

**Supplementary Table 1** Maternal sociodemographic details

	All cases (n=137)	BA (n=90)	noBA (n=47)	Sig
Maternal age at booking*	28(6)	28.2(5.9)	26.8(6.5)	0.236
Weight at booking (kg)*	66.5(13.7)	67.7(14.6)	64.6(11.2)	0.271
Height at booking (cm)*	163(7)	163(8)	163(6)	0.566
Social class 1,2 <sup>#</sup>	58(43)	41(46)	17(36)	0.311
Unemployed <sup>#</sup>	16(12)	8(9)	8(18)	0.159
Married <sup>#</sup>	38(28)	21(23)	17(38)	0.111
Smoker at booking <sup>#</sup>	51(38)	36(40)	15(34)	0.373
Primigravida <sup>#</sup>	50(37)	30(34)	20(42)	0.287
No of pregnancies <sup>^</sup>	1(2)	1(2)	1(2)	0.468
History of infertility, previous neonatal death or miscarriage <sup>^</sup>	40(29)	31(34)	9(19)	0.062
Previous termination of pregnancy <sup>#</sup>	24(18)	15(16)	9(19)	0.717
Previous uterine surgery <sup>#</sup>	33(24)	24(27)	9(19)	0.329

\* mean, standard deviation and p value (independent samples t-test)

# number, percentage and 2-tailed significance (Chi-square test)

<sup>^</sup> median, interquartile range and asymptotic 2-tailed significance (Mann-Whitney U test)

**Supplementary Table 2** Pregnancy details

	All cases (n=137)	BA (n=90)	noBA (n=47)	Sig
Unbooked or booked >15 weeks <sup>#</sup>	18(13)	12(13)	6(13)	0.926
Systolic BP at booking <sup>*</sup>	115(15)	117(16)	112(13)	0.098
Diastolic BP at booking <sup>*</sup>	68(12)	68(13)	68(10)	0.970
Multiple pregnancy <sup>#</sup>	20(15)	12(13)	8(18)	0.562
Assisted conception <sup>#</sup>	4(3)	3(3)	1(2)	1.000
Abnormal serum screening <sup>#</sup>	14(16)	8(13)	6(22)	0.371
Amniocentesis performed <sup>#</sup>	11(8)	6(7)	5(11)	0.509
Abnormal fetal anomaly scan <sup>#</sup>	21(34)	16(37)	5(26)	0.403
Antibiotics in pregnancy <sup>#</sup>	22(16)	12(13)	10(22)	0.229
Steroids in pregnancy <sup>#</sup>	35(26)	18(20)	17(38)	<b>0.039</b>
Oligohydramnios <sup>#</sup>	27(20)	14(16)	13(30)	0.091
Hyperemesis <sup>#</sup>	18(13)	7(8)	11(24)	<b>0.010</b>
Placenta praevia >grade1 <sup>#</sup>	7(5)	2(2)	5(11)	<b>0.045</b>
Pyrexia >38°C/flu-like illness during pregnancy <sup>#</sup>	13(10)	5(6)	8(18)	0.061
Anaemia <11g/dl <sup>#</sup>	14(33)	27(30)	17(39)	0.437
Polyhydramnios <sup>#</sup>	11(8)	10(11)	1(2)	0.097
Intrauterine growth restriction <3 <sup>rd</sup> centile <sup>#</sup>	19(14)	9(10)	10(23)	0.066
Loss of fetal movements reported <sup>#</sup>	14(10)	8(9)	6(14)	0.554
Premature rupture of membranes <sup>#</sup>	31(23)	21(24)	10(23)	0.808
Intrauterine or urinary tract infection <sup>#</sup>	18(13)	10(11)	8(18)	0.331
Pregnancy-induced hypertension <sup>#</sup>	14(10)	7(8)	7(16)	0.235
Antepartum haemorrhage in 2/3 trimesters <sup>#</sup>	40(29)	22(24)	18(40)	0.090
Any of the above complications of pregnancy <sup>#</sup>	112(82)	72(80)	38(81)	0.905

\* mean, standard deviation and p value (independent samples t-test)

# number, percentage and 2-tailed significance (Chi-square test)

^ median, interquartile range and asymptotic 2-tailed significance (Mann-Whitney U test)

**Supplementary Table 3** Intrapartum details

	All cases (n=137)	BA (n=90)	NoBA (n=47)	Sig
Induction of labour <sup>#</sup>	13(10)	8(10)	5(9)	0.764
No labour <sup>#</sup>	29(21)	21(23)	8(18)	0.391
Forceps/Ventouse delivery <sup>#</sup>	10(7)	7(8)	3(6)	1.000
Emergency caesarean section <sup>#</sup>	57(42)	41(45)	16(36)	0.194
Malpresentation of fetus <sup>#</sup>	48(35)	27(29)	21(47)	0.087
Meconium staining <sup>#</sup>	28(20)	23(26)	4(9)	<b>0.040</b>
CTG abnormality reported <sup>#</sup>	51/99(52)	42/71(59)	9/27(31)	<b>0.004</b>
Cord prolapse <sup>#</sup>	9(7)	7(8)	2(4)	0.718
Documented intrapartum infection <sup>#</sup>	12(9)	7(8)	5(11)	0.751
Pyrexia in labour >38°C <sup>#</sup>	11(8)	7(8)	4(9)	1.000
Bleeding in labour <sup>#</sup>	32(23)	21(23)	11(24)	0.993
1 <sup>st</sup> stage duration (h) <sup>^</sup>	2.1(6.6)	2.5(6.8)	1.6(6)	0.726
2 <sup>nd</sup> stage duration (m) <sup>^</sup>	5(28)	4(27)	7(30)	0.472
Time of ruptured membranes (h) <sup>^</sup>	2(14)	3(17)	1(6)	0.314
Ruptured membranes >24h <sup>#</sup>	28(21)	20(23)	8(18)	0.451
General anaesthetic in labour <sup>#</sup>	26(19)	19(21)	7(16)	0.378
Epidural in labour <sup>#</sup>	44(32)	33(37)	11(22)	0.115
Opiates in labour <sup>#</sup>	47(34)	28(30)	19(42)	0.276
Delivery out of hours (21:00-08:59 and weekends) <sup>#</sup>	83(61)	57(64)	26(53)	0.362

\* mean, standard deviation and p value (independent samples t-test)

# number, percentage and 2-tailed significance (Chi-square test)

^ median, interquartile range and asymptotic 2-tailed significance (Mann-Whitney U test)

**Supplementary Table 4** Infant newborn details

	All cases (n=137)	BA (n=90)	noBA (n=47)	Sig
Male sex <sup>#</sup>	84 (61)	56 (61)	28 (62)	0.763
Gestation <sup>*</sup>	31 (6.4)	32 (6.8)	29(5)	<b>0.017</b>
< 37 weeks gestation <sup>#</sup>	99 (72)	59 (44)	40 (89)	<b>0.015</b>
Weight (g) <sup>*</sup>	1779 (1193)	1971(1274)	1411 (849)	<b>0.004</b>
Occipitofrontal circumference (cm) <sup>*</sup>	27.8 (6)	28.9(6)	26.1(4)	<b>0.015</b>
Apgar 0 at 1 minute <sup>#</sup>	18 (13)	18 (20)	0	<b>0.001</b>
1 minute Apgar <sup>*</sup>	3 (3)	1(2)	6(3)	<b>&lt;0.001</b>
5 minute Apgar <sup>*</sup>	5(3)	3(3)	8(1)	<b>&lt;0.001</b>
10 minute Apgar <sup>*</sup>	5(4)	2(3)	9(1)	<b>&lt;0.001</b>
Time to establish regular respirations (m) <sup>^</sup>	1 (5)	4 (14)	0 (1)	<b>&lt;0.001</b>
Cardiac massage required <sup>#</sup>	40 (29)	37 (40)	3(7)	<b>&lt;0.001</b>
Intubation required <sup>#</sup>	113 (83)	81 (88)	32(71)	<b>0.001</b>
Age at death (h) <sup>^</sup>	15 (49.2)	10.7 (47.8)	39.1 (50.9)	<b>0.002</b>
Admitted to SCBU <sup>#</sup>	106 (77)	65 (73)	41 (87)	<b>0.046</b>

\* mean, standard deviation and p value (independent samples t-test)

# number, percentage and 2-tailed significance (Chi-square test)

<sup>^</sup> median, interquartile range and asymptotic 2-tailed significance (Mann-Whitney U test)

**Supplementary Table 5** Infant first week details

	All cases (n=106)	BA (n=65)	noBA (n=41)	Sig
< 37 weeks gestation <sup>#</sup>	80 (76)	42(63)	38 (97)	<b>0.001</b>
Initial pH within 1 <sup>st</sup> hour <sup>*</sup>	7.12 (0.25)	6.96 (0.23)	7.25 (0.12)	<b>&lt;0.001</b>
Time to reach normal pH (h) <sup>^</sup>	4 (5)	4.75 (4.88)	3 (4.32)	0.117
First mean arterial pressure <sup>*</sup>	38(15)	40(17)	36(10)	0.207
Hematuria in first 24h <sup>#</sup>	32 (30)	19 (77)	13(71)	1.000
Creatinine >120 <sup>#</sup>	23 (22)	17 (26)	6 (15)	<b>0.020</b>
Inotrope required <sup>#</sup>	35 (33)	20 (34)	15 (38)	0.644
Colloid required <sup>#</sup>	82 (77)	51 (85)	31(81)	0.362
Surfactant given <sup>#</sup>	56 (53)	26(40)	30(74)	<b>0.001</b>
Respiratory distress syndrome <sup>#</sup>	46 (43)	20(32)	26(70)	<b>0.001</b>
Ventilated for poor respiratory drive <sup>#</sup>	21 (20)	20 (33)	1(3)	<b>&lt;0.001</b>
Abnormal coagulation <sup>#</sup>	46 (43)	28 (80)	18 (78)	1.000
Abnormal infection screen <sup>#</sup>	15 (14)	9 (20)	6(17)	0.839
Abnormal liver function tests	7/97 (7)	7 (44)	0	<b>0.022</b>
Hypoglycemia <2.6 mmol/l <sup>#</sup>	40 (38)	22 (39)	18 (50)	0.480
Hyperglycemia >8 mmol/l <sup>#</sup>	36 (34)	22 (42)	14(33)	0.759
Necrotising enterocolitis <sup>#</sup>	5 (5)	4 (7)	1 (3)	0.646
Seizures <sup>#</sup>	12 (11)	11 (16)	1 (3)	<b>0.027</b>
Muscle relaxant <sup>#</sup>	22 (21)	8 (13)	14 (38)	<b>0.011</b>
Abnormal neurology (alive >12hours) <sup>#</sup>	28/45 (62)	25/30(93)	3/15(7)	<b>&lt;0.001</b>
Abnormal cranial USS <sup>#</sup>	48/68(71)	31/40 (76)	17/28 (62)	0.135
Age at death (h) <sup>^</sup>	35.6 (60.25)	18 (62.7)	43.1 (52.1)	0.175

\* mean, standard deviation and p value (independent samples t-test)

# number, percentage and 2-tailed significance (Chi-square test)

^ median, interquartile range and asymptotic 2-tailed significance (Mann-Whitney U test)

**Supplementary Table 6** Clinical & neuropathological features in neonatal deaths with putative prenatal brain damage

Case	Gestation	Clinical Features	Estimated Total Hours of Labour plus postnatal survival	Neuropathological Features
1	42	1. Normal 2. Abnormal CTG, ruptured uterus 3. Apgar 4 <sup>5</sup> , pH 6.91, Seizures, isoelectric EEG, cerebral oedema on USS, died 32h	32 Hours	Cerebral oedema; neuronal eosinophilia & karyorrhexis; microglial activation & focal macrophage infiltration in white matter.
2	40	1. Normal 2. Meconium, abnormal CTG, ruptured uterus 3. Apgar 0 <sup>1</sup> 0 <sup>5</sup> , pH 6.8, HIE 3, died 15hours	28 Hours	Cerebral oedema; fresh microhaemorrhages, neuronal eosinophilia & karyorrhexis; microglial activation; white matter gliosis & damage.
3	40	1. Normal 2. PROM, meconium, abnormal CTG, suspected infection 3. Apgar 1 <sup>5</sup> , pH 6.86, HIE 3, isoelectric EEG, seizures, died 42h	61 Hours	Neuronal eosinophilia & karyorrhexis; white matter damage; microglial activation & macrophage accumulation; focally gliotic white matter.
4	40	1. Normal 2. Abnormal CTG, cord prolapse 3. Apgar 0 <sup>1</sup> 2 <sup>5</sup> , pH 6.79, HIE 3, cerebral oedema on USS, isoelectric EEG, died 14h	21 Hours	Cerebral oedema; neuronal eosinophilia; white matter gliosis & amphophilic globules.
5	39	1. Loss FM 32,39wks, essential HT 2. No labour, meconium, abnormal CTG, fetomaternal bleed 3. Apgar 4 <sup>5</sup> , pH 7.06, HIE grade 3, died 14h	14 Hours	Neuronal eosinophilia & karyorrhexis; grey matter gliosis; microglial activation and macrophage accumulation.
6	38	1. Unbooked, severe PIH 2. No labour, abnormal CTG, multiple placental infarctions 3. Apgar 0 <sup>1</sup> 2 <sup>5</sup> , pH 6.57, seizures, HIE grade 3, bilateral echogenicity on USS, died 17h	17 Hours	Cerebral oedema, neuronal eosinophilia & karyorrhexis; white matter gliosis & macrophage accumulation.
7	38	1. Loss fetal movements 38/40		Germinal matrix haemorrhage;

		2. No labour, abnormal CTG, fetomaternal bleed 3. Apgar 0 <sup>1</sup> 0 <sup>5</sup> , pH 6.8, severe HIE, died 43h	43 Hours	neuronal eosinophilia & karyorrhexis; white matter damage & gliosis; microglial activation & macrophage accumulation.
8	37	1. Smoking 2. No Labour, abnormal CTG, uterine rupture 3. Apgar 0 <sup>1</sup> 0 <sup>5</sup> , pH 6.69, no cortical activity on EEG, seizures, died 35h	35 Hours	Cerebral oedema; neuronal eosinophilia & karyorrhexis; gliosis grey matter; microglial activation & macrophage accumulation.
9	36	1. Smoking, multiple pregnancy, APH 30-36wks 2. Green vaginal discharge, complex shoulder presentation, abnormal CTG 3. Apgar 0 <sup>1</sup> 3 <sup>5</sup> , pH 6.9, abnormal neurology, abnormal background EEG, died 45h	53 Hours	Cerebral oedema, neuronal eosinophilia & karyorrhexis; microglial activation & macrophage infiltration; white matter gliosis.
10	40	1. Previous NND 2. Unexpected poor condition 3. Apgar 7 <sup>5</sup> , pH 6.94, abnormal tone, poor respiratory drive, died 26h	39 Hours	Gangliosidosis – GM1; white matter gliosis.
11	36	1. Smoking, previous anencephalic infant, oligohydramnios, IUGR 2. Breech, meconium 3. Apgar 0 <sup>5</sup> , died <1h	4 Hours	Micromineralisation; white matter damage & macrophage accumulation.
12	35	1. Known duodenal atresia, antenatal steroids, ROM 35wks, IUGR 2. Meconium, abnormal CTG 3. Tracheal atresia, oesophageal-pulmonary fistula, Apgar 4 <sup>5</sup> , pH 6.8, died 11h	11 Hours	Cerebral oedema; white matter gliosis & microglial activation.
13	35	1. Previous SB, unbooked, massive fetal ascites on USS 2. No labour, meconium, abnormal CTG 3. Apgar 1 <sup>5</sup> , pH 6.81, abnormal neurology, died 8h	8 Hours	Mineralised neurons in basal ganglia; fresh microhaemorrhages; neuronal karyorrhexis; white matter gliosis & macrophages.

14	32	1. Known duodenal atresia, amnioreduction, polyhydramnios, antenatal steroids, severe PIH 2. No labour, abnormal CTG 3. Apgar 0 <sup>1</sup> 0 <sup>5</sup> , pH 6.9, died 1h	1 Hour	Cerebral oedema; micromineralisation; focal white matter damage; white matter gliosis.
15	28	1. Multiple pregnancy, antenatal steroids, hydropic 1 <sup>st</sup> twin 2. Breech, meconium 3. Apgar 1 <sup>5</sup> , died 2h	7 Hours	Microhaemorrhages; basal ganglia micromineralisation; white matter damage & gliosis; focal macrophage accumulation.
16	28	1. Smoking, oligohydramnios, IUGR, antenatal steroids 2. No labour, abnormal CTG, breech 3. Apgar 9 <sup>5</sup> , pH7.09, Abnormal neurology, USS showed IVH, PVL, died 70h	70 Hours	Germinal matrix haemorrhage with thrombosed vessels; white matter infarction & gliosis; neuronal eosinophilia & karyorrhexis; macrophage accumulation.
17	27	1. Previous SB 25wks, antenatal steroids, oligohydramnios, IUGR 2. No labour, meconium, abnormal CTG 3. Apgar 4 <sup>5</sup> , died <1h	0.5 Hours	Fresh microhaemorrhages; neuronal eosinophilia; focal grey matter gliosis; macrophage accumulation in grey & white matter.
18	25	1. High AFP, severe oligohydramnios, IUGR, APH at 16, 20, 25 wks, ROM 17wks 2. PROM, breech 3. Apgar 1 <sup>5</sup> , died 2h	6 Hours	Germinal matrix haemorrhage; neuronal eosinophilia; white matter gliosis; microglial activation & macrophage infiltration.
19	24	1. Unbooked, IUGR 2. Breech 3. Apgar 2 <sup>5</sup> , died<1h	2 Hours	Focal macrophage accumulation & gliosis in grey matter.
20	24	1.Oligohydramnios, APH 13/40, ROM 21/40, anemia <9g/dl, suspected infection	13 Hours	Germinal matrix haemorrhages; neuronal



		2. PROM 3. Apgar 8 <sup>5</sup> , pH 7.08, IVH, died 12h		eosinophilia; focal white matter damage & microglial activation; grey matter gliosis.
21	40	1. APH 6,29wks 2. Cord haemorrhage 3. Apgar 0 <sup>5</sup> , died at 1h	2 Hours	Focal grey matter gliosis; microglial activation; focal macrophage accumulation & white matter damage.
22	39	1. Essential HT 2. Meconium, abnormal CTG 3. Apgar 0 <sup>1</sup> 0 <sup>5</sup> , died<1h	3 Hours	White matter diffuse microglial activation & macrophage accumulation; focal gliosis of white matter.
23	26	1. Smoking, low AFP, oligohydramnios, APH 9/40, grade 3 placenta praevia, ROM 26/40, suspected infection, bicornuate uterus 2. PROM, breech, abnormal CTG 3. Apgar 7 <sup>5</sup> , pH 7.12, died 11h	29 Hours	Microhaemorrhages; focal microglial activation & macrophage infiltration of white matter.
24	25	1. Severe maternal varicella, heavily sedated and ventilated, antenatal steroids 2. Breech, delivered unexpectedly in adult ITU 3. Apgar 0 <sup>1</sup> 4 <sup>5</sup> , pH 6.9, seizures, severe PVH, died 51h	51 Hours	Neuronal eosinophilia & karyorrhexis; germinal matrix haemorrhage; focal microglial activation & macrophage accumulation.
25	42	1. Amniocentesis for low AFP, loss FM 36,41/40, PIH 2. Abnormal CTG 3. Good condition, Apgar 10 <sup>5</sup> , collapse at 1h, died 5h	5 Hours	Diffuse white matter gliosis; amphophilic globules.
26	40	1. Normal 2. Meconium, abnormal CTG 3. Apgar 1 <sup>5</sup> , died<1h	10 Hours	Fresh microhaemorrhages; white matter gliosis & focal white matter damage.
27	40	1. Normal 2. Meconium 3. Unexpected poor condition, Apgar 5 <sup>5</sup> , pH 7.04, died 13h	18 Hours	Cerebral oedema; focal white matter gliosis & microglial activation.

## Key:

1. pregnancy features
2. labour and delivery features
3. resuscitation and neonatal features

ROM rupture of membranes; PROM ruptured membranes >24hours; HT hypertension; IUGR intrauterine growth retardation; PVH periventricular haemorrhage; APH antepartum haemorrhage; FM fetal movements; SB stillbirth; AFP serum alpha fetoprotein

**Supplementary Table 7** Timing of CNS Injury after Cerebral Insult

<b>Pathological Features</b>	<b>Timing of Onset after Injury</b>	<b>References</b>
Neuronal Eosinophilia	6 – 24 hours	<p>Norman (1978) described eosinophilia in differentiated neurons 24 -36 hours after hypoxic insult (such as delay in establishing respiration) in a classic study of perinatal brain damage. In quoting the results of animal studies, she points out that these may not be applicable directly to human infants.</p> <p>Low et al (1989) suggests that eosinophilia requires at least 18 hours after a documented insult (results in 16 of 120 perinatal deaths).</p> <p>A major current text of neuropathology (Graeber et al, in Greenfield's Neuropathology 2002) quotes a period of "more than 6" hours after insult with reference to observations in the rat.</p>
Neuronal Karyorrhexis	12 – 48 hours	<p>Friede (1972) described neuronal karyorrhexis in mature infants surviving at least 22 hours after an insult.</p> <p>Low et al (1989) suggested that nuclear pyknosis requires 18 hours to become visible. This study documents the duration of labour as well as postnatal survival but suggests that histological changes do not indicate precisely the timing of the insult.</p> <p>Wigglesworth &amp; Bridger (1994) suggested this change required a time lapse of more than 24 hours from their own studies of perinatal deaths.</p> <p>Squier (2001) suggested a time interval of 12-48 hours from her own experience and a survey of the literature.</p>
Infarcts – Necrosis	3 – 8 hours	<p>Banker (1967) quotes 3 hours as the period needed for coagulation necrosis to become evident but a further 9 hours required for commencing cellular reactions.</p> <p>Norman (1978) describes smudgy eosinophilic coagulation necrosis with axonal balls and pyknotic glial nuclei arising 3-8 hours after a cerebral insult; most likely due to a failure of tissue perfusion.</p> <p>Squier (2001) describes coagulation necrosis and retraction balls occurring within 3 hours of insult, quoting other studies and her own observations.</p>
Infarcts – Cavitation	14 – 42 days	<p>Banker (1967) described cysts appearing in areas of damaged white matter two weeks after the insult.</p> <p>Ellis et al (1988) drew on their own experience to conclude that 14 days was required.</p> <p>Squier (2001) quotes the literature and her own experience in suggesting a period of 14 – 42 days.</p> <p>Kinney &amp; Armstrong (2002) described a delay of "a few weeks".</p>
Reactive Gliosis (white matter)	3 – 11 days	<p>Gilles &amp; Murphy (1969) thought that hypertrophic astrocytes required 3 days to appear and were able to attribute brain damage to the prenatal period on this basis, provided that the astrocytosis was accompanied by other evidence of white matter damage such as glial pyknosis.</p> <p>Roessman &amp; Gambetti (1986) thought that 4 days were required (for the appearance of hypertrophied astrocytes identified categorically by GFAP immunocytochemistry; sometimes present in isolation but is taken as evidence of brain damage).</p> <p>Ellis et al (1988) examined very carefully a series of infants</p>

		<p>in whom astrocytosis was graded as early, established or late. Subtle early astrocytosis could be detected by one day after insult whereas enlarged and hypertrophic astrocytes required 3-5 days.</p> <p>Low et al (1989) indicated that 3 – 5 days were required.</p> <p>Norenberg (1994) concentrated on astrocytic reactions and thought these were maximal by 4 days after injury in humans compared with 24 hours in a rat model – he emphasised that the two situations were not comparable in that the human brain was likely to suffer more widespread damage and required to recover before mounting cellular reactions.</p> <p>The consensus is that reactive astrocytosis requires around 3 days and on this basis, damage has been ascribed in several series to the prenatal period although Norman (1978) and Squier (2001) both draw attention to the potential confusion between reactive astrocytosis and “myelination” gliosis. Stress is generally laid on features accompanying gliosis eg amphophilic globules in and around the walls of vessels or macrophage infiltration in order to attribute significance to the reactive gliosis (Golden et al 1997, Gilles et al 1998).</p>
Reactive Gliosis (grey matter)	3 – 5 days	<p>Friede (1972) described a glial response occurring in pontosubicular necrosis 3-5 days after the insult. If infants with pontosubicular necrosis survived only 1-2 days, the grey matter glial response was very slight.</p> <p>Del Bigio &amp; Becker (1994) described the glial response in damaged dentate gyrus “lagging behind” a microglial response which itself required 1-4 days.</p> <p>Marin-Padilla (1999) emphasised that grey matter damage was repaired by gliosis, unlike white matter which cavitates, but found this phenomenon only in comparatively longer survivors (weeks and months after the insult).</p> <p>Kinney &amp; Armstrong (2002) suggested that 3-5 days were required for grey matter gliosis to follow on neuronal necrosis in both preterm and mature infants.</p>
Microglial Upregulation	3 hours – 3 days	<p>Banker (1967) observed microglial infiltrate about 12 hours after the onset of coagulative necrosis.</p> <p>Norman (1978) found rod cells in necrotic white matter foci only after 2-3 days following an anoxic episode.</p> <p>Ellis et al (1988), quoting animal studies compared with their own human studies, observed microglia 1-3 days after an insult.</p> <p>Low et al (1989) observed rod cells 36-72 hours after a hypoxic episode.</p> <p>Del Bigio &amp; Becker (1994) observed an increased number of rod cells only when survival exceeded 4 days following an insult which had produced grey matter infarcts. This study quotes results in animal experiments where microglial upregulation was observed to commence approximately 1 day after the insult, becoming maximal at 4 days.</p>
Macrophage Infiltration	3 – 7 days	<p>Banker (1967) observed macrophages only 1 week after a documented insult.</p> <p>Friede (1972) observed macrophage responses (foamy cells) in relation to pontosubicular damage 4-5 days after the onset of presumed clinical insult.</p> <p>Ellis et al (1988) documented early, middle and late stages from their own observations of macrophage formation and related this to animal studies.</p>

		<p>Squier (2001) observed macrophages only 4-5 days after injury.</p> <p>Kinney &amp; Armstrong (2002) suggested 3-5 days were required for a macrophage response in relation to pontosubicular necrosis, presumably based on their own experience.</p>
Fresh Haemorrhage	Minutes	<p>Fresh haemorrhage is an acute lesion which is too recent to assist in criteria for prenatal damage (Ellis et al 1988) but which can follow an episode of infarction in white or grey matter or a systemic consumption coagulopathy.</p>
Haemosiderin Deposits	2-3 days	<p>Ellis et al (1988) found that haemosiderin staining macrophages accompanied the appearance of macrophages within and around haemorrhagic lesions and that this change required 3 days to appear.</p> <p>Squier &amp; Keeling (1991) suggest that the presence of pigmented macrophages around haemorrhages requires at least 2 days.</p> <p>Vanesis (2001) states that haemosiderin containing macrophages are found within the brain 3-4 days after injury and this is later than in some other tissues. Vanesis emphasises that no reliance should be placed on animal studies in this regard since there is very considerable interspecies variation.</p>
Mineralisation	3 – 14 days	<p>Norman (1978) believed that ferrugination of neurons could occur 3 days post insult. However other authors have all assumed a longer interval.</p> <p>Ellis et al (1988) observed that a period of 14 days was required for the appearance of perivascular mineralising foci in the kitten model. These foci, and amphophilic globules, may be found in association with white matter gliosis (Gilles &amp; Murphy, 1969) and have been used to date the onset of damage in the prenatal period.</p> <p>Ellis et al (1988) thought that neuronal ferrugination required more than 14 days.</p> <p>Squier (2001) thought that mineralisation required 8-14 days. Amphophilic globules in and around the walls of small vessels may represent leaked plasma proteins.</p>

