Meningococcal vaccine failure in conjunction with an unusual meningococcal cluster in southern Tasmania

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Abstract

The following is a report of an unusual family cluster of group C invasive meningococcal disease in Tasmania. This unusual case cluster raises several important issues of public health significance regarding vaccine failure and nucleic acid amplification testing use in the setting of invasive meningococcal disease. *Commun Dis Intell* 2005;29:159–163.

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Introduction

Although not common, invasive infection with *Neisseria meningitidis* can be devastating to affected patients and families, and, despite modern treatment, has a case-fatality risk of about nine per cent.[1]

In 2001/2002, there was an outbreak of group C meningococcal disease in Tasmania. In response to this outbreak, a subsidised state-wide polysaccharide ACW135Y vaccination campaign for persons aged 13–30 years was undertaken starting in mid-2002. This program finished in September 2004. The national conjugate group C program commenced in January 2003. At the time of this meningococcal cluster, both vaccination programs were in operation in Tasmania.

The following is a report of an unusual family cluster of group C invasive meningococcal disease.

Index case

In December 2003, a 3½-year-old male presented to the Department of Emergency Medicine (DEM) of a major private hospital in Hobart. He was vaccinated with Menjugate® vaccine eight months prior to presentation. His clinical history was of four days of a febrile illness with fevers to 40° C. Twenty-four hours prior to presentation he developed irritability, neck stiffness and non-blanching red/purple lesions on his lower limbs. When he presented to the DEM he had a temperature of 37.9° C, a purpuric rash on the lower limbs and nuchal rigidity. He was administered ceftriaxone 1-gram IV and benzylpenicillin 600 mg IV before transfer to the DEM of Royal Hobart Hospital, five minutes away by ambulance.

On presentation to the Royal Hobart Hospital he had a Glasgow Coma Score of 14, and a clinical presentation as above. He was given IV fluids and a further 400 mg of benzylpenicillin IV and transferred to the Intensive Care Unit. Investigations demonstrated a normal white cell count, a mild acidosis, and cloudy cerebrospinal fluid (CSF), with a positive latex agglutination for *Neisseria meningitidis.* CSF culture and throat swab were negative for *N. meningitidis* however blood cultures subsequently grew serogroup C *N. meningitidis* sensitive to ceftriaxone, penicillin and rifampicin.

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He continued to have high fevers for the next nine days, in spite of ceftriaxone one g bd IV and benzylpenicillin 900 mg IV every four hours. His temperature eventually settled and he was discharged without sequelae.

His immunisation status was confirmed with his local doctor and appropriate administration and cold chain procedures at the practice were confirmed. The patient subsequently underwent tests for immunological deficiency (including immunoglobulins and complement). These were normal. While the general tests for immunoglobulins were normal, the *Haemophilus influenza* type b IgG (Hib) serology test undertaken during clinical convalescence was less than 0.1 ug/ml, indicating suboptimal short term and long term protection.

This was despite the fact that he had on written evidence three Hib vaccines at two, five and eight months and a booster at 16 months of age.

The patient's three siblings, a 9-year-old male, a 7-year-old male and a 16-month-old female, two parents and two grandparents, were identified as contacts. The 16-month-old had been vaccinated against group C meningococcal disease four months previously. All received chemoprophylaxis with appropriate doses of rifampicin except for the 16-month-old sibling who received 250 mg of ceftriaxone IM. Chemoprophylaxis for the contacts was commenced the day of admission of the index case.

Case 2

Four days after presentation of the index case, the patient's 7-year-old sibling presented with a history of 12 hours of mild respiratory illness, with a 'croupy' cough, low grade fevers, nausea and a fine blanching macular rash spread over most of the back. The patient had completed a 2-day course of rifampicin for chemoprophylaxis two days earlier. Within 12 hours the sibling had developed neck stiffness and mild photophobia. He was assessed in the DEM of the Royal Hobart Hospital, where he was found to have a fever of 39.9 degrees Celsius, a tachycardia of 130, mild nuchal rigidity and mild photophobia. Blood was taken but a lumbar puncture was not performed. The patient was admitted to the paediatrics ward with a provisional diagnosis of upper respiratory tract illness, but a differential diagnosis of meningococcal disease was suggested. The patient was treated with ceftriaxone one gram IV daily and benzylpenicillin 600 mg bd. He had an elevated white cell count with a neutrophilia. His fever settled within 24 hours of antibiotic treatment. His blood cultures were negative but an in-house nucleic acid antigen test (NAAT) was positive for *N. meningitidis.* This child had not been immunised against meningococcal disease.

Case 3

Six days after presentation of the index case, the child's 9-year-old sibling presented with a febrile illness. This child had completed an appropriate 2-day course of rifampicin chemoprophylaxis for meningococcal disease four days earlier. The patient presented to the DEM of the Royal Hobart Hospital with a 24-hour history of fevers, neck stiffness, sore throat, dry cough and non-specific abdominal pain. No photophobia or rash was noted. Physical examination did not demonstrate rash, photophobia or nuchal rigidity. A provisional diagnosis of upper respiratory tract illness was made, however, in view of his contact with a known case of meningococcal disease, blood cultures and NAAT for *Neisseria meningitidis* were requested and a dose of ceftriaxone 1.5 grams IV and benzylpenicillin 1.8 grams IV were given. The patient was discharged home. Blood cultures were negative however the NAAT was positive for *N. meningitidis.* The patient was recalled four days later and received daily ceftriaxone 1.5 grams IV as an outpatient for five days.

At this point the parents and grandparents of the index case were given ciprofloxacin 500 mg as a single dose as further chemoprophylaxis. The immunised 16-month-old infant did not receive further chemoprophylaxis.

Further events

By this stage, the parents of the children were extremely concerned about the safety of the 16-month-old infant and themselves. They requested a blood test be performed on the remaining family members to see if they had evidence of meningococcal infection. The paediatrician who was caring for the children acquiesced.

NAAT performed on blood taken from the father was positive for *N. meningitidis.* The Public Health Unit was contacted to report the father as a case. The father was interviewed and was found to be clinically well. He reported no fever, rash, photophobia or neck stiffness. In view of this he was treated as a suspected, rather than confirmed, case of invasive meningococcal disease. He was referred to the Infectious Diseases Physician at the Royal Hobart Hospital who performed an assessment and found no clinical evidence of invasive meningococcal disease. In view of the positive NAAT result, and family cluster of invasive disease, he was commenced on daily ceftriaxone IM for three days.

The results of the molecular typing performed on the samples confirmed that the molecular type of all subjects was C: 14D4a:P1.5–2, 10–1. Typing was performed by the Melbourne Microbiological Diagnostic Unit.

Discussion

This unusual case cluster raises several important issues of public health significance regarding vaccine failure and NAAT use in the setting of invasive meningococcal disease.

Vaccine failure

This is the first report of a meningococcal serogroup C conjugate vaccine failure in Tasmania. Meningococcal group C vaccine is effective and vaccine failure is rare. Data from the United Kingdom (UK) confirm this and demonstrate that the impact of the introduction of meningococcal serogroup C conjugate vaccines in the UK has been extremely favourable where vaccine coverage has exceeded 80 per cent in all age groups targeted and up to the end of 2001, only 25 confirmed and one probable vaccine failure had been observed.[2]

In the UK, the definition of a vaccine failure to meningococcal disease is as follows:

- True vaccine failure – invasive meningococcal serogroup C disease meeting the case definition for definite serogroup C infection with onset more than 10 days after the last dose of vaccine scheduled for that age group.
- Probable vaccine failure – failure (i.e. probable serogroup C disease meeting the above vaccination criteria) where a person develops invasive serogroup C disease within 10 days of the last dose or before the last scheduled dose.[3]

Risk factors for vaccine failure are not clearly defined but include prematurity and low birth weight, a chromosomal abnormality or other genetic disorder, malignancy, any other underlying medical condition, known IgG deficiency or other immunological abnormality, hyposplenism and ethnic subgroups.[3,4] Subjects are classified as true or probable vaccine failures according to the above case definitions, regardless of the presence of risk factors. According to this definition, the index case in this case series constitutes a true vaccine failure. None of the above risk factors were identified as leading to his vaccine failure.

The phenotype of the organism is another factor that may influence vaccine efficacy. Meningococci have a number of surface antigens. The organism is classified into serogroups, types and subtypes based on the configuration of the surface antigens:

- serogroups – based on variants in the capsular polysaccharide;
- serotypes – based on the *PorB* outer membrane protein variants;
- serosubtypes – based on the *PorA* outer membrane protein variants.[5]

Conjugate vaccine works by priming the immune system to respond to capsular polysaccharide, not the cell wall antigens.[6] Newer vaccines in development are directed against *PorA* regions (in particular, vaccine against 'B' meningococcus), however, this is not relevant to this case.[7,8] The conjugate vaccine given to the index case ordinarily would have provided protection against the organism as the organism was a definite C capsular subgroup.

The index case was tested for complement and immunoglobulin levels, which were normal. The negative Hib serology results may indicate the presence of an IgG subclass deficiency, a possible explanation of this clinical event. However, the patient was not tested for IgG subclass antibodies. In future, if a case of meningococcal vaccine failure is reported, testing for IgG subclass antibodies is recommended.[3,9]

High attack rate

The attack rate for meningococcal disease among untreated household contacts varies between 4.2 and 27.7 per 1,000 subjects.[10,11,12] Chemoprophylaxis reduces the risk of subsequent cases by 89 per cent.[13] In this family, three out of seven household contacts were NAAT positive for testing for the invasive meningococcal strain. Two of the subjects had received rifampicin chemoprophylaxis prior to testing and the third had received both rifampicin and ciprofloxacin prior to testing. Rifampicin resistance has not been reported in Tasmania. In this case, the invasive *Neisseria* strain in the index case was proven sensitive to rifampicin. Rifampicin eliminates, in most instances, the nasopharyngeal carriage of *N. meningitidis* but it is recognised that it may not abort invasive disease if already incubating.[14]

The father of the index case was asymptomatic but NAAT positive. He may have been a case of nasopharyngeal carriage with transient bacteraemia rather than invasive disease. The population rate of nasopharyngeal colonisation with meningococci varies between 10 and 30 per cent.[15,16] Rates of nasopharyngeal colonisation with invasive strains of *N. meningitidis* are much lower than this.[17,18] There are little data on the use of NAAT in the screening of asymptomatic contacts of cases. As this case series illustrates, a positive NAAT result in the absence of clinical symptoms and a negative culture presents a clinical dilemma. A positive result in this setting may represent transient bacteraemia or could be the beginning of invasive meningococcal disease. Due to the precipitous nature of the illness, the clinician in this case was obligated to treat the patient as if he had incipient invasive disease even though it was more likely he did not. It may well be the case that transient and spontaneously resolving bacteraemia is not uncommon amongst this group.

Nucleic acid amplification testing issues

In this case cluster, three out of four subjects had a positive NAAT assay result in the absence of positive blood culture result (throat swabs were not collected). This phenomenon is well recognised. Antibiotic treatment prior to transport or admission to hospital has reduced the proportion of cases of invasive meningococcal disease from which *Neisseria meningitidis* can be isolated by standard microbiological techniques.[19] Identification of meningococci by NAAT is now a common method for detection of evidence of invasive meningococcal disease. The literature reports the sensitivity of the NAAT assay for culture-confirmed cases is between 91 and 98.5 per cent. The specificity of the test is between 76 and 96 per cent based on test results for patients from whom other bacteria were isolated, children with viral meningitis and afebrile negative controls.[20,21]

The NAAT in use at the Royal Hobart Hospital amplifies a region of the *N. meningitidis* insertion sequence, IS *1106*. This is an in-house assay that was adapted from that of Newcombe.[22] The literature reports the sensitivity and specificity of this NAAT assay as ranging from 83–100 per cent and 87–100 per cent respectively. This NAAT has been extensively validated in-house with local data suggesting sensitivity and specificity of 92 per cent and 94 per cent respectively. In addition, all NAAT positive samples were tested using a second genomic target (*PorA*) as part of the typing protocol. All three samples were positive in both NAAT assays. The three NAAT positive/culture negative cases reported here are therefore likely to be genuine.

This is supported in the literature. A study examining the meaning of a positive NAAT for *Neisseria meningitidis* in the presence of a negative culture found that NAAT improves diagnosis. In the study, 35 of 39 patients suspected to have meningococcal meningitis were microbiologically confirmed. Of these, 22 were culture and NAAT positive, three were microscopically and NAAT positive, one was only microscopically positive, and nine were positive only by NAAT. By using NAAT methodology, the number of confirmed diagnoses of meningococcal meningitis increased by 23 per cent compared with those obtained by microscopic observation and culture.[23]

Although the literature demonstrates that NAAT has certainly improved case ascertainment, especially where culture negative or post antibiotics, the evidence is limited to cases who actually had some sort of febrile illness which warranted the test in the first place. Studies of the sensitivity and specificity of NAAT in well subjects are lacking.

Conclusions

Invasive meningococcal disease continues to be an illness of considerable public health importance. According to the UK definition of vaccine failure, this constitutes a true vaccine failure. There was no evidence of hereditary immune deficiency in this case, however, if future cases occur, it would be prudent to perform IgG subclass antibodies as this IgG subclass deficiency could be responsible for failure to mount an immune response to the meningococcal conjugate vaccine. Group C conjugate vaccine failure is rare and efficacy of the vaccine is good.

The use of NAAT has improved diagnosis of invasive disease. Should the father in this case cluster have been tested? There is no easy answer to this. A disease such as invasive meningococcal disease does not always afford the clinician the luxury of time. By the time the signs and symptoms of disease have developed, the pathological processes that lead to death or disability may be well established. The advent of the NAAT test has altered the consequences of precautionary testing. Testing within the broader context in which the illness occurs is an issue still to be resolved, but would appear to remain generally appropriate that such tests only be performed when clinical symptoms warrant it.

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