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Comparison of Isolates of *Neisseria gonorrhoeae* Causing Meningitis and Report of Gonococcal Meningitis in a Patient with C8 Deficiency

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We studied a previously healthy 20-year-old woman who presented with gonococcal meningitis. The gonococcal isolate, HT-1, was prototrophic by auxotyping, was protein I serovar IB-1, and agglutinated with wheat germ lectin. This isolate differed from the proline-requiring, serovar IA-1 and IB-4, wheat germ-agglutination-negative gonococcal isolates recovered from three patients during a recent outbreak of gonococcal meningitis in Philadelphia. HT-1 was killed by normal pooled human sera (≥98% at 30 min) but not effectively killed by the convalescent-phase sera of the patient (>30% survival at 30 min). Similar results were obtained when mucosal and cerebrospinal fluid isolates from a Philadelphia patient were exposed to these sera, but mucosal and blood isolates from another Philadelphia case showed increased resistance to killing by normal pooled human sera. Further characterization revealed multiple differences in outer membrane and cellular proteins and lipopolysaccharide between case isolates. Absence of the L8 lipopolysaccharide epitope was noted for all isolates. Sera of our patient were found to have low total hemolytic complement (CH_{100} = 21 U/ml; normal = 55 to 100 U/ml) due to deficiency of C8 (C8 < 1,000 CH_{50} U/ml; normal = ≥16,000 CH_{50} U/ml). This is the first reported case of gonococcal meningitis occurring in a patient with a terminal-complement deficiency. Gonococcal meningitis is a rare complication of gonococcal bacteremia. Both defects in host defenses (e.g., terminal-complement deficiency) and organisms with unusual virulence appear to contribute to the pathogenesis of this complication of gonococcal bacteremia.

Gonococcal meningitis is a rare complication of disseminated gonococcal infection (DGI). DGI develops in 1 to 3% of patients with mucosal gonococcal infections and is most often associated with arthritis or tenosynovitis with or without skin lesions (7). However, endocarditis, myopericarditis, and meningitis can be sequelae of gonococcal bacteremia (7, 10, 12). Several characteristics, such as transparent colony type, absence of outer membrane protein II, and resistance to killing by normal human sera (NHS) have been associated with the gonococcal strains that disseminate beyond mucosal surfaces (1). In addition, gonococcal strains isolated during a recent outbreak of gonococcal meningitis were found to have characteristics which distinguished them from DGI strains, most notably in serovars and lectin agglutination patterns. These isolates came from the same geographic area as the meningitis strains but did not cause meningitis (15, 16). These data suggest that study of cases of gonococcal meningitis may provide important clues to defining organism and host factors associated with cerebrospinal fluid invasion by pathogenic *Neisseria* species.

We report a case of bacterial meningitis caused by *Neisseria gonorrhoeae* in a previously healthy female. We studied the auxotype, serovar, lectin agglutination pattern, colony type, and outer membrane antigens of this isolate and compared these to those of the isolates recovered during a recent outbreak of gonococcal meningitis in Philadelphia (15). In addition, we studied bactericidal activity, complement levels, and specificity of gonococcal antibodies found in the acute- and convalescent-phase sera of our patient.

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CASE REPORT

A 20-year old woman presented to the emergency room of Grady Memorial Hospital with a 2-day history of myalgia and low-grade fever. At the time of admission she complained of a severe headache, fever, nausea, and a stiff neck. Her past medical history was unremarkable. She was on oral contraceptives, and her last menstrual period was 1 week prior to admission. On physical examination, her temperature was 38°C, and there was marked nuchal rigidity with no focal neurologic findings or papilledema. No skin lesions were present, and the rest of the examination was unremarkable.

Laboratory findings included an elevated leukocyte count of 19,100/mm^3 with 64% polymorphonuclear leukocytes, 18% bands, 2% lymphocytes, 15% monocytes, and 1% basophils. Total serum protein was 6.9 g/dl, and albumin was 4.4 g/dl. Hepatic enzymes and other serum chemistries were within normal limits.

A lumbar puncture revealed cloudy fluid with 4,500 leukocytes per mm^3 (90% polymorphonuclear leukocytes and 10% macrophages), protein of 288 mg/dl, and glucose of 7 mg/dl. A Gram stain did not show microorganisms. The patient was given ampicillin intravenously, and rapid improvement followed. Culture of the cerebrospinal fluid (CSF) grew an oxidase-positive, gram-negative diplococcus

identified as *N. gonorrhoeae*. Blood cultures were not obtained before antibiotics were given.

MATERIALS AND METHODS

Microorganisms and susceptibility testing. CSF was centrifuged for 10 min in an IEC Centra-7 Centrifuge (International Equipment Co., Div. Daman Corp., Needham Heights, Mass.), and the sediment was plated on blood (5%) and chocolate agar plates (Carr-Scarbrough Microbiologicals Inc., Decatur, Ga.). The plates were incubated at 37°C in a 3% CO_2 incubator. The CSF isolate (HT-1) from our patient was confirmed as *N. gonorrhoeae* by carbohydrate utilization and by using the Vitek NHI identification card (McDonald Douglas, Hazelwood, Mich.) and the GONAGEN kit (New Horizon Diagnostic Corp., Columbia, Md.). Four isolates of two patients, 84-021704 and 84-021705 (endocervical and blood isolate of patient 1) and 84-026583 and 84-026582 (endocervical and CSF isolate of patient 2), from the recently reported Philadelphia gonococcal meningitis outbreak were also used in this study (15).

Serologic classification of the gonococcal strains was done by using protein-I-specific monoclonal antibodies (9). Auxotyping and lectin agglutination studies and determination of colony type were performed as previously described (19, 21, 23). β-Lactamase production was determined by using a disk diffusion method (26). MICs of penicillin, tetracycline, spectinomycin, cefoxitin, and ceftriaxone were determined by an agar dilution method (8).

SDS-PAGE and Western immunoblotting. To assess further the characteristics of these isolates and to study the specificity of antigonococcal antibodies present in the sera of the patient, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western immunoblots were used. SDS-PAGE (12.5% acrylamide gels, silver stained) of whole-cell lysates or proteinase K digests and Western immunoblotting were performed as previously described (24, 25). Whole-cell lysates of each isolate were run after heating at 56°C for 30 min or boiling at 100°C for 3 min. Acute- and convalescent-phase (obtained 8 weeks after hospitalization) sera from our patient (1 to 50 dilution in blocking buffer), immunoglobulin G (IgG) monoclonal antibodies to antigen H.8 (kindly supplied by Janne Cannon), LPS epitope L8 (kindly supplied by Wendell Zollinger), and antisera to pilin (25) were used as probes in the Western immunoblots. Detection of IgG antibody binding to antigens immobilized on nitrocellulose was performed by using staphylococcal protein A conjugated with horseradish peroxidase and diaminobenzidine tetrahydrochloride. Both monoclonal antibodies reacted with staphylococcal protein A.

Serum bactericidal assay. A microdilution serum bactericidal assay was performed as previously described (23). Briefly, NHS from normal adult subjects with no history of gonococcal or meningococcal disease and not currently receiving antibiotic therapy was collected, divided into aliquots, and stored at −70°C prior to use. Total hemolytic activity of the NHS was at normal levels. The isolates were grown on GC agar (BBL Microbiology Systems, Cockeysville, Md.) containing 2% IsoVitaleX for 14 to 18 h at 37°C in 2 to 5% CO_2. Inocula were prepared as previously described (23), diluted to the desired concentration, and used immediately in the bactericidal assay. Serum (0.5 ml), bacterial inoculum (0.1 ml), and *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES)-minimal essential medium (0.4 ml) were mixed so that the final suspension was 1 ml with 50% (vol/vol) serum and 2×10^4 CFU/ml. The reaction mixture was incubated at 37°C in 2 to 5% CO_2 with end-over-end rotation. Triplicate samples (0.01 ml) were withdrawn from the reaction mixture after 30 and 120 min of incubation and assayed for viable organisms. Strains FA-19 and FA-899, previously characterized serum-resistant and serum-sensitive strains, respectively (24), were used as controls for the serum bactericidal assay.

Sera from the patient were analyzed for hemolytic complement and specific activity of complement components by SmithKline Bio-Science Laboratories (Tucker, Ga.).

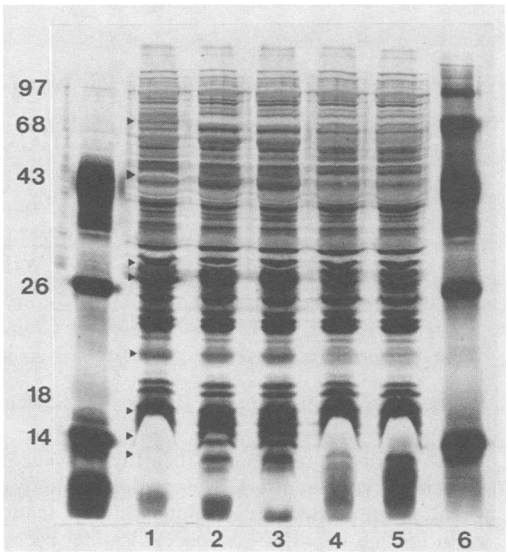

FIG. 1. SDS-PAGE profile (12.5% acrylamide gel) of whole-cell lysates of gonococcal meningitis isolates HT-1 (lane 1), 84-021704 (lane 2), 84-021705 (lane 3), 84-026582 (lane 4), and 84-026583 (lane 5). The isolates differed in multiple bands (▶), notably in the region of less than 40-kDa molecular mass. Molecular weight markers flank the isolates, and their sizes (in thousands) are noted on the vertical axis.

RESULTS

Characteristics of the gonococcal meningitis isolate HT-1. The protein I serovar of the isolate was IB-1, and the auxotype was prototrophic. The isolate agglutinated with wheat germ lectin. HT-1 did not produce β-lactamase. Meningitis isolates from an outbreak in Philadelphia (15) were proline requiring by auxotype, did not agglutinate with wheat germ lectin, and did not produce β-lactamase. Thus, HT-1 differs from the Philadelphia isolates in protein I serovar, auxotype, and lectin agglutination pattern. The MIC for HT-1 of penicillin was 0.5 μg/ml, of tetracycline 2 μg/ml, of spectinomycin 8 μg/ml, of cefoxitin 1 μg/ml, and of ceftriaxone 0.004 μg/ml.

HT-1 formed predominantly opaque colonies on clear (GCIso) agar. The SDS-PAGE profile of the whole-cell lysate of isolate HT-1 is shown in Fig. 1 compared with whole-cell lysates of 84-021704, 84-021705, 84-026583, and 84-026582. By SDS-PAGE, isolates 84-021704 and 84-021705 (from the endocervix and blood of patient 1) were similar, as were isolates 84-026583 and 84-026582 (from the endocervix and CSF of patient 2). However, isolates from each patient differed. Strain HT-1 differed from both pairs of the Philadelphia isolates, notably in the region of less than 40 kilodaltons (kDa). Some of the differences in this region were due to the presence or absence of outer-membrane protein

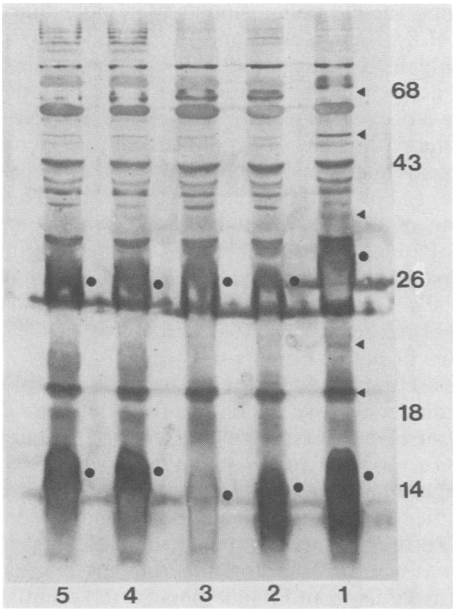

FIG. 2. Antigens of gonococcal meningitis isolates recognized by sera of the patient. Western blot of SDS-PAGE-separated whole-cell lysates of gonococcal meningitis isolates noted in Fig. 1 was probed with acute-phase sera from our patient. Multiple antigens of identical molecular weight were recognized in all isolates, but differences were noted between isolates (◀). Also, bands of variable molecular weight but similar staining characteristics were noted in the 27-to-32-kDa region and below 14 kDa (●). No differences were noted in the immunoblot pattern whether the source of antibody was acute- or convalescent-phase sera. Sizes (in thousands) of molecular weight markers are noted on the vertical axis.

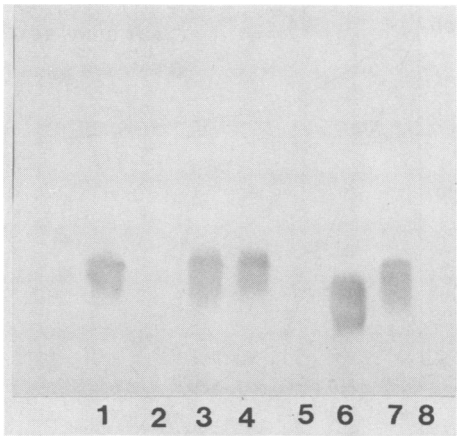

FIG. 3. LPS epitopes of gonococcal meningitis isolates recognized by sera of the patient. Western blot of proteinase K digests of gonococcal meningitis isolates was probed with acute-phase sera from our patient. Serum contained IgG antibodies which reacted with LPS of isolate HT-1 (lane 1) and each of the other gonococcal meningitis isolates (lane 3, 84-026582; lane 4, 84-026583; lane 7, 84-021704) except 84-021705 (lane 8). Sera also did not recognize LPS of gonococcal strain FA899 (lanes 2 and 5) but reacted with LPS of gonococcal strain SS-9 (lane 6). We have previously shown that FA899 and SS-9 differ in LPS structure (24).

II. However, other bands that differed did not have the heat-modifiable characteristics of outer-membrane protein II. To study further other antigens of this region, Western blots of the preparations were probed with antibodies to H.8 antigen, pilin, and LPS. In addition, proteinase K digests of these lysates were studied. The molecular mass of the H.8 antigen of HT-1 (31.5 kDa) was similar but not identical to the molecular mass of the H.8 antigen of each of the Philadelphia gonococcal meningitis isolates, 84-021704, 84-021705, 84-026582, and 84-026583 (31 kDa). Molecular weights of pilin and LPS of isolate HT-1 differed from those of both pairs of the Philadelphia isolates. Neither HT-1 nor any of the other gonococcal meningitis isolates were found to express L8, an LPS epitope which has been associated with serum resistance of *N. gonorrhoeae* (20).

Antigens of gonococcal meningitis isolate HT-1 recognized by sera of the patient. To determine whether sera from our patient contained specific antibodies to antigens of gonococcal strain HT-1 and the other gonococcal meningitis isolates, Western immunoblots of whole-cell lysates were probed with the patient's acute-phase (Fig. 2) and convalescent-phase sera. These sera recognized multiple proteins of identical molecular weight in each isolate. However, distinct bands were noted for strain HT-1 when compared with the other meningitis isolates. The molecular weight of antigens recognized by the sera in the 27-to-32-kDa range of these isolates was consistent with the molecular weights of the H.8 antigen seen with the monoclonal antibody. The 19.5-kDa identical bands did not appear to represent a common pilin (pilus or fimbriae subunit) epitope when antisera to the CNBR-2 fragment of pilin was used as a probe. The staining characteristics of the bands of less than 14 kDa suggested binding to LPS. Immunoblot patterns were identical when probed with acute- or convalescent-phase sera. These data indicate that acute- and convalescent-phase sera from our patient contained IgG antibodies possibly directed at H.8, LPS, and several gonococcal proteins and that these antigens were not identical among the isolates. When NHS was used to probe these preparations, minimal reactivity with cellular proteins or LPS was noted (data not shown).

To study further anti-LPS antibodies present in the sera of the patient, proteinase K digests of the whole-cell lysates were probed with the acute-phase sera of the patient. Except for that of the blood isolate 84-021705, LPS of all gonococcal meningitis isolates reacted (Fig. 3). These data suggest that, although identical by other methods (antibiotic susceptibility, serovar, serum susceptibility, and SDS-PAGE profile), strains 84-021704 (endocervix) and 84-021705 (blood) from the same patient have differences in the antigenic structure of LPS.

Complement studies. Serum complement studies performed on sera from the patient collected 15 days after the onset of illness showed a C3 level of 214 U/ml (normal = 83 to 177), a C4 level of 34 U/ml (normal = 15 to 45), and a CH_{100} level of 21 U/ml (normal = 55 to 100). These studies were repeated 2 months later, giving similar results. Assay for specific components of the complement membrane attack complex showed normal activity of C5, C6, C7, and C9 but low activity of C8 (< 1,000 CH_{50} U/ml; normal ≥ 16,000 CH_{50} U/ml).

Serum susceptibility of gonococcal meningitis isolates. Susceptibility of HT-1 to 50% NHS and 50% convalescent-phase sera from the patient is shown in Fig. 4. Strain HT-1 is susceptible to killing by NHS (<2% survival at 30 min). In contrast, when exposed to 50% convalescent-phase sera from our patient, strain HT-1 was ineffectively killed (>30% survival at 30 min; $P < 0.003$; two-tailed test). The other gonococcal meningitis isolates were also ineffectively killed by the sera of this patient (data not shown). These data suggest that strain HT-1 is serum sensitive but was resistant

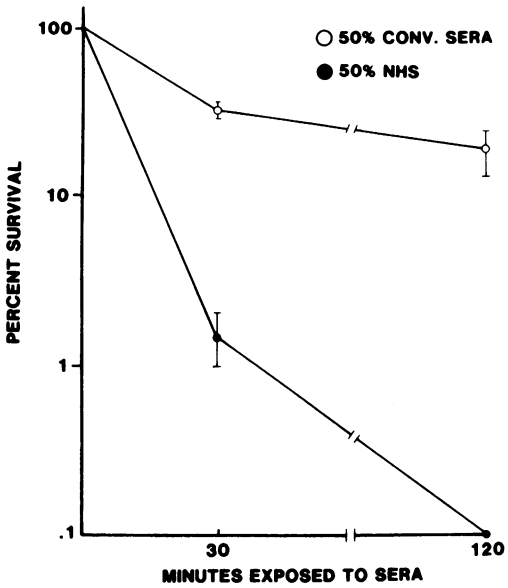

FIG. 4. Serum susceptibility of gonococcal isolate HT-1. When exposed to 50% (vol/vol) NHS, HT-1 was very susceptible (<2.5% survival at 30 min) to killing. When exposed to 50% convalescent-phase sera from the patient, HT-1 was ineffectively killed (>30% survival at 30 min; $P = 0.003$; two-tailed Student's t test).

to killing by the convalescent-phase (C8-deficient) sera from our patient. When exposed to 50% NHS, strains 84-021704 and 84-021705 had 19.1 ± 4% (mean ± standard error of the mean) and 21.0 ± 5.2% survival at 30 min, respectively. However, strains 84-026582 and 84-026583 were serum sensitive (<2% survival at 30 min). The difference in killing by NHS of HT-1 and 84-021704 and 84-021705 at 30 min was statistically significant ($P < 0.001$, two-tailed Student's t test). At 120 min, survival of all isolates was less than 4%.

DISCUSSION

The first definite case of gonococcal meningitis was reported by Smith in 1922 (22). Since then, approximately 30 additional cases have been reported (4, 7, 11, 18, 27). Two of the three patients from an outbreak in Philadelphia (3, 15) were found to have no evidence of complement deficiency. The complement status of the third patient was not determined. Gonococcal isolates from this outbreak failed to agglutinate with wheat germ, a characteristic previously described for encapsulated *N. meningitidis* (5). This finding suggested that gonococcal strains isolated from CSF have specific alterations of cell-surface carbohydrates or produce inhibitory polysaccharidelike material. The presentation of our patient led us to study further organism and host factors associated with gonococcal meningitis. Characterization of the isolate of the patient, HT-1, revealed distinct differences in protein I, wheat germ agglutination, cellular proteins, and other outer membrane antigens when compared with the Philadelphia isolates. In contrast to these isolates, HT-1 did not appear to be a member of a unique clone associated with gonococcal meningitis. We were unable to identify any unusual virulence characteristic for our isolate, and HT-1 had characteristics (e.g., serum sensitivity, MIC of penicillin, opaque colony type, serovar) normally found in isolates recovered from mucosal surfaces. It is important to emphasize the limitations of comparing characteristics of meningitis isolates from presumably normal and complement-deficient patients. We did note a similarity in molecular weights of antigen H.8 of our isolate and the Philadelphia isolates. The H.8 antigen, first described by Cannon et al. (2), was present on gonococci and meningococci but absent in nonpathogenic *Neisseria* species. However, the role of this antigen in the pathogenesis of gonococcal and meningococcal infections remains unclear.

Our patient showed that gonococcal meningitis can be a complication of DGI associated with terminal-complement deficiency. Patients with deficiencies of the terminal complement system proteins (C5, C6, C7, or C8) have been shown to be at increased risk for disseminated *Neisseria* infections (13). A review by Ross and colleagues (17) of 242 homozygotes or heterozygotes with an apparently inherited absence of a complement protein identified 23 episodes of DGI (including one case of endocarditis but no cases of meningitis) in 11 patients. Two of the blood isolates of the patients were reported to be serum resistant. The authors suggested that meningococcal bacteremia and disseminated *Neisseria* infections in complement-deficient patients were not due to serum-sensitive strains. Our data suggested this may not always be the case. In our serum bactericidal assay, one pair of isolates from Philadelphia were serum sensitive (84-026582 and 84-026583), while the second pair (84-021704 and 84-021705) showed resistance to killing at 30 min but were killed at 120 min by NHS. We observed a similar phenotype previously in transformants of gonococcal strain FA19 (serum resistant up to 120 min) when DNA from a serum-sensitive strain was used to transform this organism (24).

It was interesting to note that serum-sensitive organisms were recovered from the CSF. Rice et al. (14) noted that isolates from joint and mucosal surfaces of patients with gonococcal septic arthritis were more serum sensitive than those recovered from blood or mucosal surfaces of patients who presented with dermatitis and arthralgias.

The difference in LPS observed between isolates 84-021704 (endocervix) and 84-021705 (blood) is intriguing. LPS epitopes, like other gonococcal surface antigens (e.g., outer membrane protein II) are known to undergo phase variation in vitro and in vivo (M. A. Apicella, M. Shero, J. F. Breen, G. F. Brooks, C. Fenner, and P. A. Rice, Abstr. 6th Int. Pathogenic Neisseria Conf. 1988, P13, p. 13). This phenotypic shift in LPS epitopes, which may be selected for by the host, could account for the observed difference.

Meningitis occurred in our patient despite the presence at the time of infection of IgG antibodies which reacted with antigens of the infecting isolate. In patients with urethral gonococcal infection, IgG antibodies reactive with several gonococcal antigens including H.8 were present in the sera prior to infection (6). These antibodies did not prevent mucosal infection. In our patient with a complement system deficiency, these antibodies did not prevent DGI or meningitis.

Gonococcal meningitis is a rare complication of gonococcal bacteremia. Its occurrence may suggest an underlying complement deficiency or an organism with unusual virulence characteristics.

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