

Case report

Case report on Hoagland's sign: a useful clinical sign for the early diagnosis of infectious mononucleosis. Pediatric report

DOI: 10.5377/alerta.v9i3.23310

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0009-0008-9606-6739

OPEN ACCESS

Signo de Hoagland: signo clínico útil para el diagnóstico temprano de mononucleosis infecciosa. Informe pediátrico

Suggested citation:

Barahona de Figueroa J. Case report on Hoagland's sign: a useful clinical sign for the early diagnosis of infectious mononucleosis. Pediatric report. Alerta. 2026;9(3):172-178. DOI: 10.5377/alerta.v9i3.23310

Editor:

Naida Rodríguez

Received:

September 11, 2025.

Accepted:

June 13, 2026.

Published:

July 31, 2026.

Author contribution:

JBF: study conception, manuscript design, literature search, data collection, data management or software, data analysis, writing, revising, and editing.

Conflicts of interest:

No conflicts of interest.

Abstract

Infectious mononucleosis is characterized by the triad of fever, pharyngotonsillitis and cervical lymphadenopathy. However, some early manifestations, such as bilateral eyelid edema (Hoagland's sign), may go unnoticed, especially in the pediatric population, leading to diagnostic delays and the unnecessary use of antibiotics. **Case presentation.** A 7-year-old female patient presented with acute, non-inflammatory bilateral eyelid edema that was painless and lacked local signs of inflammation, accompanied by fever, pharyngotonsillitis, and cervical lymphadenopathy. The identification of Hoagland's sign led to an early suspicion of Epstein-Barr virus infection. A complete blood count with peripheral blood smear revealed 15 % reactive atypical lymphocytes, a hematologic finding characteristic of the disease. A cervical ultrasound showed multiple bilateral enlarged lymph nodes in the anterior and posterior cervical chains. **Diagnosis.** The diagnosis was confirmed by the detection of heterophile antibodies during the second week of the illness. **Treatment.** Symptomatic treatment with nonsteroidal anti-inflammatory drugs was prescribed; corticosteroids, antivirals, or antibiotics were not required. **Outcome.** The course was favorable, with progressive resolution of symptoms. The patient was discharged on the sixth hospital day, with no complications or sequelae during follow-up. Recognition of Hoagland's sign can facilitate a timely diagnosis and appropriate management.

Keywords

Infectious Mononucleosis; Epstein-Barr Virus Infections; Edema; Eyelids.

Resumen

La mononucleosis infecciosa se caracteriza por la tríada de fiebre, faringoamigdalitis y linfadenopatía cervical. No obstante, algunas manifestaciones tempranas, como el edema palpebral bilateral o signo de Hoagland, pueden pasar inadvertidas, especialmente en la población pediátrica, lo que favorece retrasos diagnósticos y el uso innecesario de antibióticos. **Presentación del caso.** Paciente femenina de siete años que consultó por edema bpalpebral bilateral agudo no inflamatorio, indoloro y sin signos inflamatorios locales, concomitante con fiebre, faringoamigdalitis y linfadenopatías cervicales. La identificación del signo de Hoagland orientó precozmente la sospecha de infección por el virus de Epstein-Barr. El hemograma con frotis de sangre periférica mostró 15 % de linfocitos atípicos reactivos, hallazgo hematológico característico de la enfermedad. La ecografía cervical evidenció múltiples adenomegalias bilaterales en las cadenas cervicales anteriores y posteriores. **Diagnóstico.** Se confirmó mediante la detección de anticuerpos heterófilos durante la segunda semana de evolución. **Intervención terapéutica.** Se indicó tratamiento sintomático con antiinflamatorios no esteroideos, sin requerir corticosteroides, antivirales ni antibióticos. **Evolución clínica.** Fue favorable, con resolución progresiva de los síntomas. La paciente recibió el alta al sexto día de hospitalización, sin complicaciones ni secuelas durante el seguimiento. El reconocimiento del signo de Hoagland puede facilitar un diagnóstico oportuno y un manejo apropiado.

Palabras clave

Mononucleosis Infecciosa, Virus de Epstein-Barr, Edema, Párpados.

Introduction

Infectious mononucleosis (IM), primarily caused by the Epstein-Barrvirus (EBV), is characterized by mononuclear lymphocytosis, with the presence of atypical lympho-

cytes. Although it is generally benign and resolves spontaneously, its wide clinical variability and potential complications require close monitoring. The classic presentation includes the triad of fever, pharyngitis, and generalized lymphadenopathy.¹

Hoagland's sign, defined as soft, non-inflammatory bilateral upper eyelid edema, is a finding of high diagnostic value that may precede typical symptoms, making the initial diagnosis difficult if it goes unrecognized.¹ First described in 1952, this sign appears in approximately 5 % to 30 % of cases.² Its strategic value lies in being an early manifestation, identifiable before serological tests become positive, which is key to avoiding misdiagnoses.²

In pediatrics, mononucleosis is often underdiagnosed due to atypical presentations.^{3,4} Identifying Hoagland's sign allows for distinguishing IM from other viral pharyngitides and streptococcal tonsillitis,⁵ in addition to enabling an early diagnosis of the disease, for appropriate follow-up and screening for complications. It usually appears even before the onset of exudative pharyngitis and cervical lymphadenopathy.^{5,6} Early recognition is essential to avoid the unnecessary use of aminopenicillins, which are associated with the induction of a characteristic rash in these patients.⁶

Pathophysiologically, bilateral eyelid edema is associated with viral replication in the nasopharynx and transient lymphatic obstruction, frequently presenting with atypical lymphocytosis and no proteinuria.⁶

Clinicians should consider this edema not only as a clinical marker of the early course of the disease, but also be alert to its potential for prolonged progression.⁷ Therefore, we present this case to describe the clinical presentation, diagnostic approach, treatment, and course of a pediatric patient with infectious mononucleosis, highlighting Hoagland's sign as an early and key manifestation for the timely recognition of suspected Epstein-Barr virus infection.

Case presentation

A seven-year-old female patient who had been experiencing fever, a productive cough, and nasal congestion for four days. Three days prior to admission, she developed painless bilateral eyelid edema, with no signs of inflammation or ocular discharge. During the 48 hours preceding hospitalization, she also experienced intermittent abdominal pain, vomiting, and a syncopal episode.

No rash or evidence of hemorrhagic manifestations was documented. Upon admission, her vital signs were as follows: heart rate of 90 beats per minute, respiratory rate of 28 breaths per minute, oxygen saturation of 96 % on room air, temperature of 38.4 °C, blood pressure of 100/60 mmHg, weight of 31.5 kg (85th-97th percentile), and height of 130 cm (50th percentile). The patient was alert, febrile, appeared acutely ill, and was complaining. She presented with marked bilateral non-inflammatory eyelid edema; there were no signs of respiratory distress, and she was eupneic but irritable and uncooperative during the physical examination.

In the emergency department, a preliminary diagnosis of tonsillitis was made, and outpatient treatment was prescribed with amoxicillin and clavulanic acid in 500 mg/125 mg tablets, to be taken orally every twelve hours. Twelve hours later, the patient reconsulted due to persistent fever and the onset of a headache, prompting the decision to admit her to the hospital.

As illustrated in Figure 1, the patient's symptoms exhibited a clear progression. Eyelid edema was the most persistent symptom, lasting for 15 days. This was followed by lymphadenopathy, which persisted for 14 days, then tonsillar hypertrophy, which lasted for 10 days, and finally fever, which lasted for 7 days.

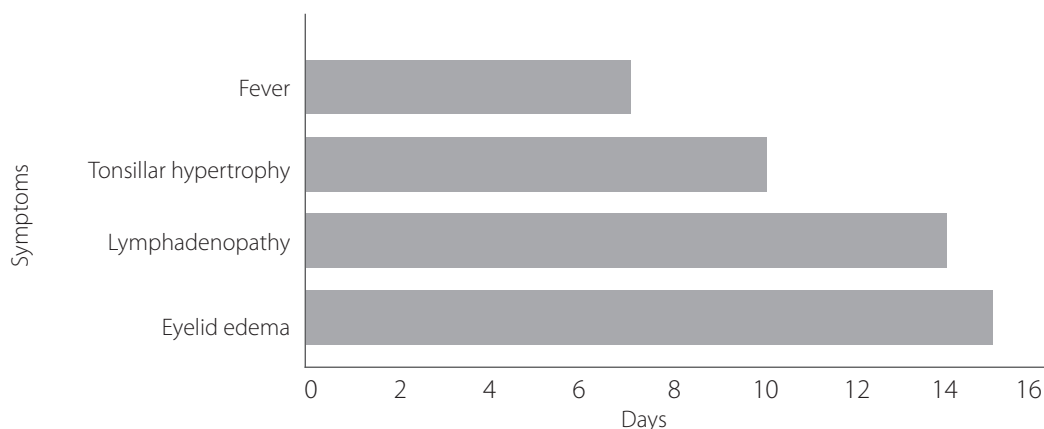


Figure 1. Duration of symptoms expressed in days during the clinical course.

During the evaluation, bilateral eyelid edema was observed without local heat or erythema, without proptosis, or restriction of extraocular movements (Figure 3A). The patient also presented with grade III tonsillitis with tonsillar exudate (Figure 2). Physical examination revealed tender cervical lymph nodes measuring approximately 5 cm x 5 cm on the right side of the neck and 2 cm x 2 cm on the left. In addition, dullness on percussion was noted in the splenic area, suggestive of splenomegaly. No rash, malleolar edema, or anasarca was observed.

Following the initial evaluation by pediatric surgery, the presentation was interpreted as parapharyngeal ganglionic cellulitis and tonsillitis, and treatment was initiated with benzathine penicillin (1 200 000 IU intramuscularly), oxacillin (200 mg/kg/day), and ketorolac (1.5 mg/kg/day). However, after twelve hours of hospitalization, a new pediatric evaluation led to a revision of the diagnosis to IM upon identification of the characteristic clinical triad of fever, exudative tonsillitis, and lymphadenopathy, along with the presence of Hoagland's sign.

The complete blood count showed white blood cell and platelet counts within normal limits: white blood cells: 8130 μ L; monocytes: 8.1 %; lymphocytes: 31 %; neutrophils: 60.2 %; platelets: 185 000/ μ L; with hemoglobin at 12 g/dL. The throat culture obtained before the start of antibiotic therapy was negative for *Streptococcus pyogenes* (group A beta-hemolytic streptococcus). A general urinalysis ruled out proteinuria and hematuria.



Figure 2. Tonsillitis caused by the Epstein-Barr virus. Infectious mononucleosis in a pediatric patient. Zacamil National Hospital, El Salvador.

No measurements of C-reactive protein, lactate dehydrogenase, or erythrocyte sedimentation rate were performed. The suspected diagnosis was supported by a peripheral blood smear showing > 15 % atypical lymphocytes, a finding characteristic of infectious mononucleosis (Figure 4).

Confirmation was obtained on the ninth day of the illness through the detection of positive heterophil antibodies for Epstein-Barr virus (Monotest), a test performed during the second week of illness, when it achieves the highest diagnostic sensitivity.

Treatment

Given the presence of fever, exudative tonsillitis, cervical lymphadenopathy, and Hoagland's sign, a clinical diagnosis of IM was established 12 hours after hospital admission. After ruling out bacterial superinfection and a cervical abscess through clinical and ultrasound evaluation, oxacillin was discontinued following the initial dose. Symptomatic treatment with nonsteroidal anti-inflammatory drugs was initiated for five days: intravenous ketorolac 1.5 mg/kg/day for three days, followed by dextketoprofen 1.5 mg/kg/day for two additional days, as the patient demonstrated adequate oral tolerance.

Clinical evolution

The patient remained hospitalized for six days under close observation. Management focused on monitoring and controlling the persistent fever and the imminent risk of airway compromise secondary to large lymphadenopathy located in an anatomically high-risk area.

The fever lasted seven days (Figure 1). Tonsillar hypertrophy temporarily progressed to grade IV on the sixth day of illness, then regressed to grade II by the tenth day of illness, as confirmed during an outpatient follow-up visit (Figure 2).

The cervical lymphadenopathy decreased in size by the eighth day of illness to 3.5 cm by 3.5 cm, achieving clinical resolution during an outpatient follow-up visit fourteen days after the onset of symptoms. Eyelid edema began to subside on the seventh day after onset, with a decrease by the twelfth day and complete resolution by the fifteenth day of illness, as verified during an outpatient follow-up visit (Figure 3B).

The identification of Hoagland's sign was crucial for early diagnosis, as it led to the suspicion of infectious mononucleosis. Recognition of this finding optimized decision-making by eliminating the need for unnecessary intravenous antibiotic therapy.



Figure 3. Hoagland's sign caused by the Epstein-Barr virus. (A) Bilateral, painless eyelid edema without conjunctivitis, on the third day of the illness. (B) Clinical resolution on the fifteenth day of the illness. Source: Zacamil National Hospital. Photograph: Dr. Jeannette Barahona de Figueroa.

from the first day of hospitalization, and an effective symptomatic treatment regimen was established, which also facilitates timely monitoring for potential complications of the disease.

Discussion

The Epstein-Barr virus is the most common cause of infectious mononucleosis; it has a worldwide distribution and primarily affects children and young adults. With a seroprevalence of over 90 % in the adult population,³ humans are its sole reservoir. Viral replication in B cells and the reactive T-cell response induce lymphoproliferation manifested in lymphoid tissue and the spleen. Transmission mainly via oral secretions.³

Although mononucleosis is characterized by the classic triad of fever, tonsillitis, and cervical lymphadenopathy,⁸ it is important to note the occurrence of atypical signs such as the Hoagland sign, or bilateral bipalpebral edema, which occurs in one-third of patients with IM.⁷

The significance of this sign lies in the fact that it usually precedes tonsillitis and cervical lymphadenopathy,^{7,8} as observed in this patient. The pathophysiology of Hoagland's sign has not been fully established. It has been proposed that bilateral eyelid edema results from lymphocytic infiltration of the periorbital tissue and the lacrimal glands, leading to the development of dacryoadenitis, associated with a transient alteration in local lymphatic drainage. These mechanisms would promote fluid accumulation in the eyelids and explain its bilateral, painless presentation, which is typically devoid of erythema or other local inflammatory signs.^{9,10-14} Therefore, unlike other forms of edema, it is not accompanied by conjunctivitis or pain, which aids in the differential diagnosis from allergic conditions.

Hoagland's sign is characterized by bilateral bipalpebral edema and is considered an early manifestation of IM caused by the Epstein-Barr virus, with a generally self-limiting duration of days to a few weeks.^{7,8,15-17}

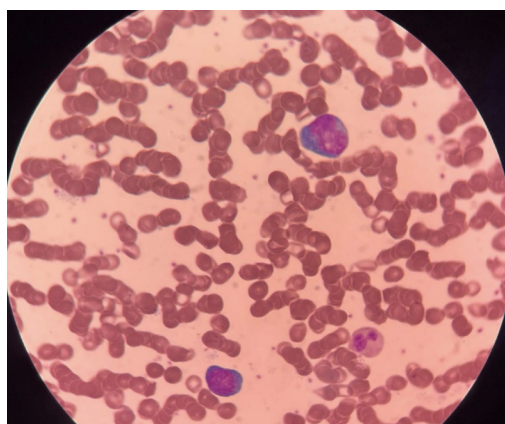


Figure 4. Peripheral blood smear. Atypical polymorphic lymphocytes with irregular nuclei and hyperbasophilic cytoplasm are observed.¹⁴ Source: Clinical Laboratory, Zacamil National Hospital. Photo: Dr. Luis Enrique Martínez Valle.

The prevalence of Hoagland's sign is not well established, especially in the pediatric population, and is likely underestimated due to its early onset, transient nature, and limited clinical recognition.¹ Published estimates vary considerably depending on the study design and the timing of the evaluation. In one series, Hoagland's sign, eyelid edema, was documented in approximately one-third of the patients evaluated prospectively, while a more recent prospective series documented it in 14 of 26 patients with confirmed IM (54 %).¹¹ These results suggest that systematic and early clinical screening could increase its detection. Some reviews report an incidence of Hoagland's sign in about 30 %, ^{2,7} while others indicate that half of patients with infectious mononucleosis present with this sign.¹⁷

The patient's course was consistent with the literature, in which Hoagland's sign was an early finding.^{10,12} The presence of 15 % atypical lymphocytes supported the theory of an active cellular immune response.^{8,12} It has been reported that pediatric EBV infection is usually asymptomatic,^{13,14} the patient exhibited the classic triad of mononucleosis, along with Hoagland's sign; this should be considered

an early, transient, and likely underrecognized manifestation. It may precede or accompany the classic triad, but it is not usually the predominant reason for seeking medical care. Although it can be observed relatively frequently when systematically sought, it is not the predominant presentation in adolescents, in whom fever, pharyngotonsillitis, cervical lymphadenopathy, and fatigue typically prevail.^{15,18-21}

The differential diagnosis included preseptal and orbital cellulitis, nephrotic syndrome, angioedema or an allergic reaction, and Kawasaki disease. Preseptal and orbital cellulitis were considered unlikely due to the bilateral and non-inflammatory nature of the edema, as well as the absence of erythema, local warmth, eye pain, proptosis, abnormalities in extraocular motility, and visual impairment; the latter are characteristic warning signs of orbital involvement. Nephrotic syndrome was ruled out due to the absence of generalized edema and findings consistent with nephrotic-range proteinuria and hypoalbuminemia. Furthermore, the absence of pruritus, urticaria, labial edema, recent exposure to potential allergens, or associated respiratory symptoms made an allergic reaction or angioedema unlikely. Finally, Kawasaki disease was excluded due to the absence of persistent fever and its main mucocutaneous manifestations, such as bilateral non-purulent conjunctivitis, oral lesions, polymorphic exanthem, and changes in the extremities.^{1,11}

The diagnosis of infectious mononucleosis was based on the presence of 15 % atypical lymphocytes in the peripheral blood smear and the detection of heterophil antibodies via the Monotest during the second week of the illness. A proportion of atypical lymphocytes greater than 10 % is a highly suggestive finding, while the Monotest has a specificity of approximately 90 %. Its performance improves after the first week, as heterophil antibodies typically become detectable between days six and ten and increase during the second and third weeks.^{3,8,9,19}

Recognition of Hoagland's sign is crucial to avoid the unnecessary use of antibiotics. The erroneous administration of amoxicillin in patients with IM causes, in up to 80 % - 100 % of cases, a maculopapular rash that leads to a false diagnosis of lifelong penicillin allergy.²¹

As a clinical sign, it allows for early diagnosis before seroconversion, thereby optimizing resources. Eyelid edema generally resolves spontaneously within a few days and, in some cases, may persist for up to two weeks. In rare instances, prolonged courses lasting up to eight weeks have been

reported. In the absence of complications, it usually does not require specific treatment, and management is primarily symptomatic. Early recognition allows it to be distinguished from potentially serious causes of periorbital edema, avoids unnecessary diagnostic tests and treatments, and provides reassuring guidance to the patient and their family.^{1,15,17}

Hoagland's sign is an easily identifiable, common, and likely useful clinical sign in the early stages of EBV-induced IM; therefore, it is necessary to raise awareness of this sign among physicians.^{9,14,16,18}

Once a diagnosis has been made clinically or through laboratory tests, treatment for infectious mononucleosis includes rest, hydration, and management of fever and pharyngitis.⁸ Severe complications of infectious mononucleosis caused by the Epstein-Barr virus are rare but potentially serious. These include upper airway obstruction secondary to tonsillar hypertrophy, neurological complications such as encephalitis or Guillain-Barré syndrome, hematological abnormalities such as autoimmune hemolytic anemia and severe thrombocytopenia, as well as splenic rupture, which is considered a medical emergency.^{8,16} Hepatic complications may also occur, and, in rare cases, immunological syndromes such as hemophagocytic lymphohistiocytosis.¹⁹

Management options for the patient consisted of the pharmacological measures recommended for this disease, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Corticosteroids were not used as anti-inflammatory agents, as they are recommended for patients with severe complications of infectious mononucleosis, such as airway obstruction, autoimmune hemolytic anemia, and thrombocytopenia.

The use of steroids for symptom relief is not considered standard practice and has been reported to have varying degrees of efficacy.²⁰

Hoagland's sign is a useful early clinical finding in IM caused by EBV, as it can guide the diagnosis in the early stages, even before the full clinical picture emerges.

Its timely recognition can allow for a primarily conservative management approach, avoid unnecessary tests or treatments, and ensure adequate clinical monitoring for the early detection of potential complications.

It is recommended that assessment of Hoagland's sign be incorporated into the routine physical examination of pediatric patients with suspected IM, as it is a useful clinical finding for diagnosis, especially in the early stages of the disease.¹¹

Its timely identification can help establish the clinical diagnosis, reduce the need for unnecessary additional tests, and facilitate a particularly conservative management approach⁸ while monitoring for possible complications.

Ethical Considerations

For the publication of this case, written informed consent was obtained from the patient's mother both for hospital care and for the purpose of publishing the case, with a commitment to respect the patient's privacy, confidentiality, and dignity, in accordance with the guidelines of the Declaration of Helsinki.

Funding

No external funds were received for this work.

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