Neurodevelopment of children born very preterm and free of severe disabilities: the Nord-Pas de Calais Epipage cohort study.

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ABSTRACT

Aim: to describe the development of very preterm children free of cerebral palsy or severe sensory impairment in the domains of gross and fine motor functions, language and sociability at a corrected age of 2 years; to identify factors associated with performances in each domain.

Methods: 347 children born in 1997 before 33 weeks of gestation, part of the EPIPAGE population-based cohort study, had their psychomotor development assessed with the Brunet-Lezine scale.

Results: The study population had a mean gestational age of 30.1 ± 2.0 weeks. Lower developmental quotients (DQ) were observed in the study group compared to the reference sample (96 ±13 vs 104 ± 8, $p<0.01$). Fine motor function, language and sociability were all affected with a p value <0.01. Multivariate analysis showed that duration of intubation and parents' educational and occupational level were the only variables significantly related to each developmental domain ($p<0.01$).

Conclusions: Children very preterm and free of severe disabilities had mild delays in multiple areas of development. The mechanisms by which neonatal factors played a role need further investigation. However socioeconomic status had a great impact on development and our results underline the need for improved support of socioeconomically disadvantaged parents after a preterm birth.

Keywords: neurodevelopmental outcome; follow-up studies; premature infant; social-environmental risk factors

There is mounting public and professional concern worldwide regarding the long-term outcome of preterm babies. The prevalence of sequelae reported in different countries is very similar, with cognitive impairment being the most common disability.(1) Cognitive impairment now requires assessment that extends beyond traditional intelligence quotients (IQ).(2) Indeed, executive and sensorimotor functions, attention, language, visuospatial processes, memory, behavioral adjustment may all contribute to this deficit.(2)

Follow-up data available from epidemiological studies carried out in the first two years after a preterm birth mainly focus on detection of serious impairment: cerebral palsy (CP), severe sensory impairment or developmental delay. Recent epidemiological research is mainly directed towards children born at an extremely low gestational age (GA), because of ethical concerns about resuscitation of these children. Data available for this population around two years of age show that their mean developmental quotient (DQ) is below 70 in 15 to 46 % of cases.(3) However, the vast majority of the prematurely born population with cognitive deficits and associated learning disorders is made up of children born at a greater GA. Most of the data available from population based cohorts of children born very preterm involve children who were born before prenatal corticotherapy and surfactants were widely used.(4,5). However it has been shown recently that neurodevelopmental impairments by the age of four years are still common in children born before 33 weeks of GA in the late 1990’s.(6,7) These data have to be confirmed by others in Europe. The Epipage population-based cohort provided large amounts of data on babies born before 33 weeks in 1997 in nine French areas. Overall, 2357 infants surviving at discharge were enrolled in a follow-up study. The overall outcome at 5 years has already been published.(8) In the Nord Pas-de-Calais area, one of the study areas, an evaluation of global development was made on children at a corrected age (CA) of two years.(9) The magnitude of the cohort allowed us to study in more detail the development of children free of CP or severe neurosensory impairment and who were therefore considered to have ‘normal’ development. We hypothesized that minor impairments could be observed in multiple domains as early as two years of age. We compared the results with those obtained from babies born at term, and tried to identify factors related to development in each domain studied.

METHODS

Population

Our study population was described elsewhere.(9) During the study period, 634 children were born alive at a GA of less than 33 weeks. Two children with congenital anomalies interfering with development were excluded and 546 surviving children were included in the follow up.

Evaluation at two years CA

Pediatricians from the neonatal teams performed standardized neurological examinations as well as an assessment of hearing and vision on children at a CA of two years. CP was defined according to the European Cerebral Palsy Network.(10) Severe sensory impairments were blindness or requirement of a hearing aid. The revised Brunet-Lézine (BLR) scale was used to evaluate development.(11) Written informed consent was obtained from families of all children participating in the study. The study received the approval of the “Commission Nationale de l’Informatique et des Libertés”.

The revised Brunet-Lézine scale (BLR scale)

This early childhood psychomotor development scale covers four domains of development: gross motor function (GM), fine motor function (FM), language (L), and sociability (S). Four separate DQs can be calculated for children aged 2 to 30 months that, combined, yield a global DQ. Means and standard deviations of sub scores according to age are available for each domain and for the global quotient.(11) The distribution of the differences between the global DQ and each of the separate DQ are tabulated, enabling children with specific patterns of developmental delay to be identified. Children were considered to have an achievement discrepancy if the difference between the global DQ and at least one partial DQ was a value obtained by only 5 % of the reference sample. The test was revised between 1994 and 1996 on a sample of 1032 French children born at term, from single pregnancies with a birth weight greater than 2400g.(11)

Factors associated with global and partial DQs

The following variables were selected *a priori* and studied in relation to DQs: GA, sex, small for gestational age (SGA), clinical risk index for babies (CRIB), duration of intubation, educational level and parents’ occupation, severe cerebral ultrasound abnormalities, postnatal administration of corticosteroids and breastfeeding at discharge. Gestational age refers to completed weeks of amenorrhea and was the best obstetric estimate based on the date of last menstrual period and an early prenatal ultrasound scan, which is a routine practice in France. Birth weight scores, as a function of sex and GA, were derived from our own population of admitted babies. Children SGA were defined as babies having a birth weight < 10^{th} percentile for sex and GA. Severe cerebral ultrasound abnormalities included cystic leukomalacia and severe intraventricular haemorrhage defined as Papile's grade III or IV.(12) These medical and social factors were selected because they are known to be associated with the overall neurological outcome of very preterm children, although their relationship with development in each domain remains unknown.(9)

Statistical analysis

We first described the population in terms of global and partial DQs. The Student's t-test was used to compare results with those obtained by children of the reference sample. For all quantitative data, results were given as mean ± standard deviation (SD).

STATA, version 9.0, was used to perform univariate and multivariate regression analyses (Stata Corp, college Station, Texas, USA), to identify factors associated with variations in global and partial DQs. Relationships between each factor and the DQ were first studied using t-tests or analysis of variance. Factors associated with DQs with a $p < 0.20$ were included in the multivariate model. GA had to be one of the variables, because of its central role.(1) The multivariate model presents mean variations of scores for each factor after adjustment for other factors.

RESULTS

Population

The population is described in figure 1. A clinical examination was performed on 461 children with a CA of 24 months ± 5 weeks. Four hundred and sixteen were free of CP or neurosensory impairment. A BLR test was performed on 347 (83 % of those free of CP or neurosensory impairment). These 347 children were born at a mean GA of 30.1 ± 2.0 weeks with a mean birth weight of 1390 ± 403 g ; 80 % received corticosteroids antenatally, and 41 % received surfactant ; 177 (51 %) underwent intubation, with a mean duration of 7.7 ± 11.4 days (median = 3 days). Compared with these 347 children, the 45 children with CP and/or severe sensory impairment were born at a significantly lower GA of 29.0 ± 2.2 weeks ($p<0.01$).

Children lost to follow-up and who refused the test

Children lost to follow-up (N=85) together with children who refused the test (N=69) differed from those involved in the study in a number of ways: they were more frequently boys ($p=0.03$) and SGA ($p=0.02$). They had a higher CRIB score ($p<0.01$), and were more often diagnosed as having severe ultrasound abnormality ($p=0.02$). Their parents had a lower educational ($p<0.01$) and occupational ($p<0.01$) level.

Results of the BLR scale

Global DQ was significantly lower in the study population than that of the reference sample ($p<0.01$) (Table 1). Significant differences between very preterm babies and babies born at term were observed in all the domains except GM function. Eight children (2.3 %) had a DQ < 70 and 62 (17.9 %) had a DQ < 85.

Twenty-four children (6.9 %) had an achievement discrepancy in at least one developmental domain. All but one had a global DQ > 85. Six had a delay in only one domain (FM: n = 5, L: n =1). The 18 others showed high performance in at least one domain compared to the global DQ.

Factors associated with partial DQs

As no difference in GM function was observed between the study population and the reference sample, the analysis of risk factors focused on the three other domains evaluated with the BLR scale. Results of the univariate analysis are shown in Table S1 (in Supplementary Material online). All the factors studied, except being SGA, were related to global DQ ($p <0.20$). In the multivariate analysis (Table 2), global DQ was related to sex ($p=0.01$), duration of intubation, parental educational level and occupation ($p<0.01$). The three latter factors were all significantly related to FM, L and S DQs. LDQ was lower in babies born before 32 weeks ($p=0.05$), in boys ($p<0.01$) and in children born SGA ($p=0.02$). S DQ was higher in girls ($p<0.01$). Although breastfeeding at discharge was associated at $p <0.20$ with each of the partial DQs in the univariate analysis, this relation was no more significant after multiple adjustment.

DISCUSSION

This large cohort included children born very preterm in the late 1990's, free of CP or severe sensory impairment. The mean DQ at 2 years CA was within the average range but approximately 0.5 SDs below the mean for term birth weight children born during the same period of time. Developmental delay, although small, was statistically significant and may be clinically meaningful for the individuals.(13) All but one of the areas of development evaluated on the BLR scale were delayed. Factors consistently associated with the partial DQs were: duration of intubation and parental level of education or occupation. GA < 32 weeks and being SGA were associated with lower LDQ. Language and sociability DQs were significantly lower in boys.

The results of this study indicating that very preterm birth is associated with deficiencies in a wide range of abilities are consistent with previous reports.(5,14) However, this is a cohort established in the post-surfactant era and not only extremely preterm babies were included but all very preterm children born up to 33 weeks GA. Recent Magnetic Resonance Imaging findings in preterm are in favor of a reduction in total tissue volume, and thus neuroimaging as well as neurodevelopmental abnormalities detected in preterm babies appear to be relatively diffuse, involving multiple neural systems.(15,16) The population was geographically determined and thus not subject to referral bias. Developmental delay was observed as early as 2 years of age and this may lead to early intervention.

Only children free of CP or severe neurosensory impairment were included in our cohort. Although mild CP cannot always be diagnosed at 2 years CA, GMDQ of the study group was not different from the reference sample.(11) It has been shown that an assessment of gross motor function considerably increases the reliability of CP diagnosis, especially in mild CP.(17) Thus, underestimation of CP is mild in our cohort. We assume that most of the children with moderate developmental delay were excluded. Indeed, only 2.3% of the children had a DQ <70 which is considerably lower than described by others.(18) Moderate developmental delay have been shown to be over represented in children unable to perform the full test. These children, who represented 16.5 % of the study group, together with those lost to follow up may have contributed to an overestimation of the DQs for the global population.

We found no significant impact of GA on development, except in the domain of language. However our group of extremely preterm babies which is at highest risk of later cognitive impairment, was too small to observe any difference.(19) We observed apparent highest LDQ in children born at 32 weeks compared to children born earlier. Being SGA was also related to LDQ but not to performance in other domains. The temporal lobe which is responsible for language process is among the latest to develop mature gyri, and shows increased vulnerability to hypoxic injury.(20) This may explain partly why children born SGA or before 32 wks had lower LDQs, but this still has to be confirmed. Being a boy was related to language and sociability DQ. No sex differences were observed in the reference sample in the different domains.(11) There are several explanations for male vulnerability and for example the role of estrogens in brain maturation has been recently studied.(21, 22)

Much of the improvement in survival observed along the years is attributed to the increased use of antenatal steroids, more aggressive approaches to delivery room resuscitation and surfactant replacement.(23) However, these measures did not appear to have improved the cognitive outcome of preterm babies.(24) The causes of adverse outcomes are multiple. Neonatal morbidity, social and environmental factors have to be considered, as well as the type of long-term problems experienced by children who require neonatal intensive care. In our group of children the duration of intubation was associated with a lower DQ in each of the domains studied. In a previous study, the total number of days of assisted ventilation was correlated with altered behavior around term in very preterm infants.(25) The relationship between duration of intubation and outcome is complex, with numerous confounding factors. Duration of intubation is obviously linked to the severity of respiratory distress and associated disorders. It may also be a marker of stress and painful events experienced by the baby. The impact of pain on neurodevelopment has been the subject of recent research. Pain enhance neuronal cell death and it has been suggested that cumulative brain damage during infancy leads to a reduction in brain volume, abnormal behavioral and neuroendocrine regulation, and poor cognitive outcomes in childhood and adolescence.(26) Decreasing stress in the Neonatal Intensive Care Units may improve the neurodevelopment of preterm babies and more research is required in this promising area.(27)

Socio economic status (SES) was also correlated with DQs. Other variables may have improved model accuracy. For example, the contribution to development of environmental factors, such as family functioning, social climate and resources, is well-known and found to be associated with outcome.(2) The lack of significant relation between breastfeeding and partial DQs in the multivariate analysis may be explained by the adjustment on SES.(28) It was suggested that socioeconomically disadvantaged groups have fewer personal resources to cope with strenuous life situations and that this influences breastfeeding duration in mothers of very preterm infants.(28, 29) This highlights the need for improved support for socioeconomically disadvantaged parents after a preterm birth.

It is unclear whether data collected at 2 years of age are predictive of later cognitive function. Twenty-four months is a critical transition period in cognitive development when skills in symbolic function, language development and early concept formation emerge.(30) The relationship between development at 2 years of age and cognitive function at 5 and 8 years is currently being studied in our cohort.

Our results suggest that preterm children born in the 1990s with essentially average development display subtle difficulties in multiple domains as early as 2 years CA which can only be traced by appropriate follow-up programs. In that group of children the influence of GA was minimal. Environmental factors after discharge appeared to have a major role in determining the outcome. Interventions aimed at enhancing parent-infant relationship and the self regulatory competence of the baby may give promising results with this population and require careful analysis.

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CONTRIBUTORS

PT and VP were responsible for the protocol development, patient screening, enrollment and outcome assessment. AF participated in the analytic framework for the study. MLC, VP, PYA and PT analyzed and interpreted the results. MLC drafted the report. VP contributed to the writing of the manuscript. All authors participated in revision and critical review of the report, and all have seen and approved the final version

LIST OF ABREVIATIONS

IQ, intelligence quotient; CP, cerebral palsy; GA, gestational age; DQ, developmental quotient; CA, corrected age; BLR : revised Brunet-Lézine; GM, gross motor; FM, fine motor; L, language; S, sociability; SGA, small for gestational age; CRIB, clinical risk index for babies; SD, standard deviation; MRI, magnetic resonance imaging; SES : socio economic status; NICU, neonatal intensive care unit.

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Table 1: Results obtained with the Brunet-Lezine Revised-test for the study population and the reference sample.

	Very preterm children N=347	**Calibration sample** N=57	p
Global DQ*	96 ± 13	104 ± 8	<0.01
Partials DQs*			
Gross motor	101 ± 15	102 ± 13	0.39
Fine motor	95 ± 14	102 ± 10	<0.01
Language	92 ± 17	101 ± 16	<0.01
Sociability	101 ±16	111 ± 9	<0.01

*: developmental quotient

Table 2: Multivariate analysis of the relationship between global DQ* and separate DQs* of the variables included (p<0.20 after univariate analysis).

	GLOBAL DQ* N=295			FINE MOTOR FUNCTION N=295			LANGUAGE N=311			SOCIABILITY N=295		
	Coefficient	CI 95 %	p	Coefficient	CI 95 %	p	Coefficient	CI 95 %	p	Coefficient	CI 95 %	p
Gestationnal age												
32 weeks												
30 - 31 weeks	-2	[-6 ; +1]		-1	[-5 ; +3]		-5	[-9 ; -1]		-2	[-6 ; +2]	
28 - 29 weeks	-3	[-6 ; +1]		-2	[-7 ; +2]		-5	[-10 ; -1]		-1	[-6 ; +4]	
<28 weeks	-3	[-8 ; +2]	0.37	-1	[-7 ; +5]	0.32	-4	[-10 ; +2]	0.05	-1	[-7 ; +6]	0.80
Sex												
girls												
boys	-4	[-6 ; -1]	<0.01				-5	[-9 ; -2]	<0.01	-5	[-9 ; -2]	<0.01
Growth in utero												
AGA†												
SGA ‡							-10	[-18 ; -1]	0.02			
CRIB§ score												
<5												
5 – 10	-1	[-6 ; +4]		1	[-4 ; +7]					-2	[-9 ; +4]	
> 10	8	[-3 ; +19]	0.26	6	[-6 ; +18]	0.57				10	[-4 ; +23]	0.24
Duration of intubation												
< 3 days												
3 to 9 days	-4	[-7 ; 0]		-5	[-9 ; -1]		-4	[-9 ; 0]		-7	[-9 ; 0]	
> 9 days	-11	[-17 ; -5]	<0.01	-11	[-17 ; -4]	<0.01	-8	[-14 ; -1]	0.02	-12	[-19 ; -4]	<0.01
Postnatal Corticosteroids												
No												
Yes	-2	[-8 ; +4]	0.46							-1	[-7 ; +8]	0.86
Severe ultrasound abnormalities												
No												
Yes	-2	[-10 ; +6]	0.61							-2	[-9 ; +12]	0.78
Breastfeeding at discharge												
No												
Yes	2	[-2 ; +5]	0.30	3	[-1 ; +7]	0.11	2	[-3 ; +6]	0.44	0	[-4 ; +5]	0.86
Highest parental educational level												
Beyond high school diploma												
High school diploma or less	-6	[-10 ; -2]	<0.01	-4	[-8 ; 0]	0.07	-9	[-13 ; -4]	<0.01	-7	[-12 ; -3]	<0.01
Highest parental occupation												
Intellectual or intermediate												
Employee, worker	-5	[-9 ; -2]		-5	[-9 ; -1]		-7	[-12 ; -3]		-3	[-8 ; +1]	
Unemployed	-12	[-17 ; -5]	<0.01	-11	[-17 ; -4]	<0.01	-18	[-25 ; -10]	<0.01	-11	[-19 ; -4]	0.01

*: developmental quotient; †: appropriate for gestational age; ‡: small for gestational age; §: clinical risk index for babies

Figure 1: Study population.

634 children born < 33 wks

Deaths in delivery room
(n = 37)
Deaths in NICU
(n = 49)

Surviving at discharge
N = 548
(86%)

Down's syndrome
(n = 1)
Agenesis of the corpus callosum
(n = 1)

Inclusion in follow up
N = 546

Lost to follow-up
(n=85)

Evaluated at a corrected age of 2 years
N = 461
(84%)

Cerebral Palsy
Quadriplegia (n=15)
Diplegia (n=20)
Hemiplegia (n=4)
Sensory impairment
Hearing aid (n=7), one associated with CP
Blind (n=2), both associated with CP

Free of cerebral palsy
and/or severe sensory impairment
N = 416

Refused the test
(n=69)

Brunet-Lézine test
N = 347
(83%)