CASE REPORT

Meningococcal meningitis in two patients with primary antibody deficiency treated with replacement intravenous immunoglobulin

S Lear, E Eren, J Findlow, R Borrow, D Webster, S Jolles

J Clin Pathol 2006;59:1191–1193. doi: 10.1136/jcp.2005.031054

The current treatment of primary antibody deficiency (PAD) is the early recognition of the condition and replacement immunoglobulin combined with prompt treatment of infections and complications. The route of administration (intravenous or subcutaneous), dose and frequency of administration of immunoglobulin still vary between centres and countries. Most infections in patients with PAD are reduced but not entirely prevented by replacement immunoglobulin, with sinopulmonary infections accounting for the bulk of the remainder. Although there have been reports of meningitis in patients with PAD before replacement treatment, we describe the first two cases of bacterial meningitis (group B *Neisseria meningitidis*) on adequate immunoglobulin replacement and discuss the involvement of potential cofactors.

Bacterial meningitis is a serious, life-threatening disease resulting in an estimated 171 000 deaths per year worldwide.¹ Many organisms are capable of invading and infecting the meninges, and their prevalence varies geographically and within populations. *Streptococcus pneumoniae* and *Neisseria meningitidis* account for most post-neonatal infections in the UK. The course and outcome of infection reflects many variables—for example, bacterial virulence factors, host immune competence, vaccination, access to antibiotics and intensive care. Even in industrialised countries, the mortality and long-term complication rates remain notable. Meningitis is described in patients with primary antibody deficiency (PAD) before the use of replacement immunoglobulin treatment.² However, there are no reports of meningitis in patients with PAD who receive immunoglobulin replacement. We describe two patients with PAD who, despite adequate antibody replacement, developed meningitis with group B *N meningitidis*.

CASE REPORTS

Case 1

A 29-year-old man initially developed respiratory and ear infections as a child aged 4–7 years. He had hepatosplenomegaly at 13 years and underwent several investigations, including a lung and lymph node biopsy, which showed a chronic inflammatory cell infiltrate with small granulomas and follicular hyperplasia, but with no evidence of infection or malignancy. A bone marrow trephine biopsy was normal. He was, in the light of his accompanying hypogammaglobulinaemia, diagnosed with granulomatous common variable immunodeficiency and was started on intravenous immunoglobulin, Sandoglobulin (ZLB Behring, Kankakee, Illinois, USA), 18–24 g every 3 weeks. Immunoglobulin (Ig) G trough levels were maintained at >7 g/l. His most recent IgG trough

level was 10.4 (7–16) g/l with IgA <0.1 (0.7–4) g/l and IgM <0.1 (0.4–2.3) g/l. Lymphocyte phenotyping showed a mild CD4 lymphopenia at 0.281×10^6 (0.4×10^6 – 1.5×10^6)/l. Complement studies were normal and the level of mannan-binding lectin (MBL) was 4 (0–4) mg/dl.

Over the next 10 years, he had recurrent sinusitis and chest infections. In 1997, he underwent ethmoidectomy and middle meatal anastomies, and intermittently required antibiotics and nasal steroids. Subsequently, he was started on oral antibiotic prophylaxis for recurrent respiratory tract infections, remained generally well, and was able to complete his schooling and university degree.

In February 2001, he was unwell for about 2 weeks, with vague upper respiratory tract symptoms. He increased his prophylactic antibiotics (doxycycline, in view of reactions to a range of alternative drugs), but did not improve. On 5 February 2001, he awoke feeling unwell with a sore throat, myalgia and mild headache. By 16:00 h that day he developed a blanching rash and his temperature was 39°C; he vomited thrice during the day and attended the accident and emergency department, where he was assessed specifically for evidence of meningitis. He denied other symptoms, including neck stiffness and photophobia. A blanching maculopapular rash over the torso and limbs was noted but physical examination, including neurology, was otherwise normal. He remained feverish, but cardiovascular observations were normal. His blood tests showed a raised white cell count, with a neutrophilia of 14.1×10^9 /l, and he was treated symptomatically with the primary diagnosis of a viral illness. When seen in the morning by the Infectious Diseases team, the rash was considered to be erythema multiforme; the possibility of a drug reaction was raised, but viral infection remained the primary diagnosis and oral prednisolone was started late on 7 February 2001. The next morning, the rash had improved, his temperature remained normal and his white cell count was normal despite a C reactive protein level of 282 mg/l from the previous day. On 8 February 2001, he was considered well enough to be discharged. However, that evening he developed an acutely swollen left index metacarpophalangeal joint and his temperature rose to 38°C. He remained systemically well and the joint swelling had almost resolved by the morning. Blood samples taken the next day showed little change; his C reactive protein level had dropped to 209 and his IgG trough level was 7.7 g/l. That evening his condition deteriorated, he had headache, neck pain and vomiting; overnight he became agitated and confused, with a Glasgow Coma Score of 13 out of 15. Observations remained normal, with no evidence of circulatory collapse. An unenhanced computed tomography scan of the head was reported to be normal. On the morning of 10 February 2001,

Abbreviations: CSF, cerebrospinal fluid; MBL, mannan-binding lectin; PAD, primary antibody deficiency

Table 1 Summary of meningitis cases in patients with common variable immunodeficiency before and after immunoglobulin replacement

Group	Patients (n)	Patients with meningitis before immunoglobulin replacement (n)	Patients with meningitis after immunoglobulin replacement (n)
Hermazewski and Webster ³	240	1	0
Cunningham-Rundles ²	248	2	0
ESID Registry	419	6	0
UK Audit ⁴	1247	20	0

microbiology reported a Gram-negative coccobacillus from blood culture and, limited by his history of antibiotic reactions, he was started on intravenous chloramphenicol 1 g thrice daily. A lumbar puncture was carried out, the results of which were consistent with bacterial meningitis (cerebrospinal fluid (CSF) protein 4.1 (0.1–0.4) g/l; glucose 0.1 mmol/l (2.5–3.9); and white cell count 860 cu/mm with 70% polymorphs and 5% lymphocytes; Gram stain, negative); over the next 24 h his condition improved, the Glasgow Coma Score returned to normal and temperature settled. On 11 February 2001, the bacterium was confirmed to be group B *N meningitidis* from blood culture, which was sensitive to penicillin and chloramphenicol; there was no growth in the CSF sample. On skin prick testing for ceftriaxone, the patient had no local reaction and was switched to intravenous ceftriaxone 2 g twice daily. He was well enough to be discharged on 16 February 2001 with no neurological sequelae, and has remained well when seen in clinic for follow-up.

Case 2

A 28-year-old Indian woman born in 1975 of consanguineous parents was diagnosed with common variable immunodeficiency in 1982 at the age of 7 years. She was referred to hospital after recurrent otitis media and sinusitis, and was found to have hypogammaglobulinaemia. She remained systemically well and was started on intravenous immunoglobulin in 1982 and has been receiving Sandoglobulin at 21 g every 3 weeks at the Royal Free Hospital, London. She remained well until 1995 when she was diagnosed with discoid lupus erythematosus, having developed some typical lesions on the skin and ears. She also had positive autoantibodies for anti-Ro, anti-ribonucleoprotein, anti-smooth muscle and anti-thyroid, all of the IgM class. Over the next few years, she also developed a variable positive IgM anti-cardiolipin antibody, but remained rheumatoid factor negative. She was treated with aspirin, hydroxychloroquine

and mepacrine with good effect, apart from some fluctuation in her cutaneous lesions. Sinopulmonary infections were infrequent, she did not require prophylactic antibiotics and her lung function tests remained stable. The months preceding her admission were unremarkable, with stable IgG trough levels >7 g/l. Her treatment was unchanged and her sinus and skin condition were quiescent. Her most recent immunology shows IgA 0.1 (0.7–4.0) g/l; IgG 10.1 (7–16) g/l; IgM 17.8 (0.4–2.3) g/l (IgM is polyclonal) with a mild lymphopenia of 0.913×10^9 (1×10^9 – 3.2×10^9)/l predominantly due to low CD4 T cells at 0.232×10^9 (0.4×10^9 – 1.5×10^9)/l. Complement studies show normal classic and alternative pathway function and normal C3, with C4 slightly low at 15 (16–54) mg/dl and MBL 0 (0–4) mg/dl. The raised IgM level prompted a search for hyper-IgM syndrome and the patient was found to have a mutation in the region coding for activation-induced cytidine deaminase, confirming this diagnosis.

On 4 February 2004, she awoke feeling generally unwell and by mid-day had developed classic symptoms of meningitis. In the emergency department, she was found to have headache, neck stiffness and photophobia, with no evidence of systemic disease—there was no rash, neurological examination was unremarkable, she had no fever and cardiovascular observations were normal. Meningitis was suspected, she was started on intravenous ceftriaxone 2 g twice daily and investigations proceeded. However, her condition deteriorated dramatically, she became acutely confused and agitated, and required sedation and intubation so that a computed tomography scan of her head and lumbar puncture could be carried out. CSF results were consistent with bacterial meningitis (CSF protein 3.04 (0.1–4) g/l; glucose 2.1 (2.5–3.9) mmol/l; white cell count 6400 cu/ml; polymorphs 98%; and Gram stain, negative) and blood culture confirmed the presence of *N meningitidis* group B type 4 subtype P1.4. She made a gradual recovery, with a prolonged period of intubation, and was able to go home after 10 days, with no neurological sequelae.

DISCUSSION

In the normal population, meningococcal meningitis occurs in 1–5 patients/ 10^5 people/year.⁵ Despite high levels of public awareness, prompt primary care and advanced tertiary care, the disease has a high morbidity and mortality. Patients with antibody deficiency are at a greater risk of contracting meningitis. However, once established on immunoglobulin replacement, the incidence of meningitis seems to be low—from the three large surveys undertaken in the literature and the European database currently being compiled, it is apparent that meningitis is reported before but not after treatment with immunoglobulin is started (table 1). Similarly, isolated case reports of bacterial meningitis occur as a presenting infective episode before diagnosis with an antibody deficiency.

It is not routine practice to vaccinate patients with PAD with the meningococcal group C conjugate vaccine, as it has

Table 2 Serum bactericidal antibody titres and anti-outer membrane vesicle immunoglobulin G titres from the second patient, before and after intravenous immunoglobulin infusion

Designation	Phenotype	SBA titre		OMV ELISA	
		Before IVIg infusion	After IVIg infusion	Before IVIg infusion	After IVIg infusion
M01 240013	B:NT:P1.19-1, 15-11	8	16	27.7	55.7
M01 240101	B:NT:P1.22, 9	16	16	31.0	66.6
M01 240149	B:4:P1.7-2, 4	32	32	59.7	109.6
M01 240185	B:1:P1.22,14	<4	<4	35.7	73.3
M01 240355	B:2a:P1.5-1, 10-8	32	32	30.1	62.3

IVIg, intravenous immunoglobulin; OMV, outer membrane vesicle; SBA, serum bactericidal antibody.

been thought that a response is unlikely and that they may be afforded some protection from regular intravenous immunoglobulin replacement.⁶

Risk factors identified for contracting *N meningitidis* fall into three groups.

- Increased risk of exposure as in outbreaks seen in schools, prisons and army barracks.
- As colonisation of the human nasopharynx is a feature of some species of *Neisseria* and is a prerequisite of invasive meningococcal disease,⁷ factors associated with enhanced colonisation or barrier disruption in the upper respiratory tract have also been associated with an increased risk—for example, smoking or respiratory tract infection. Both patients reported here had recurrent sinusitis; the first was under the care of an ear, nose and throat department and had undergone sinus washout procedures in the past, although not related to this admission.
- Factors associated with an increased risk of meningococcal disease relate to host genetic factors,⁸ which determine bacterial handling, the extent of the immune response and the eventual degree of clinical disease.

Less is known regarding the factors that permit the progression of nasal carriage to invasive disease.

The second patient was deficient in MBL, and, although relatively common, it is conceivable that this may have acted as a cofactor. Deficiency of MBL is probably the most common human immunodeficiency. MBL has been shown to bind to *N meningitidis*⁹ and its deficiency is associated with an increased risk of mucosally acquired infections, including meningococcal disease;¹⁰ additionally, a 2–3-fold increase in MBL deficiency has been reported in patients with systemic lupus erythematosus.¹¹ It has also been shown that antibody-mediated classic pathway activation can compensate for impaired target opsonisation through the MBL pathway in MBL-deficient patients, and that therefore MBL deficiency may become clinically relevant in the absence of a concomitant adaptive immune response.¹² Although the main effector mechanisms in the defence against *N meningitidis* are mediated by the complement and antibody, patients with common variable immunodeficiency are also known to have variable levels of T cell impairment, and this also needs to be borne in mind.

Serum samples from the second patient, before and after intravenous immunoglobulin infusion, were tested in the serum bactericidal antibody assay¹³ and the outer membrane vesicle ELISA.¹⁴ Samples were assayed against a panel of *N meningitidis* strains, representative of the most prevalent disease isolates in the UK. Anti-outer membrane vesicle IgG antibodies were detected against all strains tested (table 2) and rose after intravenous immunoglobulin infusion. In addition, functional bactericidal activity was confirmed at levels likely to correlate with protection before and after intravenous immunoglobulin infusion for four of the five strains (table 2), including a strain phenotypically identical to the infecting organism.

Clearly, meningococcal meningitis can occur in patients with PAD receiving adequate intravenous immunoglobulin replacement, and appropriate consideration is needed as the initial presentation may be non-specific. It is worthwhile searching for cofactors and treating these aggressively where possible (eg, sinusitis), as well as identifying subgroups of patients who may benefit from vaccination strategies when these become available.

Take-home messages

- Antibody and complement are the main immunological effector mechanisms against meningitis.
- Meningitis can occur in PAD patients on replacement IVIg with trough IgG in the normal range.
- The presentation of meningitis in PAD may be non specific.
- Chronic sinusitis and low MBL levels may act as cofactors.

ACKNOWLEDGEMENTS

We thank Dr A Durandy for analysis of class switching, somatic hypermutation and *AID* gene sequencing in case 2.

Authors' affiliations

S Lear, E Eren, D Webster, Department of Clinical Immunology, Royal Free Hospital, London, UK

J Findlow, R Borrow, Vaccine Evaluation Department, Health Protection Agency North West, Manchester, UK

S Jolles, Department of Biochemistry and Immunology, University Hospital of Wales, Cardiff, UK

Competing interests: None declared.

Patient consent was received for publication of this study.

Correspondence to: S Jolles, Department of Biochemistry and Immunology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK; stephen.jolles@cardiffandvale.wales.nhs.uk

Accepted for publication 8 September 2005

REFERENCES

- 1 Jodar L, Feavers IM, Salisbury D, *et al*. Development of vaccines against meningococcal disease. *Lancet* 2002;**359**:1499–508.
- 2 Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunologic analyses of 248 patients. *Clin Immunol* 1999;**92**:34–48.
- 3 Hermaszewski RA, Webster AD, *et al*. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q J M* 1993;**86**:31–42.
- 4 Spickett MA, Chapel HM. Audit of patients with primary antibody deficiency in the United Kingdom 1993–1996. *Consensus document for the diagnosis and management of patients with primary antibody deficiencies*, October 1995.
- 5 Warrell DA, Farrar JJ, Crook DWM. Bacterial meningitis. In: Warrell DA, Cox TM, Benz EJ, eds. *Oxford textbook of medicine*. 4th edn. Oxford: Oxford University Press, 2003.
- 6 Matejschuk P, Chidwick K, Prince A, *et al*. A direct comparison of antigen-specific antibody profiles of intravenous immunoglobulins derived from US and UK donor plasma. *Vox Sang* 2002;**83**:17–22.
- 7 Townsend R, Goodwin L, Stevanin TM, *et al*. Invasion by *Neisseria meningitidis* varies widely between clones and among nasopharyngeal mucosae derived from adult human hosts. *Microbiology* 2002;**148**:1467–74.
- 8 Emonts M, Hazelzet JA, de Groot R, *et al*. Host genetic determinants of *Neisseria meningitidis* infection. *Lancet Infect Dis* 2003;**3**:565–77.
- 9 Estabrook MM, Jack DL, Klein NJ, *et al*. Mannose-binding lectin binds to two major outer membrane proteins, opacity protein and porin, of *Neisseria meningitidis*. *J Immunol* 2004;**172**:3784–92.
- 10 Jack DL, Lee ME, Turner MW, *et al*. Mannose-binding lectin enhances phagocytosis and killing of *Neisseria meningitidis* by human macrophages. *J Leukoc Biol* 2004;**77**:328–36.
- 11 Kilpatrick DC. Mannan-binding lectin: clinical significance and application. *Biochim Biophys Acta* 2002;**1572**:401–13.
- 12 Roos A, Garred P, Wildenberg ME, *et al*. Antibody-mediated activation of the classical pathway of complement may compensate for mannose-binding lectin deficiency. *Eur J Immunol* 2004;**34**:2589–98.
- 13 Findlow J, Lowe A, Deane S, *et al*. Effect of sequence variation in meningococcal PorA outer membrane protein on the effectiveness of a hexavalent PorA outer membrane vesicle vaccine in toddlers and school children. *Vaccine* 2005;**23**:2623–7.
- 14 Davenport V, Guthrie T, Findlow J, *et al*. Evidence for naturally acquired T cell mediated mucosal immunity to *Neisseria meningitidis*. *J Immunol* 2003;**171**:4263–70.