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Group A streptococcal meningitis: a case report

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SUMMARY

Streptococcus pyogenes (Group A streptococcus, GAS) is a rare cause of bacterial meningitis, accounting for less than 1% of cases. GAS meningitis has rarely been reported in children, and is associated with a high (46%) rate of morbidity and a high (10-17%) case fatality rate. This paper describes a case of meningitis caused by GAS in a previously healthy child; M protein genotyping demonstrated an *emm* type 12. Although not common, GAS meningitis must be considered in children vaccinated for other invasive pathogens. Continuous monitoring of the molecular epidemiology of circulating invasive GAS strains is of crucial importance for planning intervention policies.

KEY WORDS: Streptococcus pyogenes, E*mm* type, Meningitis, Case report.

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INTRODUCTION

Streptococcus pyogenes (Group A streptococcus, GAS) is a major cause of global morbidity and mortality, being responsible for different clinical manifestations ranging from pharyngitis and mild soft tissue infections to severe diseases, such as bacteraemia, meningitis, pneumonia, peritonitis, puerperal fever, necrotizing fasciitis and streptococcal toxic shock syndrome (Carapetis *et al.,* 2005).

Meningitis is an unusual presentation for invasive GAS disease, accounting for less than 2% of all streptococcal systemic infections in Europe (Lamagni *et al.,* 2008).

In recent decades an increase in invasive GAS diseases has been recorded both in Europe and in North America (O'Loughlin *et al.,* 2007; Luca-Harari *et al.,* 2009). The overall incidence is similar in developed countries such as USA, Canada and Europe, ranging from 2.79 to 3.5 cases per 100,000 (Laupland *et al.,* 2006; O'Loughlin *et al.,* 2007; Lamagni *et al.,* 2008).

Invasive GAS disease has a high mortality rate. The overall case fatality rate (CFR) in Europe is 19%, being highest in patients with streptococcal toxic shock syndrome (44%) and necrotizing fasciitis (31%) (Luca-Harari *et al.,* 2009). The higher risk of severe GAS disease is linked to host factors: older age, underlying diseases such as diabetes, varicella or other acute or chronic skin lesions, and intravenous drug use. Nevertheless, GAS has the ability to cause severe diseases in otherwise healthy subjects: a quarter of cases report no factor predisposing to severe infections (Lamagni *et al.,* 2008).

A known GAS virulence factor is the M protein, a surface constituent sustaining the bacterial resistance to phagocytosis. M protein is widely used as a marker to type GAS isolates by sequencing the 5' end of the emm gene encoding the M protein (*emm* typing) (Bisno *et al.,* 2003). Recent international studies reported that few *emm* types, such as *emm*1 and *emm*3, are involved more frequently in severe GAS disease, and infections with these organisms are associated with increased mortality (Creti *et al.,* 2007; Luca-Harari *et al.,* 2009).

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In Italy, during a nationwide surveillance program for GAS invasive diseases in 2003-2005 no case of GAS meningitis was recorded (Creti *et al.,* 2007; Lamagni *et al.,* 2008). This paper describes a case of GAS meningitis in a previously healthy child.

CASE REPORT

A previously healthy 4-year-old boy had a recent history of remittent fever, vomiting, headache, pharyngitis and otalgia lasting for 7 days. Since clinical conditions worsened, the child was referred to the Emergency Unit of Trieste Children's Hospital owing to suspected meningitis. On admission the patient was alert and responsive, but showed meningeal signs. Cardio-pulmonary and abdominal examinations were negative as well as neurological signs of focal disorders and skin lesions were absent. The child had undergone the complete schedule of vaccination including the *Haemophilus influenzae* type b and 7-valent pneumococcal vaccines.

The patient underwent a lumbar puncture and the cerebrospinal fluid (CSF) was turbid as for bacterial meningitis; thus, treatment was started with intravenous ceftriaxone (1.5 grams per day for 10 days) and dexamethasone. A white blood cell count showed 23200 cells/mm^3 with 95% polymorphonuclear neutrophils. The inflammation indexes sharply increased (erythrocyte sedimentation rate = 109 mm/h; C-reactive protein =10.97 mg/L). CSF examination showed 2400 leucocytes/mm^3 with 60% neutrophils; protein concentration was 56.6 mg/dL and glucose was 25 mg/dL. Gram stain showed Gram-positive cocci in chains and polymorphonuclear cells. Overnight culture led to the growth of a strain identified as *Streptococcus pyogenes* by biochemical and serological tests. Antimicrobial susceptibility to penicillin, ceftriaxone, erythromycin, chloramphenicol, tetracycline and vancomycin was tested by disk-diffusion on Mueller–Hinton agar supplemented with 5% sheep blood; minimal inhibitory concentration (MIC) was determined for ceftriaxone by Etest. The strain proved to be sensitive to all the antimicrobials tested. Blood culture was negative.

The child responded quickly to treatment both in terms of clinical and laboratory response: he soon became afebrile and showed a rapid decrease in both neutrophil count and inflammation indexes. At discharge, the patient was in good general conditions. He did not develop any neurological sequelae and the audiological test was normal two months after recovery.

The isolate was sent to the national reference laboratory for molecular typing and was confirmed as Lancefield group A Streptococcus *emm* type12.

DISCUSSION

Starting from the 1980s, invasive GAS disease in children and adults has been increasingly reported, though meningitis has remained rare (Lamagni *et al.,* 2008; Luca-Harari *et al.,* 2009). GAS bacterial meningitis accounts for less than 1% of all culture-proven bacterial meningitis (Schlech *et al.,* 1985; Santos *et al.,* 2009). A recent study on GAS meningitis in Brazilian children reported an incidence of 0.06 cases per 100,000 children per year (Almeida Torres *et al.,* 2013); a similar incidence (0.05/100,000/y) has been observed in Norway (Bruun *et al.*, 2010).

The most common predisposing factors for GAS meningitis in children are otitis media, mastoiditis and sinusitis, cochlear implants and skin conditions like chickenpox and penetrating traumas. In many cases GAS invasive diseases can be due to a focal infection, with or without bacteraemia. Nevertheless, in 10-25% of cases GAS can cause meningitis in healthy children without overtly recognizable foci of infection (Perera *et al.,* 2005; Lamagni 2008)

GAS meningitis shows a high (46%) rate of morbidity and a high (10-17%) case fatality rate (*van* Zitteren *et al.*, 2011). The outcome is still rather unfavourable in spite of early and appropriate antibiotic treatment, leading to adverse outcomes (death and neurological sequelae) in about 30% of cases, reaching 43% in poorer countries (Perera *et al*., 2005; de Almeida Torres *et al.,* 2013).

This paper described a rare case of group A Streptococcus genotype *emm*12 meningitis with a favourable outcome in a paediatric patient. Our patient did not require intensive care and recovered well after antimicrobial therapy, without neurological sequelae. Blood cultures remained sterile and fever ceased after few days of antibi-

otic treatment. The pathogenesis of this GAS invasive case remained undetermined, although a focal origin of meningitis could not be fully ruled out, in spite of the lack of a documented bacteraemia, due to the history of otalgia suggesting a middle ear infection.

Several bacterial virulence determinants associated with invasive GAS infections have been identified; the surface M protein has proven a critical GAS virulence factor. The M protein has been widely used as a target for the standard molecular typing method called *emm*-typing, and more than 200 *emm* types have already been described (de Almeida Torres *et al.,* 2013). Nevertheless, only strains of certain *emm* types are epidemiologically associated with particular clinical syndromes. Few GAS *emm* types such as 1, 3, 28 and 89 have been frequently, although not exclusively, isolated from patients with severe invasive disease, and infections with these organisms are associated with increased mortality (Luca-Harari *et al.*, 2009). In Europe, only four *emm* types (*emm*1, 3, 4 and 12) account for the majority (57%) of paediatric cases; the case fatality rate (CFR) is highest in infections caused by *emm*3 (36%) and *emm*1 (29%) genotypes. The GAS genotype *emm*12 described here represents 11% of invasive isolates and usually displays an intermediate virulence level with a CFR of about 17% (Luca Harari *et al.*, 2009). A variation in the geographical distribution of *emm* types among different European countries and dynamic changes over time have been reported (Siljander *et al.*, 2010). In Italy *emm*12 has been frequently found in asymptomatic carriers (Blandino *et al.,* 2011) and has been increasingly recognized as a cause of invasive disease (Creti *et al.,* 2007).

GAS are universally susceptible to all beta-lactam antibiotics with no published report of resistance to date, but relatively high rates of macrolide and tetracycline resistance were found in Italy and in other European countries (Jasir *et al.*, 2005; Creti *et al.,* 2007). Therefore, penicillin is the first-choice drug once GAS meningitis has been diagnosed (Wajima *et al.,* 2008). In our case, the patient promptly responded to antimicrobial therapy with ceftriaxone.

Invasive GAS disease has a significant impact on the health care system since most patients require hospitalization (O'Loughlin *et al.,* 2007). Due to the burden of GAS disease, epidemiological surveillance is a crucial issue to detect differences in its distribution in distinct populations. An important part of epidemiological surveillance is devoted to typing bacterial isolates. Knowledge of the incidence of the disease and *emm* type distribution is necessary for planning immunization strategies by development of GAS vaccines.

Two types of vaccines have entered or are nearing clinical investigation: the N-terminal M protein-based multivalent vaccines (26-valent and 30-valent vaccines) and the conserved M protein vaccines (Dale *et al.*, 2013). Serotypes included in the 26-valent vaccine have been chosen since they were commonly involved in invasive GAS disease or uncomplicated pharyngitis or associated with rheumatic fever in the USA (O'Loughlin *et al.,* 2007).

Epidemiologic surveys suggest that the 26-valent vaccine would provide a good coverage of circulating strains of GAS in industrialized countries (over 72%); according to a recent national survey, such a vaccine would cover about 75-79% of invasive infections in Italy (Creti *et al.,* 2007). Due to the different *emm* types distribution in many developing countries, the 26-valent vaccine has been reformulated into a 30-valent vaccine to increase coverage of circulating GAS in these areas. In preclinical studies, the 30-valent vaccine has shown to be highly immunogenic, inducing the production of antibodies which opsonize all *emm* types represented in the vaccine and even a proportion of nonvaccine *emm* types of GAS, possibly conferring cross-protection (Steer *et al.,* 2009; Steer *et al.,* 2013).

In conclusion, GAS meningitis remains an unusual form of invasive GAS disease in children, frequently occurring in association with other focal infections, mostly otitis media. Careful clinical diagnosis and improved epidemiological surveillance of GAS infections could describe disease trends and identify conditions or groups at risk. In addition, the *emm* gene typing system for GAS isolates represents the best tool for GAS molecular epidemiology description.

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