

ORIGINAL ARTICLES

Evidence of Occurrence of Intradural and Subdural Hemorrhage in the Perinatal and Neonatal Period in the Context of Hypoxic Ischemic Encephalopathy: An Observational Study from Two Referral Institutions in the United Kingdom

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Received August 2, 2008; accepted November 9, 2008; published online November 19, 2008.

ABSTRACT

The occurrence of subdural hemorrhage (SDH) on the convexities of the cerebral hemispheres is not an unusual finding in the setting of intrauterine, perinatal, or neonatal deaths, the hemorrhage usually presenting either as a thin film over the occipital poles or as a small infratentorial bleed. Working in 2 referral centers with over 30 000 deliveries per year, we routinely examine the dura macroscopically and histologically in nonmacerated fetuses over 24 weeks in gestation and in neonates. This paper describes our experience of intradural hemorrhage (IDH) and SDH associated with hypoxia. Our series comprises 25 fetuses and 30 neonates with obvious macroscopic intradural hemorrhage and hypoxia of varying degrees of severity diagnosed by systematic examination of the brain. Fetal gestational age ranged from 26–41/40 weeks (all no more than 24 hours from intrauterine death), while the 30 neonates lived for between 1 hour and 19 days. Simultaneously with IDH, frank SDH was seen in 2 of 3 of all cases (16 fetuses and 20 neonates). Intradural hemorrhage was more prominent in the posterior falx and tentorium, most likely because of the existence of 2 venous plexus at these sites. Our findings demonstrate that SDH and cerebral hypoxia are common associations of IDH and that SDH (often seen as a thin film of hemorrhage) almost always occurs in association with diffuse falcine IDH. Diffuse IDH with SDH are more frequently associated with severe or moderate hypoxic ischemic encephalopathy (HIE), while mild or early HIE is more common with focal IDH without SDH.

Key words: asphyxia, brain hypoxia, intradural hemorrhage, neonatal, perinatal, subdural hemorrhage

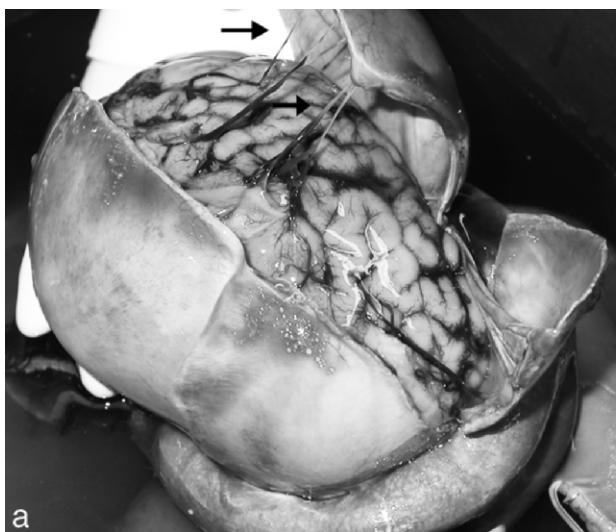
INTRODUCTION

Traditionally it has been considered that the “subdural space” is located between the arachnoid and the dura and that subdural hemorrhage (SDH) and hematoma are the result of blood accumulating in this virtual space [1]. However, experiments conducted in animals using electron microscopy have demonstrated that this concept is not accurate. A specialized layer known as the dural border cell layer, which consists of fibroblasts with few cell junctions, enlarged extracellular spaces, and no collagen, is present at the dura-arachnoid junction in humans as well as animals [2,3]. Under normal conditions, there is no evidence of a naturally occurring subdural space (either real or virtual). This space, however, may develop as a consequence of a pathological/traumatic process that damages the weak plane of the dural border cell layer between the arachnoid and the dura. Moreover, when a subdural space does develop, it is not initially “subdural” but rather lies within the dural border cell layer [2,3].

In the newborn, birth trauma can produce tentorial or falx tears, which give rise to SDH [4,5]. Birth trauma is also assumed to be responsible for SDH through damage to the bridging veins, which run from the brain to the dura mater [4,6], caused by deformation of the skull during labor.

A recent retrospective review in fetuses, infants, and toddlers with proven hypoxic ischemic encephalopathy (HIE) in the absence of trauma found no cases of SDH. This led the authors to deny that HIE can lead to SDH [7]. Despite the review covering 5 centers over a span of 17 years, the authors only managed to find 9 perinatal cases of HIE. However, in our experience and that of others [8], SDH on the convexities of the cerebral hemispheres is not an unusual finding in the setting of intrauterine, perinatal, or

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a



b

Figure 1. a. Bridging veins are assessed when opening the skull. b. Closer view depicting intact bridging veins. Case 47.

neonatal deaths. In these cases, the SDH more commonly presents as a thin film on the occipital convexity of the cerebral hemispheres or as a small infratentorial hemorrhage. In 1939 Leary [9] proposed that ruptured vessels within the dura could be a source of SDH in the newborn. He was the first to describe the occurrence of intradural hemorrhage (IDH), and he suggested that the bleeding first dissects the connective tissue of the dura before leaking into the subdural space. Kibayashi and colleagues [10] recently demonstrated the presence of IDH in the histological examination of the tentorium of children who were initially wrongly diagnosed by postmortem cranial computed tomography of traumatic subarachnoid hemorrhage.

In our daily practice we routinely examine the falx cerebri, parietal dura, and tentorium cerebelli, both macroscopically and microscopically, in all nonmacerated fetuses over 24 weeks in gestation (intrauterine and intrapartum deaths) and in neonates. We frequently observe IDH and SDH associated with brain hypoxia. Our aim is to describe the occurrence of this association and to encourage others to take these samples in their postmortem examinations.

MATERIAL AND METHODS

We describe the associations between IDH, SDH, and brain hypoxia in 25 nonmacerated (up to 24 hours following intrauterine death) fetuses of 24 weeks in gestation or more and in 30 newborns (less than 1 month of age) seen during a period of 2 years in 2 pediatric and perinatal tertiary referral centers in the United Kingdom. In this observational study, cases were selected based on the presence of IDH with or without obvious SDH. These cases comprise a representative sample of our routine practice.

To begin, we open the skull, making 2 incisions in the anterior fontanel, and then cut parasagitally without damaging the parasagittal sinus extending forward and backward on each side. The fronto-parietal and parieto-occipital suture lines are incised on each side. This allows visualization and assessment of the bridging veins (Fig. 1a,b). After the skull is incised and reflected, the falx cerebri

and tentorium cerebelli are inspected in situ. The falx is then detached from its anterior and superior insertion in the skull and, while still attached to the tentorium, is manually mobilized toward the back of the skull in order to allow removal of the brain. At this stage these membranes are examined macroscopically to search for hemorrhages (Fig. 2). We routinely sample the anterior, middle, and posterior falx; the tentorium cerebelli where the free margin joins the falx; and the parietal dura.

We grade the IDH as (1) minimal when red cells are occasionally seen spilling out of the vessels in the membrane (Fig. 3a); (2) focal when the hemorrhage is patchy; and (3) diffuse when this extensively involves the whole thickness of the dura (Fig. 3b). When a diffuse IDH exceeds the limits of the dura, the terms juxtadural and subdural hemorrhage are used in the microscopic and macroscopic description, respectively.

In the case of severe hypoxia, the brain is swollen on gross examination and there is widespread damage in characteristic sites on histology; with less severe degrees of

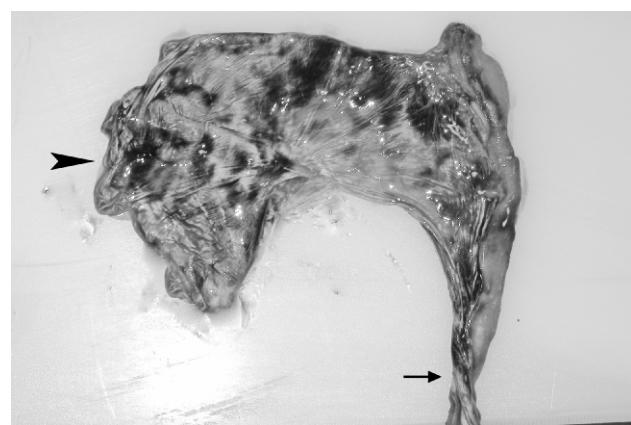


Figure 2. The falx and tentorium are inspected in situ for the presence of hemorrhages; after they are removed they are placed on the dissecting board to obtain a closer view. Arrow points to anterior falx, and the arrowhead shows the tentorium. Case 12.

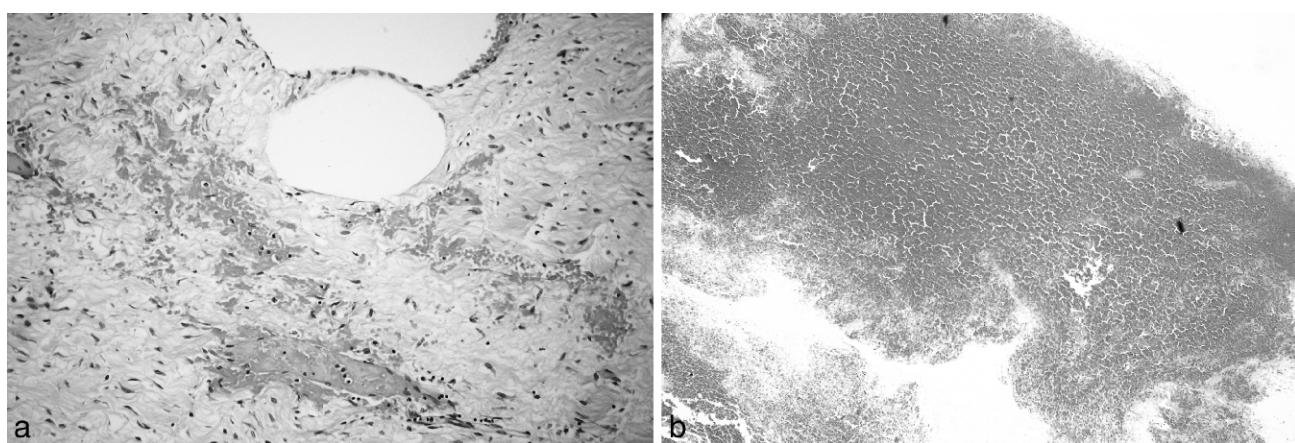


Figure 3. Hemorrhages in the falx and/or tentorium are graded as mild. **a.** Red cells are rarely seen spilling out of the vessels. Case 33. **b.** Diffuse, when the hemorrhage involves the whole thickness of the dura membrane. Case 5.

hypoxia histological changes are invariably present, although the brain weight may be within normal limits. Histologically, hypoxic neurons have a pyknotic nucleus with acidophilic cytoplasm, margination of Nissl substance, and, later, nuclear karyorrhexis [11]. We grade hypoxia as (1) mild (presence of edema [supported by increase in brain weight] and isolated hypoxic neurons in the dentate nuclei, pons, and/or inferior olfactory nuclei) (Fig. 4a); (2) moderate (neuronal pyknosis and karyorrhexis in the above areas and in the hippocampus [area CA1], commonly with vascular congestion) (Fig. 4b); and (3) severe (widespread neuronal pyknosis and karyorrhexis with endothelial swelling and reduplication in more advanced stages and frequently associated with bleeding in the cerebrum and pia matter) (Fig. 4c). Hypoxia shows a predilection for the white matter in younger fetuses and infants (28 to 36 weeks in gestation), while in term fetuses and neonates it more significantly affects the basal ganglia, thalamus, and cortex [12].

RESULTS

The gestational ages and postnatal age at death; cause of death or significant pathology; degree of IDH in the falx cerebri, tentorium, and parietal dura mater; presence or absence of SDH; and degree of hypoxia in each case are depicted in Tables 1 (fetuses) and 2 (neonates).

The gestational age of the 25 fetuses was between 26 and 41 weeks in gestation. The 30 newborns were aged between 1 hour and 19 days; of those, 26 newborns were 1 week of age or less. We initially sampled dura for microscopic examination when we could see obvious hemorrhage, but lately we have been routinely sampling the falx (anterior, middle, and posterior), right and left tentorium, and parietal dura from the sagittal sinus to the base of the brain.

In the falx cerebri IDH was absent in 2 cases (1 fetus and 1 neonate), focal in 8 (3 fetuses and 5 neonates), and diffuse in 45 (24 fetuses and 21 neonates). This sample was not taken in 2 cases (1 fetus and 1 neonate). In the tentorium IDH was graded as absent in 3 cases (1 fetus and 2 neonates), minimal in 2 (1 fetus and 1 neonate), focal in 20 (8 fetuses and 14 neonates), and diffuse in 28 cases (15 fetuses and 13 neonates). This sample was not taken in 2

cases (1 fetus and 1 neonate). As we only started taking parietal dura more recently, this sample was not taken in 19 cases (3 fetuses and 16 neonates). Hemorrhage in the parietal dura was absent in 9 cases (6 fetuses and 3 neonates), minimal in 8 (5 fetuses and 3 neonates), focal in 14 (8 fetuses and 6 neonates), and diffuse in 5 cases (3 fetuses and 2 neonates). Subdural hemorrhage was seen as a thin film over the convexities in 36 cases (16 fetuses and 20 neonates); this represents around 2 of 3 cases in fetuses (64%) and neonates (66.6%) in all cases with IDH. Brain hypoxia was graded as mild in 21 cases (12 fetuses and 9 neonates), moderate in 16 (10 in fetuses and 6 in neonates), and severe in 18 cases (3 in fetuses and 15 in neonates) (Fig. 5a–c).

In the fetal group (25 cases) there was severe hypoxia in 3 cases, moderate hypoxia in 10 cases, and mild hypoxia in 12 cases. All cases except one (in which the falx was not sampled) had falcine hemorrhage, diffuse in 21 and focal in 3 cases. All cases except 2 (in one of those tentorium was not sampled) had tentorial hemorrhage, diffuse in 15 and focal in 8 cases. Intradural hemorrhage within the parietal dura was seen in 16 cases; of these 16 cases, in only 3 cases was the IDH diffuse. In 3 cases the parietal dura was not sampled, and in the other 6 cases IDH was not seen. Thin film SDH was present in 16 cases, all of which had diffuse falcine IDH. All fetuses with severe brain hypoxia had SDH, as did half of those with moderate hypoxia and 8 with mild hypoxia.

In the neonatal group (30 cases), 15 cases had severe hypoxia, 6 had moderate hypoxia, and 9 had mild hypoxia. All cases had falcine hemorrhage (the falx was not taken in 1 case): diffuse in 22, focal in 5, and negative in 2 cases; in 1 case the falx was not sampled. Tentorial hemorrhage was present in 27 cases (in 13 as diffuse and in 14 as focal hemorrhage) and absent in 2 cases, and the tentorium was not sampled in 1 case. The 2 cases without falcine hemorrhage (either focal or diffuse) did not show SDH. Parietal dura was not sampled in 16 cases; when sampled, there was diffuse IDH in 2 cases, focal IDH in 5 cases, minimal IDH in 3 cases, and IDH was absent in 3 cases. Subdural hemorrhage was present in 20 cases. All babies with severe hypoxia and half of the babies with moderate hypoxia had SDH, but only 2 cases with mild hypoxia had

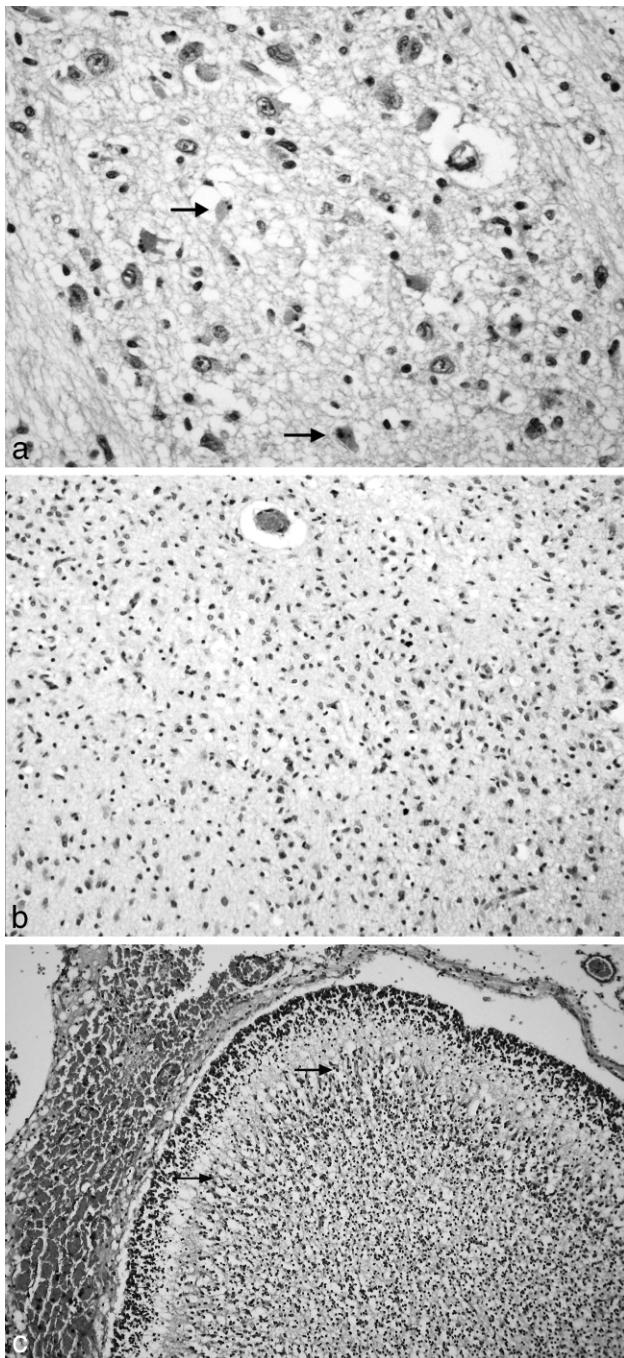


Figure 4. Hypoxia is considered mild (a) when there is edema and isolated pyknotic neurons (arrows) in the dentate nuclei, pons, and/or inferior olive nuclei (case 25: pons; hematoxylin and eosin [H&E], $\times 40$); moderate (b) when neuronal pyknosis and lysis is seen in the above areas and in the hippocampus (area CA1), usually with vascular congestion (case 11: hippocampus; H&E, $\times 20$); or severe (c) when there is widespread neuronal pyknosis and lysis (arrows) with endothelial swelling and reduplication in more advanced stages and frequently associated with bleeding in the cerebrum and pia matter (case 6: cerebellar cortex; H&E, $\times 20$).

SDH. The 2 neonates with mild hypoxia had both diffuse falcine and parietal dura IDH, while none of the other cases with mild hypoxia had this combination of IDH. Falcine hemorrhage was present in all SDH cases in which it was

sampled (19/20), as diffuse hemorrhage in 17 cases and focal hemorrhage in 2; when falcine hemorrhage was focal, there was also IDH in tentorium and parietal dura. Tentorial hemorrhage was present in 18 cases with SDH (9 diffuse IDH and focal in 9 cases); one case did not have tentorial hemorrhage (this had diffuse falcine IDH), and the tentorium was not sampled in the other case.

DISCUSSION

In the newborn, SDH associated with tentorial or falx tears represents one of the more classic forms of cranial birth trauma [4,5]. This can arise as a result of a combination of different circumstances: a large baby and a small birth canal, a compliant skull, rigid pelvic structures, labor that is too long or too brief (thus not allowing dilatation of the pelvic structures), abnormal presentations, or assisted delivery [5]. With improving obstetrical care this condition is more rarely seen. The tears of one or both leaves of the tentorium usually involve the free margin close to the junction with the falx [4]. Subdural hemorrhage has been described in hemophilic newborn infants and in thrombocytopenia. Tears in the bridging veins, which form short trunks passing directly from the brain to the dura mater [4,6], have also been blamed for SDH in cases of birth trauma. However, there is little evidence for this occurrence, and ruptured bridging veins are not generally identified upon autopsy. On the contrary, intact bridging veins can be identified if the skull is opened carefully (Fig. 1).

A recent review of 82 fetuses, infants, and toddlers with HIE in the absence of trauma found no evidence of SDH. These cases were searched over a 17-year period in 5 centers. The authors [7] did not differentiate between fetuses/neonates and older infants and children, but they only had 8 cases of intrauterine/delivery asphyxia and 1 case of prematurity, indicating that their routine practice does not seem to involve a large number of fetal and neonatal autopsies. The authors had not addressed in depth their criteria for diagnosing brain hypoxia, and no photographs were shown. Furthermore, there was no sampling of the dura in any of the cases reported. This paper concludes that HIE cannot lead to SDH [7]. Our combined practice covers areas with more than 30 000 births per year, and during 2007 we performed more than 300 postmortems of fresh fetuses >24 weeks in gestation and of neonates. The view of these investigators [7] is contrary to what we and others with large numbers of perinatal autopsies [8,15] recognize. The cases described in the current study had features of brain hypoxia (graded as mild in 21 cases; moderate in 16 cases; and severe in 18 cases), illustrated in Figure 4a through c. Diffuse IDH was seen in the falx of 21 fetuses (84%) and 22 neonates (73.3%), in the tentorium of 15 fetuses (60%) and 13 neonates (43.3%), and in the parietal dura of 3 fetuses and 2 neonates. Interestingly, SDH was seen in 16 fetuses (64%) and 20 neonates (66.6%) (see Fig. 5), always associated with diffuse falcine hemorrhage in the fetuses and in 19 of 22 neonates; one of the neonates had no dural samples and the other 2 neonates had focal posterior falx hemorrhage, one with diffuse tentorial hemorrhage and the other with focal tentorial hemorrhage.

Since Geddes and colleagues [16,17] demonstrated that

Table 1. Intradural hemorrhage, subdural hemorrhage (SDH), and hypoxia in 25 fetuses

| Case No. | Age (years) | Cause of death or significant pathology | Falx focal | Falx diffuse | Tent focal | Tent diffuse | PD focal | PD diffuse | SDH | Hypoxia | Brain weight ¹³ |
|----------|-------------|---|------------|--------------|------------|--------------|----------|------------|-----|---------|----------------------------|
| 15 | 33/40 | SD hematoma | — | + | — | + | — | + | + | S | nl |
| 51 | 35/40 | IVH, DIC | — | + | — | + | — | + | + | S | ↑ |
| 6 | 26/40 | IUGR, Breus mole | — | + | — | + | — | — | + | S | ↑ |
| 1 | 39/40 | SGA, IUGR, HFPR | — | + | — | + | + | — | + | M | ↑ |
| 3 | 33/40 | IUGR, HFPR, velamentous cord | — | + | + | — | ± | — | + | M | ↑ |
| 12 | 40/40 | Intrapartum asphyxia | — | + | — | + | + | — | + | M | nl |
| 18 | 37/40 | Intrapartum asphyxia | — | + | + | — | + | — | + | M | nl |
| 44 | 27/40 | HFPR, thrombi | — | + | — | + | + | — | + | M | ↑ |
| 28 | 27/40 | GBS, chorioamnionitis | — | + | — | + | + | — | + | m | ↑ |
| 34 | 36/40 | IUGR, HFPR, fibrin thrombi | — | + | — | + | ± | — | + | m | ↑ |
| 41 | 41/40 | Chorioamnionitis, HFPR | — | + | — | + | — | — | + | m | ↑ |
| 34 | 36/40 | IUGR, HFPR, fibrin thrombi | — | + | — | + | ± | — | + | m | ↑ |
| 49 | 39/40 | HFPR, cord accident | — | + | — | + | + | — | + | m | ↑ |
| 50 | 26/40 | IUGR, HFPR | — | + | + | — | ND | ND | + | m | ↑ |
| 53 | 40/40 | Fibrin thrombi | — | + | — | + | — | + | + | m | nl |
| 55 | 39/40 | Abruptio | — | + | + | — | ND | ND | + | m | nl |
| 2 | 41/40 | Chorioamnionitis, intrapartum death | — | + | — | + | + | — | — | M | nl |
| 33 | 38/40 | Hypercoiled cord with thrombi | + | — | + | — | ± | — | — | M | ↑ |
| 26 | 38/40 | Abruptio | + | — | ± | — | ± | — | — | M | ↑ |
| 31 | 40/40 | SGA, IUGR, hypoxia | — | + | — | + | — | — | — | M | ↑ |
| 32 | 41/40 | IUD hypoxia, hypercoiled cord | ND | ND | + | — | — | — | — | M | ↑ |
| 23 | 37/40 | Abruptio, HFPR | — | + | ND | ND | — | — | — | m | ↑ |
| 46 | 37/40 | Abruptio, VUE | + | — | + | — | — | — | — | m | ↑ |
| 48 | 36/40 | HFPR, IUGR, chorioamnionitis | — | + | — | + | ND | ND | — | m | ↑ |
| 52 | 36/40 | Abruptio | — | + | — | — | + | — | — | m | nl |

Tent indicates tentorium; PD, parietal dura; SD, subdural; —, absent; +, present; S, severe; nl, normal; IVH, intraventricular hemorrhage; DIC, disseminated intravascular coagulation; ↑, increased; IUGR, intrauterine growth restriction; SGA, small for gestational age; HFPR, high feto:placental ratio; M, moderate; ±, minimal; GBS, Group B streptococcus; m, mild; ND, not done; IUD, intrauterine death; VUE, villitis of unknown etiology.

the histological abnormality underlying all cases of SDH with brain edema in suspected cases of shaking in children under 1 year of age was hypoxic and not traumatic, the association between brain hypoxia and SDH has become a controversial subject [18]. Subdural hemorrhage in shaken baby syndrome is said to be a bilateral thin film of liquid blood, sometimes no more than 2 ml. These hemorrhages are common along the interhemispheric fissure and over the convexities [19], and sometimes they are missed on magnetic resonance imaging (MRI) [16,20]. All of our fetuses with SDH and 17 of our neonates with SDH had diffuse falcine hemorrhage, which is seen on MRI as a high signal in the interhemispheric fissure [21], further emphasizing the possible mechanism of oozing from fragile falcine capillaries as a source of the SDH over the convexities.

Geddes and colleagues [22] found IDH not related to trauma in 72% of children younger than 5 months of age and suggested that, in the great majority of the cases, hypoxia-induced alterations in the permeability of the vessels, exacerbated by severe elevations in central venous pressure, caused blood to leak into the extravascular compartment, resulting in IDH and SDH.

They suggested that critical to hypoxia causing IDH was a rise in central venous pressure. This may be transient or severe and prolonged. This situation may arise in labor: during the 2nd stage of labor, once the head is out in the birth

canal and the thorax and abdomen are still in the uterus, the baby is highly vulnerable because the maternal “pushing” pressure (Valsalva maneuver) is superimposed on the pressure produced by uterine contractions. Increased thoraco-abdominal pressures in the child will be transmitted directly to its cerebral venous system and therefore would predispose the child to venous hemorrhage [23,24]. If labor is prolonged the hypoxia will render the capillaries more susceptible to leaking and bleeding (see below). The rise in the central venous pressure would explain why bleeding starts in the richly vascularized falcine plexus and in the parasagittal area in the parietal dura [25]. The increase in central venous pressure also explains the percentage of retinal hemorrhages seen after normal delivery [26]. It has been postulated that the florid hemorrhages in several organs in cases of placental abruption are the consequence of sudden increases in fetal blood volume due to the compression of fetal venous return by the retroplacental clot [27]. We consistently see IDH and frequently thin film SDH in placental abruption. Four of the 5 cases of placental abruption presented here only had evidence of mild hypoxia, as babies die before developing substantial brain hypoxia. In these cases the main mechanism of bleeding would be the increase in central venous pressure. Cord compression and obstruction may represent another example of transient increase in venous pressure, and both situations were

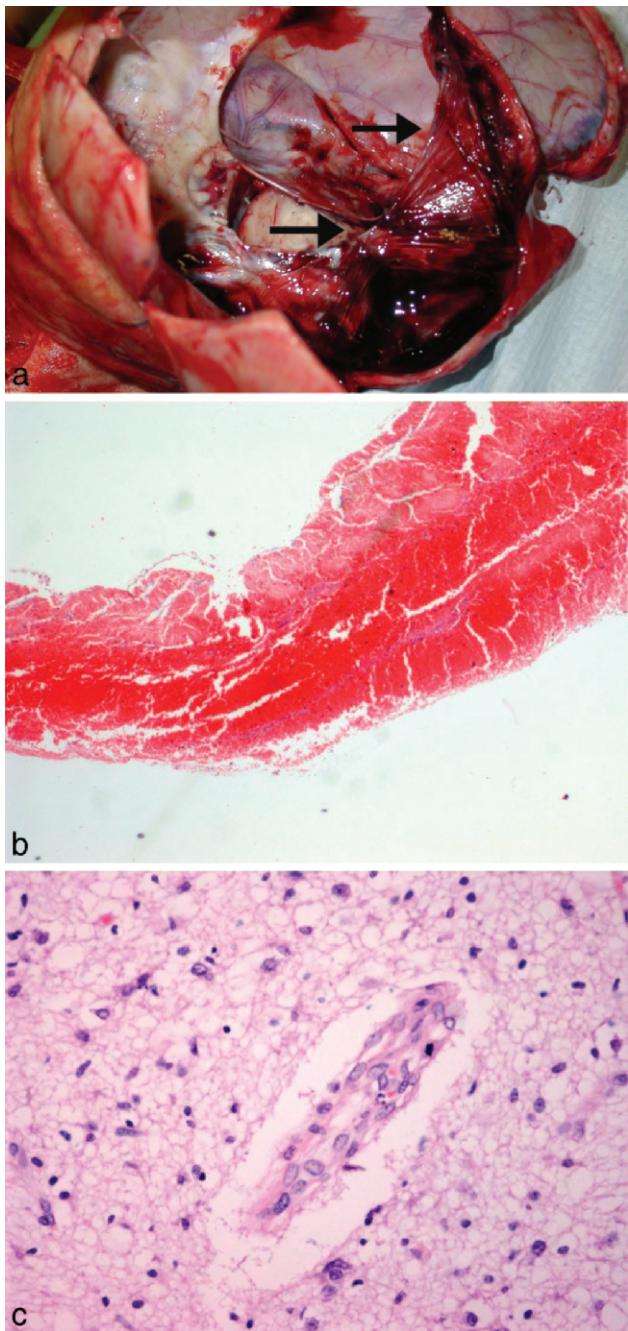


Figure 5. Case 7 showing (a) hemorrhages were clearly seen in the tentorium and posterior falx when inspected in situ (arrows). (b) Histology confirmed the presence of diffuse hemorrhages in the dural membranes (hematoxylin and eosin [H&E], $\times 10$). (c) Severe hypoxia with widespread neuronal pyknosis and lysis with endothelial reduplication was seen in the pons, cerebellum, and medulla oblongata (H&E, $\times 4$).

identified in several of our intrauterine deaths before labor. The lack of increased central venous pressure would explain why not all cases of brain hypoxia present with IDH/SDH. A more systematic study is required to elucidate the cause of IDH and SDH in cases of abruption with increased central venous pressure but very few signs of brain hypoxia.

The brain weight was increased in 18 fetuses and 15 neonates. In 1 case the weight was in the upper limit of

normality. Increased brain weight as a marker of edema and early hypoxia was present in 9 fetal cases; in 3 other cases the brain weight was within normal limits, and we cannot completely rule out autolytic artifact due to intrauterine death. However, 2 of those cases involved intrauterine death due to abruption, in which the increased venous pressure due to the retroplacental clot appears to be the main mechanism of bleeding. Other factors, not involving increased pressure, including inflammation and hemorrhagic disorders, may have been involved in the 21 fetuses or neonates who did not have an increase in brain weight. In the neonatal group only 1 case with SDH and early hypoxia had a normal brain weight (a baby with acinar dysplasia). Two cases with normal brain weight, early hypoxia, and IDH, but not SDH, had an infection, which may have played a substantial role in the development of IDH.

We recently described the combined approach to examining the pediatric central nervous system, using MRI with T2 weighted images at autopsy, and demonstrated the occurrence and associations between IDH, SDH, and hypoxia in this age group [21]. As in the fetus and neonate cases described in the present study, the SDH in the older group was usually of small volume and was more commonly seen as a thin film on the occipital convexity of the cerebral hemispheres or as a small infratentorial SDH. Histological examination of the dural folds revealed that the blood leaked from dural vascular channels. In those cases in which the IDH was diffuse, this occupied the whole thickness of the falx cerebri and/or tentorium and eventually became subdural. Our findings indicated that, in the absence of trauma, the origin of this bleeding was in the vascular plexus of the falx cerebri and tentorium cerebelli. A ruptured tentorium in 1 case and likely torn bridging veins in another case with much more severe hemorrhage than a thin film contributed to the bleeding in these cases associated with birth trauma. In the cases with HIE and intraventricular bleeding it is likely that the blood occupying the subarachnoid space floods into the subdural space at the level of the cisterna magna, adding another source for the SDH.

In our experience, IDH is most prominent or is only present in the posterior falx. This can be explained by the presence of a rich venous plexus in the posterior third of the falx cerebri and, within this, in the inferior part [28]. This falcine venous plexus always communicates with the inferior sagittal sinus, but in 63% of cases it also communicates with the superior sagittal sinus [28]. In most of our cases IDH was also common in the free anterior border of the tentorium cerebelli, where a venous plexus connects the straight sinus with the left and right transverse sinuses [29].

Two studies [30,31] using MRI to investigate the frequency of silent SDH in term live-born infants as a result of delivery have recently been published. The 1st study [30] demonstrated 9 asymptomatic SDH among more than 100 scanned neonates, 6 of whom were associated with the use of ventouse. The SDH was most often infratentorial, all cases had resolved after 4 weeks, and the babies had normal neurological examinations. The 2nd study [31] found a prevalence of 19% of asymptomatic intracranial hemorrhages in normal vaginal deliveries (16 SDH, 2 subarach-

Table 2. Intradural hemorrhage, subdural hemorrhage (SDH), and hypoxia in 30 neonates

| Case | Age | Cause of death or significant pathology | Falx focal | Falx diffuse | Tent focal | Tent diffuse | PD focal | PD diffuse | SDH | Hypoxia | Brain weight ¹⁴ |
|------|-----------------|---|---------------|-----------------|---------------|-----------------|-------------|---------------|-----|---------|-------------------------------|
| 5 | 14 hours | Intrapartum asphyxia | — | + | — | + | + | — | + | S | nl |
| 7 | 3 days | HIE, HFPR | — | + | — | + | + | — | + | S | ↑ |
| 8 | 2 days | HIE, IVH | — | + | + | — | ND | ND | + | S | nl |
| 9 | 7 days (35/40) | FMH, DIC, HIE | — | + | — | + | + | — | + | S | nl |
| 16 | 1 day | Rupture tentorium | — | + | — | + | ND | ND | + | S | ↑ |
| 17 | 2 day | HIE | ND | ND | ND | ND | ND | ND | + | S | ↑ |
| 19 | 1 day | HIE, rupture vertebral disc 6 | — | + | — | + | ND | ND | + | S | nl |
| 24 | 1 day | HIE | — | + | — | + | ND | ND | + | S | nl |
| 27 | 4 days | HIE | + | — | — | + | + | — | + | S | ↑ |
| 29 | 5 days | HIE, IVH | — | + | + | — | ND | ND | + | S | ↑ |
| 35 | 1 day | HIE | — | + | + | — | ND | ND | + | S | ↑ |
| 36 | 2 day | HIE | — | + | + | — | ND | ND | + | S | ↑ |
| 37 | 3 day | HIE | — | + | + | — | ND | ND | + | S | ↑ |
| 42 | 4 weeks (25/40) | Congenital CMV, microcephaly | — | + | + | — | ± | — | + | S | nl |
| 43 | 17 days (42/40) | HFPR, HIE | — | + | — | + | — | — | + | S | nl |
| 11 | 6 days | SGA, HIE, microcephaly | — | + | — | + | — | + | + | M | nl |
| 20 | 3 days (24/40) | IVH | — | + | + | — | — | — | + | M | nl |
| 40 | 1 day | Lung hypoplasia, congenital pneumonia | + | — | + | — | ± | — | + | M | nl |
| 14 | 1 hour | Intrapartum asphyxia, T 21, cord coil | — | — | — | + | + | — | — | M | nl |
| 13 | 18 hours | HIE, abruption | — | + | — | + | ND | ND | — | M | ↑ |
| 39 | 1 day | Congenital pneumonia | — | + | + | — | ND | ND | — | M | ↑ |
| 25 | 5 hours | Acinar dysplasia | — | + | — | — | ND | ND | + | m | nl |
| 45 | 6 hours | Intrapartum trauma, hypovolemic shock | — | + | + | — | — | + | + | m | ↑ |
| 4 | 3 days | HFPR, post-term | + | — | ± | — | ± | — | — | m | ↑ |
| 10 | 13 days | SUDI | — | + | + | — | ND | ND | — | m | ↑ |
| 21 | 5 days | SUDI (withdraw symptoms) | — | + | — | — | ND | ND | — | m | ↑ |
| 22 | 6 days | CHD | — | — | — | + | ND | ND | — | m | ↑ |
| 38 | 1 day | GBS pneumonia | — | + | — | + | + | — | — | m | nl |
| 47 | 1 day | GBS pneumonia | + | — | + | — | — | — | — | m | nl |
| 54 | 19 days | Bilateral lung hemorrhage | + | — | + | — | ND | ND | — | m | nl/↑ |

Tent indicates tentorium; PD, parietal dura; —, absent; +, present; S, severe; nl, normal; HIE, hypoxic ischemic encephalopathy; HFPR, high feto:placental ratio; ↑, increased; IVH, intraventricular hemorrhage; ND, not done; FMH, feto maternal hemorrhage; DIC, disseminated intravascular coagulation; CMV, cytomegalovirus; ±, minimal; M, moderate; SGA, small for gestational age; m, mild; SUDI, sudden unexpected death in infancy; CHD, congenital heart disease; GBS, Group B streptococcus.

noid, and 6 parenchymal hemorrhages). As in many of our cases, the SDH was infratentorial and over the occipital lobe.

Other convincing evidence that HIE and SDH are related is shown by other authors [32] who have used carbon dioxide asphyxiation in rats to demonstrate the occurrence of a variety of cranial hemorrhages that were prominent in the dura, thus confirming that the IDH appears to be a consequence of the hypoxia/asphyxia process. Hauser and colleagues [32] suggested that the hemorrhages develop in the dyspnea phase of the asphyxia and are associated with a temporary rise in blood pressure. Kibayashi and colleagues [10] described the occurrence of increased density of the tentorium on postmortem cranial computed tomography in 4 children. This was originally interpreted as corresponding to a subarachnoid hemorrhage. At autopsy, none of the children showed head injuries. The tentorium was thick and congested in all of them, and histology revealed the presence of IDH. Interestingly, “pseudo-subarachnoid hemorrhage,” described as increased density of the tentorium on computed tomography scan, has been described in comatose children with brain swelling due to

HIE [33]. Other investigators have also shown the presence of SDH and intracranial hemorrhages in children with congenital heart disease and in the setting of nontraumatic brain hypoxia [34]. More recent experimental research has shown that hypoxia induces cerebral microvascular changes in permeability and tight junctions [35]. More specifically, the expression of claudin-5, a key component of tight junctions between neural endothelial cells, is a target molecule for hypoxia. Experiments conducted *in vivo* revealed that claudin-5 molecules were present in normoxia but were significantly reduced in hypoxic conditions [35]. The authors of this latter study also demonstrated that hypoxia induces a breakdown of claudin-5 molecules in the microvasculature of the retina. This indicates that hypoxia may also play a role in the etiology of some retinal hemorrhages.

CONCLUSION

The cases described here seen in our routine practice show that IDH is a frequent finding in fetal, perinatal, and

neonatal postmortems in the context of brain hypoxia. When present, the IDH is always more prominent in the posterior falx and tentorium as a result of the existence of 2 venous plexuses at these levels. It seems that there is a clear correlation, particularly in neonates, between the degree of hypoxia and the extent of IDH and the presence of SDH, such that all babies with severe hypoxia had falcine IDH (diffuse in 87% of cases), and all had SDH. Bleeding in the parietal dura mater starts near the parasagittal sinus. If the bleeding is diffuse, this appears to be a more ominous sign, which tends to develop when hypoxia is more severe or prolonged. A diffuse IDH will eventually damage the weak plane of the dural border cell layer between the arachnoid and the dura and give rise to SDH. The cases described from our routine practice show that hypoxic damage to immature blood vessels is related to IDH and SDH, and these cases provide evidence for a causal relationship between HIE and the development of IDH and SDH in fetal life and in neonatal life, particularly when associated with transient or sustained rises in central venous pressure. We would encourage our colleagues to routinely sample the falx (posterior, middle, and anterior), tentorium, and parietal dura in all nonmacerated >24 week-gestation fetuses and neonates. As other factors (particularly in the cases with mild hypoxia) are likely to be important in the development of IDH, research should be undertaken into the different mechanisms involved in IDH/SDH, looking at different postnatal ages, focusing on differences in cranial physiology once the skull bones fuse. This research should also inquire into the causes and mechanisms in cases of brain hypoxia without IDH and the relevance of IDH in intrauterine death in macerated fetuses (more than 24 hours before delivery).

REFERENCES

- Gilbert-Barness E, Debich-Spicer DR. Central nervous system. In: *Handbook of Pediatric Autopsy Pathology*. Totowa, NJ: Humana Press, 2005;362.
- Haines DE. On the question of the subdural space. *Anat Rec* 1991; 230:3–21.
- Haines DE, Harkey HL, Al-Mefty O. The “subdural” space: a new look at an outdated concept. *Neurosurgery* 1993;32:111–120.
- Larroche JC. Fetal and perinatal brain damage. In: Wigglesworth JS, Singer DB, eds. *Textbook of Fetal and Perinatal Pathology*. Boston: Blackwell Scientific Publications, 1991;807–842.
- Volpe JJ. *Neurology of the Newborn*. Philadelphia: WB Saunders Company, 1981.
- Yamashima T, Friede RL. Why do bridging veins rupture into the virtual space? *J Neurol Neurosurg Psychiatr* 1984;47:121–127.
- Byard RW, Blumbergs P, Rutty G, et al. Lack of evidence for a causal relationship between hypoxic ischemic encephalopathy and subdural hemorrhage in fetal life, infancy and early childhood. *Pediatr Dev Pathol* 2007;10:348–350.
- Cohen M, Cox P, Kiho L, et al. Lack of evidence for a causal relationship between hypoxic ischemic encephalopathy and subdural hemorrhage in fetal life, infancy and early childhood. A response. *Pediatr Dev Pathol* 2007;10:500–501.
- Leary T. Subdural or intradural hemorrhages? *Arch Pathol Lab Med* 1939;28:808–820.
- Kabayashi K, Shojo H, Sumida T. Dural hemorrhage of the tentorium on postmortem cranial tomographic scans in children. *Forensic Sci Int* 2005;154:206–209.
- Larroche JC. Fetal and perinatal brain damage. In: Wigglesworth JS, Singer DB, eds. *Textbook of Fetal and Perinatal Pathology*. Boston: Blackwell Scientific Publications, 1991;807–842.
- Squier W. *Pathology of Fetal and Neonatal Brain Damage: Identifying the Timing in Acquired Damage to the Developing Brain. Timing and Causation*. London: Arnold, 2002.
- Singer DB, Sung CR, Wigglesworth JS. Fetal growth and maturation: with standards for body and organ development. Means and standard deviations of weights and measurements of liveborn infants. In: Wigglesworth JS, Singer DB, eds. *Textbook of Fetal and Perinatal Pathology*, 2nd ed. Boston: Blackwell Science Publications, 1998;28.
- Stocker JT, Dehner LP. *Pediatric Pathology*, Vol. 2. Philadelphia: J.B. Lippincott, 1992.
- Smith C, Bell JE, Keeling JW, Risdon RA. Dural haemorrhage in nontraumatic infant deaths: does it explain the bleeding in “shaken baby syndrome”? A response. *Neuropathol Appl Neurobiol* 2003;29: 411–413.
- Geddes JF, Hackshaw AK, Vowles GH, Nichols CD, Whitwell HL. Neuropathology of inflicted head injury in children. I. Patterns of brain damage. *Brain* 2001;124:1290–1298.
- Geddes JF, Vowles GH, Hackshaw AK, Nichols CD, Scott IS, Whitwell HL. Neuropathology of inflicted head injury in children. II. Microscopic brain injury in infants. *Brain* 2001;124:1299–1306.
- Geddes JF, Whitwell HL. Inflicted head injury in infants. *Forensic Sci Int* 2004;146:83–88.
- Gerber P, Coffman K. Non accidental head trauma in infants. *Child’s Nerv Syst* 2007;23:499–507.
- Hart BL, Dudley MH, Zumwalt RE. Postmortem cranial MRI and autopsy correlation in suspected child abuse. *Am J Forensic Med Pathol* 1996;17:217–224.
- Cohen MC, Whitby E. Hypoxia, intradural hemorrhage and subdural bleeding in the pediatric and perinatal post-mortem: Are they related? A study combining the use of autopsy and post mortem magnetic resonance. In: British Association in Forensic Medicine, Winter Meeting, Bath, United Kingdom, November 24, 2007.
- Geddes JF, Tasker RC, Hackshaw AK, et al. Dural hemorrhage in non-traumatic infant deaths: does it explain the bleeding in “shaken baby syndrome”? *Neuropathol Appl Neurobiol* 2003;29:14–22.
- Geddes JF, Talbert DG. Paroxysmal coughing, subdural and retinal bleeding: a computer modeling approach. *Neuropathol Appl Neurobiol* 2006;32:625–634.
- Bakker PCA, Kurver PHJ, Kuik DJ, Van Geijn HP. Elevated uterine activity increases the risk of fetal acidosis at birth. *Am J Obstet Gynecol* 2007;193:313.e1–313.e6.
- Fox R, Walji A, Mielke B, et al. Anatomic details of intradural channels in the parasagittal dura: a possible way for flow of cerebrospinal fluid. *Neurosurgery* 1996;39:84–91.
- Emerson MV, Pieramici DJ, Stoessel KM, Berreen JP, Gariano RF. Incidence and rate of disappearance of retinal hemorrhage in newborns. *Ophthalmology* 2001;108:36–39.
- Morrison JE. Foetal and neonatal pathology. (1970). Cited in: JS Wigglesworth, DB. Singer, *Pathology of Intrapartum and Early Neonatal Death. Textbook of Fetal and Perinatal Pathology*, 2nd ed. Boston: Blackwell Science Publications; 1998;251–268.
- Tubbs RS, Loukas M, Louis RG Jr, et al. Anatomy of the falcine venous plexus. *J Neurosurg* 2007;107:155–157.
- Kaplan HA, Browder J, Krieger AJ. Venous channels within the intracranial dural partitions. *Radiology* 1975;115:641–645.
- Whitby EH, Griffiths PD, Rutter S, et al. Frequency and natural history of subdural haemorrhages in babies and relation to obstetric factors. *Lancet* 2004;363:846–851.
- Looney Ch B, Smith JK, Merck LH, et al. Intracranial hemorrhage in asymptomatic neonates: prevalence on MR images and relationship to obstetric and neonatal risk factors. *Radiology* 2007;242:535–541.
- Hauser R, Jankowski Z, Gos T, Krzyżanowski M. Hemorrhages in head tissues during the asphyxiation process. *Forensic Sci Int* 2001; 124:235–236.
- Avrahami E, Katz R, Rabin A, Friedman V. CT diagnosis of non-traumatic subarachnoid haemorrhage in patients with brain edema. *Eur J Radiol* 1998;28:222–225.
- McQuillen PS, Barkovich AJ, Hamrick EGS, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. *Stroke* 2007;38:736–741.
- Koto T, Takubo K, Ishida S, et al. Hypoxia disrupts the barrier function of neural blood vessels through changes in the expression of claudin-5 endothelial cells. *Am J Pathol* 2007;170:1389–1397.