

ORIGINAL ARTICLE

Prevalence, causes, and outcome at 2 years of age of newborn encephalopathy: population based study

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Objectives: To ascertain the prevalence of newborn encephalopathy in term live births, and also the underlying diagnoses, timing, and outcome at 2 years of surviving infants.

Design: Population based observational study.

Setting: North Pas-de-Calais area of France, January to December 2000.

Patients: All 90 neonates with moderate or severe newborn encephalopathy.

Results: The prevalence of moderate or severe newborn encephalopathy was 1.64 per 1000 term live births (95% confidence interval (CI) 1.30 to 1.98). The prevalence of birth asphyxia was 0.86 per 1000 term live births (95% CI 0.61 to 1.10). The main cause of newborn encephalopathy was birth asphyxia, diagnosed in 47 (52%) infants. It was associated with another diagnosis in 11/47 cases (23%). The timing was intrapartum in 56% of cases, antepartum in 13%, ante-intrapartum in 10%, and postpartum in 2%. In 19% of cases, no underlying cause was identified during the neonatal course. Twenty four infants died in the neonatal period, giving a fatality rate of 27% (95% CI 17% to 36%). Three infants died after the neonatal period. At 2 years of age, 38 infants had a poor outcome, defined by death or severe disability, a prevalence of 0.69 per 1000 term live births (95% CI 0.47 to 0.91). In infants with isolated birth asphyxia, this prevalence was 0.36 per 1000 term live births (95% CI 0.20 to 0.52).

Conclusions: The causes of newborn encephalopathy were heterogeneous but the main one was birth asphyxia. The prevalence was low, but the outcome was poor, emphasising the need for prevention programmes and new therapeutic approaches.

Neonatal encephalopathy (NE) in term newborn infants is a significant public health problem. Variable prevalences have been reported in the United States, Britain, and Sweden¹ but the most recent was 3.8 per 1000 term live births in Western Australia.² During recent years, a growing interest in neural rescue treatments which can be applied after birth asphyxia has emerged. From these therapeutic perspectives, it is important to know whether perinatal hypoxia-ischaemia (HI) is due to acute asphyxia only, associated with subacute or chronic asphyxia, or due to other disorders. Badawi *et al*³ suggested that many pathways leading to NE begin in the antepartum period, but this is still controversial.^{4–5} It is generally accepted that HI accounts for only a small proportion of cerebral palsy (CP),⁶ but it is a potentially avoidable cause of CP.

The aims of our study were to describe the prevalence of NE in term babies in a French population, to define the spectrum of diagnoses associated with this syndrome and the timing of NE, and to describe the outcome of surviving infants at 2 years of age.

SUBJECTS AND METHODS

Between January and December 2000, we conducted a population based study of term infants with NE born in the North Pas-de-Calais area in France. This region is densely populated with 4 million inhabitants. The birth rate is 13.6 per 1000 population, representing 7.5% of all infants born in France. The population is one of the youngest in France but the level of education is among the lowest, with 30% of pregnant women having a post secondary diploma, which is significantly different from the 38.7% for the whole country.⁷

The area is served by 46 delivery units. Of these, four are level III perinatal centres. There are six neonatal intensive

care units, including the four perinatal centres, four level II and nine level I neonatal units. Many efforts have been made during the last 15 years to improve the regional organisation of perinatal care, and 12 delivery units were closed between 1990 and 2000. The planning of the study was elaborated with at least one colleague from each level II and III neonatal unit and after regular discussions before the start of the study to complete referral and recruitment of patients. One obstetrician was involved in these discussions, and information was sent to the Regional College of Obstetricians.

Cases included in the study were those of term babies (≥ 37 weeks) who, during the first week of life, fulfilled the following criteria:

- Either seizures alone or
- Any two of the following criteria lasting more than 24 hours:
 - Abnormal consciousness
 - Difficulty maintaining respiration (of presumed central origin)
 - Difficulty feeding (of presumed central origin)
 - Abnormal tone and reflexes

Infants with chromosomal abnormalities recognisable at birth, open neural tube defects, or neonatal abstinence syndrome were excluded. Other major congenital malformations were included, but minor congenital abnormalities were not systematically documented. Most neonates with drug withdrawal syndrome stay with their mothers in the

Abbreviations: CP, cerebral palsy; HI, hypoxia-ischaemia; IUGR, intrauterine growth retardation; NE, neonatal encephalopathy

Table 1 Perinatal characteristics of 90 cases of newborn encephalopathy

	No	%
Boys	42	47
Small for gestational age	13	14
Twin pregnancy	2	2
Spontaneous labour	64	71
Caesarean section (CS)	37	41
Emergency CS	25	28
Forceps	12	13
Vacuum	7	8

maternity unit or are referred to the nearest neonatal unit, including level I units, and we could not assume that we would document all these infants. The severity of NE was graded as moderate or severe as described by Sarnat and Sarnat.⁸ All cases of severe NE are referred to level III neonatal units. Moderate encephalopathy can be admitted to either level II or level III neonatal units.

HI was defined as NE with at least three of the following criteria:

- Late decelerations on fetal monitoring or meconium staining
- Delayed onset of breathing
- Arterial cord blood pH < 7.1 or base deficit ≥ 12
- Apgar < 7 at five minutes
- Multiple organ failure defined as involvement of at least two organs including kidney, liver, gut, and heart
- Acute hypoxic event occurring immediately before or during labour—for example, massive ante-intrapartum haemorrhage or ruptured uterus

Deaths due to medical termination of pregnancy are recorded in a regional register.

All cases included in 2000 were reviewed, and deaths associated with brain pathology extracted. Postmortem examinations of neonates who died per-partum or during the first week of life are performed in the regional department of histopathology (Lille University Hospital), but not all cases are referred to the centre. The unit databases were browsed again for term babies with NE.

To increase the accuracy of the material, a phone call was made to each unit every month. All level I neonatal units were informed and regularly contacted to be sure that no infant with NE was admitted to these units. At the end of the study, data were cross checked and supplemented by the hospital databases of level II and III units.

The causes of NE were reviewed by two of the authors and discussed with the neonatologist involved in patient management in the case of a disagreement. The event leading to NE was defined as antepartum, intrapartum, postpartum, or

Table 3 Aetiology of 90 cases of neonatal encephalopathy

Cause	All cases	Cases associated with HI (n = 8)
Birth asphyxia	39 (3*)	0
Infectious disease	7	2
Birth defects		
Biochemical	3	0
Structural	10	4
Genetic	3	1
Others	11	1
Unknown	17	0

Values are number of subjects.

*Three of the 39 were small for gestational age.

HI, Perinatal hypoxia-ischaemia.

unknown. Associations were possible. Antepartum causes included birth defects and coagulation disorders. Birth defects were defined as structural, chromosomal, genetic, and biochemical.⁹ Coagulation disorders were those leading to antenatal bleeding as in neonatal alloimmune thrombocytopenia. Intrapartum cases were those involving HI, early onset infections, or intracranial haemorrhage during delivery. All were posterior fossa haematomas after instrumental extraction or subarachnoid haemorrhage. Intrauterine growth retardation (IUGR) is much more a risk factor for than a cause of NE, but neonates with HI and birth weight below the 3rd centile¹⁰ were included in the ante-intrapartum cases. A postnatal origin was retained for cases in which a clear acute postnatal event occurred that compromised the brain and was followed by signs of NE and occurring within 7 days of birth. Sometimes we were unable to identify any underlying cause, and these cases were labelled NE of unknown origin.

Follow up

Survivors were included in a follow up study until the age of 2 years. Assessments were made by the neonatologists usually involved in the follow up of at risk newborns during a routine outpatient visit. They included a standard clinical and neurological examination. They were completed with a structured follow up questionnaire planned to collect birth defects which could have been diagnosed after the neonatal period. A systematic evaluation of sensorineural and cognitive functions was not planned. CP was defined as described by Hagberg *et al.*¹¹ Minor neurological dysfunction was defined as strabismus or slight abnormality of tone. Head circumference was compared with the growth curves of Sempé.¹² The list of infants lost to follow up was sent to the North Pas-de-Calais Registries for handicapped children (CDES) to obtain information about the occurrence of sequelae. This register includes all handicapped children requiring special education. By 2 years of age, only children with severe handicap are included in this register.

Table 2 Features of neonatal encephalopathy in 90 newborns with or without perinatal hypoxia-ischaemia (HI)

Features	With HI* (n = 47)	Without HI* (n = 43)	p Value	OR (95% CI)
Seizures	28 (59)	34 (79)	0.04	0.39 (0.14 to 1.09)
Abnormal tone	45 (96)	31 (72)	0.001	8.71 (1.66 to 60.85)
Respiratory difficulties	26 (55)	14 (33)	0.02	2.56 (1 to 6.65)
Feeding difficulties	24 (51)	26 (60)	0.36	0.68 (0.27 to 1.71)
Abnormal consciousness	35 (74)	13 (30)	<0.0001	6.73 (2.44 to 19.04)

Values are numbers (%).

*Categories not mutually exclusive.

Table 4 Diagnosis associated with antenatal causes of neonatal encephalopathy

Birth defects (n = 16)			
Biochemical (n = 3)	Structural (n = 10)	Genetic (n = 3)	Others (n = 5)
Non-ketotic hyperglycaemia (2)	Cortical dysplasia (1)	Willi-Prader syndrome* (1)	Non-immune hydrops fetalis* (1)
Ornithine transcarboxylase deficiency (1)	Congenital post-haemorrhagic hydrocephalus (1)	Costello syndrome (1)	Intrauterine growth retardation (3)*
	Unilateral absent kidney, megaloureter, ventriculomegaly (1)	Benign familial neonatal seizures (1)	Early onset hypocalcaemia (1)
	Cerebro-oculofacial skeletal syndrome (1)		
	Facial dysmorphism, microcephaly (1)		
	Facial dysmorphism, dysmorphic fingers, hypospadias* (1)		
	Pierre Robin syndrome, hypoplasia of the corpus callosum* (1)		
	Dysgenesis of the corpus callosum* (1)		
	Pierre Robin syndrome, atrophied brainstem* (1)		
	Epileptic encephalopathy (1)		

Values are number of subjects.

*Cases associated with perinatal hypoxia-ischaemia.

Statistical analysis

In 2000, 58 235 live births were registered in North Pas-de-Calais. The number of premature births was extrapolated from the results of the 1998 National Perinatal Investigation, which gave a 5.4% rate of premature births in this area.⁷ The prevalence of NE among term live births was calculated assuming that 54 624 term neonates were born in 2000. Main outcome measures are given as odds ratios with 95% confidence intervals (CI). Rates were compared by the χ^2 test.

RESULTS

Ninety infants fulfilled the inclusion criteria. Eighty eight were admitted to a neonatal care unit, and two died in the delivery room. Mean (SD) gestational age was 39 (1) weeks for a mean (SD) birth weight of 3118 (618) g. None of the infants was born after 41 weeks gestation. Table 1 summarises the perinatal characteristics. HI was diagnosed in 47 infants (52%). Twenty three had moderate, and 24 severe NE. Apgar score at one minute was ≤ 3 in 30 infants (33%). All but one had signs of HI. Clinical seizures (69%) and abnormal tone (84%) were the most common features of NE. Table 2 gives the distribution of the entry criteria for infants with or without HI. Abnormal consciousness or tone level was more often diagnosed in neonates with HI ($p < 0.001$, $p = 0.001$).

Prevalence

The birth prevalence of moderate or severe NE was 1.64 per 1000 term live births (95% CI 1.30 to 1.98). The prevalence of moderate or severe HI was 0.86 per 1000 term live births (95% CI 0.61 to 1.10). During the same period of time, termination of pregnancy in fetuses with severe brain

malformation was performed in 23 cases. If one assumes that all of these neonates would have developed signs of NE, the prevalence would have been 2.06 per 1000 term live births (95% CI 1.68 to 2.44).

Causes of NE

Table 3 presents the causes. The main cause of NE was perinatal HI (52%). It was isolated in 36 cases (77%), associated with IUGR in three cases (6%), and associated with another diagnosis in eight cases (17%). A birth defect was diagnosed in 16 cases (18%). Infectious diseases (8%) were always severe early onset infections with either septicaemia or meningitis. Of the 11 infants with other causes (12%), four had subarachnoid haemorrhage, two had brain injury after forceps extraction, one had a focal infarction, two had HI during neonatal surgery, one had non-immune hydrops fetalis, and one had early onset hypocalcaemia. In 17 cases (19%), no underlying cause of NE was identified during the neonatal period. All but three had moderate encephalopathy. Fourteen had seizures, confirmed by an electroencephalogram in 10 cases. In six cases there was evidence that the neonates had experienced a significant intrapartum event which may have been associated with intrapartum hypoxia, although our definition of HI was not strictly fulfilled. Eight had mild abnormalities on cranial ultrasound compatible with HI lesions.¹³

Timing of NE

The main event leading to NE occurred during the intrapartum period in most of the cases ($n = 50$, 56%) (fig 1). A significant antenatal cause of NE was diagnosed in 18 infants (table 4). Three neonates with IUGR and HI were included in this subgroup and consequently 21 cases (23%) were labelled antenatal. It was the only identified cause in 12 cases (13%), but was associated with HI in nine cases (10%). Two cases (2%) were defined as postnatal. Both were infants with congenital anomalies and HI hypovolaemia during surgery. In 19% of the neonates, no clear cause was recognised and the timing of NE was designated as unknown.

Outcome

Twenty four infants died in the neonatal period, giving a fatality rate of 27% (95% CI 17% to 36%). All of them

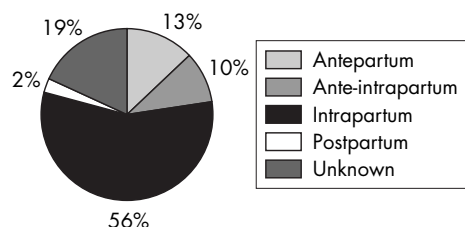


Figure 1 Distribution of origin of newborn encephalopathy.

Table 5 Outcome at 2 years of age in cases of neonatal encephalopathy according to cause

Outcome	Group I (n = 39)	Group II (n = 17)	Group III (n = 34)
Death	16 (41)	0 (0)	11 (32)
Normal	15* (38)	12 (70)	13 (38)
Minor neurological dysfunction	3 (8)	3 (18)	2 (6)
Cerebral palsy	4 (10)	1 (6)	6 (18)
Lost to follow up	1 (3)	1 (6)	2 (6)
Age at walking (months)	10.2 (1.4)	12.3 (1.7)	16.6 (6.7)
Head circumference (m)	0.11 (1.6)	0.19 (1.1)	0.37 (1.05)

All values are number (%) except for age at walking and head circumference, which are mean (SD). Group I, infants with hypoxia-ischaemia as the only recognised cause; group II, infants with an unrecognised cause during the neonatal period; group III, others.

*One case with renal failure due to birth asphyxia.

had severe NE. Intensive care was withdrawn in 13 cases (54%). Details of these children can be found at <http://adc.bmjjournals.com/supplemental/>. In 16 cases with birth asphyxia, three with metabolic disorders, three with congenital malformation, one with infectious disease, and one with postnatal HI, death occurred. A brain malformation was diagnosed in two of the infants with congenital malformation.

Table 5 shows the outcome at 2 years of age for the 66 neonatal survivors. Outcome was analysed separately in three subgroups: infants with HI as the only recognised cause (group I), with an unrecognised cause during the neonatal period (group II), and in others (group III). Three infants in group III with congenital anomalies died after the neonatal period. Among the survivors at 2 years, 15 infants in group I (15/23, 65%), 12 in group II (12/17, 70.5%), and 13 in group III (13/23, 56.5%) were considered to be neurologically normal. Four infants in group I (4/23, 17%), one in group II (1/17, 6%), and six in group III (6/23, 26%) developed CP. All but one in group I had quadriplegia, with dystonic features in one of them. The other had a pure dystonic CP. The infant with CP in group II had a hypotonic form, and a brain defect was diagnosed after the neonatal period. In group III, hypotonic CP was diagnosed in four infants. Two had quadriplegia with severe mental retardation. Mean age at walking was slightly delayed in group III. Two infants in group I and one in group III had a microcephaly. None of the infants lost to follow up was known at the CDES.

The overall incidence of death or severe disability at 2 years of age was 42% (95% CI 32% to 52%) which represents 0.69 per 1000 term live births (95% CI 0.47 to 0.91). Twenty infants (51%) with birth asphyxia alone (95% CI 35% to 67%) had a poor outcome, defined by death or severe disability, which gave an incidence of 0.36 per 1000 term live births (95% CI 0.20 to 0.52).

DISCUSSION

Our findings show that over 50% of term infants with NE had evidence of HI, which was associated with another specific diagnosis in 23% of the cases. The outcome of children with moderate or severe perinatal HI without any other recognised diagnosis was poor, with 51% of them having died or with severe disabilities at 2 years of age. Such a large proportion of neonates with NE and HI is controversial, but is in agreement with observations in Sweden,¹⁴ the United Kingdom, and the Netherlands.⁵ In the eighth Swedish population based cerebral palsy report, 36% of CP in term infants was considered to be of perinatal or neonatal origin.¹⁴ In a large hospital based study, using magnetic resonance imaging, Cowan *et al*⁵ found that 90% of term infants with NE, seizures, or both, but without specific syndromes or major congenital defect had evidence of perinatally acquired insults

and a very low rate of established brain injury acquired before birth. As our study was population based, we were not able to obtain the same quality of neuroimaging for all the infants, but because of the lack of standardised protocol, we have chosen not to report the neuroimaging data. Consequently we cannot assume that none of them had lesions acquired antenatally. Nevertheless, only one congenital defect was diagnosed during the follow up in this subgroup of infants, and those who developed CP exhibited types recognised by the Cerebral Palsy Task Force¹⁵ to be associated with an intrapartum cause of CP. The diagnosis of perinatal HI is still a matter of debate, but we have tried to follow as far as possible the definitions used by others.³ It would have been interesting to standardise the measurements of acid-base status, which is an essential criterion to define an acute intrapartum hypoxic event,^{4, 15} but this was not possible in this clinical observational study. Indeed cord pH was not measured in every maternity unit.

Other investigators^{2, 16, 17} have reported that only 8–28% of term infants with NE have evidence of asphyxia immediately after birth, with antepartum risk factors being recognised in 69% of the cases.² In our population, an antenatal cause of NE was clearly found in only 23% of the cases. In 19% of the infants, the cause of NE was not identified. One could assume that some of these cases were of antenatal origin, but a brain defect was diagnosed after the neonatal period in only one of them. At least six of them experienced a possible intrapartum event, and such babies have been included by others³ in the group of neonates with HI. This would leave us with 12% of neonates with NE, and no clear cause at 2 years of age, but a longer follow up is needed to eventually exclude other diagnoses, particularly epileptic encephalopathies. Among term children in Sweden,¹⁴ the origin of CP was unclassifiable in 14% of the cases, and 16% of neonates with NE had a normal scan in the British-Dutch cohort.⁵ However, only 2% of neonates in the Western Australian study³ had unrecognised risk factors.

In this study, we chose a broad but widely accepted definition of NE to enable comparisons with other studies and to investigate the aetiological classification associated with this syndrome. The features of encephalopathy were similar to those observed by others,² with seizures and abnormal tone being the most common criteria, although we cannot assume that all seizures were diagnosed with confidence in ventilated infants. A full picture of NE was more often associated with HI, and this is in agreement with the experience of Cowan *et al*.⁵

The overall prevalence of NE (1.64 per 1000 term live births) was lower than the latest published prevalence (3.8 per 1000)² with similar inclusion criteria. Apart from the fall in incidence that can be assumed between 1993–95 and 2000, several other factors could account for the differences. Our exclusion criteria were somewhat different, as we excluded

infants with an isolated drug withdrawal syndrome. These neonates were not identified as a single clinical entity in the Western Australian cohort, but it was recorded that 27% of the mothers consumed alcohol during pregnancy. The absence of post-term neonates in our population is notable. There is now a consensus on interventions for improving the outcome of delivery at or beyond term, and Crowley¹⁸ suggested that routine induction of labour after 41 weeks gestation appears to reduce perinatal mortality. This policy is largely applied in France. In 1998, the overall incidence of birth ≥ 42 weeks was 1.1%,¹⁹ compared with 9.8% of the cases and 2.5% of the controls in the Western Australian study.² Our observed prevalence of HI was similar to the 0.82 per 1000 reported in Trent in 1997.²⁰

The causes of NE were heterogeneous, but most were related to perinatal HI. IUGR was over-represented in this population, compared with the expected distribution in France.¹⁹ This is in accordance with previous studies, where a strong association between NE and restriction of intra-uterine growth has been described,^{2,21} and we found it relevant to include HI with IUGR in the group of NE of ante-intrapartum origin. The proportion of birth defects was higher in the Western Australian study²² than in our population (27.5% v 15.5%, $p = 0.02$). However, we did not include minor defects in this group and probably underestimated the group with ante-intrapartum origin. Although term infants who later present with CP of apparent antenatal origin rarely had symptoms as a neonate,¹⁴ we estimated the prevalence of NE assuming that all terminations of pregnancy in fetuses with a brain defect would develop NE. This allowed comparisons with countries with different policies. The proportion of infants with a metabolic disorder (3%) was comparable to others.⁵⁻²²

The overall outcome was poor, with death or severe disability observed in 42% of the cohort and in 51% of children with HI. Three infants with birth defects died after the neonatal period, but this population is already recognised to be at greater risk of poor outcome.²²⁻²³ We were not able to evaluate the developmental quotient for all the children included in this cohort, and, clearly, our long term follow up is insufficient and does not reflect the magnitude of sequelae in this population. Recently, Dixon *et al*²⁴ have shown that 15.5% of children with NE but without CP at follow up have a Griffiths general quotient score below the significant developmental delay cut-off point compared with 2.5% of control subjects.

Our definition of encephalopathy was broad, the study was population based, newborns were followed until the age of 2 years, and the results suggest that most of the cases arose in the intrapartum period. The outcome at 2 years emphasised the need for prevention programmes such as the confidential enquiry method and for new intervention approaches. It also suggests that careful follow up of this population is required to enable appropriate early interventions and educational provisions as they grow up.

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CONTRIBUTORS

VP had the original idea for the study, designed the study, reviewed all the files, and wrote the paper. NH assisted with the design of the study, reviewed the files, coded the data, entered data into files for

analysis, and carried out the analysis. AL contributed to the day to day running of the study and facilitated data collection. DT reviewed all cases of antenatal deaths in the regional register. DS assisted with the obstetric elements of the design of the study and provided expert obstetric interpretation of the data. PT assisted with the design and supervised the analysis and writing of the paper.

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