A complicated course of meningitis caused by *Haemophilus influenzae* serotype a

Hannah Van Roeyen, Ivo Corthouts, Sybien Lampmann, Bart Rutteman

AZ Sint Blasius, department of Pediatrics, Dendermonde, Belgium

hannah.vanroeyen@student.kuleuven.be

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Abstract

We describe a case of bacterial meningitis caused by Haemophilus influenzae serotype A with a complicated fever sequence in a 22-month-old otherwise healthy boy. We will discuss the epidemiology of different H. influenzae serotypes and the possible causes of the resurgence of the fever. Surveillance of such invasive infections remains important in order to improve the general vaccination scheme.

Introduction

Bacterial meningitis in young children has become an uncommon, yet life-threatening condition that should be recognized and treated promptly. Since the introduction of generalized vaccination, cases of meningitis caused by the most common bacterial pathogens, such as *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* serotype b, have declined significantly. Other causative micro-organisms remain very rare. We present a case of *H.influenzae* serotype a bacterial meningitis with a complicated fever sequence.

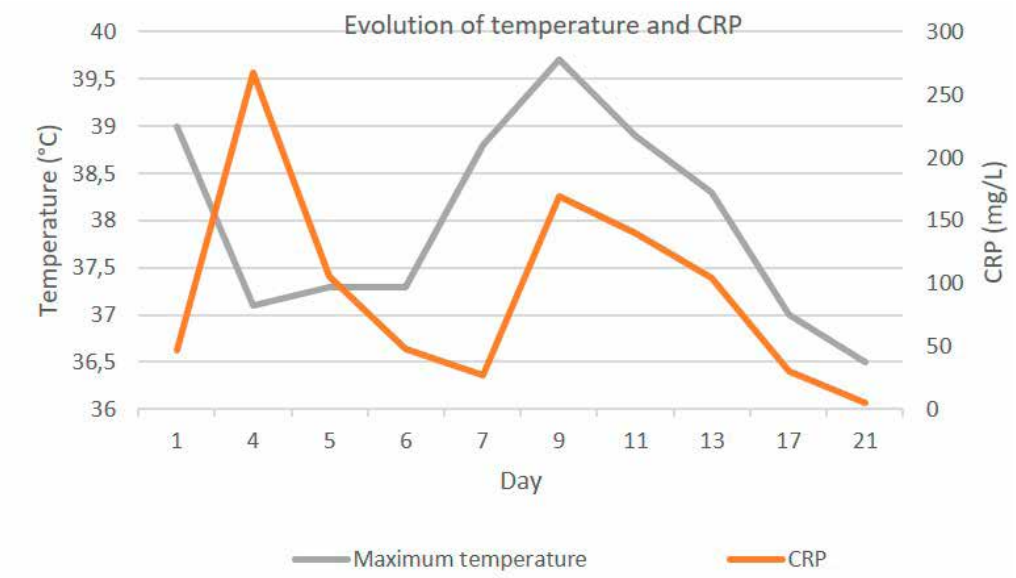
Case presentation

A 22-month-old boy, with no relevant medical history, presented with fever and vomiting since several hours. No other symptoms were reported. Initial clinical examination showed no abnormalities. Laboratory evaluation showed a raised CRP-value (46.8 mg/L; reference value < 5 mg/L) with a normal white blood cell count (5.500/µl; reference value 5.000-15.000/µl). Urine analysis was negative. The boy was admitted to the pediatrics department for observation and supportive treatment. Several hours after admission, his clinical condition deteriorated rapidly with increasing somnolence, global hypotonia and nuchal rigidity. Blood culture and lumbar puncture were performed and empiric treatment, consisting of dexamethasone, ceftriaxone and acyclovir was started.

On day 3, blood and cerebrospinal fluid cultures turned positive for *H. influenzae* (three weeks later, after subtyping in a reference lab, it turned out to be *H. influenzae* serotype a). Ceftriaxone monotherapy was continued, dexamethasone was stopped after 4 days. A central venous catheter was placed on day 4 given prolonged need for intravenous antibiotic therapy and parenteral nutrition.

Initially, the boy improved and defervesced rapidly. However, after 5 days, a second febrile episode occurred with resurging of CRP (from 26.8 mg/l on day 7 to 168.8 mg/L on day 9; figure 1). Urgent neuroimaging (CT-scan) was performed to exclude an intra-cranial abscess. Except for prominent bifrontal subdural effusion of up to 4 millimeters (compared to

Figure 1: Graphical representation of the evolution of CRP-value and maximum temperature.



a CT scan performed 5 days earlier) no abnormalities were found (figure 2). A tertiary hospital was consulted: there were no arguments for subdural empyema and thus no need for immediate therapeutic interventions. In case of persistent fever and/or clinical deterioration, there would be a need for detailed neuroimaging (MRI) and transfer to tertiary hospital.

The central venous line was removed because of a suspected central line infection. However, culture of the catheter tip and blood cultures drawn through the central catheter all stayed negative. Clinical symptoms and additional investigations (microbiological examination of urine, stool and nasopharyngeal samples) did not reveal an alternative cause for the fever. Therefore, we concluded that the fever was based on notable subdural effusion rather than (a new) infection or therapy failure. Hence, antibiotic treatment was continued with addition of systematic acetylsalicylic acid as anti-inflammatory drug.

Antibiotic therapy (ceftriaxone) was continued intravenously for a total of 21 days (cf. antibiotic treatment duration guidelines: treatment duration of 7-10 days in case of uncomplicated *H. influenzae* meningitis, up to 2-4 weeks in case of a complicated course) (1). The fever progressively disappeared within 7 days after the second febrile episode. The boy recovered completely, without neurological impairment at discharge and at follow-up after 2 weeks.

Discussion

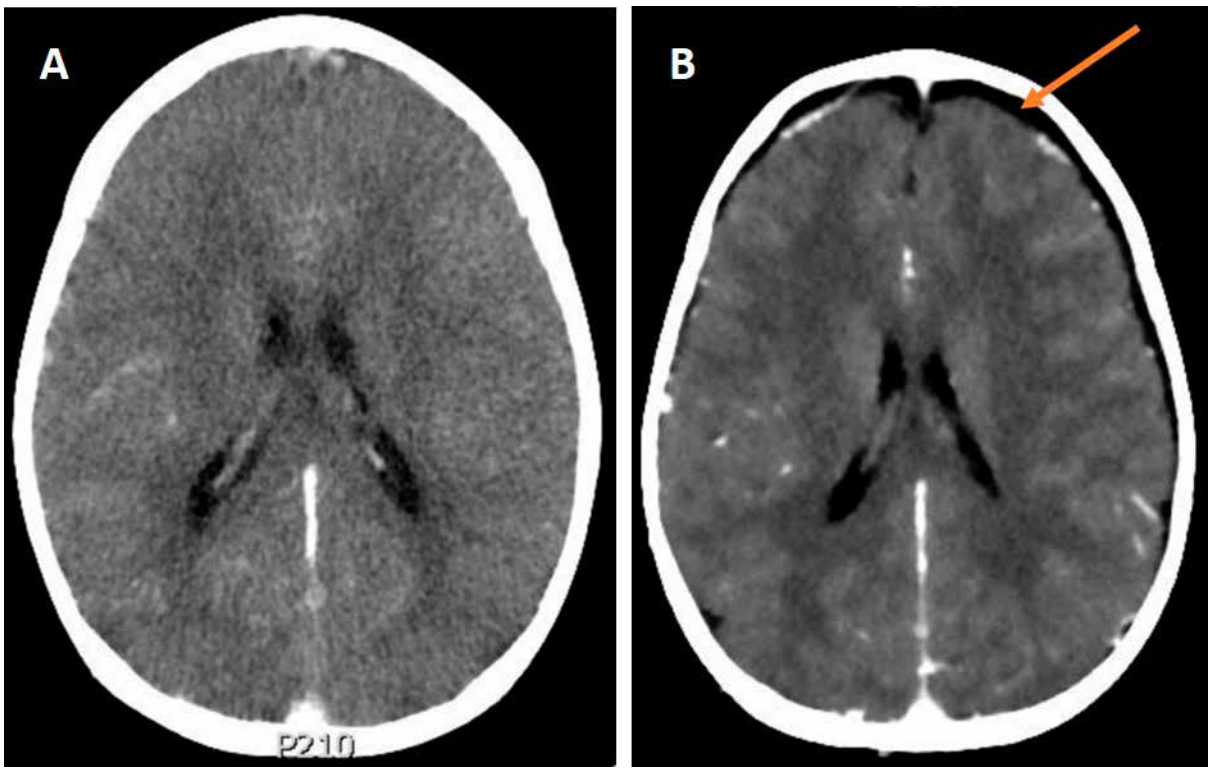
Bacterial meningitis in children older than 3 months has become rare, but it stays important to recognize and treat it rapidly and appropriately. Causative pathogens of bacterial meningitis vary by age group. In children aged 2 months to 10 years the main pathogens are *N. meningitidis, S. pneumoniae* and *H. influenzae* type b. After introducing vaccinations against these 3 main pathogens, a significant decrease was observed in the incidence of bacterial meningitis (2).

This report presents a rare case of meningitis caused by *H. influenzae* serotype a, one of the encapsulated subtypes of the *Haemophilus* strain. The different strains of *H. influenzae* are either encapsulated (6 different serotypes, ranging from a to f) or non-encapsulated (also called 'non-typeable'). The virulence of *H. influenzae* serotype a is comparable to serotype b, given that the capsule has similar characteristics. That is why it equally can cause serious invasive infections, such as sepsis and meningitis (3).

After the introduction of generalized vaccination against *Haemophilus influenzae* serotype b in 1993, there were concerns about a subsequent increase in serious infections with other serotypes. Surveillance of *H. influenzae* invasive infections in Belgium showed a significant decrease in type b infections since generalized vaccination. In 2018, there were 129 invasive *H. influenzae* infections in Belgium, of which only 10 were serotype b (7.8 %). In the remaining cases, the pathogen is non-typeable (74.4%) or serotype f (10.9%). In only 3.8% - i.e. 5 cases including 2 children <5y – of these cases *H. influenzae* type a was involved. This is in contrast to the pre-vaccine period from 1990 to 1992, where there were 250-300 *H. influenzae* type b invasive infections per year. At present in Belgium, we note that there is very limited increase in non-b serotype *H. influenzae* invasive infections (more specifically mainly non-typeable, i.e. non-encapsulated, strains). No absolute numbers are given in the Sciensano report. This has to be monitored closely through ongoing surveillance (4).

A study between 1996 and 2006 in 14 European countries – in which Belgium did not participate – showed an increase in invasive *H. influenzae* infections with non-encapsulated forms, especially in neonates and elderly individuals (relative increase of 3.6% per year in invasive non-b *H. influenzae* infections). Nevertheless, invasive infections with encapsulated serotypes remained very rare, with infections mainly due to serotype e and f (5). Likewise, a population-based study in Utah reveals an increase in non-b invasive infections, with mainly serotype a invasive infection (for invasive *H. influenzae* serotype a in children under 5 years of age: mean incidence increased from 0.8 cases per 100,000 child-years in 1998 to 2.6 cases per 100,000 child-years in 2008) (6). The same observation of increase especially in serotype a invasive infections was seen in a large scale study in The United States and Alaska, with an increase mainly in

Figure 2: Comparison between CT scan of brain at day 2 (A) and day 7 (B), when the second fever episode occurred. The arrowhead on figure B shows a prominent bifrontal subdural effusion, noticeably increased compared to figure A.



young children < 5 years of age (relative increase of 11.1% per year) (7). Although absolute numbers remaining low, worldwide there seems to be an increase of non-b serotype *H. influenza*e invasive infections. A possible explanation for this increase in non-b *H. influenzae* invasive infections may be that *H. influenzae* type b vaccination would reduce carrier status at the throat allowing other strains to establish themselves there. From the throat, these strains can then cause invasive disease. Also, more infections may be reported, due to more accessible surveillance systems

Literature regarding the occurrence of a second febrile episode within the course of a bacterialmeningitis is very limited. The most common reasons for such a relapsing fever are intercurrentnosocomialinfections (viral respiratory tract infections, gastroenteritis, urinary tract infection, infectionsof catheters, ...) and subdural effusions. Rarely, this is due to inadequate treatment, drug fever(diagnosis of exclusion) or subdural empyema. In theory,discontinuation of corticoid therapy may alsobe the cause of the resurgence of fever(8). However, in most cases the exact origin of thesecondaryfever remains uncertain.

There is no well-documented treatment in literature in case of fever due to subdural effusions. Our choice to treat with systematic acetylsalicylic acid as anti-inflammatory drug was hence based on theoretical advantages rather than protocols or evidence based treatment. Given the favorable outcome in our patient, this treatment may be an option in other cases, although we cannot reliably draw conclusions based on one case.

There is no significant difference in the occurrence of a secondary fever among the 3 most important pathogens (*H. influenzae, N. meningitidis and S. pneumoniae*). Persistent initial fever (after starting appropriate antibiotic therapy) > 5 days occurs more in *H. Influenzae* infections than in streptococcal or meningococcal infections (9).

Conclusion

We present a case of *H. Influenzae* serotype a meningitis with a complicated fever sequence in a 22-month-old healthy boy. After 3 weeks of intravenous antibiotic therapy, he recovered completely.

A second febrile period during treatment was noted, causing concern for (re-)infection or therapy failure. We concluded that it was most probably caused by prominent subdural effusion, which is a phenomenon known to occur in bacterial meningitis.

To date, there is limited epidemiological evidence for a slight increase in non-b *H. influenzae* invasive infections in Belgium. Longitudinal studies in the United States of America also show increases in non-b infections, with mostly type a invasive infections. Although serotype a being a rare subtype, concerns are that the prevalence may rise as a result of generalized vaccination targeting serotype b. This should be monitored closely by (inter)national surveillance systems.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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