Case Report

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Hepatobiliary infections due to non-capsulated Haemophilus influenzae

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We present two cases of non-capsulated *Haemophilus influenzae* hepatobiliary infection and review the literature. Such cases are rare, and prior to routine immunization against *H. influenzae* serotype b invasive *Haemophilus* disease was largely caused by capsulated strains. The epidemiology of invasive *Haemophilus* infections has changed and the number of cases of intra-abdominal and hepatobiliary infection may be underestimated due to current microbiological processing practices.

Received 2 March 2011 Accepted 26 April 2011

Case reports

Case 1

A 52-year-old male patient was admitted following a 6 week history of gradually worsening right upper quadrant pain. In the preceding 24 h he had experienced fever and rigors, but with no other symptoms. Four years previously he had developed gall stone-induced pancreatitis that necessitated a cholecystectomy. Since then he was an insulin-dependent diabetic. His other past medical history included hypothyroidism that was well controlled with levothryoxine. On examination he had a temperature of 39.5 °C and was tachycardic with a pulse rate of 120 beats min⁻¹. He was hypoxic on room air with a pO₂ (partial pressure of O₂ in arterial blood) of 7.4 kPa and had respiratory alkalosis. There was no jaundice or abdominal tenderness. Blood tests revealed a raised white cell count of 19.2×10^9 cells l^{-1} (neutrophilia) and a C-reactive protein level of 185 mg l^{-1} . Liver function tests showed an elevated alkaline phosphatase level of 247 IU l⁻¹ with normal bilirubin (8 μ mol l⁻¹) and alanine transaminase (8 IU l⁻¹). His international normalized ratio was elevated at 1.5, and he had an albumin level of 34 mg l^{-1} . Blood cultures taken on admission were sterile after 5 days incubation. An abdominal ultrasound scan identified a large cystic lesion (12 by 15 cm) also visualized by computed tomography (CT) scanning in segments 5, 6, 7 and 8 of the liver with appearances consistent with an abscess (Fig. 1). A CT pulmonary angiogram was normal (performed in view of the hypoxia). A percutaneous drain was inserted under ultrasound guidance that revealed pus that on culture gave a pure growth of *Haemophilus influenzae*. Empirical treatment had already been started with intravenous coamoxiclav (1.2 g three times daily) and this was continued for 14 days before the patient was discharged with a further 14 days of oral co-amoxiclav (625 mg three times daily). The patient's inflammatory markers normalized and a repeat liver CT scan 6 weeks later showed resolution of the abscess. Magnetic resonance cholangiopancreatography revealed no apparent biliary aetiology for the liver abscess.

Case 2

A 32-year-old female patient presented with a 6 day history of severe, colicky epigastric and left-sided upper quadrant pain that was exacerbated by movement and lying on her left side. This was associated with vomiting, fever and rigors. She had experienced similar but less severe bouts of pain over the preceding 2 years. Her past medical history included polycystic ovarian syndrome and a hiatus hernia, and her only regular medication was a proton pump inhibitor. On examination she had a temperature of 38.4 °C and a sinus tachycardia of 118 beats min⁻¹. The abdomen was tender on palpation, with guarding in the epigastrium and left upper quadrant. Blood tests revealed a raised white cell count of 11.9×10^9 cells l⁻¹ (neutrophilia) and a C-reactive protein level of 483 mg l^{-1} . Her liver function was abnormal with 86 µmol bilirubin l^{-1} , 159 IU alkaline phosphatase l^{-1} and 158 IU alanine transaminase l⁻¹. Serum amylase and calcium levels were normal. A CT scan of her abdomen revealed marked intrahepatic and extrahepatic biliary duct dilatation (Fig. 2), some enhancement of the gallbladder wall, with a degree of peri-cholecystic oedema and a single gallstone within Hartmann's pouch. The findings were consistent with a diagnosis of ascending cholangitis, with the most likely aetiology being common bile duct (CBD) stones.

Abbreviations: CBD, common bile duct; CT, computed tomography; Hib, Haemophilus influenzae serotype b; NTHi, non-typable Haemophilus influenzae.



Fig. 1. CT scan showing a large liver abscess.

Blood cultures taken on admission grew *H. influenzae.* In view of a severe penicillin allergy, the patient was initially treated empirically with intravenous gentamicin (5 mg kg⁻¹ once daily) and metronidazole (500 mg three times daily). As imaging suggested biliary dilation, she underwent urgent endoscopic retrograde cholangiopancreatography. This confirmed the diagnosis of a CBD stone. A sphincterotomy was performed and the CBD stone removed; and CBD clearance was confirmed by a balloon trawl. The patient improved clinically and was discharged with a 7 day course of oral ciprofloxacin (500 mg twice daily) (to which the



Fig. 2. CT scan showing intrahepatic and extrahepatic biliary duct dilatation.

isolate was sensitive) to await a laparoscopic cholecystectomy. She presented again 4 days later with abdominal pain, and had a further endoscopic retrograde cholangiopancreatography and sphincterotomy to remove a bile duct stone, which resulted in complete resolution of her symptoms without additional antibiotic therapy.

Microbiology

Both H. influenzae isolates were susceptible to amoxicillin, tetracycline and ciprofloxacin, but resistant to erythromycin. MICs for gentamicin were 4 and 2 mg l^{-1} for cases 1 and 2, respectively (there are no British Society for Antimicrobial Chemotherapy or European Committee on Antimicrobial Susceptibility Testing guidelines for interpreting the results of the use of gentamicin against Haemophilus spp.). The isolates were identified by API 20NH (bioMérieux) and confirmed at Health Protection Agency's Haemophilus Reference Unit by species-specific PCR (Hobson et al., 1995), and typed as a non-capsulated strain (Falla et al., 1994). Further characterization by biotyping (Kilian, 1976) and multilocus sequence typing (Meats et al., 2003) revealed that the isolate from case 1 belonged to biotype I and sequence type 559, whereas the isolate from case 2 belonged to biotype V and sequence type 536.

Discussion

H. influenzae is a small Gram-negative coccobacillus whose growth on laboratory media requires haem (factor X) and NAD (factor V) (Oksuz *et al.*, 2005). There are six serotypes (a–f) determined by capsular polysaccharide composition and also non-capsulated strains (Pittman, 1931). It is part of the normal upper respiratory tract flora and can cause meningitis, otitis media, pneumonia, endocarditis, bacteraemia, osteomyelitis and septic arthritis (Oksuz *et al.*, 2005). *H. influenzae* has also rarely been associated with hepatobiliary infections (Bradley *et al.*, 1987; Cantón *et al.*, 1989; Oksuz *et al.*, 2005).

The majority of invasive H. influenzae infections, prior to routine immunization of infants with conjugate H. influenzae serotype b (Hib) vaccines, were caused by Hib and occurred in children under 5 years of age (Peltola, 2000). By contrast, non-type b strains and in particular non-typable H. influenzae (NTHi) strains were typically responsible for infections in older individuals, especially elderly individuals with predisposing comorbid conditions such as chronic respiratory disease (Ladhani et al., 2010). European surveillance programmes now show that the incidence of invasive non-type b H. influenzae is higher than that of Hib and this is associated with a higher case fatality seen mainly in infants (Ladhani et al., 2010). In the UK, after the introduction of Hib immunization in children, invasive Hib infections in unimmunized adults have also declined. but the overall rate of invasive H. influenzae disease in adults increased, with most infections being caused by noncapsulated strains (Sarangi et al., 2000). A contemporary population-based epidemiological study of *H. influenzae* bacteraemia in seven regions globally has identified an important burden of disease, particularly with NTHi in the elderly, but ongoing population-based surveillance worldwide is needed in order to evaluate continuing changes in *H. influenzae* epidemiology (Laupland *et al.*, 2011).

Cases of H. influenzae hepatobiliary infection have generally been reported in more elderly patients with significant comorbidities, such as diabetes mellitus and malignancy. Severe infections requiring intensive care unit management have been reported, with Oksuz et al. (2005) reporting cholecystitis in a 73-year-old lady with diabetes mellitus, and De Sa Pereira et al. (1981) reporting biliary infection following percutaneous liver biopsy in a 46 year old with underlying malignancy. Other similar cases have been reported in elderly patients (Crowe & Levitz, 1987; Garces Garmendia et al., 1996; Gómez-Garcés et al., 1992). There is a single report of a case of cholecystitis in a 65year-old patient without significant past medical history (Sigwart & Raslavicius, 1972). Our second patient with cholangitis differs in being younger and without significant predisposing disease.

There are two cases of hepatic abscess in the literature (from 1987 and 1989), reported in an 83-year-old female patient with a history of hydatid disease and in a 70-year-old male patient with recent nasal surgery (Bradley *et al.*, 1987; Cantón *et al.*, 1989). Both patients had a history of cholecystectomy and, in both cases, the causative organism was found to be *H. influenzae* type b. Both had a good outcome, the former treated with abscess drainage and antibiotics, and the latter receiving just parenteral antibiotics. This is consistent with our first case who had also had prior cholecystectomy, though he was younger and had diabetes mellitus.

The two reported cases of hepatic abscess in the literature were due to encapsulated strains of *H. influenzae* type b (Bradley *et al.*, 1987; Cantón *et al.*, 1989), and our report is, to the best of our knowledge, the first report of a non-capsulated strain causing this presentation. The majority of cases of other hepatobiliary infections reported were similarly caused by encapsulated strains (Gómez-Garcés *et al.*, 1992; Oksuz *et al.*, 2005). Therefore, our case series is believed to be unique as both our patients were infected with non-capsulated strains of *H. influenzae*. There is, however, one earlier report of acute cholecystitis due to a non-a, b or c serotype isolate reported in 1972 (Sigwart & Raslavicius, 1972).

The epidemiology of invasive *H. influenzae* infections has changed since routine vaccination against Hib was introduced in the 1990s, with a higher proportion of disease being caused by non-Hib and non-capsulated strains. We report here two cases of invasive disease caused by NTHi and show that NTHi may cause intra-abdominal infections. The incidence of intra-abdominal infection could be underestimated if specimens are not appropriately processed in the laboratory (due to *H. influenzae*'s fastidious growth requirements). The pathogenesis of hepatobiliary infections due to H. influenzae strains may involve direct spread from the gastrointestinal tract or haematogenous seeding following colonization of the oropharynx. In these cases, the absence of positive cultures from blood samples support the hypothesis that these infections may have originated in the gastrointestinal tract. All reported cases of H. influenzae liver abscess have occurred in cholecystectomized patients and it may be that this distortion of normal anatomy is a predisposing factor or that surgery allows for colonization with *H. influenzae*. It has been shown that bile contains the essential growth factors X and V (Sigwart & Raslavicius, 1972). Additionally, microbiological factors may be implicated but a detailed analysis of virulence factors and how these may influence the site of infection is beyond the scope of this article. There are no published data to suggest that the biotypes and multilocus sequence types in these infections are associated with more invasive disease.

Our cases show that non-capsulated strains may be responsible for atypical presentations of invasive disease. The processing of microbiological specimens from these infections should take this into account.

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