Infants dying suddenly and unexpectedly share demographic features with infants who die with retinal and dural bleeding: a review of neural mechanisms

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ABBREVIATIONS

CPR	Cardiopulmonary resuscitation
5-HT	5-hydroxytryptamine
OCR	Oxygen-conserving reflexes
RDH	Retinodural haemorrhage
SBS	Shaken baby syndrome
SDH	Subdural haemorrhage
SIDS	Sudden infant death syndrome
SUDI	Sudden unexpected death in infancy

The cause of death in infants who die suddenly and unexpectedly (sudden unexpected death in infancy [SUDI]) remains a diagnostic challenge. Some infants have identified diseases (explained SUDI); those without explanation are called sudden infant death syndrome (SIDS). Demographic data indicate subgroups among SUDI and SIDS cases, such as unsafe sleeping and apparent life-threatening events. Infants dying suddenly with retinal and dural bleeding are often classified as abused, but in many there is no evidence of trauma. Demographic features suggest that they may represent a further subgroup of SUDI. This review examines the neuropathological hypotheses to explain SIDS and highlights the interaction of infant oxygen-conserving reflexes with the brainstem networks considered responsible for SIDS. We consider sex- and age-specific vulnerabilities related to dural bleeding and how sensitization of the dural innervation by bleeding may influence these reflexes, potentially leading to collapse or even death after otherwise trivial insults.

The term sudden unexpected death in infancy (SUDI) is defined as the sudden unexpected (or unclassified) death of an infant of younger than 1 year of age, and includes explained and unexplained deaths. All of these infants share the characteristic feature that 24 hours before death (or collapse that led to death), the caregivers were unaware that there was a risk of the infant dying.[1]

The group includes infants who have some kind of disease process identified (explained SUDI), infants who have no explanation and are classified as sudden infant death syndrome (SIDS), and infants who die in unsafe sleeping conditions (co-sleeping or overlaying). A further subgroup may be represented by infants who have had an apparent life-threatening event.[2] Sudden unexplained death in infancy, overall, is the most common cause of death in infants of 1 month to 1 year of age in the USA.[3]

The cause of death in infants who die suddenly and unexpectedly in infancy remains a diagnostic challenge, despite many years of research. Explanations proposed for SUDI include accidental and non-accidental causes, sepsis, and abnormal gut microbiome.[4–6] Cardiac disorders are identified in some, including mutations in cardiac ion channel genes and delayed maturation of the cardiac conduction system.[7,8] Almost 10% of infants diagnosed as SIDS carry functionally significant genetic variants in long QT syndrome genes.[9] Metabolic conditions such as medium-chain acyl-CoA dehydrogenase deficiency may be responsible for a very small percentage of sudden deaths.[10] Exposure to tobacco smoke[11] and to drugs of addiction during pregnancy[12] may increase the risk of sudden death in infants. In a small but unknowable proportion, sudden death results from intentional suffocation.[13] Subtle hippocampal abnormality has been described in a proportion of SIDS deaths,[14] and seizures may play a role in the terminal pathway in a subset of victims.[15,16] Central nervous system mechanisms that might mediate sudden infant death have been reviewed by Thach.[3]

If thorough investigation (including complete autopsy and death scene examination) is negative, the definition is one of SIDS. Although there are controversies over the use of this term it remains of assistance, with the caveat that it represents a group of causes of death, some of which will eventually be identifiable as specific medical conditions.[17] Some also include in the definition of SIDS that death occurs during sleep.[18] For the last two decades, the prevailing hypothesis to explain SIDS is a triple risk model, in which death occurs when an infant with an underlying intrinsic vulnerability is exposed to an exogenous stressor

or trigger at a critical developmental stage.[19] Abnormality of specific brainstem neuronal networks has been described in SIDS.[20]

Both explained and unexplained sudden infant deaths may result from the intersection of multiple factors which lead to the same terminal process likely involving hypoxic-ischaemic encephalopathy.[1] Analysis of pooled data from the UK, USA, Norway, and Germany suggests that both share genetic and age-related physiological vulnerabilities that interact with environmental factors. When an infant is faced with, for example, hypoxic challenge in the early months of postnatal life, these vulnerabilities lead to failure of the brainstem neuronal networks; reflex respiratory responses fail and lead to sudden death.[1]

Based on the sex ratio, infants who die while co-sleeping with a carer or in an unsafe situation form a distinct subgroup, with potentially different lethal mechanisms from those who die alone;[21] the sex ratio of infants who die while sleeping alone was 2:1 (males to females), compared with 1:1 of those sleeping with another. While bed-sharing is more common among males, both those who die of SIDS and controls, the male predominance in SIDS is confined to infants who do not co-sleep.[22] The co-sleeping group makes up an increasing proportion of SIDS deaths and is associated with a decrease in the peak age of SIDS.[23] The risks of bed-sharing are complicated by parental exposure to tobacco, alcohol, and drugs.[22,23]

Another group of infants who die suddenly and unexpectedly have retinodural haemorrhage (RDH). These infants are often classified as victims of abusive head trauma, and labelled as non-accidental head injury or shaken baby syndrome (SBS). While trauma may be an obvious diagnosis in some, in others there is no physical or historical evidence of trauma. Where there is no objective evidence of trauma, it is appropriate to be cautious; early presumption of trauma risks incomplete assessment of the cause of death. Full regard should be given to the empirical clinical and pathological evidence; infants with RDH without evidence of trauma are better classified objectively as having RDH of infancy. Infants with RDH share the same distinct age and sex characteristics as SIDS and SUDI cases, which suggests that they might be considered a subgroup of SUDI classification. This proposition is limited by the lack of case–controlled epidemiological studies of infants with RDH compared with the many studies of explained and unexplained SUDI. We, at the outset, set forth that this proposition is not an attempt to reclassify deaths in infants who have RDH. Instead what follows is an exploration of how dural bleeding may present a risk factor for sudden infant death in this age group by its influence on the caudal brainstem 5-hydroxytryptamine (5-HT) networks responsible for maintaining respiration.

BRAINSTEM CONTROL OF RESPIRATION DURING THE TRANSITION TO AIR BREATHING

Fetal breathing movements first begin at 10 weeks' gestation and increase in frequency as pregnancy progresses.[24]

What this paper adds

- There is wide demographic overlap of infants with sudden unexpected death and those with non-traumatic subdural haemorrhage.
- In some cases of sudden unexpected death, the mechanism of subdural haemorrhage can be explained.
- Subdural bleeding may cause exaggerated and potentially harmful oxygen-conserving reflexes.
- Oxygen-conserving reflexes act via the brainstem neuronal networks considered responsible for sudden infant death syndrome.

At birth the fetal breathing pattern changes virtually instantaneously to a continuous pattern; the stimuli for this remain incompletely defined.[25] In the weeks after birth a regular breathing pattern and cardiorespiratory coupling are coordinated with sucking and swallowing through pattern generating neuronal networks in the brainstem.[26] Breathing patterns are not controlled by individual neuronal nuclei but by multiple pathways in neuronal networks including the preBötzinger complex and the Kölliker-Fuse, as well as some cortical and cerebellar networks.[27–29] In response to stresses such as hypoxia, these networks are able to reconfigure, generating multiple breathing patterns and facilitating auto-resuscitation.[30] These networks are part of the caudal 5-HT system, which undergoes significant developmental changes throughout late fetal and early infant life. There is a reduction in 5-HT receptor binding from mid-gestation to the neonatal period and from infancy to childhood.[19] The networks have a critical role, not only in cardiorespiratory control, but also in autonomic function, sleep and arousal, and in regulating upper airway protective reflexes.

Factors responsible for maintaining the neuronal networks include brain derived neurotropic factor, which mediates communication between neurons and astrocytes and is thought to be responsible for stable respiratory rhythm.[31] The neuropeptides orexin A and B are critical for maintaining levels of arousal, waking, and sleeping states. They are expressed in the hypothalamus and brainstem nuclei. Recent studies on infants dying with SIDS showed reduction of up to 50% in orexin levels in the pons compared with age- and sex-matched infants dying from other causes.[32]

Instability in the early control of breathing is reflected in the frequency with which apnoea occurs in young infants. Brief apnoeic spells are common within the first few minutes after birth, later more prolonged episodes of apnoea are seen in association with prematurity, laryngeal chemoreflex activity, or 'breath holding' apnoeic episodes which may be associated with bradycardia and loss of muscle tone ('near-miss SIDS' or apparent life-threatening events).[33,34] Prospective monitoring has demonstrated episodic apnoea and bradycardia days or weeks before death in infants who subsequently died of SIDS.[35]

While the system is still immature, life-threatening challenges such as hypoxia, hypercapnia, or regurgitation during sleep provoke the caudal 5-HT networks to generate reflex responses leading to arousal and auto-resuscitation.[30] Failure of these reflex responses is currently accepted as the final

common pathway in SIDS, supported by observation of significantly decreased levels of 5-HT, altered neuronal density and neuronal maturation in the caudal 5-HT system in 50% to 75% of SIDS cases.[19,20] However, the caudal 5-HT network is part of a wider 'serotonin axis' including the rostral 5-HT system in the midbrain and pons, and throughout the brain including the limbic system, hippocampus, and neocortex.[15] Abnormalities in the rostral 5-HT system, including the dorsal motor nucleus of the vagus, nucleus of the solitary tract, and arcuate nucleus, which have important roles in cardiorespiratory control and chemosensation, have been shown in SIDS cases.[36,37] An increase in the neuropeptide substance P in the spinal trigeminal nucleus and nucleus tractus solitaries has been described in SIDS, and is significantly associated with astroglial proliferation in the medullary reticular formation.[38] This is potentially highly significant with respect to the interrelationship between the trigeminal nerve-mediated oxygen-conserving reflexes (OCR) and the caudal 5-HT system.

UPSTREAM INFLUENCES ON THE MEDULLARY 5-HT SYSTEM

Higher systems projecting into the brainstem 5-HT system may contribute to the mechanisms of sudden death in infants. Two have received increasing attention in recent years and are worthy of further consideration in the context of this review. These are the temporal lobe and hippocampus with the inherent capacity to generate seizures, and the sensory system of the airways, face, and head as part of the upper airway and OCR system.

The hippocampus, seizures, and apnoea

It has been proposed that seizures may influence the brainstem 5-HT pathways in some SIDS cases, sudden death resulting from temporary dysfunction of 5-HT neurones because of seizure activity, or failure of the 5-HT system to respond to stressors in the post-ictal state.[15] Infants with apparent life-threatening events show considerable demographic overlap with infants with sudden unexpected death from epilepsy.[16] Febrile seizures may, in conjunction with 5-HT deficiencies, cause failure of auto-resuscitation. Several clinical examples indicate seizures as a cause of sudden death in infants; pathological abnormalities and asymmetry have been described in the hippocampus in both infants and toddlers who die unexpectedly.[14] Reduction in hippocampal microtubule-associated protein 2-positive (MAP-2) neurones has been described in SIDS victims and infants with hypoxic-ischaemic injury but not in normal controls.[39] Apnoea may be the only manifestation of seizure activity and has been described in infants with temporal lobe haemorrhage associated with focal epileptic activity identified on electroencephalography.[40]

Sensory afferents from the upper airway: oxygen-conserving reflexes

Sensory nerves from the upper respiratory tract, nasal passages, face, and head project into the brainstem centres controlling respiration and form the afferent arm of the OCR. This is a set of finely-tuned responses, which are most pronounced in the immature infant and which protect the brain against oxygen deprivation during the transition to air breathing in the first months of life. These reflexes include the laryngeal chemoreflex, the trigeminocardiac reflex, and the dive reflex.[41–44]

The trigeminal sensory system

Electrical or mechanical stimulation of the trigeminal nerve evokes dramatic bradycardia, hypotension, apnoea, and gastric hypermotility in experimental animals and in humans.[45] The OCR are mediated by a powerful excitatory and polysynaptic pathway via the vagal nuclei and are modulated and facilitated by the caudal 5-HT network. Abnormal 5-HT function could lead to an exaggerated endogenous facilitation of the OCR in SIDS victims.[41,46,47]

The OCR are activated by stimulation of any sensory branch of trigeminal nerve: examples include airflow stimulation of the face, cold or water on the face and in the nasal passages, craniofacial surgery, and dural inflammation.[48,49] Application of a facemask in newborn term infants causes a reduction in respiratory frequency because of facial trigeminal stimulation,[50] and the dive reflex is exploited in treatment of supraventricular tachycardia in infants by applying ice to the face to lower heart rate.[51] While many studies have addressed the effects of gastric contents on the laryngeal sensory receptors,[52] the effect of gastric contents on nasal trigeminal receptors during reflux does not appear to have been studied.

The predominance of OCR in early life corresponds with far denser sensory innervation of the face and head than in later life. In the rat model, the extensive arterial and forehead trigeminal innervation in the rat at birth is 'pruned' by postnatal remodelling involving retraction of nerves, cell death in the trigeminal ganglion, and re-specification of neuropeptide expression.[53,54] Similarly, human dural innervation increases between 31 weeks of gestation and term, is greatest at term, and subsequently decreases in the first 5 postnatal months.[55]

The concept that protective reflexes may be fatal is paradoxical, but dysfunction of these reflexes is implicated in SIDS and in cerebral hypoxia after intubation of young infants.[41,42,56] Clinically, OCR are observed during ophthalmic and craniofacial surgery, but their incidence is under-recognized because of routine use of prophylactic anticholingeric medication when anaesthetising infants.[43] Clinical case reports of OCR in infants are rare; significant sudden hypotension and bradycardia have been described in an adult after drainage of a subdural empyema and in an 18-month-old child after repeat intracranial surgery on the dura. In both cases inflammatory sensitization of dural trigeminal afferents was considered to be an important predisposing factor.[49,57] 'Delayed dive reflex' was described in an infant who died after cold water immersion and at autopsy had brainstem gliosis.[58] Krous et al.[59] describe five infants with 'awake SIDS', in four of whom nasal or

laryngeal stimulation was implicated in triggering a response; one infant collapsed shortly after having saline sprayed into the nostrils followed by syringe bulb suction, and three collapsed during feeds. Reversible cerebral vasoconstriction is described in children after water immersion (such as swimming and diving) or use of a nasal spray.[60]

The responses of the trigeminal sensory afferents may be modified and enhanced if they are exposed to inflammatory mediators and become sensitized. In the laboratory, application of 'inflammatory soup' to the exposed dura causes trigeminal sensitization and increased responsiveness, so that dural afferents can be strongly activated by mechanical and other stimuli that initially had evoked little or no response.[61,62] This may be highly relevant in human disease. Trigeminal sensitization by inflammation is considered to be one of the pathways to migraine.[63] Bleeding in the human dura, which produces an inflammatory response and increased mast cell numbers,[64,65] may potentially sensitize the trigeminal system,[66] and has been implicated in inducing the trigeminocardiac reflex.[49,57]

Laryngeal chemoreflex

The larynx guards the lower respiratory tract and protects it from aspiration of fluids. The laryngeal epithelium is richly endowed with sensory nerve endings that project into the nucleus of the tractus solitarius, which is closely associated with the dorsal motor nucleus of the vagus and projects to the caudal 5-HT networks.[19,67] When stimulated chemically or mechanically, laryngeal afferents give rise to rapid and profound protective responses, including startle, rapid swallowing, apnoea, laryngeal constriction, hypertension, and bradycardia.[44] Upper respiratory infections, hypoxia, and anaemia may lead to a prolonged and more severe apnoeic response.[52] Anaemia has been found in infants suffering apparent life-threatening events.[68]

In clinical practice, stimulation of the larynx by intubation of young infants can lead to unstable bradycardia and the risk of secondary cerebral ischaemia; these effects are exacerbated by extreme prematurity, hypoxia, sepsis, and raised intracranial pressure.[56] The laryngeal reflex response is important in the fetus to prevent amniotic fluid aspiration; while prolonged laryngeal closure and apnoea does little harm to the fetus, after birth this would be harmful to the infant who is dependent on air breathing. During early postnatal life the laryngeal chemoreflex is modified, and neonates respond to the presence of water in the larynx with increased swallowing, bradycardia, apnoea, and little or no coughing, but by adult life the same stimulus generally elicits coughing and only a brief interruption of breathing.[35,52] Similarly, immaturity of vagal irritant reflexes has been implicated as a cause for silent aspiration and apnoea in infants born preterm.[69] Gastro-oesophageal reflux may trigger the laryngeal chemoreflex when gastric contents pool around the larynx.[70] Gastro-oesophageal reflux is common in the first months of postnatal life, peaking at 3 to 4 months. It is associated with apnoea and cyanosis and, with other feeding difficulties, forms the most common cause of apparent life-threatening event in infants.[2] Gastro-oesophageal reflux is also associated with sudden death.[71,72] It has been proposed that laryngeal chemoreflex may play a role in some cases of SIDS[35,52]; 14% of SIDS cases have evidence of aspiration.[73]

DEMOGRAPHICS OF SBS AND SIDS

Exogenous triggers

Many of the demographic features represent exogenous stressors such as minor infections, maternal smoking, alcohol and drug use, and social deprivation (Table I). Unsafe sleeping may introduce the risks of hypoxia, hypercapnia, and hyperthermia. Many of these demographic features have not been fully studied for either group. Nutrition may be important and congenital vitamin D deficiency is now being recognized increasingly in Western populations.[74] Not only may this cause abnormal bone development but it is also linked to immunodeficiency and abnormal blood clotting.[75,76] Animal studies have demonstrated abnormal brain development in congenital vitamin D deficiency.[77] In older studies of infant subdural haemorrhage (SDH), malnutrition and economic deprivation were noted in more than a third of patients, and infections, considered to reflect poor general health and malnutrition, were seen in almost one-half.[78] Vitamin C and D deficiency, sepsis, and specific infections were considered important.[79]

Intrinsic vulnerabilities: age, sex, and prematurity

Byard et al.[21] have noted the importance of demographic features in distinguishing subgroups of sudden infant deaths. There is a long list of intrinsic demographic factors common to both SIDS and infants who die with unexplained RDH (when classified as SBS) – notably age, sex, prematurity, and congenital anomalies.[35,80–83]

Age

There is a remarkable overlap of age at death in infants with SIDS and RDH, with the peak incidence in both at

Table I: Demographics of shaken baby syndrome (SBS) and sudden infant death syndrome (SIDS)

SBS[80–82,87]	SIDS[17,83,86]
Less than 1 year of age	First year of life
Male infants	Male infants
Prematurity	Prematurity
Young mothers	Young maternal age
Single mothers	Single mothers
Multiple births	Multiple births
Low birthweight	Low birthweight
More than three children	High parity
Smoking during pregnancy	Tobacco exposure
Disability in the child	Congenital anomalies noted at birth
Minor respiratory symptoms	Minor infections
Anaemia	Anaemia
Socioeconomic factors:	*Socioeconomic factors:*
Low maternal education	Low parental education
Unstable families	Unemployed parent/s
Extended family in the home	Drugs/alcohol
Parent in the military	

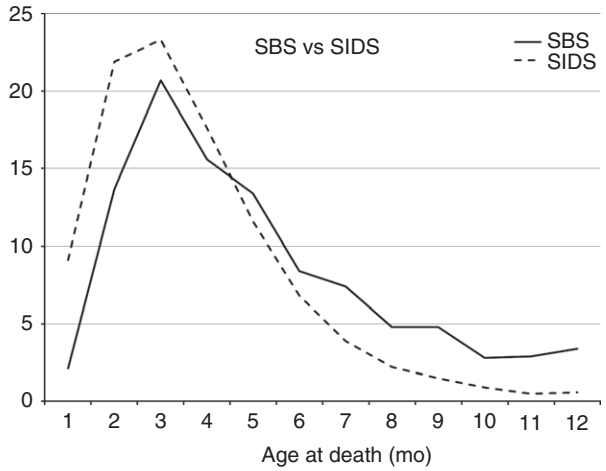

Figure 1: Percentage of deaths caused by sudden infant death syndrome (SIDS) or shaken baby syndrome (SBS) for each month of age in the first year of life.[84] See also: http://www.babywill.org/sids-information/what-is-sids/sids-statistics.

12 weeks (Fig. 1).[17,80,81,83–87] The average age of the explained SUDI cases is higher (median 127d) with a higher proportion of deaths in the first month of life (18%) and after 196 days (35%).[83] Recent studies have shown that the peak age of SIDS has declined, possibly because of an increased proportion of infants who are co-sleeping.[23]

The brainstem neuronal networks controlling respiration are still undergoing developmental changes in infancy and childhood.[19,20] The density of human dural innervation increases throughout late fetal life to a maximum around birth.[55] This suggests that there are specific age-related functions of the dura and its innervation. In preliminary studies we have shown expression of the neuropeptides substance P and calcitonin gene related peptide in dural nerve fibres to be highest in fetuses and neonates, coupled with greater neural density and a greater mast cell population in this age group. These facts suggest that the fetal and infant brain may have the potential for a far greater range of responses to stimulation of the dural trigeminal innervation than in later life (Davidson J, Mack J, Varatharaj A, Squier W. Age specific responses of the dural trigeminal innervation to dural bleeding. Unpublished).

Sex

Males consistently account for two-thirds of both SIDS and RDH. Epidemiological and experimental evidence points to potential sex differences in physiology related to hypoxia and SIDS risk; males predominate in deaths caused by respiratory distress syndrome, bronchopulmonary dysplasia, accidental suffocation, acute respiratory infection, and inhalation of food.[30] Males also predominate in infants born preterm dying out of hospital in the post neonatal period.[86] The substrate for male vulnerability to SIDS has been suggested to be specifically reduced 5-HT binding in the brainstem.[20]

As noted above, Byard et al.[21] have indicated a distinction between SIDS and co-sleeping infants on the basis of the sex ratios in these two groups. Several conditions which involve the trigeminovascular system show a degree of sex specificity. After adolescence, migraine is twice as prevalent in females. This is not seen in children, where migraine rates are the same in males and females.[88]

There is male predominance of infant SDH,[78,89–92] and infants with increased head circumference caused by intracranial bleeding show a male excess of 3:2 M:F.[93] Infants with enlarged extra-axial spaces (an imprecise category which includes subdural fluid collections) show striking male excess, generally far over 2:1 M:F.[93–95] A pathogenetic link between these groups may be explained by dural bleeding causing neurogenic inflammation, which leads to increased vascular permeability, dural effusion, and enlargement of the extra-axial spaces.[66] Our unpublished results also showed variation in neuropeptide expression with sex: substance P was lower in female than male children and higher in female than male adults. Fetuses did not show any sex differences (Davidson J, et al. Unpublished). The density of nerve fibres expressing trigeminal neuropeptides in rat cerebral arteries has been shown to be influenced by sex and by pregnancy,[96] indicating that female hormones may upregulate neuropeptide expression.

Male predominance in retinodural haemorrhage: SBS, trauma, and natural causes

The data on sex ratio suggest differences between infants with SBS and those who have evidence of trauma, but a major pitfall lies in the definition of SBS and head trauma. Retinal and dural bleeding occur in natural conditions but are often used as the basis for a diagnosis of inflicted head trauma and SBS. In some reports it is possible to identify infants with clear evidence of trauma, such as external signs of head trauma, fractures, and thoracoabdominal trauma. These reports indicate that male and female infants equally suffer head injuries where there is clear evidence of impact. Vinchon et al.[92] found epidural bleeding and fractures (characteristically associated with trauma) in almost equal numbers in male and female infants (M:F 1.36), while subdural and subarachnoid haemorrhage were significantly more common in male infants (M:F 2.7). Vinchon et al. suggested that head injuries are not much more common in males, but more often cause intracranial bleeding. They interpreted their observations as indicating a greater fragility of meningeal structures in males, possibly in relation with a larger head with enlarged arachnoid spaces, a hypothesis shared by Miller and Miller.[90] Vinchon et al.'s series included cases classified as abuse on the basis of RDH and the absence of history of trauma; they admits the circular reasoning of their study and that some of these cases may not have been victims of trauma.

These findings suggest that in infants with RDH, SDH shows a male predominance which is not seen when there

is independent evidence of trauma such as fractures and bruises.

Prematurity

Infants born preterm undergo the transition to air breathing when they are physiologically ill-equipped. Very preterm infants are at greater risk from SIDS (odds ratios [OR] 2.57 times higher than term infants), but show a much higher risk from 'other' sudden deaths (OR 6.8 times higher than term infants); the most common 'other' cause of death being asphyxia.[86]

The neuropathology of infants born preterm shows diffuse white matter injury as a common substrate for cerebral palsy.[97] The brainstem is highly vulnerable; neuronal loss and gliosis are commonly seen in infants born preterm both by neuropathology and by advanced magnetic resonance imaging in survivors.[98,99] Loss or impairment of the function of the cells involved in the networks controlling respiration provides a likely cause of the increased risk of sudden death in infants born preterm, and may explain the high incidence of 'asphyxial' deaths in this group.

RETINODURAL HAEMORRHAGE IN INFANCY

The demographic features of infants with SIDS show striking overlap with infants who present with unexplained retinal and subdural bleeding.[80,81] The difficulties in distinguishing infants with unexplained RDH from those with traumatic causes were discussed above.

While these infants are most often thought to have suffered from SBS or abusive head trauma, this mechanism is speculative and has faced increasing criticism.[100–102] Therefore, a comparative analysis and pathological reassessment is overdue.

The most striking similarity between infants with SIDS and those with RDH is the mean age at presentation (Fig. 1). Infants in both groups present at a peak age of 12 weeks; in both there is a male predominance of 60%, and in both a mild prodromal illness is often described. The many other common demographic features suggest that we should consider whether infants with RDH and no associated evidence of trauma may represent a subgroup of infants at risk for unexpected death (Table I).[35,83] If this is the case, then explanations for mechanisms of RDH and SDH in these infants must be sought.

Five potential explanations need to be considered for RDH in the absence of evidence of trauma: (1) RDH is part of the secondary cascade of effects after collapse and prolonged hypoxia with cardiopulmonary resuscitation (CPR); (2) The dural blood is related to birth and is a bystander, coincidental and unrelated to cause of death; (3) The dural blood is related to birth and is not simply a bystander but by causing dural inflammation makes the infant more vulnerable to apnoea and subsequent collapse through overstimulation of OCR; (4) Intradural bleeding may be misinterpreted on scans as SDH; and (5) A coexisting disease or diseases are present and associated with RDH but missed because of the diagnostic focus on suspected trauma.

Prolonged hypoxia and advanced resuscitation

The diagnostic criteria for SIDS include absence of any pathological finding and death in sleep or a sleep-related state;[18] these infants have no resuscitation. On the contrary, infants who die with unexplained RDH are usually found recently collapsed or still awake and have a history which usually involves aspirating a feed, choking, seizures, gasping respiration, or apnoea, followed by a prolonged period of hypoxia and CPR. Severe and prolonged hypoxia is associated with a secondary cascade of reactive processes and these infants also may have superimposed advanced resuscitative measures. Experimental models of reperfusion injury confirm that the longer the periods of ischaemia, the greater is the small vessel damage and breakdown of the blood–brain barrier. This is exacerbated by resuscitation and reperfusion.[103,104] Two studies have examined SIDS cases who died after CPR after collapse. In five cases who died of 'awake SIDS', CPR did not exceed 18 minutes. The dura was described in only one infant and this infant had intradural haemorrhage. In 'delayed SIDS', 12% had intradural bleeding and 4% subdural bleeding, defined as 3–5mL of parafalcine blood.[59,105] These may be underrepresentations because both were retrospective reviews of autopsy reports.

Because CPR produces surges of raised intrathoracic pressure, which are transmitted via the venous system to the dural sinuses,[106] patients who undergo extended CPR may experience abnormal dural venous sinus pressures exacerbated by reperfusion. Increased dural venous pressures combined with reperfusion injury may predispose to bleeding from the intrinsic dural venous plexus (the most likely source of SDH described in healthy newborn infants). A similar and statistically significant association among CPR, reperfusion, and cerebral oedema with retinal and optic nerve sheath haemorrhage has been outlined by Matshes (Matshes E. American Association of Forensic Sciences Conference, 24 February 2010).

Some studies have suggested that hypoxia does not cause RDH.[107–109] There are several caveats to this suggestion. First, hypoxia alone is not proposed as a cause of subdural bleeding, although there does appear to be an association between the two. Second, these studies are retrospective reviews and may underestimate small volume SDH, which can only be identified using careful techniques to open the skull with detailed examination of the dura and subdural compartment at the time of autopsy.[110,111] The period of hypoxia, whether or not CPR was employed, and for how long are important factors which are not addressed in these studies. Kelly et al.[112] found no association between SDH and hypoxaemia in infants with congenital heart disease who had undergone surgery. However, these infants had no recorded acute collapse or advanced resuscitation in the period of study.

The dural blood is related to birth and is a bystander, coincidental and unrelated to cause of death

Radiological observations in the last 10 years have demonstrated that almost half of healthy asymptomatic newborn infants have dural bleeding.[113–115] Kelly et al.[112] showed a similar proportion of neonatal SDH in infants with congenital heart disease, confirming the observation by pathologists that intradural and subdural bleeding is extremely common in neonates, even those who lack evidence of either trauma or overt hypoxia.[116–119]

That dural bleeding is so common as to be regarded as almost normal in the newborn leads to the question of whether it may represent a provision to protect the brain during birth. The dural venous plexuses, which are the likely source of this bleeding, are larger and more complex at birth than at any other time, and are particularly extensive around the confluence of sinuses, in the posterior falx, cerebellar falx, and tentorium.[120,121] These are not only the most common sites of SDH identified in healthy neonates, but also are the characteristic sites of SDH in infants diagnosed as SBS/abusive head trauma.[80,114,122]

Venous blood flows from the brain to the dural sinuses and intradural venous tributaries via valveless communications, finally flowing into the extracranial venous system to return to the heart. Dural venous sinus pressure is increased by pressure on the head, altered head position, obstruction of the jugular veins, and also by positive pressure ventilation.[106] It is likely that the pressures exerted on the infant during labour and delivery would similarly compromise venous return and increase pressure in the dural venous system. Were these pressures to be transmitted to the brain, the smallest terminal vessels in the cerebral parenchyma would bleed. The large venous lakes in the immature dura may represent reservoirs[106] that accommodate venous blood and thereby reduce the risk of reflux into the cerebral parenchyma. Sphincters at the outflow cuffs of the bridging veins, which are active during raised intracranial pressure, may assist in preventing reflux into the brain.[123–126] As there are no such sphincters on the small intrinsic dural vessels draining into the dural sinuses,[127,128] increased pressure within the sinuses likely results in preferential flow into these small dural vessels. When the capacity of the intradural venous reservoir is surpassed, intradural bleeding can occur. Intradural bleeding, if extensive, can leak into the subdural compartment and routinely accompanies SDH in non-traumatic cases.[116] The presence of a reservoir for venous blood accommodating the pressure fluxes of birth is clearly an advantage for survival if it protects the brain. The slow regression of the intradural plexuses comprising this reservoir during the first years of life may protect the brain during a period of rapid growth and high blood flow,[121,129] but also confers an increased risk of intradural bleeding during this period, which is reflected in the higher incidence of SDH in young patients.[128]

Almost a third of infants who collapse with SIDS are harbouring the residua of old dural bleeding; this is regarded as the most common birth-related pathology identified at routine autopsy of SIDS victims.[130,131] Old SDH is also common in cases attributed to non-accidental injury.[81,122,132,133]

Healing subdural membranes are characterized pathologically by numerous thin-walled blood vessels and foci of repeated bleeding in the absence of trauma.[134,135] The presence of small amounts of fresh blood in conjunction with chronic SDH must not, therefore, be construed as direct evidence of trauma, either accidental or abusive.

The dural blood is related to birth and is not simply a bystander

While chronic SDH may be a totally innocent bystander, dural bleeding may itself play a more active role in triggering collapse by contributing to increased vulnerability to collapse after what might otherwise be considered a minor and innocuous event in an infant.

Chronic infant SDH is associated with a range of clinical symptoms, many rather non-specific, such as feeding difficulties and reflux. The cause is not clear because the blood is separated from the brain by the arachnoid barrier membrane, so does not cause direct cerebral irritation. The signs are not apparently caused by increased pressure because they are identified in infants who do not show evidence of increased head size or full fontanelle.[78,91]

SDH induces an inflammatory response which is recognized by pathologists.[135] Dural inflammation, even an acellular 'inflammatory soup', both stimulates and sensitizes dural trigeminal sensory afferent fibres, causing them to be activated by stimuli that previously evoked little or no response.[62] Mast cells in particular can evoke prolonged activation of trigeminal pathways,[136] and their density is increased in response to dural haemorrhage.[65] The infant dura may be particularly prone to sensitization because it is more densely innervated than in later life.[55] Chronic SDH may be more than an innocent bystander; overactivity of trigeminal afferent innervation may provoke aberrant or exaggerated OCR and lead to apnoea, bradycardia, and sudden death after otherwise trivial events. Chronic subdural inflammation is considered to be an important predisposing factor for the trigeminocardiac reflex.[49,57]

Intradural bleeding may be interpreted on scans as SDH

The bleeding seen on scans and interpreted as SDH of traumatic origin in living infants may be intradural. Clinical brain scanning does not have sufficient resolution to distinguish with certainty small amounts of subdural blood from intradural blood; in some cases subarachnoid blood may be confused with subdural blood.[137,138] The misidentification of the location of the haemorrhage is particularly likely with small volume SDH, and therefore it is important to recognize that in some infants only 2–3mL may be present and diagnosed as SBS.[110] Because coagulation parameters may be altered in the hours and days before death in ventilated infants, one must be cautious in

assuming that all blood seen at autopsy was present on admission to hospital. Intradural bleeding that extends into the subdural compartment should be evaluated in the context of any disturbance of the coagulation parameters.

Focal intradural bleeding that extends into the subdural compartment is a reflection of the volume of blood present and does not denote cause. Intradural bleeding can be seen in non-traumatic conditions; focal and diffuse intradural bleeding is so common in neonates at autopsy as to be considered virtually normal.[118,119,137] In addition, any complication of intradural bleeding should be evaluated with the understanding that stimulation of the trigeminal nerve may result in dural vasodilation and increased vascular permeability leading to leakage of plasma proteins.[139,140]

A coexisting disease or diseases associated with RDH may be missed because of focus on suspected trauma

There are many causes for subdural bleeding, some extremely rare but which must be considered and excluded in the full evaluation of these infants.[141] Venous thrombosis is reported in association with subdural and subarachnoid haemorrhage[142–144] and can be difficult to diagnose. Failure to investigate these conditions may deny the infant and other family members accurate diagnosis and the opportunity of treatment.

THE SIGNIFICANCE OF RETINAL BLEEDING

Retinal haemorrhage so often accompanies SDH in the infant that it has been described as pathognomonic for it.[91] Like SDH, retinal haemorrhage is common after birth, occurring in about a third of all neonates.[145–147] It is described in 75% of vacuum, 33% of vaginal, and 7% of Caesarean deliveries, with no association with asphyxia or traumatic cyanosis at birth.[146,147] Critchley found a striking male predominance, but the sample was small.[148]

The concordance between SDH and retinal haemorrhage is not surprising given that the eye develops from, and is part of, the brain. The eye is surrounded by the same membranes as the brain, the sclera being a modification of the dura which surrounds the optic nerve. Clinical examination of the eye provides a unique opportunity to visualize directly, in life, a part of the brain, its vascular system, and its responses to disease. The retinal vessels have a similar structure and cellular and extracellular components as the blood vessels of the brain,[149] and share the same innervation and capacity for neurogenic inflammation as cerebral vessels.[150] Venous drainage from the eye is in part via the dural sinuses. In most infants, the cavernous sinus is not yet connected to the cerebral veins, resulting in less reserve and increased vulnerability within the venous drainage system.[144] Severe brain swelling while on life support is associated with enhanced blood flow in the superior ophthalmic veins, thought to be caused by diversion of blood from the internal carotid to the ophthalmic arteries and impaired venous drainage through the cavernous sinus.[151] These factors could predispose to retinal haemorrhages in ventilated infants.

Although the way in which infant retinal haemorrhage develops is a matter of debate, the anatomy of the eye suggests that it develops in much the same way as other intracranial haemorrhages. The venous drainage of the retina and anterior optic nerve is almost exclusively via the central retinal vein. This vein is surrounded by the subarachnoid space and dura, which is subject to fluxes of intracranial pressure. Pathological studies have indicated that venous hypertension, stasis, and leakage from retinal vessels are likely mechanisms.[152,153] The blood vessels of the brain respond to raised venous pressure by diapedesis of cells – that is, leakage of blood around them – causing localized perivascular haemorrhages. Similar leakage in response to pressure changes in the eye would provide an anatomical and pathological explanation for the observed orderly pattern of infant retinal bleeding along vascular arcades.

As with SDH, the patterns of retinal haemorrhage described in abusive head trauma and birth-related bleeding are similar. Both are found around the disc and vascular arcades and may be similarly severe, extending anteriorly to the ora serrata.[145–147,154]

The similarity between birth-related haemorrhages, and the haemorrhages that may be seen with RDH should prompt consideration that their mechanisms are similar and may include, as pointed out by Emerson et al.,[152] hemodynamic and biochemical alterations. In the cases of unexplained deaths that include dural haemorrhage, retinal haemorrhage may be part of a cascade of responses by the immature brain to destabilization of the intracranial environment whether by pressure fluxes, altered vascular perfusion, oxygen deprivation, or, most likely, some combination of these factors.

FUTURE ASPECTS

Further studies are needed to better understand the epidemiology of infants with RDH and whether risk factors for SIDS are also risk factors for RDH. For example, prenatal exposure to nicotine is a risk factor for SIDS and in animal models induces an exaggerated bradycardic response to hypoxia.[155] Whether intrauterine exposure to tobacco has further effects on the likelihood of dural bleeding or its failure to rapidly resolve remains unknown.

CONCLUSIONS

The most compelling current hypothesis for SIDS is failure of the final common pathway of neuronal networks in the infant brainstem which are responsible for respiration, cardiorespiratory coupling, and auto-resuscitative responses to hypoxic threats to the brain. Projections into these networks from higher centres, for example the hippocampus and pathways which mediate the OCR, may be responsible for sudden infant death.

Infants with SIDS share many common demographic features with infants who die suddenly with RDH who may have no other evidence of a traumatic cause. There are several mechanisms that help to explain why some

SIDS cases also may have RDH. Our increased understanding of the infant dura suggests that its specific anatomy may protect the brain, as a reservoir for blood during surges in pressure at birth and during infancy, preventing reflux bleeding into the brain. However, this function also predisposes to intradural bleeding which may not always be benign. Sensitization of the dura by chronic haemorrhage and inflammation may provoke aberrant OCR and lead to apnoea, bradycardia, and asystole. These newly emerging concepts may help to explain sudden death from dysfunction of these reflexes in the early postnatal months.

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