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# SHORT REPORTS

## Seven-week interval between acquisition of a meningococcus and the onset of invasive disease. A case report

K. R. NEAL[1]*, J. S. NGUYEN-VAN-TAM[1], R. C. B. SLACK[2], E. B. KACZMARSKI[3], A. WHITE[4] AND D. A. A. ALA'ALDEEN[5]

[1] *Department of Public Health Medicine and Epidemiology, University of Nottingham, Nottingham NG7 2UH, UK*
[2] *Nottingham Health, 1 Standard Court, Park Row, Nottingham NG1 6GN, UK*
[3] *PHLS Meningococcal Reference Unit, Public Health Laboratory, Withington Hospital, Manchester M20 2LR, UK*
[4] *Cripps Health Centre, University of Nottingham NG7 2RH, UK*
[5] *Meningococcal Research Group, Division of Microbiology, University of Nottingham, Nottingham NG7 2UH, UK*

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### SUMMARY

Invasive meningococcal disease (IMD) is thought to occur within a few days of pharyngeal acquisition of *Neisseria meningitidis*. During a longitudinal study of carriage and acquisition among 2453 first-year undergraduates we identified a male student from whom *N. lactamica* was isolated in October 1997 followed by *N. meningitidis* in December 1997. In mid-January 1998 this student suffered a mild episode of IMD (meningitis) during which *N. meningitidis* was isolated from his CSF. The meningococcus carried in December 1997 was phenotypically and genotypically indistinguishable from the invading organism, suggesting the possibility that the organism may have been carried for 7 weeks prior to the onset of invasive disease. Further studies are needed to assess more accurately the range of asymptomatic carriage prior to disease onset.

Invasive meningococcal disease (IMD), either meningitis or septicaemia, is believed to occur within a few days of pharyngeal acquisition of *Neisseria meningitidis*. This is supported by evidence from studies of military recruits undergoing regular testing for meningococcal carriage in which all those developing IMD were negative for meningococci on their last swab prior to onset of illness [1, 2] and from laboratory-acquired cases [3]. In addition, it has been shown that meningococci can stop expressing some virulence factors such as capsular polysaccharide during adaptation to long-term colonization [4]. We report a case where a meningococcus was isolated from an asymptomatic patient 7 weeks prior to the onset of meningococcal meningitis.

In October 1997 pharyngeal swabs were taken from 2453 first-year university undergraduates during the first week of term as part of a study to investigate acquisition and carriage of meningococci. These students attended a traditional campus-based university with nearly 2000 catered hall places and an annual incidence of IMD during the academic years 1994–9 of 19·6 per 100000. In November and December randomly sampled groups of students in halls of residence were re-swabbed. Pharyngeal swabs were plated immediately onto a selective plate: GC agar (Oxoid) containing vancomycin, colistin, nystatin and trimethoprim and cultured using routine methods.

* Author for correspondence.

During the academic year 1997/8, three first-year students developed microbiologically confirmed invasive meningococcal disease caused by unrelated strains after recruitment to the study. One of these was a 19-year-old male who developed acute signs and symptoms of meningitis on 22 January 1998. His illness was characterized by no decrease in conscious level, no haemodynamic disturbance and a rapid response to parenteral antibiotics. In his CSF, 1000 polymorphs/ml were seen in addition to Gram negative diplococci.

The student had been swabbed twice previously and was shown to have been carrying *N. lactamica* on 1 October 1997 and a meningococcus on 5 December 1997. When this isolate was compared by the Meningococcal Reference Unit (Manchester PHLS) with the infecting meningococcus isolated from CSF on 22 January 1998, the strains were found to be phenotypically indistinguishable: *Neisseria meningitidis* B: NT:P1.4 with identical penicillin, rifampicin, ciprofloxacin and sulphonamide MICs.

Additional characterization was carried out by pulsed field gel electrophoresis of *Spe1* digests (PFGE) and sequencing of the *porA* [5] and *dhps* [6] genes. Multilocus sequence typing (MLST) was undertaken at the National Institute for Biological Standards and Control (NIBSC), Potters Bar, UK [7]. The two strains produced identical PFGE patterns, the *porA* and *dhps* gene sequences of the two isolates were identical, as were alleles at the loci examined as part of MLST.

No antibiotics had been prescribed to this student between his starting university in October 1997 and developing invasive disease in January 1998. Paired sera taken 6 weeks apart demonstrated no evidence of recent infection with any of the influenza (A or B) viruses, adenovirus, psittacocisis/LGV, *Coxiella burnetii*, RSV, mycoplasma, herpes simplex, varicella/zoster, CMV, measles or mumps. Though insufficient serum from an admission blood specimen was available for testing, the PHLS Meningococcal Reference Unit used an in-house assay to show an antibody titre against serogroup B meningococcal polysaccharide of 1363 units per ml in a convalescent serum taken on 5 March 1998 ($>$ 1000 units/ml is typically seen following recent infection) demonstrating an effective humoral response to this antigen.

There was no history of underlying disease or previous increased susceptibility to infectious diseases as a child and no health problems were noted in the 18 months after his illness. Complement activity as assessed by the $CH_{50}$ test was normal. Lymphocyte counts were within expected ranges and subset proportions were normal.

This case demonstrates the onset of invasive meningococcal disease 7 weeks after carriage of an indistinguishable meningococcus in the nasopharynx. One of a number of possible scenarios may have occurred. It is recognized that asymptomatic carriage of meningococci can be prolonged but also that changes in the predominant carried strains occur [8]. The supposition is that this patient carried his strain asymptomatically and that it subsequently invaded. It is possible, however, that the patient cleared the meningococcus naturally and then became re-infected from another source with an indistinguishable strain. This latter sequence of events is thought unlikely since, of 963 students swabbed in December 1997, none was carrying the phenotypically identical strain B:NT:P1.4. Whereas five other students carried *N. meningitidis* B:4:P1.4.

The finding that the patient had carried *N. lactamica* in October is interesting and indicates that protective immunity is not reliably induced by this means. The widely perceived view that carriage of meningococci lasting beyond a few days protects against invasion by the same strain is also not supported by the case we report, though the mild disease experienced in this case may reflect partial immunity induced by earlier carriage of either or both organisms.

Recent respiratory infections with pathogens such as influenza [9] have been associated with invasive meningococcal disease. However, the patient's clinical history and serology results showed no evidence of any recent respiratory tract infections that could have predisposed to invasion by the meningococcus or have been responsible for immune anergy.

A long period of meningococcal carriage before the onset of clinical illness may be more common than is generally thought as there are few published longitudinal studies of carriage which have been powerful enough to detect this phenomenon. More longitudinal studies in high-risk populations would help to determine how often IMD is preceded by a long period of nasopharyngeal carriage.

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