Neonatal death after hypoxic ischaemic encephalopathy: does a postmortem add to the final diagnoses?

Dawn E. Elder,a Jane M. Zuccollo,b Thorsten V. Stanleya

Background Case review after fatal perinatal asphyxia may have medicolegal implications. Accurate diagnosis of cause of death is therefore essential.

Objective To determine consent rate and utility of autopsy after fatal grade III hypoxic ischaemic encephalopathy (HIE) presumed to be secondary to birth asphyxia.

Design A retrospective clinical review from January 1995 to December 2002.

Setting Regional tertiary referral neonatal unit, Wellington, New Zealand.

Population Inclusion criteria were gestation ≥37 weeks, resuscitation after delivery, and clinical course of grade III HIE. Exclusions were a recognised major lethal malformation.

Methods Review of clinical records including the autopsy report.

Main outcome measures Consent for autopsy, change in diagnosis after autopsy.

Results Twenty-three infants died during the time period with a major diagnosis of grade III HIE. Three did not meet inclusion criteria. Of the remaining 20, 11 were female. Median gestation at birth was 40 weeks (range 38–42 weeks) and median birth weight was 3568 g (range 2140–4475 g). In 8/17 of the infants for whom length and head measurements were available, the Ponderal Index suggested intrauterine growth retardation. The 16/20 infants had an autopsy. Four of these were Coroner’s cases giving an autopsy rate of 80% with a rate by consent of 60%. In 10 (62.5%) infants, significant new information was added to the clinical diagnoses.

Conclusions Neonatal HIE is a symptom rather than a final clinical diagnosis. A full autopsy is required to fully explore the reasons for fatal neonatal HIE and may provide information that is important medicolegally.

INTRODUCTION

Neonatal paediatricians are well aware that the outcomes of the newborns they care for with severe hypoxic ischaemic encephalopathy (HIE) may have medicolegal significance. It is therefore of some concern that when these infants die, there has not always been a push by clinicians for an autopsy to confirm the clinical diagnoses despite recent reports suggesting that other unexpected pathologies may mimic the clinical course of perinatal asphyxia.

A number of retrospective and prospective reviews of neonatal autopsy have now been published and all have confirmed that after neonatal death from a variety of clinically determined causes, new information is frequently obtained at postmortem. In our own review of neonatal autopsies over a three-year period, we found that in 59% of cases new information was found at autopsy. The chance of finding new information appears to be at least partly dependent on the quality of the autopsy and therefore the experience of the pathologist. Despite this clear evidence of the utility of the neonatal autopsy, neonatal autopsy rates appear to be falling rather than increasing in their 10-year review found the autopsy rate in the first five-year period to be significantly higher than that in the second five-year period (71.2% vs 47.7%, P < 0.001).

When a neonate dies after documented perinatal asphyxia associated with neonatal HIE it is appropriate for a clinical review of the case to occur. This does not always include information from a postmortem examination unless the case has been referred to the Coroner. Even then, Coroners may not order a postmortem in such circumstances. Not all reported neonatal autopsy series have broken down consent rates according to clinically determined cause of death. When this has been done, reported autopsy rates after perinatal asphyxial deaths have varied widely from 19% to 83%. In one of these studies, autopsy after HIE was found to have a high yield because of the recognition of old undiagnosed central nervous system lesions.

The aim of this study therefore was to investigate the autopsy rate for infants dying after a clinical diagnosis of...
severe birth asphyxia followed by grade III HIE who were
cared for in our own institution and to see what impact the
pathological findings had on the final diagnoses.

METHODS

A retrospective audit was undertaken of all term infants
who died in the Wellington metropolitan area after care in the
Wellington tertiary neonatal unit with a clinical diagnosis
listed as perinatal asphyxia or neonatal HIE grade III.
The audit included an eight-year period from January 1995
until December 2002. Inclusion criteria for subjects were
gestation ≥37 weeks, need for resuscitation at delivery, suc-
cessful resuscitation and a clinical course consistent with
grade III HIE as defined by Sarnat and Sarnat.14 Infants
with a recognised major lethal malformation were excluded
as were neonates with encephalopathy not thought to be
related to perinatal asphyxia. Clinical decisions regarding
the severity of the asphyxial insult were based on a com-
bination of clinical course, cerebral function as determined
by a cerebral function monitor (CFM) or electroencepha-
logram (EEG) and computerised tomography (CT) head scan
findings at 72 hours of age. The medical record, including
the postmortem report, was reviewed for clinical data re-
lated to the perinatal and neonatal course. Obstetric data
collected included mode of delivery and maternal ethnicity.
Neonatal data collected included gestation at birth, sex,
weight, length and head circumference at birth. Data were
also collected concerning the resuscitation of the infant and
the neonatal clinical course. All postmortems were under-
taken by an experienced perinatal pathologist (JZ).

RESULTS

A search of the neonatal unit database revealed 23 babies
coded as dying after serve birth asphyxia. Of these three
were excluded, one because of a major lethal malforma-
tion, one because resuscitation was not successful and one
because no resuscitation was required at birth and the as-
phyxial insult was thought to have occurred after the im-
mediate perinatal period. This left 20 infants, 11 female and
9 male. The median gestation at birth was 40 weeks (range
38–42 weeks). Median birthweight was 3568 g (range
2140–4475 g). Length measurements were available for
17 infants. For 8 (47%) of these 17 infants the Ponderal
Index (PI), calculated retrospectively, suggested intrauterine
growth retardation (PI < 10th centile15). Only four of the
eight also had a birthweight below the 10th centile. There
were 11 (55%) infants born by vaginal delivery, 6 (30%) by
emergency caesarean section and 3 (15%) by assisted vag-
nal delivery. In 11 infants no heartbeat was detectable prior
to the commencement of resuscitation.

Two infants died at home at four and five weeks of age,
respectively. The other 18 infants died at a median
of 52.5 hours of age (range 24–151 hours). All infants died
after the parents opted for withdrawal of intensive care. The
primary clinical diagnosis and cause of death was deter-
ted to be grade III HIE secondary to severe perinatal
asphyxia in all cases prior to the autopsy. An autopsy was
completed in 16 of the 20 infants, an autopsy rate of 80%.
Of these cases four were referred to the coroner and 12
were autopsied after parental consent (autopsy rate by
consent 60%). Consent was obtained for all four Maori
infants and neither of the two Pacific Island infants. The
consent rate for the 10 Caucasian infants was 80%.

All infants had evidence of global cerebral asphyxia on
histology, indicating that the final reason for death in all
infants related to the clinically evident HIE. There were
six infants for whom no significant new information was
found at autopsy. These infants are listed in Table 1. In
the two infants who died at four and five weeks of age,
the autopsy confirmed the clinical diagnosis of severe
hypoxic ischaemic brain injury with extensive organising
parenchymal necrosis. In four infants there was confirm-
ation of the diagnosis but no new information found. In two
of these infants a significant antemortem clinical diagnosis
was excluded by the autopsy. In one case an echocardio-
gram had been equivocal but the postmortem confirmed

<table>
<thead>
<tr>
<th>Age at death</th>
<th>Wt (g)</th>
<th>GA (weeks)</th>
<th>Sex</th>
<th>Pertinent clinical findings</th>
<th>Clinical diagnoses considered antemortem but excluded by autopsy</th>
<th>Other pathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>98 hours</td>
<td>3080</td>
<td>40</td>
<td>F</td>
<td>Cardiac echo done-still concern about inflow and outflow tracts</td>
<td>? Congenital heart disease</td>
<td>Nil</td>
</tr>
<tr>
<td>4 weeks</td>
<td>3660</td>
<td>39</td>
<td>F</td>
<td>Nil</td>
<td>Bronchopneumonia (infant 4 weeks old)</td>
<td>Nil</td>
</tr>
<tr>
<td>5 weeks</td>
<td>2660</td>
<td>42</td>
<td>M</td>
<td>Intrauterine growth retardation</td>
<td>Nil</td>
<td>Aspiration pneumonia (infant 5 weeks old)</td>
</tr>
<tr>
<td>36 hours</td>
<td>3545</td>
<td>40</td>
<td>F</td>
<td>Placental abruption</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>46 hours</td>
<td>3050</td>
<td>40</td>
<td>F</td>
<td>Hypoglycaemia, lactic acidosis</td>
<td>Inborn error of metabolism</td>
<td>Nil</td>
</tr>
<tr>
<td>84 hours</td>
<td>4400</td>
<td>40</td>
<td>M</td>
<td>Gestational diabetes</td>
<td>Intracerebellar haemorrhage</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Wt = weight; GA = gestational age.

Table 2. Autopsy findings in 10 infants for whom there was significant information added to the clinical diagnoses after autopsy.

<table>
<thead>
<tr>
<th>Age at death (weeks)</th>
<th>Wt (g)</th>
<th>GA</th>
<th>Sex</th>
<th>Pertinent clinical findings</th>
<th>Clinical diagnoses considered antemortem but excluded by autopsy</th>
<th>Other pathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>2800</td>
<td>39</td>
<td>M</td>
<td>Initially thought wt was not &lt;10th centile as was thought to be 37/40</td>
<td>Nil</td>
<td>Fetal malnutrition</td>
</tr>
<tr>
<td>57</td>
<td>3230</td>
<td>41</td>
<td>M</td>
<td>Weight borderline 10th centile</td>
<td>Nil</td>
<td>Two-tone liver</td>
</tr>
<tr>
<td>77</td>
<td>3710</td>
<td>39</td>
<td>F</td>
<td>Cord tight around the neck three times</td>
<td>Nil</td>
<td>Fetal malnutrition</td>
</tr>
<tr>
<td>100</td>
<td>2780</td>
<td>41</td>
<td>F</td>
<td>Weight above 50th centile</td>
<td>Nil</td>
<td>Fetal malnutrition CNS changes 5–8 days old</td>
</tr>
<tr>
<td>43</td>
<td>2800</td>
<td>39</td>
<td>M</td>
<td>Initially thought wt was not</td>
<td>Nil</td>
<td>Fetal malnutrition</td>
</tr>
<tr>
<td>57</td>
<td>3230</td>
<td>41</td>
<td>M</td>
<td>Weight borderline 10th centile</td>
<td>Nil</td>
<td>Two-tone liver</td>
</tr>
<tr>
<td>77</td>
<td>3710</td>
<td>39</td>
<td>F</td>
<td>Cord tight around the neck three times</td>
<td>Nil</td>
<td>Fetal malnutrition CNS changes 5–8 days old</td>
</tr>
<tr>
<td>100</td>
<td>2780</td>
<td>41</td>
<td>F</td>
<td>Weight above 50th centile</td>
<td>Nil</td>
<td>Fetal malnutrition CNS changes 5–8 days old</td>
</tr>
<tr>
<td>130</td>
<td>3590</td>
<td>38</td>
<td>F</td>
<td>Ruptured membranes &lt;6 hours Peak CRP 363 Initial culture no growth</td>
<td>Nil</td>
<td>Periventricular white matter necrosis</td>
</tr>
<tr>
<td>34</td>
<td>3900</td>
<td>39</td>
<td>F</td>
<td>Mother, Gp B streptococcal carriage Intrapartum antibiotics given No clinical chorioamnionitis Coagulopathy Subgaleal haemorrhage</td>
<td>Nil</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>32</td>
<td>2975</td>
<td>40</td>
<td>M</td>
<td>No antenatal care Ruptured membranes 1 hour Weight &lt;10th centile</td>
<td>Nil</td>
<td>Congenital pneumonia Two-tone liver</td>
</tr>
<tr>
<td>48</td>
<td>3865</td>
<td>40</td>
<td>M</td>
<td>Failed forceps delivery/LUSCS Subarachnoid haemorrhage Intraventricular haemorrhage Left parietal haemorrhage</td>
<td>Nil</td>
<td>Bilateral tentorial tears Infra and supratentorial haemorrhage Left occipital osteodiastasis Subdural haemorrhage Subarachnoid haemorrhage Bilateral asymmetric tentorial tears Subdural haemorrhage</td>
</tr>
<tr>
<td>151</td>
<td>3620</td>
<td>40</td>
<td>F</td>
<td>Undiagnosed breech home delivery Subdural haemorrhages</td>
<td>Nil</td>
<td>Placenta examination — multiple chorioangioma</td>
</tr>
<tr>
<td>48</td>
<td>2140</td>
<td>38</td>
<td>F</td>
<td>Intrauterine growth retardation noted</td>
<td>Tentorial haemorrhage was queried on CT scan</td>
<td>Placenta examination — multiple chorioangioma</td>
</tr>
</tbody>
</table>

Wt = weight; GA = gestational age; CNS = central nervous system; CRP = C-reactive protein; LUSCS = lower uterine segment caesarean section; CT = computed tomography.

In two cases there was evidence of significant intracranial trauma, the extent of which had not been fully appreciated antemortem. In one infant there had been an attempted high forceps delivery followed by an emergency caesarean section. The autopsy findings indicated the injury was more severe than suggested by the CT scan and also revealed an occipital osteodiastasis. The second of these infants was an undiagnosed breech delivered at home and the autopsy findings provided more specific detail about the nature of the cerebral injury. In two infants the microscopic changes in the brain strongly suggested that an asphyxial insult preceded delivery. These findings were capillary proliferation, early breakdown of the cortex and fibrillary gliosis. In one of these infants there was evidence of previous haemorrhage with haemosiderin laden macrophages in the germinal matrix. In two infants, including one who also had

normal cardiac anatomy. In the other case a diagnosis of intracerebellar haemorrhage had been made on the basis of a CT scan but no haemorrhage was found at autopsy.

New information was found in 10 infants (62.5%). These findings are listed in Table 2. In four infants there was evidence of fetal malnutrition at autopsy that had not been appreciated clinically. All infants with a low PI had an autopsy but only 3/8 had evidence of fetal malnutrition determined postmortem. The other infant who had evidence of fetal malnutrition had both a normal PI and a normal birthweight. In two infants the postmortem findings were those of congenital infection, most likely due to Gp B streptococcus. In a further infant the findings were suggestive of infection as there was congenital pneumonia noted at postmortem. In one case there was evidence of contributory placental pathology with multiple chorioangioma.
evidence of older CNS lesions, the presence of a two-tone liver indicated that the asphyxial insult had definitely occurred prior to delivery. There were no differences noted in the histological distribution of the central nervous system asphyxial lesions between those who had evidence of acute asphyxia alone and those who had added findings.

DISCUSSION

We have shown that in our unit an autopsy added new information in 62.5% of neonatal deaths for which severe perinatal asphyxia, followed by grade III HIE in survivors, was thought to be the main clinical diagnosis antemortem. All this new information could have had medicolegal significance in the context of clinical review. It is therefore surprising that a recent multidisciplinary case review of cases of fatal neonatal encephalopathy can be reported without consideration of information gained at autopsy.16

In the past a minimum recommended postmortem rate of 75% for this age group has been suggested.17 Our autopsy rate at 80% is in line with these recommendations although many perinatal units find it difficult to attain this gold standard over the range of neonatal deaths.6,8 In a multicentre study from the Netherlands, 181 neonatal deaths were reviewed over a one-year period. There were 37 cases listed as perinatal asphyxia. In 146 (81%) cases treatment was withheld or withdrawn because of the poor prognosis or lack of expectation for survival. An autopsy was determined in only 46% of cases.18 The role of the autopsy as an audit of the final diagnosis is not discussed. Although it may be argued that a target autopsy rate of 75% is not necessarily appropriate in 2004 for all causes of neonatal death, in our opinion, death after perinatal asphyxia is an important condition to be documented at autopsy because of the medicolegal issues that can be associated with this diagnosis.

In contrast, Dhar et al.3 achieved an autopsy rate of 83% for cases dying after HIE. In this institution, deaths caused by perinatal asphyxia or birth trauma in which questions were raised about preventability of injury were referred to the coroner. For HIE infants there was an overall 24.3% discordance rate between the clinical and pathological diagnoses. In this series, 5% of the term HIE group who were autopsied had old unrecognised CNS lesions. We found two such infants (12.5%) in our series and this raises the possibility that a central nervous system insult occurring prior to labour may make the infant more vulnerable to asphyxia in labour or possibly be the initiator of labour. This hypothesis is supported by recent data from the Scottish perinatal neuropathology study.19 In this cohort of 174 early neonatal deaths 62% of 21 autopsied asphyxiated term infants who died ≤3 days of age had histological evidence of CNS damage consistent with onset before the start of labour. The utility of the autopsy in determining the timing of the perinatal asphyxial insult has been discussed previously,20,21 and in more detail in a recent review.22 The timing of the asphyxial insult in infants found to be asphyxiated at birth has important medicolegal implications.

In two infants the presence of a two-tone liver was noted. This timmertime reflects the pallor that occurs in the relatively less well-oxygenated right lobe of the liver when hypoxia occurs in utero. It confirms that the hypoxic episode occurred when the fetal liver was still dependent on umbilical vein flow. This pathological finding when first described in 1969 was found to be more commonly seen in postmature infants dying during delivery.23 In situations where the need for extensive resuscitation of an infant soon after birth is unexpected, this autopsy finding clearly indicates that the asphyxial event occurred prior to delivery.

The most common added finding at autopsy was that of evidence of fetal malnutrition. Fetal malnutrition was determined at autopsy by an apparent loss of subcutaneous fat and the presence of dry skin with loss of turgor. The brain/liver weight ratio was not used to determine fetal malnutrition as these babies had not suffered from asymmetrical fetal growth restriction earlier in utero. We were interested in evidence of loss of condition just prior to delivery as we felt that this might assist in explaining why the infant was more vulnerable to asphyxia during labour. This condition could have been recognised clinically by the attending physician but the impression from the medical record was that the symptoms of the neonatal ischaemic encephalopathy were so striking and the need for intensive management so immediate that the finer points of examination of these infants seemed to be overlooked and were poorly documented. Interestingly, one of these infants also had the two-tone liver as described above and two infants may have sustained a CNS insult prior to labour. These findings together suggest these infants probably should have been delivered earlier but the difficulty is in being able to predict this outcome antenatally.

We also had three cases that presented as neonatal HIE but were found to have evidence of congenital infection at autopsy. In one case, the C-reactive protein (CRP) level had been high in life, suggesting infection, but this was not discussed in detail in the medical record, as the clinical picture was still one of neonatal HIE. There were none of the usual risk factors for infection noted. In the second case, the initial CRP was not raised and although there was evidence of maternal colonisation with group B streptococcus there was no clinical evidence recorded of the chorioamnionitis that was subsequently diagnosed by placental histology. Intrapartum antibiotics had been given. In the third case, infection was suspected because of the congenital pneumonia but could not be proven conclusively. Congenital infection has been reported previously as mimicking perinatal asphyxia.2,8 This is an important diagnosis to make, not only to avoid the clinician managing labour being inappropriately accused of mismanagement of labour, but also because it may have implications for management of the next pregnancy.
We were pleased to find that all four Maori families felt able to consent to autopsy. We believe this is most likely because we were able to offer a seven-day a week service from morning into the early evening. Maori parents were therefore able to consent to autopsy and still have their baby returned to them quickly so that they could have the infant on the marae for the tangi as soon as 3–4 hours after death.

McHaffie et al.24 studied the perceptions of parents about the value of autopsy after withdrawal of treatment in the newborn period. In this study in Scotland, data were collected from 1996 to 1998 before the publicity about organ retention in paediatric centres in England. Of the 81 eligible families, 59 (73%) participated. All but one couple were asked for permission for autopsy. Of the 58 families asked 22 (38%) refused permission for autopsy. One or both parents in a further 11 (19%) families were initially reluctant but were subsequently persuaded that it was the right thing to do. Consent for autopsy was obtained for 5/11 babies with asphyxia or brain injury. The main reasons for refusal were fear of mutilation of the body and a perception that no further answers were required as to the cause of death. The ability to obtain permission for autopsy appeared to vary between consultants. No parent appeared to subsequently regret the decision to grant autopsy permission. This study indicates that there is some onus on the clinician to allay the reasonable concerns that parents have about the autopsy. Others have shown that autopsy consent is more likely to be obtained by more experienced physicians.25 In the light of recent controversies about organ retention after postmortem in Australasia and Britain, full and complete discussion with parents about the procedure must occur before consent is sought.a6'27 In New Zealand, Maori parents may be particularly concerned about the issue of organ retention but can be reassured if the issue is discussed openly.

In a survey of women who had had a perinatal loss and been offered autopsy, it was apparent many did not have enough understanding about what the postmortem involved to make an informed choice.38 Counselling parents regarding the role of postmortem takes time and requires skill. Parents need to understand that the autopsy is important not just because new information can be obtained but also because confirmation of the clinical diagnosis is in itself important especially if it has been the basis of a decision to withdraw treatment. Many parents feel guilt about the decision to withdraw treatment and the confirmation that the CNS injury was extremely severe may assuage that. We have also found this information important as clinicians. Having our clinical judgement about the severity of likely outcome confirmed for each infant enables us to be more confident in counselling the next family about the management of their infant with severe neonatal HIE.

A recent paper looking at the attitudes of neonatologists to autopsy in the context of clinical trials clearly shows the ambivalence many have to the role of autopsy after neonatal death.28 Particularly concerning was the lack of awareness of the range of information that could be obtained from autopsy after the death of an infant. Clinicians are more likely to obtain consent for autopsy if they are convinced of the role of autopsy and therefore able to convey this to the parents. In our series there was little new information gained from the infants who had an autopsy after dying after a month of life. However, even in these cases it was still reassuring to see the extent of the cerebral damage and be reassured that the decision against active treatment was appropriate. The information regarding fetal malnutrition should be able to be determined by more careful clinical examination but two of these infants also had evidence suggesting an older cerebral injury that was relevant to an understanding of the aetiology of the asphyxia. Perhaps the most important change was for the infants where infection was found at autopsy. This information may be the most useful medicolegally. The other two cases for which the information gained at postmortem was important medicolegally were the infants with serious intracranial injury. In both these cases the findings at autopsy were pertinent to fully defining the extent of the intracerebral injury and its contribution to the severity of the asphyxial insult.

CONCLUSION

This small study confirms the importance of infant autopsy when perinatal asphyxia is implicated in neonatal death. Neonatal HIE is a symptom rather than a final clinical diagnosis. A full postmortem is required to fully explore the reasons for fatal neonatal HIE and may provide information that is important medicolegally. All perinatal units caring for these infants should review their clinical practice in this area.

References


Accepted 17 November 2004