CASE REPORT

Haemophilus influenzae type f meningitis in a previously healthy boyAndreas Ronit,¹ Ronan M G Berg,¹ Helle Bruunsgaard,² Ronni R Plovsing³¹Centre of Inflammation and Metabolism, Department of Infectious Diseases, University Hospital of Copenhagen, Copenhagen Ø, Denmark²Tissue Typing Laboratory 7631, Department of Clinical Immunology, University Hospital of Copenhagen, Copenhagen Ø, Denmark³Intensive Care Unit 4131, University Hospital of Copenhagen, Copenhagen Ø, Denmark**Correspondence to**Dr Ronni Plovsing,
drplovsing@gmail.com**SUMMARY**

Non-serotype b strains of *Haemophilus influenzae* are extremely rare causes of acute bacterial meningitis in immunocompetent individuals. We report a case of acute bacterial meningitis in a 14-year-old boy, who was previously healthy and had been immunised against *H influenzae* serotype b (Hib). The causative pathogen was identified as *H influenzae* serotype f (Hif), and was successfully treated with ceftriaxone. An immunological evaluation revealed transient low levels of immunoglobulins but no apparent immunodeficiency was found 2 years after the clinical insult.

BACKGROUND

Haemophilus influenzae (Hi) colonises the nasopharynx of healthy individuals, and encompasses six encapsulated serotypes (a–f), as well as several non-encapsulated (ncHi). In the prevaccine era, *H influenzae* serotype b (Hib) was the most common cause of invasive *H influenzae* infection, and occurred almost exclusively in children of less than 5 years of age. The incidence of invasive disease due to Hib decreased dramatically in the early 1990s when the conjugate Hib vaccine was introduced, and since then, infections caused by ncHi strains have been reported more frequently.¹ Infection caused by non-serotype b strains is rare¹; however, an increase in *H influenzae* serotype f (Hif) has recently been reported.² Cases of invasive disease due to Hif have principally been opportunistic infections confined to young children or adults >65 years of age.² Here, we present a case of Hif meningitis in a 14-year-old boy with no underlying disease or predisposing condition. This is the first report of meningitis due to Hif in an adolescent with no apparent immunodeficiency.

CASE PRESENTATION

A previously healthy 14-year-old boy was admitted to the emergency department with a reduced level of consciousness after a day of flu-like symptoms, headache and vomiting. After arrival to the hospital, he appeared somnolent with a Glasgow Coma Score (GCS) of 9. Physical examination revealed nuchal rigidity with no focal neurological deficits. Cardiovascular and respiratory function was unremarkable, there was no fever and no signs of macular or petechial rash. He was transferred to the intensive care unit due to a consistent reduction in GCS, and was intubated shortly thereafter to protect his airway.

INVESTIGATIONS

At admission, biochemical analyses revealed a neutrophil leucocytosis, elevated C reactive protein and procalcitonin levels (table 1), and arterial blood gas analysis showed a slight metabolic acidosis. Lumbar puncture revealed a cloudy cerebrospinal fluid (CSF) with elevated white blood cell count and protein levels, and a decreased CSF–serum glucose ratio, together indicating acute bacterial meningitis (table 1). A contrast-enhanced CT scan of the brain was negative for signs of bleeding, oedema or hydrocephalus. Bacteria isolated from both CSF and blood cultures were subsequently identified as Hif.

The boy had previously received immunisations according to the children's vaccination schedule in Denmark, and the Hib antibody titre was high (above the detection range). He exhibited lymphocytopenia, hypogammaglobulinaemia and low serum levels of mannose-binding lectin (MBL) upon admission (table 1). In contrast to the absolute lymphocyte count, which returned to normal levels within 1 week, levels of IgM, IgG and IgA were still below age-corrected reference values 1 month after the patient had presented with symptoms, as was the IgG 1 subclass. A screening test for total complement function based on the ELISA format³ showed normal activity of the classical, lectin and alternative pathway (table 1). The MBL genotyping revealed a variant (YA/B) that is associated with low levels of serum MBL.

TREATMENT

The patient was successfully treated with ceftriaxone for 10 days, ampicillin (until Hif was definitely identified) and dexamethasone for 4 days.

OUTCOME AND FOLLOW-UP

He was extubated after 3 days and was discharged with no sequelae on day 10.

A 2-year follow-up revealed a marginally low IgM, but otherwise normal levels of antibodies including IgG-subclasses. There was no history of recurrent infections, including upper and lower respiratory tract infections.

DISCUSSION

Here, we report a case of Hif meningitis in an adolescent man who recovered completely. He had no prior history of recurrent infections or other signs that could indicate a pre-existing immunodeficiency, and immunological evaluation after 2 years revealed no laboratory evidence of immunodeficiency. To assess previously reported cases of Hif meningitis we used the following search criteria in

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Table 1 Laboratory test results

Blood	Unit	Admission	One-month follow-up	Two-year follow-up	Age-corrected reference values
Antibodies					
P-IgG	g/l	4.9*	3.8*	8.5	6.40–15.2
P-IgM	g/l	0.31*	0.41*	0.42*	0.49–2.85
P-IgA	g/l	0.62	0.52*	1.10	0.58–2.56
IgG subclasses					
IgG1	g/l		2.0*	3.9	3.7–10.2
IgG2	g/l		1.2	2.58	1.10–5.90
IgG3	g/l		0.21	0.8	0.15–1.3
IgG4	g/l		0.08	0.3	0.06–1.9
Lymphocyte subsets					
B cells	$\times 10^9/l$	0.12	0.25		0.11–0.57
T cells	$\times 10^9/l$	0.29*	1.60		1.0–2.2
CD4 T cells	$\times 10^9/l$	0.21*	1.00		0.53–1.3
CD8 T cells	$\times 10^9/l$	0.07*	0.57		0.33–0.9
NK-cells	$\times 10^9/l$	0.093	0.47		0.07–0.48
Complement system					
S-MBL	ng/ml	152			0–9000
MBL genotype		YA/B			
Classical pathway†	%	99			69–129
Lectin pathway†	%	52			3–125
Alternative pathway†	%	101			30–113
CSF					
Neutrophils	$\times 10^6/l$	14 790*			<3
Protein	g/l	>6.00*			0.15–0.5
Glucose	mmol/l	0.1*			2.2–3.9
CSF/S-glucose ratio		<0.01*			>0.4

*Signifies values different from reference values.

†A functional assay based on the ELISA format was used to determine the total activity of the three pathways.

APTT, activated partial thromboplastin time; CRP, C reactive protein; CSF, cerebrospinal fluid; INR, international normalised ratio; MBL, mannose-binding lectin; PCT, procalcitonin; WBC, white blood cells.

PubMed: ‘*Haemophilus influenzae* (sero) type f’, ‘*Haemophilus influenzae* f’ or ‘*Haemophilus influenzae*, limit: case reports’. All articles were examined for references and cross-references and citations were further assessed using the citation database Scopus. This yielded 25 articles, in which a total of 28 cases were reported. All cases were evaluated for predisposing conditions, if an immunological evaluation was carried out and the outcomes (table 2, refs. 4–28 included).

Predisposing conditions, including impaired immunity, have previously been reported in more than two-thirds of patients with invasive Hif disease, for example, meningitis, pneumonia or sepsis.² In comparison, we found this to be less common in Hif meningitis (9 of 28, 32%), primarily attributed to the even lower occurrence in children <5 years of age (4 of 19, 21%). Accordingly older children and adults were much more likely to have a predisposing condition (5 of 9, 56%). This discrepancy might indicate that meningitis due to Hif is caused by strains that may be more pathogenic in nature, at least in infants.

Immunodeficiency usually presents with signs and symptoms of infection that may be severe, that is, invasive disease. Moreover, antibody or early complement deficiencies may first be recognised by the occurrence of Hif meningitis.²⁹ Immunological evaluation with a clear indication of levels of antibodies was, nonetheless, performed only in five cases of meningitis (5 of 28; 18%), and lymphocyte subsets and complement function were described in three and one of those cases, respectively. In the present case, laboratory examinations revealed low levels of antibodies and T-cells after admission, which might have been caused by the

severe infection per se.³⁰ The patient had an MBL variant genotype that is associated with low levels of serum MBL. The susceptibility to invasive Hif disease is, however, not known to be associated with low levels of MBL, and later (2 year) follow-up revealed no history of or signs that would indicate immunodeficiency in this patient.

The proportion of patients with long-term sequelae after Hif meningitis was 7 of 28; 25%, and the types of sequelae is shown in table 2. Only two fatal cases of meningitis were identified (2 of 28; 7%), which is comparable to the case–fatality ratio previously reported in Hif meningitis.² In the present case the patient survived with no sequelae.

Hif meningitis is rare and may be associated with a predisposing condition, especially in patients over 5 years of age.² Hence, an immunological evaluation may be warranted in a patient presenting with Hif meningitis; this should include a complete blood count to determine the lymphocyte count, and quantitative serum immunoglobulin levels (IgM, IgG and IgA). Further immunological workup should be considered if immunodeficiency is suspected, for example, if an episode of meningitis occurs at an age that is uncharacteristic for the causative pathogen. This may include measurement of IgG-subclass levels, quantitative and qualitative assessment of B cells, assessment of total complement function or individual complement components, as well as HIV testing. Nonetheless, Hif may exhibit significant virulence, and cause infection in an individual with no apparent evidence of immunodeficiency, as illustrated in the present case report.

Table 2 Clinical characteristics of *Haemophilus influenzae* type f (Hif) meningitis

Reference	Age	Sex (M/F)	Predisposing condition(s)	Immunological evaluation	Outcome
4	3 weeks	M	Mother with autoimmune disease and ongoing immunosuppressive treatment	n/a	Survived Cerebral paresis
5	6 months	M	Recurrent bronchitis	n/a	Survived. No sequelae
6	18 months	F	Cranial defects Leakage of CSF	n/a	Survived. No sequelae
7	2 years	F	Sinusitis Recurrent upper respiratory infections	n/a	Survived. No sequelae
8	8 years	F	Hypogammaglobulinaemia	Immunoglobulins IgG subclasses B and T cells	Survived. No sequelae
9	55 years	F	Primary biliary cirrhosis Splenectomised	Immunoglobulins Complement	Survived. No sequelae
10	55 years	F	Multiple myeloma Chemotherapy treatment	n/a	Died
11	60 years	F	Neurosurgery Leakage of CSF	Immunoglobulins	Died
12	67 years	F	Recurrent otitis media Cortical mastoidectomy	n/a	Survived. No sequelae
13	3 months	F	None	n/a	Survived Mild left hemiparesis
14	4 months	F	None	n/a	Survived. No sequelae
15	5 months	M	None	Immunoglobulins IgG subclasses B and T cells	Survived. No sequelae
16	5 months	M	None	n/a	Survived. No sequelae
17	6 months	M	None	n/a	Survived. No sequelae
5	6 months	M	None	n/a	Survived. No sequelae
18	9 months	F	None	Immunoglobulins B and T cells	Survived Persistent subdural effusions
19	10 months	F	None	n/a	Survived. No sequelae
20	10 months	F	None	n/a	Survived. No sequelae
21	10 months	F	None	n/a	Survived. No sequelae
13	17 months	M	None	n/a	Survived Possible bilateral hearing loss
22	3 years	F	None	n/a	Survived Right ear deafness
23	3 years	M	None	n/a	Survived. No sequelae
23	5 years	n/a	None	n/a	Survived. No sequelae
24	5 years	M	None	n/a	Survived Cognitive impairment
25	17 years	M	None	n/a	Survived. No sequelae
26	43 years	F	None	n/a	Survived Hearing loss
27	55 years	F	None	n/a	Survived. No sequelae
28	59 years	F	None	n/a	Survived. No sequelae

Upper panel: patients with a known predisposing condition. Lower panel: patients without a known predisposing condition.
CSF, cerebro spinal fluid; n/a, data not available.

Learning points

- Invasive disease, for example, meningitis, pneumonia or sepsis, caused by non-serotype b strains of *Haemophilus influenzae* is increasing.
- Infection caused by *H Influenza* serotype f (Hif) is the most common of the non-serotype b strains.
- Hif meningitis may be associated with a predisposing condition including impaired immunity, especially in patients above 5 years of age.
- An episode of meningitis at an age that is uncharacteristic for the causative pathogen should warrant further immunological evaluation.

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