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Evaluation of Temporal Association Between Vaccinations and Retinal Hemorrhage in Children

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Abstract

Importance—Vaccinations have been proposed as a cause of retinal hemorrhage in children, primarily as part of a defense strategy in high-stakes abusive head trauma cases. If vaccination injections cause retinal hemorrhage, this consideration would affect the evaluation of children for suspected child abuse.

Objectives—To describe the prevalence and causes of retinal hemorrhage among infants and young children in an outpatient ophthalmology clinic and to test the hypothesis that, if vaccination injections cause retinal hemorrhage, then retinal hemorrhage would be seen frequently and be temporally associated with immunization.

Design, Setting, and Participants—Retrospective cohort study between June 1, 2009, and August 30, 2012, at The Children's Hospital of Philadelphia pediatric ophthalmology clinics among 5177 children 1 to 23 months old undergoing a dilated fundus examination as an outpatient for any reason. Children with intraocular surgery or active retinal neovascularization were excluded from the study.

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Main outcomes and Measures—The prevalence and causes of retinal hemorrhage, as well as the temporal association between vaccination injection within 7, 14, or 21 days preceding examination and retinal hemorrhage.

Results—Among 7675 outpatient fundus examinations, 9 of 5177 children had retinal hemorrhage for a prevalence of 0.17% (95% CI, 0.09%-0.33%). All 9 had abusive head trauma diagnosable with nonocular findings. Among a subset of 2210 children who had complete immunization records and underwent 3425 fundoscopic examinations, 163 children had an eye examination within 7 days of vaccination, 323 within 14 days, and 494 within 21 days. No children had retinal hemorrhage within 7 days of vaccination, 1 child had hemorrhage within 14 days, and no additional child had hemorrhage within 21 days. There was no temporal association between vaccination injection and retinal hemorrhage in the prior 7 days ($P > .99$), 14 days ($P = .33$), or 21 days ($P = .46$).

Conclusions and Relevance—Retinal hemorrhage was rare among outpatients younger than 2 years. Considering both immediate and delayed effects, no temporal association existed between vaccination injection and retinal hemorrhage. Vaccination injections should not be considered a potential cause of retinal hemorrhage in children, and this unsupported theory should not be accepted clinically or in legal proceedings. Ophthalmologists noting incidental retinal hemorrhage on an outpatient examination should consider a child abuse evaluation in the absence of other known ocular or medical disease.

Vaccinations have been proposed as a cause of retinal hemorrhage among children in the medical literature and as part of a defense strategy in court in high-stakes cases of abusive head trauma.[1-3] If true, such an association could influence the interpretation of retinal findings during child abuse evaluations because retinal and intracranial hemorrhage is an important sign of abusive head trauma in infants.[4-9]

Aside from speculative editorials lacking primary data,[1,2] only a handful of case reports of retinal hemorrhage after vaccination exist. In 1948, Rosen[10] reported a case of retinal hemorrhage that appeared 10 days after a vaccination injection. However, abusive head trauma had not yet been described in the contemporary literature and therefore was not excluded. Almost 50 years later, 6 cases were reported of central or branch retinal vein occlusion occurring in adults shortly after hepatitis B vaccination.[11-13] In their case series, Granel et al[13] found no single potential mechanism–among which they considered immunocomplexes, antigenic cross-reactions, immediate hypersensitivity, and pathogenic lymphocyte stimulation–to be “entirely satisfactory” to explain ocular manifestations after vaccination. Retinal vein occlusion, often diagnosed as an idiopathic condition in adults, is rare in children and features a characteristic pattern of retinal hemorrhage distinguishable from the patterns typical of abusive head trauma.[7] Moreover, no comparative data have been reported to assess for a potential association between vaccination injection and retinal hemorrhage, to our knowledge.

We reasoned that, if vaccination injections cause retinal hemorrhage, then retinal hemorrhage would be observed with some frequency among children having eye examinations during infancy and early childhood and would be temporally associated with immunization. Therefore, we sought to describe the prevalence and identifiable causes of

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retinal hemorrhage among infants and young children undergoing retinal examinations in an outpatient ophthalmology clinic and to determine any association between vaccination injection and retinal hemorrhage.

Methods

We conducted a retrospective cohort study of children evaluated at the outpatient pediatric ophthalmology clinics of The Children's Hospital of Philadelphia (CHOP) between June 1, 2009, and August 30, 2012. The study was approved by the Committees for the Protection of Human Subjects, which granted a waiver of informed consent, and was carried out in compliance with the principles of the Declaration of Helsinki and the US Health Insurance Portability and Accountability Act of 1996.

Eligible study participants were children 1 to 23 months old who had a dilated fundus examination by a pediatric ophthalmologist using indirect ophthalmoscopy as an outpatient during the study period. The children were seen for various reasons typical of young children referred to a pediatric ophthalmologist, including the evaluation of strabismus or pseudostrabismus, amblyopia, red eye, trauma, tear duct obstruction, poor visual behavior, history of systemic disease associated with ocular findings, and others. These children were included in a study of the prevalence of retinal hemorrhage among outpatient eye examinations. A few children were seen for follow-up of an ophthalmological condition diagnosed as an inpatient, including trauma and child abuse. A subset of these children was also included in a temporal analysis of vaccination exposure and retinal hemorrhage. The criterion for being included in this subset was the availability of vaccination records in the electronic medical record, which occurred when the child's pediatrician was within the CHOP primary care network. Children were excluded from the study a priori if they had a history of direct eye trauma, intraocular surgery (eg, for cataract or glaucoma), or known active retinal neovascularization (eg, stage 3 or worse retinopathy of prematurity) because these conditions are known to be a potential cause of retinal hemorrhage. We did not exclude children with a history of suspected abusive or accidental head trauma, regressed retinopathy of prematurity, or prematurity in general so as not to bias the study results. Regressed retinopathy of prematurity and prematurity without retinopathy were not exclusion criteria because these conditions do not generally cause retinal hemorrhage.

The prevalence of retinal hemorrhage was calculated as the proportion of children with any retinal hemorrhage on fundus examination. The 95% CI of the prevalence was calculated using the method by Wilson,[14] which is appropriate when the observed proportion is low. The causes of retinal hemorrhage were determined by reviewing the entire medical record, including inpatient records if necessary. The subset of children with immunization records was divided into anexposed group (examination occurring within 7 days after a vaccination injection) and an unexposed group. The prevalence of retinal hemorrhage was compared between groups to determine if there was an association between vaccination injection and retinal hemorrhage. Fisher exact test for comparison of proportions was used to assess for statistical significance, defined as $P < .05$. As a precaution, the association was secondarily evaluated by defining the exposure as having an examination within 14 days and within 21 days after a vaccination injection. This evaluation was conducted to assess for possible

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delayed effects of vaccinations, although we know of no such delayed association. Many children had multiple vaccination dates, each of which represented an additional “exposure,” and multiple dilated fundus examinations, each of which represented an additional assessment of “outcome.” The date of the first retinal hemorrhage diagnosis was used for the analysis, and once retinal hemorrhage was diagnosed, subsequent examinations for that child were excluded. If the diagnosis of retinal hemorrhage was first made as an inpatient, the inpatient visit date was used for the analysis. All statistical analyses were performed using a software program (SAS, version 9.2; SAS Institute Inc).

Results

In total, 5177 children met the study criteria and had 7675 fundus examinations. The mean (SD) age was 19.1 (9.4) months, and 47.4% (2453 of 5177) were female.

Overall, 9 of 5177 children had retinal hemorrhage. Therefore, the prevalence of retinal hemorrhage was 0.17% (95% CI, 0.09%-0.33%). All 9 children with retinal hemorrhage were victims of abusive head trauma unambiguously diagnosable with nonocular clinical and historical findings, including the following: acute or acute with chronic intracranial hemorrhage (n = 9), skull fracture (n = 5), bruises (n = 3), hypoxic-ischemic brain injury and watershed brain infarction (n = 2), spinal fracture (n = 1), spinal hematoma (n = 1), and perpetrator confession (n = 1). All 9 children had first been examined and diagnosed as having retinal hemorrhage and abusive head trauma as inpatients.

Of the 5177 children studied, a subset of 2210 had vaccination records available and were included in the temporal immunization analysis. The mean (SD) age of this subset was 18.2 (9.7) months, and 47.2% (1044 of 2210) were female. These children underwent 3425 fundus examinations (Table). In total, 41 673 vaccination injections were administered on 14 173 immunization days. These injections included the following: pneumococcus (n = 8417); combination diphtheria, tetanus, and pertussis (n = 8130); *Haemophilus* influenza type B (n = 7790); polio (n = 6743); hepatitis B virus (n = 6671); combination measles-mumps-rubella (n = 1965); and varicella (n = 1957). Eighty-nine percent (1968 of 2210) of the children received vaccinations on 5 or more separate days, and all children received immunization on at least 1 day. Multiple immunization injections were administered on the same day for 9638 of the 14 173 days (68.0%) when children were vaccinated, and 4 or more injections were given simultaneously for 6288 (44.4%) of these days. Of the 3425 retinal examinations, 163 occurred within 7 days of a vaccination injection, 323 within 14 days, and 494 within 21 days.

In total, 4 of the 2210 children with vaccination records had retinal hemorrhage (Table). Therefore, the prevalence of retinal hemorrhage was 0.18% (95%CI, 0.70%-0.46%).These 4 children were included among the 9 children described above in the second paragraph of the Results section, and all 4 had been previously diagnosed as having abusive head trauma. None of the 4 children had a vaccination in the 7 days preceding the diagnosis of retinal hemorrhage. One of the children had a vaccination within 14 days before diagnosis, and the other 3 children did not have a vaccination in the 21 days preceding the diagnosis. There was

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no association between receiving a vaccination injection and the presence of retinal hemorrhage in the subsequent 7 days ($P > .99$), 14 days ($P = .33$), or 21 days ($P = .46$).

Discussion

We found that retinal hemorrhage is very rare among infants and young children undergoing outpatient ophthalmological examinations. If retinal hemorrhage was caused by immunization, we would expect retinal hemorrhage to be a somewhat common finding among children of ages at which vaccinations are routinely and repeatedly administered, but it was not frequently observed. The prevalence of retinal hemorrhage was only 0.17% (9 of 5177), and it would have been 0% if children with abusive head trauma, who all had non-ocular findings, had been excluded. If retinal hemorrhage was caused by immunization, we also would expect there to be a temporal association between vaccination injection and retinal hemorrhage, but there was no such relationship. We found no association between vaccination injection and the presence of retinal hemorrhage during periods of 7, 14, or 21 days after immunization. For these reasons, we conclude that vaccination injections do not cause retinal hemorrhage. While the low prevalence of retinal hemorrhage results in lower statistical power to detect an association with immunization, the exceedingly low prevalence in and of itself supports the conclusion that vaccination does not cause retinal hemorrhage.

Alternative hypotheses, such as vaccinations, regarding the etiology of retinal hemorrhage in young children diagnosed as having abusive head trauma are commonly presented in legal proceedings and the medical literature without scientific data to support the claims.[1-3,15] We sought to obtain objective data about one such hypothesis. To our knowledge, there are no comparative studies in the literature against which to evaluate our results. The Institute of Medicine's extensive report on adverse effects of vaccinations does not mention retinal hemorrhage.[16] The case reports cited in the Introduction herein do not establish an association.[11-13] Furthermore, there is little biologic plausibility to suggest that an association might exist between vaccination injection and retinal hemorrhage. In an editorial, Clemetson[2] speculated that vitamin C deficiency combined with injection of foreign proteins from multiple vaccines leads to elevated histamine levels, causing capillary fragility and bleeding as well as bone fragility and fractures. No data support this hypothesis.[17] It should be noted that our cohort included many children who received multiple vaccines at one time. In another editorial to suggest a correlation between vaccination and retinal hemorrhage, Gardner[1] attempted to draw rough parallels between variations in the timing of injections and peak ages of reported abusive head trauma in the United States, Japan, and France. These correlations are weak, and secular trends provide a low level of evidence when measured against a comparative study.

Numerous causes are commonly cited and routinely considered in the differential diagnosis of retinal hemorrhage in infancy.[7,8] We found that the only cause of retinal hemorrhage among a cohort of 5177 outpatients was abusive head trauma after a priori exclusion of children with active retinopathy of prematurity or recent intraocular surgery. This result does not exclude the possibility of another cause, but it suggests that an incidental finding of retinal hemorrhage in an infant undergoing an outpatient eye examination should raise suspicion for trauma, birth trauma in the first few weeks of life, and inflicted trauma

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afterward.[6,7,9,18] Even mild hemorrhages are potentially significant as a sign of occult trauma. In contrast, the incidental finding of retinal hemorrhage in an adult is commonly suggestive of diabetes mellitus, hypertension, or vascular occlusive disease.

Although the background context for the study involved a proposed alternative cause of retinal hemorrhage relative to abusive head trauma, which is commonly characterized by intracranial hemorrhage or encephalopathy, the study question was specifically whether vaccination injections are associated with retinal hemorrhage in young children. Therefore, an outpatient population (and not an inpatient population) was explicitly chosen a priori because such a population most directly fit the study question, which did not involve intracranial hemorrhage or encephalopathy from possible head trauma.

The study had multiple strengths. The study cohort was large and of an age range matching that of children with abusive head trauma.[4,9] Children younger than 1 month were excluded so as not to confound the results with birth trauma–related retinal hemorrhage. Children diagnosed as having abusive head trauma were not excluded so as not to potentially bias the study results. Head trauma was not an exclusion criterion because the hypothesis proposed was that vaccination injections are the cause of retinal hemorrhage rather than abusive head trauma, so exclusion of such children could unfairly bias the results against finding an association if the hypothesis was true. Dilated fundus examinations were performed by experienced pediatric ophthalmologists, and findings were recorded in a standardized fashion in the medical record. Detailed vaccination records were used. The analysis was performed for immediate (7 days) and delayed (14 days and 21 days) effects of vaccination injections and allowed multiple immunization events and multiple retinal examinations for each child to be considered separately, maximizing the opportunity for an association to be found. Numerous types of immunization were administered, and multiple vaccinations were given on the same day, so a potential effect of coincident administration of different vaccinations would be represented in our study sample. Although vaccination records were directly verifiable only for the 2210 children with a pediatrician in the CHOP primary care network, the proportion of the 2967 remaining infants who received immunization was likely high because vaccination rates are very high in the Philadelphia, Pennsylvania, region (96% for measles-mumps-rubella and 89% for 4 doses of diphtheria and tetanus toxoids and pertussis).[19]

The study had potential limitations to consider as well. The participants were children who had been referred to an ophthalmologist for an eye concern (eg, strabismus, poor tracking, tearing, ptosis, or infection) or a genetic or systemic disorder with known ocular associations (eg, chromosomal abnormality, metabolic disease, or hearing loss). However, the prevalence of retinal hemorrhage would likely be biased either upward or not at all, so the study conclusions would not change. Similarly, the children with vaccination records all had a primary care provider in the CHOP network, so those records would be available. Although the CHOP primary care providers see many healthy children in the surrounding communities, these children may be more likely to have a systemic disease compared with children with a non-CHOP primary care provider. Again, the prevalence of retinal hemorrhage would likely be biased upward or not at all; therefore, such selection bias would not change the study conclusions. The cohort was consecutive with regard to outpatient eye

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examinations; it was not a consecutive series of patients having vaccinations. However, because most children receive vaccinations,[19] sampling a large nonconsecutive series of children based on the need for an eye examination would not be expected to create a selection bias that would make it less likely to identify retinal hemorrhage. The far retinal periphery is not consistently visualized in pediatric outpatients, so hemorrhage limited to this area may be missed. However, the patterns of retinal hemorrhage associated with abusive head trauma and hypothesized by some to be caused by vaccinations include posterior pole hemorrhage and not simply isolated peripheral hemorrhage. Intraretinal hemorrhage can clear quickly, so it is possible that hemorrhages would not be identified if the examination was performed more than a few days after the vaccination injection. However, many children had examinations within a few days of injection, and retinal hemorrhage still was not seen. Finally, children with acute neovascular retinopathy of prematurity or a history of intraocular surgery were excluded because these conditions can cause retinal or vitreous hemorrhage. Clinically, such conditions would be clearly identifiable based on patient history or examination findings.

Conclusions

We found that retinal hemorrhage is very rare in infants and young children undergoing outpatient eye examinations and that the most likely cause when present is trauma. We suggest that ophthalmologists noting incidental retinal hemorrhage in the absence of active retinopathy of prematurity, a history of intraocular surgery, or other obvious cause should consider a child abuse evaluation. The very low prevalence of retinal hemorrhage among children receiving immunization and the lack of a temporal association between vaccination injection and retinal hemorrhage indicate that immunization does not cause retinal hemorrhage.

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At a Glance

- Vaccinations have been proposed as a possible cause of retinal hemorrhage in children, which if true would influence child abuse evaluations. If vaccination injections cause retinal hemorrhage, then retinal hemorrhage would be common during the first 2 years of life and be temporally associated with immunization.
- Among 5177 young outpatients undergoing fundus examinations, the prevalence of retinal hemorrhage was 0.17%, and the only cause was abusive head trauma as diagnosed with nonocular findings.
- In a subset of 2210 children with vaccination records, there was no temporal association between immunization and retinal hemorrhage.
- Pediatric ophthalmologists finding incidental retinal hemorrhage in young children undergoing outpatient fundus examinations should consider child abuse as a cause.

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Table

Assessment of an Association Between Vaccination Injection and Retinal Hemorrhage (RH) in 2210 Children With Complete Immunization Records

Variable	Retinal Examinations (N = 3425)	No. (%)		*P* Value[a]
		No RH (n = 3421)	RH (n = 4)	
Within 7 d preceding examination				
Vaccination	163	163 (100)	0	>.99
No vaccination	3262	3258 (99.9)	4 (0.1)	
Within 14 d preceding examination				
Vaccination	323	322 (99.7)	1 (0.3)	.33
No vaccination	3102	3099 (99.9)	3 (0.1)	
Within 21 d preceding examination				
Vaccination	494	493 (99.8)	1 (0.2)	.46
No vaccination	2931	2928 (99.9)	3 (0.1)	

[a]Fisher exact test.