Neonatal Infection and 5-year Neurodevelopmental Outcome of Very Preterm Infants

WHAT'S KNOWN ON THIS SUBJECT: Neonatal infections are frequent complications in very preterm infants, already at high risk of neurologic and cognitive disabilities. Few studies have linked neonatal infections and neurodevelopmental outcomes. Those that did evaluated children only to the age of 22 months.

WHAT THIS STUDY ADDS: This study assessed the respective effects of early- and late-onset sepsis and their association with 5-year neurodevelopmental outcomes. We identified a significant and cumulative risk of cerebral palsy when episodes of early- and late-onset sepsis were associated.

abstract

FREE

OBJECTIVE: To determine whether neonatal infections are associated with a higher risk of adverse neurodevelopment at 5 years of age in a population-based cohort of very preterm children.

METHODS: We included all live births between 22 and 32 weeks of gestation, from 9 regions in France, in 1997 (EPIPAGE study). Of the 2665 live births, 2277 were eligible for a follow-up evaluation at 5 years of age: 1769 had a medical examination and 1495 underwent cognitive assessment. Cerebral palsy and cognitive impairment were studied as a function of early-onset sepsis (EOS) and late-onset sepsis (LOS), after adjustment for potential confounding factors, in multivariate logistic regression models.

RESULTS: A total of 139 (5%) of the 2665 live births included in the study presented with EOS alone (without associated LOS), 752 (28%) had LOS alone (without associated EOS), and 64 (2%) displayed both EOS and LOS. At 5 years of age, the frequency of cerebral palsy was 9% (157 of 1769) and that of cognitive impairment was 12% (177 of 1495). The frequency of cerebral palsy was higher in infants with isolated EOS (odds ratio [OR]: 1.70 [95% confidence interval (CI): 0.84−3.45]) or isolated LOS (OR: 1.71 [95% CI: 1.14−2.56]) than in uninfected infants, and this risk was even higher in cases of combined EOS and LOS (OR: 2.33 [95% CI: 1.02−5.33]). There was no association between neonatal infection and cognitive impairment.

CONCLUSIONS: Neonatal infections in these very preterm infants were associated with a higher risk of cerebral palsy at the age of 5 years, particularly in infants presenting with both EOS and LOS. *Pediatrics* 2013;132:e372–e380

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KEY WORDS

cohort study, neonatal infection, neurodevelopmental outcome, population-based study, very preterm infants

ABBREVIATIONS

CI—confidence interval
EOS—early-onset sepsis
EPIPAGE—Etude Epidémiologique sur les Petits Ages Gestationnels
K-ABC—Kaufman Assessment Battery for Children
LOS—late-onset sepsis
MPC—mental processing composite Scale
OR—odds ratio

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Very preterm infants have a high risk of neurodevelopmental impairment, including cognitive and psychomotor delay.[1] Cerebral palsy, the most common and severe motor sequela, occurs in ~80 to 90 per 1000 very preterm births.[1–3] Cerebral white matter damage, identified principally by using magnetic resonance imaging but also by cranial ultrasound scans, is a powerful predictor of cerebral palsy in very preterm infants.[4–6] Recent studies have identified perinatal infection and inflammation as risk factors for cerebral white matter damage.[7–10] Preterm infants born to mothers with clinical or histologic chorioamnionitis are at risk for adverse neurodevelopmental outcomes, with a particularly high risk of cerebral palsy.[11]

Very preterm infants have a high risk of multiple infections between birth and hospital discharge. More than 50% of extremely low birth weight infants (<1000 g) are treated for clinical or proven neonatal infection during their hospitalization,[12] and the associated mortality is high (20%–40%).[13–15] Follow-up studies of preterm infants have suggested an association between inflammation, cerebral white matter damage, and cerebral palsy,[16–19] but very few studies have directly addressed the possible links between neonatal infections and neurodevelopmental outcomes.[8,20] The objective of the current study was to evaluate the impact of neonatal infections on 5-year neurodevelopmental outcomes in a large population-based cohort of very preterm infants.

METHODS

Study Population

EPIPAGE (Etude Epidémiologique sur les Petits Ages Gestationnels) is a population-based cohort study in which children were followed up from birth to 5 years of age.[21] This study included all live births between 22 and 32 completed weeks of gestation in all the maternity units of 9 French regions (more than one-third of the regions in the country) from January 1, 1997, to December 31, 1997. Overall, 127 (4%) of the 2901 live-born children recorded died in the delivery room, and information about neonatal infection was missing for another 109 infants; these children were all excluded (Fig 1). Thus, 2665 live births were included in the study. There were 291 neonatal deaths during hospitalization, leaving 2374 infants who were discharged from the hospital alive. Follow-up was proposed at hospital discharge for all the surviving infants in 7 of 9 regions. In the remaining 2 regions, follow-up was proposed for one-half the infants born at exactly 32 weeks of gestation, selected at random. The population included in this follow-up study therefore consisted of 2302 very preterm infants, 25 of whom died before the age of 5 years, leaving a total of 2277 survivors for follow-up at 5 years.

The study was approved by the French data protection agency (Commission Nationale de l'Informatique et des Libertés). The parents received written information about the study and provided oral consent for participation.[22]

Neonatal Infections

The data concerning neonatal infection were collected from neonatal records by using a standardized questionnaire. Two types of infection were studied: infections of maternal (ie, vertically transmitted) origin and postnatally (ie, horizontally) acquired infections. For infections of maternal origin, each child was classified as having no infection, confirmed infection, probable infection, or colonization. Early-onset sepsis (EOS) was defined as confirmed infection of maternal origin (vertically transmitted), on the basis of medical records. Late-onset sepsis (LOS) was defined as a postnatally acquired infection (horizontally acquired) treated with antibiotics for at least 7 days, also on the basis of medical records.

Maternal and Neonatal Data

Data for mothers, pregnancy, birth, and neonatal outcomes were recorded on standardized questionnaires at each maternity unit. Maternal data included antenatal corticosteroid therapy, premature rupture of membranes, maternal hemorrhage, spontaneous preterm labor, and type of pregnancy (singleton or multiple). Neonatal data included gender, gestational age (determined from the last menstrual period and findings from early prenatal ultrasound scans, calculated in completed weeks), small for gestational age (defined as a birth weight less than the 10th percentile for gender and gestational age in the EPIPAGE population), duration of central venous line use, and cranial ultrasound abnormalities. Cranial ultrasound scans were routinely performed during the neonatal period, and abnormalities were classified as major or moderate lesions in cases of periventricular leukomalacia or periventricular parenchymal hemorrhage, intraventricular hemorrhage with ventricular dilation or isolated ventricular dilation, or echodensity lasting >14 days. They were classified as minor lesions when intraventricular hemorrhage without ventricular dilation or germinal matrix layer hemorrhage was reported.[6]

Neurodevelopmental Outcomes

At 5 years of age, a complete medical and neuropsychological assessment was performed by trained physicians and psychologists at centers specifically set up for the study in each region. A medical questionnaire was completed by the physician after the clinical assessment, which included a

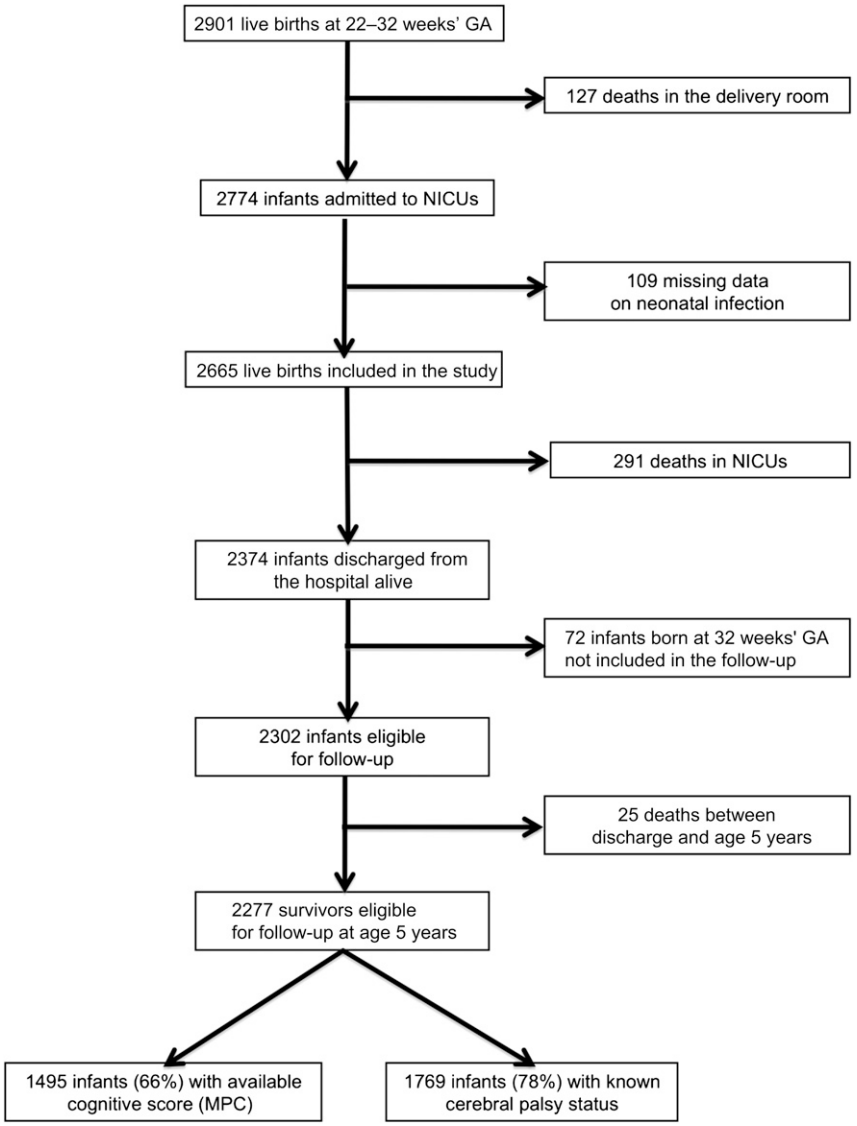

FIGURE 1
The study group. MPC of the Kaufman Assessment Battery for Children was used for analysis. GA, gestational age.

standardized neurologic examination (tone, reflexes, posture, and movements). We used the definition of cerebral palsy established by the European Cerebral Palsy Network,[23] which requires the presence of at least 2 of the following: abnormal posture or movement, increased tone, and hyperreflexia. Cerebral palsy status was known for 1769 very preterm children (78% of the children who survived to follow-up at 5 years of age).

The Kaufman Assessment Battery for Children[24] was used to assess cognitive function, expressed as a mental processing composite (MPC) score, which is an IQ equivalent. The MPC score provides a global measurement of cognitive ability, standardized to a mean ± SD of 100 ± 15.[24] MPC scores <70 indicate severe cognitive impairment.[1] Children who did not complete all of the tests in the battery were not included in the analysis of cognitive impairment. Cognitive scores (MPC) were available for 1495 (66%) children who survived to follow-up at 5 years of age.

Statistical Analysis

We first studied the associations between maternal and neonatal characteristics, and then neonatal infections and neurologic outcomes (cerebral palsy and MPC score). The goal was to identify potential confounders in the relationship between neonatal infections and neurologic outcomes. Early- and late-onset neonatal infections were studied independently (EOS, yes/no; LOS, yes/no) and together. We used a combined indicator to assess the respective effects of EOS and LOS and their association. Infants were classified as follows: uninfected, EOS alone (no associated LOS), LOS alone (no associated EOS), or both EOS and LOS.

The associations between neonatal infections and neurologic outcomes (cerebral palsy and MPC score) were studied by using logistic regression models, which were constructed separately for each outcome. For cerebral palsy, models were adjusted for maternal and neonatal variables selected in the univariate analysis (preterm rupture of membranes, spontaneous preterm labor, gender, gestational age, and small for gestational age) and other factors previously reported to be associated with short- and long-term outcomes (eg, antenatal corticosteroid therapy). For cognitive impairment, models were adjusted for maternal and neonatal variables selected in the univariate analysis (maternal age at birth, maternal level of education, parity, preterm rupture of membranes, gender, gestational age, small for gestational age, and duration of central venous catheter use) and other factors previously reported to be associated with short- and long-term outcomes (eg, antenatal corticosteroid therapy).

Associations were quantified according to odds ratios (ORs) and 95% confidence intervals (CIs). Analyses of MPC scores <70 were repeated after the exclusion

of children with cerebral palsy. Weights were used to take into account the differences in the proportion of children born at 32 weeks included in the different regions. Only weighted percentages are presented in the tables. Data from infants who were alive but did not complete their follow-up were compared with data from those who completed follow-up. All statistical tests were 2-tailed, with $P < .05$ regarded as significant. Stata version 11.0 software (Stata Corp, College Station, TX) was used for analysis.

RESULTS

Of the 2665 very preterm children born alive, 203 (8%) had EOS, which was not associated with LOS in 139 (5%); 816 (31%) had LOS, which was not associated with EOS in 752 (28%); and 64 (2%) had both EOS and LOS. Bacteriologic results were known in 84% (171 of 203) of EOS cases and 75% (614 of 816) of LOS cases. The most frequently detected organisms were group B *Streptococcus* (34%) and *Escherichia coli* (33%) for EOS and coagulase-negative *Staphylococcus* (46%) and *Staphylococcus aureus* (20%) for LOS.

For cerebral status and cognitive assessment, infants who were alive but did not complete their follow-up visit had a slightly higher gestational age and a lower maternal level of education than those who did complete follow-up. There were no differences in terms of infections (EOS and LOS), antenatal corticosteroid therapy, gender, small for gestational age, or cerebral lesions (Table 1).

Maternal and neonatal characteristics differed between the EOS and LOS groups (Table 2). EOS was more frequent in cases of premature membrane rupture. LOS was significantly more frequent in children who were small for gestational age. Rates of EOS and LOS infections increased with decreasing gestational age.

Cerebral palsy was found in 157 (9%) of the 1769 infants with known cerebral status, and 177 (12%) of the 1495 infants for whom a cognitive score (MPC) was available were found to have severe cognitive impairment. Maternal and neonatal characteristics differed as a function of neurologic outcome (cerebral palsy and MPC score) (Table 3). Cerebral palsy was significantly more frequent in cases of spontaneous preterm labor and in male infants. Severe cognitive impairment was significantly more frequent in cases of low maternal level of education and in children born to multiparous mothers. The frequencies of cerebral palsy and severe cognitive impairment increased with decreasing gestational age.

The risk of cerebral palsy was higher in children with EOS or LOS than in uninfected children, but these associations were no longer significant after adjustment for potential confounders (Table 4). However, if both EOS and LOS were considered (Table 5), children with isolated LOS or associated EOS and LOS had a higher risk of cerebral

TABLE 1 Characteristics of Survivors Seen at the Follow-up Visit at 5 Years and Infants Alive But Lost to Follow-up

Characteristic	Medical Examination					Cognitive Assessment				
	Infants With Known Cerebral Palsy Status (n = 1769)		Infants Alive But Lost to Follow-up (n = 508)		P	Infants With Known Cognitive Score (n = 1495)		Infants Alive But Lost to Follow-up (n = 782)		P
	%	n/N	%	n/N		%	n/N	%	n/N	
EOS	7	131/1769	6	29/508	.19	7	109/1495	7	51/782	.49
LOS	31	557/1769	31	155/508	.76	31	467/1495	31	245/782	.97
Gestational age, wk					<.01[a]					.01[a]
23–28	25	436/1769	18	93/508		24	365/1495	21	164/782	
29–30	26	467/1769	26	133/508		27	410/1495	24	190/782	
31–32	49	866/1769	55	282/508		48	(720/1495	55	428/782	
Cranial ultrasound abnormalities					.53					.08
Major or moderate	19	340/1750	19	93/496		18	266/1481	22	167/765	
Minor	16	275/1750	14	69/496		16	234/1481	14	110/765	
No	65	1135/1750	67	334/496		66	981/1481	64	488/765	
Antenatal corticosteroid therapy	75	1305/1739	74	361/488	.63	76	1110/1469	73	556/758	.25
Gender of child					.17					.16
Male	51	907/1769	55	278/508		51	762/1495	54	423/782	
Female	49	862/1769	45	230/508		49	733/1495	46	359/782	
Small for gestational age	8	138/1769	6	28/508	.08	8	113/1495	7	53/782	.50
Maternal level of education					<.01[a]					<.01[a]
University	31	538/1722	20	74/376		32	476/1468	22	136/630	
High school	22	371/1722	16	61/376		22	321/1468	18	111/630	
Middle school	42	715/1722	54	201/376		41	595/1468	51	321/630	
Primary school or no school	6	98/1722	11	40/376		5	76/1468	10	62/630	

[a] XXXX

TABLE 2 EOS and LOS as a Function of Maternal, Pregnancy, and Neonatal Characteristics

Characteristic	EOS			LOS			EOS and LOS		
	%	*n*/*N*	*P*	%	*n*/*N*	*P*	%	*n*/*N*	*P*
Antenatal corticosteroid therapy									
Yes	7	143/1908		31	601/1908		3	48/1908	
No	8	56/685	.57	30	204/685	.40	2	16/685	.79
Preterm rupture of membranes									
Yes	14	139/980		29	282/980		5	45/980	
No	4	61/1645	<.01[a]	32	526/1645	.09	1	19/1645	<.01[a]
Maternal hemorrhage									
Yes	7	22/313		32	100/313		2	7/313	
No	8	181/2352	.68	30	716/2352	.59	2	57/2352	.84
Spontaneous preterm labor									
Yes	6	47/780		28	221/780		2	15/780	
No	8	153/1850	.05[a]	32	586/1850	.09	3	49/1850	.27
Type of pregnancy									
Singleton	8	145/1830		31	564/1830		3	50/1830	
Multiple	7	58/835	.38	30	252/835	.74	2	(14/835	.10
Gender of child									
Male	7	104/1410		31	440/1410		3	31/1410	
Female	8	99/1253	.61	30	375/1253	.47	2	33/1253	.46
Gestational age, wk									
23–28	12	88/741		51	381/1741		5	40/741	
29–30	7	47/657		33	214/657		2	14/657	
31–32	5	68/1267	<.01[a]	17	221/1267	<.01[a]	1	10/1267	<.01[a]
Small for gestational age									
Yes	4	9/228		43	98/228		3	63/2435	
No	8	194/2435	.03[a]	29	717/2435	<.01[a]	0.4	1/228	.04[a]
Duration of central venous catheter use, d									
<11				8	74/960		0.5	5/960	
11–20				21	131/638		1	7/638	
>20				58	577/994	<.01[a]	5	47/994	<.01[a]
Cranial ultrasound abnormalities									
Major or moderate	10	61/602		40	240/602		4	26/602	
Minor	10	38/391		39	154/391		3	13/391	
No	6	94/1607	<.01[a]	26	422/1607	<.01[a]	2	25/1607	<.01[a]

[a] XXXX

palsy than uninfected children. These associations remained significant after adjustment. There was no association between neonatal infection and severe cognitive impairment before or after adjustment (Table 6).

DISCUSSION

We found that neonatal infections in these very preterm infants were associated with a higher risk of cerebral palsy at 5 years of age, particularly when both EOS and LOS were present. There was no association between neonatal infection and cognitive impairment.

Our study was based on data from the EPIPAGE cohort, one of the largest population-based studies of very preterm infants, with an accurate assessment of the gestational age of all very preterm children. In France, early ultrasound assessments of gestational age are routinely conducted, and gestational age determination according to this method is considered highly satisfactory.[25] Children enrolled in the EPIPAGE study were evaluated at the age of 5 years, with standardized, validated criteria, for the detection of cerebral palsy and cognitive impairment.[23,24]

Loss to follow-up is a common issue in longitudinal studies and may bias the results. However, medical data were available at 5 years for more than three-quarters of the very preterm children, and an MPC score was available for almost two-thirds of these children. This follow-up rate should be viewed in light of the large number of children investigated, their geographic dispersion, and the frequent movement of parents with young children. Moreover, our follow-up rate is similar to that of other population-based studies.[26,27] However, studies in which complementary investigations are conducted for children who were initially lost to follow-up have reported worse outcomes for these children.[28] This finding

TABLE 3 Cerebral Palsy and Cognitive Impairment (MPC <70) as a Function of Maternal, Pregnancy, and Neonatal Characteristics

Characteristic	Cerebral Palsy			MPC <70		
	%	*n*/*N*	*P*	%	*n*/*N*	*P*
Maternal level of education						
University	7	38/538	.37	6	29/476	<.01[a]
High school	9	32/371		8	25/321	
Middle school	10	70/715		17	103/595	
Primary school or no school	10	10/98		24	18/76	
Maternal age at birth of the infant, y						
<25	10	39/377	.45	13	37/295	.03[a]
25–34	9	96/1106		10	100/963	
>34	8	21/276		17	38/229	
Parity						
Primiparous	9	86/975	.94	9	78/833	<.01[a]
Multiparous	9	70/784		15	99/656	
Antenatal corticosteroid therapy						
Yes	10	44/434	.33	13	45/359	.68
No	9	112/1305		12	130/1110	
Preterm rupture of membranes						
Yes	10	65/653	.24	11	60/565	.28
No	8	91/1096		12	114/912	
Maternal hemorrhage						
Yes	9	19/211	.94	9	16/183	.17
No	9	138/1558		12	161/1312	
Spontaneous preterm labor						
Yes	12	59/498	<.01[a]	13	51/400	.49
No	8	95/1250		11	123/1075	
Type of pregnancy						
Singleton	10	116/1219	.16	12	127/1033	.42
Multiple	7	41/550		11	50/462	
Gender of child						
Male	10	95/907	.01[a]	13	97/762	.28
Female	7	62/862		11	80/733	
Gestational age, wk						
23–28	14	63/436	<.01[a]	19	68/365	<.01[a]
29–30	9	40/467		10	42/410	
31–32	6	54/866		9	67/720	
Small for gestational age						
Yes	6	8/138	.18	15	17/113	.27
No	9	149/1631		12	160/1382	
Cranial ultrasound abnormalities						
Major or moderate	24	81/340	<.01[a]	22	59/266	<.01[a]
Minor	9	26/275		15	34/234	
No	4	49/1135		9	84/981	

[a] XXXXX

may have led to an underestimation of cognitive impairment, because loss to follow-up was more common in socially disadvantaged children, and these children have a higher risk of lower cognitive scores. Children lost to follow-up had a slightly higher gestational age at birth than did those remaining in the study, but neonatal cerebral lesions and neonatal infections did not differ between the 2 groups. Thus, any bias in our assessment of the prevalence of cerebral palsy is probably small.

Our study is the first to focus on the association between neonatal infections and 5-year neurodevelopmental outcomes in very preterm children. Children presenting with both EOS and LOS had a higher risk of cerebral palsy than uninfected children. Moreover, children with isolated LOS also had a higher risk of cerebral palsy than uninfected children. The association with isolated EOS was no longer significant after adjustment, but we cannot exclude the possibility that this finding was due to a lack of statistical power. Very few studies have directly investigated the potential links between neonatal infection and neurodevelopmental outcome.[8,20] Stoll et al[8] conducted a large cohort study of 6093 extremely low birth weight infants (from the Eunice Kennedy Shriver National Institute of Child Health and Human Development) comparing uninfected infants with those presenting with isolated clinical infection, sepsis, sepsis and necrotizing enterocolitis, or meningitis (with or without sepsis). They found that infants with infections of these types were significantly more likely to have adverse neurodevelopmental outcomes at follow-up visits at 18 to 22 months of corrected gestational age, including cerebral palsy (range of significant OR: 1.4–1.7), low mental development index (OR: 1.3–1.6), and psychomotor development index (OR: 1.5–2.4) on the Bayley Scales. In a more recent Swiss national cohort of 541 extremely premature infants born at gestational ages of 24 to 27 weeks,[20] proven sepsis per se increased the risk of cerebral palsy (OR: 3.23 [95% CI: 1.23–8.48]) at a corrected age of 2 years. In both studies,[8,20] neurodevelopmental status was assessed in early childhood, an approach that is known to be less strongly predictive than the later assessment of long-term neurodevelopmental outcome.[29]

We studied very severe cognitive impairment (MPC score <70), potentially accounting for the lack of association between neonatal infections and cognitive impairment. However, the mechanisms underlying cognitive impairment are more complex, probably involving a combination of brain

TABLE 4 Relationship Between Cerebral Palsy, EOS (yes/no), and LOS (yes/no)

Status	No. of Infants		OR, 95% CI	*P*	OR,[a] 95% CI	*P*
	%	*n*/*N*				
EOS						
No	8	137/1638	1	.01	1	.12
Yes	15	20/131	1.92,[c] 1.15–3.20		1.55, 0.90–2.67	
LOS						
No	7	84/1212	1	<.01	1	.08
Yes	13	73/557	2.11, 1.51–2.95		1.45, 0.95–2.20	

[a] EOS: adjusted for antenatal corticosteroid therapy, preterm rupture of membranes, spontaneous preterm labor, sex, gestational age, small for gestational age. LOS: adjusted for antenatal corticosteroid therapy, preterm rupture of membranes, spontaneous preterm labor, type of pregnancy, sex, gestational age, small for gestational age and duration of central venous catheter use.

TABLE 5 Relationship Between Cerebral Palsy and Neonatal Infection (Uninfected Versus Infected)

Status	No. of Infants		OR, 95% CI	*P*	OR,[a] 95% CI	*P*
	%	*n*/*N*				
Uninfected	6	73/1126	1	<.01	1	.03
EOS alone (without associated LOS)	13	11/86	2.05, 1.04–4.05		1.70, 0.84–3.45	
LOS alone (without associated EOS)	12	64/512	2.15, 1.50–3.07		1.71, 1.14–2.56	
Associated EOS and LOS	20	9/45	3.63, 1.68–7.86		2.33, 1.02–5.33	

[a] Adjusted for antenatal corticosteroid therapy, preterm rupture of membranes, spontaneous preterm labor, sex, gestational age, small for gestational age.

TABLE 6 Relationship Between Severe Cognitive Impairment (MPC<70), EOS, and LOS (After the Exclusion of Children With Cerebral Palsy)

Status	No. of Infants		OR, 95% CI	*P*	OR,[a] 95% CI	*P*
	%	*n*/*N*				
EOS						
No	11	140/1297	1	.97	1	.95
Yes	11	11/98	0.99, 0.51–1.90		0.98, 0.47–2.04	
LOS						
No	11	103/972	1	.65	1	.31
Yes	11	48/423	1.09, 0.75–1.57		0.79, 0.50–1.24	

[a] EOS: adjusted for maternal age at birth, maternal level of education, parity, preterm rupture of membranes, antenatal corticosteroid therapy, gender, gestational age, and small for gestational age. LOS: adjusted for maternal age at birth, maternal level of education, parity, antenatal corticosteroid therapy, gender, gestational age, small for gestational age, and duration of central venous catheter use.

damage, persistent inflammation, and epigenetic changes resulting in the impairment of brain maturation and development.[30] Studies in a number of experimental animal models have suggested that there is a relationship between cytokine responses, hypotension, and white matter injury.[31–33] Studies in premature infants have also shown a relationship between inflammatory cytokine levels and white matter injury,[34,35] which is known to be associated with cerebral palsy.[4,6] Glass et al[36] found that exposure to multiple episodes of culture-positive infection increased the risk of progressive white matter injury. Another recent study, by Chau et al,[37] provides further evidence that postnatal infection, even in the absence of positive culture results, is an important risk factor for widespread abnormalities of brain development in premature infants.

The frequency of EOS differs considerably between studies, depending on the population considered; published values range between 1% and 15%. The high frequency of EOS (8%) in our study may be accounted for by the use of a diagnostic procedure less specific than the criteria used in previously published studies. The frequency of LOS was 31% in the 2665 very preterm infants included in our study, a rate consistent with published data (21%–66%),[12,38,39] even though the diagnosis of neonatal infection was not based on highly specific criteria (ie, a positive blood culture result or 2 positive culture results for coagulase-negative staphylococcal infections).[40] The diagnosis of a bloodstream infection in adults is based on a single positive result on blood culture, but this criterion cannot be transposed directly to newborn children in general and to preterm infants in particular. Indeed, the mean volume of blood dispensed into blood culture bottles for preterm infants is <0.5 mL,[41,42] greatly limiting the discrimination possible with this test. This limitation may lead to errors in the diagnosis of infections, due to misclassification (false-positive and false-negative results). These misclassifications are independent of neurodevelopmental outcome but are likely to result in a lack of power in studies of associations between neonatal infections and long-term outcomes.

CONCLUSIONS

The originality of the current study resides in the use of an indicator combining the 2 types of neonatal infections in relation to cerebral palsy and cognitive impairment at 5 years of age. The higher risk of cerebral palsy in cases of neonatal infection is consistent with the neurotoxic effects of infectious and inflammatory mediators on cerebral white matter, particularly in children suffering both early- and late-onset infections. The development of appropriate strategies for reducing infection rates would thus help to improve the neurodevelopment outcomes of these vulnerable infants. The evaluation of such strategies should be validated in randomized trials.

ACKNOWLEDGMENTS

The composition of the EPIPAGE Study Group was as follows: INSERM U953: B. Larroque (national coordinator), P. Y. Ancel, B. Blondel, G. Bréart, M. Dehan, M. Garel, M. Kaminski, F. Maillard, C. du Mazaubrun, P. Missy, F. Sehili, K. Supernant, and L. Marchand; Alsace: M. Durant, J. Matis, J. Messer, and A. Treisser (Hôpital de Hautepierre, Strasbourg); Franche-Comté: A. Burguet, L. Abraham-Lerat, A. Menget, P. Roth, J.-P. Schaal, and G. Thiriez (CHU St Jacques, Besançon); Haute-Normandie: C. Lévêque, S. Marret, and L. Marpeau (Hôpital Charles Nicolle, Rouen); Languedoc-Roussillon: P. Boulot and J.-C. Picaud (Hôpital Arnaud de Villeneuve, Montpellier), A.-M. Donadio, and B. Ledésert (ORS Montpellier); Lorraine: M. André, J. Fresson, and J.M. Hascoët (Maternité Régionale, Nancy); Midi-Pyrénées: C. Arnaud, S. Bourdet-Loubère, and H. Grandjean (INSERM U558, Toulouse), M. Rolland (Hôpital des enfants, Toulouse); Nord-Pas-de-Calais: C. Leignel, P. Lequien, V. Pierrat, F. Puech, D. Subtil, and P. Truffert (Hôpital Jeanne de Flandre, Lille); Pays de la Loire: G. Boog, V. Rouger-Bureau, and J.-C. Rozé (Hôpital Mère Enfants, Nantes); and Paris-Petite-Couronne: P.-Y. Ancel, G. Bréart, M. Kaminski, and C. du Mazaubrun (INSERM U953, Paris), M. Dehan and V. Zupan-Simunek (Hôpital Antoine Béclère, Clamart), and M. Vodovar, M. Voyer (Institut de Puériculture, Paris).

We are indebted to the women and children who participated in the study. We are grateful to all the members of the EPIPAGE group, including the study designers and investigators.

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(Continued from first page)

Dr Mitha conceptualized and designed the study, drafted the initial manuscript, carried out the initial analyses, and reviewed and revised the manuscript; Dr Foix-L'Hélias conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Arnaud, Marret, Vieux, Aujard, Thiriez, Larroque, Cambonie, Burguet, Boileau, Rozé, Kaminski, and Truffert critically reviewed the manuscript; Dr Ancel critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-3979

doi:10.1542/peds.2012-3979

Accepted for publication May 28, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: Funding for this study was obtained from INSERM (French National Institutes of Health and Medical Research), Directorate General for Health of the Ministry for Social Affairs, and "Hospital Program for Clinical Research 2001" (A0M01117) of the French Department of Health. None of the funding bodies was involved in the design or running of the study; data collection, analysis, or interpretation; or the preparation, review, or approval of the manuscript.

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Pediatrics 2013;132;e372
DOI: 10.1542/peds.2012-3979 originally published online July 22, 2013;

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DOI: 10.1542/peds.2012-3979 originally published online July 22, 2013;