Patterns of retinal hemorrhage associated with pediatric cerebral sinovenous thrombosis

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BACKGROUND Cerebral sinovenous thrombosis (CSVT) has been proposed as an alternative cause of retinal hemorrhage (RH) in children being evaluated for abusive head trauma. This study investigated the prevalence and characteristics of RH in children with CSVT.

METHODS The medical records of children >6 weeks of age with newly diagnosed CSVT and fundus examination by an ophthalmologist were examined retrospectively. Primary outcomes were presence and patterns of RH.

RESULTS A total of 29 children (median age, 9 years; range, 7 weeks to 17 years) were studied. Of these, 5 (17%) had RH, in 4 of whom RH were peripapillary, superficial, intraretinal, and adjacent to a swollen optic disk. In the fifth child, who had meningitis, sepsis, and multiple cerebral infarcts, there were a moderate number of posterior pole intraretinal hemorrhages. Eighteen children (62%) had optic disk swelling. In 13 children, cerebrospinal fluid opening pressure was recorded (range, 27–59 cm H_2O). CSVT risk factors included meningitis, mastoiditis, and hypercoagulability.

CONCLUSIONS RH in pediatric CSVT was uncommon. When RHs were present, the appearance matched RH patterns known to be caused by medical conditions, such as raised intracranial pressure and sepsis, also present in these children. These findings suggest that the RHs are due to these other causes and not directly to CSVT itself. In children with CSVT, if RHs are multilayered, extend beyond the peripapillary region into the rest of the posterior pole or retinal periphery, or occur in the absence of optic disk swelling, another etiology for the RH should be sought. (J AAPOS 2017;21:23-27)

Retinal hemorrhage (RH) is an important finding in young children with intracranial hemorrhage. The most common causes of RH in such children are birth trauma in the first month of life and abusive head trauma (AHT) in older infants, but numerous other, less common, causes have been reported.[1-3] The specific pattern and extent of RH help to delineate the cause of the eye findings.[1,2,4-6] RH in AHT may range from a few intraretinal, dot-and-blot, or flame-shaped posterior pole hemorrhages to hemorrhages that are multilayered (pre-, intra-, and subretinal), too numerous to count, or extend to the retinal periphery. In more severe cases, RH may be accompanied by retinal folds, retinoschisis, or hemorrhagic macular cyst. The majority of AHT hemorrhages occur without optic nerve head edema.[7,8] In contrast, RH related to increased intracranial pressure (ICP) are characteristically superficial intraretinal hemorrhages located on or adjacent to a swollen optic nerve head.[8]

Cerebral sinovenous thrombosis (CSVT) is a rare disease, affecting just 0.67 children per 100,000 per year.[9] It occurs when thrombi occlude a vein or sinus in the intracranial venous system, resulting in decreased venous blood and cerebrospinal fluid drainage and a retrograde rise in venous pressure and congestion (Figure 1). These effects may stay regionalized in the brain, or, in the case of major sinovenous occlusion, more global effects may occur, resulting in increased ICP.[10] Papilledema, or optic nerve head swelling from raised ICP can be observed in children with CSVT, and formal ophthalmologic evaluation is often conducted in the diagnostic evaluation of children with suspected or radiographically confirmed CSVT.

CSVT has been proposed in the courtroom as an alternative explanation for RH in children being evaluated for AHT, but formal investigation of this hypothesis has yet to be presented in the literature. If

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FIG 1. Cerebral sinovenous thrombosis seen on "time of flight" magnetic resonance venogram as a filling defects (arrows) in the superior sagittal sinus, extending into the left transverse and sigmoid sinuses.

CSVT were associated with RH, it could affect the interpretation of ocular findings in children being evaluated for possible abusive injuries. The present study sought to describe the prevalence and patterns of RH associated with pediatric CSVT.

Subjects and Methods

We conducted a two-center retrospective cross-sectional study at the Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (CHOP), and Nationwide Children's Hospital, Columbus, Ohio. The study was approved by the institutional review boards of both institutions and conformed to the requirements of the US Health Insurance Portability and Accountability Act of 1996.

Subjects were identified using ICD-9 codes to search a clinical database at Nationwide, and a separate search was conducted of a prospective, consecutive Pediatric Stroke Registry at CHOP for children with CSVT between January 2009 and December 2013. The inclusion criteria for the study included age >6 weeks and <18 years; a new diagnosis of CSVT as evidenced by thrombus or interruption of flow with cerebral veins or dural venous sinuses on computed tomography (CT) or magnetic resonance (MR) venography; and dilated fundus examination with indirect ophthalmoscopy by a pediatric ophthalmologist. Children were excluded if the eye examination occurred more than 10 days from the time of diagnosis of CSVT. Children were not excluded if there was suspected AHT, because doing so could introduce a selection bias. In all cases, the ophthalmologist's examination of the retina was completed prior to fundus imaging. The primary outcomes were the presence of RH, pattern of RH, presence of macular pathology, and presence of optic disk swelling. The pattern of RH was assessed by the quantity, type (disk splinter hemorrhage, superficial intraretinal [flame] hemorrhages, deeper intraretinal [blot] hemorrhages, and subretinal hemorrhage), and location (on the disk, peripapillary, along the vascular arcade, in the macula, near periphery, mid periphery, far periphery). Macular pathology included circumlinear macular retinal folds, macular retinoschisis, or hemorrhagic macular cyst.

Medical records were reviewed for demographics, clinical presentation, signs of elevated ICP, past medical history, and results from diagnostic evaluations, including lumbar puncture (LP) and brain imaging studies. Headache, nausea, emesis, altered level of consciousness, diplopia, abducens nerve palsy, esotropia, seizure, and optic disk swelling were considered clinical symptoms and signs of raised ICP. Risk factors associated with CSVT were identified from the abstracted medical records.

An institutional Pediatric Stroke Service was consulted on all suspected CSVT cases at both hospitals in this study, and the Pediatric Stroke Service confirmed the diagnosis and the associated risk factors. In both institutions, all children suspected of having an abusive injury are evaluated by multidisciplinary assessment.

Results

A total of 29 children (16 girls) with CSVT met inclusion criteria (Table 1). The mean age at presentation was 9 years (range, 7 weeks to 17 years). Six children were <3 years of age, none of whom had retinal hemorrhages. Associated CSVT risk factors included head and neck infection in 11 subjects (38%), chronic systemic disease in 8 (28%), prothrombotic state in 4 (14%), head trauma (snow ball to head) in 1 (4%), and were uncertain in 5 (17%). AHT was not suspected in any of these cases. Twenty-seven children (93%) had a clear history of clinical symptoms or signs of raised ICP. Eighteen (62%) had papilledema ranging from mild to severe. Thirteen (45%) had opening pressures recorded at time of lumbar puncture, with a mean opening pressure of 37 cm H_2O (range, 27–59 cm H_2O).

Fundus examination occurred <48 hours from radiographic confirmation of CSVT in 17 (60%) cases, 2-5 days from diagnosis in 6 (20%), and 6-10 days from diagnosis in 6 (20%). A total of 5 (17%) subjects had RH, of whom 4 had a few splinter disk hemorrhages or superficial intraretinal hemorrhages directly adjacent to a swollen optic disk (Figure 2). Of these 4, 1 had systemic lupus erythematosus, 1 had mastoiditis, and 2 did not have an identified CSVT risk factor. The fifth child with RH had meningitis, sepsis, and multiple coincident ischemic cerebral infarctions. This child had a moderate number of (approximately 30-35) intraretinal hemorrhages in the posterior pole of each eye (Figure 3). The diagnosis of sepsis and meningitis was made based on clinical grounds and response to treatment. The infant was 7 weeks old, born at 33 weeks' gestational age, with a prior history of necrotizing enterocolitis; he presented with poor feeding, decreased activity,

Table 1. Demographic and clinical features of 29 children with cerebral sinovenous thrombosis

	N	%
Subjects	29	
Age, years		
Mean ± SD	9.2 (0.7)	
Minimum	0.15	
1st quartile	4	
Median	11	
3rd quartile	14	
Maximum	17	
Risk Factors		
Infection	11	38
Mastoiditis	9	31
Meningitis	4	14
Sinusitis	2	7
Otitis media	1	3
Sepsis	1	3
Systemic disease	8	28
Asthma	2	7
Malignancy	1	3
Nephrotic syndrome	1	3
Lupus	1	3
Cobolamine B deficiency	1	3
Immunodeficiency	1	3
Other	1	3
Prothrombotic state	4	14
Oral contraceptive	3	10
Familial hypercoaguability	1	3
Trauma	1	3
Uncertain	5	17
Clinical symptoms		
Headache	18	62
Emesis	13	45
Diplopia/esotropia	8	28
Lethargy	6	21
Ear pain	5	17
Fever	4	14
Seizure	3	10
Photophobia	2	7
Dizziness	1	3
Hypothermia	1	3
Hypoxia	1	3
Sinus pain	1	3
Extremity weakness	1	3
Neck pain	1	3
Transient visual obscurations	1	3
Myalgias	1	3
Loss of milestones	1	3
Aphasia	1	3
Global developmental delay	1	3
Macrocephaly	1	3
Ataxia	1	3
Radiographic findings		
Sinovenous thrombosis	29	100
Hemorrhagic infarction	2	7
Cerebellar hemorrhage	1	3
Subdural empyema	1	3

SD, standard deviation.

enlarging abdomen, hypothermia (87° F), apneic episodes, emesis, seizure-like movements, and hypoxia. Brain imaging showed multifocal venous infarctions due to thrombosis, involving the superior sagittal sinus and frontal cortical veins. There was no subdural hemorrhage, and there were no additional physical examination findings that raised suspicion of trauma. Initially, the infant was too unstable to undergo lumbar puncture, and intravenous antibiotics were begun, resulting in clinical improvement and recovery.

Discussion

We found that RH is uncommon in children with CSVT. When it was present, the children also had medical conditions known to cause RH, including elevated ICP and sepsis, and the RH patterns observed were consistent with the specific patterns of RH associated with those conditions. Four of the 5 children had a RH pattern consistent with raised ICP: disk hemorrhages or superficial peripapillary intraretinal hemorrhages adjacent to a swollen optic disk.[8] One child with sepsis had a RH pattern consistent with sepsis: a moderate number of intraretinal hemorrhages limited to the posterior pole.[11,12] These observations suggest that the RH associated with CSVT results from these other causes, not from CSVT itself. Regardless of whether or not there is a causal link, the RH patterns seen in CSVT cases are not consistent with the severe RH patterns frequently seen in AHT. No subject in our study had RHs that were preretinal, subretinal, peripheral, or too numerous to count. Nor did any subject have retinal folds, retinoschisis, or hemorrhagic macular cysts. Furthermore, the raised ICP pattern of RH observed in CSVT is not consistent with the milder RH patterns that can be seen in cases of AHT, as AHT can also feature deeper blot intraretinal hemorrhage extending elsewhere in the posterior pole, not just superficial peripapillary RH.

Our findings are similar to prior case reports describing the pattern of RH seen in CSVT. In one case, an 11-year-old child with CSVT and elevated ICP developed optic disk swelling with superficial peripapillary hemorrhages.[13] In another, a 3-year-old child presenting with encephalopathy, elevated ICP, and associated midline shift on neuroimaging was found at time of diagnosis to have fewer than 5 retinal hemorrhages associated with disk swelling in one eye.[14] One adult patient with severe papilledema and venous sinus thrombosis also had classic peripapillary RH with optic disk swelling.[15]

Our cohort was representative of children with CSVT. In published population-based[9] and multicenter[16] cohorts studied by pediatric stroke experts, the most commonly identified risk factors for CSVT are intracranial infection (otitis media/mastoiditis, meningitis), dehydration, anemia, prothrombotic disorders, and chronic systemic diseases such as malignancy and exposure to chemotherapy, autoimmune disorders, and protein-losing states (enteropathy, nephropathy, liver failure). Some cases are diagnosed incidentally, after surveillance neuroimaging has been performed after neurosurgery. In many children, multiple risk factors are present.

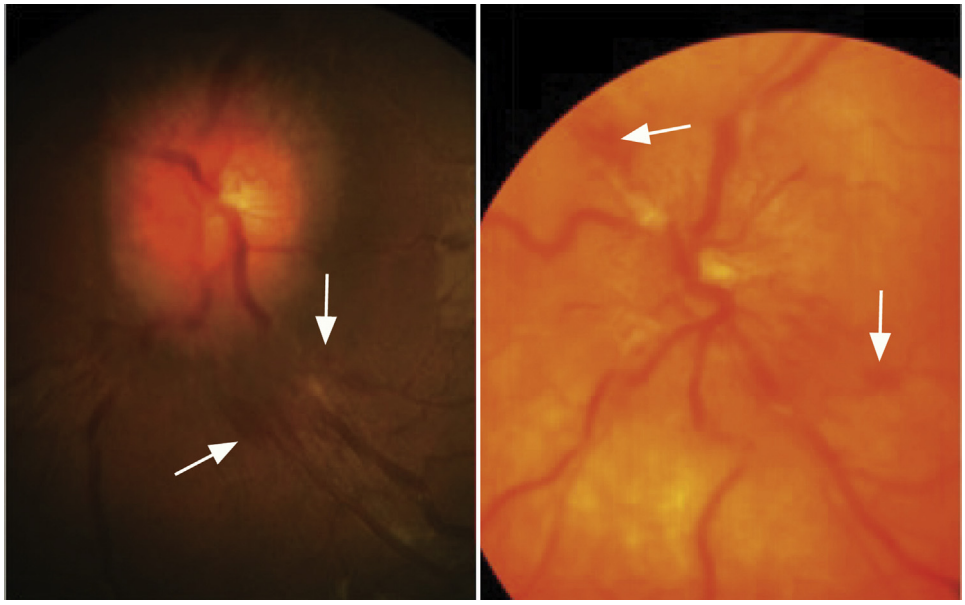

FIG 2. Two children with papilledema and cerebral sinovenous thrombosis showing small, superficial intraretinal hemorrhages adjacent to the swollen optic nerve head (arrows).

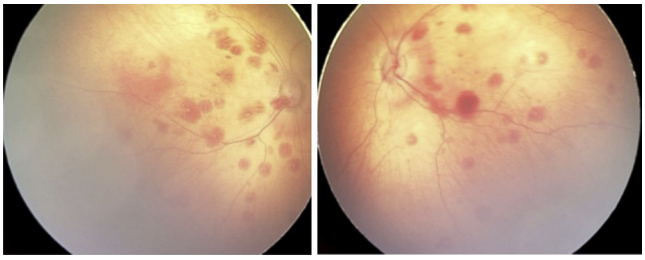

FIG 3. Child with sepsis and cerebral sinovenous thrombosis showing a moderate number of intraretinal hemorrhages in the posterior pole of both eyes.

AHT has not been identified as a risk factor for CSVT, although more generally head trauma has been reported in association with CSVT. As part of a 217-patient single-center cohort, Xavier and colleagues[17] reported on 20 children with head-injury associated CSVT, only 1 of whom was <2 years of age: none had AHT. Similarly, Matsushige and colleagues[18] reported on 7 children, of whom 3 were <2 years of age, and none was identified as having AHT. Choudhary and colleagues[19] described the cortical venous and sinus abnormalities in 45 children with AHT using magnetic resonance imaging and magnetic resonance venography; although common findings included displacement or compression of cortical veins and sinuses from subdural hemorrhage or edema, CSVT was not a feature.

As shown in our series, the majority of children with CSVT have at least one identifiable risk factor; however, even after an exhaustive review of the clinical history and physical examination findings, some children are classified as idiopathic and spontaneous CSVT. Pediatric stroke specialists usually suspect they harbor an unknown prothrombotic disorder, and many such patients are kept on anticoagulation indefinitely. The mode of CSVT presentation varies by age but in general, it is nonspecific. In neonates, the most common presentation is seizures, followed by encephalopathy.[9] In older infants and children, encephalopathy (including headache) is the most common presentation, followed by focal neurologic signs (visual disturbance, abducens nerve palsy, or hemiparesis or hemisensory loss related to venous infarction) and seizures. All subjects in our study had clinical symptoms compatible with CVST (Table 1).

The strengths of our study include the large number of subjects with this relatively uncommon disease and outcomes assessed with dilated fundus examinations performed by pediatric ophthalmologists experienced in examining children and in recognizing the relevant types and patterns of RH. Although the RH data were collected retrospectively, the ophthalmologists routinely perform systematic examinations of the posterior, equatorial, and, if possible, far peripheral retina, and document findings in a standardized manner. With regards to generalizability to children with CSVT, as discussed above, the demographic and risk factor profile of our subjects is consistent with prior population-based and multicenter cohort studies of CSVT.[9,16,17] The findings also are generalizable to children being evaluated for possible abuse. While children with AHT are typically <3 years of age, we are unaware of retinal or neuroanatomical differences between younger and older children that would provide a pathophysiological mechanism by which RHs would be more likely to arise in CSVT in younger

children than in older children. In addition, only 6 children in the study were <3 years of age, and none had retinal hemorrhages.

The study has potential limitations. Six retinal examinations were performed 6-10 days after CSVT diagnosis, and it is possible that some intraretinal hemorrhages may have cleared by that time. However, most children (17/29) were examined within 2 days of CSVT diagnosis, and the majority (23/29) were examined within 5 days. Moreover, preretinal hemorrhage, retinal folds, retinoschisis, and hemorrhagic macular cysts last for weeks and would not have resolved within 10 days of CSVT diagnosis.[20,21] Another limitation is that only about half of the subjects in the study had an LP to measure ICP directly, given that LP may not be necessary once CSVT has been radiographically confirmed. However, all but 2 children had clinical evidence of raised ICP, and the children who had available opening pressure data had elevated ICP.[9,18]

RHs are uncommonly seen in association with CSVT. Based on the RH patterns observed in this cohort, RH associated with CSVT is likely the result of an associated medical condition, such as elevated ICP or sepsis. Therefore, the presence of CSVT should not change the current clinical interpretation of RH patterns and severity with regard to the differential diagnosis and specificity for AHT. In children with CSVT, when RHs are multilayered, extend beyond the peripapillary region into the rest of the posterior pole or retinal periphery, occur in the absence of optic disk swelling, or are associated with macular pathology such as retinoschisis or retinal folds, another etiology for the RH should be sought.

Literature Search

PubMed, MEDLINE, Scopus, Web of Science, Embase, and Google Scholar were searched on October 1, 2016 using the following terms: *cerebral venous thrombosis*, *sinovenous thrombosis*, *cortical vein thrombosis*, *retina*, and *retinal hemorrhage*.

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