Extramedullary Hematopoiesis in Abusive Head Trauma

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Abstract
Extensive unilateral extramedullary hematopoiesis of the choroid was observed in an otherwise clear cut case of abusive head trauma with bilateral retinal hemorrhage, optic nerve sheath hemorrhage and peripapillary intrascleral hemorrhage. Review of 60 archival cases of suspected abusive head trauma identified two more examples of extramedullary hematopoiesis in abusive head trauma that initially had been diagnosed as uveitis. Extramedullary hematopoiesis of the choroid may have a relation to premature birth, possible anemia or may be a reaction to intracocular bleeding due to earlier trauma. Choroidal extramedullary hematopoiesis may easily be confused for choroidalis and interpreted as a sign of infectious disease. Awareness of the possibility of extramedullary hematopoiesis of the choroid should prevent misdiagnosis.

Keywords
Child abuse; Retinal hemorrhage; Extramedullary hematopoiesis

Abbreviations
AHT: Abusive Head Trauma; NAHI: Non-Accidental Head Injury; SBS: Shaken Baby Syndrome; EMH: Extramedullary Hematopoiesis

Introduction
Ocular pathology, mostly in the form of retinal hemorrhages, vitreous hemorrhages or optic nerve sheath hemorrhages, has long been linked with child abuse, in particular with abusive head trauma /non-accidental head injury/shaken baby syndrome (AHT/NAHI/ SBS) in toddlers and infants [1-3]. In autopsy cases, removal and histological study of the eyeballs is mandatory. The diagnosis of AHT requires a trias of subdural hemorrhage, acute encephalopathy and retinal hemorrhages. The children usually are below the age of two years and may show sparse signs of external injury. There is an inadequate or inconsistent history of the caregiver and there is no plausible history of trauma to explain the symptoms. Retinal hemorrhages related to AHT typically are bilateral-symmetrical, may be pre-, sub- or intraretinal near the optic nerve or Ora serrata. Often hemorrhage in the optic nerve sheath and peripapillary intrascleral hemorrhages are observed. The differential diagnosis of retinal hemorrhages in neonates and infants include amongst others severe accidental head trauma, birth, coagulopathy, increased intracranial pressure, retinopathy of prematurity and meningitis. We describe three examples of extramedullary hematopoiesis (EMH) in a series of 60 autopsy cases of retinal hemorrhage in AHT of which two had been initially diagnosed as uveitis.

Material and Methods
The electronic laboratory management system (FlexLab/ Sympathy, Tieto Corporation, Helsinki, Finland) of the department of pathology of the Erasmus MC University was searched for forensic post mortem eye examinations evaluated for signs of AHT since the year 2005. A cohort of 60 consecutive cases of known or presumed child abuse was identified. Uveitis had been diagnosed in 8 cases. These cases were retrieved and examined for the presence of EMH.

Special stains comprised Prussian blue staining for iron, Ledererase and Giemsa. Sections of deparaffinized formalin-fixed paraffin embedded tissue, 4 µm thick were stained using a BenchMark automated immunostainer (Ventana, Tucson, AZ, USA) with the Ultraview Universal diaminobenzidine detection kit (Ventana). Primary mouse monoclonal antibodies directed against human CD3, CD20, CD34, CD61, CD68, CD117, glycophorin C and myeloperoxidase (Dako, Carpinteria, CA, USA) were applied to the sections for 32 minutes. Human tonsillar tissue served as a control. Antigen retrieval was performed with Ultra Conditioner (Ventana 97°C for 64 min). Endogenous peroxidase activity was blocked with blocking solution (Ventana). Sections were counterstained with haematoxylin.

Results
Report of a case
A 7 week old male infant was presented to the emergency department with complaints of peculiar crying behavior, loss of eye contact and loss of consciousness. The patient was transferred to a pediatric intensive care center with severe neurological deficit. CT-scan showed intracranial hemorrhage and diffuse edema. Ophthalmologic evaluation showed retinal hemorrhages. The caregiver stated that two weeks before admittance the infant had made a fall from the parental bed to the floor.

Postmortem findings
Male infant with a relative low weight (P2) and normal length (P50) for the age. There were multiple bruises, subdural and subarachnoid hematoma, cerebral edema and signs of tonsillar herniation.

Macroscopy
The eyes measured 2 x 1,8 x 1,8 cm and 1,9 x 1,9 x 1,9 cm respectively with a corneal diameter of 9 mm. The orbital fat and optic nerve sheath showed red-brown discoloration. The cut sections showed red-brown streaks and dots of the retina compatible with severe retinal hemorrhage.

Histopathology
There are diffuse bilateral hemorrhages affecting all retinal layers, most severe at the periphery. There is hemorrhage in the optic nerve sheath and peripapillary intrascleral hemorrhage (Figure 1). There are...
focal erythrocyte extravasations in the orbital fat. The right eye shows a diffuse EMH of the choroid with extensive myeloid progenitors; rare erythroid precursors and megakaryocytes (Figure 2A). Early eosinophil and neutrophil myelopoiesis could easily be mistaken for active inflammation, especially when autolysis is present. The presence of erythroblasts and earlier erythroid progenitors lead to the recognition of EMH. Additional Lederesterase stains confirmed myelopoiesis. Immunohistochemical stains for glycophorin C identified erythroid progenitor cells (Figure 2B), CD61 identified megakaryocytes and CD34 identified rare positive myeloblasts (Figure 2C). Lymphoipoiesis stained positive for CD3 and CD20. Macrophages, essential for the production of cytokines, are essential to hematopoiesis stained positive or CD68 (Figure 2D). Prussian blue staining showed iron laden macrophages in the choroid (Figure 2E).

Upon review of 60 preceding cases of forensic postmortem eye studies, uveitis had been diagnosed in 8 cases. In 6 cases AHT could not be implicated based on histopathologic studies. In two cases of AHT the inflammatory cells proved EMH upon revision of the slides.

Discussion

EMH was identified in three cases of suspected AHT with severe bilateral retinal hemorrhages involving all retinal layers, optic nerve sheath hemorrhage and most importantly peripapillary intrascleral hemorrhage. Meningitis can lead to retinal hemorrhages, but these are expected to be more restricted to the posterior pole and are usually fewer in number. The peripapillary intrascleral hemorrhage cannot be explained this way. The presence of inflammatory cells associated with EMH in the choroid could be mistaken with infection; however the clinical histories and autopsy did not indicate an infectious illness.

The earliest cases of intraocular hematopoiesis were described in a series of syphilitic children [4], interpreted at the time as mobilized immature myelocytes because of prematurity. Intraocular EMH has been described in other infectious conditions of the eye [5]. Intraocular hematopoiesis was first recognized by Böck [6] in trabecular bone of a phthisical eye and has been confirmed repeatedly as a common finding [7]. Hematopoiesis has been described during normal embryological development in the orbital fat around the eye [8] and has an important role in the development of the choriocapillaris up to week 9 of gestation [9]. Reese and Blodi describe the occurrence of hematopoiesis in the eye in 19 out of 122 perinatal eyes [10], of which 2 were prematurely born infants respectively two and three months old suffering from persistent anemia. Of seven other term infants with intraocular EMH only two had lived for two days and died after massive blood loss. Heimann and Terheggen later showed in an seldom cited paper that the choroid of the fetal eye is a common site of (focal) hematopoiesis throughout pregnancy [11]. EMH has been described in the uvea of adults after inflammation, operation or trauma to the eye [12-14] and in a case of hemorrhage in ocular intravascular B-cell lymphoma [15]. Relevant to the current case is a recent series that describes intraocular EMH in 35 out of 102 postmortem pediatric examinations, of which many cases of SIDS (22/35) [16]. This series only describes two cases of AHT that did not show EMH [16]. The oldest child with intraocular EMH was two years of age. Only eight cases showed EMH in other organs, 6 liver, 1 spleen and 1 thymus. We describe EMH in the choroid of 3/60 (5%) of post mortem eyes investigated on the suspicion of AHT. The most probable explanation of this phenomenon is a chance finding that may have a relation to the premature birth and possible anemia [10]. An alternative explanation may be a reaction to intraocular bleeding due to earlier trauma [12]. An important consequence of EMH is the presence of iron in special stains which may hinder the interpretation of the age of the retinal hemorrhages in AHT.

Conclusions

Extensive unilateral EMH of the choroid was observed three out of 60 cases of AHT (5%) with retinal hemorrhage, optic nerve sheath hemorrhage and/or peripapillary intrascleral hemorrhage. This may be a chance finding, or it may have a relation to premature birth, possible anemia or may be a reaction to intraocular bleeding due to earlier trauma. Awareness of the possibility of EMH in AHT may prevent misdiagnosis of active uveitis or meningitis.
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