Origin and timing of brain lesions in term infants with neonatal encephalopathy

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Summary

Background The role of intrapartum asphyxia in neonatal encephalopathy and seizures in term infants is not clear, and antenatal factors are being implicated in the causal pathway for these disorders. However, there is no evidence that brain damage occurs before birth. We aimed to test the hypothesis that neonatal encephalopathy, early neonatal seizures, or both result from early antenatal insults.

Methods We used brain MRI or post-mortem examination in 351 fullterm infants with neonatal encephalopathy, early seizures, or both to distinguish between lesions acquired antenatally and those that developed in the intrapartum and early post-partum period. We excluded infants with major congenital malformations or obvious chromosomal disorders. Infants were divided into two groups: those with neonatal encephalopathy (with or without seizures), and evidence of perinatal asphyxia (group 1); and those without other evidence of encephalopathy, but who presented with seizures within 3 days of birth (group 2).

Findings Brain images showed evidence of an acute insult without established injury or atrophy in 197 (80%) of infants in group 1, MRI showed evidence of established injury in only 2 infants (<1%), although tiny foci of established white matter gliosis, in addition to acute injury, were seen in three of 21 on post-mortem examination. In group 2, acute focal damage was noted in 62 (69%) of infants. Two (3%) also had evidence of antenatal injury.

Interpretation Although our results cannot exclude the possibility that antenatal or genetic factors might predispose some infants to perinatal brain injury, our data strongly suggest that events in the immediate perinatal period are most important in neonatal brain injury.

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See Commentary page 713

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Introduction

Until recently, hypoxic-ischaemic events in the perinatal period were assumed to be the main cause for early neonatal encephalopathy, seizures, or both. They were also thought to be a major cause of brain damage in infants with a clinical diagnosis of cerebral palsy. For the normally developed non-dysmorphic infant born at term who develops neonatal encephalopathy or early seizures after an uneventful pregnancy, an insult to the brain of perinatal origin seems the logical conclusion. Results from Hagberg and colleagues'[1] study of the prevalence, cause, and timing of cerebral palsy in Sweden lend support to this view. These investigators reported a perinatal origin for cerebral palsy in 36% of affected term infants, and asphyxia of intrapartum onset was judged to be the cause of the disorder in most. However, there is often an absence of evidence of severe intrapartum asphyxia in infants with neonatal encephalopathy, and conversely, many infants who do have signs of fetal distress and asphyxia do not develop neurological sequelae.[2-6] These observations, together with evidence that there is a higher incidence of maternal illness, antenatal complications, and adverse social factors in infants with neonatal encephalopathy, seizures, or both[7] have led to the view that the main causes of such conditions occur before birth.

Our aim was to test the hypothesis that neonatal encephalopathy, early neonatal seizures, or both in the term infant are the result of early antenatal insults.

Methods

Patients

Between Jan 1, 1992, and Dec 31, 1998, we recruited 351 fullterm infants born in, or referred to, two tertiary referral intensive care units—Wilhelmina Children's Hospital, Utrecht, Netherlands, and Hammersmith and Queen Charlotte's Hospitals, London, UK. Both units provide a regional specialist service for the investigation of neurologically abnormal neonates.

All infants in the study were born after more than 36 weeks' gestation and presented within 72 h of birth with neonatal encephalopathy, seizures, or both. We divided the infants into two groups. The first consisted of infants with neonatal encephalopathy, defined by abnormal tone pattern, feeding difficulties, altered alertness, and at least three of the following criteria: (1) late decelerations on fetal monitoring or meconium staining, (2) delayed onset of respiration, (3) arterial cord blood pH less than 7·1, (4) Apgar scores less than 7 at 5 min, and (5) multiorgan failure.

The second group consisted of infants who had seizures within 72 h of birth but did not meet the criteria for neonatal encephalopathy.

We excluded infants with neural tube defects, alcohol and drug embryopathies, serious cardiac abnormality, hydrops, important gastrointestinal malformations, and immediately diagnosable chromosome abnormalities. If chromosome abnormality was diagnosed after the neonatal period, we excluded the infants retrospectively.

We also excluded ten infants who were treated with hypothermia[8] because the effects of this novel treatment on scan observations are not known. We did include infants with minor congenital abnormalities or those not part of a recognised syndrome—eg, undescended testicles, hypospadias, or sacral dimple.[9] Proven bacterial or viral infection was not a reason for exclusion.

Procedures

We checked medical notes of mothers and infants for antenatal risk factors associated with neonatal encephalopathy[7] to establish whether there is a correlation between such factors and antenatal lesions on early brain MRI, or with disorders of antenatal, genetic, or neurometabolic origin. Risk factors were family history of fits or neurological disorders, parity, maternal age, race, infertility, twin pregnancy, hypertension, thyroid disease, bleeding and infections in pregnancy, and infant gestational age, sex, birthweight, and head circumference percentile. Maternal age, gestational age, birthweight, and head circumference were analysed as continuous variables and in percentile[10] or age ranges.[6,7]

In London, MRI was done with a 1 Tesla HPQ system (Picker, Cleveland, Ohio, USA) and in Utrecht, a 1·5 Tesla Gyroscan ACS-NT system (Phillips, Best, Netherlands) was used. The scan was done with age-related, conventional T1-weighted and T2-weighted spin echo, and inversion recovery (IR) sequences in the transverse and sagittal planes with slice thickness 4–5 mm. All scans were done within 2 weeks of birth, but most were done within the first week. If necessary, infants were sedated with either oral chloral hydrate (30–50 mg/kg) or a mixture of 20 mg pethidine, 5 mg chlorpromazine, and 5 mg promethazine per mL (0·1 mL/kg, intramuscularly). Care provided in the neonatal intensive-care unit was continued during the scan, and a paediatrician was present throughout. All scans had local ethics committee approval and the verbal consent of a parent and were a routine investigation for these clinical conditions. Three study investigators not involved in the clinical care of the infants (MR, GMB, and LCM) interpreted the scan.

Scans were assessed for abnormalities consistent with established insults or developmental abnormality, and for evidence of an acute perinatal insult. Panel 1 shows details of the criteria we used to assess scans. Post-mortem examinations were done whenever possible. For infants in London, standard sample blocks were taken from the cortex, white matter, basal ganglia, and thalami. For infants in Utrecht, who were part of a study to compare ultrasonography[11] and MRI with histopathology, the brain was cut in alignment with imaging slices, and blocks of periventricular and subcortical white matter, cortex, basal ganglia, and basal thalami were taken from throughout the brain. Transverse sections of 1–2 cm thickness were cut and the areas of interest were taken out, routinely processed, and embedded in paraffin. Slices with a thickness of 4 μm were stained with haematoxylin and eosin. In several cases, additional sections were stained with monoclonal antibodies reacting against CD68 or glial fibrillary acidic protein for evaluation of macrophage reaction or gliosis, respectively. Eosinophilia of neurons and nuclear pyknosis were regarded as early signs of hypoxic-ischaemic damage (evident up to 24 h after insult), and karyorrhexis was assumed to occur between 24 h and 48 h and macrophages to appear and gliosis to begin just after 72 h.[12,13] Evidence of longstanding damage included established gliosis, mineralisation, and cyst formation.

Panel 1: Scan abnormalities suggestive of an antenatal insult or developmental abnormality

Signs of antenatal insult or developmental abnormality
Irregular ventricular dilatation, widening of the interhemispheric fissure, enlarged extracerebral space

Established cystic lesions: porencephaly, germinolytic cysts, cystic periventricular leucomalacia

Focal infarction with atrophy

Longstanding haemorrhage

Marked asymmetries—eg, in ventricular shape or size, hemispheric size, cerebellum, brain stem, or operculum

Developmental anomalies—eg, in cortical dysplasia, midline structural anomalies, abnormal cerebellar development

Signs of acute perinatal insult

Brain swelling

Cortical highlighting

Focal or global loss of grey-white matter differentiation

Abnormal signal intensity in the basal ganglia and thalami—typically the posterior putamen and ventrolateral nucleus of the thalamus (VLNT) but could include the caudate nucleus and globus pallidus

Loss of normal signal intensity in the posterior limb of the internal capsule (PLIC) associated with the above cortical, white matter or basal ganglia and thalami abnormality

Acute and subacute parenchymal, intraventricular, or extracerebral haemorrhage

Acutely evolving focal infarction in an arterial territory or in a parasagittal or watershed distribution.

Statistical analysis

For antenatal factors that could be analysed as continuous variables, we used a two-tailed t test to compare the two groups—ie, infants who had evidence of an acute insult only and those with evidence of antenatal lesions or disorders of antenatal, genetic, or neurometabolic origin. For categorical or nominal variables, Fisher's exact test or χ^2 test was used (SPSS version 9.0). The level of significance was set at 0·05.

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Results

We included 351 infants. 261 infants met our criteria for neonatal encephalopathy and 90 had seizures within 72 h of birth.

Infants with neonatal encephalopathy (group 1)

245 had a brain MRI scan, 29 both MRI and post-mortem examination and 16 had port mortem only (Utrecht patients only). Gestational ages ranged from 37·0 to 42·9 weeks (median 40·0, mean 40·0 SD 1·4). Birthweight ranged from 2000 to 4900 g (3330 g, 3385, 575). Head circumference at birth ranged from 31·4 to 38·5 cm (35·0 cm, 35·0, 1·4). 197 (80%) infants with encephalopathy who had scans had evidence of acutely evolving lesions that were compatible with a hypoxic ischaemic insult. These lesions were mostly bilateral

Panel 2: **Additional findings in nine infants with image abnormalities consistent with encephalopathy**

Findings from MRI, post mortem, or both	Diagnosis
Hemicerebellum (1)	Possible antenatal thrombosis or infarction
Haemorrhage (1 cerebellar, 2 subdural)	
Cerebellar hypoplasia (3)	Walker-Warburg syndrome (1) Consanguinous parents (1) Complex I deficiency (1)
Abnormal and atrophied basal ganglia, thalami, and brainstem with schizencephalic appearance (1)	Antenatal insult caused by a severe car accident at 22 weeks' gestational age
Abnormal and atrophied basal ganglia, thalami and brainstem (1)	Microcephalic twin—probable antenatal insult

abnormalities in basal ganglia, thalami, cortex, or white matter, although eight infants had focal infarction. Scans in 40 (16%) infants in this group were normal, nine (4%) showed damage that was in addition to a recent hypoxic ischaemic insult (panel 2) and eight (3%) had evidence of another disorder (panel 3).

Three infants with imaging evidence of hypoxic ischaemic insult were mildly dysmorphic without a specific diagnosis, one did not have a femur, but all four were included in the study. Two had evidence of group B streptococcal septicaemia, and another two infants had clinical signs that were highly suggestive of infection (not confirmed on culture or serology). One infant had signs of congenital cytomegalovirus infection, but a brain scan did not show the major abnormalities that might be associated with that disease. Another with enterovirus had severe lesions of the basal ganglia and thalami but histological examination showed that these changes were consistent with a viral infection.

Eight infants in group 1 had an abnormal scan but the findings were not consistent with an acute hypoxic ischaemic insult. Panel 3 shows the diagnoses made on the basis of imaging, clinical, and biochemical data.

45 infants in group 1 had post-mortem examinations, 24 from London and 21 from Utrecht. The Utrecht group included 16 infants for whom there was no MRI scan. All examinations showed evidence of acutely evolving lesions thought to be of hypoxic-ischaemic origin. The infants from Utrecht had been included in a study designed to detect even small foci of established damage that clearly predated labour and delivery.[11] Three of these 21 had, in addition to an acutely evolving lesion, evidence of an established lesion that consisted of very small foci of established gliosis in the periventricular white matter. An MRI was not available for these cases.

Panel 3: **Diagnoses and abnormal MRI findings, not compatible with hypoxic ischaemia in eight infants with encephalopathy**

Diagnosis	MRI findings
Non-ketotic hyperglycinaemia (2)	Dysgenesis of the corpus callosum or absent corpus callosum, and absent signal in posterior limb of the internal capsule (2)
Mitochondrial disorder (1)	Basal ganglia cysts
Congenital myotonic dystrophy (1)	Haemorrhage and ventricular dilatation
Nemaline myopathy (1)	Subarachnoid and thalamic and haemorrhage ventricular dilatation
No diagnosis (3)	Delayed myelination, abnormal white matter

Infants with seizures only within 72 h of birth (group 2)

All 90 infants who had seizures within 72 h of birth but did not meet all the inclusion criteria for neonatal encephalopathy had an MRI scan.

The gestational ages ranged from 37·0 to 42·0 weeks (median 40·0, mean 39·8 SD 1·4) Birthweight ranged from 1700 to 4650 g (3210, 3170, 560). Head circumference at birth ranged from 30·5 to 38·6 cm (35·0, 34·7 1·6). In infants with evidence of a recent ischaemic or haemorrhagic insult, 35 had focal cerebral infarction in an arterial or parasagittal distribution, 12 had small focal areas of white matter haemorrhage (two in association with hypoglycaemia), eight had extensive parenchymal haemorrhage, two had posterior fossa haemorrhage, three had subarachnoid haemorrhage, and two had an intraventricular haemorrhage. Thus, acute ischaemic or haemorrhagic lesions were noted in 62 (69%) of infants in group 2. Furthermore, concomitant evidence of antenatal injury was present in only two of these 62 (one had a very small cystic lesion in the lentiform nucleus, and the other a small lesion in the mid and upper brain stem on the side ipsilateral to the acutely evolving middle cerebral artery infarction).

Seizures had various causes in the remaining 28 infants in group 2 (panel 4). In 13 infants, the scan findings indicated a specific, non-hypoxic ischaemic diagnosis. 15 infants had a normal scan, five in association with hypoglycaemia and ten without a specific diagnosis. Seven of these ten infants have a persistent seizure disorder.

Antenatal risk factors and early MRI findings

In both groups, 306 infants had scans that showed evidence of acute findings only, and 45 had scans that

Panel 4: **Specific diagnoses, syndromes, and scan findings in infants with seizures**

Normal scan (n=15)
Hypoglycaemia (5)
Persistent seizure disorder (3)
Epileptic encephalopathy (5)
Transient seizures disorder (2)

Abnormal scan (n=13)
Bleed related to Rendu-Osler syndrome (1)
Multiple intracerebral haemangiomas (1)
Aicardi-Goutière syndrome (1)
Meningitis (1)
Herpes encephalitis (1)
Tuberous sclerosis (1)
Incontinentia pigmenti (1)
Zellweger syndrome (2)
Neonatal adrenoleucodystrophy (1)
Non-ketotic hyperglycinaemia (2)
Cortical dysplasia (1)

	Acute (%) (n=306)	Non-acute (%) (n=45)	p (95% CI)
Maternal factors			
Age* (years)			
<20	5 (2%)	5 (11%)	..
20–24	30 (10%)	4 (9%)	..
25-29	79 (26%)	6 (13%)	..
30-34	97 (31%)	16 (36%)	..
>35	48 (16%)	4 (9%)	..
Missing	47 (15%)	10 (22%)	0·002†
Age (years)‡	30·2 (4·8)	28·5 (6·5)	0·157 (–0·7 to 4·2)
Parity			
0	185 (60%)	25 (56%)	..
1	63 (21%)	9 (20%)	..
2	31 (10%)	9 (20%)	..
Missing	27 (9%)	2 (4%)	0·190†
Race			
White	233 (76%)	35 (78%)	..
Asian	48 (16%)	9 (20%)	..
Afro Carib	25 (8%)	1 (2%)	..
Missing	0	0	0·311†
Family history of seizures			
No	287 (93%)	34 (76%)	..
Yes	8 (3%)	5 (11%)	..
Missing	11 (4%)	6 (13%)	0·011¶
Infertility			
No	288 (94%)	37 (82%)	..
Yes	13 (4%)	4 (9%)	..
Missing	5 (2%)	4 (9%)	0·133¶
Hypertension			
No	266 (87)	40 (89)	..
Yes	25 (8)	1 (2)	..
Missing	15 (5)	4 (9)	0·225¶
Thyroid disorder			
No	276 (90%)	41 (91%)	..
Yes	2 (1%)	0	..
Missing	28 (9%)	4 (9%)	1·00¶
Bleeding			
No	265 (87%)	40 (89%)	..
Yes	25 (8%)	1 (2%)	..
Missing	16 (5%)	4 (9%)	0·225¶
Infection			
No	271 (88%)	37 (82%)	..
Yes	18 (6%)	4 (9%)	..
Missing	17 (6%)	4 (9%)	0·498
Infantile factors			
Gestational age* (weeks)			
37	15 (5%)	3 (7%)	..
38	33 (11%)	11 (24%)	..
39	61 (20%)	8 (18%)	..
40	114 (37%)	14 (31%)	..
41	62 (20%)	6 (13%)	..
42	21 (7%)	3 (7%)	..
Missing	0	0	0·155†
Gestational age‡ (weeks)	40·0 (1·3)	39·7 (1·4)	0·149 (–0·1 to 0·7)§
Birthweight* (percentile)			
>90	25 (8%)	2 (4%)	..
10–90	193 (63%)	28 (62%)	..
3-10	46 (15%)	5 (11%)	..
<3	39 (13%)	7 (16%)	..
Missing	3 (1%)	3 (7%)	0·73†
Birthweight (g)‡	3380 (560)	3125 (455)	(75 to 430, 0·006)§
Head circumference* (percentile)			
>90	17 (6%)	3 (7%)	..
10–90	192 (62%)	19 (42%)	..
3–9	17 (6%)	6 (13%)	..
<3	17 (6%)	3 (7%)	..
Missing	63 (20%)	14 (31%)	0·083†
Head circumference* (percentile)			
⩾10	209 (68%)	22 (49%)	..
<10	34 (12%)	9 (20%)	..
Missing	63 (20%)	14 (31%)	0·03
Head circumference‡ (cm)	35·0 (1·5)	34·6 (1·5)	0·217 (–0·2 to 0·9)§
Sex			
Male	165 (54%)	24 (53%)	..
Female	141 (46%)	21 (47%)	0·941†
Singleton			
Yes	294 (95%)	40 (89%)	..
No	9 (3%)	2 (4%)	..
Missing	3 (2%)	3 (7%)	0·630¶

*Analysed as non-continuous data. †χ^2 test. ‡Analysed as continuous data; data are mean (SD). §95% CI of difference; p value derived from *t* test. ¶Fisher's exact test.

Antenatal risk factors in infants with evidence of acute brain injury only, or non-acute antenatal injury, or other diagnoses

suggested some developmental, metabolic, or other diagnoses of antenatal origin (non-acute group, panels 2, 3, and 4). Of the antenatal risk factors assessed (table), a positive family history for seizures or neurological disorder, a low mean birthweight (compared as continuous data), a head circumference below the tenth percentile and a low maternal age band were significantly more common in infants with evidence of lesions of antenatal origin or disorders of antenatal, genetic, or neurometabolic origin than in those who had evidence only of acute injury (table). We did not note a difference between patients with acute and those with non-acute injuries for the proposed risk factors of maternal parity, race, history of infertility, hypertension, thyroid disease, bleeding, infection, twin pregnancy, or infant sex, gestational age, birthweight percentile, or head circumference (compared as means).

Discussion

Our findings show that more than 90% of term infants with neonatal encephalopathy, seizures, or both, but without specific syndromes or major congenital defects, had evidence of perinatally acquired insults, and there was a very low rate of established brain injury acquired before birth. Reasons for injuries of perinatal onset remain poorly understood. The frequency of risk factors in infants with and without established brain abnormality did not differ greatly, but the study was not designed to explore antenatal aspects of perinatal brain injury. Our data do not exclude the possibility that antenatal factors could initiate a causal pathway for perinatal brain injury and that they, possibly together with genetic predispositions to hypoxic-ischaemic injury, might make some infants more susceptible than others to the stresses of labour and delivery.

Some investigators[2,3] have reported that only 8–15% of term infants with neonatal encephalopathy, and far fewer with early neonatal seizures,[14,15] have evidence of asphyxia immediately before birth. Furthermore, others[6,7] have suggested that many neurological signs once thought to be caused by intrapartum asphyxia are a manifestation of a process begun during the antenatal period. However, we have found little evidence for the two proposals that acute perinatal injury is uncommon in such infants, and that injurious processes have been taking place antenatally.

Because referral patterns from local hospitals differed, our study is not population-based. However, both study centres provide a regional neurological diagnostic service, and have a policy to provide easy access and rapid admission for all newborn babies referred with seizures or even subtle signs of neonatal encephalopathy, and to do brain MRI within 1–7 days of admission. We acknowledge that these features of treatment and care make our study different from population-based studies in which all infants within a region are enrolled. However, this disadvantage is offset by the detailed investigations and specific diagnoses for all infants, ensuring that there was no ambiguity about their inclusion in a study of infants with encephalopathy.

We chose to separate infants who presented with an encephalopathy (group 1) from those without (group 2), because our previous clinical experience has shown that this separation is clinically relevant. The two groups present differently and, as borne out by our findings, the diagnoses and types of lesions seen in the two groups are different, with many more diagnoses of non-hypoxic ischaemia or haemorrhage in group 2 than in group 1. Other investigators,[6,7] have not differentiated between children who have seizures only, and those with encephalopathy.

Patterns and types of acute injuries were consistent with those reported by other investigators.[14–24] The most common pattern of severe acute injury that we saw was damage to the basal ganglia and thalami, and cortex. Some infants also had damage to the midbrain, brain stem, and hippocampal region. A less common pattern was that of widespread damage to white matter with relative sparing of the central grey matter. Evidence of atrophy did not appear within 2 weeks of birth. Infants scanned within 24 h of birth might have had normal scans, even though scans obtained later in the first week showed severe injury.[16,18] This finding accords with evidence for secondary energy failure and delayed neuronal injury available from data derived from magnetic resonance phosphorous tests.[25] We used a very early scan only if a later scan was not available.

Post-mortem examination showed very small foci of established gliosis in the white matter of three infants, who, unfortunately, had not had an MRI scan. Because these small focal areas might not have been identified on neonatal MRI, and because most infants only had a scan, we might be underestimating the overall occurrence of such lesions. However, our experience of a large number of infants with neonatal encephalopathy shows that those who have what we deem a normal brain appearance on MRI done in the neonatal period are normal at preschool follow-up.[18,24] Although we cannot be certain that these small foci do not have an important role in the genesis of neurodevelopmental disorders, results of follow-up to age 6 years in a large proportion of the group do not suggest late onset of neurological disorders.[26]

Squier and Keeling[13] noted that prenatal damage was implicated in 22% of 90 early neonatal deaths, but this group included both preterm and fullterm infants and no diagnoses are reported. In a study of neonatal encephalopathy in term infants that compared neonatal cranial ultrasonography and post-mortem findings,[11] only three of 30 (10%) had lesions of prepartum origin at post mortem. Lesions were small and very localised, and in isolation would not have been sufficiently large to explain the infants' encephalopathy and death that was caused by acutely evolving lesions in the central grey matter. Had the infants survived with the small white matter lesions alone, we would not have expected the child to have a motor deficit, because the type and pattern of lesions leading to cerebral palsy after neonatal encephalopathy in term infants is well recognised.[18,24] In a study from the Hammersmith group[27] to assess the accuracy of MRI in detection of specific abnormality in children with neonatal encephalopathy, the positive predictive value of MRI was 1·0 and the sensitivity 0·79, despite the fact that the median interval between scan and death was 1·5 days (range 0–4) and the median interval between scan and post mortem was 4·5 days (3–7). The Hammersmith group examined very specific regions of the brain, and they did not report whether, the small areas of focal white matter abnormality described by Eken and colleagues[11] were seen on their scans.

In group 2, most infants (69%) had evidence of an acutely developing region of focal infarction in an arterial territory or in a parasagittal distribution: a finding that accords with the data of other workers.[14,15] Only 8 (3%) of the infants who presented with low Apgar scores and neonatal encephalopathy had such focal lesions. The time course of changes seen with MRI is well established in newborn babies with focal infarction. In those for whom diffusion-weighted imaging was done, the most abnormal scans results, indicating very recent insult, arose in the first 1–5 days of life. Thereafter, the abnormal high signal

intensity on the diffusion-weighted images dropped until age 2 weeks.[20] This time course accords with that for adult stroke patients for whom the precise time of stroke onset is known. Only two infants in group 2 also had evidence of established antenatal injury. However, a substantial proportion (31%) who presented with seizures, but not neonatal encephalopathy, had an identifiable metabolic, neurocutaneous, vascular, or developmental disorder that was clearly of genetic or congenital origin. None of these infants had areas of focal infarction. About half of these infants had abnormal scans that aided the diagnosis. In the remainder of the infants with seizures, scans were normal and the diagnosis was made from clinical electrophysiological and biochemical data. The overall proportion of infants with a metabolic disorder (2·6%) is much the same as that recorded by Felix and colleagues[9] in a study of birth defects and neonatal encephalopathy. These investigators do not distinguish between infants with neonatal encephalopathy and those with seizures alone.

Badawi and colleagues[6,7] in a large study of antenatal and intrapartum factors in infants with encephalopathy concluded that, for most infants with this disorder, the causal pathway began before birth. Although our study was not specifically designed to determine the role of antenatal risk factors in neonatal encephalopathy, we noted that the frequency of risk factors, such as maternal thyroid disease, was very low in our total cohort. Compared with infants who had only an acute insult, those with evidence of antenatal lesions or genetic or neurometabolic disorders had lower mean birthweight, a head circumference more often in the lowest decile, lower maternal age, and a significantly higher rate of seizures or neurological disorders in their family history.

That our results suggested a different importance of antenatal risk factors than did those of Badawi and colleagues could, in part, be attributable to the differences in inclusion criteria. These investigators used a definition of encephalopathy that was less restrictive than ours. We deliberately selected a group of infants whose clinical signs were likely to be a result of difficulties that arose during birth. Badawi and colleagues, however, included infants with obvious neurodevelopmental and chromosome abnormalities, and those who presented with the disorder late in the first week of life. Furthermore, infants with problems such as low tone and feeding difficulties, which are common to many disorders, were included as encephalopathic. Therefore, the population in Badawi's study probably included many infants with genetic and developmental anomalies, which would have reduced the proportion of infants in whom difficulties during birth was the most important factor, and increasing the chance that antenatal factors would be significant. Felix and colleagues[9] report that birth defects arise in 28% of infants with neonatal encephalopathy compared with 4% of those without the disorder. We did not exclude infants with minor birth defects, but would have excluded most infants that Felix lists with birth defects.

Unlike our study, Badawi's[6,7] were population based and had controls. We could not use this study design because to image the required large number of control infants would not have been feasible. We did not set out to do a case control study, but rather to define the spectrum of diagnoses in a large number of encephalopathic infants. We accept that a few term infants will have established lesions at birth, but our point was to determine whether having such lesions predisposed a fetus to present with encephalopathy; the low rate of established lesions suggests that there is no relation between lesions and presentation with encephalopathy. This observation is in accordance with Hagberg and colleagues' data[1] who noted that term infants who later present with cerebral palsy of apparent antenatal origin rarely had symptoms as a neonate.

Badawi and colleagues attribute the cause of neonatal encephalopathy to antenatal factors rather than any intrapartum abnormality, despite the fact that they recorded a significant difference between cases and controls in frequency of postmaturity beyond 42 weeks, acute intrapartum events, Apgar score, onset of respiration, need for resuscitation, and birth trauma. Furthermore, they identified an inverse association between elective caesarean section and neonatal encephalopathy,[6] a relation also suggested by Gaffney and colleagues.[28] Moreover, in Gaffney's study when the presence or absence of neonatal encephalopathy was taken into account, there was no difference in antenatal risk factors. The seriousness of intrapartum complications and the pattern and severity of motor and intellectual deficit was significantly worse in the neonatal encephalopathy group, strongly suggesting that events during birth do affect infant outcome. Nelson and colleagues[5] have noted that a tight nuchal cord at delivery was seen significantly more often in infants with neonatal encephalopathy than in controls, which lends further support to the explanation that events late in labour are important in neonatal encephalopathy. Some data show that infants born at night are more than twice as likely to die from asphyxia than those born during the day, a finding that might be attributable to tiredness and inexperience of night time staff, or a delay in appropriate treatment.[29] Evidence from confidential inquiries into neonatal encephalopathy and neonatal deaths in term infants documents a high proportion of less than optimum care during labour.[30]

Focal infarction was diagnosed in over a third of infants with early onset seizures but without neonatal encephalopathy. Such infarction is the second most common cause of seizures in the neonatal period and is generally thought to be unrelated to intrapartum difficulties or the presence of neonatal encephalopathy; although in our studies, the rate of antenatal and intrapartum problems is higher than in a control population.[15] There is increasing evidence that having an inherited thrombophilic abnormality increases the risk of focal infarction, and 30% of our infants with infarction had some thrombophilic abnormality, usually heterozygosity for Factor V Leiden or a high Factor VIII concentration.[31] Because these abnormalities exist in the healthy population, most of whom are asymptomatic, their presence does not necessarily mean that focal infarction will result; however, they might identify an infant susceptible to such difficulties in the presence of additional stresses. Only two of 35 infants that we scanned and who had focal infarction showed evidence of an existing lesion of antenatal origin, whereas all had evidence of an acutely evolving lesion. Thrombophilic abnormalities have been implicated in all forms of cerebral palsy,[32] although other data[33] for infants with neonatal encephalopathy, many of whom will develop cerebral palsy, do not show the thrombophilic abnormalities noted for infants with focal lesions.

Our study does not focus on outcome, but some of the infants will eventually be included in registers used to investigate the risk factors for cerebral palsy and early neonatal death. We have followed up all infants and know that of those with a hypoxic-ischaemic pattern of lesions, 66 died and 85 had evidence of cerebral palsy at a minimum of 18 months' follow-up. The injury in those

who died was largely to central grey matter and brain stem. No infant with only cortical or white matter injury on MRI scan died, and only two with focal infarction died. The severity of cerebral palsy in these infants is consistent with published data that relates to patterns of injury with imaging findings.[15,18,24] Our data therefore, do not support findings suggesting that the main causes of cerebral palsy in term infants with intrapartum hypoxic events arise in the antenatal period.

We believe that our data provide a robust phenotypic description of the brain injury in infants with neonatal encephalopathy; we hope they will form a basis for epidemiological and genetic studies into disorders that often have tragic sequelae.

Contributors

F Cowan, L de Vries, M Rutherford, and L Dubowitz designed the study. G Bydder, L Meiners, and M Rutherford analysed MRIs. F Groenendaal, F Cowan, L de Vries, and M Rutherford cared for the infants during the MRI and contributed to image analysis. F Cowan, P Eken, L de Vries, E Mercuri, and L Dubowitz saw the children clinically. P Eken gathered and interpreted data. F Groenendaal and E Mercuri did the statistical analysis. F Cowan and L de Vries wrote the paper.

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