sometimes develop late-onset SNHL, long-term auditory outcomes are needed to investigate in this study subjects to show the association between VD on brain CT images and all congenital CMV-associated SNHL. Finally, because MRI provides more information of white matter lesions and malformations of cortical development in addition to VD and calcifications simultaneously, quantitative evaluation of ventricle size for CCMVI infants should be studied using MRI in the early postnatal period.

Conflict of interest

The authors have no financial or personal relations that could pose a conflict of interest.

Acknowledgments

This work was supported in part by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (I.M. and A.M.), the Ministry of Health, Labor and Welfare of Japan (H23-Jisedai-Ippan-001), and the Japan Association of Obstetricians and Gynecologists (H22, 23-Ogyah-Kenkin).

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who died had renal failure before ET. Recently, Taffarel et al[11] in Argentina presented a review of 41 infants with pertussis cared for in their PICU between January 2003 and March 2011. Nine of the infants received ET in their management. The 4 ETs before 2011 were done as "rescue therapy in very ill patients," and all of these infants died. The 5 ETs performed in 2011 were done preemptively, and the ET was based on a WBC count >95,000mm^3 without requiring severe cardiopulmonary compromise; 4 of 5 of this group survived.

Although we present data on the largest number to date of young infants who received ET for the treatment of severe pertussis, our data are insufficient to address efficacy of the procedure. To determine efficacy, a controlled trial is needed. If ET is planned in an infant it should be done before organ failure has occurred.

In our opinion, ET for management of very severe pertussis in young infants is a biologically sound procedure. Findings in a number of case studies show that ET lowers the extreme leukocytosis, which would reduce aggregates of leukocytosis in the small pulmonary vessels.[3,5–10] In addition, it reduces circulating pertussis toxin, which inhibits other G-proteins, that might also contribute to cardiac or pulmonary failure.[3]

The data presented here as well as data in our previously published work[3] indicate that the decision for ET should be based on the early appearance of pneumonia, the presence of pulmonary hypertension and the rapidity in the rise of the WBC count. This requires that WBC counts to be performed every 12 to 24 hours. Rapidly rising counts that reach 30,000 cells/mm^3 should prompt immediate consideration of ET. Also rapidly increasing pulse and respiratory rates should also be considered as indicators form performing ET.

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CLINICOEPIDEMIOLOGIC STATUS OF MOTHER-TO-CHILD INFECTIONS: A NATIONWIDE SURVEY IN JAPAN

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Abstract: We conducted a nationwide survey of the present status of 10 representative mother-to-child infections in Japan. Congenital syphilis, vertical human T-cell leukemia virus type 1 infection, congenital rubella and vertical HIV infection, for which effective preventative strategies have been established, were rare. Cytomegalovirus was the most common congenital pathogen in Japan, although most infants with congenital cytomegalovirus infection may remain undiagnosed.

Key Words: mother-to-child infection, congenital cytomegalovirus infection, neonatal herpes, hepatitis B virus, human T-cell leukemia virus type I

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This study was financially supported by Japanese Society for Pediatric Infectious Diseases. The authors have no other funding or conflicts of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

DOI: 10.1097/INF.0b013e3182897c36

Mother-to-child infections, often represented by the TORCH complex, can have severe sequelae and have substantial socioeconomic burdens. The epidemiological features of mother-to-child infections vary greatly from region to region and over time. For example, introduction of the universal rubella vaccination program has led to a dramatic decrease in congenital rubella syndrome in many countries, including Japan.[1] Hepatitis B virus (HBV) is another example of vaccination that can prevent transmission from mother to child.[2] Serologic screening for syphilis, hepatitis C virus, HIV and human T-cell leukemia virus type 1 (HTLV-1) is also available all over Japan: 99.8%, 99.7%, 99.1% and 87.8% of pregnant women were tested in 2009 for those infections, respectively (annual report of the Ministry of Health, Labour and Welfare, Japan). However, no effective screening systems have been established for other congenital or perinatal infections, such as cytomegalovirus (CMV), neonatal

TABLE 1. Case Numbers of Mother-to-child Infections According to the Primary Survey

Infection	Number of Reported Cases				Adjusted Cases/100,000 Live Births*
	2006	2007	2008	3-yr Total	
Congenital CMV infection	46	37	57	140	9.5
Vertical HBV infection	23	28	26	77	5.2
Vertical hepatitis C virus infection	19	7	27	53	3.6
Neonatal herpes	6	17	15	38	2.6
Congenital syphilis	8	6	11	25	1.7
Congenital toxoplasmosis	3	5	8	16	1.1
Congenital parvovirus B19 infection	8	3	0	11	0.75
Vertical HTLV-1 infection	4	1	3	8	0.54
Congenital rubella	2	0	3	5	0.34
Vertical HIV infection	0	1	1	2	0.14

*Calculated from the mean annual reported number of live births during the 3-year period and adjusted by the collection rate (45.1%).

herpes, congenital toxoplasmosis and congenital parvovirus B19 infection.

Understanding of the current clinicoepidemiologic status of such infections is essential for planning effective strategies against them. In this study, we conducted a nationwide survey of the present status of the aforementioned 10 representative mother-to-child infections in Japan.

MATERIALS AND METHODS

A retrospective survey for the period from January 2006 to December 2008 was performed using questionnaires. In December 2009, a questionnaire as a primary survey was sent to a key respondent from each medical facility in Japan that had a pediatric and/or neonatal department (n = 2624 facilities). This primary survey inquired about the number of patients with the following mother-to-child infections during the indicated period: congenital rubella syndrome, congenital syphilis, vertical HIV infection, vertical HTLV-1 infection, vertical HBV infection, vertical hepatitis C virus infection, congenital toxoplasmosis, congenital parvovirus B19 infection, congenital CMV infection and neonatal herpes. Definition and diagnosis of each disease were based on the manual of pediatric infectious diseases published by the Japanese Society for Pediatric Infectious Diseases.[3] Patients born during the study period were included regardless of the timing of the diagnosis. Stillbirth cases were excluded from this study. The number of cases reported annually was calculated using an adjustment for data collection and mean live birth rates during the 3 years of the study (2006 to 2008).[4] Statistical analyses were performed using SPSS, version 18.0 (SPSS Inc., Chicago, IL).

A secondary survey was performed to evaluate the following 4 infections: congenital toxoplasmosis, congenital CMV infection, congenital parvovirus B19 infection and neonatal herpes. In June 2010, the secondary survey questionnaire was sent to all facilities that reported having cases of these infections in the primary survey (n = 134 facilities). This secondary survey inquired about clinical details of both the mothers and patients, including histories, symptoms, diagnostic procedures, therapies and outcomes. The questionnaire was completed by 1 physician at each facility, using data obtained from medical records. All questionnaire data were collected and analyzed at Nagoya University Graduate School of Medicine. This study was approved by the institutional review board of Nagoya University Graduate School of Medicine and by the Japanese Society for Pediatric Infectious Diseases.

RESULTS

Primary Survey of 10 Mother-to-child Infections

We received replies from 1183 of 2624 (45.1%) facilities, including approximately 77% of those with neonatal intensive care units and 70% of university hospitals. Responding hospitals accounted for 62% of the total number of hospital beds. The numbers of cases reported are shown in Table 1. The adjusted case number was highest for congenital CMV infection (9.5/100,000 live births), followed by vertical HBV infection, hepatitis C virus infection and neonatal herpes. Other mother-to-child infections were rare (less than 2/100,000 live births). The geographic distributions of the 4 major infections are shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/B497. Vertical HBV infection was more frequently reported from the mid and western parts of Japan.

Secondary Survey of 4 Selected Congenital and Perinatal Infections

We received replies from 109 of 134 (81.3%) facilities, which indicated 89 cases of congenital CMV infection, 31 of neonatal herpes, 8 of congenital parvovirus B19 infection and 5 of congenital toxoplasmosis.

Of 89 reported congenital CMV infection cases, 10 were excluded due to limited data or unconvincing diagnosis. The characteristics of the 79 cases eligible for further analysis of congenital CMV infection are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/B498. These cases included 72 symptomatic and 7 asymptomatic patients. Diagnosis of congenital CMV infection relied on polymerase chain reaction assays in approximately 80% (63) of cases. Notably, dried umbilical cord, which is traditionally preserved as a symbol of the mother–child bond in Japan, was used for polymerase chain reaction–based diagnosis in 16 cases. Auditory function during the neonatal period was evaluated by auditory brainstem response and automatic auditory brainstem response in 47 and 32 cases, respectively. Nearly half (38) of cases received antiviral therapy (ganciclovir only, 34 cases; valganciclovir only, 3 cases; both ganciclovir and valganciclovir, 1 case).

Of 31 reported neonatal herpes cases, 5 were excluded due to limited data or an unproven diagnosis. One case was congenital herpes simplex virus infection. The remaining 25 cases were eligible for further analysis of neonatal herpes (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B499). The ratio of disseminated disease, localized central nervous system disease and localized disease to the skin, eyes and mouth was 2:2:1. Patients

with disseminated disease (3 cases; 30%) had high mortality, and those with localized central nervous system disease (6 cases; 60%) had notable morbidity.

DISCUSSION

This is the first comprehensive nationwide survey that aimed to clarify the present status of mother-to-child infections in Japan. The numbers of reported cases of congenital syphilis, congenital toxoplasmosis, congenital parvovirus B19 infection, vertical HTLV-1 infection, congenital rubella and vertical HIV infection were very small, and their adjusted cases per 100,000 live births were less than 2 (Table 1). Annual numbers of congenital syphilis, congenital rubella and vertical HIV infection in this study were similar to those reported by the Infectious Disease Surveillance Center in Japan (Infectious Agents Surveillance Report, http://idsc.nih.go.jp/iasr/index.html), confirming the reliability of this study and the low prevalence of these infections. The prevalence of HTLV-1, which causes adult T-cell leukemia, is high in Japan, especially in the Kyushu district. Because this virus is transmitted mainly via breast-feeding, withholding breast-feeding can significantly reduce mother-to-infant transmission of this virus. The prevalence of HTLV-1 has been decreasing steadily in the younger generation,[5] partly because of this type of intervention. These results indicate that preventive strategies have successfully decreased or controlled mother-to-child infections with *Treponema pallidum*, rubella virus, HIV and HTLV-1 in Japan.

The low incidence of congenital toxoplasmosis may be explained by the low seroprevalence of *Toxoplasma gondii* in the Japanese population[6]; however, it is possible that this disease has been underdiagnosed due to a lack of effective screening systems. Similarly, congenital parvovirus B19 infection may also be underdiagnosed because no effective screening system during pregnancy exists for it and stillbirth cases were not included in this study. Because we did not collect data from obstetricians in this study, we may have missed many cases of congenital parvovirus B19 infection. In Japan, outbreaks of erythema infections occur periodically. A prospective study of pregnant women with suspected parvovirus B19 infection indicated that the incidence of adverse outcomes (including hydrops fetalis and fetal death) was 7% of those infected.[7]

Mother-to-child transmission of HBV infection, despite having the second highest incidence among those investigated in this study, has dramatically decreased since 1985, when the national immunization program for babies born to HBV carrier mothers started in Japan. Shiraki[2] estimated that the number of HBV carrier babies decreased from 260/100,000 live births in 1986 to 24/100,000 in 1995. In our study, the adjusted case number of mother-to-child HBV infections was 5.2/100,000 live births, indicating that the immunization program remains effective in preventing vertical transmission.

The adjusted case number (9.5/100,000 live births) of congenital CMV infection was highest in this study. However, this number is much smaller than the estimated number of infants with symptomatic congenital CMV infection. A prospective study recently performed in Japan showed that 0.31% of neonates have congenital CMV infection,[8] of which approximately 23% were symptomatic. Therefore, the incidence of symptomatic congenital CMV infection is estimated to be more than 7 times larger than that estimated here. CMV seroprevalence in pregnant women has been decreasing gradually in Japan.[9] However, this does not seem to account for the increase in reported cases because the incidence of congenital CMV infection has barely changed during the last 30 years.[8]

In conclusion, we report here the first comprehensive nationwide survey of mother-to-child infections in Japan. Congenital syphilis, vertical HTLV-1 infection, congenital rubella and vertical HIV infection, for which effective prevention strategies have been established, were quite rare. CMV was the leading congenital pathogen in Japan, although most infants with congenital CMV infection may still be unrecognized. Data from the present study will help us address mother-to-child infections in Japan.

ACKNOWLEDGMENTS

We thank all the facilities that participated in this survey. We are also grateful to F. Ando for her secretarial assistance.

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PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2013) **55**, 566–571 doi: 10.1111/ped.12122

Original Article

Risk factors for poor outcome in congenital cytomegalovirus infection and neonatal herpes on the basis of a nationwide survey in Japan

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Abstract ***Background***: Congenital cytomegalovirus (CMV) infection and neonatal herpes are major mother-to-child infections, and analyses of the important clinical issues, including risk factors for prognosis, are essential.

Methods: A secondary survey of congenital CMV infection and neonatal herpes was performed using questionnaires for cases reported in the primary survey between 2006 and 2008.

Results: Univariate analysis of 71 cases of congenital CMV infection showed that intrauterine growth restriction (IUGR) or other specific findings on fetal ultrasonography (US), microcephaly, intracranial calcification, disseminated intravascular coagulation, abnormal findings on computed tomography, and the use of i.v. gammaglobulin were all significantly correlated with poor outcome (death or severe sequelae). Multivariate analysis showed that only IUGR was significantly associated with poor outcome. Hearing impairment is one of the major abnormalities associated with congenital CMV infection. Automatic auditory brainstem response (automatic ABR) appeared to be useful for detection of hearing impairment in comparison with conventional ABR. Moreover, univariate analysis showed that specific fetal US or abnormal magnetic resonance imaging findings were correlated with sensorineural hearing loss. In 24 cases of neonatal herpes, fever and seizure were correlated with poor outcome on univariate analysis. All patients received acyclovir treatment, although substantial numbers of patients in severe clinical categories (disseminated or central nervous system diseases) received a low dose of acyclovir (<60 mg/kg per day).

Conclusions: This secondary survey has identified the risk factors associated with outcome and important issues in diagnosis and treatment of two mother-to-child infections: congenital CMV and neonatal herpes, in Japan.

Key words congenital cytomegalovirus infection, intrauterine growth restriction, multivariate analysis, nationwide survey, neonatal herpes.

Mother-to-child infection is a significant cause of fetal and neonatal mortality and an important contributor to early and later childhood morbidity. Congenital cytomegalovirus (CMV) infection is the leading non-genetic cause of sensorineural hearing loss (SNHL) in children in many countries.[1] Approximately 1% of all live-born infants are infected *in utero*, and 10% of infants with congenital CMV infection have involvement that is evident at birth with various manifestations, including SNHL.[1] Herpes simplex virus (HSV) is transmitted to the neonate most often during birth through the infected maternal genital tract, and the incidence is estimated to range from 1 in 3000 to 1 in 20 000 births.[2] Neonatal herpes is often severe, with attendant high mortality and morbidity rates, even when antiviral therapy is used.[2] Given that understanding of the current clinico-epidemiological status of these infections is essential to plan effective treatment strategies, we recently conducted a nationwide survey to investigate the present status of 10 representative mother-to-child

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Received 7 March 2013; revised 13 April 2013; accepted 23 April 2013.

infections, including congenital CMV and neonatal herpes.[3] During the 3 year study, data on 89 cases of congenital CMV infection and on 38 of neonatal herpes were analyzed in the secondary survey. Clinical features were also reported in this survey.[3] In this study, univariate and multivariate analysis were performed to determine the risk factors associated with outcome of congenital CMV infection and neonatal herpes. Moreover, important clinical issues in diagnosis and treatment of these two mother-to-child infections were also analyzed.

Methods

Data collection

A retrospective survey for the period January 2006 to December 2008 was performed using questionnaires sent to 2624 Japanese medical facilities. This primary survey identified the numbers of patients, including those with congenital CMV infection and neonatal herpes.[3] A secondary survey of congenital CMV infection and neonatal herpes was performed: the secondary survey questionnaire was sent to all facilities that had reported cases of these two infections. This secondary survey solicited clinical details of the mothers and patients, including histories, symptoms, diagnostic procedures, therapies, and outcomes. In cases in which the data were ambiguous or insufficient to confirm the diagnosis and evaluate outcome, telephone interviews were held with the physicians when possible. Outcome was evaluated at the time of death or at the last visit (>18 months old). Morbidity was defined as follows: no sequelae; mild sequelae that did not necessitate support for daily life; and severe sequelae that necessitated support for daily life. The general characteristics of the two infections were reported.[3]

The data were collected and analyzed at Nagoya University Graduate School of Medicine. This study was approved by the institutional review board of Nagoya University Graduate School of Medicine and by the Japanese Society for Pediatric Infectious Diseases.

Statistical analysis

Statistical analysis was performed using SPSS, version 18.0 (SPSS, Chicago, IL, USA). For univariate analysis, Mann–Whitney *U*-test was used to compare continuous variables, and Pearson's chi-square test or Fisher's exact test was used to compare categorical variables. Logistic regression was used for multivariate analysis. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Risk factors associated with outcome in congenital CMV infection

Of 89 reported cases in the secondary survey, 10 were excluded due to limited data or unproven diagnosis. After a mean observation period of 29.1 months, five patients (6.3%) died and 18 (22.8%) had severe sequelae. Twenty-four (30.3%) had mild sequelae and 25 (31.6%) had no sequelae (outcomes in eight cases were unknown). The risk factors associated with the outcomes of congenital CMV infection were estimated in these 71 cases (Table 1). Univariate analysis showed that intrauterine growth restriction (IUGR) detected on fetal ultrasonography (US), other specific findings on fetal US (including hydrocephalus/ventriculomegaly, microcephaly or ascites), microcephaly, intracranial calcification, disseminated intravascular coagulation, abnormal findings on computed tomography (CT), and the use of i.v. gammaglobulin were all significantly correlated with poor outcome (death or severe sequelae). Multivariate analysis showed that only IUGR was significantly associated with poor outcome. The risk factors associated with the development of SNHL were also determined in 56 cases in which outcome of hearing acuity was available (Table 1). Univariate analysis showed that specific fetal US or abnormal magnetic resonance imaging (MRI) findings were correlated with SNHL, but these were not significant on multivariate analysis (Table 2).

Use of automatic auditory brainstem response for detection of hearing impairment

Hearing impairment is one of the major abnormalities associated with congenital CMV infection, and auditory brainstem response (ABR) is used for diagnosis. In Japan, automatic auditory brainstem response (AABR) is widely used for screening of hearing impairment during the early neonatal period because of its ease of application. Auditory functions during the neonatal period were evaluated on ABR in 47 individuals and on AABR in 32 individuals. Sensitivity, specificity, positive predictive value, and negative predictive value for detection of hearing impairment were 93.3%, 82.4%, 82.4%, and 93.3%, respectively. These values were comparable to those of ABR. Therefore, AABR appeared to be useful for detection of hearing impairment (Table 3).

Risk factors associated with outcome in neonatal herpes

Of 31 reported cases in the secondary survey, five were excluded due to limited data or unproven diagnosis. One case was of congenital HSV infection. The remaining 25 cases were eligible for further analysis of neonatal herpes. Three patients (12%) died and four (16%) had severe sequelae. Five patients (20%) had mild sequelae and nine (36%) had no sequelae (the outcome in one case was unknown). We estimated the risk factors associated with poor outcome (death or severe sequelae) in these 24 cases. On univariate analysis, fever and seizure were correlated with poor outcome (Table 4). Multivariate analysis could not be performed due to the small number of cases.

Treatment and outcome among clinical categories

Neonatal herpes is classified into three main categories for therapeutic and prognostic reasons: localized skin, eye, and mouth (SEM); central nervous system (CNS) with or without SEM; and disseminated disease, which may involve the CNS and SEM in addition to other organs.[2] The ratio of disseminated disease/CNS/SEM was 2:2:1. I.v. acyclovir was given in all cases. Acyclovir dosage and outcome for each disease type are given in Figure 1. Substantial numbers of patients with disseminated and CNS disease received a low dose of acyclovir (<60 mg/kg per day).

Table 1 Factors associated with poor outcome[†] in infants with congenital CMV infection

Covariates	No. patients (with risk factor/total)	No. patients with poor outcome	Univariate analysis		Multivariate analysis	
			OR (95%CI)	*P*	OR (95%CI)	*P*
Sex (male)	33/71	10	0.84 (0.31–2.27)	0.73		
Low APGAR score (<7 at 5 min)	4/71	3	1.33 (0.20–8.71)	0.56		
IUGR on fetal US	**26/71**	**4**	**5.33 (1.73–16.4)**	**<0.01**	**4.33 (1.04–18.1)**	**0.045**
Specific findings on fetal US[‡]	**23/71**	**12**	**3.67 (1.27–10.6)**	**0.01**	1.39 (0.22–8.78)	0.73
Light-for-date[§]	**29/71**	**29**	**3.25 (1.12–9.44)**	**0.03**		
Gestational age (mean 37.3 weeks)			N.A	1.00		
Birthweight (mean 2365 g)			N.A	0.23		
Maternal age (mean 29.0 years old)			N.A	0.42		
Primary symptoms						
Hepatomegaly	18/71	7	1.47 (0.48–4.49)	0.50		
Dyspnea	18/71	7	1.47 (0.48–4.49)	0.50		
Purpura	15/71	4	0.71 (0.20–2.52)	0.42		
Microcephaly	**12/71**	**9**	**9.64 (2.29–40.6)**	**<0.01**	3.60 (0.36–36.1)	0.28
Splenomegaly	10/71	3	0.88 (0.21–3.76)	0.59		
Anemia	4/71	0	0.65 (0.55–0.78)	0.20		
Jaundice	8/71	3	1.29 (0.28–5.94)	0.51		
Laboratory findings						
Abnormal CT[§]	**31/43**	**15**	**10.3 (1.18–89.9)**	**0.02**		
Abnormal MRI	31/40	14	6.59 (0.73–59.2)	0.07		
Thrombocytopenia	28/71	11	1.67 (0.61–4.59)	0.32		
Intracranial calcification	**22/71**	**14**	**7.78 (2.51–24.1)**	**<0.01**	4.60 (0.83–25.3)	0.080
Hydrocephalus/ventriculomegaly	20/71	9	2.16 (0.74–6.33)	0.16		
Elevated transaminase enzymes	17/71	5	0.83 (0.25–2.73)	0.76		
DIC	**6/71**	**5**	**13.06 (1.43–120)**	**0.01**	16.4 (0.72–371)	0.079
Treatment						
Ganciclovir/valganciclovir	38/71	13	1.20 (0.44-3.25)	0.73	1.76 (0.38–8.25)	0.47
I.v. gammaglobulin	**14/71**	**8**	**3.73 (1.11–12.5)**	**0.03**	0.68 (0.08–5.82)	0.72

[†]Death or severe sequelae. **Bold**, $P < 0.05$. Factors with $P < 0.05$ after univariate analysis and treatment were included in multivariate analysis. [‡]Specific findings on fetal US included hydrocephalus/ventriculomegaly, microcephaly or ascites. [§]These factors were excluded from multivariate analysis because they were closely associated with other covariates. CI, confidence interval; CMV, cytomegalovirus; CT, computed tomography; DIC, disseminated intravascular coagulation; IUGR, intrauterine growth restriction; MRI, magnetic resonance imaging; NA, not applicable; OR, odds ratio; US, ultrasonography.

Patients with disseminated disease had a high mortality rate (30%), and those with localized CNS disease had poor morbidity (60%; Fig. 1b).

Discussion

Features associated with outcome of congenital CMV infection include gestational age at the time of maternal infection,[4] type of maternal infection (primary vs recurrent),[5] and specific newborn clinical findings.[6] Although several clinical manifestations, such as microcephaly, intracranial calcification, and disseminated intravascular coagulation, were associated with poor outcome in this study, their significance was reduced on multivariate analysis. Regarding treatment, i.v. gammaglobulin was associated with poor outcome in this study, but significance was reduced on multivariate analysis. It is interesting to note that multivariate analysis identified IUGR detected on fetal US as the only independent risk factor associated with poor outcome. This information is useful, not only for determining prognosis but also for prenatal diagnosis of symptomatic CMV infection. Prenatal diagnosis of congenital CMV infection can be made by identifying IUGR via non-invasive fetal US, followed by maternal serological examination and by testing for CMV-DNA in amniotic fluid.[7] This is highly significant because successful intrauterine treatment using CMV-specific immunoglobulin has recently been reported.[8,9]

I.v. ganciclovir treatment can improve hearing acuity and psychomotor development in infants with congenital CMV infection,[10–12] and oral use of its prodrug, valganciclovir, is expected to have comparable therapeutic effects.[12] These observations highlight the importance of early diagnosis of congenital CMV infection during the neonatal period. Hearing impairment is one of the most frequent manifestations. In this study, AABR was shown to detect hearing impairment in neonates with congenital CMV infection as effectively as conventional ABR. AABR is increasingly being introduced into maternity clinics and hospitals in Japan, although its use is not yet mandatory. Screening by AABR and subsequent detection of CMV-DNA on polymerase chain reaction appear to be effective and reasonable methods of detecting congenitally CMV-infected infants requiring observation and/or treatment. But, given that sensorineural hearing impairment associated with congenital CMV infection often develops after the neonatal period and is progressive, neonatal auditory screening alone is insufficient. Therefore, universal screening using detection of CMV-DNA in blood, urine, or saliva

Table 2 Factors associated with sensorineural hearing loss in infants with congenital CMV infection

Covariates	No. patients (with risk factor/total)	No. patients with SNHL	Univariate analysis		Multivariate analysis	
			OR (95%CI)	*P*	OR (95%CI)	*P*
Sex (male)	28/56	13	0.56 (0.19–1.62)	0.28		
Maternal age (mean 29.0 years old)			NA	0.09	1.14 (0.88–1.47)	0.33
IUGR by fetal US (29/79)	21/54	13	1.73 (0.57–5.26)	0.34		
Specific findings on fetal US[†]	**17/56**	**13**	**4.21 (1.16–15.2)**	**0.02**	0.99 (0.14–7.00)	0.99
Gestational age (mean 37.3 weeks)			NA	0.92		
Birthweight (mean 2365 g)			NA	0.28		
Light-for-date	25/56	15	1.60 (0.55–4.65)	0.39		
Low APGAR score (<7 at 5 min)	4/47	2	0.87 (0.11–6.75)	0.65		
Primary symptoms						
Hepatomegaly	13/56	6	0.68 (0.20–2.36)	0.54		
Dyspnea	12/56	9	3.29 (0.78–13.8)	0.09	4.77 (0.37–61.2)	0.23
Purpura	10/56	5	0.84 (0.21–3.30)	0.54		
Microcephaly	10/56	8	4.36 (0.83–22.8)	0.07	3.35 (0.16–72.6)	0.44
Splenomegaly	9/56	4	0.65 (0.15–2.71)	0.41		
Anemia	4/56	2	0.86 (0.11–6.56)	0.64		
Jaundice	7/56	5	2.40 (0.42–13.6)	0.28		
Laboratory findings						
Abnormal CT[‡]	22/34	15	14.3 (0.96–19.18)	0.05		
Abnormal MRI	**27/35**	**21**	**24.5 (2.50–240)**	**<0.01**	14.16 (0.89–225)	0.06
Thrombocytopenia	22/56	11	0.79 (0.27–2.31)	0.67		
Intracranial calcification	15/56	10	2.10 (0.61–7.23)	0.24		
Hydrocephalus/ventriculomegaly	14/56	10	2.75 (0.74–10.2)	0.12		
Elevation of transaminases	13/56	6	0.68 (0.20–2.36)	0.54		
DIC	3/56	2	1.79 (0.15–20.9)	0.55		
Treatment						
Ganciclovir/valganciclovir	31/56	19	2.02 (0.69–5.88)	0.20	1.43 (0.21–9.75)	0.72
Intravenous gammaglobulin	9/56	5	1.10 (0.26–2.61)	0.59	3.28 (0.14–74.7)	0.46

Bold, $P < 0.05$. Factors with $P < 0.10$ on univariate analysis and treatment were included in multivariate analysis. [†]Specific findings on fetal US included hydrocephalus/ventriculomegaly, microcephaly or ascites. [‡]This factor was excluded from multivariate analysis because of close associations with other covariates. CI, confidence interval; CMV, cytomegalovirus; CT, computed tomography; DIC, disseminated intravascular coagulation; MRI, magnetic resonance imaging; NA, not applicable; OR, odds ratio; SNHL, sensorineural hearing loss.

is desirable;[13–15] this has cost implications, however, and requires increased effort. Moreover, determination of which infants with congenital CMV infection actually require treatment remains controversial, because most remain asymptomatic throughout their lives.

In the secondary survey of neonatal herpes, univariate analysis showed that fever and seizures were associated with poor outcome, probably because these symptoms usually indicate disseminated or localized CNS disease. Acyclovir was used in all cases reported, but the dosage varied from 30 to 60 mg/kg per day. Although the American Academy of Pediatrics recommends an acyclovir dosage of 60 mg/kg per day to treat neonatal herpes,[2,16] such a high dose was not officially approved in Japan during the study period, which is probably why many infants with neonatal herpes received low doses of acyclovir in this study. There were no differences in outcome between infants receiving a high dose of acyclovir and those receiving low-to-intermediate doses (Table 4). This could be explained by physician tendency to treat severely infected patients with high doses of acyclovir.

Conclusion

The risk factors associated with outcome of congenital CMV infection and neonatal herpes were identified from the results of

Table 3 Comparison of ABR and AABR for detection of hearing impairment

Method	Result	Final diagnosis of hearing ability (no. patients)		Sensitivity	Specificity	PPV	NPV
		Impaired	Normal	% (95%CI)			
ABR	Positive	29	5	100 (88.1–NA)	72.2 (46.5–90.3)	85.3 (68.9–95.0)	100 (75.3–NA)
	Negative	0	13				
AABR	Positive	14	3	93.3 (68.1–99.8)	82.4 (56.6–96.2)	82.4 (56.6–96.2)	93.3 (68.1–99.8)
	Negative	1	14				

ABR, auditory brainstem response; AABR, automatic ABR; CI, confidence interval; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

Table 4 Factors associated with poor outcome† in infants with neonatal herpes

Covariates	No. patients (with risk factor/total)	No. patients with poor outcome	OR (95%CI)	*P*
Sex (male)	12/23	4	3.50 (0.63-19.5)	0.15
Gestational age (mean 39.5 weeks)			NA	0.28
Mode of delivery (vaginal vs cesarean)	18/21 vs 3/21	11 vs 0	0.39 (0.22-0.69)	0.09
Premature rupture of membranes	2/20	1	1.00 (0.05–18.6)	0.76
Birthweight (mean 3042 g)			NA	0.21
Primary symptoms				
Fever	**13/24**	**9**	**10.1 (1.47–69.9)**	**0.01**
Low suckling	7/24	3	0.84 (0.14-4.97)	0.61
Vesicular rash	5/24	0	0.42 (0.25-0.71)	0.03
Lethargy	5/24	2	0.74 (0.10-5.49)	0.59
Consecutive symptoms				
Seizure	**9/24**	**7**	**9.63 (1.38–67.3)**	**0.02**
Respiratory distress	8/24	5	2.78 (0.48-16.0)	0.24
Hepatomegaly	6/24	3	1.25 (0.20-7.96)	0.59
Vesicular rash	4/24	1	0.33 (0.03-3.78)	0.36
Laboratory findings				
Elevated C-reactive protein	13/24	6	1.03 (0.21-5.15)	0.97
Cerebrospinal fluid pleocytosis	10/24	6	2.70 (0.51-14.4)	0.22
Elevated transaminase enzymes	9/24	5	1.86 (0.35-9.98)	0.38
DIC	8/24	5	2.78 (0.48-16.0)	0.24
Viral type (type 1 vs type 2)	4/10 vs 6/10	1 vs 4	10.0 (0.65–154)	0.12
Treatment				
Acyclovir dose (<60 mg/kg per day vs 60 mg/kg per day)	8/19 vs 11/19	6 vs 5	0.42 (0.08-2.25)	0.27
I.v. gammaglobulin	9/24	5	1.88 (0.35-9.98)	0.38
Steroid	6/23	4	2.86 (0.41-20.1)	0.28

†Death or severe sequelae. **Bold**, $P < 0.05$.CI, confidence interval; DIC, disseminated intravascular coagulation; NA, not applicable; OR, odds ratio.

the secondary nationwide survey in Japan. IUGR identified on fetal US was an independent risk factor for poor outcome on multivariate analysis, and automatic ABR was useful for detection of hearing impairment in patients with congenital CMV infection. Fever and seizure in neonatal herpes were correlated with poor outcome on univariate analysis. The data from this study will help in the management of these mother-to-child infections.

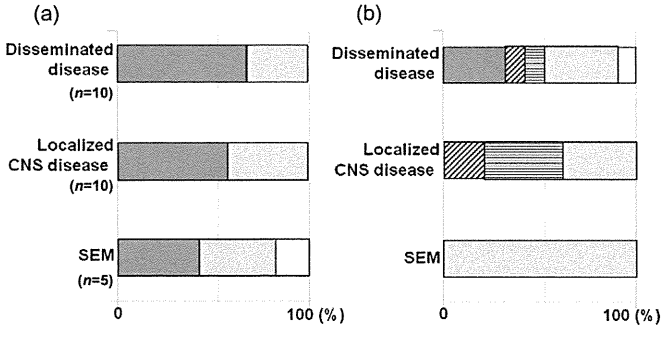

Fig. 1 Treatment and outcome for neonatal herpes. (a) Acyclovir treatment vs disease type. ▩, 60 mg/kg per day; □, ≥30 and <60 mg/kg per day; □, unknown. (b) Outcome vs disease type. ▩, death; ▨, severe sequelae; ▤, mild sequelae; □, no sequelae; □, unknown. CNS, central nervous system; SEM, localized disease to the skin, eyes, and mouth.

Acknowledgments

We thank all facilities that participated in this survey. We are also grateful to F. Ando for assistance with the manuscript. This study was financially supported by the Japanese Society for Pediatric Infectious Diseases.

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Original article

A nationwide survey of maternal screening for mother-to-child infections in Japan

Short title: Screening of mother-to-child infections

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cga.12044

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ABSTRACT

Mother-to-child infections cause congenital infection with disease and sequelae. To evaluate a state of maternal blood screening for mother-to-child infections in Japan, we for the first time conducted a nationwide survey on obstetric facilities where had regular maternity checkups. A questionnaire assessment involved an annual number of deliveries, scale of facilities and a state of maternal blood screening for 8 pathogens. A high rate (73.7%) of reply to the questionnaire was achieved from 1,990 facilities, covering 75.1% of annual number of delivery in 2011. The performance rates of blood screening were more than 99% for rubella virus, *Treponema pallidum*, human immunodeficiency virus (HIV), human T cell leukemia virus type 1 (HTLV-1), hepatitis B virus, and hepatitis C virus, while the rate were found to be only 4.5% for cytomegalovirus (CMV), and 48.5% for *Toxoplasma gondii* with large differences in regions. Most of the facilities performed blood tests for rubella virus, *Treponema pallidum*, HIV, hepatitis B virus and hepatitis C virus once in early pregnancy, while approximately 28% of the facilities performed blood tests for HTLV-1 once during 2nd or 3rd trimester. Most of the facilities used HA tests for *Toxoplasma gondii*, whereas there was a wide variation in antibody measurement methods

for CMV. Generally, the obstetric facilities in Japan have performed maternal blood screening properly according as the current recommendations. The results of this survey involve important information and are helpful of clinical practicians.

Key words: cytomegalovirus, parvovirus B19, rubella virus, *Toxoplasma gondii, Treponema pallidum*

INTRODUCTION

Mother-to-child infections, which develop if pathogens are transmitted from a mother to a fetus/neonate during pregnancy or the perinatal period, may lead spontaneous abortion, fetal death, fetal growth restriction and severe congenital diseases including anomalies and sequelae. To prevent or reduce the incidence of mother-to-child infections, maternal blood screening for pathogens capable of mother-to-child infections are usually performed at regular maternity checkups in obstetric facilities.

Recently, a Japanese study have completed a nation wide survey of mother-to-child infections on pediatric and neonatal departments, demonstrating the number of newborns with congenital infection of cytomegalovirus (CMV), *Toxoplasma gondii*, rubella virus, *Treponema pallidum*, human immunodeficiency virus (HIV), human T cell leukemia virus type 1 (HTLV-1), hepatitis B virus, hepatitis C virus, herpes smplex virus, and parvovirus B19 (Torii et al. 2013).

However, no report has evaluated a state of maternal blood screening for mother-to-child infections in Japan, we for the first time conducted this nationwide survey on obstetric facilities.

MATERIALS AND METHODS

We conducted a nationwide survey between February 2012 and July 2012 to

evaluate a state of maternal blood screening for mother-to-child infections, with the approval of the Ethical Committee of Kobe University Graduate School of Medicine (No. 1441). This survey was done for 2,714 obstetric facilities where performed regular maternity checkups in Japan. A questionnaire assessment involved an annual number of deliveries in 2011, scale of facilities, presence or absence of neonatal intensive care unit (NICU) in facilities, and a state of maternal blood screening for CMV, *Toxoplasma gondii*, rubella virus, *Treponema pallidum*, HIV, HTLV-1, hepatitis B virus, and hepatitis C virus.

The questionnaire also assessed frequency and time of maternal blood screening for each infection/pathogen; and methods of antibody measurement for CMV and *Toxoplasma gondii*. The modality of antibody measurement methods included specific IgG, IgM, complement fixation (CF) test for CMV; and hemagglutination (HA) test, specific IgG, IgM, and latex agglutination (LA) test for *Toxoplasma gondii*.

RESULTS

We received replies from 1,990 of 2,714 facilities, and found that maternity checkups had been discontinued in 13 facilities. The reply rate of the questionnaire was calculated as 73.7% (1,990/2,701) excluding these 13 facilities. According to the administrative divisions in Japan, the response rate ranged from 47% to 91% without large differences in regions. The annual number of deliveries of the 1,990 facilities in 2011

summed to 788,673. The scale of the 1,990 obstetric facilities where replied to the questionnaire is shown in Table 1.

Table 2 shows the state of maternal blood screening for mother-to-child infections in 2011. The percentages of facilities having screening in all mothers were more than 99% for Rubella virus, *Treponema pallidum*, HIV, HTLV-1, Hepatitis B virus, and Hepatitis C virus, while the percentages were found to be only 4.5% for CMV and 48.5% for *Toxoplasma gondii*. According to the administrative divisions in Japan, there was a large difference in percentages of facilities having maternal blood screening for *Toxoplasma gondii*, ranging from 6% in Akita Prefecture or 12% in Nagasaki Prefecture to 98% in Kagoshima Prefecture or 100% in Iwate Prefecture (Figure 1).

The frequency and time of maternal blood screening during pregnancy for each pathogen are shown in Table 3. The questionnaire assessment involved methods of antibody measurement for CMV and *Toxoplasma gondii*. The modality of antibody measurement methods for CMV in 90 facilities included CF test 28.9%, IgG 22.2%, IgG plus IgM 22.2%, IgM 5.6% and unknown/no reply 21.1%. Meanwhile, the modality of antibody measurement methods for *Toxoplasma gondii* in 962 facilities included HA test 78.8%, IgG 8.8%, LA 2.2%, HA plus IgM 2.0% and unknown/no reply 8.2%.

DISCUSSION

In order to evaluate a state of maternal blood screening for mother-to-child infections in Japan, we for the first time conducted this nationwide survey on obstetric facilities where performed regular maternity checkups. A high rate (73.7%) of reply to the questionnaire was achieved from 1,990 facilities, where gave a total of 788,673 deliveries covering 75.1% of annual number (1,050,806) of delivery in 2011, Japan (Kamiya 2013).

The performance rate of maternal blood screening was found to be more than 99% for rubella virus, *Treponema pallidum*, HIV, HTLV-1, hepatitis B virus and hepatitis C virus in the present survey study. The maternal blood screening in early pregnancy for rubella virus, *Treponema pallidum*, HIV, hepatitis B virus and hepatitis C virus is recommended commonly by Japan Society of Obstetrics and Gynecology (JSOG), Japan Association of Obstetricians and Gynecologist (JAOG) as well as by the Ministry of Health, Labor and Welfare of Japan. It has been confirmed that most of the obstetric facilities in Japan perform blood tests for these 5 pathogens once in early pregnancy (Tab. 2). However, approximately 28% of the facilities have performed blood tests for HTLV-1 once during 2nd or 3rd trimester, probably because they recommend that HTLV-1 screening should be completed until about 30 weeks of gestation. Therefore, the present study has demonstrated that most of the obstetric facilities in Japan perform maternal blood screening

for the abovementioned 6 pathogens properly according as the current recommendations.

The performance rate of *Toxoplasma gondii* screening was found to be 48.5% with a large difference of percentages in regions. Most of the facilities used HA tests for *Toxoplasma gondii* once in early pregnancy. In Japan, approximately 90-96% of pregnant women did not have *Toxoplasma gondii* antibody (Nishikawa et al. 2006; Sakikawa et al. 2012). The main risk factor for acute *Toxoplasma gondii* infection during pregnancy was known to be "ingestion of raw or undercooked meat" (Yamada et al. 2011). The incidence of congenital toxoplasmosis in Japan is estimated to be at least 1.26 per 10,000 births under the condition that all pregnant women receive maternal blood screening and medication if necessary (Yamada et al. 2011). However, universal screening of *Toxoplasma gondii* for all pregnant women is still not recommended by JSOG or JAOG. They describe that there are no strong evidences supporting the universal antibody screening (Guideline for Obstetrical Practice in Japan 2011). There are several uncertainties of *Toxoplasma gondii* screening methodology including diagnostic algorism of acute infection in mothers and congenital infection in newborns, and the efficacy of medications. IgG avidity and PCR assays of *Toxoplasma gondii,* of which measurement costs are not yet covered by health insurance, have not been standardized. The preventive or therapeutic efficacy of medications such as acetylspiramycin, pyrimethamine and sulfadiazine for congenital infection is limited (The SYROCOT study group 2007), and the latter 2 medications are

neither available nor manufactured in Japan. These might be the reasons why not all facilities performed maternal blood screening for *Toxoplasma gondii* and why there was a large difference of the screening percentages in regions.

The performance rate of CMV screening was found to be only 4.5%. CMV is the most common virus responsible for severe diseases with high mortality and morbidity rates in the affected fetus and newborn. Recently, a multi-center study of neonatal urine screening has revealed that congenital CMV infection develops in 0.31% of newborns in Japan (Koyano et al. 2011). The number of infants with congenital CMV infection due to primary infection may increase in Japan, because the prevalence of Japanese pregnant women with a positive test for CMV antibody has decreased to approximately 70% (Azuma et al. 2010). However, maternal CMV screening is not recommended by JSOG or JAOG. The reason might be similar to that of *Toxoplasma gondii*, in terms of unestablished screening methodology involving IgG avidity and PCR assays. Nevertheless, some facilities seem to perform CMV antibody screening in order to find women with a high risk for primary infection or women with possible acute infection during pregnancy. To prevent primary infection during pregnancy, the Centers for Disease Control and Prevention recommends that women without CMV antibody should receive counseling and education about mother-to-child CMV transmission and congenital infection. The newborns from women with possible acute infection will receive a workup for congenital infection and

follow-up for hearing difficulty if necessary. Therefore, it is likely that the modality of antibody measurement methods for CMV in the present study presented a wide variation.

This nationwide survey of mother-to-child infections has been performed for the first time on obstetric facilities. The results in the present study that demonstrated a state of maternal blood screening for mother-to-child infections in 2011 will have important information in the field of epidemiology, public health, public administration and infectious disease in Japan, and have helpful information for clinical practice as well.

ACKNOWLEDGMENTS

This work was supported in part by Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan (grant number; H23-Jisedai-Ippan-001) and Japan Association of Obstetricians and Gynecologists (grant number; H22, 23-Ogyah-Kenkin).

We appreciate all facilities cooperating on this nation wide survey and JSOG, JAOG supporting this project