Horizontal transmission of the Leningrad–Zagreb mumps vaccine strain: A report of six symptomatic cases of parotitis and one case of meningitis

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A B S T R A C T

Here we report horizontal symptomatic transmission of the Leningrad–Zagreb (L–Zagreb) mumps vaccine virus. Children who were the source of transmission had been vaccinated with the MMR vaccine (Serum Institute of India) contained L–Zagreb mumps virus. This is the first report of horizontal symptomatic transmission of this vaccine. The etiology of all seven contact cases was confirmed by epidemiological linking, serology and by F, SH, NP and HN mumps virus genes sequencing.

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1. Introduction

In Belarus a mandatory single dose of mumps vaccine was instituted in 1986 and a two-dose mandatory regimen (first dose at 12–24 months of age, second dose at 6–7 years of age) – in 1999. Since 1986, one-dose mumps-containing vaccine coverage in Belarus has ranged from 93% to 95% and for two-dose coverage has ranged from 93% to 98%. In response to the widespread use of a two dose mumps-containing vaccine regimen, the number of notified cases of mumps in Belarus has declined significantly from 190 cases per 100,000 population in the year 2000 to less than 1 case per 100,000 population upon last reporting in 2010. There has been some shift in the age distribution of mumps cases in Belarus toward the older age’s vaccinees since 2002 year [1,2]. The Russian monovalent vaccine containing the Leningrad–3 (L-3) mumps virus (MuV) strain was used until 1996, then the “Trimovax” vaccine, containing the Urabe AM-9 MuV strain, produced by Sanofi Pasteur, was used [1]. Since 2006, the MMR vaccine produced by Serum Institute of India containing the L–Zagreb MuV has been used.

Horizontal transmission of the L–Zagreb vaccine produced by the Institute of Immunology of Zagreb has been reported [3–5]. Here we report L–Zagreb vaccine virus transmission from recent recipients of the Serum Institute of India’s vaccine to close family contacts. To our knowledge this is the first report of horizontal transmission of the L–Zagreb vaccine produced by the Serum Institute of India. Earlier, L–Zagreb vaccine produced by Serum Institute of India has been found to cause mumps virus-specific adverse events, and vaccine virus has been isolated from such cases [6–10].

2. Subjects

A total of seven cases of symptomatic mumps as a result of horizontal transmission are reported here. These cases were identified between January 2010 and April 2011 in Minsk, Belarus. During this time period, 50 cases of mumps were reported in Minsk (41 cases in 2010 and 9 in the first 4 months of 2011) [11]. The seven persons acquiring mumps by horizontal transmission are referred to here as the “patients”. Six of the seven patients were adults (5 mothers and one father). The seventh patient was a 4-year-old boy. All seven patients were exposed to a child in the house vaccinated 17–34 days prior to symptom onset in the patients. Informed consent was received from all adult patients and from the parents of the one
Table 1
Data of mumps patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Status (year)</th>
<th>Source of infection</th>
<th>Time frame&lt;sup&gt;a&lt;/sup&gt; (days)</th>
<th>Clinical presentation</th>
<th>Serum IgM</th>
<th>Serum IgG&lt;sub&gt;1&lt;/sub&gt;/IgG&lt;sub&gt;2&lt;/sub&gt; (titer)</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>26</td>
<td>F</td>
<td>V (1986)</td>
<td>Daughter</td>
<td>31</td>
<td>Unilateral parotitis</td>
<td>+</td>
<td>-/1:1200</td>
<td>*oral fluid, throat swab</td>
</tr>
<tr>
<td>P2</td>
<td>28</td>
<td>F</td>
<td>V (1986)</td>
<td>Daughter</td>
<td>21</td>
<td>Fertility unilateral parotitis</td>
<td>+</td>
<td>-/1:1300</td>
<td>*oral fluid, urine</td>
</tr>
<tr>
<td>P3</td>
<td>31</td>
<td>F</td>
<td>NV</td>
<td>Son</td>
<td>34</td>
<td>Bilateral parotitis</td>
<td>+</td>
<td>-/1:2000</td>
<td>*(oral fluid)</td>
</tr>
<tr>
<td>P4</td>
<td>30</td>
<td>F</td>
<td>NV</td>
<td>Son</td>
<td>29</td>
<td>Fertility, bilateral parotitis, meningitis, pancreatitis</td>
<td>+</td>
<td>1:400/1:1200</td>
<td>*(urine, throat swab, CSF)</td>
</tr>
<tr>
<td>P5</td>
<td>32</td>
<td>M</td>
<td>NV</td>
<td>Son</td>
<td>32</td>
<td>Unilateral parotitis</td>
<td>+</td>
<td>-/1:800</td>
<td>*(throat swab)</td>
</tr>
<tr>
<td>P6</td>
<td>39</td>
<td>F</td>
<td>NV</td>
<td>Son</td>
<td>30</td>
<td>Fertility, bilateral parotitis</td>
<td>+</td>
<td>-/1:2400</td>
<td>*(oral fluid, throat swab, urine)</td>
</tr>
</tbody>
</table>

IgG<sub>1</sub>, IgG in sera collected within 1–4 days after the first symptoms developed; IgG<sub>2</sub>, IgG in sera collected 9–11 days after the first serum sample was taken.

<sup>a</sup> Time frame between the date of the first symptom developed and the date of the contact immunization.

<sup>b</sup> 17 days after the immunized contact developed acute parotitis.

child patient. Other than the aforementioned household contacts, the patients in our study had no other known contacts with persons exposed to mumps in the previous 2-month period. The most likely source of the virus was the 12–21-month-old children residing in the household who were recently vaccinated with the MMR vaccine produced by Serum Institute of India. Two of the adult patients (P1 and P2) were previously vaccinated during childhood with the Russian monovalent mumps vaccine L–3. Patient P7 (the 4-year-old boy) had previously been vaccinated with the “Trimovax” vaccine (Sanofi Pasteur) (Table 1). None of the seven patients had a history of mumps infection in the past.

Six of the seven source children vaccinated with L–Zagreb displayed no mumps symptoms post-vaccination according to the available medical records. The seventh child (contact of P7) developed unilateral parotitis within 2 weeks of vaccination.

3. Methods

Paired sera from all patients were tested in parallel. Serological detection of anti-mumps virus IgM and IgG antibodies was determined using the commercially available Enzygnost ELISA (Anti-parotitis-virus/IgM and anti-parotitis-virus/IgG, Siemens Healthcare Diagnostics Products, Marburg, Germany). A differential diagnosis was made by testing the paired sera for IgG antibodies to parainfluenza virus types 1–3 (Novagost Parainfluenza 1/2/3 IgG) and IgM antibodies to Epstein–Barr virus (Enzygnost Anti-EBV/IgM).

Mumps virus infection was confirmed by RT-PCR of RNA extracted directly from clinical specimens (throat swabs, oral fluid, urine and/or CSF) using QIAGEN RNeasy mini kit (Qiagen, Germany). Purified RNA was reverse transcribed using Senscript RT kit (Qiagen, Germany) with random hexamers (dN6) as described by the manufacturer. The resultant cDNA was amplified by nested PCR to obtain DNA fragments, representing full length F, SH, NP and HN genes with specific primers, as described earlier [12]. The purified final products were directly sequenced using PCR primers [12]. Sequencing reaction was performed with the CEQ 2000 Dye Terminator Cycle Sequencing Kit (Beckman Coulter, USA) and (Beckman Coulter, USA) according to manufacturer’s instructions. Obtained sequences were analyzed using Vector NTI v. 10.0 (InforMax, Bethesda, MD) software package. In parallel, the L–Zagreb vaccine (same genes) was sequenced from three vaccine lots used to vaccinate the presumed sources of virus transmission (the seven children listed in Table 1). These lots were acquired from the relevant public health authority.

4. Results

The clinical presentation of the mumps patients is summarized in Table 1. Six of the seven patients had typical signs of mumps such as fever and/or parotitis.

One patient, a 30-year-old female (P4) had a severe course of infection and was hospital admitted as having bacterial meningitis. Blood test showed elevated level of neutrophils (30%). Computer tomography of brain revealed no abnormalities. A lumbar puncture revealed pleocytosis (586 cells/μl, 80% neutrophils) of the cerebrospinal fluid (CSF). The patient was administered symptomatic care as well as ceftriaxone. On day 4 after admission, the patient remained febrile and complained of severe headache; neck stiffness and Kernig’s sign were still notable; nausea and vomiting developed. On day 5 the patient developed unilateral parotitis and 2 days later she developed bilateral parotitis. A second lumbar puncture revealed lymphocytosis of CSF – 784 cells/μl (94% lymphocytes). Abnormal laboratory findings included blood lymphocytosis (55%), elevated amylase 97 U/l (normal range 80 U/l) and elevated ESR, 24 mm. Abdominal ultrasound showed a distended, thick-walled edematous gallbladder. The clinical diagnosis of acute mumps infection complicated by meningitis, pancreatitis and acute acalculous cholecystitis was made. The patient continued to receive symptomatic treatment and on day 5 ceftriaxone was changed to levofloxacin. Clinical improvement was noted on day 9, when the patient revealed no Kernig’s sign and stiff neck. A third lumbar puncture (day 13) showed significant improvement, 144 cells/μl (90% lymphocytes). On day 17 the patient was discharged in a good condition with no complaints.

Clinical specimens from patients were positive for MuV RNA by RT-PCR as shown in Table 1. Complete nucleotide sequences of F, SH, NP and HN genes of MuV were obtained from the specimens, as well as from the identified vaccine lots’ samples. Sequencing of all examined RT-PCR products from the vaccine lots and clinical specimens identified the virus as the L–Zagreb mumps vaccine strain and were identical to the sequences available in GenBank for F, SH, NP and HN genes of L–Zagreb vaccine strain by Serum Institute of India (GenBank accession numbers AM181760, AM076488, AJ937822 and AY583323 correspondingly).

5. Discussion

To the best of our knowledge until now there have been only few reports of symptomatic disease developed as a consequence of horizontal transmission of mumps vaccine strains [1,3,4,12,13]. Sawada
et al. described in 1993 [13] a horizontal transmission of the Urabe AM9 vaccine strain from a symptomatic vaccinee to her younger sister, and recently, horizontal transmission of the L-3 mumps vaccine strain from healthy vaccinees to six previously vaccinated contacts resulting in symptomatic infection has been described [12]. Neither neurological, nor other extrasympathetic abnormalities were seen among those patients, and none of them had to be hospitalized. All cases occurred in children [12,13]. Recently, Kaic et al. [3,5] and Tesovic [4] described the first virologically confirmed cases of symptomatic mumps following horizontal transmission of L–Zagreb MuV vaccine strain (Institute of Immunology, Inc., Zagreb, Croatia) in adults. The data suggest that the L–Zagreb MuV vaccine strain can be transmitted horizontally, causing parotitis, as well as extrasympathetic manifestations of the disease including meningitis, even among previously vaccinated subjects.

Here we describe seven additional cases of horizontal transmission of L–Zagreb MuV vaccine strain, but these are distinct from previous reports in that (1) the vaccine in question was produced from the Serum Institute of India and (2) severe symptoms were identified in at least one case.

We support the hypothesis that horizontal transmission of the mumps vaccine is not rare [3,4,7,13,14], but rather rarely recognized as mumps virus often produces a subclinical infection in vaccinees. The rate of vaccine virus transmission may depend on population susceptibility (e.g., unvaccinated contacts, waning immunity), but also may be a consequence of the properties of the vaccine virus itself, such as its titer. A 2-fold difference in mumps vaccine potency has been suggested as biologically significant for mumps vaccine virus transmission [12]. According to the Serum Institute of India vaccine product license, mumps virus concentration per dose is not less than 5000 CCID50 (3.7 log10); however, a maximum titer per dose is not stated. In our investigation of four MMR vaccine lots used in Minsk within the same period but not associated with horizontal transmission had potencies ranging from 4.62 to 4.70 log10, with a mean value of 4.65 ± 0.23 log10. This is approximately half the potency of the three lots associated with horizontal transmission in our study (range: 4.87–5.00 log10; mean: 4.92 ± 0.20 log10, p < 0.04). It is interesting that the vaccinees who were the source of the horizontal transmission did not develop mumps-specific symptoms. One explanation could be that the vaccine virus may have acquired changes during its replication in the vaccinees that result in an increased potential for virulence, as was suggested earlier [12]. Support for this notion would require complete nucleotide sequencing of the clinical isolates and a comparison to the input virus sequence. Notably, we did not find any sequence changes in the four virus genes assessed.

It should be pointed out that only a few cases of symptomatic vaccine virus transmission were identified in our study. Clearly, the benefit of vaccination outweighs the very low risk of symptomatic vaccine virus transmission. However, this report highlights the value in monitoring household contacts of vaccinated persons, particularly during the first month post-vaccination, and particularly adults who may not have been vaccinated or whose immunity may have waned.

References