or severe encephalopathy were included in the study. The parameters studied included age, gender, schooling for those at school age, the Apgar score at the 5th minute of birth, the degree of encephalopathy according to Sarnat grade, the resuscitation maneuvers used at birth, the duration of resuscitation (in minutes), the duration of the neonatal hospitalization (in days) and the child's pathologies during the neonatal hospitalization. Child's vision, hearing and psychomotor development were assessed. Association between HIE severity and long-term outcome was assessed.

Results: Total 60 children with male: female ratio of 2:1 were included in the study. The mean age was 36.4 ± 19.0 months. Twenty-seven (45%) children were at school age. However, 19 (70.37%) of these school age children were not in school. Co-morbidities seen were cerebral palsy in 47 (78.3%), epilepsy in 17 (28.3%), blindness in 4 (6.7%) and deafness in 3 (5.0%). The majority of children with a history of perinatal asphyxia were born in a borough health center 24 (40.0%). Psychomotor assessment was normal in 8 (13.3%) children, mild retardation in 2 (3.3%), moderate retardation in 16 (26.7%) children, severe retardation in 7 (11.7%) and profound in 27 (45.0%) children. Thirty-five (58.3%) children had grade 3 HIE, 20 (33.3%) had grade 2 HIE and 5 (8.3%) had grade 1 HIE. An Apgar score of between 3 and 4 was associated with profound mental delay ($p < 0.001$). Children with Sarnat 1 HIE were at no risk of psychomotor retardation ($p = 0.001$). Sarnat 3 HIE grade increased the risk of having profound psychomotor retardation ($OR = 13.2$; $p = 0.01$). Children resuscitated for more than 20 minutes were at significant risk of developing profound delay ($OR > 1000$; $p = 0.002$). Co-morbidities strongly associated with profound psychomotor retardation were cerebral palsy ($p = 0.007$) and epilepsy ($p = 0.001$).

Conclusion: The children presenting a severe HIE had a profound mental delay. The neurological sequelae found were mainly psychomotor retardation, cerebral palsy, epilepsy and neurosensory abnormalities.

ARTICLE HISTORY

Received 23 March 2021

Accepted 30 June 2021

KEYWORDS

Psychomotor development, perinatal asphyxia, HIE.

Introduction

Psychomotor development reflects the cerebral

maturation of the child through his motor acquisitions and his psychic progress (intelligence, language, and affectivity, etc.).¹ The etiology of psychomotor retardation are mostly unknown; however, some potential causes can be found in the perinatal period.² Perinatal asphyxia is defined as an impairment of gas exchange which, when persisted, leads to fetal hypoxemia and hypercapnia.³ World Health Organization (WHO) estimates that around 3% of the 120 million newborns born each year in

Address for Correspondance: Daniel Armand Kago Tague. MD, Gynaeco-Obstetrics and Pediatric Hospital, BP: 4362 Route de Ngousso Yaounde, Yaounde - Cameroon.

Email: kagog2@yahoo.fr

 2022 Pediatric Oncall

developing countries are prone to suffocation and need resuscitation. About 900,000 of these newborns die from asphyxia. Asphyxia accounts for 23% of the 4 million annual neonatal deaths worldwide⁴, and 8% of all deaths of children under five.⁵ Today, the incidence of perinatal asphyxia remains high and seems to be influenced by the health level of countries. In the majority of African countries, like Nigeria, its incidence in 2003 was 10%⁶; Burkina Faso in 2015, 19.8%⁷; in the Democratic Republic of Congo in 2016, 15.6%.⁸ In Cameroon, perinatal asphyxia is the third leading cause of neonatal death after neonatal infection and prematurity. Chiabi et al found an incidence of 8% in 2010 at the in Cameroon.⁹ In a descriptive cohort study on the clinical and etiological aspect of cerebral palsy in 2015 at Cameroon, the authors reported that most etiologies of cerebral palsy are mainly perinatal at 80.2% dominated by perinatal asphyxia (70.1%).¹⁰ Thus, perinatal asphyxia is therefore a real public health problem. In short term, asphyxia could lead to multi-organ failure or death,^{3,11} while in the long term, children surviving hypoxic-ischemic encephalopathy (HIE) could develop either cerebral palsy, psychomotor retardation, neurosensory and intellectual abnormalities, epilepsy, learning and behavior problems^{11,12} which are heavy socio-economic, emotional, physical burdens and which constitute a source of stigmatization for the victims and their families. We undertook this study to determine the long-term outcome of neonates with HIE.

Methods & Materials

This was a descriptive cross-sectional study carried out at a tertiary referral center in Cameroon over a period of 4 months, from February 20 to May 22, 2018. We recruited consecutively 60 children aged 6 to 72 months who had survived HIE, and who were on regular follow up in the pediatric outpatient department (OPD). Children born at term (≥ 37 weeks of amenorrhea) and who got an Apgar score < 7 at the 5th minute of birth and / or mild, moderate or severe encephalopathy were included in the study.¹³ Children who presented with a pathology that could affect neurological development (kernicterus, neonatal meningitis, embryofetopathy, and metabolic disease) were excluded. After obtaining administrative authorizations and ethical clearance by the Bioethics Committee of the Faculty of Medical Sciences of Université des Montagnes, the cases were recruited using a pre-established and pretexted technical sheet, summarizing the variables linked to the specific objectives. Written informed consent was taken of the parents. All children meeting our inclusion criteria were enrolled in the study. The parameters assessed included age, gender, schooling for those at school age, the Apgar score at the 5th minute of birth, the degree of encephalopathy according to Sarnat grade¹³, the resuscitation maneuvers used at birth, the duration of resuscitation (in minutes), the duration of the neonatal hospitalization (in days), and the child's pathologies during the neonatal hospitalization from the medical records. In a quiet room, without outside intervention, the following entities were briefly examined in the child with playful materials (Cubes, pellets, bottles containing colored pellets) - The vision (using a target object, the examiner in front of the child made movements from

left to right, up and down and thus objectified the eye tracking of the child), hearing (the examiner in front of the child made small claps with his 2 hands on either side of the child's ear and observed the child's reaction to noises. For those who did not react to the noise, an auditory evoked potential was required to identify deafness.)

Psychomotor development was assessed using the Denver II scale. This test represents a diagram where the abscissa is the age and the ordinate each item, represented by a rectangle. The rectangle begins at the age at which 25% of the population takes the test, the beginning of the gray corresponds to 75% of the population and the end of the rectangle to 90% of the population.¹⁴

For each area of Denver, we administered at least three items to the far left of the line corresponding to the child's age, and those crossing the line. When the child did not complete these items, we administered other items to the left of the row until he passed three consecutive items. Then we administered the items to the right of his age line until he missed three consecutive items. At the end of the evaluation, we therefore determined the developmental age (DA) which corresponded to the age at which the child performed an item, then the development quotient (DQ) from his current age (CA) using the formula; $DQ = (DA/CA) \times 100$. This allowed us to classify mental sub normality as mild, moderate, severe or deep/profound, according to the WHO classification.¹⁵ The Denver was carried out on several entities according to age. For each age there are corresponding acquisitions. A logarithmic regression curve was thus established showing the evolution of psychomotor acquisitions according to age. A logarithmic regression curve was established of the form $\ln(1+X)$. In normal children and in asphyxiated children of the form $\ln(1+X)$. The comparison of these curves made it possible to see and estimate the percentage of acquisition that the asphyxiated children had in relation to the norms defined by the Denver II.

$X = (\text{Percentage of acquisitions}) * (\text{Corresponding developmental age})$

The diagnosis of cerebral palsy was clinical based on a history of abnormal motor development that was not progressive, coupled with the presence of abnormal neurological signs that localized the lesion to the brain.¹⁶

Data analysis: The data were analyzed by the SPSS software version 22. The Chi square test used to determine the association between two variables. Logistic regression used to eliminate the confounders. The odd ratio and their confidence interval of 95% allowed measuring the strength of association.

Results

Total 60 children with male: female ratio of 2:1 was included in the study. The mean age was 36.4 ± 19.0 months. Twenty-seven (45%) children were at school age. However, 19 (70.37%) of these school age children were not in school. Co-morbidities seen were cerebral palsy in 47 (78.3%), epilepsy in 17 (23.3%), blindness in 4 (5.5%) and deafness in 3 (4.1%). The majority

of children with a history of perinatal asphyxia were born in a borough health center 24 (40.0%) whereas 12 (20%) were born in a clinic, 15 (25%) were born in a district hospital, 7 (11.6%) were born in a central hospital and 2 (3.3%) were born in a regional hospital. Neonatal infections represented 29 (48.3%) of the pathologies developed in neonatology. The other pathologies were respiratory distress 14 (23.3%), neonatal jaundice 5 (8.3%) and neonatal meningitis 4 (6.7%). Concerning the psychomotor assessment, it was normal in 8 (13.3%) children, mild retardation in 2 (3.3%) children, moderate retardation in 16 (16.6%) children, severe retardation in 7 (11.6%) and profound in 27 (45.0%) children.

Concerning the Apgar score at 5th minute, 8 (13.3%) children had a score between 3 to 4, 14 (23.3%) between 4 to 5 and 38 (63.3%) between 5 to 6. The most widely used resuscitation maneuver was ventilation in 59 (98.3%), external cardiac massage in 35 (58.3%) and intubation 18 (30.0%). The most predominant resuscitation time was greater than 20 minutes in 34 (56.6%) whereas 15 (25%) required resuscitation between 15-20 mins, 7 (11.6%) required resuscitation between 10-15 mins and 4 (6.6%) required resuscitation between 5-10 mins. Thirty-five (59%) children had grade 3 HIE, 20 (33.3%) had grade 2 HIE and 5 (8.3%) had grade 1 HIE. Neonatal care for 7 to 14 days was required in 38 (63.3%) and the mean duration was 15.1±13.6 days whereas 7 (11.6%)

required neonatal hospital stay for <7 days. At the end of the neonatal care, 33 (55%) children had a sequela. An Apgar score of between 3 and 4 was associated with profound mental delay ($p<0.001$). Children with Sarnat 1 HIE were at no risk of psychomotor retardation ($p=0.001$). Sarnat 3 HIE grade increased the risk of having profound psychomotor retardation ($OR=13.2$; $p=0.01$). Children resuscitated for more than 20 minutes were at significant risk of developing profound delay ($OR>1000$; $p=0.002$). Co-morbidities strongly associated with psychomotor retardation were cerebral palsy and epilepsy (Table 1).

Discussion

Our study involved 60 children with a history of perinatal asphyxia complicated by hypoxic-ischemic encephalopathy. This sample is lower than that of Dongol et al in Nepal who in his study evaluated 102 infants¹⁷, and the one of Thomberg et al in Sweden who evaluated 65 children.¹⁸ But it is higher than that of TOH et al who evaluated 23 children. This difference could be explained by the difference in age group and study period.

Our study population had 67% boys. This male predominance is also reported by Yelamali B et al¹⁹ who found 65% boys. Similarly, Dongol et al¹⁷ found 57% boys. Indeed, Johnston and Hagberg suggested that sex hormones (estrogen) appear to protect the female fetal brain from anoxia and ischemia.²⁰

Table 1. Correlation between the Apgar score, the Sarnat grade, the duration of resuscitation and the level of development.

| Variables | Psychomotor Retardation | | | | Deep/ Profound | P-value | OR | IC 95% |
|----------------------------------|-------------------------|----------|-----------|----------|-------------------|---------|------|-------------|
| | Normal | Mild | Moderate | Severe | | | | |
| APGAR at 5 minute | | | | | | | | |
| [3-4] | 1 (12.5) | 0 | 0 | 0 | 7 (87.5) | 0.001 | 1.0 | [0.1-29.1] |
| [4-5] | 0 | 0 | 3 (21.4) | 2 (14.3) | 9 (64.3) | 0.9 | >10 | [0.0-NA] |
| [5-6] | 7 (18.4) | 2 (5.2) | 13 (34.2) | 5 (13.2) | 11 (28.9) | 0.03 | 0.2 | [0.0-1.3] |
| Sarnat grade | | | | | | | | |
| Sarnat1 | 4 (80) | 1 (20) | 0 | 0 | 0 | 0.001 | 0.01 | [0.0-0.1] |
| Sarnat2 | 3 (15) | 1 (5) | 12 (60) | 3 (15) | 1 (5) | 0.7 | 0.8 | [0.1-4.3] |
| Sarnat3 | 1 (2.8) | 0 | 4 (11.4) | 4 (11.4) | 26 (74.2) | 0.01 | 13.2 | [2.1-257.4] |
| Duration of resuscitation | | | | | | | | |
| [5-10] | 2 (50) | 0 | 1 (25) | 1 (25) | 0 | 0.05 | 0.1 | [0.1-1.1] |
| [10-15] | 2 (25) | 1 (12.5) | 4 (50) | 0 | 1 (12.5) | 0.3 | 0.3 | [0.0-3.07] |
| [15-20] | 4 (26.6) | 0 | 6 (40) | 1 (6.6) | 4 (26.6) | 0.09 | 0.2 | [0.0-1.5] |
| >20 | 0 | 1 (3.0) | 5 (15.1) | 5 (15.1) | 22 (66.6) | 0.002 | >10 | [0.0-NA] |
| Comorbidities | | | | | | | | |
| Cerebral palsy | 3 (6.4) | 1 (2.1) | 10 (21.2) | 7 (14.8) | 26 (55.3) | 0.007 | 9.1 | [2.1-8.2] |
| Epilepsy | 1 (5.5) | 0 | 2 (11.1) | 3 (16.6) | 12 (66.6) | 0.001 | 3.4 | [1.3-3.2] |
| Blindness | 0 | 0 | 2 (50) | 0 | 2 (50) | 0.9 | >10 | [0.0-1.4] |
| Deafness | 0 | 0 | 1 (33.3) | 1 (33.3) | 1 (33.3) | 0.9 | >10 | [0.5-1.2] |

From the place of birth, our study shows that children with a history of perinatal asphyxia were mostly born in borough health center (40%). Indeed, these health structures do not have enough human and material resources to manage neonatal resuscitation. It is in this sense that Durkin et al suggested in 2000 that the increasingly high frequency of perinatal asphyxia in developing countries would be linked to the inadequacy of the resources necessary for obstetric follow-up and treatment and burden of complications in labor and delivery.²¹

In our study, 45% children were of school age. However, 70.3% were not in school. The WHO estimates that around one million children who have suffered from perinatal asphyxia live with serious neurological sequelae such as intellectual disability, cerebral palsy and epilepsy. These consequences are sources of motor and intellectual disabilities, thus explaining the predominance of out-of-school children.²²

The most prevalent degree of HIE in our sample was Grade 3 HIE (59%). Sepeku et al in Tanzania also report a predominance of Grade 3 HIE (42.5%).²³ In contrast, Yelamali B et al in India report a predominance of Grade 1 HIE at 98.36%.¹⁹ The predominance of severe HIE in Africa can be explained by the lack of infrastructure in most health center and the level of health care which still remains precarious in our regions. Thus, perinatal asphyxia seems to be influenced by the health level of the countries.²²

Of our 60 children with a history of perinatal asphyxia, 45% had profound/deep psychomotor retardation, 11.6% had severe retardation, 26.6% had moderate retardation and only 3.3% had mild retardation. This result is close to that reported by Mah et al, who found 23% deep delay, 15% moderate and 12% mild.²⁴ This could be explained by the fact that, HIE is an important cause of permanent brain damage which can lead to psychomotor retardation, cerebral palsy or neonatal death. In addition, Nguetack et al reported in 2013 that perinatal asphyxia complicated by HIE was the leading cause of psychomotor delay in children aged 5 to 72 months with a predominance of severe psychomotor delay.²⁵

In our series, the association between the Apgar score of 3-4 and profound psychomotor retardation was extremely significant. Bissouma et al showed in his study that an Apgar score between 0 and 3 at the 5th minute multiplied the risk of psychomotor retardation by 9.²⁶ Thorngren-Jerneck et al showed in their study that an Apgar score <7 at the 5th minute exposed to the risk of psychomotor handicap, epilepsy and long-term mental retardation with Odds Ratio respectively of 31.4, 7.9, and 9.5.²⁷

Children who had a Sarnat grade 1 HIE were at no risk of psychomotor retardation. The occurrence of a severe AIE increased the risk of having profound psychomotor retardation 13 times. In fact, the degree of encephalopathy influences long-term neurological prognosis. Mild HIE have an excellent prognosis while severe AIE are associated with a very unfavorable prognosis; 100% serious sequelae or death.²⁸ This result thus agrees with the hypothesis of the literature according to which: the evolution of brain distress is

roughly parallel to the stage of initial asphyxia severity.

In our study, the comorbidities strongly associated with psychomotor retardation were mainly cerebral palsy and epilepsy with a risk multiplied by 9 and 3 respectively. Moifo et al found that cerebral palsy is associated with psychomotor retardation in 40.2% with the main risk factors being perinatal asphyxia and antenatal infections.²⁹ Also, Nguetack et al found that epilepsy represented the 2nd cause of psychomotor retardation in children.²⁵ In addition, data from the literature show that epilepsy is associated with psychomotor retardation in 60 to 66.7% of cases.³⁰ Indeed, anoxo-ischemic and gliosis lesions secondary to perinatal asphyxia are potential epileptogenic foci. The studies by Chevalier et al showed us that the existence of these lesions leads to serious consequences such as mental retardation associated with neurological disorders (cerebral palsy).³¹ However, Mazet and Houzel claim that to be successful, psychomotor development requires basic neuroanatomical equipment, the integrity of the anatomical structures and the central nervous system.³²

Children with grade 3 HIE had a greater acquisitions' delay compared to children with grade 2 or 1 HIE. Our results are comparable to those of Avebe et al in Mali, who found a significant association between the degree of HIE and the acquisitions of gross motor skills, language and social contact.³³ These results could also be explained by the topography of the lesions. This is because the extent of brain damage is influenced by the degree of asphyxia. In severe or prolonged asphyxia, more or less extensive cortical necrosis and involvement of the basal ganglia were observed. Dysfunction of the basal ganglia leads to abnormalities in the motor cortex, alterations in muscle tone, and abnormal involuntary movements.³³

Conclusion

In our study, children presenting a severe HIE were predominant, followed by moderate and mild encephalopathy. The neurological sequelae found were mainly psychomotor retardation, cerebral palsy, epilepsy and neurosensory abnormalities. We found a significant association between a low Apgar score and profound psychomotor retardation. Profound delay was associated with severe HIE.

Authors Contribution

SN: Conception and study design, reading for important intellectual content and final approval of version to be submitted. FLT: Collection of data and drafting of manuscript. DAKT: Drafted manuscript and revised the manuscript. FN, FDT, NAT: Revised the manuscript. EM: Edited the manuscript. AC: Final approval of version to be submitted.

Compliance with Ethical Standards

Funding: None

Conflict of Interest: None

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