An important diagnosis to consider in recurrent meningitis

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Meningitis, a potentially life threatening illness, requires prompt recognition and treatment. Recurrent meningitis necessitates detailed investigations to identify the underlying cause. We describe two adult patients with recurrent meningitis due to an underlying skull base abnormality.

Introduction

Meningitis may be caused by bacterial, viral and fungal infections, malignancy, medications, e.g. immunosuppressants, and chronic inflammatory diseases, e.g. sarcoidosis.¹ Meningeal inflammation can lead to severe neurological complications including altered mental state, seizures, stroke, hydrocephalus, cranial nerve palsies and cerebral herniation.²

In patients with recurrent meningitis, detailed investigations are needed to identify the underlying cause to prevent further episodes. Two important causes to be looked for include an immune defect (complement deficiency, antibody deficiency or hyposplenism) and skull base defects.

We describe two adult patients with a history of recurrent meningitis seen in our department for exclusion of an underlying immunodeficiency. Following investigation, both were found to have an underlying skull base abnormality as the cause of their recurrent meningitis.

Case reports

Case 1

A 49-year-old Greek Cypriot male was referred to us with a history of four episodes of meningitis over the past 15 years (1998, 1999, 2002 and 2009). The first three episodes had been treated elsewhere, each time presenting with headache, fever, photophobia but no rash. Though no bacterial diagnosis was ever made and no organism isolated, his episodes were associated with high cerebrospinal fluid (CSF) protein and CSF neutrophil infiltrate. He responded well to intravenous antibiotic treatment on each occasion with no neurological deficit. Computerized tomography (CT) and magnetic resonance imaging (MRI) head imaging had not detected the cause of his recurrent meningitis.

He had had two Staphylococcus aureus infections of his umbilicus in 2002 and 2009 but otherwise his medical history was unremarkable. There was no history of head trauma nor of recurrent ear or sinus infections. He did report some non-specific upper respiratory tract symptoms but none suggestive of CSF rhinorrhoea.

Detailed investigation of his immune system revealed low mannose-binding lectin (MBL) levels (0.06 mg/L, normal range 1.0–4.0 mg/L). The rest of his humoral and cellular immune tests were normal. A coronal CT sinus scan done to investigate his non-specific upper respiratory tract symptoms showed a 4 × 3 mm defect in the cribriform plate adjacent to the vertical attachment of the middle turbinate, a relatively common site for ‘congenital’ defects (Figure 1). A small rim enhancing CSF intensity sac was shown on MRI just beneath the cribriform plate defect, consistent with a meningocoele. This was confirmed at surgery. The defect was surgically repaired with temporalis fascia and inferior turbinate mucosa by an endonasal endoscopic route.
Case 2

A 21-year-old Caucasian male was reviewed in our clinic with a history of *Streptococcus pneumoniae* meningitis and bacteraemia complicated by pneumonia requiring intensive care unit admission. He recovered well following treatment with intravenous ceftriaxone. Assessment of his immune system revealed an isolated borderline low IgG level (6.3 g/L, normal range 7–16 g/L), borderline low C4 level (15 mg/dL, normal range 16–54 mg/dL) and low pneumococcal antibody titres (16 mg/L, protective range >50). At the time of his first episode, his IgG level was also noted to be low (5.1 g/L, normal range 7–16 g/L). Viral testing was negative. He was vaccinated with 23-valent pneumococcal polysaccharide vaccination and made an appropriate antibody response.

He continued to report tiredness and general malaise and just over a year later, at age 23, developed a second episode of pneumococcal meningitis.
meningitis. This again responded well to intravenous antibiotics. Serotype-specific pneumococcal antibodies were measured after the second episode and low titres to 7 of the 13 measured pneumococcal serotypes were found. There was no history of head trauma with either episode nor of CSF rhinorrhoea.

The past medical history included autoimmune hepatitis and Crohn’s disease, requiring low-dose maintenance oral steroids. Other medication intermittently used included mesalazine, mercaptopurine and methotrexate. He had had recurrent tonsillitis as a child and had a tonsillectomy at the age of 20.

Initial routine CT head was reported as normal. However, detailed sinus CT showed an anomalous, prominent right agger nasi ethmoid air cell extending up to the skull base with sclerotic thickened bony walls and opacification within (Figure 2). This was diagnosed as a mucocoele of this anomalous air cell. It was surgically decompressed.

Long-term pneumococcal antibiotic prophylaxis and pneumococcal vaccination were given as preventative measures. Currently, his IgG and complement levels are within normal range.

**Discussion**

In each patient, a small abnormality of the anterior skull base was responsible for the recurrent meningitis. This may have been exacerbated by MBL deficiency in one patient and mild antibody deficiency secondary to immunosuppressive medication in the other.

Skull base abnormalities and variants and immunodeficiency disorders are known to be linked with recurrent meningitis. Both congenital and acquired skull base defects may occur. These act as a portal for entry of pathogens into the subarachnoid space. Congenital defects include those involving the middle ear and mastoid, anterior skull base, persistent dermal sinus tracts of the vertebral column and less commonly neurenteric fistulae and cysts. These may present in childhood or later. Acquired defects arise secondary to trauma, with fracture of the cribriform plate of the ethmoid bone being the most common lesion, neurosurgery or infection.

Underlying immunodeficiency disorders include defects of the complement system and primary antibody disorders. The complement system plays an important role in defence against...
| Author          | Type of publication                  | Time period | No. of patients with recurrent meningitis | Underlying cause                                                                 | Primary organism isolated | Other organisms identified                     |
|-----------------|--------------------------------------|-------------|------------------------------------------|---------------------------------------------------------------------------------|---------------------------|------------------------------------------------|
| Kline           | Retrospective case series and literature review | 1978–1988   | 47 patients (children – 33; adults – 14) | Congenital CSF fistula – 26 (children – 23) Traumatic or surgical fistula – 8 Immunodeficiency disorders – 10 (complement deficiency – 8, IgG2 subclass deficiency – 1, lymphoma with asplenia – 1) Unknown – 3 | Streptococcus pneumoniae | Haemophilus influenzae Neisseria meningitidis Staphylococcus aureus Escherichia coli Streptococcus viridans Streptococcus agalactiae Enterobacter sakazaki |
| Drummond et al. | Retrospective case series and literature review | 1984–1995   | 6 children                              | Anatomical defects – 2 (traumatic – 1) Immunodeficiency – 2 (asplenia – 2) Unknown – 2 | Streptococcus pneumoniae | Haemophilus influenzae Streptococcus bovis       |
| Tebruegge and Curtis | Retrospective case series and literature review | 1988–2007   | 363 patients – children and adults (numbers unspecified) | Anatomical abnormalities – 112 (heterotopic brain tissue – 19, skull base defects – 11, meningioma – 1, dermoid cyst/epidermoid cyst/dermal sinus tract – 5, cranial lymphangiomatosis – 1, neuroenteric cyst – 4, inner ear abnormality (unspecific) – 42, cochlear dysplasia – 13, meningocele – 1, dermal sinus/dermoid cyst – 15) Trauma – 102 (head injury/basal skull fracture) Immunodeficiency – 132 (complement deficiency – 72, HIV infection – 43, agammaglobulinaemia – 2, IgG subclass deficiency – 3, common variable immunodeficiency – 1, IL-1 receptor associated kinase 4 (IRAK-4) – 1 deficiency, asplenia (congenital and iatrogenic) – 10) Paraventricular infections – 17 | Streptococcus pneumoniae | Neisseria meningitidis Haemophilus influenzae Escherichia coli Staphylococcus aureus Streptococci Salmonella spp. Proteus spp. Enterococcus spp. Klebsiella pneumonia |
pyogenic organisms and therefore deficiency, in particular, within the final common pathway (C3, C5-C9) increases the susceptibility to infection with encapsulated organisms. Deficiency of MBL, a protein also involved in the innate immune system, has been linked to meningococcal disease though there is still limited data on this. One study found an increased frequency of both homozygous and heterozygous MBL variant genotypes in those with such disease. Low levels of MBL were seen in the case of our first patient though the exact significance and contribution to his recurrent meningitis is unknown.

Most published reports of recurrent bacterial meningitis consist of single case reports and some case series. Details of some of the larger series are shown in Table 1. Skull base abnormalities, as found in our patients, and immunodeficiency disorders, predominate as the aetiology, the former more than the latter. In the past three years, there have been at least 16 published cases of recurrent meningitis with skull base defects being the most significant finding. Twelve of the 16 cases involved children.

Between 30 and 50% of patients in the larger case series of recurrent bacterial meningitis had an underlying skull base defect diagnosed. These defects were more frequent in children. Complement defects were found in approximately 20% of the cases.

In the review conducted by Kline, congenital skull base abnormalities were found to predominate in the paediatric population. Since then, there have been major advances in immunology, imaging and diagnostic techniques. This has allowed for better understanding and recognition of the underlying factors therefore perhaps identifying more cases in the adult population than previously. In 34 adult cases of recurrent bacterial meningitis, Adriani et al. found that head injury was the commonest feature followed by CSF leakage.

Tebruegge and Curtis conducted one of the largest case series reviews after Kline. They both found a higher incidence of congenital abnormalities in children than adults. It is unclear from their figures, probably due to the high number of cases reviewed, exactly how many adult cases there were for each individual aetiology identified. Their review highlighted the importance of
a thorough history and physical examination in detecting the underlying cause. Where no cause is obvious, further laboratory, immunological and radiological investigations are recommended. Drummond et al.\(^9\) proposed that all children with recurrent meningitis of unknown aetiology should undergo audiological evaluation, CT scan of the temporal bones, skull base and paranasal sinuses and immunological assessment. This being due to the significant number of recurrent meningitis cases in children secondary to otorhinolaryngologic aetiologies.

Our patients had no history of proven CSF rhinorrhoea. In those who do, CT cisternography is still the optimal method of localizing the site of an active leak.\(^{13}\) In the majority of anterior skull base defects, an endoscopic endonasal approach has been shown to be very successful in closing such defects.\(^{14}\)

**Conclusion**

Previous reports suggest that most skull base defects in recurrent meningitis are seen in the paediatric population. Our cases highlight the importance of considering such defects at any age, regardless of the age of presentation. High-resolution CT of the anterior skull base and temporal bones should routinely be included in the initial imaging. Where skull base defects exist, surgical correction of the underlying defect is essential so as to reduce or eliminate the risk of recurrent meningitis and prevent complications.

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