

## **Analyzing Risk Factors for Brain Damages in a Group of Newborns with High Risk of Neurodevelopmental Sequelae: A Moroccan Study**

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### Abstract

The aim of the study is to identify risk factors for occurrence of perinatal brain injury objectified in transfontanellar ultrasound (TFU) in a group of infants with high risk of neurodevelopmental sequelae. It's a retrospective study, conducted at the neonatal intensive care unit of the Children's Hospital of Rabat, during the period from 1 January to 31 December 2014. Were included newborns hospitalized for a medical condition with intrauterine croissance retardation (ICUR) more than 5 days and have survived. The neurological workup includes TFU made between day 2 and day 5 of life. Data analysis was performed on SPSS 18.0 software. The level of significance was  $p < 0.05$ . The percentage of newborns that developed neurological damage to the TFU was 36%. Patients with abnormalities in the TFU had a breakdown time, duration dependence of O<sub>2</sub>, duration of hospitalization and a higher frequency of nosocomial infections than patients without abnormality. The interest in the prevention of nosocomial infections is to try to shorten the duration of invasive ventilation, favoring fast relay noninvasive ventilation.

Keywords: brain injury; newborns; prematurity, neurodevelopmental sequelae, trans-fontanellar ultrasound.

### Introduction

With the many advances in neonatal resuscitation, and different government policies to reduce the level of infant mortality, we are faced with an increasing number of infants at high risk of neurological, sensorial and neurodevelopmental sequelae.

Advanced in perinatal intensive care have been associated with improved survival of high-risk neonates but have not resulted in decreased morbidity. Small sample sizes, heterogeneity of cohorts and methodology, diversity of perinatal clinical practice, and the high cost of randomized, controlled trials (RCTs) and follow-up care have all contributed to the lack of rigorous data on the sequelae of preterm delivery and the therapies used to improve the long-term outcome of high-risk infants.

The administration of oxygen and postnatal steroids are prime examples of interventions that may have immediate positive effects but negative long-term effects (Barrington, 2001). In addition, multicenter studies have identified significant center differences in the management and developmental outcome of high-risk infants (vohr, 2004).

In Morocco, a 2004 survey by the Ministry of Social Development, Family and Solidarity

5.2% of the general population is considered disables. These disabilities have congenital or perinatal origin in 22.8% of cases according to the studies. Various pathologies involved are represented primarily by prematurity, low birth weight, neonatal infection, perinatal asphyxia, neonatal jaundice, congenital defects and metabolic disorders ([www.social.gov.ma](http://www.social.gov.ma), 2010).

Progress was also made in the early detection of perinatal brain injury due to the transfontanellar ultrasound (TFU) and especially magnetic resonance imaging (MRI) whose access is not always easy especially in developing countries.

The objective of this study is to identify risk factors for perinatal brain injury objectified in TFU in a group of infants with high risk of neurodevelopment sequelae.

### Method

This is a retrospective study, from medical records of newborns admitted to the neonatal intensive care unit at Children's Hospital of Rabat during the period 1 January to 31 December 2014. It included all patients who survived after a hospitalization duration greater than 5 days. Exclusion criteria were:

patients who died and patients whose records were unusable.

A TFU was performed in patients at risk, between the second day (J2) and the fifth day (J5) of hospitalization. For premature, it was repeated every week until 37 weeks of corrected age.

The variables studied were as follows:

- Gestational age determined by the early fetal ultrasound, coupled with morphological examination (Dubowitz's score).
- Prematurity: defined as birth before 37 weeks of amenorrhea (SA)
- Intrauterine growth retardation (IUGR): defined by measurements (weight, height and head circumference lower than standard percentiles according to Leroy lefort curves)
- Perinatal asphyxia is defined by an Apgar score less than 7 at 5 minutes of life and the presence of neurological signs. It is classified into three stages according to Sarnat classification.
  - Grade I: Minor encephalopathy with hypotonia and moderate hyperexcitability within 48 hours.
  - Grade II: moderate encephalopathy with low consciousness, muscular hypotonia, abnormal movements and/or often seizures.
  - Grade III: severe encephalopathy with coma and often loss of reflexes of the trunk.
- Nosocomial infection: Any infection which appears beyond 48 hours of hospitalization
- Enterocolitis: Inflammation of the bowel resulting clinically by hemorrhagic gastric residue, abdominal distension and the presence of radiological images. Radiography allows a classification of lesions according to Bell stages.

• Intraventricular hemorrhage (IVH): Four degrees:

Grade I: Isolated subependymal hemorrhage.

Grade II: Moderate intraventricular hemorrhage with normal ventricles.

Grade III: Great abundance intraventricular hemorrhage with dilation of ventricles.

Grade IV: Intraventricular hemorrhage, hemorrhage grade III with intra-parenchymal extension type of periventricular hyperechogenicity.

• Antenatal maturative steroids: complete cure is defined by the administration of two doses of 12mg to 24 hours apart.

• Premature rupture of membranes (PRM): frank rupture of the amnion and chorion occurring before the start of delivery regardless of the term of pregnancy. It is pathological when the interval between rupture and delivery is more than 12 hours.

Data analysis were performed on Excel and SPSS 18.0 software. Quantitative variables were expressed as mean or median and interquartile range (M (IQ)). Qualitative variables were expressed as numbers and percentages. The comparison of variables was performed by the chi-square test, the averages, the Student test t and Mann-Whitney test. The level of significance was  $p < 0.05$ .

## Results

The neonatal intensive care unit has hospitalized during the period 1 January to 31 December 2014, 640 newborns. Of this population, 122 had included, 97 were selected, representing 15.15% of hospitalized patients.

### Maternal data

The synthesis of maternal data (Table 1) reveals that the average maternal age was  $28.95 \pm 6.6$  years (range 17 to 47 years). Among the main pathologies noted, 30.6% of mothers had hypertension, 50% had genital or urinary tract infection and 19, 4% had other pathologies.

Table 1  
*Maternal characteristics of group born with high risk of neurodevelopment sequelae*

Maternal characteristics	Values (N=97)
Maternal age (years) (M±SD)	28,95 ± 6,6
Parity (M±SD)	2,02 ± 1
Gravidity (M±SD)	2,35 ± 1,5
PIH (%)	11 (30,6%)
Maternal infection (%)	18 (50%)
Others (%)	7 (19,4%)

M±SD; Average and standard deviation.  
PIH ; pregnancy induced hypertension. % ; percentage

### Characteristics relating to pregnancy and childbirth

A preterm labor was observed in 57.7% of cases. The most represented mode of delivery was vaginal (67%) (Table 2).

Table 2  
*Characteristics relating to pregnancy and childbirth group of newborns with high risk of neurodevelopmental sequelae*

Features related to pregnancy and childbirth	Values (N=97) (%)
TPB	56 (57,7)
Followed pregnancy	73 (75,3)
Antenatal steroids	20 (20,8)
Vaginal issue	65 (67)
Cesaraen	32 (33)
Plannified cesaren	10 (10,3)
Emergency cesaren	22 (22,7)
RPM	26 (26,8)
Durée de RPM (heure)	19 (4, 72)

M±SD: Average and Standard Deviation.  
TPB: Threatened Preterm Birth.  
PRM : Premature rupture of membranes; % : percentage.

### Neonatal data

In our series, there was a male predominance (62.9%). The average weight was  $2406,8 \text{ g} \pm 995,6\text{g}$  with a minimum of 1100 g and a maximum of 5000 g. (Table 3). The main diseases that motivated hospitalization were represented by prematurity with 55.6% of cases, divided in very preterm birth in 23.3% of cases and moderate prematurity in 32.3% of cases; IUGR was noted in 24.7%; Respiratory distress in 16, 7% of cases with average of score of Silverman  $4 \pm 2$ . Perinatal asphyxia was present in 11, 1% of the population, 7 patients had stage II of Sarnat 3 patients presented stage I. The temperature at the admission was  $35.37 \pm 3.95 \text{ }^\circ\text{C}$ .

Table 3  
*Features of the new neonatal group born with high risk of neurodevelopmental sequelae*

Neonatal characteristics	Values (N=97)
Male	61 (62,9%)
Female	36 (37,1%)
Term (Weeks of amenorrhea) A±SD	34,62 ± 2,8
Dubowitz (Weeks of amenorrhea) A±SD	34,99 ± 2,6
Birth Weight (gramm) A±SD	2407 ± 996
Size(cm) A±SD	45 ± 5,4
Cranial perimeter (cm) A±SD	31,83 ± 4,8
Apgar 5 minutes : 3 – 7	10 (11,1%)
Perinatal asphyxia	10 (11,1%)
Prematurity	54 (55,6%)
RD	16 (16,7%)

A±SD : Average± standard deviation ; % : percentage ;  
RD : Respiratoy distress ; IUCR: Intrauterine croissance retardation; % : percentage

### Brain Injuries

The TFU was performed in 82 patients. The percentage of infants who developed neurological damage to the trans-fontanellar ultrasound was 36%. Twenty patients had ventricular hemorrhage, 14 newborns had a grade I, and 2 grades II, III and IV. Ten patients had other brain injuries, including 2

cases of hydrocephalus, 3 cases of periventricular leukomalacia, 2 cases of hyperechoic lesions and 3 other injuries (subdural hematoma, parietal hematoma). The intraventricular hemorrhage was more common in premature infants with 31.8% in very premature infants, 29% in moderate or late preterm and 9.5% in full-term newborns (p 0.042).

#### *Support and other morbidities*

Antibiotherapy was indicated in 98% of cases, or before an unexplained prematurity, positive infectious history. Mechanical ventilation was required in 43.3% of patients with a median of 7 days of ventilation (5-10 days). The median dependence of O<sub>2</sub> was 6 days (3-10 days). (Table 4). Morbidities during hospitalization were also dominated by nosocomial infections in 53.6% of patients. Enterocolitis was noted in 18.8% of patients. A case of premature retinopathy was noted.

Table 4  
*Care and neonatal morbidities*

Characteristics of the support	Values N=97
Non invasive ventilation	48 (49,5 %)
High flow nasal oxygen	57 (58,8%)
Ventilator	42 (43,3%)
Caffeine	52 (53,6%)
Hospitalisation's duration (day) A±SD	13,13 ±8,2
Ventilation's duration(IQ)	7,95 (5-10)
Oxygendependacy duration (IQ)	6 (3-10)
Transfontanellar ultrasound TFU (%)	
Normal	51(62,2%)
Anormal	30 (36%)
Nosocomial infection	52 (53,6%)
Enterocolitis	18 (18,8%)
Intraventricular hemorrhagea	20 (21,1%)
Monitoring	31(32%)

#### *Comparison brain injury in the initial TFU*

Patients with abnormalities in the TFU had a breakdown duration, dependence of oxygen and higher hospitalization than patients

without abnormality and a higher incidence of nosocomial infections. (Table 5). There was no significant difference in the term and birth weight between the two groups. The comparison of decision antenatal steroids, caffeine, and indication of phototherapy showed no significant differences between the two groups.

#### **Discussion**

The majority of child disabilities originate in the perinatal period. Prematurity, perinatal asphyxia and intrauterine growth retardation are the main situations exposing children to the risk of perinatal disability.

Improved knowledge on the pathophysiology and mechanism of acquired brain injury during pregnancy and childbirth has better define the risk of impairments, disabilities and subsequent disorders (Marrett, 2004).

The risk factors of appearance of lesions in the TFU in our series are nosocomial infections and a breakdown of duration, oxygen dependence and higher hospitalization. In our patients with brain damage, nosocomial infection was more common (70%). The diagnosis was made on the basis of clinical, inflammatory balance and radiological images. Infection is a major factor in the genesis of brain damage, not only in the prenatal period, but even after birth (Boog, 2005).

Leukomalacia seems to be triggered by infectious and inflammatory phenomena. They are likely via different mechanisms (cytokines, free radicals, excitotoxicity, apoptosis ...) lead to neuronal and / or glial cell death (Baud, 1998).

In recent years, the importance of the innate immune system receptors (Toll-like receptors) in the genesis of brain injury in neonatal sepsis has been demonstrated, with particular emphasis on *Escherichia coli*, coagulase-negative staphylococcus, and group B

streptococcus in the premature neonates (Ballard, 2012).

Infants with both sepsis and necrotizing enterocolitis had a risk 4.6 times higher of seizures, suggesting a possible role of infection in the pathogenesis of brain injuries in premature infants. Thus, acquiring an infection during hospitalization increases the risk of brain damages, not only through the pro-inflammatory factors but also by hemodynamic disorders it causes (Kohélet, 2006 ; Berteloite, 2009).

The genesis of intracranial hemorrhage would be secondary to changes in cerebral blood flow (CBF). This risk is further increased in older premature due to the immature brain. Also, in our children with brain injuries, the most frequent use of assisted ventilation and oxygen dependence of the longer duration, can be explained by the severity of the neurological status, but also by the superimposed morbidity represented in our context by nosocomial infection, which often requires a fairly heavy resuscitation. All this will lead to an extension of hospitalization's duration which increases the risk of invasive procedures (nasal or buccal aspiration, tracheal aspirations and the poses of the central pathways) that are subsequently gateways for nosocomial infection. Also, several studies showed that long-term oxygen dependency or assisted ventilation, exposed to neurodevelopmental risks (Carlo, 2010 ; Bozet, 1996).

Other risks of brain injury factors have been identified in several studies: infection and the ante or perinatal inflammation (Berger, 2000), Chronic perinatal hypoxia (Berger, 2000; Wilson-Costello, 1998), male sex (Pharoah, 2002), twin's pregnancies, especially monochorial, and the death of a co-twin in utero (Scher, 2002), also in case of twin-to-twin transfusion syndrome (TTS) (Cincotta, 2000), respiratory diseases, especially bronchopulmonary dysplasia (Majnemer, 2000), administration of postnatal steroids

(Doyle, 2001), and patent ductus arteriosus (Bozet, 1998).

The intraventricular hemorrhage was more common in very premature infants and in moderate prematurity in full-term neonates. The results of our study are similar with the results found in the literature (Larroque, 2003).

However, analyzing the risk factors of all brain injuries objectified, no difference was found for the small gestational age, intrauterine growth retardation and premature rupture of membranes. The sample size was not sufficiently representative would probably be the cause. Moreover, to antenatal steroids, studies report a decrease of almost 50% in the risk of intraventricular and periventricular hemorrhage in case of antenatal steroids administration (Baud, 1999). There would also have a beneficial effect on other inflammatory diseases such as necrotizing enterocolitis, or bronchopulmonary dysplasia. This has not been observed in our series probably related to the low rate of use.

## Conclusion

The role of prematurity, the IGUR and perinatal asphyxia in the occurrence of serious deficiencies was confirmed in several studies. Our study also showed the involvement of morbidities superimposed during hospitalization, in particular nosocomial infection, duration of oxygen dependency, ventilation and prolonged hospitalization in the onset of brain damage in the population at risk.

These elements justify the interest of more aseptic techniques for the prevention of nosocomial infections; try to shorten the duration of invasive ventilation and thus the duration of oxygen dependency, favoring fast relay non invasive ventilation.

## Declaration of interests

The authors declare that they have no conflicts of interest related to this article.

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Table 5

*Comparison of brain injury in transfontanellar ultrasound TFU*

Factors	Neonates with anomaly in TFU (N=30)	Neonates with normal TFU (N=67)	P
Term A±SD	34,27±2,98	34,27±2,93	0,99
Dubowitz's score A±SD	34,63±2,53	34,61±2,5	0,96
Weight ( gramm)			0,809
< 1500	5(17,2%)	10(20,8%)	
1500 à 2500	13(48,8%)	18(37,5%)	
> 2500	11(37,9%)	20(41,7%)	
APGAR 5' %			1
3-7	3(10,7%)	4(8,5%)	
>7	25(89,3%)	43(91,5%)	
Twins	3(10%)	20(41,7%)	0,13
Ventilattion	17(56,7%)	18(35,3%)	0,61
NIV	18(60%)	24(47,1%)	0,28
Ventilation duration M(IQ)	9(6 ; 13)	6(4,75 ; 7,25)	<b>0,029</b>
Oxygdependency duration M(IQ)	9(6 ; 12,5)	5(3 ; 7,5)	<b>&lt; 0,001</b>
Hospitalisation duration	16	11	<b>0,012</b>
Nosocomial infection(%)	21(70%)	21(41,2%)	<b>0,012</b>
Premature rupture of membranes (%)	10(33,3%)	15(29,4%)	0,72
Enterocolitis (%)	9(30%)	8(15,7%)	0,12
Antenatal steroids%	8(26,7%)	11(22%)	0,72
Caffeine%	18(60%)	31(60,8%)	0,94
ICUR (%)	8(26,7%)	12(23,5%)	0,75
Phototherapy (%)	13(43,3%)	24(48%)	0,68

AV assisted ventilation; NIV non invasive ventilation; IUGR intrauterine growth retardation, M (IQ), median and interquartile; % percentage