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Case Report

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Ophthalmoparesis Secondary to *Haemophilus influenzae* meningitis: A case report and review of literature

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Abstract

Haemophilus influenzae is an intracellular gram-negative coccobacillus responsible for causing mainly respiratory infections and meningitis. Initial infection begins in the respiratory tract with monocyte invasion and can spread to the central nervous system through the bloodstream. The invasive clinical syndromes caused by *H. influenzae* include bacteremia, epiglottitis, septic arthritis, purulent pericarditis, endocarditis, osteomyelitis, and meningitis. We report a case of incomplete paresis of the third cranial nerve with rapid onset and infectious etiology in an adult patient. Besides infectious causes, other possible etiologies for third cranial nerve paresis include structural lesions, cerebrovascular disease, inflammatory and traumatic conditions. Complete recovery from exotropia was noted after administration of corticosteroids. PubMed searches found other neurologic involvement related to *H. influenzae* but no reports on *H. influenzae* as an etiological agent in acute infectious ophthalmoparesis.

Keywords: *Ophthalmoparesis; Ophthalmoplegia; Oculomotor nerve diseases; Haemophilus infections; Haemophilus influenzae; Meningitis*

Introduction

Haemophilus influenzae type b (Hib) is an encapsulated intracellular gram-negative coccobacillus that rarely causes infections in children over 5-year old and adults, except in immunocompromised people [1]. It is responsible for causing respiratory infections and meningitis. Initial infection begins in the respiratory tract with the invasion of monocytes and ciliated respiratory epithelial cells [2] and can spread to the central nervous system (CNS) through the bloodstream. The TNF-alpha cytokine produced at the primary infection site is the main cause of changes in the blood-brain barrier (BBB) permeability [3-5].

Tissue invasion is a crucial pathogenic factor, especially invasion of the choroid plexus (CP) epithelial cells [6], considering that the blood-cerebrospinal fluid barrier (BCSFB) located at the choroid plexus is the place of direct contact between the cerebrospinal fluid and blood [7]. The main virulence factor of Hib is the antiphagocytic polysaccharide capsule, which contains ribose, ribitol, and phosphate, the polyribosylribitol phosphate (PRP) capsular polysaccharide of Hib [8,9].

In a population-based observational study in the United States (1997 to 2010), the incidence of *H. influenzae* meningitis decreased from 0.10 to 0.058 per 100,000 people [10]. This marked decrease is presumed due to widespread vaccination of infants. Isolation of this organism in older children and adults should suggest the presence of certain underlying conditions, including sinusitis, otitis media, epiglottitis, pneumonia, diabetes mellitus, alcoholism, splenectomy or asplenic states, head trauma with cerebrospinal fluid (CSF) leak, and immune deficiency (e.g., hypogammaglobulinemia) [11,12].

The invasive clinical syndromes caused by *H. influenzae* include bacteremia, epiglottitis, septic arthritis, purulent pericarditis, endocarditis, osteomyelitis, and meningitis [13]. Hearing impairment is a common complication of

meningitis. It is among the most common sequelae of Hib meningitis in children [14]. Sensorineural hearing loss (transient or permanent) can result from damage to the eighth cranial nerve, cochlea, or labyrinth, induced by direct bacterial invasion and/or the inflammatory response elicited by the infection [15].

Cranial neuropathies other than the eighth cranial nerve may occur. Nerves most commonly involved are the facial, abducens, and oculomotor. Other neurologic complications of bacterial meningitis include: seizures, focal neurologic deficits, impaired mental status, increased intracranial pressure and cerebral edema [16,17]. It is important to emphasize that these complications may be sudden or gradual in onset and can appear at any time after the onset of symptoms, even after the completion of therapy.

We report a case of incomplete infectious paresis of the third cranial nerve with rapid evolution in an adult patient. The methods involved research in databases and digital libraries such as Medline and PubMed with a comparative bias concerning the clinical case presented.

In addition to infectious causes, there are other etiologies of third cranial nerve paralysis, including structural injuries, cerebrovascular diseases, inflammatory and traumatic conditions [18,19]. Ischemic paralysis of the third nerve is a common cause of microvascular origin, with risk factors being advanced age, systemic arterial hypertension, and diabetes mellitus [20]. It may be the first or last sign of a posterior communicating artery aneurysm with an imminent risk of death [21].

Case Report

We admitted a 78-year old woman with a severe holocranial headache accompanied by photophobia for 4 days to the emergency department. She had not experienced any headaches in the past several years. She had a history of fibromyalgia and well-controlled chronic myeloid leucemia treated with imatinib 400mg/day. After 2 days from the symptom onset, the patient developed horizontal diplopia. No evidence of meningism, eye pain, low visual acuity, fever, vomiting, loss of consciousness, seizures, and focal motor deficits. Upon admission, neurological examination revealed left moderate eye lid ptosis and incomplete left third cranial nerve paresis, with no pupillary involvement. Fundoscopy and the rest of the neurological examination were normal.

The full blood count of this patient in the hospital admission is described in the Table 1. Contrast cranial magnetic resonance imaging (MRI) was performed with no evidence of anomalous gadolinium uptake, despite the difficulties in evaluation due to metallic artifacts. We also performed cerebral angiography, which did not indicate any changes.

	Result
Red blood cell count (x 10^{12}· L^{-1})	3,64
White blood cell count (x 109·L^{-1})	5,3
Hemoglobin (g·L^{-1})	116
Hematocrit	0,34
MCV (fL)	94,5
MCH (pg)	31,9
MCHC (g/L)	337
RDW (%)	14,6
Platelet (x 109·L^{-1})	259
Neutrophils (x 109·L^{-1})	3,6
Lymphocytes (x 109·L^{-1})	0,95
Monocytes (x 109·L^{-1})	0,37
Eosinophils (x 109·L^{-1})	0,3
Basophils (x 109·L^{-1})	0,05

Table 1: Full blood count

The cerebrospinal fluid (CSF) was clear and colorless, with pleocytosis (cellularity of 70 cells/mm^3), 3% neutrophils, and absence of eosinophils, plasmocytes, macrophages, and blasts. Slightly increased proteins (55 mg/dL, RV – reference values = 15–45 mg/dL) and normal glucose (50 mg/dL, RV = 40–70 mg/dL), as shown in Table 2.

	Result	Reference value
Leukocyte count (cells/mm^3)	70	Up to 6
Protein (mg/dL)	55,1	15-45
Glucose (mg/dL)	50	40-70

Table 2: Cerebrospinal fluid analysis

The rapid molecular panel was positive for meningitis and encephalitis with the detection of *H. influenzae* (Table 3). Other tests showed negative results, such as antibodies to human immunodeficiency virus (HIV), bacterioscopy, tests for acid-alcohol-resistant bacilli, fungal cultures, venereal disease research laboratory (VDRL) test, direct tests for *Cryptococcus neoformans*, and tests for neoplastic cells.

Bacteria	**Result**
Escherichia coli K1	Not detected
Haemophilus influenzae	Detected
Listeria monocytogenes	Not detected
Neisseria meningitidis	Not detected
Streptococcus agalactiae	Not detected
Streptococcus pneumoniae	Not detected
Viruses	**Result**
Cytomegalovirus (CMV)	Not detected
Enterovirus	Not detected
Herpes simplex virus 1 (HSV-1)	Not detected
Herpes simplex virus 2 (HSV-2)	Not detected
Herpes simplex virus 6 (HHV-6)	Not detected
Human parechovirus (HPeV)	Not detected
Varicella-zoster virus (VZV)	Not detected
Fungi	**Result**
Cryptococcus neoformans/gattii	Not detected

Table 3: Rapid molecular panel for meningitis and encephalitis (Multiplex polymerase chain reaction)

Considering the diagnosis of left third cranial nerve mononeuritis secondary to *H. influenzae* infection, we immediately started treatment with ceftriaxone 2 g IV twice daily for 7 days and dexamethasone 4 mg for 10 days. There was a partial symptom improvement on the second day of treatment, and complete improvement was noted at hospital discharge, which occurred on the seventh day of treatment.

Discussion

The classic presentation of third cranial nerve palsy is "eyes down and out" combined with ptosis, with or without pupillary involvement [9]. The absence of pupillary involvement directed our diagnosis away from compressive causes, leading us to investigate inflammatory/infectious etiologies through CSF tests.

Cranial nerve palsies can result from compression due to brain swelling or perineuritis due to the adjacent meningeal inflammatory reaction. The VI nerve is the most commonly cranial nerve affected in meningitis, probably because its long intracranial segment adjacent to the brainstem is highly vulnerable to elevated intracranial pressure and the inflammatory reaction that can occur with meningitis. Cranial nerves III, IV, and VII also may be affected [22].

Infectious causes must always be taken into account in cases of focal neurological deficits due to the involvement of specific cranial nerves. Another rare focal finding in patients with bacterial meningitis is cranial neuropathy due to reactivation of herpes zoster virus (Ramsay Hunt syndrome, also called herpes zoster oticus) [23].

Among the main infectious causes of mononeuritis of the third cranial pair are meningoencephalitis due to *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Mycobacterium tuberculosis,* and viral infections such as Herpes Zoster and cytomegalovirus [24-27]. The study by Kodosi [24] demonstrates a low incidence of third nerve paralysis associated with infectious causes (5.7%), however, in comparison with the studies Keith [26], Harley [27] and Miller [25] this association is present from 23% (25) to 25% (26,27) of the cases. We did not find in the literature studies evaluating the specific incidence of third cranial nerve mononeuritis for each bacterial agent [24-27].

Taking into consideration it was a bacterial meningitis, patient was treated with ceftriaxone and dexamethasone and had a progressive improvement of the diplopia.

Conclusion

Despite numerous citations in the literature relating *H. influenzae* to meningoencephalitis, no cases of ophthalmoparesis secondary to *H. influenzae* infection were found in PubMed searches. Therefore, we consider this report valuable to the scientific community in the sense of expanding the range of differential diagnoses in patients with motor ocular neuropathy.

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