A cluster of meningococcal disease caused by rifampicin-resistant C meningococci in France, April 2012

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In April 2012, a cluster of two cases of meningococcal disease caused by rifampicin-resistant C meningococci was reported in the Champagne-Ardenne region, France. The two cases occurred in a student population living in the same town but studying at different schools. Bacteriological and epidemiological investigations of cases have shown that the isolates of both cases were non-differentiable.

Background

Neisseria meningitidis is a strictly human bacterium encountered in the pharynx in about 10% of the general population (asymptomatic carriage) [1]. This bacterium can also cause severe infections (mainly septicemia and meningitis) [2].

In France, the annual incidence of invasive meningococcal disease (IMD) varies between 0.9 and 1.5 cases per 100,000 population. Cases are mainly due to meningococci of serogroup B and C (65% and 27% respectively for the last 10 years) [3]. Chemoprophylactic treatment with rifampicin is particularly useful in preventing secondary cases among close contacts of a patient with IMD and in stopping the spread of pathogenic N. meningitidis. Rifampicin is recommended as first-line agent for chemoprophylaxis among contacts of patients with IMD in several European countries [4]. The efficacy of the chemoprophylaxis is usually estimated by the reduction of carriage rate of meningococci. This reduction has been reported to range between 82% and 98% at 7–14 days of follow-up [5–7]. Resistant meningococcal isolates may emerge among 10–27% of treated carriers [8, 9]. However, several studies have reported that rifampicin resistance is rare in invasive meningococcal isolates [10]. According to the annual report of the National Reference Center for Meningococci (NRCM) in Paris, the incidence of rifampicin-resistant meningococci isolated in France averages one per year with no expansion of these isolates and no secondary case [11]. We describe here the detection of a cluster of two cases of rifampicin-resistant C meningococci that were reported in the Champagne-Ardenne region, France in 2012.

Case reports

A student in his early twenties (Case one) presenting with signs of meningitis was admitted mid-April 2012 to a hospital, in the Ile-de-France region. The case who lived and studied in a town in the Champagne-Ardenne region, close to the Ile-de-France region, was immediately treated with cefotaxime and amoxicillin. Cultures of the patient's cerebrospinal fluid (CSF) and blood taken upon admission, yielded serogroup C meningococci. Following the French recommendations [12], rifampicin was recommended to the family and other close contacts three days hereafter, when the health agency in the Champagne-Ardenne region had received the notification. In addition to rifampicin, vaccination with meningococcal C conjugate vaccine was recommended for household contacts.

Eleven days after the notification of Case one, the health agency in the Champagne-Ardenne region received another notification of IMD. A student in his late teens (Case two) had been admitted the day before with signs of meningitis to a hospital, in the Champagne-Ardenne region and was immediately treated with cefotaxime and amoxicillin. Case two lived and studied in the same city as Case 1 but attended a different school, The CSF and blood cultures of Case two also yielded serogroup C meningococci.

Family and close contacts of Case two were given the same recommendations as those of Case one. On the second day after admission of Case two, antibiotic sensitivity testing results showed that the strain was rifampicin-resistant. As a result, chemoprophylaxis for contacts was recommended to be repeated with ciprofloxacin or ceftriaxone [12].

At the same time, the health agency in the Champagne-Ardenne region was informed that the strain of Case

one was also rifampicin-resistant. However, it was then too late (delay >10 days), according to the French recommendations [12], to repeat chemoprophylaxis with ciprofloxacin or ceftriaxone for the contacts of the Case one.

Epidemiological investigations found that Case two had attended a party organised by the schoolmates of Case one two days after admission of the first case.

Molecular typing

Strains of both cases were sent to the NRCM in Paris where phenotyping and genotyping was performed and rifampicin resistance confirmed. The characterisation by multilocus sequence typing, PorA variable regions, penA, FetA showed that the isolates were non-differentiable. The antigenic formula (serogroup: serotype: subtype) was C: NT: P1.7, 1. The genetic typing showed PorA VR1=7-1, VR2=1, FetA= F3-6 and *penA3*, and the strains were of the sequence type ST-11 (clonal complex ST-11). The resistance was due to the same mutation in the *rpoB* (D542V) that was previously reported to confer resitance to rifampicin [9]. A retrospective analysis revealed that in March 2012, a strain with identical markers had been isolated in a neighbouring region to the Champagne-Ardenne region. The patient was also a student, but we found no epidemiological link with the first and second cases described in this report.

Discussion and conclusion

In April 2012, at an approximate interval of 10 days, we observed two cases of IMD caused by rifampicin-resistant C meningococcus in students in the Champagne-Ardenne region. Failure of chemoprophylaxis, due to antibiotic resistance, could lead to the occurrence of secondary cases [13–15]. Therefore, the use of rifampicin in chemoprophylaxis against already resistant bacteria creates a positive selection for resistant strains that may then provoke secondary cases. The detection of the cluster of two cases with non-differentiable isolates of rifampicin-resistant C meningococci suggests the possible carriage and circulation of the ST-11 strain in the student population of the Champagne-Ardenne region.

We could assume that Case one could have transmitted *N. meningitidis* to one or more of his contacts before admission. Contacts of Case one could then have transmitted it to Case two during the party organised on 18 April.

Indeed, ST-11 serogroup C isolates (rifampicin susceptible) have been circulating in the northwestern part of France during the last two years in particular among student populations (unpublished data). This circulation and the repeated use of rifampicin in chemoprophylaxis may have accounted for the selection of rifampicin resistant ST-11 serogroup C isolates. Our detection of a case in a neighbouring region to the Champagne-Ardenne region in March 2012 (but unlinked to the reported cluster) due to rifampicin resistant ST-11 serogroup C isolates is in accordance with the hypothesis of the selection of rifampicin-resistant strain [10].

It is worth to note here that ST-11 isolates belonged to a hyperinvasive genotype that was one of the reasons to recommend systemic vaccination in France in 2009 among 1-24 year-olds, which has now been implemented [16, 17]. Our report underlines the need to monitor antibiotic resistance and both bacteriological and epidemiological investigations of cases even without obvious historical links in order to adapt chemoprophylaxis to the resistance profile of locally circulating strains.

To date, no new case of IMD had been notified in the local student population. Concerning this population, it is recommended to administer ciprofloxacin or ceftriaxone as chemoprophylaxis as soon as possible to protect contacts by reducing carriage of the strain if a new case of IMD occurs. This is recommended by the French High Council for Public Health on 16 April, 2012 [18]. The French recommendations insist on the importance of vaccination against C meningococcus using meningococcal C conjugate vaccine in 1-24 year-olds. The occurrence of IMD is an opportunity to remind the population and physicians of this recommendation [17, 19].

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