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Review

Retinal hemorrhage and pediatric brain injury: etiology and review of the literature

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Summary Retinal hemorrhages have long been linked with child abuse and, in particular, the "shaken baby/shaking-impact" syndrome. However, the presence of retinal hemorrhages is neither necessary nor sufficient for the diagnosis of child abuse. Additionally, retinal hemorrhages are also associated with an ever-expanding list of conditions, each of which carries important implications for patients and their families. To correctly interpret a patient's retinal hemorrhages, the physician requires a broad knowledge base, including of child abuse, the "shaken baby/shaking-impact" syndrome, the differential diagnosis of retinal hemorrhages and the types of retinal hemorrhage and their diagnostic implications. We review the literature regarding types of retinal hemorrhage and their associated etiologies.

Keywords: retinal hemorrhage, head trauma, pediatrics, children, head injury

INTRODUCTION

Retinal hemorrhages have long been linked with child abuse and, in particular, the "shaken baby/shaking-impact" syndrome. However, retinal hemorrhages are also associated with an ever-expanding list of conditions, each of which carries important implications for patients and their families. To correctly interpret a patient's retinal hemorrhages, the physician requires a broad knowledge base. First, as the majority of retinal hemorrhages are associated with circumstances suspicious for child abuse, a firm acquaintance with the "shaken baby/shaking-impact" syndrome is necessary. Second, as retinal hemorrhages have been associated with a wide variety of conditions, a thorough familiarity with the differential diagnosis of retinal hemorrhages is required. Finally, as different types of retinal hemorrhage are associated with different etiologies, a working knowledge of the types of retinal hemorrhage and their diagnostic implications is warranted.[1,2]

Retinal hemorrhages are inextricably linked to child abuse in most physicians' minds. The presence of retinal hemorrhages, in the appropriate clinical context, indeed, strongly suggests child abuse. However, retinal hemorrhages are neither necessary nor sufficient to diagnose child abuse. Only about 40% of abused children have retinal hemorrhage. Thus, the presence of retinal hemorrhages is not necessary for the diagnosis of child abuse. Furthermore, child abuse is not the only condition with which retinal hemorrhages have been linked; the differential diagnosis of retinal hemorrhage is broad. Retinal hemorrhages have also been associated with motor vehicle accidents, birth trauma, and sudden intracranial hypertension, conditions that are not uncommon in the population of children seen by neurosurgeons. The presence of retinal hemorrhages is therefore not sufficient for the diagnosis of child abuse.[1–4]

TYPES OF RETINAL HEMORRHAGE

The first step in recognizing retinal hemorrhage is knowing where to look. Green studied the eyes of 23 children who died of intentional trauma, 12 of whom had retinal hemorrhages. The most common site of retinal hemorrhage in this group (40%) was near the ora serrata. The posterior portion of the eye, near the disk and the macula, was the second most prevalent location (20%). The remaining 40% were distributed in the remaining regions of the retinal periphery. Similar findings were reported for the 10 children with retinal detachment. These findings correlate with retinal microanatomy; the ora serrata and the optic disk are the sites at which the vitreous attaches to the retina. Thus, the absence of retinal hemorrhages at the fundus does not rule out their presence in the eye. A thorough inspection of the retinal periphery is required. Indirect ophthalmoscopy allows an excellent view of the peripheral retina and photographic documentation of the findings. Thus, in the appropriate context, it is wise to involve the ophthalmology service.[5]

The second step in recognizing retinal hemorrhage is knowing what to look for. There are many types of retinal hemorrhage. Clinically, retinal hemorrhages can be divided into intravitreal, preretinal, intraretinal, subretinal, and subretinal pigment epithelial or choroidal (Figs. 1–5). Each of these hemorrhages has a characteristic, recognizable appearance, and each carries its own distinct diagnostic and prognostic implications. Concerning diagnosis, some hemorrhages are more characteristic of some etiologies than of others. Regarding prognosis, most intraretinal hemorrhages resolve spontaneously; however, some retinal hemorrhages require intervention to prevent visual loss and amblyopia. In traumatic retinal hemorrhages, some types are associated with greater force than others; and thus may carry important implications for neurological prognosis. Therefore, it is important to recognize that there are different types of retinal hemorrhage, and each carries its own implications regarding diagnosis and prognosis.[6,7]

The retinal vasculature lies in the inner half of the neural portion of the retina. Larger vessels lie in the nerve fiber and ganglion cell layers, separated from the vitreous by a delicate layer of neural and glial tissue and, inwardly, by the internal limiting membrane. Since the internal limiting membrane does not cover the optic nerve head, at this point the vessels are separated from the vitreous by only a thin coat of neural and glial elements. Smaller vessels, the precapillary arterioles, capillaries and postcapillary venules, are located between the nerve fiber layer and inner nuclear layer. The retinal capillaries themselves tend to lie in

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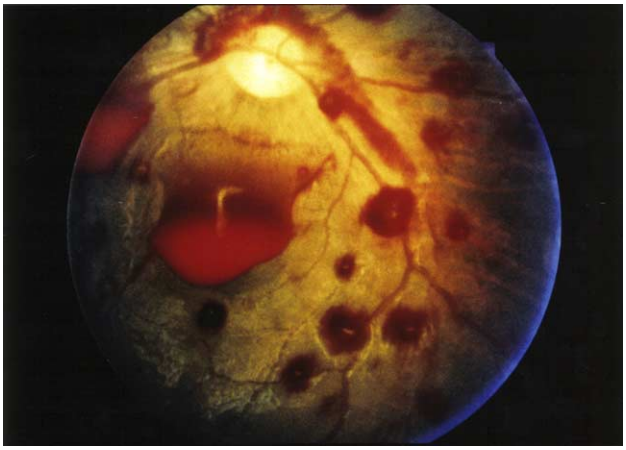

Fig. 1 Vitreous/intravitreal hemorrhage.

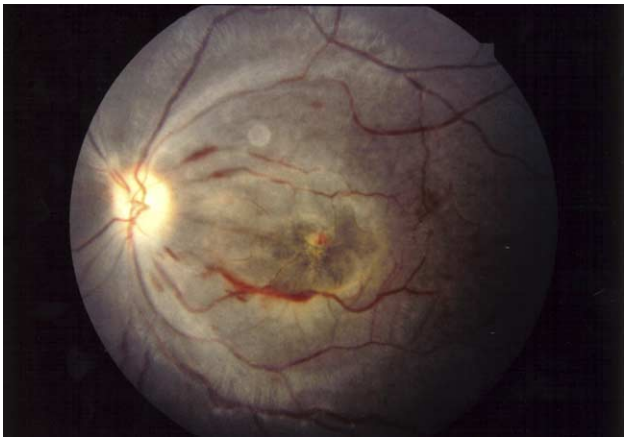

Fig. 4 Subretinal hemorrhage.

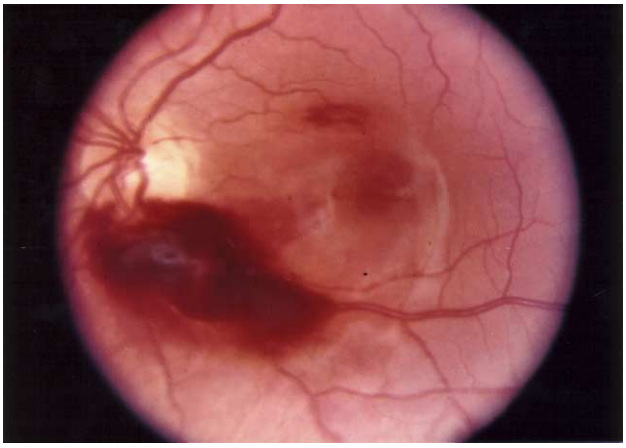

Fig. 2 Preretinal hemorrhage.

Fig. 5 Choroidal/subretinal pigment epithelial hemorrhage.

Fig. 3 Intraretinal hemorrhage.

two main layers, the inner capillaries lying within the nerve fiber and ganglion cell layers, the outer capillaries forming a denser meshwork in the inner nuclear layer. Besides these two main layers of capillaries, there is a third layer, the radial peripapillary capillaries, which form the superficial-most stratum of the retinal vasculature. The radial peripapillary capillaries follow a limited distribution, being found mostly near the major supero-temporal and infero-temporal vessels.[8]

Vitreous hemorrhages are not common in infancy. These hemorrhages occur when large retinal or preretinal hemorrhages break through into the vitreous gel (Fig. 1). On examination, vitreous hemorrhages look like curls, streaks, or diffuse patches of blood in the vitreous. Since the internal limiting membrane is relatively tough, preretinal hemorrhages must be large to break through the membrane and gain access to the vitreous. All but the most severe vitreous hemorrhages clear spontaneously. The time required for clearance of mild vitreous hemorrhages may be only a few weeks, whereas more severe hemorrhages may persist for years. Large preretinal hemorrhages that have broken through to the vitreous tend to take a long time to clear, particularly in infants, who have a comparably thick gel layer. Unfortunately, during this long clearance, the hemorrhage may become loculated and may leave white tissue or vitreous condensation at the site where the internal limiting membrane ruptured.[6,8]

Vitreous hemorrhages do not need to be severe to impair vision; only a small amount of blood can markedly reduce both the patient's vision and the fundoscopic examiner's view. For the examiner, indirect ophthalmoscopy may allow the retina to be visualized. For the patient, light perception tends to be spared, even in severe cases. As the hemorrhage slowly settles, the patient regains sight. For children with recurrent vitreous hemorrhages, clearance of the vitreous may be impaired, and the blood may collect in the back of the eye to form an "ochre membrane". Thus, early vitrectomy may be required to prevent deprivation amblyopia. In unilateral cases, occlusion of

the contralateral eye following vitrectomy has been recommended. Conditions associated with vitreous hemorrhage include hypertension, anemia, leukemia, and the retinal hemorrhages of the newborn.[6,8]

In preretinal hemorrhages, the blood lies just beneath the internal limiting membrane (Fig. 2). These hemorrhages arise from the radial peripapillary capillaries or from the superficial capillary layer. Typically, preretinal hemorrhages are found singularly or in small groups at the posterior pole of the eye. When fresh, the blood forms a round mass, most dense in the center. With time, the red blood cells sink to the bottom of the mass, and a horizontal fluid level forms, giving the hemorrhage a boat-shaped or crescent appearance. In this configuration, the inferior most portion has the densest color. The fluid level moves with the position of the head. The least dense portions of the hemorrhage will be absorbed first, thus the hemorrhage will resolve from top to bottom, leaving a delicate white curved line at the lower border. Posterior polar preretinal hemorrhage is common in children with either subdural or subarachnoid bleeding.[6,8]

A distinct type of preretinal hemorrhage is the "thumbprint" hemorrhage. These are found at the posterior pole, are usually one disk diameter in size, and usually appear in groups of 3–8. The middle of the hemorrhage is dark and its edges are frayed. At the center of each hemorrhage is a glistening light reflex. This may lead to their confusion with Roth's spots. Roth's spots are hemorrhages with a pale, white center. These spots can represent focal ischemia, an inflammatory infiltrate, a colony of infectious organisms, fibrin and platelets, or an accumulation of neoplastic cells. These often absorb without a trace. However, the white centers of Roth's spots are fuzzy, larger, and immobile, compared with the light reflex of a thumbprint hemorrhage, which is sharper, smaller, and which moves as the viewing angle changes. As thumbprint hemorrhages absorb, they fade and fragment, leaving no trace.[6,8]

Intraretinal hemorrhages (Fig. 3) are divided into superficial and deep hemorrhages. Superficial intraretinal hemorrhages originate from capillaries in the superficial capillary bed, located between the nerve fiber layer and the ganglion cell layer. These hemorrhages spread along the path of least resistance, along the nerve fibers. As the nerve fibers are more tightly bunched near the disk than they are peripherally, this gives superficial retinal hemorrhages their distinct appearance: elongated, with distal borders that fray in the direction of nerve fiber travel. Smaller superficial hemorrhages are slim and splinter-like; larger hemorrhages fan outward, like flames. The nerve fibers are bundled tightly enough to shape the "splinter" or "flame" pattern of hemorrhage only within about 7 mm from the disk. More peripherally, even superficial hemorrhages assume a rounded, irregular form. These hemorrhages have a tendency to clear quite rapidly. As they are reabsorbed, their color changes from a bright to a rusty red.[6,7]

"Dot" and "blot" hemorrhages are deep intraretinal hemorrhages, emanating, in the posterior retina, from the deep capillary layer. These hemorrhages are usually located in the outer reticular layer, but may involve either the inner or the outer nuclear layer. The blood pools vertically, between the neural fibers and cell nuclei deep in the retina. Dot hemorrhages are localized clusters of red blood cells; they are round and uniformly red. Dot hemorrhages tend to fragment and fade over the course of a few weeks, leaving no trace. Blot hemorrhages, while also red and rounded, appear domed in shape. In contrast with dot hemorrhages, blot hemorrhages are full-thickness retinal hemorrhages and are often associated with venous occlusion and retinal ischemia.[6,8]

Subretinal hemorrhages are located between the photoreceptors and the retinal pigment epithelium (Fig. 4). These hemorrhages may be derived from either the retinal circulation or the choroidal circulation. Large, deep retinal hemorrhages may break through the external limiting membrane, causing a subretinal hemorrhage. This mechanism occurs in leukemia, sickle cell disease, and Coats' disease, and is less common in retinal detachment and severe anemic retinopathy. Another source of subretinal hemorrhage is the rupture of deep neovascular growths, as in Coats' disease. Subretinal hemorrhages may arise from the choroidal vasculature as well, extension of bleeding from beneath the retinal pigment epithelium. Subretinal hemorrhages appear as red blotches beneath an elevated retina; usually, they are extensive. The borders of the hemorrhage are round and lobulated. As these hemorrhages resolve, a pale yellow, fatty exudate often forms in the retina above them. Reabsorption is slow, requiring months to complete, and leaving in its wake a mottled and damaged retina. Since these hemorrhages interfere with the function of the choriocapillaries, which nourish the outer retinal elements, they are associated with a permanent central scotoma. Subretinal hemorrhages are associated with Coats' disease, sickle cell disease, leukemia, retinopathy of prematurity, and angiomatosis retinae. Subretinal hemorrhages located in the macula are associated with trauma or choroidal subretinal neovascularization.[6,8]

Hemorrhages located beneath the retinal pigment epithelium originate in the choroid (Fig. 5). Blood may travel from the choriocapillaries through a break in Bruch's membrane into the space beneath the retinal pigment epithelium. The blood may also originate from ruptured neovascular tufts, arising from the choroid, but lying on the inner side of Bruch's membrane. This allows the blood to enter the space between Bruch's membrane and the retinal pigment epithelium. These hemorrhages are not red; rather they are a dark, slate color. As the blood collects beneath it, the retinal pigment epithelium is stretched, and often tears at the edges, allowing blood to leak through the retinal pigment epithelium beneath the retina. This produces the red corona of subretinal blood pathognomonic for subretinal pigment epithelial hemorrhages.[6,8]

The vast majority of choroidal hemorrhages are traumatic in origin. Since the choroid is more easily ruptured than the retina, choroidal hemorrhages may appear in the absence of significant retinal findings. These hemorrhages have a dim, reddish color and can be found at the posterior pole. The borders are smooth, and the hemorrhages are often extensive. Since there is usually little associated retinal pathology, choroidal hemorrhage tend to be absorbed to leave a normal fundus. However, interference with the choroidal vasculature leads to visual destruction.[6,8]

ETIOLOGIES

The association between retinal hemorrhages and head trauma is complex. In children with head trauma, retinal hemorrhages are most often associated with inflicted, rather than accidental, injury. However, retinal hemorrhages have been reported, rarely, in cases of severe accidental trauma, for example in high-speed motor vehicle accidents. Thus, the presence of retinal hemorrhages in a child with head trauma suggests, but does not prove, that the injury was inflicted. Secondly, retinal hemorrhages seem to be associated with rotational, rather than translational forces applied to the head. For example, retinal hemorrhages are rare in simple falls, a source of translational force, yet common following blows to the infant's head, a source of rotational force. Finally, the acceleration-deceleration forces involved must be substantial. In studies of accidental head trauma, in which a reliable history is more easily obtained, only the most severe cases produced retinal hemorrhages.[9]

Child abuse/non-accidental trauma

Retinal hemorrhages are common among abused children. Between 65% and 89% of abused children have retinal hemorrhages. This makes retinal hemorrhage the most common ocular manifestation of child abuse. Several different forms of child abuse can cause retinal hemorrhages, including direct blows to the head, the "shaken baby/shaking-impact syndrome", and thoracic compression, as may be seen in sexual abuse. However, retinal hemorrhages are neither necessary nor sufficient for the diagnosis of child abuse. Not all battered children have retinal hemorrhages. The retinal hemorrhages associated with child abuse are usually seen in children less than three years of age. Thus, since not all battered children have retinal hemorrhages, their absence does not exclude child abuse. Furthermore, since the retinal hemorrhages of child abuse are most commonly seen in children less than three years of age, this is the group in which retinal hemorrhages are most suggestive of child abuse. Secondly, retinal hemorrhages, while strongly suggestive of child abuse in the appropriate context, are by no means pathognomonic. There are a great many other, albeit more rare, causes of retinal hemorrhage. Thus, the presence of retinal hemorrhage does not prove the presence of child abuse. Finally, the ocular manifestations of child abuse are myriad. In addition to retinal hemorrhage, retinoscisis, retinal detachment, and dislocation of the lens, for example, are also seen. Thus, retinal hemorrhage is not the only ocular sign of child abuse.[6,10,11]

With regard to appearance, the hemorrhages of child abuse are usually intraretinal; deep intraretinal hemorrhages having a "dot" and "blot" pattern, superficial hemorrhages taking on a "splinter" and "flame" pattern. Often, all of the retinal layers are involved in the hemorrhages. In more severe cases, blood may be present in the preretinal space, in the subretinal space, or in the vitreous. The presence of blood in the vitreous is an especially important diagnostic clue: vitreous hemorrhages, otherwise rare in infancy, are a frequent finding in abused children. Another important diagnostic clue is the unusual persistence of these lesions: the retinal hemorrhages of child abuse tend to persist for several months, even years, after the injury. The hemorrhages may be either bilateral or, rarely, unilateral, and may show different ages and stages of hemorrhage and reabsorption in different areas of the retina.[6,12]

Head injuries/accidental trauma

In children with head injuries, the presence of retinal hemorrhages suggests that the injuries were inflicted, rather than accidental. In 1992, Buys and her colleagues reported their findings in a prospective study of 79 children less than 3 years of age with head injuries. Each of the infants underwent an ophthalmoscopic exam, including indirect ophthalmoscopy, within 48 hours of their injury. Seventy-five of the seventy-nine children sustained accidental head injuries. This included injuries as severe as falls from a height greater than 10 feet (5 children) and falls down stairs and onto a non-carpeted surface (10 children). None of the children with accidental head injuries had retinal hemorrhages. However, retinal hemorrhages were present in all four children who had sustained non-accidental injury.[13,14]

Among children who do not survive their injuries, the presence of optic nerve sheath hemorrhages may serve as an important clue as to the cause of death. In their 1994 report, Budenz and associates found retinal hemorrhages in 11 of the 13 infants whose death was attributed to intentional trauma. However, optic nerve sheath hemorrhages were present in all 13 of these children. Among the control group (six infants whose death was attributed to sudden infant death syndrome) a few erythrocytes were present in one eye of one of the children. In this series, the association between optic nerve sheath hemorrhage and intentional trauma was even stronger than that between retinal hemorrhage and intentional trauma. In this regard, optic nerve sheath hemorrhages may be helpful in determining the cause of death from trauma.[15,16]

While retinal hemorrhages are most strongly associated with non-accidental trauma, severe accidental trauma may also be associated with retinal hemorrhage. In 1992, Duhaime and associates reported their findings in a series of 100 children less than two years of age with head injuries. Children were studied retrospectively, and were admitted to the study based on their diagnosis at discharge, allowing the inclusion of children in whom head injury was not evident at admission. Strictly defined criteria divided children into "accidental" and "inflicted" injury categories. Criteria were intentionally defined to provide a conservative estimate of the prevalence of inflicted injury. Of the 100 patients, 24 met the study criteria for "inflicted" injury. Retinal hemorrhages were found in 10 children, nine of who met the study criteria for "inflicted" injury. The remaining patient was a passenger in a high-speed motor vehicle accident. Riffenburgh and Sathyavagiswaran reported in 1991 on the ocular findings at autopsy in 190 consecutive cases. Four of the children with retinal hemorrhages in their series had a definite history of unintentional trauma to account for their retinal findings. Of these four children, two had sustained severe head injuries in automobile accidents, one died one week after a difficult forceps delivery, and the fourth received cardiopulmonary resuscitation and ultimately died of enterocolitis.[9,17]

While retinal hemorrhages have been reported in cases of accidental trauma, retinal hemorrhages are rare in this setting, and are associated with particularly severe head injury. In 1993, Johnson and associates studied the prevalence of retinal hemorrhages in 170 children with accidental head trauma, 140 of whom were examined for retinal hemorrhages by an ophthalmologist. Although this study included older children, the median age was 4.5 years and young children were well represented: 52 of the 140 children examined by an ophthalmologist were under two years of age. Of these 140 children, only two had retinal hemorrhages, both of whom were involved in side-impact automobile accidents. Both of these children were severely injured: one died and the other sustained a cerebral contusion and subarachnoid hemorrhage.[18]

There is evidence to suggest that the presence and severity of retinal hemorrhage may predict the severity of the intracranial injury and the gravity of the neurological prognosis. Firstly, the presence of retinal hemorrhages may suggest a poor prognosis. In the 1996 study by Green et al, an autopsy study of 23 children who died of intentional injury, the prevalence of retinal hemorrhages among the 16 children who died of head trauma was 81%. Among the children whose death was attributed to other causes, the prevalence of retinal hemorrhages was only 17%. Secondly, the severity of the intraocular injury may parallel the severity of the central nervous system (CNS) injury. In 1989, Wilkinson and associates reported their findings in a series of 14 children being treated for presumed "shaken baby syndrome". There was a significant correlation between the severity of the retinal hemorrhages and the acute neurological findings. Among all of the children in the Green et al 1996 autopsy study, there was a strong correlation between ocular injury scores and CNS injury scores.[5,19]

Motor vehicle accidents

Motor vehicle accidents have been associated with retinal hemorrhage. In large studies of children with head trauma and retinal hemorrhage, intentional injury is the most common etiology.

Among the remaining children, those with accidental injuries, motor vehicle accidents are the most common etiology. In Riffenburgh and Sathyavagiswaran's 1991 autopsy study, two of the four children who sustained accidental head injury were involved in motor vehicle accidents. In the 1992 clinical study by Duhaime et al, the single child who experienced both retinal hemorrhages and accidental injury was a passenger in a high-speed motor vehicle accident. In the Johnson 1993 study of accidental head injuries, both of the children with retinal hemorrhages were passengers in side-impact motor vehicle accidents.[9,17,18]

Neonates

Babies may develop ocular hemorrhages associated with the trauma of birth. These hemorrhages are relatively common, generally transient, and ordinarily benign. Neonatal retinal hemorrhages have been reported to occur in between 2.5% and 50% of all births. Risk factors for retinal hemorrhage in the newborn include prolonged labor, forceps delivery, maternal toxemia, and older primiparae. The choice of induction agent may also affect the development of neonatal retinal hemorrhages. Protective factors include breech presentation and cesarean delivery. The types of hemorrhage most commonly associated with neonatal retinal hemorrhage are intraretinal hemorrhages, taking on "splinter", "flame", "dot", and "blot" patterns. Often, neonatal hemorrhages are a mixture of "dot" and "blot" hemorrhages and "splinter" and "flame" hemorrhages. Preretinal hemorrhages are also common among neonates; subretinal hemorrhages, however, are rare. In about 4% of births, macular hemorrhages are present. While these, too, usually resolve completely and without visual sequelae, persistent macular hemorrhage may require vitrectomy to prevent amblyopia. Subconjunctival hemorrhages are common in neonates, however, since the infant's palpebral fissure is relatively small, and covers most of the sclera, these hemorrhages are seldom recognized, even by the mother. Conjunctival and retinal hemorrhages in neonates tend to disappear rapidly and completely. Almost all neonatal retinal hemorrhages resolve within a week of birth, the remainder by about 4 to 6 weeks. Large preretinal hemorrhages take a little longer to clear.[6,13,20–22]

Among premature newborns, retinal hemorrhages are frequent. Retinal hemorrhages tend to occur in the acute phases of the retinopathy of prematurity. Retinal involvement in the retinopathy of prematurity begins at the junction between the vascularized and non-vascularized premature retina. Usually, the hemorrhages of the retinopathy of prematurity are intraretinal, occurring on the surface of the neovascular ridge located at this junction. Often, these hemorrhages are small, remaining localized on the surface of the neovascular ridge. However, they may become massive and extend into the vitreous. Often these infants endure lasting visual sequelae, usually due to other associated disease. Among premature infants, parenteral administration of vitamin E may be a risk factor for retinal hemorrhage. Extracorporeal membrane oxygenation has also been associated with retinal hemorrhage. Interestingly, the hemorrhages associated with extracorporeal membrane oxygenation are reported to be unilateral, occurring contralateral to the catheters.[6,23,24]

Cardiopulmonary resuscitation

One important question is whether cardiopulmonary resuscitation (CPR) causes retinal hemorrhages. This issue is currently the subject of vigorous debate. Some authors claim that retinal hemorrhages may be found in children who have no risk factor for retinal hemorrhage other than CPR. In 1990, Goetting and Sowa reported on their experience with CPR and retinal hemorrhage. Patients admitted to the pediatric critical care medicine service were entered into the study if they had received chest compressions, had no history or physical evidence of trauma and no history of other conditions known to be associated with retinal hemorrhages. Twenty children met the study criteria. Of these 20 patients, 2 had retinal hemorrhages, both of whom were under three years of age, and both of whom subsequently died. No evidence of preceding trauma was found at autopsy in either child. One weakness of the study was the method of retinal examination: direct ophthalmoscopy. Although the majority of retinal hemorrhages associated with increased intrathoracic pressure occur at the fundus, a significant number occur in the periphery, and are unlikely to be seen on direct ophthalmoscopy. For this reason, it is possible that the true incidence of retinal hemorrhage in this population (10%) was underestimated.[25–27]

However, several reports argue that other risk factors for retinal hemorrhages are consistently present in children who have retinal hemorrhages following CPR. As other risk factors are present, CPR cannot be proven to cause the hemorrhage. Gilliland and Luckenbach reported in 1993 on their findings in the eyes of 169 children. Of the 61 retinal hemorrhages found among children who had received prolonged resuscitation attempts, 56 had head injuries, 4 had CNS diseases and sepsis, and, although the cause of death was officially "undetermined" in the remaining child, this child came from a household with documented child abuse and two prior child deaths. In 1986, Kanter reported on his experience with 54 patients who had received CPR. Nine of these patients were victims of trauma, of whom five had retinal hemorrhages. Of the 45 remaining patients, who had no evidence of preceding trauma, one retinal hemorrhage was found. This infant was found having a seizure at home, received CPR, and subsequently developed hypertension reaching 190/120 mmHg. Interestingly, of the 9 newborns in Baum and Bulpitt's 1970 study who required CPR, intravenous bicarbonate infusion and assisted ventilation for more than 20 minutes, none had retinal hemorrhages.[20,27,28]

Seizures

Although retinal hemorrhages are often associated with conditions that cause seizures, seizures alone have not yet been shown to cause retinal hemorrhages. In 1997, Sandramouli and associates reported their findings in 32 children admitted following a seizure. Children were examined prospectively within 48 hours of admission, using both direct and indirect ophthalmoscopy, for the presence of retinal hemorrhages. No retinal hemorrhages were found. Following completion of the study, one of the investigators reports a 23-day-old premature (33 weeks) infant with a single retinal hemorrhage that may have occurred during a seizure. As no neonates were included in the study, and as neonates are at high risk for the development of retinal hemorrhages, a separate, prospective study of retinal hemorrhages in neonates with seizures is currently underway. At present, retinal hemorrhages in a child beyond the first month of life who has had seizures are unlikely to have been caused by the seizures themselves.[11]

Leukemia and blood disorders

Retinal hemorrhages are common in patients with leukemia. Fundoscopic changes occur in up to 90% of leukemia patients at some point in their disease. The retinal veins of leukemia patients become dilated and tortuous. Both the arteries and the veins take on a yellowish cast, reflecting the decreasing proportion of red blood cells and the concurrently increasing proportion of white blood cells. Cotton wool spots, occurring perhaps secondary to ischemia, commonly appear. As the neoplastic cells infiltrate the

retina and as the retinal vessel walls are damaged, impaired coagulation, hyperviscosity, and occlusion of the retinal vasculature all contribute to the formation of retinal hemorrhages in leukemia. The retinal hemorrhages of leukemia tend to occur at the posterior pole, favoring the deep layers of the retina. However, these hemorrhages may be found in any and all layers of the retina and may extend into the vitreous. Often, there is a white region at the center of the hemorrhage, corresponding to a collection of leukemic cells, to aggregates of platelets and fibrin or to septic emboli. Retinal infarcts and infiltration of other areas of the eye, especially the uvea, are also common in leukemia. Associated features will include, obviously, the systemic manifestations of leukemia, and the prognosis of the retinal lesions depends on the treatment of the malignancy.[6,29]

Retinal hemorrhages have been reported in various other blood disorders, including juvenile pernicious anemia, iron deficiency anemia, sickle cell disease, malaria, and aplastic anemia. In anemia, the hematocrit decreases and the retinal veins become dilated and tortuous and multiple bilateral intraretinal hemorrhages appear, taking on "dot", "blot", "flame", or "splinter" appearances. Some of these retinal hemorrhages may have white centers. Additional changes include swelling of the optic disc and the appearance of cotton wool spots. Among anemic patients, adults are more likely to develop retinal hemorrhages than are children. Those with a hemoglobin less than 8 g/dL are especially susceptible to the development of retinal hemorrhages. In Foster's 1970 study of 144 patients with a hematocrit of 35% or less, 29 patients had retinal hemorrhages. Coexisting thrombocytopenia or platelet dysfunction may contribute to the development of the retinopathy of anemia, thus retinal hemorrhages are more common in megaloblastic anemia, in which the platelet count is decreased, than in iron deficiency anemia, in which the platelet count is usually elevated. Of the 29 patients with retinal hemorrhages in Foster's study, only one had an iron deficiency anemia; 22 had megaloblastic anemia, and the remainder were of unclear etiology. In sickle cell disease, the transient arteriolar occlusions and reperfusions damage the retinal vasculature, permitting blood to seep through the injured arteriolar wall. In a study of children aged 5 to 13, discolored patches, thought to be the result of intraretinal hemorrhage, were common. However, recent retinal hemorrhages were an infrequent finding. It is possible that infants with sickle cell disease may already bear the retinal manifestations of their disease.[6,30–33]

Protein C deficiency is an autosomal disorder. Heterozygotes have an increased tendency toward venous thrombosis; homozygotes present in infancy with widespread thrombotic complications. A single case has been reported of a male infant, born at 37 weeks gestation, with protein C deficiency and intravitreal hemorrhages. Subarachnoid hemorrhages were also present. His protein C level was measured, and was found to be less than 5% of the normal value.[6]

Retinal hemorrhages occur with moderate frequency in hyperviscosity syndromes including cystic fibrosis, macroglobulinemia, cryoglobulinemia, and paraproteinemia. The retinal hemorrhages of hyperviscosity syndromes may involve any of the layers of the retina, with "dot" and "blot" hemorrhages and "flame"-shaped hemorrhages being the most prominent. Engorgement of the uveal vasculature and tortuosity of the retinal vessels suggest this diagnosis. Systemic findings appropriate for the various hyperviscosity syndromes indicate the diagnosis. The prognosis of the retinal hemorrhages in this context is usually good.[6]

Infection

Retinal hemorrhages are common findings in the context of retinal infections. Cytomegalovirus (CMV), herpes simplex (HSV), rickettsiae, ocular toxoplasmosis and subacute bacterial endocarditis may each cause retinal hemorrhage due to infection. In the case of subacute bacterial endocarditis, characteristic white-centered, oval hemorrhages, apparently located in the nerve fiber layer of the retina are the retinal hallmark of the disease. In general, the retinal hemorrhages found in these infections are small, intraretinal hemorrhages found in areas of retinal necrosis. These hemorrhages may span any and all layers of the necrotic retina. Systemic signs of infection and the presence of immune compromise suggest an infectious etiology.[6,34]

Other etiologies

Coats' disease is a rare form of retinal telangiectasia that may present in infancy. It is usually unilateral, and presents in childhood with poor fixation, leukocoria or strabismus. The walls of the telangiectatic blood vessels are abnormal, leading to hemorrhage, transudation of fluid, and vascular occlusion. Secondary subretinal exudates form. Retinal hemorrhages occur with moderate frequency in patients with Coats' disease. These hemorrhages tend to be intraretinal, but may extend into the vitreous. Subretinal exudate and, of course, the presence of telangiectatic vessels in the retina point are characteristic of Coats' disease. The ophthalmologic prognosis for Coats' disease is poor, usually progressing to eventual retinal detachment, and the retinal telangiectasia tend to be more aggressive in younger children.[6,35,36]

Persistent hyperplastic primary vitreous (PHPV) is a developmental abnormality. Usually PHPV is unilateral, and presents early in life with strabismus, leukocoria or poor vision. Mild microphthalmos is a common finding. Although the prevalence of retinal hemorrhage in PHPV is low, PHPV may present as vitreous hemorrhage. There are three forms of PHPV: anterior, posterior, and combined. The posterior form is the least common, and presents with leukocoria and poor vision. Behind a clear lens, retinal folds, retinal detachment, and pigmentary disturbances are found, and a dense vitreous band extends from the region of the disc to the periphery. The anterior form is characterized by a whitish retrolental mass with radial blood vessels. Most patients show a combination of these two patterns. The ophthalmologic prognosis is poor.[6,36]

Retinal dysplasia is the abnormal differentiation of the retina characterized by retinal folds, gliosis, and disorganization. The incidence of retinal hemorrhage in retinal dysplasia is high. Unilateral retinal dysplasia has been associated with radiation or Agent Orange exposure and prenatal trauma or viral infection. Bilateral retinal dysplasia is usually seen in children with systemic abnormalities, such as trisomy 13–15, trisomy 18, Norrie's disease and Meckel-Gruber syndrome. White pupils and the absence of fixation behavior are usually noticed early in life. Mild microphthalmos with a shallow anterior chamber and a clear lens are common findings. Norrie's' disease is an X-linked recessive syndrome of blindness, hearing loss, and dementia. Patients with Norrie's disease present in the first few months of life with bilateral retrolental opacities and total retinal detachment. Pathologic examination reveals retinal dysplasia and extensive retinal hemorrhage. About one third of Norrie's disease patients will develop hearing loss, and about one third will eventually develop dementia. Meckel-Gruber syndrome is an autosomal recessive disease, characterized by microcephaly, encephalocele, syndactyly, and polycystic kidneys. There is no known therapy for these severely abnormal eyes.[6,36]

Carotid-cavernous sinus fistula is also associated with retinal hemorrhage, although this condition is rare in infancy. In carotid-cavernous sinus fistula, ophthalmic venous pressure is high. This results in retinal ischemia, which leads to retinal hemorrhage. The retinal hemorrhages of carotid-cavernous sinus fistulae tend

to be peripapillary. Associated with the hemorrhage are proptosis, papilledema, vascular engorgement, and glaucoma. Traumatic skull lesions, cranial nerve palsies, and bruit may also be present. The prognosis of the retinal lesions is good, provided the fistula remits.[6]

Retinal hemorrhages are highly prevalent in the context of hypertension. Hypertensive retinopathy may be seen in infants with renal disease. The retinal hemorrhages of hypertension tend to be peripapillary and "flame"-shaped, occasionally extending into the vitreous. Associated ocular findings include retinal infarcts and choroidal infarcts. The presence of hypertensive encephalopathy and renal disease further point to hypertension as the etiology of the retinal hemorrhages.[6]

Myopia is rare in infancy. Earlier onset of myopia is associated with faster progression and greater severity. Thus, infants with myopia are at risk for developing associated choroidal neovascularization and subretinal hemorrhages. Yellow, linear "lacquer cracks", later appear at the site of previous subretinal hemorrhage. Myopia has been associated with Down, de Lange's, Marshall-Smith, Noonan's, Schwartz, Sticker's, Kniest's, and Marfan's syndromes. In general, the incidence of retinal hemorrhages in the context of myopia is low. When present, the hemorrhages may be found intraretinally, as subretinal disciform lesions, or extending into the vitreous. In Marshall-Smith, Noonan's, Schwartz, Sticker's and Kniest's syndromes, there is a high risk of retinal detachment. In Down, de Lange's, and Marfan's syndrome, lens dislocation is common. Premature infants, particularly those infants who develop the retinopathy of prematurity, are at risk for developing myopia. The ophthalmologic prognosis is favorable, except in the case of disciform lesions.[6,37,38]

Vitreous hemorrhage may be seen at the onset of retinoblastoma, and may be the presenting sign. Optic disc hamartoma, tuberous sclerosis, von Hippel-Lindau disease, and juvenile X-linked retinoschisis may cause retinal hemorrhage. Retinal hemorrhages have been reported in a case of ruptured spinal cord arteriovenous malformation. Primary arteriovenous malformations of the retina itself may also lead to macular and vitreous hemorrhage. Anticoagulants and hypercapnia both predispose to retinal hemorrhage. Retinal hemorrhages have also been associated with the use of epidural anesthesia. White-centered retinal hemorrhages have been reported in association with difficult or prolonged intubation during anesthesia, ruptured cerebral arteriovenous malformation, and idiopathic central hemorrhagic retinopathy. The white centers in these conditions may represent collections of fibrin and platelets at the site of repair.[6,10,39–42]

Acute altitude sickness may result in retinal hemorrhage as well as cerebral edema. Acute altitude sickness rarely occurs at elevations of less than 8000 feet (2,438 m). Symptoms, commonly nausea and vomiting in children, usually appear around 4 to 6 hours after the individual reaches high altitude, peak at 2 or 3 days, and last about four days. High altitude cerebral edema rarely occurs below 12,000 feet (3,658 m). Signs and symptoms begin 2 or 3 days after reaching high altitude, and include severe headache, weakness, ataxia, papilledema, and engorged retinal vessels. High altitude cerebral edema can be fatal and requires immediate return to a lower altitude. High altitude retinal hemorrhage occurs at higher elevations than high altitude cerebral edema. Hallmarks include dilation of the retinal vasculature, preretinal or papillary hemorrhage, peripapillary hyperemia and papilledema. More severe hemorrhages may extend into the vitreous. Chronic high-altitude hemoconcentration may also contribute to the formation of retinal hemorrhages. The presence of a high hematocrit after exposure to altitude supports this possibility.[43,44]

Retinal and optic nerve ischemia and hemorrhages have also been associated with sudden reduction in systemic blood pressure. While sudden lowering of intraocular pressure during surgery in the presence of healthy retinal vessels seldom results in retinal hemorrhage, the combination of anoxia and increased transmural pressure is reported to cause retinal hemorrhage.[6]

Retinal hemorrhages have been associated with subarachnoid hemorrhage of both traumatic and non-traumatic etiology in adults and may serve as an important prognostic indicator. About 20% of adults with subarachnoid hemorrhage have retinal hemorrhages. They may appear simultaneously with the subarachnoid hemorrhage or may lag a few days behind. The overall mortality rate reported for subarachnoid hemorrhage is 25%, however, if retinal hemorrhages are present, the mortality is 50%. Furthermore, the mortality for patients with bilateral retinal hemorrhages exceeds that for patients with unilateral lesions. The retinal hemorrhages associated with subarachnoid hemorrhages are usually located near the disc, are usually either retinal or preretinal in origin and may occasionally break through into the vitreous. Larger vitreous hemorrhages may require vitrectomy.[6]

Sudden increases in intracranial pressure, regardless of etiology, have been associated with retinal and optic nerve hemorrhage in adults. In 1974, Muller and Deck reported on their findings at the autopsies of 23 patients who had experienced sudden intracranial hypertension. Four cases of severe cranial trauma, eight cases of massive spontaneous intracerebral hemorrhage, nine cases of ruptured berry aneurysms, and two cases of internal carotid artery occlusion were included. Of the 46 eyes from cases of sudden intracranial hypertension, 40 had optic nerve sheath hemorrhage and 17 had intraocular hemorrhage. Of the retinal hemorrhages associated with sudden intracranial hypertension, most are intraretinal and resolve without incident in surviving patients. However, some of these retinal hemorrhages break through into the vitreous, with consequent loss of visual acuity.[45,46]

SUMMARY

In general, the presence of retinal hemorrhages in an infant with head trauma strongly suggests a diagnosis of child abuse. However, retinal hemorrhages also occur after severe accidental head trauma, for example, that sustained in motor vehicle accidents. In the infant with no signs of head trauma, other causes of retinal hemorrhage must be sought. Among these are conditions that predispose to retinal injury, secondary either to ischemia or to infection. In cases of suspected child abuse, it is wise to remember that the differential diagnosis of retinal hemorrhage is vast, and to suspend judgment until all other reasonable explanations are exhausted.

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