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Title:

Anti-mumps IgM antibody positive rate with sudden sensorineural hearing loss using second-generation enzyme immunoassay: a retrospective, multi-institutional investigation in Hokkaido, Japan

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## **Abstract**

### **Objective**

Although elevated anti-mumps IgM antibody levels were reported in 5.7%–7.2% of Japanese patients with sudden sensorineural hearing loss (SSNHL), there were several reports of false-positive cases, such as the continually IgM positive case and the IgM positive case in normal adults. To improve specificity, the new enzyme immuno assay (EIA) anti-mumps IgM antibody measurement kit was introduced in December 2009. This study re-examined the frequency of anti-mumps IgM antibody test positivity with SSNHL using the new measurement kit and compared the results with those from a previous report that used old kit.

### **Methods**

This is a retrospective multi-institutional study involving patients diagnosed with SSNHL who exhibited the anti-mumps IgM antibody. We compared the positive rate of anti-mumps IgM antibody and the annual average number of mumps cases per sentinel in Hokkaido between the patients in the present study and patients previously evaluated.

### **Results**

Overall, 100 patients with SSNHL were enrolled. One case (1.0%) was positive for anti-mumps IgM antibody. Of the 69 patients evaluated in the previous study, 5 cases (7.2%) were positive for anti-mumps IgM antibody. The positive rate of the anti-mumps IgM antibody in the present cases was significantly lower than that previously reported ( $p = 0.042$ ). The annual average number of mumps cases per sentinel in Hokkaido of the present and previous surveillance period was 34.47 and 42.77, respectively; no significant difference was seen in these data ( $p = 0.4519$ ).

### **Conclusion**

The present study revealed that 1.0% of SSNHL was positive for the anti-mumps IgM antibody using the new EIA-IgM measurement kit. After the introduction of the new EIA-IgM measurement kit, anti-mumps IgM antibody positive rate with SSNHL significantly decreased, indicating that the proportion of asymptomatic mumps among etiology of SSNHL may be lower than those previously reported.

### **Keywords**

Mumps deafness; Asymptomatic mumps; Anti-mumps IgM antibody; Sudden

sensorineural hearing loss (SSNHL); Vaccination

## **Introduction**

Mumps, a common childhood infection caused by the mumps virus, is characterized by swelling of the parotid gland[1]. Aseptic meningitis, encephalitis, pancreatitis, sensorineural hearing loss, orchitis, and oophoritis are common complications of mumps, which can occur in adults.

Detection of virus-specific IgM antibody is a useful means for definitive diagnosis. Mumps is an acute viral infection that does not present persistent infection except in the rare case of encephalitis[2]. Some reports suggest that the anti-mumps IgM antibody can be reliably detected by the onset of clinical disease[3] and the anti-mumps IgM antibody becomes negative after several months.

Previous studies in Japan demonstrate that the anti-mumps IgM antibody level is elevated in 5.7%–7.2% of patients with sudden sensorineural hearing loss (SSNHL)[4–6]. Such SSNHL was judged to be caused by asymptomatic mumps infection, which did not show any symptoms of parotitis. Additionally, 22.4% of patients were reportedly diagnosed with hearing loss due to asymptomatic mumps infection based on the anti-mumps IgM antibody level in the sera[7] according to criteria for diagnosis of mumps deafness established by Acute Severe Hearing Loss Study Group of the Japanese Ministry of Health, Labor and Welfare in 2013 (Table 1)[8].

In Japan, the anti-mumps IgM antibody in the sera was measured by enzyme immuno assay (EIA), and a measurement kit manufactured by Denka Seiken Co., Ltd. has been widely used on a commercial basis. However, SSNHL case with persistent positivity of the anti-mumps IgM antibody for over a year was reported[9]. Furthermore, 4.0% of normal adults who did not show any clinical signs of mumps were reportedly positive for anti-mumps IgM antibody[10]. These reports have raised the suspicion of existence of false-positive cases in the patients diagnosed with hearing loss due to asymptomatic mumps infection.

Continually IgM positive case and the IgM positive case in normal adults were detected only when the Denka Seiken Co., Ltd. kit was used; therefore, upgrading the measuring kit for anti-mumps IgM antibody has been demanded to reduce the nonspecific positive cases. Therefore, the new EIA-IgM measurement kit with

improved specificity was introduced in December 2009 by Denka Seiken Co., Ltd. Some reports already indicated that the cutoff value of the new EIA-IgM kit matched the clinical course well compared with that of the old kit[11]. In the present study, we re-examined the frequency of anti-mumps IgM antibody test positivity with SSNHL using the new EIA-IgM measurement kit and compared with previous findings based on the older kit.

## **Materials and Methods**

### **Patients**

This is a retrospective, multi-institutional study with patients diagnosed with SSNHL who exhibited the anti-mumps IgM antibody at the Otorhinolaryngology departments of five hospitals in Hokkaido between January 2010 and October 2016. This study design adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board at each participating hospital (IRB No.017-0130).

Patients who satisfied the criteria for acute low-tone hearing loss established by Acute Severe Hearing Loss Study Group of the Japanese Ministry of Health, Labor and Welfare on 2011[12] were excluded. It was reported that the sensitivity of the new EIA-IgM measurement kit did not reach 100% within 2 days of the onset and reached 100% on day 3 or subsequent days for unvaccinated patients with acute parotitis in whom the mumps virus was isolated from saliva[11]. Thus, patients whose interval between the date of onset and blood test was within 2 days were excluded from this analysis.

### **Anti-mumps IgM antibody evaluation**

The anti-mumps IgM antibody in the sera was measured using a new EIA-IgM measurement kit of Denka Seiken Co., Ltd. The sample was added to the anti-human IgM solid-phased plate first. Next, the mumps virus antigen was added, and it combined with the viral antigen specific IgM antibody in caught IgM. Subsequently, the peroxidase-labeled antiviral antibody was added. Finally, substrate was added and mumps virus-specific IgM was measured as enzyme activity. The results were expressed as antibody indexes and evaluated as follows: <0.80, negative; 0.80–1.20, indeterminate; >1.20, positive.

### **Severity classification**

Hearing results at the patient's first visit were assessed following a grading

system for sudden deafness established by the Research Group on Sudden Deafness of the Japanese Ministry of Health and Welfare[13]. The pure tone average was calculated as the mean of thresholds at 0.25, 0.5, 1, 2, and 4 kHz and classified into four grades: Grade 1, <40 dB; Grade 2, 40–60 dB; Grade 3, 60–90 dB; Grade 4, ≥90 dB.

### **Incidence rate of mumps**

In Japan, mumps is designated as a sentinel-reporting disease by the Japanese Ministry of Health, Labor and Welfare, and weekly cases of mumps per sentinel by prefecture has been reported since 1981. Herein, we calculated the annual average number of mumps per sentinel in Hokkaido according to the reports of National Epidemiologic Surveillance of Infections Disease.

### **Statistical analysis**

We compared the positive rate of anti-mumps IgM antibody between the patients in the present study and 69 patients with SSNHL previously evaluated in Hokkaido between February 1992 and December 1999[6] as a historical control using Fisher's exact test. The anti-mumps IgM antibody of the previous 69 patients was measured using the old measurement kit. In addition, we compared the annual average number of mumps cases per sentinel in Hokkaido between the present surveillance period (2010–2016) and previous surveillance period (1992–1999) using Mann–Whitney U test. Statistical analysis was performed using JMP pro 12 (SAS Institute, Inc., Cary, NC, U.S.A.), with  $p < 0.05$  chosen as the measure for statistical significance.

### **Results**

Overall, 100 patients with SSNHL were enrolled. Of them, 51 patients were male and 49 were female, with a mean age of 57 years (range, 14–85 years). The interval between the date of onset and blood test was 2–54 days (mean, 8 days). An average hearing level of all 100 cases at their first visit was 66.7 dB (Grade 1: 12 cases; Grade 2: 33 cases; Grade 3: 37 cases; and Grade 4: 18 cases). One case (1.0%) was positive and two (2.0%) were indeterminate for anti-mumps IgM antibody. The indeterminate cases were not re-examined.

Of the 69 patients evaluated in the previous study, 42 were male and 27 were female, with a mean age of 42 years (range, 4–81 years). The interval between the date of onset and blood test was 0–63 days (mean, 4 days). An average hearing level of all 69 cases at their first visit was 74.4 dB (Grade 1: 5 cases; Grade 2: 10 cases; Grade 3: 39

cases; and Grade 4: 15 cases). Five cases (7.2%) were positive and two (2.9%) were indeterminate for anti-mumps IgM antibody. The indeterminate cases were not re-examined[6].

The positive rate of the anti-mumps IgM antibody in the present 100 cases was significantly lower than that in the past 69 cases ( $p = 0.042$ ) (Table 2). The annual average number of mumps cases per sentinel in Hokkaido of the present and previous surveillance period was 34.47 and 42.77, respectively, and no significant difference was seen in these data ( $p = 0.4519$ ) (Fig. 1).

## Discussion

In the present study, we assessed the anti-mumps IgM antibody positive rate with SSNHL using the new EIA-IgM measurement kit and compared the results with the previous report that used the old measurement kit. Of the 100 SSNHL patients, one case (1.0%) was positive for anti-mumps IgM antibody. This case was believed to be sensorineural hearing loss due to asymptomatic mumps. The positive rate of the anti-mumps IgM antibody in the present cases was significantly lower than that of the previous report (7.2%) ( $p = 0.042$ ).

Various factors that may have influenced the decrease of the anti-mumps IgM antibody positive rate with SSNHL should be taken into consideration. First, because the specificity of the old measurement kit was lower than that of the new kit, false-positive cases may have been captured in the previous study. Second, the sensitivity of the new measurement kit was lower than that of the old kit; therefore, false-negative cases may have been captured in the present study. Last, the incidence rate of mumps in the present surveillance period may be lower than that of the previous surveillance period.

Ihara *et al* compared the sensitivity and specificity of the new EIA-IgM measurement kit with that of the old kit for unvaccinated patients with acute parotitis in whom the mumps virus was isolated from saliva[11]. They reported that the sensitivity and specificity of the new kit were 79.2% and 86.4%, respectively, and those of the old kit were 91.1% and 81.8%, respectively, indicating the drop in the sensitivity of the new kit. However, they also noted that the sensitivity of the new measurement kit reached 100% on day 3 or subsequent days. Patients, the interval between the date of onset and blood test of which was within 2 days, were excluded from present analysis. Therefore,

the decrease of sensitivity may not influence the present anti-mumps IgM antibody positive rate.

In addition, although the annual average number of mumps per sentinel in Hokkaido in the present surveillance period was slightly lower than that of the previous surveillance period, no significant difference was found among both periods ( $p = 0.4519$ ). Therefore, the incidence rate of mumps among surveillance periods may not affect the decrease of the present anti-mumps IgM antibody positive rate.

Thus, the present study indicates that non-mumps cases existed in the previous cases that had been diagnosed as hearing loss due to asymptomatic mumps. In other words, because false-positive cases were excluded, the present anti-mumps IgM antibody positive rate was lower than the previous one.

There is no doubt that a certain number of patients with sensorineural hearing loss due to asymptomatic mumps exist. Sensorineural hearing loss due to mumps is typically profound, and hearing prognosis is quite poor[7,14,15]. Mumps infection is preventable by vaccine, and mumps vaccination is almost universally used in developed countries. However, routine vaccination against mumps in Japan is not yet performed for historical reasons[15]. Present data shows that outbreaks of mumps in Hokkaido have remained uncontrolled, and the introduction of routine vaccination against mumps is strongly recommend.

There are some limitations of our study. First, the present study was a retrospective study. Second, this study compared patients in the present study to a historical control; therefore, the number of patients and the severity of hearing impairment differed between the present and the previous cases. Moreover, the comparison among the anti-mumps IgM antibody tests was not made under the same patients. To reveal the proportion of asymptomatic mumps among etiology of SSNHL, further investigations are required for the evaluation of a large number of samples by a nationwide prospective survey.

## **Conclusion**

The present study revealed that 1.0% of SSNHL was positive for the anti-mumps IgM antibody using the new EIA-IgM measurement kit. After the introduction of the new EIA-IgM measurement kit, anti-mumps IgM antibody positive rate with SSNHL significantly decreased. The present study indicates that the proportion of

asymptomatic mumps among etiology of SSNHL may be lower than that of previous reports.

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### **Conflict of interest**

The authors declare no conflict of interest associated with this manuscript.

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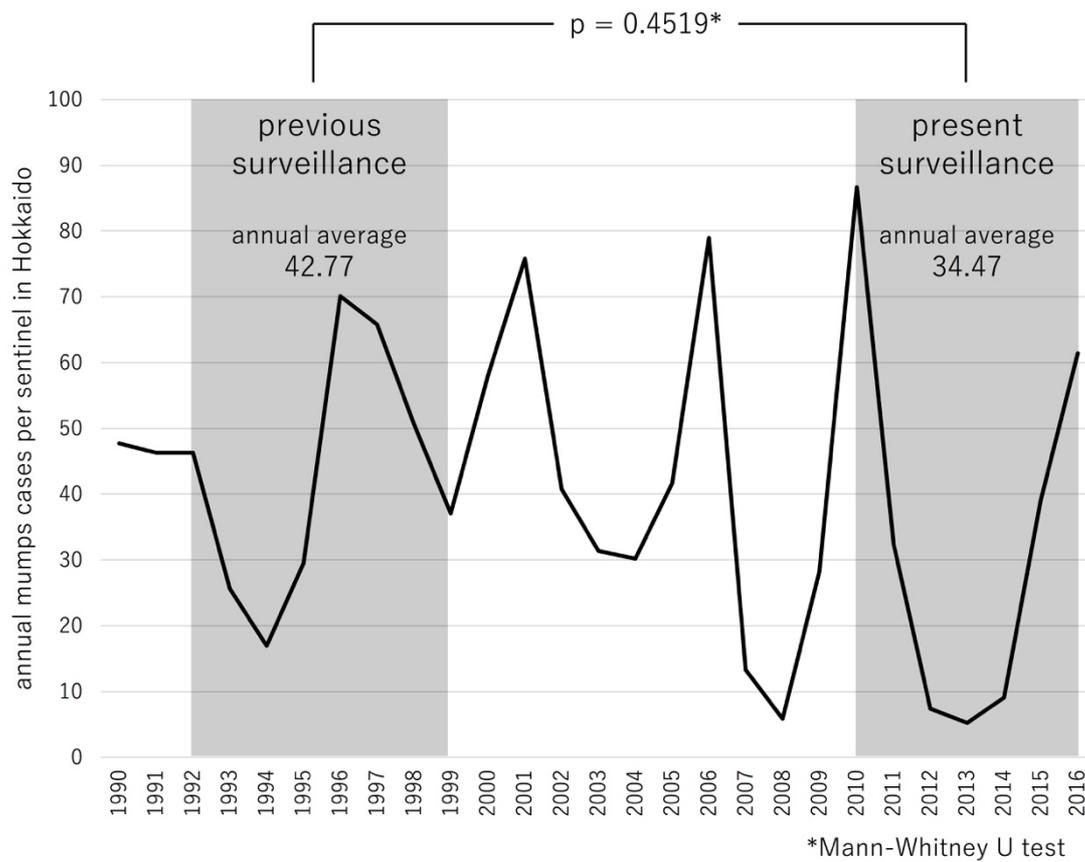


Fig. 1. The annual average number of mumps cases per sentinel in Hokkaido of the present and previous surveillance period was 34.47 and 42.77, respectively, and no significant difference was seen between these data ( $p = 0.4519$ ).

Table 1. Criteria for diagnosis of mumps deafness (revised in 2013)

*Definite*

- 1) Patients with evident clinical signs of mumps, such as swelling of the parotid gland and submandibular gland, and acute severe hearing loss during the period from 4 d before to 18 d after the appearance of such swelling.
- 2) Patients without evident clinical signs of mumps, but IgM antibodies against mumps virus are detected within 3 months after the onset of acute severe hearing loss.

*Referent case*

Patients in whom mumps deafness is suspected clinically.

- 1) Patients whose family members or friends have mumps infection
- 2) Patients who have different periods to Definite 1)

Table 2. Results of anti-mumps IgM antibody examination

Mumps IgM antibody	Present study (2010–2016) n = 100		Previous study (1992–1999) n = 69		
Positive	1	(1.0%)	5	(7.2%)	$p = 0.042^*$
Intermediate	2	(2.0%)	2	(2.9%)	
Negative	97	(97.0%)	62	(89.9%)	

\*Fisher's exact test