

Ophthalmological and Biological Features of the Oculorespiratory Syndrome after Influenza Vaccination

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We report the ophthalmological and laboratory findings of 6 patients who, after influenza vaccination, were affected by oculorespiratory syndrome (ORS), complaining of red eyes, photophobia, blurred vision, palpebral edema, ocular pain and itching, and conjunctival secretions. The conjunctivae were mildly hyperemic with few follicles, but the ophthalmological examination findings were otherwise normal. Patients had lymphopenia and decreased levels of the total hemolytic complement and the third and fourth component of the complement. We conclude that ORS causes conjunctivitis and seems to involve the complement.

During the autumn of 2000, oculorespiratory syndrome (ORS), a new adverse event associated with influenza vaccination, was identified in Canada [1–5]. The clinical case definition required that, within 24 h after influenza vaccination, the patient develop ≥ 1 of the following symptoms: bilateral red eyes, respiratory symptoms (i.e., cough, wheezing, difficulty breathing, difficulty swallowing, hoarseness, chest tightness, and/or sore throat), and facial edema [5]. We report the findings for 6 patients with ORS with red eyes who had a complete ophthalmological examination and a standardized laboratory blood investigation.

Methods. Patients with an acute episode of ORS with red eyes were referred for ophthalmologic evaluation by private and public clinics and emergency departments in Quebec City. All ophthalmological examinations were performed by a single investigator (M.J.F.) and included an examination of visual acuity

with the Snellen Chart; examinations of pupillary reflex, motility, and confrontation visual fields; an external examination; a palpation examination; a biomicroscopic examination with the slit lamp; a phenylephrine test; an intraocular pressure (IOP) test with Goldman applanation tonometry; and an eye fundus exam after administration of dilation drops. Blood investigations included a complete blood count (CBC), determination of the sedimentation rate, counts of the third and fourth component of the complement (C3 and C4), the total hemolytic complement (CH50) assay, an IgE test, and a C-reactive protein and antinuclear antibody (ANA) test. For the complement, because of its lability (in particular, that of CH50), all blood samples were centrifuged and the plasma frozen at -80°C within 30 min after being obtained. Specimens were processed within 1 week after being obtained.

Results. Six individuals (3 women and 3 men), with a mean age of 39 years, were examined. The average delay between vaccination and onset of symptoms was 4 h (range, 1.5–12 h). Ocular examinations were performed between 5 h and 8 h (average, 6 h) after onset of symptoms for patients 1–5 and 4 days after onset of symptoms for patient 6. Symptoms lasted from 3.5 h to 2 days, except for patient 6, whose symptoms lasted 11 days. Three patients had a history of allergy, and 2 patients wore contact lenses. Five patients had received influenza vaccination for the first time.

After the onset of their episode, all patients complained of red eyes, 3 had a sensation of palpebral fullness, and 3 had ocular pruritus. Five patients complained of ocular secretions, without tears, that ranged from white and fluid (2 of 5 patients) to light yellow and sticky (3 of 5 patients). Five patients complained of ocular soreness; 2 described it as a burning sensation and 3 felt pain only when rubbing their eyes. None complained of pain during eye movements or blinking. Two patients complained of photophobia and blurred vision, which they further described as difficulty in focusing. One patient even had a car accident that she attributed to this visual problem.

In all patients, visual acuity with the Snellen chart was 6/6 (distance vision in meters) and 0.37 (near vision in meters). The ocular motility and visual fields were normal in all patients. The pupils were equally reactive to light and accommodation. No palpebral edema was visible. All patients had hyperemic conjunctivae (figure 1); for 5 patients, this was mild and symmetric, and, in 1 patient, it was asymmetric (moderate in one eye and mild in the other). Hyperemia resolved with phenylephrine treatment in all cases, except for that of the patient with asymmetric hyperemia. This latter patient (patient 6, table

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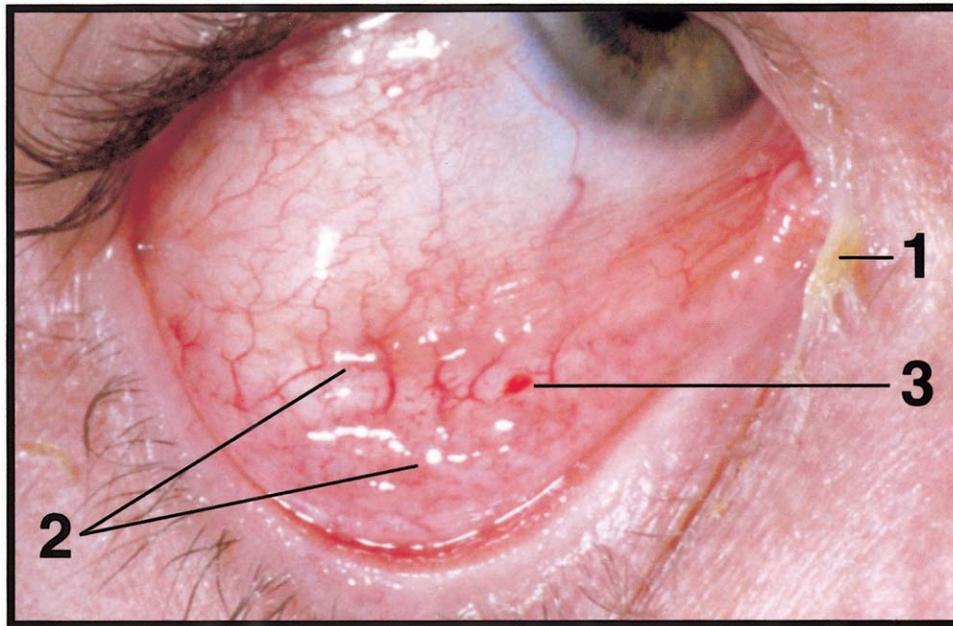


Figure 1. Ophthalmologic features found in patients with oculorespiratory syndrome. In addition to generalized conjunctival hyperemia, there were (1) thick secretions, (2) follicles, and (3) hemorrhages.

1) had dilated episcleral and scleral vessels in the upper nasal area of one eye, as well as pain at pressure in that area, and her symptoms lasted 11 days. Thick yellow secretions (indicated by 1 in figure 1) were present in 3 patients. Five patients had follicles (indicated by 2 in figure 1), 3 patients had small papillae, and 2 patients had small, well defined conjunctival hemorrhages (indicated by 3 in figure 1). The corneas were clear and the anterior chambers were free of cells and flare in all patients. The IOP was normal in all patients, ranging from 9 to 15 mm Hg. The lenses were clear, and fundoscopic examination findings were normal. Therefore, according to these signs and symptoms, 5 patients had conjunctivitis—associated with conjunctival hemorrhage in 2 of them—and 1 patient (patient 6) had sectorial scleritis (characterized by localized dilated episcleral and scleral vessels, positive results of a phenylephrine test, and pain on palpation of the globe). None of the patients had uveitis.

Four patients reported a sore throat, accompanied by difficulty in swallowing and a dry cough. The patient with the most severe pain underwent nasopharyngeal laryngoscopy, which showed mild-to-moderate edema of the epiglottis.

The patient with sectorial scleritis (patient 6) had normal laboratory results for all tests except for the ANA test (titer, 2560). She was known to have received positive ANA test results before immunization but had never had any ocular problem. Among the remaining 5 patients, laboratory tests showed an increase in WBCs in 3 patients (table 1). The patient with the most-severe respiratory manifestations had the highest WBC

count. Lymphopenia was observed in all patients, and the proportion of immature neutrophils ranged between 2% and 9%. Monocyte, basophil, eosinophil, and platelet counts were all normal, as was the sedimentation rate. The C-reactive protein level was slightly greater than 10 mg/L (normal value, <10 mg/L) in 3 patients. The CH50 level was <340 kU/L (normal range, 340–580 kU/L) in 3 patients and borderline (344 kU/L) in 1 additional patient. C3 and C4 levels at the lower end of the normal range (C3 normal range, 0.60–1.35 g/L; C4 normal range, 0.15–0.55 g/L) or just below it were observed in 4 patients and 3 patients, respectively. IgE levels were normal in all patients. All patients had positive test results for ANA, but at very low titer (10–100).

Discussion. Although limited, this ophthalmological and laboratory investigation is, to our knowledge, the only one performed among ORS patients in 2000. Despite symptoms like photophobia and blurred vision, which may suggest an involvement of internal structures of the eyes, the red eyes associated with ORS were caused by a conjunctivitis in all but 1 patient, who needed treatment for a sectorial scleritis. This patient had red eyes beginning 12 h after vaccination, but the evolution of his case was different from that of other cases, being the only case with an asymmetric presentation and a duration >2 days. This scleritis may be either a temporal coincidence or a more severe and rare manifestation of ORS in a predisposed individual (ANA titer, 2560) that was triggered by the vaccine.

The short duration of ORS symptoms and their rapid onset

Table 1. Laboratory findings for 6 patients with oculorespiratory syndrome.

Patient	WBCs				Complement levels						C-reactive protein level, mg/L
	Total count (× 1000)	Differential proportions, %			Hemoglobin level, g/L	CH50, kU/L	C3, g/L	C4, g/L	IgE	ANA type (titer)	
		Lymphocytes	Neutrophils	Immature neutrophils							
1	20.3	3	93	3	136	344	0.64	0.15	5	Speckled (10)	13
2	9.7	4	84	9	127	388	0.57	0.15	17	Speckled (10) and nucleolar (100)	10
3	14.0	5	91	2	144	194	0.63	0.23	34	Speckled (10)	25
4	15.3	0	91	6	148	259	0.67	0.14	<5	Speckled (10)	NA
5	9.6	4	89	3	127	226	0.62	0.21	<5	Speckled (10) and homogenous (10)	12
6 ^a	8.9	29	65	0	131	556	0.79	0.35	38	Homogenous (2560)	11

NOTE. ANA, antinuclear antibody; NA, not available.

^a Patient with scleritis.

after vaccination, as well as the ocular itching, papillae, and follicles, suggested an allergic reaction. However, normal levels of IgE and thick secretions are not typical of type I hypersensitivity. This type of hypersensitivity was also excluded by skin testing [6]. Viral or bacterial contamination of the vaccine was ruled out by extensive investigations conducted by both the manufacturer and Health Canada [5]. The presence of ANA, the lymphopenia, the absence of eosinophils, and the low C3, C4, and CH50 levels raise questions regarding the physiopathology of ORS. In the absence of vaccinated but unaffected control subjects, it is difficult to know whether these laboratory abnormalities are peculiar to ORS or are part of the normal response to influenza vaccine.

The low C3, C4, and CH50 levels indicate an activation of the complement system, a phenomenon known to happen with viral infections and antigens [7]. Complement activation may lead to an inflammatory response and changes in capillary permeability, which could explain the ocular findings of conjunctival injection and hemorrhages. Dysfunction or deficiencies of the C1 inhibitor that cause activation of the complement result in angioneurotic edema with bouts of nonpruritic edema of the face and the extremities, as well as edema of the larynx and bowel wall, that generally last 48–72 h [8]. These clinical features are similar but not identical to those of ORS. Nonpruritic facial edema is common in ORS, but edema of the extremities is not [2–4]. The presence of a mild-to-moderate edema of the epiglottis in 1 of our patients may resemble a mild variant of laryngeal involvement of the angioneurotic edema. It may explain the throat-tightening sensation, the difficulty swallowing,

and the hoarseness often reported by patients with ORS [2–5]. Further investigation is needed to better characterize the immunopathology of ORS.

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