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Léa Decollogne

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Année : 2020

**NEURODEVELOPMENTAL OUTCOME AT 2 YEARS OLD FOR CHILDREN
BORN BEFORE 29 GESTATIONAL WEEKS AT GRENOBLE HOSPITAL**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Léa DECOLLOGNE

[Données à caractère personnel]

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Résumé

Introduction : Les enfants très grands prématurés sont à haut risque de séquelles neurologiques. L'objectif de cette étude était d'évaluer à 2 ans d'âge corrigé le devenir neurologique des enfants nés avant 29 semaines d'aménorrhée (SA), suivi dans le réseau Naitre et Devenir. **Matériel et méthode :** Il s'agissait d'une étude rétrospective, épidémiologique, descriptive et analytique incluant les enfants hospitalisés au centre hospitalier universitaire de Grenoble, nés avant 29 SA entre 2010 et 2015, inclus dans le réseau Naitre et Devenir et atteints de dysplasie broncho-pulmonaire (DBP) à 28 jours de vie. Le développement neurologique non optimal à 2 ans incluait un quotient de développement (QD) au test de Brunet-Lézine revisité < 85 , ou une cécité, ou une surdité, ou une paralysie cérébrale (CP) ≥ 3 selon la Gross Motor Function Classification System. **Résultats :** 119 enfants ont été inclus et 99 étaient suivis à 2 ans : 31.9% de la population avait un développement neurologique non optimal dont 4% avec une CP sévère. La médiane et les interquartiles des 95 QD réalisés étaient 90 (82-97). Les facteurs associés à un développement neurologique non optimal en analyse univariée étaient un faible âge gestationnel, un faible poids et taille de naissance, un pH au cordon < 7.2 , un traitement pour un canal artériel persistant, une oxygénothérapie longue et une chorioamniotite. **Discussion :** Ces résultats sont similaires à ceux de la cohorte française EPIPAGE-2 de 2011. L'extrême immaturité et l'infection, par le biais de l'inflammation, restent des facteurs de risque alors que la corticothérapie postnatale, dans cette étude, n'est pas associée à un mauvais devenir neurologique. De plus, la prescription de corticoïdes postnataux diminue, avec une utilisation plus large d'hydrocortisone, à plus faibles doses et pour des durées plus courtes qu'auparavant. **Conclusion :** Dans une population de très grands prématurés, un tiers a un développement neurologique non-optimal à 2 ans. Ce résultat souligne l'importance des réseaux de suivi.

Abstract

Introduction: Very preterm children are at a high risk for neurological impairment. The main goal of this study was to evaluate the neurodevelopmental outcome for 2 years corrected age children born before 29 gestational weeks (GW) in the Naitre et Devenir (RND) monitoring network. **Material and methods:** This was a retrospective, descriptive and analytic epidemiologic study about children hospitalised in the university hospital in Grenoble, born before 29 GW between 2010 and 2015, included in the RND and affected with bronchopulmonary dysplasia (BPD) at 28 days of life. Non-optimal neurodevelopmental outcome at 2 years corrected age was defined with a global developmental quotient (DQ) at the revisited Brunet-Lézine scale < 85 , or blindness, or deafness, or cerebral palsy (CP) ≥ 3 over five levels according to the Gross Motor Function Classification System. **Results:** One hundred and nineteen children were included and 99 were monitored at age 2 years: 31.9% of the population had non-optimal neurodevelopment. 4% of whom had CP. The median and interquartile of the 95 DQ tests performed was 90 (82 -97). Factors associated with non-optimal neurodevelopment in univariate analysis were low gestational age, low birth weight, small birth length, a cord pH < 7.2 , a treatment of persistent ductus arteriosus, a longer oxygenotherapy, and chorioamnionitis. **Discussion:** These results were similar to the main French EPIPAGE-2 cohort of 2011. Extreme immaturity and infection, through inflammation, were still risk factors whereas postnatal steroid use, in our study, was not associated with non-optimal neurodevelopment. Postnatal steroid prescription also decreased, with more widespread use of hydrocortisone and lower doses for a shorter time than before. **Conclusion:** In a population of very preterm children, one third had a non-optimal neurological outcome at 2 years of corrected age. This result highlights the importance of monitoring networks.

Introduction

Very preterm children, born before 29 gestational weeks (GW), especially those with bronchopulmonary dysplasia (BPD), are at high risk of motor deficiencies during childhood, for example cerebral palsy (CP) and more often neurodevelopment and behavioural disabilities [1,2]. Follow-up networks have been created in order to screen for these pathologies early with scales such as the Revisited Brunet-Lézine (RBL). These networks are important to evaluate the frequency of sequelae, to inform parents and to improve our medical practices.

The Réseau Naitre et Devenir (RND) was created in 2006 to monitor the preterm children born before 34 GW in the greater Grenoble area. It has created a cohort of preterm infants with new characteristics because the preterm population has evolved in recent years: more antenatal steroids [3], more inborn births [4], more individualized developmental care and parent implication [5] and less cystic periventricular leukomalacia (10.5% for children < 26 GW in 1997 [6] compared to 2.4% in 2011 in France [3]). Moreover, there was a decrease in invasive ventilation, creating the new BPD [7], which is still a main risk factor for neurological impairment [8]. In France, CP had decreased from 9% of 24-31 GW children to 5.4% in the 2011 EPIPAGE-2 cohort [1] but neurodevelopmental and cognitive impairment remained stable [8].

Practices within Neonatal Intensive Care Units (NICU) and the preterm population itself have evolved over the years. It was interesting to frequently evaluate children with these new characteristics in order to learn the new follow-up and check for new potential risk factors.

The main goal of this study was to evaluate neurodevelopmental outcomes for 2 years old children born before 29 GW between 2010 and 2015 with BPD at 28 days of life in the RND monitoring network. The secondary aim was to look at the risk factors especially postnatal steroid (PNS) administration.

Material and methods

1. Study population and inclusion criteria

Our study was a retrospective, descriptive and analytic epidemiologic study about children hospitalised in the NICU at the university hospital in Grenoble (CHUGA), born before 29 GW between 2010 and 2015, who were included in the RND and affected with BPD at 28 days of life.

2. Main objective

The main objective was to evaluate neurodevelopmental outcomes for children at 2 years corrected age born before 29 GW with BPD at 28 days of life in the RND monitoring network and to look for the risk factors, especially PNS administration.

The non-optimal neurodevelopmental outcome at 2 years of corrected age was defined with a global developmental quotient (DQ) at the RBL test < 85 , or blindness, or deafness, or CP ≥ 3 over five levels according to the Gross Motor Function Classification System (GMFCS) expanded and revisited in 2007 [9].

The RBL test is used to evaluate the DQ and also cover four sub-scores on movement and posture, language, socialisation and coordination [10]. The mean and maximal global scores were 100 and 140, whereby DQ values ≤ 85 define neurodevelopmental impairment. They could be divided into 3 levels: DQ < 70 (severe impairment), DQ between 70 and 84 (moderate impairment) and DQ > 84 (no impairment). The RBL test was performed by the RND psychologist during the 24th month of corrected age consultation, planned for all children during the follow-up at the RND network.

Blindness or deafness was defined by a specialized consultation with an ophthalmologist or an oto-rhino-laryngologist during the RND follow-up.

CP was assessed on the diagnostic sheet completed by the neonatologist at 24 month of corrected age, according to the different RND consultation reports and with the observation from the Centres d'action médico-sociale précoce (CAMPS) by a neurological physician. In case of uncertainty, the child's file was discussed during a meeting (TD, CE, and LD).

3. Data collection

Data collection was retrospective on hospital reports during the neonatal period, on consultation reports of RND written by a neonatologist or a paediatrician who monitored each child.

Ante- and post-natal potential risk factors were analysed. Gestational age was defined by using the 1st trimester ultrasound of the pregnancy. Antenatal steroid administration was completed with 2 doses of betamethasone 24 hours apart before birth. Spontaneous prematurity was defined as spontaneous labour. Outborn birth was defined as birth out of level III maternity. Intra-Uterine Growth Restriction was defined as birth weight $\leq 10^{\text{th}}$ percentile according the French growth curve of Audipog [11].

Ductus arteriosus treatment was surgical or medical with ibuprofen or paracetamol. Amines treatment included dopamine, dobutamine, adrenaline and noradrenaline. Hydrocortisone used for hypotension (1 mg/kg/day then 0.5 mg/kg/6h for 48 hours) in the first 10 days of life was also collected in this section. Chorioamnionitis was defined as positive blood or placenta culture, or a treatment with antibiotics for at least 5 days according to the clinic and paraclinic context in the first days of life (anamnesis, symptoms, inflammatory syndrome, and evolution). Secondary infection was assessed if at least one blood culture was positive and 5 days or more of antibiotics were administrated.

PNS was defined as steroid systemic administration after birth except supplementation with hydrocortisone in the first days for hypotension. BPD was defined as oxygen requirement or respiratory support evaluated at 28 days of life. Mild BPD was defined by $< 30\%$ oxygen

requirement at 36 GW and severe BPD as $\geq 30\%$ oxygen requirement and/or respiratory support at 36 GW [12]. Oxygenotherapy was defined as use of oxygen with nasal Continuous positive airway pressure, high flow oxygen therapy or low flow oxygen therapy.

Intra-Ventricular Haemorrhage (IVH) was evaluated by transfontanellar ultrasound and graduated from I to IV according to Papile classification. Extra-Uterine Growth Restriction (EUGR) was defined as a weight at the hospital discharge \leq the 10th percentile for the corrected age according to the Audipog growth curve.

4. Ethical statements

We received the authorization from the research department of CHUGA, as a MR004 study according to the Jardé law. When parents agreed to the RND follow-up, they signed an agreement about the collection and use of their child's data in an authorized file by the French data protection authority (Commission nationale de l'informatique et des libertés). Moreover, parents were informed of the study by letter in the NICU. Anonymization was performed as soon as the data were registered.

5. Statistical analyses

Univariate and multivariate analyses were performed. Statistical analyses were performed using Epiinfo v7.2.2 software for univariate analysis and Stata v15 software for multivariate analysis. Percentages and Odds Ratios (OR) results were given with their exact 95% binomial confidence intervals (95% CI) and medians with interquartile ranges. A p value < 0.05 was considered significant. A chi-square test was used to compare proportions. For smaller numbers of data, Fisher's test was used. A Mann-Whitney test was used to compare medians.

We used the stepwise backward method to perform a multivariate logistic regression. We had selected clinically relevant variables among significant variables for the logistic regression.

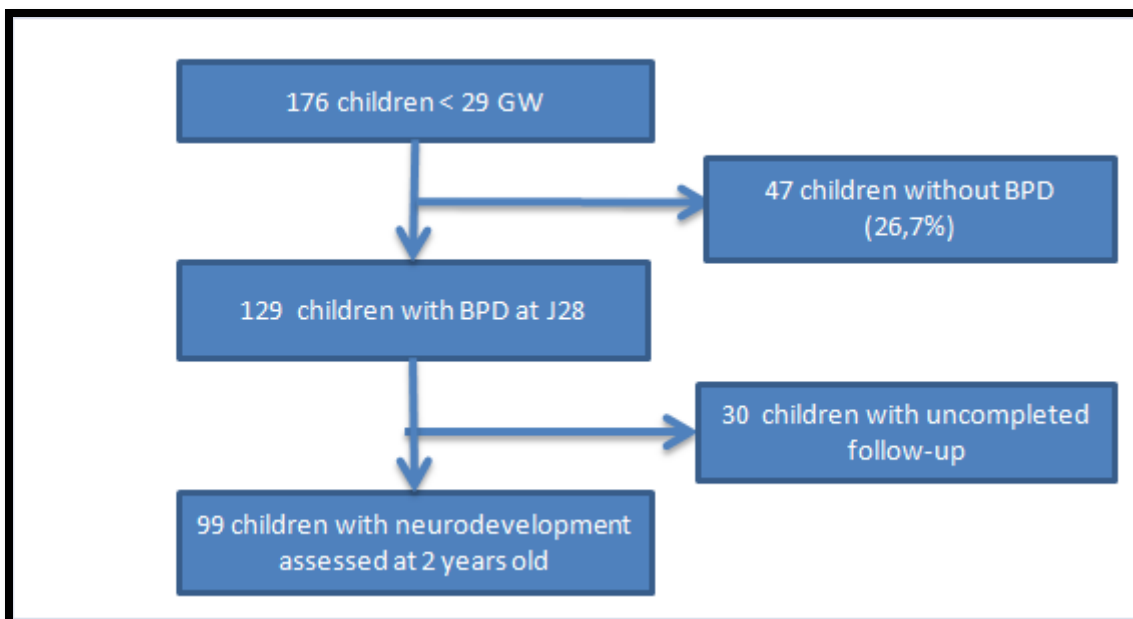
Contrary to what we had expected, we did not include the pH cord because there were too many missing data. The variables chosen to perform the multivariate logistic regression were gestational age, birth weight, the number of days of oxygenotherapy and chorioamnionitis.

Results

1. Population

One hundred and seventy six children born before 29 GW were hospitalised in our NICU between 2010 and 2015. Among these children, 129 (73.3%) had BPD at 28 days of life and they were all monitored at the RND upon discharge from the hospital (Figure 1).

Figure 1 - Flow chart. GW: Gestational Weeks. BPD: Bronchopulmonary dysplasia.



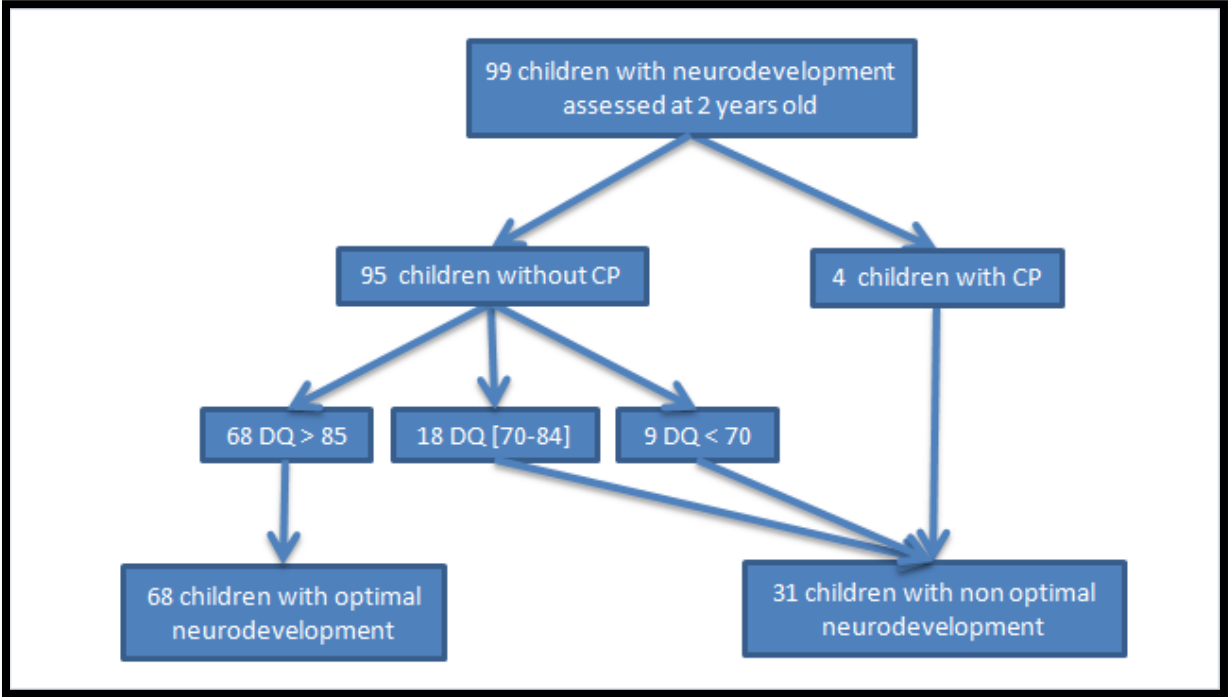
Among the children included, 99 were monitored at 2 years of corrected age and 95 performed RBL test. The 4 children (4% of the children monitored) without RBL test had CP, so they were included in the analysis. None of them was able to perform the RBL test or it was untreatable. One of them had blindness. There was no child with deafness.

Thirty other children had an incomplete follow-up: 6 without data available, 5 with an untreatable RBL test, 18 were monitored in the RND but did not come to the RBL test appointment and 4 were monitored in another network without RBL. Among the 4 children monitored in a different network, none had CP, 1 had communication disability and 3 had an optimal neurodevelopment.

There was no difference between the monitored children and those lost to follow-up, except for the EUGR (Table 1).

There were 31 children (31.9% of the population) with non-optimal neurodevelopment: 4 with CP, 18 with DQ between 70 and 84 (18.9%) and 9 with DQ below 70 (9.5%). The median and the interquartile range of the 95 DQ tests performed was 90 (82 -97). 68 children had a normal DQ (71.6%) (Figure 2).

Figure 2- Follow-up at 2 years old. DQ: Developmental Quotient at Revisited Brunet-Lézine test. CP: Cerebral Palsy.



2. Associated factors

Factors associated with non-optimal neurodevelopment in univariate analysis, were a low gestational age, specifically before 26+6 GW, low birth weight, small birth length, a cord pH < 7.2, a treatment for persistent ductus arteriosus, a longer oxygenotherapy, and chorioamnionitis. (Table 2) PNS administration was not associated with non-optimal neurodevelopment in our study. Children with non-optimal neurodevelopment without CP (only DQ < 85) had the same risk factors (Supplemental data, Table 3).

In the multivariate logistic regression, low birth weight (OR = 0.67, CI 95% 0.51-0.87, p = 0.003) and chorioamnionitis (OR = 5.11, CI 95% 1.11-23.51, p = 0.036) were associated with non-optimal neurodevelopment.

3. Postnatal steroid treatment

Nineteen children were treated by PNS. Fifteen children received a 3 day treatment, on average at J22, and three children received a 2nd treatment, on average at J54. One child received a 3rd treatment per os. Children received small doses (on average 0.13 mg/kg/day) over 3 days, with betamethasone.

Children treated by PNS had a lower gestational age, smaller birth weight, smaller length and a smaller head circumference at birth (Supplemental data, Table 4). Moreover, they were all treated for a persistent ductus arteriosus, needed more amines, had more surfactant doses, had more severe BPD and had longer invasive ventilation and oxygenotherapy than the untreated children. In this study, they did not have more risk of non-optimal neurodevelopment, IVH, Necrotizing Enterocolitis (NEC) or spontaneous intestinal perforation.

We also compared the 4 children who received at least 2 PNS treatments with those who received only one. There was no difference between them, especially the neurodevelopment at

2 years of corrected age, the number of surfactant doses, BPD severity and the duration of invasive ventilation.

Discussion

In this study, 31.3% of children had non-optimal neurodevelopment: 4% of children born between 24 and 28+6 GW had severe CP, and 27 with DQ below 85. The main risk factors associated with non-optimal development were a low gestational age (before 26+6 GW), low birth weight, small birth length, a cord pH < 7.2, a treatment of persistent ductus arteriosus, a longer oxygenotherapy, and chorioamnionitis. Moreover, in this study, the PNS treatment was not significantly associated with non-optimal neurodevelopment.

1. Comparison with literature

In the EPIPAGE-2 study, children born between 24 and 26+6 GW had a CP rate of 6.9% and 1.8% rate for severe CP (GMFCS ≥ 3) [1]. In the Swedish EXPRESS cohort [13], 7% of preterm children born before 27 GW had CP. These results were similar with our CP rate of 4% for children between 24 and 28+6 GW even through the populations were slightly different.

In this study, there was less blindness (0.01%) than in the EPIPAGE-2 study (0.4% of children born between 24 and 31 GW). We had no deaf children, whereas they were 0.7% of the preterms in the French cohort.

In our study, as in the literature, the low gestational age was the most important risk factor for non-optimal neurodevelopment, along with the associated low birth weight [14] and small

length. In the EPIPAGE-2 cohort [1], each GW decreased the risk of CP or ASQ scores below threshold significantly from 24 to 31 GW.

The other associated factors were coherent with the literature: a cord pH < 7.2 [15], a treatment of persistent ductus arteriosus [16], a longer oxygenotherapy [17], and chorioamnionitis.

In the multivariate analysis, low birth weight and chorioamnionitis were associated with non-optimal neurodevelopment outcomes. It was proved that chorioamnionitis was linked to periventricular leukomalacia and then to CP [18]. However, in our study, there was no leukomalacia and few cases of CP. Nowadays, chorioamnionitis seems to also be associated with cognitive impairment, but not necessarily with cystic periventricular leukomalacia or motor impairment, as in our study. It suggests new lesions of cognitive impairment due to inflammatory response. Indeed, in the Pappas et al. study [19], histological and clinical chorioamnionitis and histological chorioamnionitis alone were associated with an increasing risk of cognitive impairment (according to Bayley Scales of Infant Development, 3rd edition), adjusted for gestational age.

In our study, outborn birth tended to be associated with non-optimal neurodevelopment, which was also found in the Japanese study on cognitive impairment [20]. In the same way, the invasive ventilation duration seemed to be associated with non-optimal neurodevelopment as in the Dutch study [21].

2. Evolution of neurological impairment and associated factors

The children in current cohorts have less severe disabilities than those born in the 2000s in France. For example, in the EPIPAGE-1 cohort in 1997 [22], 9% of 24-31 GW children had CP compared to 5.4% in the 2011 cohort. This could be explained by the new BPD [7], which

is an important neurological impairment risk factor and the incidence of which decreased in France (from 47.8% in 1997 to 33.5% in 2011 for children between 24 and 26 GW in the EPIPAGE-2 cohort [3]). Indeed, there is a new management of BPD: more surfactant and antenatal corticosteroids, less invasive ventilation and PNS administration. We can also suppose that severe disabilities in the 2000s were linked, in some factors, to the frequent use and high doses of PNS, mostly dexamethasone. In the Yeh et al. trial [23], children who received 0.5 mg/kg/day of dexamethasone for 4 weeks had a lower intelligence quotient than the placebo group. Similarly, in the Murphy et al. study [24] MRI showed impaired gray matter for children treated with dexamethasone. Perhaps the decrease of PNS use [3] had influenced the decrease of neurodevelopmental impairment in France. In our study, according to the current recommendations [25], children mostly received only 3 days of PNS administration, with small doses, case-by-case. This is a possible explanation for the non-identification of PNS treatment as a risk factor for neurodevelopment impairment in our cohort.

Another protocol of PNS therapy is a substitutive administration such as hydrocortisone, with lower doses and for shorter time [26]. However, this early alternative treatment for all children is quite different from the treatment for selected children after a few weeks of invasive ventilation. In the 2 year follow-up of the PREMILOC study [27], children between 24 and 25 GW treated with hydrocortisone (1mg/kg/day for 7 days then decreasing) had a better neurodevelopmental outcome than those treated with placebo: 79% had DQ > 85, 21% with DQ between 70 and 84 and none with DQ < 70. Moreover, only 4% of treated children between 24 and 25+6 GW had CP.

Our results were coherent with the recent studies that showed no difference between children treated with lower doses of PNS, with hydrocortisone, for a shorter period: 1mg/kg/day for 12

days in the Watterberg study [28], 2 mg/kg/day for 2 days then decreasing for 8 days in the Peltoniemi trial [29] and 3 mg/kg/day for 4 days then decreasing in the Parikh trial [30].

3. Limits

We analysed only children with BPD because we wanted to focus on very ill, high risk children in order to avoid some confusion factors. This choice made the population of the study more homogenous. This population has also more CP and complications than the French EPIPAGE-2 cohort [1].

In the follow-up, 23% of the children had an uncompleted follow-up. However, the two populations were comparable.

We did not include parental socio-economic status or educational attainment in our study. However, these criteria could influence the neurodevelopment of children [1].

Moreover, in our study, the male sex and small weigh for gestational age were not significant risk factors; although they were highlighted in the literature [1]. This could be link to the lake of statistical power of our study.

This study is monocentric around the greater Grenoble area. It could be interesting to include children from the other hospitals in the Auvergne-Rhône-Alpes area to improve the power of the study.

THÈSE SOUTENUE PAR : Léa DECOLLOGNE

TITRE :

NEURODEVELOPMENTAL OUTCOME AT 2 YEARS OLD FOR CHILDREN BORN BEFORE 29 GESTATIONAL WEEKS IN GRENOBLE HOSPITAL

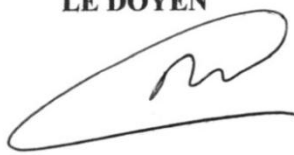
CONCLUSION:

In a population of preterm children born before 29 GW with BPD at 28 days of life, 31% had non-optimal neurological outcomes at 2 years of corrected age. 4% of whom had severe CP. These results show the importance of monitoring networks in preventing and diagnosing these complications early in at-risk populations. If possible, we would like to study the neurological outcome at age 5 and compare that data with the 2 years corrected age outcome.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 11/03/2020


LE DOYEN



Pour le Président
et par délégation
Le Doyen de Médecine
Pr. Patrice MORAND

Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



CHU de Grenoble Alpes
Hôpital Couple Enfant
Clinique de Néonatalogie
et de Réanimation Pédiatrique
Pr Th. DEBILLON

Pr. Thierry Debillon

Table 1- Characteristics of patients studied and lost to follow-up. Data are n (%) or median (inter quartiles). BPD: Bronchopulmonary dysplasia. NEC: necrotizing Enterocolitis.

| | Completed follow-up (n = 99) | Lost to follow-up (n= 30) | p |
|--|-------------------------------|----------------------------|-------|
| Antenatal characteristics | | | |
| No antenatal steroids | 9 (9.1%) | 3/29 (10.3%) | |
| Uncompleted antenatal steroids | 18 (18.2%) | 6/29 (20.7%) | |
| Completed antenatal steroids | 72 (72.7%) | 20/29 (69%) | |
| No or uncompleted antenatal steroids vs completed antenatal steroids | 27 (27.3%) | 9/29 (31.0%) | 0.429 |
| Age of mother (median, years) | 30 (27-34) | 30 (27-33) | 0.463 |
| Spontaneous prematurity | 64/97 (66%) | 22/29 (75.9%) | 0.316 |
| Outborn | 8 (8.1%) | 5 (16.7%) | 0.171 |
| Caesarean section | 47 (47.5%) | 14 (46.7%) | 0.938 |
| Birth characteristics | | | |
| Gestational age (weeks) | 27 (25.9-27.9) | 27.4 (25.6-28.1) | 0.821 |
| Gestational age < 26 + 6 gestational weeks | 49 (49.5%) | 13 (43.3%) | 0.554 |
| Male sex | 51 (51.5%) | 17 (56.7%) | 0.621 |
| Multiple birth | 35(35.4%) | 13 (43.3%) | 0.428 |
| Birth weight (median, grams) | 900 (750-1015) | 885 (675-1070) | 0.98 |
| Intra-Uterine Growth Retardation | 12 (12.1%) | 5 (16.7%) | 0.355 |
| Birth Length (median, centimetres) | 35 (32.5-37) | 33.8 (32-39) | 0.463 |
| Birth head circumference (median, centimetres) | 24 (23-25.5) | 24 (22-25) | 0.245 |
| 5 minute Apgar score < 5 | 3/98 (3.1%) | 0 | 0.456 |
| Median of cord pH | 7.34 (7.27-7.39) | 7.37 (7.33-7.41) | 0.078 |
| cord pH < 7.2 | 9/65 (13.8%) | 1/17 (5.9%) | 0.338 |
| Hemodynamic treatments | | | |
| Ductus arteriosus treatment | 73/97 (75.3%) | 18/27 (66.7%) | 0.372 |
| Amines treatment | 25/93 (26.9%) | 8 (26.7%) | 0.981 |
| Respiratory characteristics | | | |
| Treatment ≥ 2 surfactants | 39/98 (39.8%) | 15 (50%) | 0.322 |
| Post natal steroids | 13 (13.1%) | 6 (20%) | 0.255 |
| Severe BPD vs mild or moderate BPD | 25 (25.3%) | 6 (20%) | 0.555 |
| Invasive ventilation (median, days) | 7 (1-23) | 4 (1-22) | 0.652 |
| Oxygenotherapy (median, days) | 71 (49-90) | 69.5 (52 -90) | 0.843 |
| Infectious complications | | | |
| Chorioamnionitis | 9 (9.1%) | 2 (6.7%) | 0.677 |
| Secondary infection | 46/98 (47.0%) | 19/29 (65.5%) | 0.08 |
| Digestive and growth characteristics | | | |
| NEC or spontaneous intestinal perforation | 8/98 (8.2%) | 1 (3.3%) | 0.33 |
| Exclusive breastfeeding at discharge | 21/96 (21.9%) | 4 (13.3%) | 0.306 |
| Extra-Uterine Growth Retardation | 36/95 (37.9%) | 4 (13.8%) | 0.015 |
| Neurologic complications | | | |
| Intra-Ventricular Haemorrhages grad III or IV | 6 (6.1%) | 1/29 (3.45%) | 0.501 |

Table 2-Factors associated with non-optimal neurodevelopment in univariate analysis.

Data are n (%) or median (inter quartiles). BPD: Bronchopulmonary dysplasia. NEC: necrotizing Enterocolitis.

| | Non-optimal neurodevelopment (n=31) | Optimal neurodevelopment (n=68) | OR | 95% CI | p |
|--|---|---------------------------------------|------|------------|--------|
| Antenatal characteristics | | | | | |
| No or uncompleted antenatal steroids vs completed antenatal steroids | 11 (35.5%) | 16 (23.5%) | 1.79 | 0.71-4.51 | 0.215 |
| Age of mother (median, years) | 32.0 (27-38) | 30.0 (27-33) | | | 0.34 |
| Spontaneous prematurity | 22 (71%) | 42/66 (63.6%) | 1.4 | 0.55-3.52 | 0.477 |
| Caesarean section | 13 (42%) | 34 (50%) | 0.72 | 0.31-1.70 | 0.456 |
| Outborn | 5 (16.1%) | 3 (4.4%) | 4.17 | 0.93-18.7 | 0.061 |
| Birth characteristics | | | | | |
| Gestational age (median, weeks) | 25.9 (25.4-27.3) | 27.1 (26.4-28.3) | | | <0.001 |
| Gestational age < 26 + 6 gestational weeks | 21 (67.7%) | 28 (41.2%) | 3 | 1.23-7.34 | 0.014 |
| Male sex | 15 (48.4%) | 36 (53%) | 0.83 | 0.36-1.95 | 0.674 |
| Multiple birth | 12 (38.7%) | 23 (33.8%) | 1.24 | 0.51-2.98 | 0.638 |
| Birth weight (median, grams) | 780 (650-950) | 943 (805-1030) | | | 0.002 |
| Intra-Uterine Growth Retardation | 4 (12.9%) | 8 (11.8%) | 1.11 | 0.31-4.01 | 0.555 |
| Birth Length (median, centimetres) | 33.5 (32-36.5) | 35 (33-37) | | | 0.227 |
| Birth head circumference (median, centimetres) | 23.7 (23-25) | 24 (23-25.5) | | | 0.074 |
| 5 minute Apgar score < 5 | 2/30 (6.7%) | 1 (1.5%) | 4.79 | 0.42-54.9 | 0.221 |
| Median of cord pH | 7.32 (7.15-7.4) | 7.34 (7.28-7.39) | | | 0.082 |
| cord pH < 7.2 | 6/19 (3.16%) | 3/46 (6.5%) | 6.62 | 1.45-30.2 | 0.015 |
| Hemodynamic treatments | | | | | |
| Ductus arteriosus treatment | 27/30 (90%) | 46/67 (68.7%) | 4.11 | 1.12-15.07 | 0.024 |
| Amines treatment | 11/30 (36.7%) | 14/63 (22.2%) | 2.03 | 0.78-5.24 | 0.142 |
| Respiratory characteristics | | | | | |
| Treatment ≥ 2 surfactants | 14/30 (46.7%) | 25 (36.8%) | 1.51 | 0.63-3.59 | 0.356 |
| Post natal steroids | 5 (16.1%) | 8 (11.8%) | 1.44 | 0.43-4.83 | 0.381 |
| Severe BPD vs mild or moderate BPD | 10 (32.3%) | 15 (22.1%) | 1.68 | 0.65-4.33 | 0.279 |
| Invasive ventilation (median, days) | 14 (2-30) | 4.5 (1-19.5) | | | 0.069 |
| Oxygenotherapy (median, days) | 79 (64-97) | 62.5 (43.5-88.5) | | | 0.0039 |
| Infectious complications | | | | | |
| Chorioamnionitis | 6 (19.4%) | 3 (4.4%) | 5.2 | 1.21-22.4 | 0.025 |
| Secondary infection | 17/30 (56.7%) | 29 (42.7%) | 1.76 | 0.74-4.19 | 0.2 |
| Digestive and growth characteristics | | | | | |
| NEC or spontaneous intestinal perforation | 4/30 (13.3%) | 4 (5.9%) | 2.46 | 0.57-10.6 | 0.197 |
| Exclusive breastfeeding at discharge | 5/30 (16.7%) | 16/66 (24.2%) | 0.63 | 0.21-1.91 | 0.291 |
| Extra-Uterine Growth Retardation | 13/30 (43.3%) | 23/65 (35.4%) | 1.4 | 0.58-3.38 | 0.458 |
| Neurologic complications | | | | | |
| Intra-Ventricular Haemorrhages grad III or IV | 3 (9.7%) | 3 (4.4%) | 2.32 | 0.44-12.2 | 0.276 |

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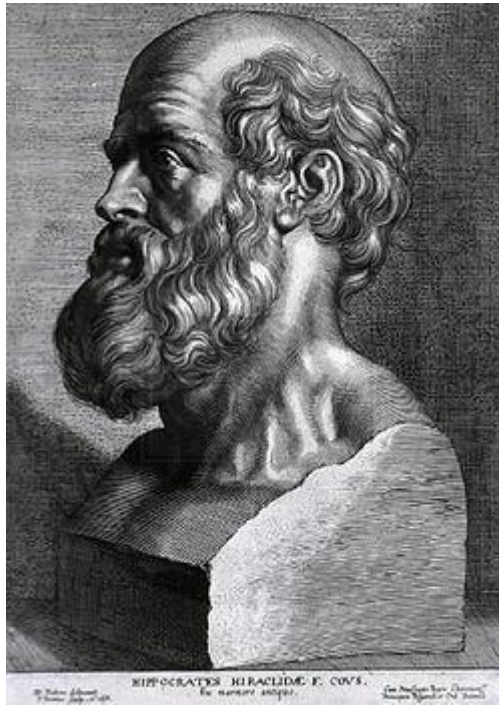
Supplemental data:

Table 3- Factors associated with non-optimal neurodevelopment without CP, in univariate analysis. Data are n (%) or median (inter quartiles). BPD: Bronchopulmonary dysplasia. NEC: necrotizing Enterocolitis.

| | Non-optimal neurodevelopment without CP (n=27) | Optimal neurodevelopment (n=68) | OR | IC (95%) | p |
|--|--|---------------------------------|------|-----------|--------|
| Antenatal characteristics | | | | | |
| No or uncompleted antenatal steroids vs completed antenatal steroids | 9 (33.3%) | 16 (23.5%) | 1.63 | 0.61-4.32 | 0.328 |
| Age of mother (median, years) | 32 (27-38) | 30 (27-33) | | | 0.389 |
| Spontaneous prematurity | 19 (70.4%) | 42/66 (63.6%) | 1.36 | 0.52-3.57 | 0.535 |
| Caesarean section | 12 (44.4%) | 34 (50%) | 0.8 | 0.33-1.96 | 0.625 |
| Outborn | 4 (14.8%) | 3 (4.4%) | 3.77 | 0.78-18.1 | 0.1 |
| Birth characteristics | | | | | |
| Gestational age (median, weeks) | 25.9 (25.4-27.3) | 27.1 (26.4-28.3) | | | <0.001 |
| Gestational age < 26 + 6 gestational weeks | 19 (70.4%) | 28 (41.2%) | 3.39 | 1.30-8.83 | 0.01 |
| Male sex | 14 (51.9%) | 36 (53%) | 0.96 | 0.39-2.34 | 0.924 |
| Multiple birth | 12 (44.4%) | 23 (33.8%) | 1.56 | 0.63-3.89 | 0.333 |
| Birth weight (median, grams) | 770 (650-900) | 944 (805-1030) | | | <0.001 |
| Intra-Uterine Growth Retardation | 4 (14.8%) | 8 (11.8%) | 1.3 | 0.36-4.75 | 0.686 |
| Birth Length (median, centimetres) | 33.5 (32-36.5) | 35 (33-37) | | | 0.226 |
| Birth head circumference (median, centimetres) | 23.2 (23-24.5) | 24 (23-25.5) | | | 0.053 |
| 5 minute Apgar score < 5 | 1/26 (3.9%) | 1 (1.5%) | 2.68 | 0.16-44.5 | 0.479 |
| Median of cord pH | 7.30 (7.16-7.38) | 7.34 (7.28-7.39) | | | 0.08 |
| cord pH < 7.2 | 5/16 (31.3%) | 3/46 (6.5%) | 6.52 | 1.35-31.5 | 0.022 |
| Hemodynamic treatments | | | | | |
| Ductus arteriosus treatment | 24/26 (92.3%) | 46/67 (68.7%) | 5.48 | 1.19-25.4 | 0.018 |
| Amines treatment | 9/26 (34.7%) | 14/63 (22.2%) | 1.85 | 0.68-5.05 | 0.225 |
| Respiratory characteristics | | | | | |
| Treatment ≥ 2 surfactants | 12/26 (46.2%) | 25 (36.8%) | 1.47 | 0.59-3.68 | 0.405 |
| Post natal steroids | 5 (18.5%) | 8 (11.8%) | 1.7 | 0.50-5.77 | 0.289 |
| Severe BPD vs mild or moderate BPD | 9 (33.3%) | 15 (22.1%) | 1.77 | 0.66-4.73 | 0.254 |
| Invasive ventilation (median, days) | 14 (2-30) | 4.5 (1-19.5) | | | 0.072 |
| Oxygenotherapy (median, days) | 80 (65-97) | 62.5 (43.5-88.5) | | | 0.004 |
| Infectious complications | | | | | |
| Chorioamnionitis | 3 (11.1%) | 3 (4.4%) | 2.71 | 0.51-14.3 | 0.221 |
| Secondary infection | 15/26 (57.7%) | 29 (42.7%) | 1.83 | 0.73-4.58 | 0.191 |
| Digestive and growth characteristics | | | | | |
| NEC or spontaneous intestinal perforation | 4/26 (15.4%) | 4 (5.9%) | 2.91 | 0.67-12.6 | 0.144 |
| Exclusive breastfeeding at discharge | 4/26 (15.4%) | 16/66 (24.2%) | 0.57 | 0.17-1.90 | 0.264 |
| Extra-Uterine Growth Retardation | 13/26 (50%) | 23/65 (35.4%) | 1.83 | 0.73-4.59 | 0.198 |
| Neurologic complications | | | | | |
| Intra-Ventricular Haemorrhages grad III or IV | 2 (7.4%) | 3 (4.4%) | 1.73 | 0.27-11 | 0.441 |

Table 4- Factors associated with Post Natal Steroids (PNS), in univariate analysis. Data are n (%) or median (inter quartiles). NEC: necrotizing Enterocolitis.

| | Children with PNS (n=19) | Children without PNS (n= 110) | p |
|--|-----------------------------|----------------------------------|--------|
| Antenatal characteristics | | | |
| No or uncompleted antenatal steroids vs completed antenatal steroids | 5 (26.3%) | 31/109 (28.4%) | 0.849 |
| Age of mother (median, years) | 30 (27-33) | 30 (27-34) | 0.850 |
| Spontaneous prematurity | 9/18 (66.7%) | 74/108 (68.5%) | 0.876 |
| Caesarean section | 9 (47.4%) | 52 (47.3%) | 0.994 |
| Outborn | 2 (10.5%) | 11 (10%) | 0.944 |
| Birth characteristics | | | |
| Gestational age (median, weeks) | 25.9 (24.4-27.3) | 27.1 (26.1-28.1) | 0.012 |
| Gestational age < 26 + 6 gestational weeks | 14 (73.7%) | 48 (43.6%) | 0.015 |
| Male sex | 8 (42.1%) | 60 (54.6%) | 0.316 |
| Multiple birth | 9 (47.4%) | 39 (35.5%) | 0.321 |
| Birth weight (median, grams) | 720 (610-947) | 930 (760-1050) | 0.006 |
| Intra-Uterine Growth Retardation | 5 (26.3%) | 12 (10.9%) | 0.067 |
| Birth Length (median, centimetres) | 32 (30-34.5) | 35 (33-37) | 0.003 |
| Birth head circumference (median, centimetres) | 23 (22-24) | 24 (23-25.5) | 0.013 |
| 5 minute Apgar score < 5 | 0 | 3/108 (2.8%) | 0.612 |
| Median of cord pH | 7.38 (7.31-7.39) | 7.34 (7.27-7.39) | 0.331 |
| cord pH < 7.2 | 1/12 (8.3%) | 9/70 (12.9%) | 0.658 |
| Hemodynamic treatments | | | |
| Ductus arteriosus treatment | 19 (100%) | 72/105 (68.6%) | 0.001 |
| Amines treatment | 11 (57.9%) | 22/104 (21.2%) | <0.001 |
| Respiratory characteristics | | | |
| Treatment ≥ 2 surfactants | 16 (84.2%) | 38/109 (34.9%) | <0.001 |
| Severe BPD vs mild or moderate BPD | 16 (84.2%) | 15 (13.6%) | <0.001 |
| Invasive ventilation (median, days) | 29 (20-49) | 4 (1-15) | <0.001 |
| Oxygenotherapy (median, days) | 107 (90-127) | 64.5 (45-82.5) | <0.001 |
| Infectious complications | | | |
| Chorioamnionitis | 2 (10.5%) | 9 (8.2%) | 0.735 |
| Secondary infection | 12/18 (66.7%) | 53/109 (48.6%) | 0.156 |
| Digestive and growth characteristics | | | |
| NEC or spontaneous intestinal perforation | 2 (10.5%) | 7/109 (6.4%) | 0.518 |
| Exclusive breastfeeding at discharge | 3 (15.8%) | 22 (20.6%) | 0.451 |
| Extra-Uterine Growth Retardation | 4 (21.1%) | 36 (34.3%) | 0.256 |
| Neurologic complications | | | |
| Intra-Ventricular Haemorrhages grad III or IV | 1 (5.3%) | 6/109 (5.5%) | 0.685 |
| Median of RBL | 90 (80-97) | 90 (83-97) | 0.533 |
| Children with non-optimal neurodevelopment | 5/13 (38.5%) | 26/86 (30.2%) | 0.381 |
| Cerebral palsy | 0 | 4 (3.64%) | 0.524 |



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.