Case Report

Gemella morbillorum: an underestimated aetiology of central nervous system infection?

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A case is reported of cerebellar abscess and diffuse cerebritis due to *Gemella morbillorum*. The clinical course was 'biphasic', developing with an acute meningeal infection followed shortly afterwards by suppurative in the cerebellar and cerebral parenchyma; this pattern seemed to suggest a latent survival of the aetiological agent, probably within the central nervous system (CNS), despite systemic antibiotic therapy. Based upon a review of cases so far described, infections of the CNS caused by *G. morbillorum* appear to be an emerging reality.

Introduction

Gemella morbillorum is a Gram-positive, catalase-negative, facultatively anaerobic, non-motile and non-spore-forming coccus, and can occur singly, in pairs and in short chains. It was first isolated in 1917 from the blood of a patient with measles (Tunncliffe, 1917). *G. morbillorum* was previously named *Diplococcus morbillorum*, *Peptococcus morbillorum*, *Peptostreptococcus morbillorum* and *Streptococcus morbillorum*. It was eventually transferred from the genus *Streptococcus* to the genus *Gemella* (also including *Gemella haemolysans* and several recently described organisms) in 1988 on the basis of its biomolecular features and physiological properties (Kilpper-Balz & Schleifer, 1988). Noticeably, these bacteria are easily decolorized during Gram staining and may therefore appear to be Gram-variable and even Gram-negative and can sometimes appear as elongated cocci. *G. morbillorum* usually behaves as a commensal organism of the mucous membranes and is part of the normal flora of several surfaces, including that of the oropharynx and the gastrointestinal and female genital tracts. However, *Gemella* species are able to cause severe localized and generalized infections as opportunistic pathogens. They may also cause clinical disease more frequently than is presently recognized, because they are sometimes incorrectly identified or left unidentified. In particular, differentiation from viridans group streptococci may be difficult and require a sophisticated PCR-based approach (La Scola & Raoult, 1998; Woo *et al.*, 2003).

The first reports on the role of microaerophilic streptococci as significant human pathogens which can cause intracra-

nial suppuration, both in adults and in children, date from the 1980s (Ariza *et al.*, 1986). Since then, reports of clinical infections due to *G. morbillorum*, especially cases of infective endocarditis (Al-Hujailan & Lagacé-Wiens, 2007; Kofteridis *et al.*, 2006; Akiyama *et al.*, 2001), have continued; poor dental health, dental manipulation or dental surgery, colorectal disease or procedures, steroid therapy, diabetes mellitus and hepatorenal dysfunction have been recognized as predisposing factors for this (Lopez-Dupla *et al.*, 1996). *G. morbillorum* has been identified as the aetiological agent even for cases of pericarditis (Condoluci *et al.*, 1995), arthritis (Roche & Smyth, 2005), pleural empyema (Valipour *et al.*, 2005), liver abscess (Hsu *et al.*, 2007), peritonitis (Azap *et al.*, 2005; Velayos Jiménez *et al.*, 2008), pneumonia (Famularo *et al.*, 2006), Ludwig's angina complicated by mediastinitis (Sofianou *et al.*, 2005), septic shock (Vasishtha *et al.*, 1996), spondylodiscitis (Eisenberger *et al.*, 1998) and soft tissue infection (Bachmeyer *et al.*, 2005).

Recently, the ability of both viridans group streptococci and *Gemella* species to be important reservoirs of genes encoding resistance to macrolides and other antibiotics has been demonstrated. Such resistance can be easily transferred to other pathogens that share their habitat, such as *Streptococcus pneumoniae* and *Streptococcus pyogenes*, raising important therapeutic issues, particularly in cases of central nervous system (CNS) infections (Cerdà Zolezzi *et al.*, 2004; Asensi *et al.*, 1996).

As of 1 June 2009, to our knowledge 11 cases of CNS infection caused by *G. morbillorum* have been described in the literature (Garavelli, 1990; Debast *et al.*, 1993; Asensi *et al.*, 1996; Murray *et al.*, 1998; Martínez Beneito *et al.*,

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid.

2002; Messori *et al.*, 2002; Spagnoli *et al.*, 2003; Liberto *et al.*, 2006; Lopes *et al.*, 2007; Villegas *et al.*, 2008) (Table 1). We report here a fatal case of meningitis caused by this organism, complicated by multiple brain and cerebellar abscesses.

Case report

In November 2008, a 77-year-old Italian male presented at our Unit with overt clinical signs of acute meningitis (fever, severe headache and neck stiffness). His past medical history documented that he had had pulmonary tuberculosis at the age of 35; in 2002 he had been hospitalized for a pleural empyema caused by polymicrobial flora (*Serratia marcescens*, *Stenotrophomonas maltophilia* and methicillin-sensitive *Staphylococcus aureus*). Two recurrences of polymicrobial pleuritis were recorded thereafter. A tubercular aetiology of this was searched for but excluded by both repeated direct examination and culture of the pleural fluid and bronchoalveolar lavage for acid-fast bacilli. Six years later (June 2008), the patient was rehospitalized due to headache and high fever with spikes at 39 °C. He presented with overt signs of meningeal irritation and a lumbar puncture was performed after a cerebral CT scan, which was negative for focal lesions. The cerebrospinal fluid (CSF) obtained was purulent and exhibited an increased pressure; it also showed a marked increase in white blood cell count (6000 cells mm⁻³, 90% neutrophils), proteins (292 mg mm⁻³) and lactic acid (10.5 mmol l⁻¹). Two CSF samples drawn by sequential lumbar punctures were cultured. After detecting bacterial growth, samples were subcultured at 37 °C on sheep blood agar and chocolate agar incubated in CO₂; after 48 h of incubation, an α -haemolytic organism grew on all plates and was further characterized as being a Gram-variable coccus that was catalase-negative and non-bile-soluble. The biochemical identification system API 20 Strep (bioMérieux) identified the organism from both CSF

cultures as being *G. morbillorum*. Molecular identification of the CSF isolates was also performed and both partial and full 16S rRNA gene sequencing also identified the micro-organisms as *G. morbillorum* after comparison to the reference strain in the MicroSeq database. Repeated blood cultures were negative and endocarditis was excluded by both transthoracic and transoesophageal echocardiograms. The patient appeared cured after a 3-week medical treatment with i.v. meropenem, after which he was discharged. Then, 2 months later (September 2008), the patient was rehospitalized for a febrile episode that appeared to resolve after empirical therapy with i.v. piperacillin/tazobactam administered for 1 week; however, a few days after the discharge the patient had to be readmitted for low fever (maximum 37.7 °C) and headache. Upon observation (5 November 2008), he complained of a severe occipital headache and displayed a slight dizziness; neurological examination at that time was negative for signs of meningeal irritation but revealed bilateral dysmetria of vision and serious ataxia. Cerebral CT scanning was performed, which documented compression of the fourth ventricle by a hypodense mass, localized in the left cerebellar hemisphere and showing peripheral enhancement after contrast injection (Fig. 1). No signs of sinusitis and/or mastoiditis were documented by specific CT examination, and a chest X-ray did not reveal focal pulmonary lesions. Urine culture and repeated blood cultures were negative. Three days after hospital admission, the patient underwent neurosurgery for the evacuation of a gross cerebellar abscess, from which *G. morbillorum* was cultured; the biochemical identification was confirmed by 16S rRNA sequencing. The strain was fully sensitive to all agents tested including penicillin, ampicillin, cefotaxime, ceftriaxone, gentamicin, streptomycin, ciprofloxacin and vancomycin. The patient subsequently displayed a progressively worsening septic state complicated by frequent gastrointestinal haemorrhages, and died 2 weeks after neurosurgery despite antibiotic treatment with i.v. penicillin and cefotaxime. The autopsy documented, in addition

Table 1. Cases of CNS infection due to *G. morbillorum* (reported as of 1 June 2009)

Case	Reference	Clinical setting	Concomitant morbidity	Outcome
1	Garavelli (1990)	Meningitis	Not reported	Cure
2	Debast <i>et al.</i> (1993)	Leptomeningitis	Sinusitis maxillaris	Death
3	Asensi <i>et al.</i> (1996)	Brain abscess	Periodontitis, alcoholism	Cure
4	Murray <i>et al.</i> (1998)	Brain abscess, meningitis	Septic arthritis	Cure
5	Martínez Beneito <i>et al.</i> (2002)	Subdural empyema	Sinusitis	Cure
6	Messori <i>et al.</i> (2002)	Brain abscess	Sinusitis	Cure
7	Spagnoli <i>et al.</i> (2003)	Brain abscess	Dental abscess	Cure
8	Spagnoli <i>et al.</i> (2003)	Brain abscess	None	Cure
9	Liberto <i>et al.</i> (2006)	Brain abscess	Dental abscess, pleuritis	Cure
10	Lopes <i>et al.</i> (2007)	Brain abscess	Inter-atrial communication	Cure
11	Villegas <i>et al.</i> (2008)	Meningitis, pituitary apoplexy	Pansinusitis	Cure
12	This case	Meningitis, cerebellar abscess, multiple brain abscesses	None	Death

Fig. 1. Cerebellar abscess caused by *G. morbillorum*. Cerebral CT scan revealing a hypodense mass localized in the left cerebellar hemisphere (a) and showing peripheral enhancement after contrast injection; compression of the fourth ventricle is also visible (b). (c) Post-craniectomy CT control showing reduction in size of the abscess after surgical aspiration.

to the cerebellar focus, diffuse cerebritis with multiple micro-abscesses spread in the parenchyma. Histology revealed perivascular microglial infiltration with large haemorrhagic and necrotic areas (Fig. 2).

Discussion

The clinical course in this patient was 'biphasic', developing with an acute meningeal infection followed shortly afterwards by suppuration in the cerebral parenchyma. This pattern, which has already been noted previously

(Murray *et al.*, 1998), seems to suggest a latent survival of the aetiological agent, probably within the CNS, despite systemic antibiotic therapy. In fact, a focus of septic infection external to the CNS could not be demonstrated, on the basis of radiological examinations and of clinical and laboratory findings. In retrospect, had a developing brain abscess rather than meningitis been suspected during the first phase, a 3-week duration of antibiotic therapy would have been inadequate.

The pathogenesis of *G. morbillorum* infections has been rarely investigated. In a case of shunt nephritis (Nagashima

Fig. 2. Histology of the cerebellar abscess caused by *G. morbillorum*. (a) Abscess wall surrounded by parenchyma showing inflammatory infiltrate. (b) Focus of cerebritis with reactive gliosis, micro-haemorrhages and perivascular infiltrate (haematoxylin and eosin, $\times 10$ – 20).

et al., 2001), the organism was proven to act as a trigger for the production of autoantibodies to proteinase 3 (PR3-ANCA), which are widely recognized as able to induce small vessel vasculitides associated with focal necrotizing damage via the release of PR3 from neutrophils and monocytes, which leads to detachment and cytolysis of endothelial cells, probably through a mechanism of apoptosis (Yang *et al.*, 1996). Another study (Ribeiro Sobrinho *et al.*, 2002) documented an effect of down-regulation of IL-12 and IFN- γ following the inoculation of *Gemella* strains isolated from patients with pulpal necrosis into germ-free mice. These cytokines are well known to play a crucial role in the eradication of many different pathogens by stimulating cell-mediated immunity through an enhancement of the cytolytic activity of natural killer and T cells (Del Vecchio *et al.*, 2007). Even in an experimental model of abscess development in the rat brain, pyogenic bacteria have been shown to elicit pleiotropic effects on cells within the CNS by the production of proinflammatory cytokines. In fact, exposure of the CNS vasculature to IL-1 β and TNF- α has led to increased adhesion and migration of inflammatory cells into the CNS, and overexpression of IL-6 has been proven to cause several detrimental conditions including reactive gliosis, neurodegeneration, and breakdown of the blood-brain barrier (Kielian & Hickey, 2000). Finally, members of the genus *Gemella* share with the viridans group streptococci and other important mucosal pathogens the ability to produce specific IgA1 protease (Lomholt & Kilian, 2000), which enables bacteria to evade the adherence-inhibitory activity of secretory IgA *in vitro* and is assumed to constitute an important virulence determinant in bacterial meningitis (Kilian *et al.*, 1996). All these mechanisms probably participate in determining the neurotropism of *Gemella*, particularly in the background of impaired immunity and/or predisposing factors for septic spread. In fact, it seems reasonable that, in the presence of an impaired mucosal immunity, the combined effect of both endothelial damage and downregulation of inflammatory response may result in an enhanced ability of *Gemella* to pierce the blood-brain barrier and invade the CNS. Infections of the CNS caused by *G. morbillorum* appear to be an emerging reality that is likely to be confirmed by future observations performed with accurate speciation and a renewed attention to the differentiation from viridans streptococci.

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