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Epidemiological Report

An Epidemiological Study on Japanese Autism concerning Routine Childhood Immunization History

Hiroshi Takahashi*, Syunsuke Suzumura[1], Fumiko Shirakizawa[1], Noriyuki Wada[2], Keiko Tanaka-Taya[3], Satoru Arai[3], Nobuhiko Okabe[3], Hironobu Ichikawa[1] and Taizo Sato[1]

Institute for International Cooperation, Japan International Cooperation Agency, Tokyo 162-8433,
[1]Tokyo Metropolitan Umegaoka Hospital, Tokyo 156-0043,
[2]Wada Pediatric Clinic, Tokyo 121-0812 and
[3]Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo 162-8640, Japan

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SUMMARY: To assess the causal association of autism with measles, mumps, and rubella (MMR) vaccine versus that with monovalent measles, mumps, and rubella immunization, a 1:2 sex-adjusted logistic regression analysis was conducted using data on subjects who were growing up in the Tokyo area between 1988 and 1992. When MMR immunization was used as a reference, monovalent measles immunization (odds ratio [OR] = 5.33, 99% confidence interval [CI]: 1.03-27.74), non-mumps immunization (OR = 8, 99% CI: 1.33 - 48.2), and non-rubella immunization (OR = 8.57, 99% CI: 1.30 - 56.4) with development of autistic spectrum disorders (ASD) were significantly increased. These results suggest a decreased risk of developing ASD with MMR compared to monovalent antigens. However, our findings may reflect potential selection bias due to requiring written consent, possible delayed vaccination in suspected autism cases, and small sample size (case = 21). For the case group and the control group, immunization completeness rate of each antigen, regardless of the timing of immunization, was 90.5% versus 100% in measles, 42.9% versus 78.6% in mumps ($P < 0.01$), 52.3% versus 83.3% in rubella ($P < 0.01$), 14.3% versus 45.2% in varicella ($P < 0.01$), 100% versus 90.5% in polio≥2, 100% versus 97.6% in Diphtheria (D), pertussis, and tetanus (T) ≥3, 85.7% versus 66.7% in DT, 95.2% versus 92.9% in BCG, and 52.4% versus 81.0% in Japanese encephalitis ≥3 ($P<0.01$). Only two case subjects and four control subjects received their measles, mumps, and rubella immunizations separately, suggesting that few Japanese parents might have had concerns about the safety of MMR vaccine. A nation-wide study would be a practical measure to scientifically judge the safety of MMR and other routine childhood immunizations.

INTRODUCTION

The etiology of autism with special attention to infection/immunization has been vigorously discussed. Wakefield and colleagues speculated that persistent measles virus infection of the gastrointestinal tract could have resulted in ileocolonic lymphonodular hyperplasia that allowed gastrointestinal absorption of toxic neuropeptides, which then caused central nervous system damage followed by neurodevelopmental regression (1). The authors hypothesized that combined measles, mumps, and rubella (MMR) vaccine might cause autism, and recommended alternative use of a monovalent measles vaccine. However, to date, no published report has supported their hypothesis (2).

The Japanese mother-child health law (article 12) regulates that all children are to receive a health check including a neurodevelopment assessment by their local health authority at least twice, once between the ages of 12 and 23 months and again around 3 to 4 years of age. Development and immunization history are recorded in "Boshitecho", the Maternal and Child Health (MCH) handbook.

From 1989 to 1993, MMR vaccine sold on the Japanese market contained AIK-C (measles), Urabe AM9 (mumps), and TO-336 (rubella) strains. At the same time, a monovalent measles vaccine with AIK-C, Schwarz FF8, TD97, or the Tanabe CAM strain was simultaneously in use in the Japanese national childhood immunization program. We considered that if the immunization data of autistic children's MCH handbook were available, the data on children who were born during that period constitute a good birth cohort for analysis of vaccine implications (3). Causal association of autism with immunization can be assessed in terms of immunization history. When the catchment areas of the case and the control populations, respectively, are geographically matched, any possible bias involving environmental factors would be minimized.

This paper summarizes immunization trends and the results of a case-control study of autistic children who were growing up in the Tokyo area from 1988 to 1992, with special attention to the causal association between autism and MMR/monovalent measles, mumps, and rubella vaccines, respectively.

METHODS

During the period from 1989 to 1993, the Japanese national immunization program recommended MMR vaccine or monovalent measles vaccination be given at the age of 12 months, diphtheria-tetanus-pertussis (DTP) vaccine at 2, 4, and 6 months old, oral polio vaccine (OPV) at 3 and 9 months, and BCG at 3 months. Monovalent mumps and rubella vaccine remained optional for those who did not receive MMR

*Corresponding author: Mailing address: Institute for International Cooperation, Japan International Cooperation Agency, Ichigaya-honmura cho 10-5, Shinjuku-ku, Tokyo 162-8433, Japan. Tel: +81-3-3269-3851, Fax: +81-3-3269-6992, E-mail: takahashi.hiroshi@jica.go.jp

vaccination. Diphtheria-tetanus toxoid (DT) was given at 12 years of age, and Japanese encephalitis (JE) vaccine was administered 3 times between 3 and 4 years.

The Tokyo Metropolitan Umegaoka Hospital is a specialized pediatric psychiatry facility in the Tokyo area. Approximately 130 school-aged children visit the hospital for treatment of and care for autistic spectrum disorders (ASD). From July 2001 to February 2002, the attending physicians of the hospital requested that the caregivers of ASD patients born between 1988 and 1992 disclose the patients' clinical records. After the caregivers had received an explanation of the study's purposes, they gave their written informed consent to release the records. Subsequently, year of birth, age at initial onset of autistic symptoms, age of diagnosis according to the ICD10 code, and family history of ASD were reviewed. The infantile autistic symptoms were defined using the criteria of the hospital (Table 1). Diagnosis was made based on the definition set out in the diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV). Immunization records including vaccination date, vaccine type, lot number, provider's name, and adverse events and any unusual episodes, if any, were collected from the MCH handbooks.

A sex-adjusted logistic regression analysis was planned. If immunization was given after ASD diagnosis, those cases were regarded as non-vaccination in each relevant antigen setting. The control group was selected from the same birth year cohort (approximately 1,700 children born between 1988 and 1992), of children who were attending one of the two pediatric clinics in Tokyo. Using a randomized table (Fisher and Yates 1974), the eligible boys and girls were selected by their last two-digit registration number, and among those selected, only those who had no neuropsychiatric disorders and whose guardians had consented to disclosure of the MCH hsandbook data were enrolled in the control population. For both males and females, this process was repeated until the sample size for the control reached twice as those of the case.

Using MMR immunization as a reference, odds ratios (OR) with a 99% confidence interval (CI) for development of ASD were calculated for each immunization antigen setting (i.e., immunization with monovalent vaccine or non-immunization for measles, mumps, and rubella antigens). The data were summarized by using Micorosoft Excel (Microsoft Japan Co., LTD, Tokyo), then analyzed using SPSS ver.11.5J (SPSS Co., LTD, Tokyo).

Table 1. Abnormal infantile behavior check list for autistic spectrum disorders (ASD), Tokyo Metropolitan Umegaoka Hospital

1. lack of social smiling
2. hypersensitivity to soft sounds
3. hyposensitivity to loud sounds
4. lack of babbling
5. lack of stranger anxiety
6. aloneness or indifference
7. disinterest in or inattention to parents
8. no response to being called by name
9. expressionless face
10. no response to "peek-a-boo" game
11. lack of anticipatory motor adjustment (e.g., when held in arms)
12. lack of eye-to-eye contact
13. no use of finger pointing
14*. speech delay: 2 to 3-word vocabulary at 2 years of age
15**. loss of verbal expression
16. difficulty in mimicking movements of others
17. autostimulation behavior: flapping and staring at hands
18. extreme withdrawal, indifference to others
19*. rejection of others' intervention during play
20. no symbolic play
21. insistence on sameness
22*. hyperactivity
23*. Sudden laughing and crying without apparent reason
24*. Irregular and disturbed nocturnal sleep patterns

Numbering in developmental order: #1-12 before the age of 12 months. #13-24 after the age of 1 year.
* May be observed in normal children.
**Often seen in regressive ASD.

RESULTS

Case and control selection: A total of 21 autistic children were enrolled in the case-control study (Table 2). Response rate with informed consent was 87.5% (21/24). Among those 21 cases, four (19%) were female, which ratio corresponded to the previously reported sex ratio in Japan (male:female = 3 - 4:1) (4). Distribution of birth year was as follows: 1 in 1988, 2 in 1989, 3 in 1990, 9 in 1991, and 6 in 1992. Two cases were diagnosed with Asperger's syndrome (ICD10 84.5). One case (No. 13) had a regressive clinical course (i.e., history of loss of verbal expression at 18 months of age). The average age at which the initial autistic symptom appeared and diagnosis was made 2.46 years (median = 2 years, standard deviation = 1.65 years) and 6.57 years (median = 5 years, standard deviation = 2.79 years), respectively.

For the control matching, 8 females and 34 males were selected, based on a response rate of 58% (42/72). Distribution of birth year was as follows: 26 in 1988, 9 in 1989, 2 in 1990, 4 in 1991, and 1 in 1992.

Measles antigens given to the case and control groups included: AIK-C (case = 9, control = 30), Schwarz FF8 (case = 5, control = 7), TD97 (case = 2, control = 2), Tanabe CAM (case = 1, control =2), and unknown (case = 3, control = 1).

Table 2. List of the autistic cases (n = 21)

Case No.	Sex	Onset of initial symptom	Age of diagnosis	ICD10
1	F	11 mo	9 yr	84.0
2	M	18 mo	5 yr	84.0
3	M	3 yr	9 yr	84.0
4	F	2 yr	10 yr	84.5
5	M	3 yr	5 yr	84.0
6	M	2 yr	6 yr	84.0
7	F	2 yr	9 yr	84.0
8	M	5 yr	8 yr	84.0
9	M	5 yr	10 yr	84.0
10	M	5 yr	10 yr	84.0
11	M	12 mo	10 yr	84.0
12	M	18 mo	2 yr	84.0
13	M	18 mo	7 yr	84.0
14	M	2 yr	5 yr	84.0
15	M	18 mo	3 yr	84.0
16	M	2 yr	5 yr	84.0
17	M	7 yr	8 yr	84.0
18	M	2 yr	8 yr	84.5
19	M	12 mo	4 yr	84.0
20	M	18 mo	3 yr	84.0
21	F	14 mo	2 yr	84.0

Table 3. The immunization completeness rate of the case group and the control group, and the estimated rate of immunization for the general population in Tokyo, 1988-1992 birth cohort

Antigen	Case (n = 21)	Control (n = 42)	Tokyo (mean±SD)
Measles	95.2%	100%	77.4 ± 5.86%
Mumps	42.9%	78.6%	N/A
Rubella	52.3%	83.3%	70.4 ± 2.19%
Varicella	14.3%	45.2%	N/A
Oral Polio≥2	100%	90.5%	90.8 ± 1.81%
DTP≥3	100%	97.6%	77.8 ± 8.65%
DT	85.7%	66.7%	83 ± 10.9%
BCG	95.2%	92.9%	95.7 ± 1.74%
JE≥3	52.4%	81.0%	78.8 ± 5.72%

JE: Japanese encephalitis.
N/A: data not available.

Table 4. Association of autism to measles, mumps, and rubella immunization settings

Immunization setting	Case Group	Control Group	Odds Ratio	99% Confidence Interval
MMR	4	24	Ref.	–
Monovalent measles	16	18	5.33	1.03-27.7
Monovalent mumps	4	9	3.33	0.45-24.6
Monovalent rubella	4	12	3.82	0.59-24.7
Non-measles	1	0	∞	immeasurable
Non-mumps	13	9	8	1.33-48.2
Non-rubella	13	7	8.57	1.30-56.4

No specific lot number was recorded for any subject in the case group or the control group.

Immunization records: For the case group versus the control group, immunization completeness rate of each antigen, regardless of timing of immunization, was 90.5% versus 100% in measles, 42.9% versus 78.6% in mumps (P < 0.01), 52.3% versus 83.3% in rubella (P < 0.01), 14.3% versus 45.2% in varicella (P < 0.01), 100% versus 90.5% in polio ≥2, 100% versus 97.6% in DTP ≥3, 85.7% versus 66.7% in DT, 95.2% versus 92.9% in BCG, and 52.4% versus 81.0% in JE ≥3 (P < 0.01). No adverse events or unusual episodes were recorded after immunization. The Tokyo Metropolitan Annual Report of Hygiene summarized the estimated rate with standard deviation for each antigen during the observation years as: 77.4 ± 5.86% (measles), 70.4 ± 2.19% (rubella), 90.8 ± 1.81% (polio), 77.8 ± 8.65% (DTP), 83 ± 10.9% (DT), 95.7 ± 1.74% (BCG), and 78.8 ± 5.72% (JE) (Table 3).

Statistical analysis: A total of four shots (i.e., one mumps and three rubella immunizations) were given after ASD diagnosis; in this study, this was regarded as non-vaccination. Among subjects in the control group, all had received either MMR vaccine or monovalent measles vaccine; therefore, the OR for measles antigen was immeasurable. When MMR immunization was regarded as a reference, monovalent measles immunization (OR = 5.33, 99% CI: 1.03 - 27.74), non-mumps immunization (OR = 8, 99% CI: 1.33 - 48.2), and non-rubella immunization (OR = 8.57, 99% CI: 1.30 - 56.4), respectively, to development of ASD was significantly increased. All the other associations were statistically non-significant (Table 4).

DISCUSSIONS

This is the first epidemiological study to analyze the causal association between routine immunization history and Japanese autism.

The results of this study contradicted the hypothesis by Wakefield's group, and allayed concerns about the reintroduction of MMR to the Japanese immunization schedule. However, the statistically significant association of ASD with monovalent measles immunization, non-mumps, and non-rubella immunization might be exaggerated in our study, due to the small sample size and possible bias due to the informed consent process; in both the case group and the control group, the informed consent process might have discouraged caregivers from enrolling children with a poor or incomplete immunization history. For instance, mumps and rubella immunization were to be given after the age of 12 months, and whether these immunizations were obtained during the observation years was the parent's or caregiver's choice. The difference in immunization completeness rates between the case group and the control group (P < 0.01) could be explained that the case group caregivers were satisfied with the minimal required antigens, especially after they became aware of the child's abnormal autistic symptoms, whereas the control group parents wished to have their children receive the maximum antigens available via MMR immunization, and these circumstances created a possible bias in this study. The relatively poor response rate (58%) of the control population presents another possible bias, though the estimated immunization rate for the general Tokyo population during the same time period was similar to that of the control group. The measles immunization rate is exceptionally lower among the Tokyo population, probably because many healthy infants might have been infected naturally before the age of 12 months. The immunization rates for mumps and varicella were not available, because these immunizations were optional.

In the United States, the vaccine safety data link project revealed that the vaccination rate begins to fall off significantly for neurologically abnormal children right around the age of 12-15 months (Dr. Robert Davis, personal communication, October 31, 2002). In fact, the immunization completeness rate of JE, which is given 3 times between the ages of 3 and 4 was 52.4% in the case group, and 81.0% in the control group (P < 0.01). Of 17 JE-immunized subjects in the case group, only five received JE immunizations after ASD diagnosis. Such a clearly intentional delay in immunization could present another bias. The presence of such a trend in the infantile period would suggest that immunization with MMR appeared less attractive after the second year of life, and many have been actively withheld due to either the caregivers' or the physicians' concerns. However, this study demonstrated that only two case subjects and four control subjects received all measles, mumps, and rubella vaccines separately, suggesting that few parents had special concerns about the safety of MMR vaccine.

The causal-effect association, i.e., the timing of the initial onset of autistic symptoms relative to that of immunization, is a crucial focus of this study. Diagnosis of ASD using DSM-IV criteria is often difficult at the infantile stage. Some researchers argue that autism has a strong genetic component and that the associated neurological defects probably occur early in the course of embryonic development (5, 6). In most cases, abnormal symptoms are present at birth, although autism migth not be diagnosed until later in life when communi-

cation delays and characteristic behaviors become apparent (7). If this is the case, the effect of immunization would contribute little more than some modification to a congenital disorder. If regressive autism occurs in conjunction with one or more congenital abnormalities (5), analysis of biological plausibility, consistency, and strength of the association would be greatly complicated.

A population-based study using a rigorous case series methodology is one way to assess the relative incidence of autism within predifined time periods (8). However, such a study should address the loss of subjects to follow up over a long time period. A study design with a shorter observation period should address potential confounding factor of normal children with temporary symptoms. For example, it is noteworthy that infants with autism-like symptoms often resume normal development after 1 year of age.

In conclusion, the former Japanese MMR and other immunizations have demonstrated no harmful causal association with ASD in Japanese children. A nation-wide study would be a practical measure to scientifically confirm the safety of MMR and other routine childhood immunizations.

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