Case Study

Laboratory-Acquired Serogroup A Meningococcal Meningitis

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Neisseria meningitidis causes fulminant meningitis and sepsis. Worldwide, N. meningitidis serogroup A is responsible for large epidemic outbreaks (e.g., sub-Saharan Africa) and serogroups B, C, Y and W-135 cause epidemic and endemic disease. Meningococci are usually transmitted from person to person through close contact with contaminated aerosols and secretions from the human nasopharynx. Laboratory-acquired infection has been reported infrequently but laboratory technicians are at increased risk. Most of the reported cases of laboratory-acquired infections occur in clinical microbiology laboratories and have been due to serogroups B and C. For reasons that are unclear, the reported mortality of laboratory-acquired N. meningitidis sepsis or meningitis is ~50%, which is higher than mortality from endemic infections.

We present the first reported case of laboratory-acquired serogroup A N. meningitidis meningitis in a 21 yr-old research laboratory assistant.

Case Report

A 21-yr old previously healthy student presented to the emergency room with a 5-d history of progressively worsening headache, fever, vomiting and confusion. He lived in a student dormitory and was working in a meningococcal research laboratory for the summer. Patient initially had reported to his physician and to his laboratory supervisor that he had been previously vaccinated against meningococcus. He denied taking any medications including antibiotics prior to his presentation. Upon admission to the hospital he was lethargic and febrile to 39.2°C. Physical examination was remarkable for abnormal mental status and severe nuchal rigidity. A lumbar puncture revealed significantly elevated opening pressure (over 30 cm of H2O) and cloudy cerebrospinal fluid. Laboratory analysis of the cerebrospinal fluid (CSF) showed 14,000 white blood cells (95% polymorphonuclear leukocytes) and 367 red blood cells/mm3. Cerebrospinal fluid (CSF) protein was 265 mg/dl and the glucose level was 4 mg/dl. Gram stain, culture and bacterial antigen testing of CSF were negative as were blood cultures, all taken reportedly before initiation of antibiotics.

The patient was started on antibiotic coverage for bacterial meningitis with ceftriaxone and vancomycin and required external ventricular drain placement for intracranial pressure reduction. On hospital day two, meningococcal polymerase chain reaction (PCR) performed on the initial CSF by the Centers for Disease Control and Prevention (CDC) was reactive for N. meningitidis serogroup A. During the hospitalization, the patient reported plating N. meningitidis serogroup A in the research laboratory and admitted that this was not conducted under a biosafety cabinet. He also then denied previous vaccination with meningococcal vaccine. He completed a 10-d course of antibiotics with intravenous penicillin, and rifampin was given to eradicate nasopharyngeal colonization; he had a full recovery. Significant contacts were traced and given chemoprophylaxis, and there were no secondary cases.

Discussion

Laboratory-acquired meningococcal disease is infrequent but the risk appears to be underappreciated. A case of laboratory-acquired meningococcal infection is defined as meningococcal disease in a laboratory worker who had laboratory exposure to a N. meningitidis isolate within 14 d before the onset of illness and who has illness with the serogroup that matches the source isolate. We report the first recent case of laboratory acquired serogroup A meningococcal disease infection. Boutet et al. in Great Britain demonstrated that laboratory workers exposed to N. meningitidis are at significantly higher risk of developing infection than the general population. Recently, these data were expanded. A total of 16 cases were described in the literature since 1985, with six cases reported in the United States. Nine of the 16 cases were caused by serogroup B and seven by serogroup C. Individuals with laboratory-acquired meningococcal disease had performed the following procedures: organism identification and reading of plates (50%), subculturing (50%), and performing serogroup determination (38%). Eight cases (50%) were fatal and in 15 of 16 reported cases, these procedures were not performed within a level 2 biosafety cabinet. A median number of 4 d (range 2–10 d) occurred between handling the isolate and symptom onset. Source isolates were from blood or CSF with carriage isolates potentially less pathogenic. Currently, N. meningitidis is considered a biosafety level-II organism and CDC guidelines recommend using a biosafety cabinet when manipulating...
samples that have a high potential for droplet or aerosol production such as centrifuging, grinding and blending procedures and for activities involving production of quantities or concentrations[5–7]. Both microbiology and research laboratory workers handling meningococcal isolates should strongly consider vaccination with the quadrivalent meningococcal vaccine or quadrivalent meningococcal conjugate vaccine which includes serogroup A, C, Y and W-135 capsular polysaccharides[6–8]. Antibodies generated from vaccines, as opposed to conjugate vaccines, are usually not persistent, meningococcal polysaccharide therefore, revaccination should be considered 3–5 yr after receipt of the initial dose of meningococcal polysaccharide vaccine in persons with ongoing meningococcal exposure[6, 18]. Meningococcal PCR has significant value in diagnosing meningococcal infections, serogroup determination and penicillin susceptibility and should be developed for clinical laboratories.

The length of protection of the recently released quadrivalent meningococcal conjugate vaccine is unknown but it has immunologic features predicting longer protection: induction of immunologic memory, higher antibody avidity and herd immunity. It is likely this vaccine will replace the polysaccharide vaccine for prevention of laboratory-associated disease[6].

The definitive diagnosis of meningococcal infection has relied on the isolation of N. meningitidis from a sterile body fluid. However, the sensitivity of routine diagnostic studies such as Gram stain and culture from blood and/or CSF yielded meningococci in only 62% of patients with clinically suspected meningococcal disease[9, 10]. Previous administration of parenteral antibiotic therapy or inadequate collection/handling of the samples are possible reasons for the low sensitivity of the Gram stain and culture. Latex agglutination has been found to be less sensitive (61%) than Gram stain in diagnosing meningococcal meningitis; further, it is associated with a significant number of false positive results (up to 54%)[10]. The first report of meningococcal meningitis diagnosed by PCR in a patient with a culture-negative CSF was reported by Kristensen in 1991[11]. Currently several oligonucleotides primer targets are being used for the detection and serogrouping of meningococci (NM1, NM2, IS1106, ctrA, sia(syn)D, crgA), with excellent sensitivity (89–96.7%) and specificity (91–100%)[12–17]. In Great Britain the development of a national PCR-based service increased the number of laboratory confirmed cases of meningococcal disease by 35%[18]. In addition, PCR is useful in meningococcal serogroup determination[4, 10]. Real-time PCR may further enhance PCR sensitivity in diagnosing meningococcal disease[15, 17]. Finally, PCR has also been used for detection of penicillin resistance in N. meningitidis with five out of 12 isolates with penicillin MIC of 0.2–0.25 mg/dl and all nine isolates with MIC >0.25 mg/dl successfully identified based on PCR[19]. Unfortunately, meningococcal PCR is not yet routinely available in many clinical laboratories.

Different serogroups of N. meningitidis have different epidemic potential, public health importance, and geographic distribution. Most meningococcal infections in the United Stated are currently caused by serogroups B, C and Y, with serogroup A meningococcal disease being extremely rare since the end of World War II. From 1977 to 1981 serogroup A infections represented 4.7% of all the meningococcal infections in the United States[2]. More recent surveillance data from 1992–1996 identified only two unconfirmed cases of serogroup A meningococcal disease[3]. The reasons for the disappearance of serogroup A disease in the United States are not clear, but disappearance of disease has been accompanied by the disappearance of serogroup A nasopharyngeal carriage. Epidemics of serogroup A meningococcal disease continue to occur in other parts of the world. Serogroup A outbreaks have occurred in association with the religious pilgrimages to Mecca in 1987 and 1992 with subsequent serogroup A outbreaks in Sudan, Chad, Ethiopia, and other parts of sub-Saharan Africa[1]. Sporadic serogroup A meningococcal disease associated with these outbreaks also occurred in France and Sweden but no cases were reported in the United States. However, the potential for serogroup A meningococcal epidemic disease merits aggressive eradication of potential carriers.

Laboratory-acquired meningococcal infection is associated with a case fatality rate of 50%/4, 5/. This may reflect the small number of cases, underreporting of mild cases, exposure to highly virulent strains and/or high concentration of organisms encountered in the laboratory setting[5]. It was recently estimated that the attack rate of meningococcal disease among microbiologists in U.S. laboratories between 1996 and 2001 was 13/100,000, compared to 0.2/100,000 among U.S. adults in general[8]. Laboratory workers handling meningococcal isolates should be vaccinated with the quadrivalent meningococcal vaccine and should conduct procedures with this organism under a certified biosafety class II containment cabinet[20, 21]. Alternative methods of respiratory protection, such as splash guards and masks require additional assessment[3]. If a biosafety cabinet or other means of protection are not available, manipulation of these isolates should be minimized and workers should consider sending specimens to laboratories that are appropriately equipped[3]. Exposure to isolates of N. meningitidis, rather than patient samples, increases the risk of infection. Education of microbiologists and strict adherence to these safety guidelines would be emphasized.

If a laboratory worker has a percutaneous exposure to an invasive N. meningitidis isolate from a sterile site, he or she should receive treatment with penicillin; if there
is a known mucosal exposure they should also received chemoprophylaxis\(^5\). If a microbiologist has manipulated invasive isolates in a manner that could result in aerosolization and/or droplet formation (such as plating, subculturing and serogrouping) in an open bench top in the absence of respiratory protection, he or she should also consider appropriate antimicrobial prophylaxis\(^5\).

In summary, we present a case of lab-acquired serogroup A meningococcal meningitis infection which was diagnosed by PCR, and which occurred in a student working for the summer in a research laboratory. Our case illustrates the value of meningococcal PCR in diagnosing meningococcal infections, serogroup determination and penicillin susceptibility and should be available for clinical laboratories. Our case is a reminder that employees who will be handling highly infectious or toxic materials undergo mandatory training in occupational safety measures, and if available, be offered preventative immunization. This is as important for temporary employees as it is for permanent ones and should not be overlooked by Supervisors and by Institutional occupational health and safety offices.

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References