Group A β-Hemolytic Streptococcus Meningitis: Clinical and Microbiological Features of Nine Cases

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Group A β-hemolytic streptococcus (GAS) meningitis is a rare disease in adults. We conducted a retrospective study to describe clinical and microbiological features of nine cases of GAS meningitis in Switzerland. Of nine patients, six had neurosurgical conditions, and five had upper respiratory tract infections. Eight cases were community-acquired. The outcome of GAS meningitis was favorable; only one patient died of neurosurgical complications. No patient presented with toxic shock syndrome. Serotyping failed to reveal a dominant strain, and genotyping revealed that two strains carried the gene encoding the streptococcal pyrogenic exotoxin C and that one strain carried the gene encoding the streptococcal pyrogenic exotoxin A. Our observations suggest that GAS meningitis in adults is associated with neurosurgical conditions and/or an upper respiratory tract infection.

During the last two decades, group A β-hemolytic streptococcus (GAS) invasive disease has been observed with an increasing frequency. It is associated with soft-tissue involvement, bacteremia, and streptococcal toxic shock syndrome (STSS) [1, 2]. Other sites of involvement are the lungs, middle ear, joints, and bones.

Despite the ability of GAS to invade soft tissues, CNS infection remains a rare event in adults. In recent studies describing invasive GAS disease, meningitis was not mentioned [2–4]. In a MEDLINE search of the world literature, we found 40 cases of GAS meningitis, which occurred mostly in children. In an extensive review, Chow and Muder [5] described only eight cases in adults. Very little is known about the predisposing factors and clinical features of GAS meningitis. The aim of our study was to identify conditions associated with GAS meningitis and to analyze the strains involved.

Patients and Methods

Cases were identified through results of CSF cultures performed in all main Swiss hospitals from 1983 to 1998. Identification of GAS by CSF culture was the inclusion criterion. Associated conditions, clinical features, and outcomes were reported on standardized case report forms. GAS was identified biochemically by using API 20 STREP Strips (bioMérieux, Marcy l'Etoile, France), and streptococcal antigens were determined by rapid antigen extraction and latex agglutination testing (Slidex, Strepto-kit, bioMérieux).

If the original strain was available, serotyping and genotyping were performed. Serotyping was performed by the PHLS Laboratory (London) according to standard procedures. Genotyping was carried out in the same laboratory by amplifying streptococcal pyrogenic exotoxin A, B, or C with a multiplex PCR [6].

Results

Nine cases of GAS meningitis were identified in five females and four males; the median age of the patients was 37 years. GAS meningitis was community-acquired in eight cases, and case 1 occurred 18 days after discharge from the hospital (table 1). One patient was pregnant, one had HIV infection, and another had ischemic heart disease. No chronic underlying diseases were present in any other patient.

Clinical signs of CNS infection were present in all cases but one. Organ failure or septic shock was not observed, and no case met the criteria for STSS [7].

Six patients (67%) had prior or concomitant neurosurgical conditions, four of whom had skull fractures. Three of these patients had proven or highly probable CSF leaks. Four patients underwent neurosurgery: several years before, two; and during hospitalization for meningitis, two.

Five patients also had ear, nose, and throat infections (table 1). All together, eight patients had histories or diagnoses of frontobasilar skull fracture and/or ear, nose, and throat infection before the onset of GAS meningitis. Cerebral CT scans were obtained for seven patients. Four of these scans showed neurosurgical abnormalities. Results of CSF analyses are presented in table 1. All patients were treated with β-lactam antibiotics. Outcomes were favorable for eight patients, and one died several weeks later following surgery for a cerebral abscess. Only one patient had mild residual left-hand paresis.

Blood cultures were performed in seven cases. Of these cultures, three (for which specimens were obtained before

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Table 1. Clinical features of and microbiological results for nine adults with GAS meningitis.

Patient no./year of diagnosis, age (y)	Associated condition(s)	CSF analysis				Other site(s) of GAS identification	M and T types	Pyrogenic exotoxin gene(s)	Therapy (duration)
		Gram staining	Cell count (/mm^3)	% PMNs	Glucose level (mmol/L)				
1 (1996), 38	Hypophysectomy for Cushing's disease	Negative	575	83	2.8	None	M6 and T6	B and C	Pen (2 w)
2 (1995), 40	Frontobasilar skull fracture, CSF leak and sinusitis	Cocci	1,700	87	4.5	None	NA	NA	Ctri/Amp then Pen (2 w)
3 (1997), 40	HIV infection, posttraumatic subdural hematoma, otitis media	Cocci	456	93	5.11	Blood	NT	B	Pen then Ctri (6 w)
4 (1990), 30	Chronic frontal fistula after frontobasilar skull fracture	Cocci	25	14	NA	Brain abscess	M2 and T2/28	B	Flox (3 w)
5 (1998), 15	Occipital skull fracture 3 y before and suspicion of CSF leak	Cocci	26,112	92	2.8	Blood	NA	NA	Ctri then Amox (3 w)
6 (1989), 17	Pharyngitis and sinusitis, jugular phlebitis, cavernous thrombosis	Cocci	40,960	93	1.1	Throat and conjunctiva	M1 and T1	A and B	Ctri/Pen (3 w)
7 (1983), 63	Otitis media and mastoiditis, ischemic heart disease	NA	938	67	2.7	Mastoid bone	PT4245 and T11	B	Pen (4 w)
8 (1998), 63	Pharyngitis	Cocci	28,500	98	NA	Blood	None and T28	B and C	Pen/Cm (4 w)
9 (1995), 30	Pregnancy	Cocci	3,925	100	1.88	None	NA	NA	Ctri (3 w)

NOTE. Amox = amoxicillin; Amp = ampicillin; Cm = clindamycin; Ctri = ceftriaxone; Flox = floxacillin; GAS = group A β-hemolytic streptococcus; NA = not available; NT = nontypeable strain; Pen = penicillin; PMNs = polymorphonuclear cells.

antibiotic therapy was started) yielded GAS, and four (for which specimens were obtained after therapy was started) remained negative. All nine CSF strains were susceptible to penicillin; six were available for characterization, serotyping, and genotyping. M types were variable; the *spe*C gene was identified in two strains, and the *spe*A gene was identified in one strain (table 1).

Discussion

We describe the clinical and microbiological features of nine sporadic cases of GAS meningitis in adults. Six patients had neurosurgical conditions, mainly sequelae of skull fractures or complications arising from neurosurgical procedures; three of these patients with neurosurgical conditions and two additional patients had bacterial upper respiratory tract infections. Apart from one HIV-infected patient, no chronic underlying condition was present, thus suggesting that GAS meningitis can occur in otherwise healthy adults.

Invasive GAS disease is often associated with STSS [3, 8]. In our series, three patients had associated bacteremia, and none had soft-tissue infection, severe organ failure, or criteria for STSS. These findings suggest that GAS meningitis is not a complication of invasive GAS disease but rather follows infection and/or colonization of the ear, nose, and throat sphere. The fact that three patients had basilar skull fractures and one other had undergone transsphenoidal surgery supports this hypothesis. Upper respiratory tract infections, neurosurgical conditions, and CSF leaks are well-known causes of acute bacterial meningitis and streptococcal meningitis [5, 9–11]. These ob-

servations also suggest that patients carrying GAS in their nasopharynx would probably benefit from antibiotic prophylaxis before surgical procedures.

The outcome, in comparison with the high mortality rate observed in cases of invasive GAS disease, was favorable. A similar outcome was also observed in previous case reports [5, 9]. The mortality rate associated with GAS meningitis also appears to be lower than that associated with pneumococcal or nosocomial meningitis.

Genotyping failed to reveal a dominant strain, and the M types were variable. All strains analyzed were found to contain the *spe*B gene, which is consistent with findings of previous studies showing that >90% of GAS strains produce the *spe*B gene [12, 13]. However, two strains were found to contain the *spe*C gene, and only one had the *spe*A gene. These results are surprising since most previous studies on invasive GAS disease reported high incidences of strains producing the *spe*A gene [12]. Our investigations suggest that production of the *spe*A gene is not a determinant in causing GAS meningitis but more likely is due to locally invasive strains. Recent reports on the virulence factors produced by GAS support this hypothesis [14].

Virulence factors such as the fibronectin-binding proteins (SfbI) and the F1 protein contribute to the increased adherence of GAS strains, which may explain the potential of this microorganism to locally invade host tissues [14]. In addition, the fact that two strains contained the *spe*C gene suggests that in some instances exotoxin C may have been a virulent factor promoting this streptococcal disease. The *spe*C gene is a virulent factor that has already been associated with streptococcal disease [15]. Several other toxins or virulence factors including the streptococcal superantigen are also associated with invasive streptococcal diseases. In the present study, we did not investigate if the streptococcal superantigen was present.

Our observations suggest that GAS meningitis in adults is not a complication of sustained bacteremia but rather is associated with neurosurgical conditions and/or upper respiratory tract infections. GAS meningitis does not seem to be associated with STSS or strains producing the *spe*A gene. Adults with GAS meningitis have a favorable prognosis if antibiotic therapy is promptly initiated.

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