Retinal haemorrhages associated with fatal paediatric infections

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Abstract
For many physicians, retinal haemorrhages (RHs) in infants and young children remain highly diagnostic of non-accidental (abusive) head trauma. Because clinicians have applied indirect ophthalmoscopy selectively to cases of suspected child abuse, the association between RH and other conditions such as infection, coagulopathy and accidental trauma has encountered habitual bias, creating the potential for iatrogenic misdiagnosis of child abuse. We present an autopsy case series of four children, aged three years old or younger, in whom RHs were detected by post-mortem monocular indirect ophthalmoscopy after the patients had died from infections. We discuss the laterality, number, type and location of RHs in these cases, and summarize proposed mechanisms of RH formation in fatalities from paediatric infection. We demonstrate that many of the ophthalmological findings that have been considered diagnostic of abusive head trauma can also occur in association with infective processes.

Keywords
Forensic science, intraocular haemorrhage, retinal haemorrhage, infection, sepsis, meningitis, encephalitis, abusive head trauma, non-accidental head injury, shaken baby syndrome

Introduction
Post-mortem indirect ophthalmoscopy allows pathologists to identify conditions associated with retinal haemorrhages (RHs), thus mitigating bias when considering the specificity of RHs. Since Kiffney’s paper on ‘the eye of the battered child’,¹ clinicians and pathologists alike have associated retinal pathology with non-accidental head injury (NAHI) in children. Subsequent publications have stressed this association, and for many physicians, RHs remain highly diagnostic of abusive head trauma (AHT) or shaken baby syndrome (SBS).²–⁶ Published reports of RHs are, however, now accumulating in association with accidental injury⁷–¹⁰ and disease processes, including infection and septicemia,¹¹–¹⁴ aneurysmal haemorrhage,¹⁵,¹⁶ raised intrathoracic pressure associated with extreme coughing or choking,¹⁷ compressive forces of labour or perinatal distress¹⁸,¹⁹ and haematological conditions such as leukaemia.²⁰,²¹ RHs in these conditions can go unrecognized because post-mortem ocular examinations are seldom performed, except in cases of suspected abuse.

RHs can occur in a variety of bacterial, viral, fungal and parasitic infections, sometimes in the absence of florid septicemia and coagulopathy.¹¹–¹⁴,²²–²⁹ Associated pathogens include group C Neisseria meningitidis,¹²,¹³,¹⁴ Streptococcus pneumoniae,¹⁴ Staphylococcus spp., Escherichia coli,²⁸ Brucella spp.,²⁹ polymicrobial bacteremia,²⁸ Herpesviridae,²²,²⁵ West Nile virus,²⁴ Candida albicans²⁸ and malaria.²⁶,²⁷

We present an autopsy case series of four children aged three years old or younger in whom RHs associated with fatal infections were detected by post-mortem monocular indirect ophthalmoscopy (PMIO).

Case studies
Case 1
A 10-week-old female infant presented to the Emergency Department (ED) following a short history of fussiness and constipation. She was discharged after receiving a prescription for glycerin suppositories. Later that day, her father found her unresponsive. Resuscitative efforts, including cardiopulmonary resuscitation (CPR), were initiated by emergency medical services (EMS) and continued for 90 minutes. Pressor medication and ventilator support were

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initiated upon arrival at the ED. Her initial coagulation studies showed a prothrombin time (PT) of 18.9 s (normal 8.9–12.1 s), a partial thromboplastin time (PTT) of 85 s (normal <30 s) and a platelet count of $155 \times 10^3$ (normal 160–360 $\times 10^3$). Seizure activity commenced shortly thereafter, and her condition continued to deteriorate until life-sustaining support was withdrawn 21 hours after presentation. No clinical fundal examination was documented in the medical record. Blood cultures drawn at her second presentation to the ED were eventually positive for group B Streptococcus.

The post-mortem interval at the start of her autopsy was 24 hours. Her external examination was unremarkable except for superficial skin abrasions consistent with resuscitative efforts. There was no other evidence of trauma.

Examination at autopsy revealed a single transverse hairline fracture of the anterolateral left second rib with minimal surrounding soft-tissue haemorrhage, consistent with injury incurred during CPR. No skull fracture or intracranial haemorrhage was present. A skeletal survey revealed no acute or healing fractures. Histology revealed dense acute inflammatory infiltrate, focal microabscess formation and venous inflammatory thrombi in the retropharyngeal soft tissues.

Histological examination did not identify meningitis or encephalitis. Her cause of death was sepsis complicating retropharyngeal cellulitis due to group B Streptococcus.

PMIO of the left fundus revealed innumerable, diffuse RHs extending past the equator in all quadrants (Fig. 1(a) and (b)). The right fundus contained no RHs. No perimacular retinal folds or retinoschisis were present in either fundus. Ocular examination following formalin fixation and sectioning revealed innumerable RHs and ciliary body haemorrhages of the left globe. Splinter, dot and flame-shaped haemorrhages in the left retina extended outward from the disc in all quadrants (Fig. 1(c) and (d)). Dot haemorrhages in a cluster the width of the disc were documented along the inferotemporal vascular arcade. Although fewer haemorrhages appeared at the equator, the ora serrata showed near-confluent haemorrhages circumferentially. Haemorrhages were located predominantly in the nerve fibre layer and were often confluent. Additional haemorrhages involved the ganglion cell and inner nuclear layers. The right fundus had a solitary area of hyperaemia and possible extravasated blood overlying the optic disc. No other abnormalities of the right fundus were identified. Optic nerve sheaths were hyperaemic bilaterally with small petechiae in the perineural fat and extraocular muscles.

**Figure 1.** Retinal haemorrhages (RHs) observed in Case 1. Projected aerial image during indirect ophthalmoscopy revealing multiple superficial RHs over the posterior pole of the left fundus (a). Direct ophthalmoscopic image of left posterior fundus showing peripapillary numerous splinter and flame-shaped RHs (b). Left eye following formalin fixation and removal of the cornea, ciliary body and lens demonstrating innumerable RHs over the posterior pole (c) and abutting the ora serrata (d). The linear, elevated papillomacular fold (c) is a post-mortem artefact.
**Case 2**

Following a two-week history of coryza and congestion, an eight-month-old male infant was found unresponsive by his father. Although resuscitative efforts began immediately and continued for 30 minutes following arrival at the ED, he failed to respond and was pronounced dead. No clinical fundal examination was documented in the medical record.

The post-mortem interval at the start of his autopsy was 17 hours. His external examination was unremarkable, with no traumatic injuries identified. A skeletal survey revealed no acute or healing fractures. Microscopically his lungs had engorged alveolar capillaries, and a few alveoli contained extravasated blood. There were increased numbers of chronic inflammatory cells within the airway walls and beneath the respiratory epithelium, characteristic of a mild bronchitis/bronchiolitis.

No scalp trauma, skull fractures, intracranial haemorrhage, cerebral oedema or injury to the underlying brain or spinal cord was found (Fig. 2(a) and (b)). However, microscopically, his cerebrum, brainstem and cerebellum showed diffuse multifocal T-cell inflammatory infiltrate with microglial nodules and neuronophagia. Inflammatory foci were found in the midbrain, pons and medulla (Fig. 2(b), inset). Lymphocytic involvement of the cerebral leptomeninges was evident, with small perivascular collections deep to the ependyma. Cerebral spinal fluid bacterial culture was negative, suggesting a viral aetiology. However, immunohistochemical staining and polymerase chain reaction were negative for enteroviruses and parechovirus. His cause of death was lymphocytic meningoencephalitis.

PMIO of the left fundus revealed numerous flame-shaped RHs. The right fundus had two small superficial RHs over the posterior pole. Subsequent ocular examination following formalin fixation revealed innumerable flame-shaped and splinter haemorrhages extending from the posterior left pole, past the equator, and abutting the ora serrata in all quadrants (Fig. 2(c) and (d)). The majority of these haemorrhages occupied the nerve cell layer, with a few foci in the ganglion cell layer. The right fundus showed two superficial, punctate, flame-shaped RHs near the equator. A solitary blot haemorrhage was also evident near the ora serrata. Optic nerve sheaths were free of haemorrhage.

**Case 3**

A three-year-old boy developed disseminated intravascular coagulation (DIC) in hospital while being treated for meningococcemia. His initial coagulation studies showed a PT of >60 s (normal 10.8–13.9 s), a PTT of >100 s (normal <34 s) and a platelet count of...
56 × 10³ (normal 160–360 × 10³). Despite aggressive treatment with antibiotics, blood products and blood pressure support, he developed a subarachnoid haemorrhage with underlying haemorrhagic infarct (Fig. 3(a)). His final coagulation studies showed a PT and PTT of 20.8 and 69.9s respectively. His condition continued to deteriorate until brain death was pronounced 39 hours after presentation to the ED. No clinical fundal examination was documented in the medical record.

The post-mortem interval at the start of the autopsy was 46 hours. There was no evidence of trauma on external examination but diffuse petechiae and purpura were on the face, trunk, neck and extremities. Scattered petechiae were on the palpebral and bulbar conjunctivae. Multiple petechiae were on the surfaces of the pericardium, pancreas, gastrointestinal tract and kidneys. The medullae of the adrenal glands were haemorrhagic.

An area of subarachnoid haemorrhage measuring 6.5 cm was over the right frontal lobe (Fig. 3(b)). The gyri were flattened, and mild tonsillar herniation was identified. A 3.5 cm × 5.5 cm haemorrhagic infarct bordered the area beneath the subarachnoid haemorrhage (Fig. 3(c)). The infarct was associated with a right-to-left midline shift and effacement of the ventricles. The cerebellum contained microscopic foci of tissue necrosis, neutrophils and Gram-negative diplococci. His cause of death was disseminated intravascular coagulopathy with cerebral intraparenchymal haemorrhage due to meningococcemia (*N. meningitidis*).

PMIO revealed multiple RHs over the right posterior pole but none in the left fundus. Following formalin fixation, ocular examination of the right fundus revealed multiple peripapillary and peripheral haemorrhages (Fig. 3(d)). The left fundus showed ill-defined areas of hyperaemia, but no haemorrhages were identified. Subdural and subarachnoid optic nerve sheath haemorrhages were present bilaterally, with greater prominence on the right than the left.

**Case 4**

A 14-month-old female with a two-week history of *Salmonella typhimurium* diarrhoea was found unresponsive while co-sleeping with her brother. Her parents were instructed to commence CPR immediately, and aggressive resuscitation efforts continued during transport by EMS. She did not respond to...
intervention at the ED, and was pronounced dead following one hour of resuscitative efforts in the ED. No clinical fundal examination was documented in the medical record.

The post-mortem interval at the start of the autopsy was seven hours. External examination was unremarkable except for two non-patterned bruises on the left forehead, each less than 1.0 cm in diameter. The post-mortem skeletal survey revealed no fractures, but mesenteric and intrahepatic portal venous gas was prominent (Fig. 4(a)).

Post-mortem blood culture was positive for \textit{S. bovis}. She had mild hyponatraemic dehydration based on a vitreous sodium of 129 mEq/L, chloride of 89 mEq/L and urea nitrogen of 24 mg/dL. Bilateral costochondral fractures of ribs 2–5 were characteristic of resuscitative chest compressions. The small and large intestines were markedly distended by gas, and lymphoid aggregates within the submucosa of the large bowel were enlarged and elevated. Microscopically, increased numbers of chronic inflammatory cells were in the colonic lamina propria. Her lungs exhibited oro-gastric aspiration but no pneumonia, and the liver contained a few loosely formed granulomas. Her cause of death was oro-gastric aspiration due to \textit{S. bovis} bacteria complicating \textit{S. typhimurium} enteritis.

PMIO revealed three posterior superficial RHs in the right fundus (Fig. 4(b)). No fundal haemorrhages were identified in the left eye. Ocular examination confirmed that the right fundus had three superficial flame-shaped RHs located in the superior half of the posterior globe (Fig. 4(c)). The left fundus contained no RHs. No optic nerve sheath haemorrhages were present.

**Discussion**

Although the number, type, and location of RHs have been considered diagnostic indicators of non-accidental trauma in children, confidence in the specificity of RHs continues to decline as additional associations emerge. \cite{2014SalvatoriandLantz} This case series provides autopsy and ophthalmological findings for a paediatric population aged three years and younger who exhibited RHs with fatal infections. Although all the children died in the hospital, none had documented clinical fundal examinations, and the RHs were detected by PMIO.

Recent publications have reported RHs in association with adult and paediatric infections, \cite{2014SalvatoriandLantz} although not in large numbers. A prospective study by Agrawal et al.,\cite{2014SalvatoriandLantz} for example, reported RH in only 15% of critically ill children admitted to a paediatric intensive care unit, excluding children with suspected NAHI or penetrating eye injuries and elective admissions. A prospective study by Curcoy et al.\cite{2014SalvatoriandLantz} similarly reported no evidence of RH among 108 children presenting with signs and symptoms of an apparent life-threatening event. Like Agrawal, the Curcoy study excluded suspected abuse victims, as well as children with a history of trauma or ‘other recognized causes of retinal haemorrhages’. Both of these studies looked at mixed populations of children with both infective and non-infective sources of critical illness. A prospective study limited to children with meningococcal septicaemia, by Dinakaran et al.,\cite{2014SalvatoriandLantz} reported a much higher incidence, with RH identified in 42% of cases.

The clinical and forensic literature shows little consensus regarding the significance of unilateral versus bilateral RH findings. A review of the diagnostic accuracy of ocular signs in paediatric abusive head trauma by Bhardwaj et al.\cite{2014SalvatoriandLantz} suggests that bilateral, extensive and multilayered RH are highly specific for non-accidental trauma. Conversely, Gilles et al.\cite{2014SalvatoriandLantz} report that RHs are distributed asymmetrically or unilaterally in 90% of confirmed non-accidental head trauma cases, with haemorrhages found ipsilateral to the site of injury. At the same time, both bilateral RH\cite{2014SalvatoriandLantz} and unilateral RH\cite{2014SalvatoriandLantz} have been reported in cases of infection. Two of our four cases showed unilateral RHs, and two cases showed

![Figure 4](https://example.com)
asymmetrical bilateral findings. Although the SBS literature reports that patients with unilateral RHs show less extensive haemorrhaging, we observed innumerable, multilayer, unilateral haemorrhage in one infection case.

Some researchers have suggested that the number of haemorrhages per fundus can distinguish non-accidental trauma from other causes of RH. Bhardwaj et al., for example, proposed that extensive, multilayer haemorrhage is highly specific for inflicted head trauma, and Agrawal et al. reported that children with infection and sepsis often showed fewer than five haemorrhages per fundus. Dinakaran et al. reached similar conclusions, reporting fewer than 20 haemorrhages per fundus in their sample of children with meningococcal septicemia. Our findings suggest, however, that numerous RHs can occur in the context of infection. In two of our cases, the fundi showed extensive RHs considered specific for non-accidental injury.

Several types of traumatic ocular and periocular haemorrhage have been described in the paediatric ophthalmology literature, including intraretinal and preretinal haemorrhage, perimacular folds, vitreous haemorrhage, dome-like haemorrhages under the internal limiting membrane/retinoschisis, white centred haemorrhages, optic nerve sheath haemorrhages and orbital haemorrhage. Although all have been reported in association with AHT, perimacular folds, vitreous haemorrhage, dome-like haemorrhages/retinoschisis and optic nerve sheath haemorrhages are not specific for non-accidental injury. Reports of vitreous haemorrhage and dome-shaped haemorrhage in association with paediatric infection cast doubt on the specificity of these haemorrhage types. In our case series, two children with fatal infections exhibited bilateral optic nerve sheath haemorrhages, with one showing associated orbital haemorrhage, findings once thought to be highly diagnostic of abuse. Diagnostic significance has also been attributed to the topography of RH in affected fundi. Posterior pole haemorrhages were considered highly indicative of non-accidental trauma, for example, although similar findings have been reported in association with meningitis. Likewise, peripheral RHs that extend to the ora serrata have been identified as a marker of severe abuse or acceleration-declaration injury, observed more frequently in autopsy than in clinical studies. Posterior pole haemorrhages were observed in all four of our cases, and three cases exhibited RHs extending to the ora serrata in all four quadrants. The topography of these infection-related RHs has thus mimicked patterns observed in non-accidental trauma. This association is corroborated by reports from Lopez et al. of extensive RHs in cases of pneumococcal meningitis.

Histological investigation has also allowed for the analysis of RH layering. We observed both superficial and multilayered haemorrhages in our cases. Similar findings were reported by Dinakaran et al. in children with meningococcal septicaemia. The presence of both superficial and multilayered haemorrhages resembles the pattern described in cases of non-accidental trauma.

Unfortunately, our autopsy series does not afford us the opportunity to investigate the pathogenesis of RH in paediatric infection. Several aetiological mechanisms have been proposed, including vasculitis, DIC, intracranial hypertension, central retinal vein occlusion, raised intrathoracic pressure and capillary damage. There seems to be little consensus, although sepsis with subsequent DIC does not appear to be necessary nor sufficient to cause RH. Further investigation is required to elucidate the aetiological mechanisms involved.

Our autopsy series has several limitations that must be considered when interpreting the results. Although the presence of an infective process was confirmed in each case via culture or histology, we cannot exclude the possibility that other factors contributed to the child’s death. Two of the cases involved histories of co-sleeping, a practice often associated with sudden infant death syndrome in infants younger than six months. The children in our cases were older than six months at the time of death, reducing the likelihood that co-sleeping was a contributing factor. Second, as coagulopathy studies were not available for all of the children, sepsicaemia with subsequent DIC cannot be ruled out as a factor in the development of RH. Finally, three of the four cases had documented histories of emergency intervention, CPR and advanced life-support efforts, which have been identified as a possible cause of RH – although other studies have claimed that CPR rarely causes RH in the absence of other causal factors. In two of the cases presented, CPR was performed with sufficient force to cause rib fractures. Terminal seizure activity was also reported in one case, although RH is believed to occur infrequently following convulsions.

We have presented an autopsy case series of four children, aged three years old and younger, who showed RHs after succumbing to complications of infections. No clinical fundal examinations were documented in the medical records, and the RHs were identified only at autopsy using indirect ophthalmoscopy. We have shown that many of the ophthalmological findings that are thought to be highly indicative of abuse can occur in association with fatal paediatric infections. Although a high index of suspicion is prudent when investigating the possibility of child abuse, forensic pathologists must recognize that an exaggerated association between RH and non-accidental trauma can bias judgement unless fundi are systematically examined. We agree with the observation by Agrawal et al. that ‘because the majority of studies describing RH focus on patients with acute head trauma, there is potential for selection bias with a risk of circular reasoning’. The routine...
performance of indirect ophthalmoscopy during all paediatric autopsies allows pathologists to recognize better the full spectrum of conditions that may present with RHs. Maintaining an appropriate differential diagnosis when investigating RHs will minimize the likelihood of iatrogenic misdiagnosis of child abuse.

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**References**


