

# The “Shaken Baby” syndrome: pathology and mechanisms

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**Abstract** The “Shaken Baby” syndrome (SBS) is the subject of intense controversy; the diagnosis has in the past depended on the triad of subdural haemorrhage (SDH), retinal haemorrhage and encephalopathy. While there is no doubt that infants do suffer abusive injury at the hands of their carers and that impact can cause catastrophic intracranial damage, research has repeatedly undermined the hypothesis that shaking per se can cause this triad. The term non-accidental head injury has therefore been widely adopted. This review will focus on the pathology and mechanisms of the three physiologically associated findings which constitute the “triad” and are seen in infants suffering from a wide range of non-traumatic as well as traumatic conditions. “Sub” dural bleeding in fact originates within the deep layers of the dura. The potential sources of SDH include: the bridging veins, small vessels within the dura itself, a granulating haemorrhagic membrane and ruptured intracranial aneurysm. Most neuropathologists do not routinely examine eyes, but the significance of this second arm of the triad in the diagnosis of Shaken Baby syndrome is such that it merits consideration in the context of this review. While retinal haemorrhage can be seen clinically, dural and subarachnoid optic nerve sheath haemorrhage is usually seen exclusively by the pathologist and only rarely described by the neuroradiologist. The term encephalopathy is used loosely in the context of SBS. It may encompass anything from vomiting, irritability, feeding difficulties or floppiness to seizures, apnoea and fulminant brain swelling. The spectrum of brain pathology associated with retinal and

subdural bleeding from a variety of causes is described. The most important cerebral pathology is swelling and hypoxic–ischaemic injury. Mechanical shearing injury is rare and contusions, the hallmark of adult traumatic brain damage, are vanishingly rare in infants under 1 year of age. Clefts and haemorrhages in the immediate subcortical white matter have been assumed to be due to trauma but factors specific to this age group offer other explanations. Finally, examples of the most common causes of the triad encountered in clinical diagnostic and forensic practice are briefly annotated.

**Keywords** Shaken baby syndrome · Subdural haemorrhage · Retinal haemorrhage · Infant encephalopathy · Axonal injury · Subcortical haemorrhage · Cerebral venous sinus thrombosis · Subpial haemorrhage

## The triad

Shaken Baby syndrome is generally, but not exclusively, diagnosed in infants under 1 year of age, the peak age being 10–16 weeks. Boys represent 65% of cases and are younger at presentation [153, 158]. The diagnosis is characterised by the triad of retinal haemorrhage (RH), thin-film bilateral or multifocal subdural haemorrhage (SDH) and encephalopathy. A mechanistic explanation and pathological description of the three components of the triad will be discussed in the context of our current understanding of the anatomy and physiology of the brain and its coverings in the first year of life. Not all babies presenting with the triad will die, and neuroradiology rather than neuropathology is the cornerstone of diagnosis in babies who survive. Interpretation of imaging depends on

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understanding the neuropathology and wherever possible reference will be made to the correlation of pathological with radiological appearances.

### The origins and history of the “Shaken Baby” hypothesis

In the early 70s Guthkelch [63] and later Caffey [18] suggested that this triad could result from whiplash or shaking injury. Guthkelch, noting that not all babies with SDH had external marks of injury to the head, suggested that shaking rather than striking the infant might be the cause. Extrapolating from the results of contemporaneous biomechanical studies on adult primates, he suggested that the whiplash of shaking may shear bridging veins leading to bilateral thin-film subdural haemorrhage, which he noted was quite unlike the unilateral subdural bleeding typically described in adults. He wrote “Moreover, since one would expect that the child is often grasped more or less symmetrically by chest or limbs the rotation-acceleration strains on the brain would tend to occur fairly symmetrically also, in an anteroposterior direction. This may be the reason why infantile subdural haematoma is even more often bilateral—for example in 14 of 18 cases (78%) of my earlier series—than subdural haematoma in adults for which the proportion of bilateral cases does not exceed 50%”.

Duhaime studied both biomechanical and clinical aspects of Shaken Baby syndrome and wrote perhaps the most exhaustive studies and reviews of the condition in the late 80s. In a review of 57 patients with suspected shaking injury, all 13 who died had evidence of impact head trauma. Eight had skull fractures and bruises, five had externally visible scalp bruises and six had “contusions and lacerations” of the brain. Her biomechanical studies led her to conclude that the acceleration force generated by impact exceeded that caused by shaking by a factor of 50. The following year, Duhaime wrote “it is our opinion, based on the clinical data and the studies outlined, that the “Shaken Baby syndrome” is a misnomer, implying a mechanism of injury which does not account mechanically for the radiographic or pathological findings” [38].

Others have repeated these biomechanical studies and shown that an adult shaking a dummy cannot generate the forces considered necessary to produce subdural bleeding [31, 125]. In contrast, Roth, using finite element modelling of the material properties of bridging veins and the angular velocities measured by Prange [125], calculated that shaking could generate sufficient force to cause BV rupture. The peak force considered necessary to do so in this model was equivalent to that generated by a 1.25 feet fall [133].

Duhaime devised an algorithm for the diagnosis of non-accidental injury on which many subsequent studies have been based. It assumes that a short fall cannot explain the triad: “falls clearly described as less than 3 feet in height were designated as “trivial” trauma and when given as an explanation of a high-force injury, along with variability in the history or a developmentally incompatible scenario, non-accidental injury was presumed” [39]. Clinical and biomechanical studies have demonstrated the error in this assumption; there are many reports of babies suffering intracranial bleeding, sometimes fatal, after low falls [3, 55, 66, 168] and laboratory studies have shown that the forces generated by even a 25-cm fall are twice those generated by maximal shaking and impact onto a soft surface [147].

An exhaustive study of the published literature over a period of 32 years found only 54 cases of confessed shaking, of which only 11 had no evidence of impact and could be considered pure shaking. There are only three published reports of witnessed shaking; all three infants were already collapsed before the shaking event [91, 140].

Since the initial work of Guthkelch, the importance of “rotational forces” as the mechanism of intracranial injury has been emphasised. Many have mistakenly assumed that rotational forces require shaking. There is no doubt that rotation is a potent cause of intracranial injury, but virtually any impact to the head will also cause rotation because the head is hinged on the neck. Holbourn wrote in 1943 “rotations are of paramount importance” and “If the head is so well fixed that it cannot rotate at all when it receives a blow there will be no rotational injury” [70]. It is reasonable to assume that the infant with a weak neck would be even more vulnerable to hinging of the head on the neck than the adult with developed musculature and full head control. While rotational acceleration/deceleration is important in causing brain damage, there is absolutely no evidence that it requires shaking or swinging. While shaking does cause rotational forces, their magnitude is insufficient to cause intracranial injury; biomechanical studies have shown that impact and falls cause far greater rotational forces [31, 37, 125].

Neuropathological studies have had enormous implications for the shaking hypothesis. Geddes showed that brain swelling and HII were virtually universal in babies thought to have suffered non-accidental injury, but very few had traumatic axonal injuries. Where, the present axonal injury was at the craniocervical junction [57, 58]. The clinical implication is that the signs of encephalopathy are due to hypoxia and brain swelling. As the pace at which swelling occurs is variable, there is an opportunity for a “lucid interval”, in contrast to immediate concussion as expected from diffuse axonal injury. In the majority of infants with the triad, the brain damage is non-specific and unless there

is injury at the craniocervical junction, the diagnosis of shaking can be no more than speculation.

In 2009 the American Academy of Paediatricians, followed in early 2011 by the UK Crown Prosecution Service, accepted that the term Shaken Baby syndrome should be dropped because it did not exclusively explain the triad of findings, although confessions supported the role of shaking. The term non-accidental head injury (NAHI) has since been widely adopted [27, 32].

While shaking is no longer a credible mechanism for NAHI, there remains no doubt that inflicted head injury does occur, but its clinical recognition remains problematic. “There is no diagnostic test for inflicted brain injury, the diagnosis is made on a balance of probability and after careful exclusion of other possible causes of the clinical presentation” [99] and “there is no absolute or gold standard by which to define NAHI” [69].

In arguing “The Case for Shaking” Dias [35] began with the statement “Unfortunately, nobody has yet marshalled a coherent and comprehensive argument in support of shaking as a causal mechanism for abusive head injury” and concluded “the consistent and repeated observation that confessed shaking results in stereotypical injuries that are so frequently encountered in AHT-and which are so extraordinarily rare following accidental/impact injuries-IS the evidentiary base for shaking”.

This very definite statement indicates that, 40 years after it was first proposed, the shaking hypothesis now rests upon confession evidence.

How reliable are confessions? Clinical evidence of impact is found in up to 63% of confessions of shaking only [35] and when imaging evidence is considered “No correlation was found between repetitive shaking and SDH densities.” [2]. This review will take a pragmatic approach, addressing the evidence provided by detailed examination of the tissue in babies who manifest the triad.

### Brain examination in the triad

The foregoing discussion illustrates the considerable responsibility for the pathologist who may be presented with a clinical diagnosis based on dubious criteria, the reliability of which will depend on the extent to which other possible causes have been excluded.

The differential diagnosis of a baby with the triad is wide and includes birth difficulties, coagulopathy, arterial occlusive disease and venous thrombosis, metabolic and nutritional disorders, infections, hypoxia–ischaemia (e.g. airway, respiratory, cardiac, or circulatory compromise) and seizures. Multifactorial and secondary cascades are common, for example “trivial trauma” in the context of predisposing or complicating medical conditions such as

prematurity, pre-existing subdural haemorrhage, coagulopathy and infectious or post-infectious condition (e.g. recent vaccination). Death occurring within the context of a recent vaccination should be reported to the appropriate agencies.

A complete and thorough review of current and past medical history involving scrutiny of perinatal and neonatal records, laboratory tests and the clinical management of the child is required. If the baby dies the gold standard is a thorough and complete autopsy where neuropathology has a key role.

Many alternative diagnoses may not have been considered or test results may not be available before pathological opinion is required. Once pathological conclusions have been reached, they can be assessed in the context of all the available information.

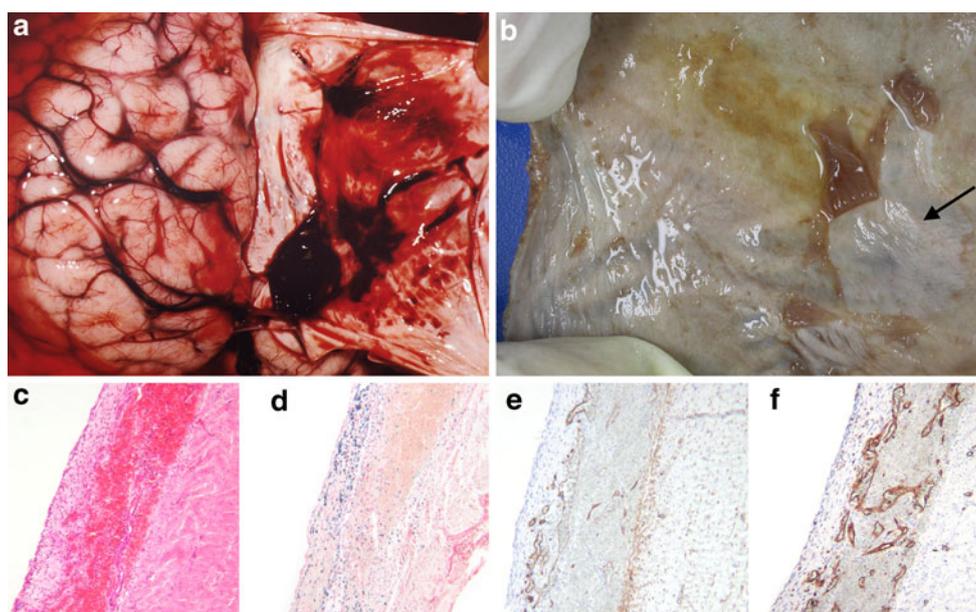
Neuropathologists may not have the advantage of attending the autopsy to see for themselves the evidence from other sites and particularly to be present when the skull is opened to identify bleeding and its potential sources. The brain may be received whole and fixed; if giving a second opinion, only blocks and slides may be submitted. Residual fixed brain slices should be requested; they frequently yield evidence that may not have been appreciated on the first examination. In my experience, cortical veins and focal congestion or thrombosis are often overlooked. The dura and spinal cord are essential parts of the examination.

### Sampling

Standard representative blocks should be taken from all brain areas and all levels of the brainstem and spinal cord, with at least three blocks from each level of the brainstem and the cervical cord, to include nerve roots and dorsal root ganglia.

The dura must be carefully examined by naked eye as well as microscopically. Old, healing subdural membranes can be difficult to see with the naked eye as they form a thin, light brown and often uniform layer (Fig. 1b). The dural sinuses must be carefully examined and sampled. Intradural bleeding is the most common posteriorly, in the spongy tissue around the torcula, in the posterior falx and in the tentorium and these areas, as well as convexity dura, should be sampled.

Dura from the spinal cord is informative for two main reasons. First, unlike the cranial dura, it is not routinely stripped from the underlying arachnoid barrier membrane during autopsy. Foci of the normal *in vivo* apposition of these membranes, as well as minor bleeding into the subdural compartment may be seen in spinal dura (Fig. 2). Second, it is common for intracranial subdural blood to track into the spinal subdural compartment, and sometimes this blood is the only evidence of old subdural haemorrhage.



**Fig. 1** Healing subdural haemorrhage. **a** Fresh bleeding into a thin, healing subdural membrane. The dura has been lifted off the brain at autopsy. There is a large area of fresh bleeding on the arachnoid surface of the dura. A faint brown/yellow tinge at the edges indicates older bleeding. Female 10 months old with head trauma 3 weeks before death. **b** A thin, light brown membrane covers the deep dural surface. The membrane could easily be overlooked but where a small area has lifted its delicate nature can be appreciated as well as the contrast with the normal light grey dura beneath (*arrow*). Fifteen months baby with head trauma 4 weeks before death from inflicted

abdominal injury. **c** Male 3 months: H&E stained section showing fresh bleeding into a membrane on the subdural surface. The uniform pink dura is on the right side of the panel. **d** Perl's positive material is most abundant on the free edge of the membrane with fresh bleeding beneath. **e** CD 34 demonstrates vessels in the membrane crossing the underlying fresh haemorrhage and, at its junction with the dura. The dura shows finely speckled fibroblast staining. **f** CD31 highlights the wide, sinusoidal vessels within the membrane and straddling the fresh bleed. The dura itself is unstained. (c-f 4×)

## Staining methods

### Brain and spinal cord

As well as standard H&E stain, the most helpful stains for identifying subtle areas of early tissue damage are CD68 and  $\beta$ APP, which draw the eye to even the smallest collections of macrophages and damaged axons. Reticulin and CD34 stains demonstrate proliferating capillaries in damaged tissue, and reticulin is invaluable for demonstrating subpial bleeding. Endothelial markers CD31 and CD34 demonstrate reactive blood vessels; smooth muscle actin (SMA) is a useful adjunct in the detection of very early organisation of intravascular clot.

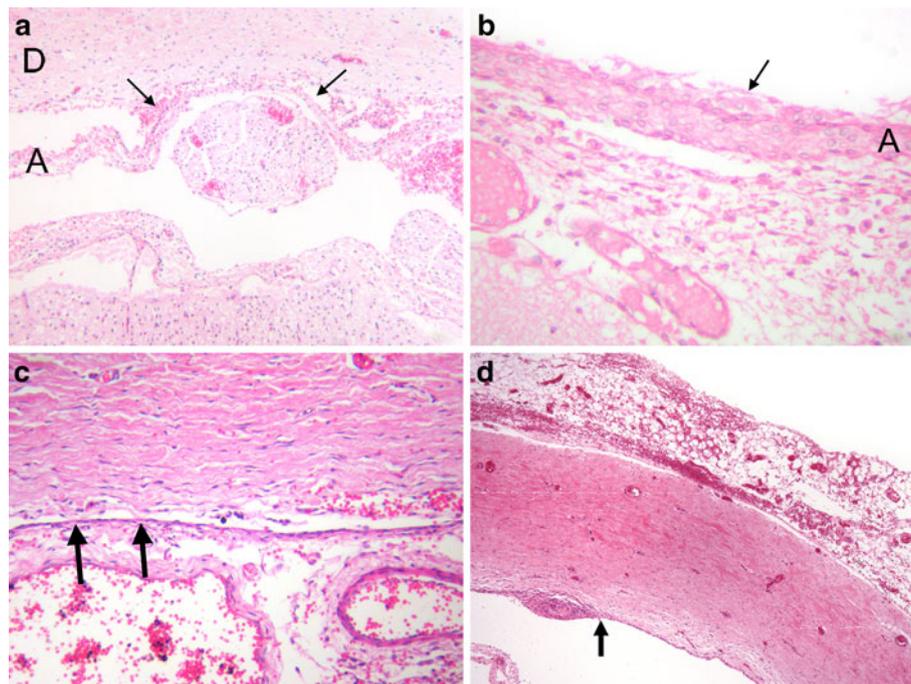
### Dura

A somewhat different panel of stains is required if subtle healing subdural membranes are to be identified. Both thin, early membranes and old-fibrosed membranes are hard to differentiate from normal dura with H&E alone. A recommended panel includes Perl's stain for iron, CD 68 for macrophages and an endothelial marker to show newly formed and reactive vessels. CD31 is preferred to CD34 as an endothelial marker, since the latter also labels

dural fibroblasts, making interpretation more difficult (Fig. 1c, d). Perl's stain indicates altered blood and previous haemorrhage, and is generally identifiable from 48 h after the bleed. Sometimes this stain is negative even when there appears to be a well-developed healing membrane. There are two explanations for this paradoxical finding: Perl's stain may be less reliable in certain fixation protocols and, rarely, CSF leaks promote development of a non-haemorrhagic but vascular subdural membrane [110]. Neurofilament stain demonstrates the luxuriant innervation of the infant dura; evidence of its involvement in the regulation of venous outflow from the brain and of functions as yet unknown, but clearly far more than just providing physical protection for the brain.

### Subdural haemorrhage

At the outset, it is important to appreciate the anatomical location of subdural bleeding, which, in fact, originates within the deep layers of the dura. The skull bones, periosteum and meninges develop by condensation from the same mesenchymal layer and the dura forms a single functional unit with the arachnoid barrier layer [98]. In life there is no subdural space; "the traditional concept of a



**Fig. 2** The dura-arachnoid interface. **a** Fetal spinal cord. The arachnoid (A) is being lifted off the dura (D) by fresh bleeding (arrows). There is a little fresh subarachnoid bleeding and the nerve root is congested (4 $\times$ ). **b** Fetal cranial arachnoid. The barrier layer is an avascular membrane (A). Above it loosely adherent flaky cells of the dural border layer are seen (arrow). The subarachnoid space is relatively cellular (10 $\times$ ). **c** Spinal cord. Several contact sites between

dura and arachnoid are indicated by arrows. Note fresh bleeding between the cells of the dural border layer at the right of the picture (10 $\times$ ). **d** Spinal dura showing adherent arachnoid cells (arrow). The dura is less vascular than the cranial dura. Note fresh bleeding into the epidural fat (4 $\times$ ) (c and d are from the spinal cord of a male baby of 4 months who died after prolonged seizures. There was no evidence of proximate trauma)

virtual, slit-like subdural space is in error” [53, 65]. When the dura is stripped from the brain surgically, at autopsy and by bleeding, the loosely adherent cells of the dural border layer are torn apart and an artificial space is created. A careful examination of the outer surface of the arachnoid membrane will reveal cellular remnants of the dural border cell layer. Similarly, adherent arachnoid cells can sometimes be identified on the deep dural layers. (Fig. 2)

### Distribution and patterns of dural and subdural haemorrhage

When a baby presents to hospital, it is often the radiological diagnosis of SDH that raises the question of NAHI and significantly influences subsequent management. The importance of this element of the triad places an onus on the pathologist to establish and describe the sources and nature of infant SDH.

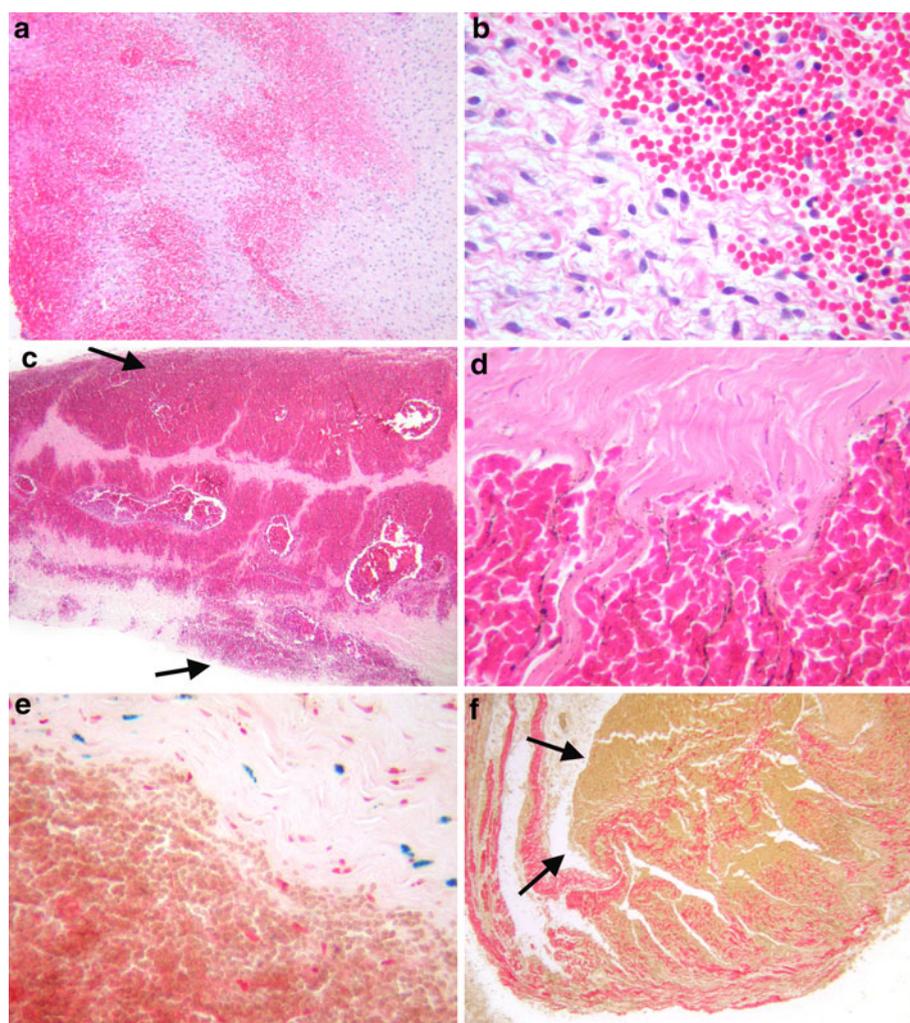
The typical pattern of subdural haemorrhage in babies with the triad is of a bilateral thin film over the cerebral convexities and in the posterior interhemispheric fissure [22, 40, 189].

The distribution of subdural blood is not a reliable indication of its cause. Rather, radiological studies have

demonstrated that the distribution is a function of age and that redistribution occurs by gravity and sedimentation [33, 47, 167]. MRI studies show spinal subdural haemorrhage in almost half of babies with intracranial subdural haemorrhage, sometimes in direct continuity with posterior fossa blood. The location in the most dependent spinal areas, dorsally at the thoracolumbar level, indicates gravitational redistribution [86]. The spinal dura extends beyond the dorsal root ganglia where it blends with the sheath of the nerve roots, allowing subdural blood to track out into them (see Fig. 10).

The bilateral widespread thin film distribution of infant SDH differs from the adult form, where subdural haemorrhage generally forms a unilateral localised mass within the convexity dura [63]. There are several potential explanations for this difference. First, the mechanism for SDH in an infant may be fundamentally different from that in an older child or an adult with a mature skull. Second, the infant dura is far less collagenised than the adult dura, and its fibroblasts are widely separated by a loose matrix (Fig. 3) allowing ready dispersion of blood. Finally, infant subdural haemorrhage is frequently not solid but “thin and easily tapped” [155, 167] allowing easy dispersion.

SDH does not need to be large or space occupying to cause clinical symptoms. Although the blood is physically



**Fig. 3** Intradural bleeding. **a–d** Dural bleeding at 20 weeks gestation and 20 months of postnatal life. **a, b** The foetal dura is cellular, with delicate, loosely interwoven fibroblast-like cells and little collagen. This allows ready dispersion of blood (foetus 20 weeks) (**a** 4 $\times$ , **b** 10 $\times$ ). **c, d** 20 month baby with acute demyelinating encephalomyelopathy with severe brain swelling but no trauma. There is extensive bleeding into the dura, most of it originating in the plexuses between the dural leaflets. In several areas, blood extends to the free edges of the dura (*arrows*). **d** The cells of the dura are less numerous than in the foetus, the dura consists largely of dense bands of collagen; in

**d** red cells are seen between these dense fibrous bands (**c** 2 $\times$ , **d** 10 $\times$ ). **e** There is fresh bleeding in the lower left of the panel but also many flecks of Perl's positive material between the fibres of the dura indicating much earlier bleeding, probably from birth. 5 month infant with sinus thrombosis. (Perl's stain 10 $\times$ ). **f** Infant of 3 months. Elastic van Gieson stain demonstrates intradural blood as yellow, standing out against the bright pink collagen of the dura. The fibres of the dura are split apart by fresh blood which is also spilling on to the dural surface (*arrows*) (4 $\times$ )

separated from the surface of the brain by the arachnoid barrier layer, it causes cerebral irritation, and clinical manifestations may occur without obviously raised intracranial pressure.

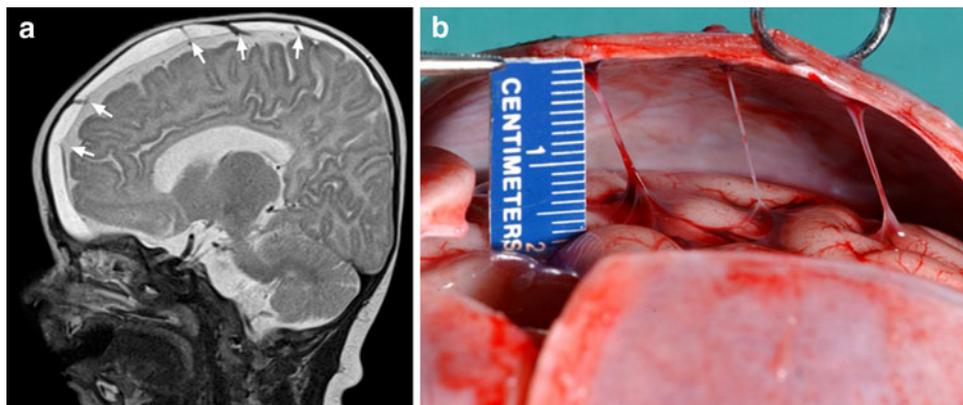
#### Autopsy identification of subdural haemorrhage

The volume of blood seen on scans may be very small, 2–3 ml of blood are sufficient for its radiological identification; between 1 and 80 ml (median 10 ml) was found in babies with blunt force injuries to the head [111]. This poses

a problem for the pathologist as this small volume of blood could readily be overlooked as the skull is opened and large vessels are cut, as they inevitably will be if special autopsy techniques are not employed. “At autopsy, the subdural hemorrhage may consist of only 2 to 3 ml of blood and may not be observed if the prosector does not personally inspect the subdural space as the calvarium is being removed. Extreme caution should be taken to not misinterpret as premortem subdural hemorrhage the blood draining from the dural sinuses when these are incised at autopsy” [22].

Needling the cisterna magna before opening the skull may identify extracerebral blood or fluid collections. In

**Fig. 4** Radiological and autopsy demonstration of bridging veins. **a** MRI: sagittal view demonstrating five bridging veins (*arrows*) crossing large extracerebral fluid collections in both the subarachnoid and subdural compartments. **b** By carefully opening the skull at autopsy with parasagittal cut it is possible to demonstrate the integrity of bridging veins



order to examine the bridging veins, the skull is opened by parasagittal cuts lateral to the superior sagittal sinus [82]. By carefully lifting the midline bony strip, the bridging veins can be visualised and any extracerebral blood and fluid identified before veins or sinuses are cut (Fig. 4). Some claimed to be able to establish the integrity of bridging veins by retrograde dye injection via the superior sagittal sinus [104, 154].

### Origin of subdural haemorrhage

The four most important potential sources of subdural bleeding are the bridging veins (BV), the dura itself, the vascular membrane of a healing subdural haemorrhage, and a ruptured intracranial aneurysm.

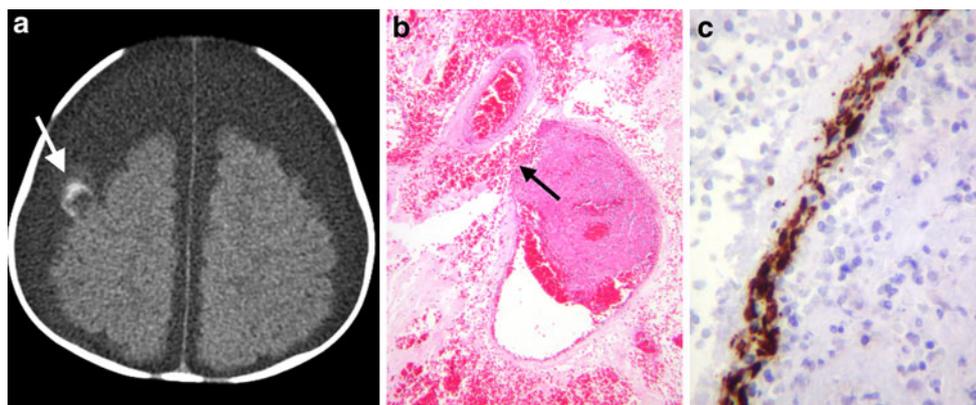
### Bridging veins

It is widely believed that subdural bleeding results from mechanical tearing of bridging veins [23]. However, it is extremely hard to find any pathological description of ruptured BV in infants with SDH. Cushing, describing his surgical and pathological observations in the newborn wrote “In two of the cases that I have examined I have satisfied myself that such ruptures were present. “A positive statement, however, cannot be given even for these cases, since the dissection and exposure, difficult enough under any circumstances, owing to the delicacy of the vessels, is the more so when they are obscured by extravasated blood”. We have not moved a long way on this issue in the last century. Voigt [171] described disruption of bridging veins in adults, but they were characterised by local subarachnoid bleeding, and he wrote “Most striking in these cases is the absence of a noteworthy subdural hematoma”. Duhaime [38] did not demonstrate BV rupture in her autopsied cases, but hypothesised that the point of bridging vein rupture is in the subarachnoid space, giving rise to both subarachnoid and subdural bleeding. Bell [9]

illustrates a thrombosed bridging vein which she described as the site of traumatic rupture, but venous thrombosis is common in hypoxic and ventilated infants and does not provide robust evidence of BV rupture. Maxeiner [105] claimed to demonstrate ruptured BV using autopsy dye injection studies. His images indicate that the dye is in the subarachnoid rather than the subdural compartment and his autopsy description of less than 5 ml of blood in the subdural space where “nearly all the parasagittal bridging veins were completely torn” suggests that his methods are unreliable. Unless the BV are visualised before brain removal, artefactual rupture at autopsy cannot be excluded.

Not only are there no convincing pathological examples of BV rupture associated with thin film subdural bleeding but also there are physiological and anatomical objections to this hypothesis. Bridging veins are few in number—about 8–11 each side—and carry high blood flow (Fig. 4). In a 6-month baby, nearly 260 ml of blood flows into the dural sinuses per minute and the majority of cortical blood flows via the parasagittal BV into the superior sagittal sinus, where flow rate is 9.2 cm per second in the infant [90, 160, 178]. It is clear that rupture of even a single BV will cause massive space occupying clot, not a thin film, and the bleeding will be at least partly subarachnoid [37]. The suggestion that BV are weak at their dural junction was derived from studies of four elderly patients [181]; in fact, this junction consists of a smooth muscle sphincter which controls cerebral venous outflow when intracranial pressure is increased, maintaining the patency of the cortical veins [7, 141, 166, 183].

There appear to be circumstances when large cortical veins may ooze blood. Cushing observed that subdural haemorrhage “may occur when too great strain has been put upon the vessels by the profound venous stasis of postpartum asphyxiation; just as in later months they may rupture under the passive congestion brought about by a paroxysm of whooping-cough or a severe convulsion” [33]. Imaging and pathological observation support the suggestion of venous leakage under tension; radiological



**Fig. 5** Leakage of red cells across distended and thrombosed vein walls. **a** CT scan. A tiny flare of blood (*white arrow*) within a wide extra-axial fluid collection suggests leakage from a bridging vein. 5 months infant with cortical vein thrombosis. **b** Thrombosed surface vein with fresh bleeding into adjacent subarachnoid space (4×). **c** The

vein wall indicated by an *arrow* in **b** is stained for smooth muscle actin and shows red cells which appear to be escaping between the cells of the vein wall into the surrounding subarachnoid space. Three month baby with cortical vein thrombosis who died 7 days after head trauma

observations occasionally show small bleeds associated with BV crossing dilated extracerebral spaces and pathology of severely congested and thrombosed surface veins shows leakage of red cells across them into the subarachnoid space. In both circumstances, the bleeding is predominantly subarachnoid. (Fig. 5)

#### The dura

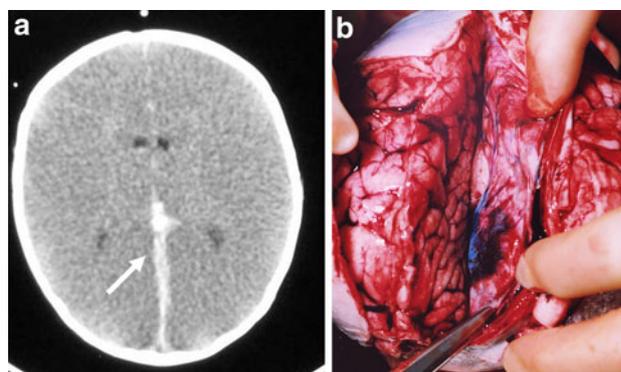
Intradural bleeding is common in the young infant and an almost universal finding at foetal and neonatal autopsy [28, 29, 59, 144, 149]. The anatomical and physiological basis for intradural bleeding in the infant has been discussed in detail [98]. In understanding the propensity for the infant dura to bleed, it must be borne in mind that the dura is not just a tough fibrous membrane providing physical support for the brain but it is the route of all venous outflow from the brain, via the dural sinuses.

The dura has two communicating vascular networks: the meningeal arteries, veins, and outermost periosteal plexus, which are superficially located, and the vascular plexus located between its periosteal and the meningeal leaflets, the remnant of a much more extensive network of the foetal dura [14]. The dense innervation of the dura is most abundant on the intradural sinuses and blood vessels. The dura also contains rounded fluid channels which may have a role in CSF uptake or monitoring [50, 120] and appears to be related both to age and to frequency and extent of intradural bleeding [148].

The dura at birth is very different from the dura after the end of the first year of life. At birth, the structure is of loosely arranged cells with a little collagen and the dural vascular plexuses and innervation are very much more extensive than in later life (unpublished observations); arachnoid granulations are not formed until about 7 months

of postnatal life [14, 118]. These continuing developmental features may all influence the predisposition of the young baby to dural haemorrhage in the first months of life.

The posterior falx and tentorium are frequent sites of bleeding in both the foetus and the young infant dying of natural causes [28, 29]. These are also the sites of the posterior interhemispheric haemorrhage, originally regarded as characteristic of SBS. This radiological sign is most likely to be due to intradural bleeding or congestion of the abundant venous sinuses which are part of the normal anatomy in this age group. It is impossible for either MRI or CT scans to distinguish between intradural and thin film subdural bleeding. Figure 6 illustrates the case of a baby who collapsed with brain swelling and febrile convulsions. Thin film interhemispheric haemorrhage was identified as subdural bleeding on scan but at autopsy the blood was entirely intrafalcine. The detailed anatomy of the infant dura questions the validity of the belief that posterior



**Fig. 6** Intrafalcine bleeding. **a** CT scan shows interhemispheric high signal which was interpreted as SDH. **b** Autopsy demonstrated all of the bleeding to be intradural in the posterior falx. Four months baby, sudden death with pyrexia and brain swelling. No evidence of trauma

interhemispheric bleeding is evidence of bridging vein rupture.

When it is extensive, intradural blood can almost always be seen seeping onto the subdural surface. Flecks of Perl's positive material, often extracellular and close to the walls of the sinuses may represent older, or birth-related bleeding (Fig. 3).

Subdural bleeding is often seen adjacent to the lateral recesses of the superior sagittal sinus at the vertex [170], the sites where arachnoid granulations will develop towards the end of the first year of life. The functions of arachnoid granulations remain unclear; their role in resorption of CSF under normal conditions had long been disputed [34]; there is ample evidence that CSF is resorbed from cranial and spinal nerve roots [80, 186]. Arachnoid granulations have mechanoreceptors and may monitor CSF pressure, or act as valves preventing reflux of blood from the sinus into the CSF compartment. As young infants have no arachnoid granulations, venous blood from the superior sagittal sinus or the lateral lacunae may reflux into the dura and seep into the subdural compartment [148, 175].

#### Healing subdural membrane

Dural bleeding promotes an inflammatory response that leads to development of a granulating membrane with a variable content of fibroblasts, macrophages, and wide thin-walled capillaries (Fig. 1c–f). Friede distinguished subdural neomembranes from granulation tissue elsewhere in the body on the basis of these distended capillaries and its looser structure [53]. The capillaries are far easier to see if endothelial markers are used, indeed such markers are necessary to determine not only the existence, but also the thickness and precise composition of a healing membrane, features which assist in assessing its age.

It is usual to see foci of bleeding of multiple ages in infant healing neomembranes, reflecting episodic rebleeding in the absence of trauma and leading to the “vicious circle” of healing which converts a recognisable reactive membrane to a fibrosed scar [53]. Fresh bleeding is an almost invariable finding at autopsy, even in babies who have been nursed on a ventilator for their past days or weeks, and is likely to be the result not of trauma, but of normal nursing or the swings of blood pressure and hypoxia which accompany brainstem death.

If sufficient, bleeding from a healing membrane will leak into, and mix with, older subdural fluid collections and effusions leading to a mixed density appearance on scans. There is a variable balance of influx and efflux as part of the natural evolution of subdural collections [75]; the number and severity of rebleeds will determine the rate of this process.

Healing subdural membranes of unknown cause are more common than generally recognised [131] and are the

most commonly encountered residuum of birth injury in SIDS autopsies [81]. Keeling warns that the “appearance should be commensurate with the age of the infant, i.e it will be red brown and recognizable as a haematoma, probably 1–2 mm thick, for two possibly up to 4 weeks post partum” and “Later than that, brown staining of the dura is apparent. This may persist for several months” (Fig. 1). Ikeda [77] suggested that most infant SDH after minor trauma resulted from fresh bleeding into pre-existing subdural collections.

#### Ruptured intracranial vascular malformation

Cerebral vascular malformations occur in the brain and meninges of very young babies and may rupture and present with subdural haemorrhage, encephalopathy or the triad [106, 124], but the true frequency of the triad in association with aneurysmal rupture is impossible to assess because the eye examination is not usually described [15, 190].

#### Is hypoxia a cause of subdural haemorrhage?

An important and almost invariably overlooked part of the clinical history in babies presenting with the triad is a prolonged period of hypoxia, often 30 min or more between the baby being found collapsed and arriving in hospital and receiving advanced resuscitation. This sequence sets babies with the triad apart from cot death babies who are, by definition, found dead and have no pathology or intracranial bleeding. Prolonged hypoxia and resuscitation have been shown to be significantly associated with retinal haemorrhages [102] and may also explain the encephalopathy in babies with the triad. Experimental models of reperfusion injury confirm that longer periods of ischaemia cause greater small vessel damage and breakdown of the blood-brain barrier, exacerbated by resuscitation and reperfusion [97, 137].

Geddes proposed that in some infants with fatal head injury, the combination of severe hypoxia, brain swelling and raised central venous pressure is the cause of dural and retinal haemorrhage [59]. Geddes was not the first to make this observation; it had already been made by Cushing in 1905. There has been a tendency, notably in the Courts, to oversimplify this hypothesis to assume that hypoxia alone is a cause of subdural haemorrhage. This is misleading, as the physiological consequences of hypoxia are more complex. Subsequent research demonstrates an association between hypoxia and dural bleeding in young infants [28, 29]. Byard [16] found no SDH in hypoxic infants, but retrospective review of autopsy reports is unreliable in detecting small volume bleeds [22]. Hurley [74], in a

retrospective autopsy and imaging study, found only one subdural haemorrhage and two intradural bleeds in 47 babies up to 4 years of age. Data regarding duration of hypoxia and resuscitation were incomplete. Neurological outcome is known to be far worse in children suffering out-of-hospital compared with in-hospital cardiac arrests, probably due to prolonged hypoxia and less effective CPR in the former group. [100].

### Birth-related SDH

A degree of subdural bleeding is extremely common after birth and seen on imaging in up to 46% of asymptomatic neonates after normal, instrumental and caesarean delivery [96, 132, 177]. More cases of SDH would be expected among symptomatic infants [24]. Two MRI studies have followed a total of just 27 babies with birth-related bleeding with repeated scans at 1–3 months of age. One baby developed further subdural bleeding [132, 177]. Due to the very small numbers used in these studies compared with the overall frequency of birth-related bleeding, meaningful interpretation is difficult and we have no good data on the natural history of birth-related SDH. It is obvious that most heal without any significant morbidity, although birth-related bleeding has been shown to be the cause of between 14 and 17% of infant chronic subdural haemorrhage [4, 69].

Studies of later onset infant subdural haemorrhage show that untreated small volume bleeds develop into chronic fluid collections. Loh [95] found chronic collections between 15 and 80 days after onset, the mean being 28 days. Hwang [75] described three cases of accidental subdural haemorrhage which resolved in CT scans only to reappear up to 111 days later. It seems likely that birth-related subdural haemorrhage will behave similarly.

### Timing subdural bleeding

Dating healing subdural haemorrhage by pathology alone is difficult and cannot constitute reliable evidence of the timing of an injury. In clinical practice, it is important to take into account the entire clinical history and the other clinical and pathological findings. Several guidelines for timing the cellular reactions to subdural haemorrhage are published [92, 108, 114].

### Clinical signs of chronic SDH

The neuropathologist needs to be aware that there may not always be a clinical history to indicate pre-existing

subdural haemorrhage. Chronic SDH can be extremely difficult to diagnose in infants and, unless specifically sought, the diagnosis is readily missed. Symptoms are non-specific and are sometimes purely systemic mimicking gastroenteritis, malnutrition or bronchopneumonia [68]; “Most often, the infant’s history includes failure to gain weight; refusal of feedings followed by frequent episodes of vomiting, some of which might be projectile; irritability; progressive enlargement of the head; and, ultimately, a seizure” [108].

Obstetric and birth records and brain scans should be reviewed. Head circumference charts are critical for the identification of extra-axial fluid and blood collections in life [184] and should be consulted in considering the possibility of pre-existing subdural haemorrhage.

### Subdural hygroma/chronic subdural haemorrhage

The terminology of these entities is confused with no clear distinction between chronic subdural haemorrhagic collections, subdural hygromas and effusions. Subdural effusions may be xanthochromic or haemorrhagic and may evolve into frank subdural haematomas [19, 122]. Conversely, acute subdural haemorrhages may evolve into clear or xanthochromic protein-rich fluid collections or hygromas. The primary mechanism for the formation of hygromas remains unknown, it has been suggested that any pathologic condition at the dural border layer; fresh bleeding, lysis of pre-existing bleeding, inflammation or exudation from dural vessels can lead to effusion and fluid accumulation [48, 176].

### Enlarged extra-axial spaces

Large fluid collections around the infant brain may be identified in otherwise normal babies and are usually self-limiting. Males outnumber females by 2–1. The causes are not known and include abnormalities in growth rates of the brain, the skull or the surrounding membranes, immaturity in the mechanisms of cerebrospinal fluid production and resorption, and old subdural bleeding. The many names, wide range of associated clinical findings and many aetiological hypotheses underscore the heterogeneity of the condition [60, 185]. Extra-axial fluid collections, whatever their cause, may predispose to SDH. Fresh bleeding into large extracerebral fluid collections after no, or only minor, trauma has been described [76, 107, 169]. Pittman [123] warned that acute SDH in the context of such a fluid collection around the brain could not be taken as evidence of abuse. A proposed mechanism for bleeding into extracerebral collections is leakage from over-stretched bridging

veins which cross them [121]. Evidence from imaging and microscopy suggests that large surface veins may leak when their walls are stretched. Figure 5 demonstrates red cells passing between the cells of a congested and thrombosed cortical vein wall into the subarachnoid space.

### Subarachnoid haemorrhage (SAH)

In adults, the most common causes of SAH are trauma and ruptured aneurysm [43]. Hypoxia is a particularly frequent cause in the young infant, as are trauma and venous and sinus thrombosis.

### Subpial haemorrhage

Subpial bleeding receives a little attention in the pathological literature and is not generally distinguished from subarachnoid haemorrhage. Larroche [89] considered the pathogenesis and clinical implications to be the same. Subpial bleeding can be mistaken both radiologically and pathologically for contusion and erroneously support a diagnosis of trauma.

Friede described subpial bleeding as representing 15% of perinatal intracranial haemorrhage [52]. He considered that the bleeding dissected through the superficial astrocytic foot processes, and was a variant of, subarachnoid bleeding due to respiratory distress syndrome. Lindenberg [94] described similar bleeding into the outer part of cortical layer 1 in babies under 5 months and Voigt [171] described it in adults. Superficial bleeding, assumed to be subpial or subarachnoid, is described in temporal pole haemorrhage (see below) [73, 89].

Subpial bleeding is macroscopically well circumscribed, and often seen at the edge of a gyrus. I have seen it in association with cortical vein thrombosis, beneath space occupying subdural haematoma and beneath fractures occurring during forceps delivery. Larroche [89] considered occlusion or compression of superficial veins as a potential mechanism. The cortical veins, unlike cortical arteries, have little or no leptomeningeal investment around them [188] and bleeding around their deep cortical tributaries can track directly into the subpial space. (see Figs. 11, 13).

### Epidural haemorrhage: cranial and spinal

The skull bones develop within the outer mesenchymal layer which forms both the periosteum and the outer leaflet of the dura [98]. As the cranial dura is so intimately associated with the periosteum epidural bleeding is

uncommon except where there has been surgery or fracture. Old trauma may not be obvious and there may be no history; skull fractures are associated with normal delivery and low falls and may be asymptomatic in the neonate [41, 135]. Rarely, cranial epidural bleeding is seen beneath an intact skull bone and is considered to result from inbending of the pliable infant skull (ping-pong fracture) which tears off the periosteum in the absence of fracture.

The relationship of the spinal dura to the vertebral bones is quite different. There is a wide epidural space which contains fat and the epidural plexus. This extensive, valveless plexus communicates above with the cranial venous outflow and is responsible for cerebral venous return to the heart in the upright position [163]. It becomes massively congested when intracranial pressure is reduced or when intra-abdominal pressure is increased [156, 157, 179].

Spinal epidural bleeding has been described in infants who are thought to have suffered non-accidental injury and has been considered to be evidence of shaking [64, 117]. However, spinal epidural haemorrhage is common in infants dying from all causes and is not diagnostic of trauma [136], but is probably a response to physiological and pathological variations in intracranial pressure (Fig. 2d).

### Retinal haemorrhage

Eisenbrey [45] was the first to suggest that retinal haemorrhages in a child under 4 years of age suggest abuse. Caffey [17] was prescient when he wrote “The retinal lesions caused by shaking will undoubtedly become valuable signs in the diagnosis of subclinical inapparent chronic subdural hematoma, and also become a productive screening test for the prevalence of whiplash dependent mental retardation and other types of so-called idiopathic brain damage”. Unilateral or bilateral retinal and vitreous haemorrhages, retinal folds and retinoschisis are indeed regarded as characteristic of Shaken Baby syndrome, and are estimated to be present in 65–90% of cases [40, 93, 134].

Vinchon [168] highlighted a pitfall in the use of RH in the diagnosis of abuse: “The importance of an RH for the diagnosis of child abuse is well established; however, the evaluation of its incidence in child abuse is almost impossible because the diagnosis of child abuse is in great part based on the presence of an RH, providing a circularity bias”. A further stumbling block in ascertaining the real significance of RH in abusive as compared to other forms of injury is that they may only be sought where abuse is suspected. In a study of SDH, ophthalmological opinion was sought in 94 of 106 cases of suspected NAHI but in

only a quarter of babies with SDH of any other cause [69]. In a meta-analysis of 1,283 children funduscopy was performed in 670 cases of suspected NAHI and only 328 cases with all other causes of brain injury [99].

All aspects of intraocular haemorrhage have been shown to occur without shaking [11, 127, 174]. A detailed, but yet unpublished, autopsy study found natural diseases to greatly outnumber inflicted injury in association with RH in infants under 1 year of age [87]. Thus, there is no diagnostic ocular neuropathology for SBS.

The pathologist must bear in mind that the ocular pathology resulting from the initial insult may be considerably modified by prolonged hypoxia, resuscitation, reperfusion, and a variable period of life support and must be interpreted in the context of the clinical findings closest to the time of injury. Clinical recognition of RH depends on the examination by an experienced physician using pupillary dilatation [168]; the timing of examination is crucial, as RH extend after initial injury [61].

A central issue is the mechanism of RH. The experimentally verified hydraulic theory is that retinal bleeding results from alterations in intracranial, intrathoracic and intra-abdominal pressure and blood pressure [146]. Muller and Deck [113] concluded that intraocular and optic nerve sheath haemorrhages result from the transmission of intracranial pressure into the optic nerve sheath and retinal venous hypertension. The alternative theory is that shaking causes vitreo-retinal traction, which tears the retina from its connections, disrupting the integrity of the blood vessels of the eye [93]. Ommaya [119] considered it biomechanically improbable that the levels of force generated by shaking would damage the eye directly and that a sudden rise of intracranial pressure is more likely to cause bleeding than the “shaken eye” hypothesis.

Observations of unilateral RH with ipsilateral intracranial haemorrhage or brain swelling indicate that RH may be due to the transmission of raised pressure along the optic nerve, potentially obstructing the central retinal vein [26, 61]. Pathology has not substantiated the theory of vitreo-

retinal traction during shaking, but implicates a secondary phenomenon due to raised intracranial pressure or venous stasis and leakage from retinal vessels [46]. This hypothesis is consistent with findings in the brain, whose capillary structure and physiology resembles that of the retina, where parenchymal bleeding tends to be associated with venous obstruction and tissue compression (see below and Fig. 15).

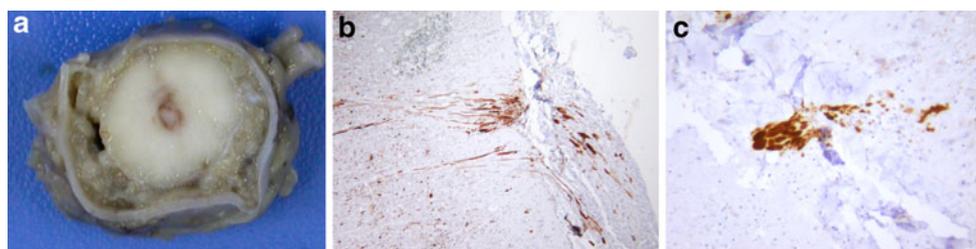
A statistically significant relationship between retinal and optic nerve sheath haemorrhage and reperfusion, cardiopulmonary resuscitation (CPR) and cerebral oedema has been demonstrated [102].

## Encephalopathy

### Brain swelling

The most common pathology encountered in babies with the triad is brain swelling which, together with congestion and neuronal death is regarded as consistent with hypoxic–ischaemic injury (HII) [57, 58, 117]. These findings are non-specific and may result from any insult leading to release of neurotransmitters and neuropeptides which promote a secondary cascade of vascular leakiness leading to brain swelling [129, 161]. Vasogenic oedema results from movement of water across capillary walls into the parenchyma of the brain. Cytotoxic oedema involves a shift of water from the extracellular to intracellular compartment and by itself does not result in a net increase in brain water content or swelling [101]. Brain swelling, which may take between 24 and 72 h to reach its maximum, can obstruct arterial inflow and lead to a perfusion failure and is the most important determinant of mortality and morbidity after head trauma.

Cerebellar tonsillar herniation can compress and distort the cervical cord and put tension on the nerve roots. Fragments of necrotic cerebellar cortex are often displaced around the spinal cord at all levels (Fig. 7).



**Fig. 7** Cervical spinal cord damage due to compression by brain swelling and tonsillar herniation. Baby 20 months acute demyelinating encephalomyelitis, who died in hospital with severe brain swelling but without trauma. **a** The lower cervical spinal cord contains a central haemorrhagic, necrotic area just ventral to the

dorsal columns. The yellow/grey tissue around the cord and beneath the dura is displaced and fragmented cerebellar cortex. **b, c** Dorsal nerve roots from **b** upper and **c** lower cervical levels show axon swellings expressing  $\beta$ APP at the exit zone (10 $\times$ )

## Parenchymal bleeding

Parenchymal bleeding is uncommon in the infant brain, except in those with prolonged cerebral death who have been nursed on a ventilator. Focal perivascular haemorrhage is seen in compressed and distorted tissues of the herniated cerebellum, brainstem and medial temporal lobes in brain swelling. Perivascular bleeding elsewhere is uncommon and other causes should be sought. Parenchymal bleeding cannot be used as a surrogate for axonal injury as has been suggested [30]. Bleeding and axonal damage are independent of one another.

### *Hypoxic–ischaemic injury (HII)*

Haemorrhage due to HII is usually minimal, perivascular and follows the pattern of neuronal necrosis, being the most common in the inferior olives and the cranial nerve nuclei. The features of infant HII have been described in detail [145].

### *Cortical vein thrombosis (CVST)*

Subpial, cortical perivascular bleeding and bleeding in the immediate subcortical white matter are seen where cortical veins are compressed or thrombosed.

### *Diffuse intravascular coagulation (DIC)*

The characteristic haemorrhages of DIC are typically round and centred on a damaged blood vessel in which a small amount of amorphous pink material may be seen.

### *Acute necrotising encephalopathy*

This is a life-threatening complication of infection. Though rare, it is a significant differential diagnosis in a baby who collapses and dies soon after a short-pyrexial illness with no signs of injury. The bleeding is perivascular and characteristically in the tegmen of the pons and the thalamus.

## Traumatic brain damage

Trauma causes brain damage in two distinct stages: primary mechanical tissue disruption and a complex secondary cascade which evolves over hours or days and is the primary target of therapy. Deformation and membrane depolarization lead to the activation of ion channels and disturbances in ionic fluxes which, if sustained, lead to oedema and secondary neurogenic inflammation.

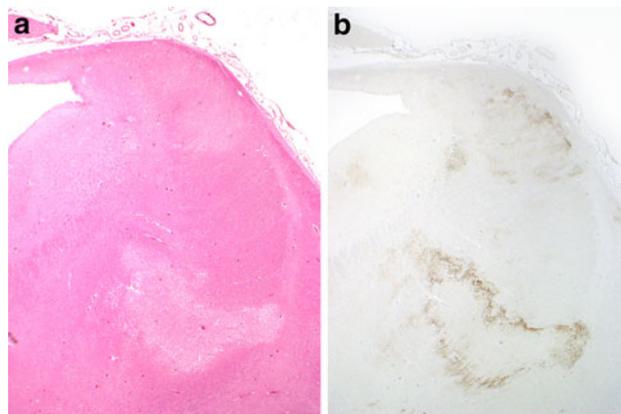
In the vast majority of infants with the triad, hypoxic–ischaemic injury and oedema, rather than traumatic axonal injury, are the predominant cerebral pathologies [57, 58]. Axonal injury may cause immediate loss of consciousness [1]

but the variable pace of swelling means that the clinical manifestations of brain injury can be delayed. This is recognised in clinical practice as a “lucid interval” in which the infant may display only subtle and non-specific signs which a parent or carer may not recognise [5]; the potential for a lucid interval in SBS has recently been acknowledged [42]. Normal neurological examination and maintenance of consciousness do not preclude significant intracranial injury [142].

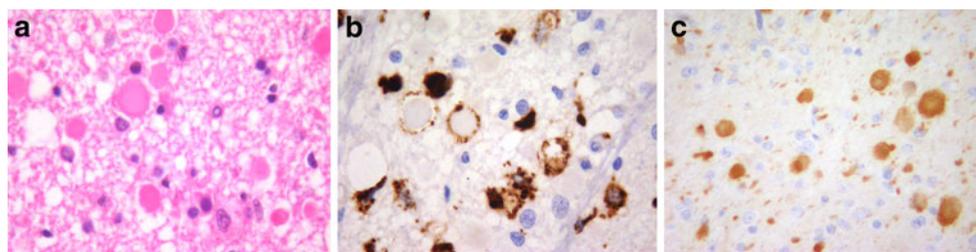
A number of genetically determined conditions may predispose children to severe brain swelling after minor trauma [85, 152].

## Axonal injury

Axonal injury, identified histologically by axonal swellings, has been considered characteristic of trauma in the adult, but in infants it is far more commonly due to hypoxia, ischaemia or metabolic disturbance [36, 128]. Large axonal swellings may be identified in routine H&E stained sections, but are much more readily seen with the use of immunocytochemistry for  $\beta$ APP. The appearance of the axonal swellings does not identify their cause. In adults, their pattern and distribution may enable a diagnosis of diffuse traumatic axonal injury [56], but similar patterns have not been established in the infant brain. Geddes [58] described axonal swellings restricted to the corticospinal tracts in the brainstem and cervical nerve roots in a minority of infants considered to have NAHI, Oehmichen [117] and Johnson [79] were unable to distinguish traumatic axonal damage in the presence of hypoxic injury. An example of ischaemic axonal damage in a site where traumatic injury is characteristic is shown in Fig. 8.



**Fig. 8** “Geographical” axonal injury in the brainstem sections through the upper pons showing infarction in the superior cerebellar peduncle, a characteristic site for traumatic axonal injury in the adult. However, in this case, areas of ischaemic injury seen as tissue oedema and pallor in the H&E preparation (**a**) map precisely to the “geographical” pattern with bands of  $\beta$ APP positive axons sweeping around the areas of infarction in **b** (2 $\times$ ). 3-year-old male with multiple episodes of impact trauma



**Fig. 9** Old brainstem axonal injury. **a** Clusters of axonal swellings are readily identified in the corticospinal tracts with H&E staining. **b** The majority of swellings are surrounded by CD68 positive cells processes indicating that they are at least 10 days old and may be much older. **c** The swellings are pale or granular with  $\beta$ APP. This plus

the macrophage reaction suggests that these swellings could be at least 2–4 weeks old (**a–c**  $\times 10$ ). One month infant born with ventouse assistance at 36 weeks and died aged 25 days. There was an old skull fracture thought to be birth related

Axon swellings may develop very soon after injury, perhaps within 35 min [72]. Early swellings stain uniformly brown and persist for up to 10–14 days. After this, the staining fades or becomes granular then disappears, although some granular staining may be seen for up to 3 years after injury. A macrophage reaction around axonal swellings begins from 10 to 11 days after injury and persists for up to 5 months [25, 56] (Fig. 9). Routine use of a marker for microglia and macrophages such as CD68 together with  $\beta$ APP greatly assists in identifying subtle axonal injury.

#### Brainstem and cervical cord damage

This is the site that shaking must damage if it is to also cause SDH and an encephalopathy since it is the point where the head hinges on the neck [57, 64]. The reported incidence of neck injury in suspected abuse is between 2.5 and 71% [13, 111]. The more inclusive definition of spinal cord injury as “any cervical cord contusion, laceration, or transection; vertebral artery injury; nerve root avulsion/dorsal root ganglia hemorrhage; and meningeal hemorrhage (epidural, intradural, subdural, and/or subarachnoid)” may explain the high incidence in the latter study. Hadley [64] described 13 infants with no direct cranial trauma. 6 had autopsies, of whom 5 had epidural and/or subdural haemorrhage at the cervico-medullary junction and 4 had high cervical spinal contusions. Among infants thought to have suffered NAHI Geddes [57] described axonal injury localised to the corticospinal tracts of the caudal pons and the cervical spinal cord and/or dorsal nerve roots in 31%, Shannon [140] described damage to the cervical spinal cord and dorsal nerve roots in 7 of 11 cases and Oehmichen [117] identified focal axonal injury in 2 of 5 cases where the cervical spinal cord was examined.

The upper cervical cord is vulnerable to infarction in severe brain swelling; there is a watershed between the arterial supply descending from the vertebral system and the radicular vessels. When the brain becomes very swollen

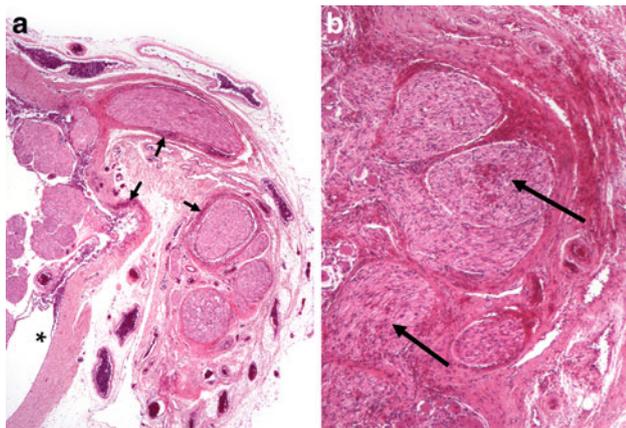
the descending vessels are obstructed; this is not uncommon in “respirator brain” [92]. Figure 7 illustrates cervical cord and nerve root damage due to brain swelling and herniation in the absence of trauma.

Axonal injury in the lower brainstem appears, perhaps surprisingly, to be compatible with survival. Geddes [58] identified swellings of several days old in one case. I have seen old axonal swellings in the brainstem of four babies who survived between 4 days and 4 months before death. Two had suffered traumatic delivery and two had been the subjects of witnessed head trauma (Fig. 9). The clinical effects of this axonal injury are unknown. This part of the brain contains centres controlling vital functions and the reflexes governing breathing and swallowing are still developing in the first year of life. While brainstem axonal injury is clearly survivable, it is likely to make the baby vulnerable and less able to recover from life-threatening events than normal babies, as has been suggested in SIDS [83, 84]. Gliosis and smallness of the brainstem is virtually universal in premature babies with white matter disease [172]. A history of prematurity is not uncommon in babies presenting with the triad and any examination of the brain of a baby dying suddenly, must pay meticulous attention to the possibility of brainstem injury and gliosis as a factor in collapse.

#### Spinal nerve root pathology

Axonal swellings in spinal nerve roots are sometimes said to represent independent evidence of trauma, either due to shaking and hyperflexion of the neck, or as an indication of direct spinal trauma [103]. However, spinal nerve root swelling has been identified where death is due to natural causes with neither a history nor evidence of trauma [151]. There are no published studies to assist in distinguishing traumatic from other causes of axonal swellings in spinal nerve roots.

Spinal nerve roots are the sites of CSF resorption and surrounded by a dense, valveless vascular plexus



**Fig. 10** Spinal nerve root bleeding. **a** Intradural bleeding is seen in the spinal dura and extending out into the nerve root sheath at several sites (*arrows*) close to a dorsal root ganglion. There is fresh intraneural bleeding. An *asterisk* marks the site of bleeding into the spinal dural border layers. Note the very vascular and congested epidural fat. (2 $\times$ ). **b** At higher power bleeding is seen into the nerve root sheath as well as within and around the nerve roots themselves (*arrows*) (4 $\times$ ). Male 4 months who died after prolonged seizures. There was no evidence of proximate trauma

[164, 187] and so are prone to bleeding, usually as they cross the dura. Spinal subdural haemorrhage can track out along nerve roots beyond the dorsal root ganglia. Further, intraneural bleeding is seen when there has been venous congestion due to raised intrathoracic pressures during resuscitation and ventilation (Fig. 10).

#### Cerebral contusions/contusional tears

Superficial cortical contusions as seen in adults are not seen in pathological studies of infants, but subcortical contusions (or contusional tears) have been described in infants under 5 months of age. They are rare; Geddes described only 4 in 53 infants, and Oehmichen did not describe any in 18 babies thought to have been abused [57, 117].

Lindenberg originally described contusional tears as clean-walled cysts found just beneath an intact cortex, usually frontal and bilateral, which “could hardly be differentiated from artefact except for some bleeding into the defect and occasionally its margins” [94]. He described microglial hypertrophy but very rare macrophages, and no vascular or oligodendrocyte proliferation. In particular he, and others since, failed to identify axonal injury in relation to subcortical clefts; the axons “simply terminated at the margins”. [20, 173]. Of note, Lindenberg recorded that “The brains of those infants who died shortly after the injury were markedly swollen”. These clefts have similar pathological characteristics to “subcortical leucomalacia” which is associated with brain swelling in the young infant and is not specifically associated with trauma [150].

In a radiological study Jaspan [78] suggested that subcortical contusions are pathognomonic of shaking. The proposed mechanism, gliding of the grey matter over the white matter, defies all known anatomy of the cortex. More recently, this group described subcortical cysts in young infants which were thought to be the result of birth injury. None had any objective evidence of birth or inflicted trauma [6].

Figure 11 illustrates subcortical “contusions” beneath parietal bone fractures. The relative preservation of the cortex indicates that the bleeding beneath it was not due to the direct mechanical forces associated with fracture. Rather, the pattern of bleeding resembles that seen in obstruction of cortical venous drainage (see Figs. 12, 13) and suggests that the cause may have been transient obstruction of the superior sagittal sinus during delivery [126, 159].

#### Temporal lobe haemorrhage

Bleeding in the temporal pole is sometimes seen in babies with the triad, mistakenly diagnosed as contusion and ascribed to trauma. Superficial (subarachnoid, subpial and subcortical) bleeding over one or both temporal lobes is described in neonates with seizures and apnoea [71, 73, 143]. There is not usually an obvious history of birth trauma, although scalp swelling is sometimes described.

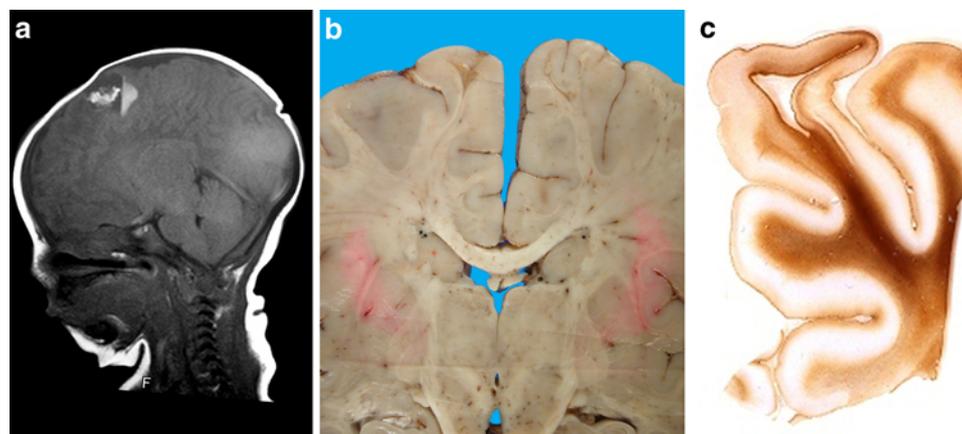
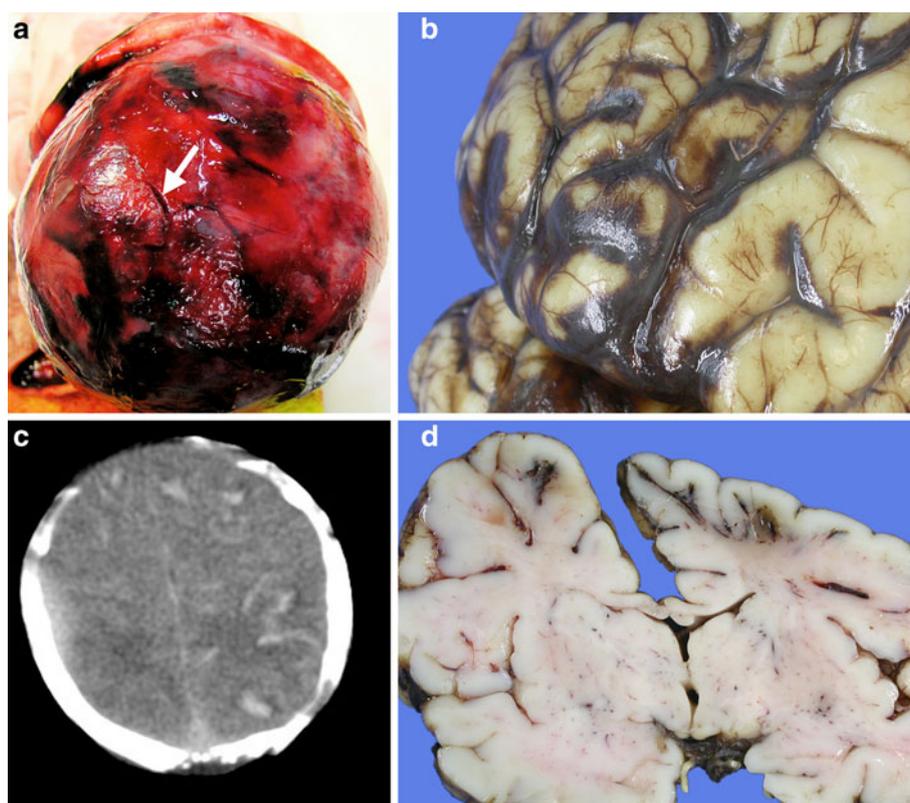
The pathophysiology of this haemorrhage has not been explained but appears to be venous in origin. Veins of the anterior temporal lobe drain into the small and variable sphenoparietal sinuses which connect with the anterior temporal diploic veins [162]. The diploic veins are delicate and superficial and are particularly vulnerable to compression before the outer table of the skull develops at about 5 years of age [67]. Larroche [89] described temporal lobe subarachnoid bleeding in 33 neonates without evidence of trauma and concluded that the pathology was likely to be the result of venous hypertension. Figure 13 illustrates examples of temporal lobe bleeding with radiological correlation.

#### Cortical vein and/or sinus thrombosis (CVST)

Superficial cortical vein and/or sinus thrombosis (CVST) are discussed together. They are, in my experience, one of the most frequently overlooked pathologies, clinically and pathologically, in babies with the triad.

Radiological studies show extraparenchymal bleeding, including subdural, subarachnoid and subpial haemorrhage and subdural effusion in association with CSVT [8, 44, 68, 130]. Parenchymal damage is usually venous infarction which may become haemorrhagic [109, 159]. Subcortical bleeding may be confused with traumatic

**Fig. 11** Subcortical and subpial bleeding. **a** Parietal bone fractures (*arrow*) in a term infant who died 5 days after birth by emergency caesarean section with forceps lift-out. **b** The surface of the fixed brain showing congested veins with sharply defined surrounding bleeding which tends to be seen on the edges of sulci. Histology confirmed subpial bleeding. **c** CT scan of this baby shows multiple patches of superficial high signal which was described as “shearing injury”. No tissue shearing was found histologically, there were no axonal swellings. **d** Coronal slice through the fixed brain shows perivascular haemorrhages and blood filled cysts in the immediate subcortical white matter. The overlying cortex, which was beneath the skull fractures, is intact



**Fig. 12** Subcortical clefts. **a** CT scan. Lateral view showing a fluid containing cyst in the immediate subcortical white matter. Infant 28 days old with pneumonia and no evidence of trauma. **b** The baby died a year later. Residual collapsed clefts are seen in the parasagittal subcortical white matter bilaterally. The cortex is almost completely

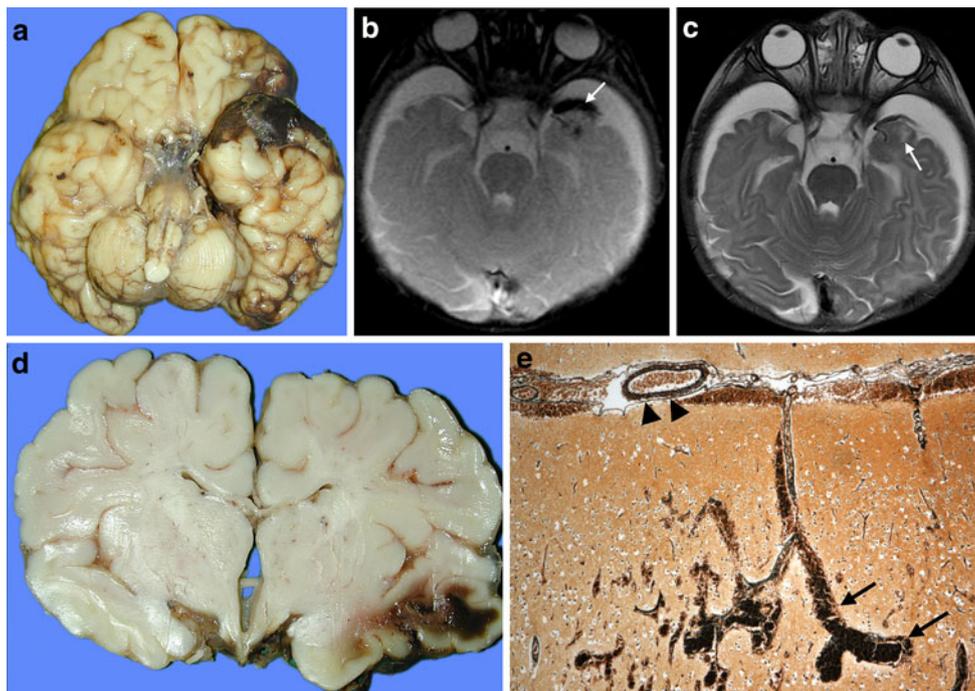
spared. **c** Male 3 months. This twin boy had a history of poor head control since the neonatal period. A section of frontal lobe stained with GFAP shows parasagittal subcortical clefts with the overlying cortex intact but focally thin and gliotic

shear injuries and misdiagnosed as “cortical contusions” [8] (see Fig. 11c).

Parietal veins are commonly thrombosed as these veins turn at an acute angle and pass into a dural sleeve for some distance prior to entering the sinus. Compression of the superior sagittal sinus by the upper occipital bone close to the posterior fontanelle has been associated with the development of CVST [159]. Reduced flow in the superficial veins or

sinuses causes damage in the immediate subcortical white matter which is the watershed of the deep and superficial venous systems. This leads to local oedema which can be transient and reversible, or to venous infarction with or without haemorrhage [126]. Bleeding around small cortical veins may track into the subpial areas [171] (Fig. 13e).

There is a striking male predominance (up to 75%) in infant CVST [10, 182]. Clinical diagnosis is difficult in



**Fig. 13** Temporal lobe haemorrhage. **a** Surface bleeding over the left temporal pole. A corresponding coronal slice of the fixed brain is seen in **d**. **b, c** Radiological appearance of temporal lobe haemorrhage in a 5-month infant with thrombosis of the superficial middle temporal vein. **b** T2\*/GRE (haem sensitive sequence) shows a thrombosed vein (arrow). **c** T2 shows fluid/oedema in the immediate subcortical white matter (arrow), the cortex apparently intact. **d** Bleeding is seen in a

very fine subpial layer as well as in the immediate subcortical white matter; the cortex appears intact. **e** Subpial bleeding in a sulcus beneath a space-occupying subdural haemorrhage. Arrowheads indicate where the pia is lifted off by a thin fresh surface bleed. There is blood around the venous tributaries in the deep cortical levels and extending up towards the surface (arrows) (Reticulin 4 $\times$ ). Female of 20 months with head impact due to a fall

infants; at least 10% of babies are asymptomatic, and others have non-specific presentations including depressed consciousness, lethargy, poor feeding, vomiting or seizures [139, 165].

Venous thrombosis is associated with a number of common illnesses. 75% have infections, 33% prothrombotic disorders and 4% recent head trauma [139]. Neonates have additional risk factors, including asphyxia, complicated delivery and altered sinus flow during skull moulding [10, 180].

Timing of intravascular clot by pathology alone is difficult and reliable, but may assist in understanding the totality of a case by relating the pathology to the clinical evidence. Old organising cortical vein thrombosis and associated subcortical damage is shown in Fig. 14. Histological criteria for timing, derived from studies of adult and animal CVST, have been published [49, 115, 116, 138].

#### Respirator brain

Not infrequently a baby is kept alive on a ventilator for several days after the brain has become severely swollen and is no longer receiving an adequate blood supply. There is little inflammatory response in the brain due to the

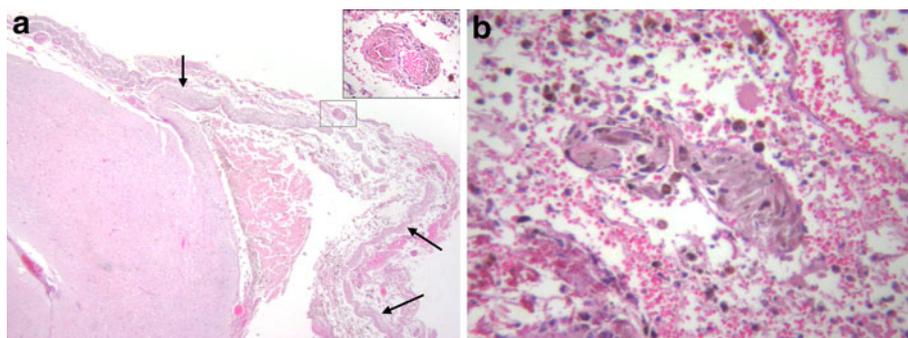
absence of circulation. However, there may be reactive change around the spinal cord and at the vascular watershed in the cervical spinal cord where central necrosis can be mistaken for traumatic damage [92]. The dural blood supply is preserved and timing of the pathology here may be more reliable than in the brain where lack of a blood supply makes timing impossible as the normal sequence of cellular processes is inactive.

#### Conditions which may present with the triad

The list of conditions which may cause an infant to develop the triad is exhaustive. Below are brief notes on the most common causes of the triad which I have encountered in my own clinical diagnostic and forensic practices. Many others are discussed elsewhere [8, 51].

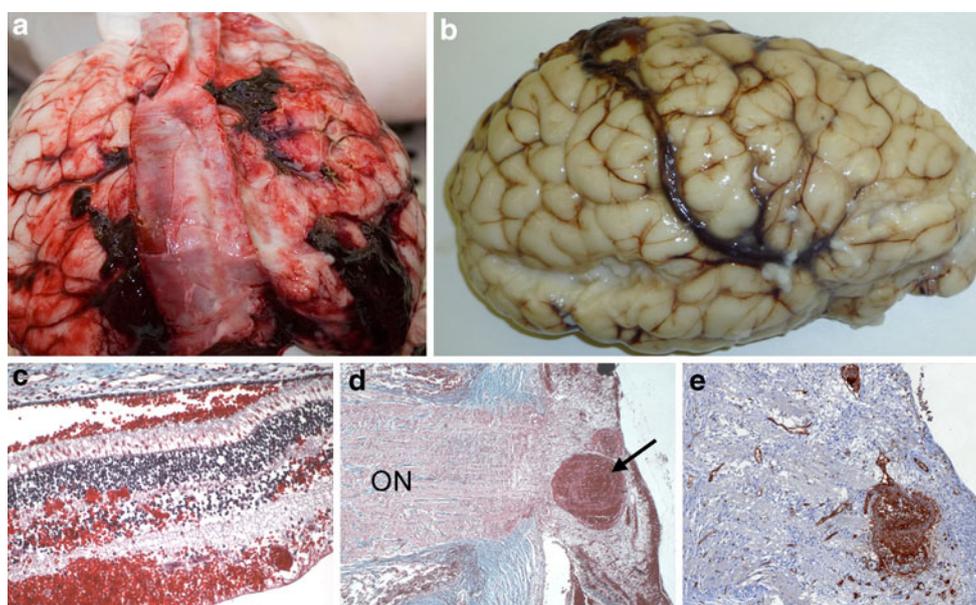
#### Chronic subdural haemorrhage

The majority of babies with the triad, perhaps 70–80% have chronic SDH. In the absence of any recent or remote evidence of trauma the question of residual consequences of birth related bleeding must be considered.



**Fig. 14** Old cortical vein thrombosis. A cleft in the parasagittal cortex contains fresh blood beneath a residual band of thinned and gliotic cortex (*arrows*). The overlying leptomeninges are thickened

and cellular with many pigment-containing macrophages. Recanalised vessels are seen within them. An example in the box is seen in **a**, another in **b**. (H&E **a** 2 $\times$ , **b** 10 $\times$ )



**Fig. 15** Cortical vein and sinus thrombosis. Male infant aged 4 weeks who collapsed and became floppy in a public park. Subdural bleeding was diagnosed on CT scan. **a** The autopsy showed dural sinus thrombosis. There is patchy bleeding over the surface of the brain related to thrombosed cortical veins. **b** Fixed brain; the right superficial middle (anastomotic) cerebral vein is thrombosed. This

baby also had retinal haemorrhage which was due to central retinal vein thrombosis. **c** Haemorrhage at all levels of the retina (H&E 4 $\times$ ). **d** There is thrombus in the central retinal vein in the optic nerve head (*arrow*). ON optic nerve (Masson's trichrome). **e** CD31 staining shows organisation and early recanalisation of the central retinal vein (**d**, **e** 2 $\times$ )

### Accidental falls

There is evidence that even low level falls may cause intracranial damage in the infant. Skull fractures may be asymptomatic and symptoms non-specific. The carer's account should be considered "The clinical history is perhaps the most important clinical tool available to the clinician and to reject the carer's version of events in favour of another requires the highest possible level of medical evidence. After all, the Doctor is effectively accusing the carer of lying" [54].

### Resuscitated SIDS

The difference between SIDS and SBS may be due to the long period of hypoxia and subsequent resuscitation that most SBS babies experience. Both share demographic factors such as age, male predominance and mild illness prior to the presentation. Certain clinical circumstances are particularly common in babies with the triad for example:

- *Aspiration* of stomach contents or pooled secretions have been implicated in SIDS through activation of the oxygen conserving reflexes such as the laryngeal

chemo reflex which are particularly powerful in infants. [62, 83]. In many cases, a parent gives a detailed account of a baby collapsing after or during a feed, regurgitating vomit and milk. The story is accurately repeated in multiple interviews. There is often a history of feeding difficulties and “reflux” and most of these babies have a chronic subdural haemorrhage.

- *Premature* babies are likely to have brainstem compromise and may not be able to overcome events that a normal baby can. The vulnerability of even mildly premature babies has been stressed [12].
- *Vaccination* Infants may collapse with the triad in the days following immunisations, possibly due to a pyrexial response triggering seizures.

#### Cortical vein and sinus thrombosis

These conditions are frequent but are underdiagnosed both clinically and pathologically in infants. The surface veins and dural sinuses must *always* be examined.

#### Inflicted injury

Many babies suffer inflicted trauma which causes the triad. In the absence of clinical or pathological evidence of trauma, it is beyond the ability or expertise of the neuropathologist to make this diagnosis, which is a matter for the legal authorities.

#### Vitamin D deficiency

There is a newly recognised epidemic of Vitamin D deficiency among pregnant women. Experimental evidence indicates that in addition to the classical bone lesions, brain growth and immune function may be compromised [88]. Complications of Vitamin D deficiency including tetany, seizures and cardiac failure can lead to collapse with brain swelling and presentation with the triad.

#### Second impact syndrome

This syndrome describes acute hemispheric swelling beneath a thin film of subdural bleeding of heterogeneous appearance after a second head injury, often very mild, occurring days or weeks after a first [21, 112]. Most patients are adolescents but the similarities to infants with SDH who may have suffered non-accidental trauma were noted by Cantu [21]. Careful review of the clinical history often discloses an impact in the days or weeks prior to collapse from which the baby apparently recovered and which may not have been taken into account on admission.

More research is needed to define whether this syndrome may underlie the triad in some infants.

#### Aneurysm rupture

Intracranial vascular malformations can and do rupture in infants and cause the triad.

#### Rare genetic conditions

Many infant deaths have underlying genetic conditions. Disorders of cardiac rhythm, coagulation or osteogenesis are the most likely to lead to being confused with abusive injury.

#### Conclusion

Neuropathologists have the benefit of detailed study of the empirical evidence offered by the tissues. A pragmatic analysis of this evidence remains the cornerstone of the clinical and forensic diagnosis.

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