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Diagnosis and medical care for congenital cytomegalovirus infection

An observational study using claims data in Japan, 2010 to 2017

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Abstract

Although early detection and intervention may improve the outcome of the congenital cytomegalovirus (cCMV) infection, few studies assessed the real-world clinical practice for cCMV patients. We analyzed medical claims data to assess the patterns of diagnoses and medical care for cCMV patients.

We used a subset of medical claims database (JMDC Claims Database) in Japan, covering 207,547 newborns between April 2010 and March 2017 and observed for at least 6 months. The diagnosis of cCMV and related symptoms and sequelae and medical care, including essential examinations and antiviral treatment, were identified using standardized codes.

Overall, we identified 53 (25.5 per 100,000 newborns) cCMV patients diagnosed within 6 months after birth; of these, 83% were diagnosed within 1 month and 68% had at least 1 cCMV-related symptom at birth. Objective hearing tests and fundus examinations were performed within 6 months in 60% and 30% of patients, respectively. Antivirals were prescribed in 26% of patients. During the observation period (median = 33 months), sensorineural hearing loss (49%) and developmental problems (28%) were commonly identified as cCMV-related sequelae. The proportions of the patients continuously followed up with objective hearing tests up to 36 months were 30% in total and 56% in antiviral-treated patients, respectively.

The cCMV patients did not necessarily receive a timely diagnosis nor continuous follow-ups in usual clinical practice. Although the universal screening for cCMV may, if implemented, facilitate early diagnosis, it should be accompanied by strategic follow-up plans to support timely interventions.

Abbreviations: cCMV = congenital cytomegalovirus, CI. confidence interval, FY = fiscal year, ICD-10 = International Classification of Diseases 10th Revision, ID = identification, JMDC = Japan Medical Data Center, NICU = neonatal intensive care unit, PCR = polymerase chain reaction, USA = United States of America.

Keywords: claims data, clinical practice, congenital cytomegalovirus infection, Japan, newborn

1. Introduction

Congenital cytomegalovirus (cCMV) infection is the most common congenital viral infection in developed countries and a leading cause of permanent disabilities, including hearing loss and cognitive impairment.[1,2] Birth prevalence of CMV-positive infants in developed countries was estimated to be 0.2% to 0.7%: of these, 10% to 30% are considered to be symptomatic at birth, and most of these develop long-term sequelae.[1,3–9] Recent studies from Japan also reported similar estimates for the birth prevalence of cCMV (0.26%–0.31%)[7,8,10] and the proportion of symptomatic patients (24%–30%).[7,10] These estimates, however, generally come from hospital-based prospective studies where the enrolled infants underwent extensive examinations and monitoring.[3–10] Much lower prevalence was observed in the studies based on surveillance,[11–13] questionnaire surveys,[14,15] or medical claims,[16,17] raising concerns about limited awareness and underdiagnosis of the disease in real-world clinical practices.[13,16]

Likewise, there is a concern that cCMV patients may not be as intensively followed up in usual practice as in the previous prospective studies, where medical care, including essential examinations for relevant sequelae, was performed systematically according to the study protocols.[3–10,16] Recent evidence suggests that universal or targeted neonatal CMV screening can

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be an effective strategy facilitating early detection and intervention for cCMV infection.[2,18,19] However, the expected effectiveness would be attained only when the patients were appropriately followed up after the diagnosis.[2] It would be necessary to understand how the cCMV patients are followed up in usual clinical practice. Although some studies addressed the common sequelae and antiviral therapy in usual practice for cCMV patients,[11,12] the patterns of the medical follow-ups have rarely been investigated.

In this study, for a better understanding of usual clinical practices for cCMV patients and to identify the gap, if any, between the observed and the recommended practices, we provided detailed descriptions of the patterns of diagnoses and medical care for the clinically identified cCMV patients through the longitudinal observation of a large-scale claims data.

2. Methods

This is a longitudinal observational study using a medical claims database. The study protocol was approved by the Institutional Review Board of the Graduate School of Medicine, The University of Tokyo (No. 11127-3).

2.1. Setting and data

In Japan, all citizens are required to enroll in one of the social health insurance plans that are uniquely determined by their age, residential address, and profession.[20] Each medical facility monthly issues nationally-standardized claims forms for each patient, which are collected and reviewed by the insurers for reimbursements.[20] We used the JMDC Claims Database (JMDC Inc., Tokyo, Japan), which contains the claims data of several society-managed health insurance plans covering people employed in large companies and industry sectors and their dependents.[21] In this database, the claims data are collected and saved onto an anonymous and individually traceable format by using the unique ID assigned by the JMDC for each beneficiary.[21] The collected data include, but are not limited to, the patient's birth month, sex, diagnoses, examinations and procedures, and prescriptions. Diagnoses in the claims, being documented based on physician's clinical decision, are encoded with the standardized disease-code master developed by the Medical Information System Development Center, which is compliant with the International Classification of Diseases 10th Revision (ICD-10) 2003 version; the prescriptions are encoded using the Anatomical Therapeutic Chemical Classification System, and the procedures, examinations, and treatments are encoded using the standardized point codes listed in the Medical Fee Schedule[22] and the standardized procedure codes developed by the Health Insurance Claims Review & Reimbursement Services.[23]

2.2. Study cohort

There were 4,056,689 beneficiaries registered in the database between April 2010 and September 2017. Of these, 211,339 were born between April 2010 and March 2017 (fiscal year [FY] 2010–2016) and joined the health insurance plan within the month of his or her birth (about 2% of all newborns in the study period in Japan). Our study cohort consisted of 207,547 newborns who were observed for at least 6 months (the birth month and subsequent 6 months) or died $\leq$6 months after birth. Of these, we obtained all the claims data of the beneficiaries with at least 1 documented diagnosis of cCMV (ICD-10 code P35.1).

2.3. Definitions of the cCMV patients

We defined the clinically diagnosed cCMV when they had at least 1 diagnosis coded as cCMV (ICD-10 code P35.1, excluding those coded with "suspected case flag") in their claims $\leq$ 6 months after birth. As it is recommended that the diagnosis of cCMV should be established with polymerase chain reaction (PCR) assay using the sample obtained $\leq$ 3 weeks after birth,[18] we separately categorized the patients diagnosed $\leq$ 1 month after birth. We used "1 month" as the claims data were available monthly. We exclusively used the diagnosis in the claims for case identification because the PCR for cCMV had not been covered by the insurance during the study period. Additionally, we identified the patients diagnosed as cCMV later in the observation period to describe the characteristics of those with delayed diagnosis.

2.4. cCMV-related symptoms and sequelae

We also used the diagnoses in the claims to identify the cCMV-related symptoms and sequelae. We applied the following set of cCMV-related symptoms at birth in line with the recently published recommendations[18] with some modifications according to the identifiability in the claims data: thrombocytopenia, petechiae, hepatosplenomegaly, hepatitis (jaundice and/or elevated transaminase), small for date/low birth weight, and central nervous system involvement, such as microcephaly and other brain abnormalities, abnormal cerebrospinal fluid indices, chorioretinitis, and sensorineural hearing loss. We defined the patients with these symptoms at birth when they had at least 1 diagnosis with corresponding ICD-10 code in the claims $\leq$ 1 month after birth. We additionally used the standardized disease codes when the symptoms could not be identified explicitly with the ICD-10 code (Supplementary Table, http://links.lww.com/MD/D892). We also investigated the occurrences of cCMV-related sequelae,[18,24] including sensorineural hearing loss, vision impairment, seizure or epilepsy, cerebral palsy, and developmental problems, by defining these sequelae when cCMV patients had at least 1 diagnosis with corresponding ICD-10 codes throughout the observation period (Supplementary Table, http://links.lww.com/MD/D892). We regarded a patient was diagnosed as having the sequela(e) in the month when the diagnoses with corresponding ICD-10 codes were documented in the claims for the first time.

2.5. Medical care for cCMV patients

We examined whether the patients underwent essential examinations, namely, objective hearing tests, and fundus examinations, $\leq$6 months by assessing the standardized point codes as listed in Supplementary Table, http://links.lww.com/MD/D892.[18] The newborn hearing screening, though it has not yet been done universally at the national level, has been implemented outside insurance coverage in Japan.[25] Therefore, the objective hearing test for screening purpose cannot be captured by the claims, but it should be captured when provided for diagnosis and/or follow-up purposes. We also examined the admission to the neonatal intensive care unit (NICU), the types of medical facility (clinic or hospital) where the first diagnosis of cCMV was made, the prescriptions of antivirals (ganciclovir,

valganciclovir, and foscarnet), and the placement of the cochlear implant. Since the audiological testing at 6-month intervals for the first 3 years is recommended especially for those treated with antivirals,[18] we identified the patients who underwent objective hearing tests within each period of ≤6, 7–12, 13–24, and 25–36 months. We applied less stringent 12-month intervals after the first year considering the possible variation of the intervals and the decreasing number of observed patients after 12 months.

2.6. Statistical analysis

We provided the overall, sex- and year-specific frequencies of cCMV patients per 100,000 newborns (the number of the identified cCMV patients divided by the number of newborns in the observation period multiplied by 100,000) and their 95% confidence intervals (CIs). Of the defined cCMV patients, we described the proportions of those who underwent the examinations and treatments, comparing them according to the presence of related symptoms using Fisher exact tests. The proportion of each of the related symptoms was also described. We then calculated the overall proportions of the patients who developed each of the related sequelae during the observation period. We used Kaplan–Meier analysis with the log-rank test to assess the associations of the related symptoms at birth with the development of the sequelae. To evaluate whether the patients were followed up periodically, we examined the proportions of the patients who underwent the objective hearing test in each period of ≤ 6, 7–12, 13–24, and 25–36 months. Additionally, we identified the cCMV patients diagnosed after 6 months and described their characteristics. We regarded the *P* value less than .05 as statistically significant. We used Stata version 15.1 (StataCorp LP, College Station, Texas, USA) for all statistical analyses.

3. Results

We identified 53 cCMV patients among the 207,547 newborns in the observation period; the frequencies per 100,000 newborns were 25.5 (95% confidence interval [CI], 19.1–33.4) in overall, 27.2 (95% CI, 18.2–39.0) in boys and 23.8 (95% CI, 15.3–35.5) in girls, respectively (Table 1). Although not statistically significant, the frequency varied across the years ($P=.07$): it increased to 47.9 per 100,000 in FY 2014 and dropped to 13.3 per 100,000 in FY 2016. Of the 53 cCMV patients, 44 (83%) were diagnosed ≤1 month, and 36 (68%) had at least 1 cCMV-related symptom. All 6 patients had the cCMV-related symptom (s) at birth for those born in FY 2010 to 2011, whereas 64% (30/47) had related symptom(s) for those born in FY 2012 and thereafter. No death was documented in the observation period.

Table 1

The total and sex- and year-specific numbers and frequencies of congenital cytomegalovirus infection patients identified with the health insurance claims database in Japan.

Variable	Newborn n	cCMV patient		*P* value*
		Total n	Per 100,000 (95% CI)	
Total	207,547	53	25.5 (19.1–33.4)	
Sex				.68
Boy	106,813	29	27.2 (18.2–39.0)	
Girl	100,734	24	23.8 (15.3–35.5)	
Fiscal year of birth				.07 (.46)
2010	15,294	2	13.1 (1.58–47.2)	
2011	19,276	4	20.8 (5.65–53.1)	
2012	24,134	5	20.7 (6.63–48.3)	
2013	35,677	6	16.8 (6.17–36.6)	
2014	37,548	18	47.9 (28.4–75.8)	
2015	38,066	13	34.2 (18.2–58.4)	
2016	37,552	5	13.3 (4.32–31.1)	

* Fisher exact test. *P* value of test for trend is shown in the bracket.
cCMV = congenital cytomegalovirus infection, CI = confidence interval.

Table 2

Medical care provisions for the patients with congenital cytomegalovirus infection according to the status of the related symptoms at birth.

Variable	Total n (%)	With related symptom(s) n (%)	Without related symptom n (%)	*P* value*
Total	53 (100)	36 (100)	17 (100)	
Sex				.77
Boy	29 (55)	19 (53)	10 (59)	
Girl	24 (45)	17 (47)	7 (41)	
Diagnosed facility				>.99
Clinic	12 (23)	8 (26)	4 (24)	
Hospital	41 (77)	28 (78)	13 (76)	
Admission to NICU	20 (38)	17 (47)	3 (18)	.07
Examination ≤ 6 months				
Objective hearing test	32 (60)	27 (75)	5 (29)	.002
Fundus examination	16 (30)	14 (39)	2 (12)	.06
Antiviral treatment				
Ganciclovir	7 (13)	5 (14)	2 (12)	>.99
Valganciclovir	10 (19)	6 (17)	4 (24)	.71
Either of the above	14 (26)	10 (28)	4 (24)	>.99
Cochlear implant	2 (4)	1 (3)	1 (6)	.54

* Fisher exact test.
NICU = neonatal intensive care unit.
VGCV median 44.5 (11–160).

A majority (77%) of the cCMV patients were diagnosed in hospitals, and 38% of the patients were admitted to the NICU (Table 2). Not many of the patients received objective hearing tests (60%) or fundus examinations (30%) within 6 months of birth. About a quarter (26%) of the patients received antiviral medications. Treatment duration varied from 3 weeks to 6 months; 10 patients were treated for 6 weeks. No patients received foscarnet. Two (4%) patients underwent a cochlear implant. The patients with cCMV-related symptom(s) were more likely to have undergone objective hearing tests than those patients with no cCMV-related symptoms (75% vs 29%, $P=.002$). The NICU admission and fundus examinations were more frequently observed among the patients with cCMV-related symptoms than those without cCMV-related symptoms, but the differences were not statistically significant.

Table 3 shows the proportion of each of the cCMV-related symptoms. The most frequently documented symptom was sensorineural hearing loss (30%), followed by hepatitis/hepatosplenomegaly (28%), and small for date/low birth weight (19%). About two-thirds (68%) of patients had at least 1 symptom, and 25% of patients had multiple symptoms.

Table 4 shows the proportions of the patients who developed each of the cCMV-related sequelae and the median months of the first diagnosis. The median (range) of the observation period was 33 (8–88) months. Sensorineural hearing loss was documented most frequently (49%), followed by developmental problems (28%), seizure/epilepsy (13%), and cerebral palsy (11%). Two (4%) patients were diagnosed as having impaired vision. The patients with symptom(s) at birth were generally more likely to

Table 3

Proportions of the congenital cytomegalovirus infection patients with related symptoms at birth.

Symptom	n (%)
Thrombocytopenia	5 (9.4)
Petechiae	2 (3.8)
Hepatitis/hepatosplenomegaly	15 (28)
Hepatosplenomegaly	1 (1.9)
Hepatitis	14 (26)
Small for date/low birth weight	10 (19)
CNS abnormalities	24 (45)
Brain abnormality	8 (15)
Chorioretinitis	3 (5.7)
Sensorineural hearing loss	16 (30)
Any of the above symptom(s)*	36 (68)
Multiple symptoms	13 (25)

* Any of the thrombocytopenia, petechiae, hepatitis, hepatosplenomegaly, small for date/low birth weight and CNS abnormalities.
CNS = central nervous system.

develop sequelae than those patients without symptoms at birth. The median months of the first diagnosis and the Kaplan–Meier curves (Figs. 1 and 2) suggest that a majority of sensorineural hearing loss were diagnosed within the first several months, while the developmental problems were identified after 6 months and increased gradually with age.

Table 5 shows the proportions of the patients followed up with periodical objective hearing tests. About a half (56%) of the antiviral treated patients continuously were followed up to 36 months, which was higher than that in total patients (30%).

Additionally, we identified 7 patients diagnosed as having cCMV after the first 6 months during the observation period (the median [range] months of diagnosis was 11 [7–40] months). All of them developed at least one of the sequelae (3 had sensorineural hearing loss, 2 had impaired vision, 2 had cerebral palsy, and 6 had developmental problems, respectively), and the diagnosis of these sequelae preceded the diagnosis of cCMV in 6 out of the 7 patients.

4. Discussion

By analyzing a large medical claims database, we found that the cCMV patients did not necessarily receive timely diagnosis nor undergo continuous follow-ups after the diagnosis. The diagnosis and treatment of cCMV generally involve different specialties, including obstetrics, neonatology, pediatrics, otology, and ophthalmology. Hospital-based data, therefore, may not cover all the medical care unless there is a well-established referral system.[7,14,15] The claims data, on the other hand, systematically include all medical services with insurance coverage for each beneficiary, even for those provided at different facilities. This allowed us to assess the medical care for cCMV in usual clinical practice in Japan, where the hierarchical referral system is not established.

The cCMV patients identified with claims data were regarded as clinically diagnosed cases. The observed cCMV frequency (25.5 per 100,000 or 0.026%), therefore, was smaller than the prevalence of CMV-positive infants (0.2%–0.7%) reported in hospital-based studies with active case ascertainment[1,3–10] but comparable to those of symptomatic cCMV in Japan (0.042%–0.094%)[7,10,26] and other developed countries (0.07%),[1] as well as to the finding in the claims-based study in the United States.[16] Delayed (after 1 month) identification of about 20%, along with similar findings in an Australian study,[12] suggests cCMV patients are not necessarily diagnosed timely in usual practice, though it may be due to procedural delay associated with the lag between laboratory test and physicians' diagnosis. The increase of cCMV patients in FY 2014 may have been associated with the outbreak of rubella in Japan in 2012 to 2013.[27] Physicians might have tested CMV in more newborns than before as a differential diagnosis of congenital rubella syndrome, which may have resulted in incidental identification of cCMV cases. Increased proportions of the patients without symptoms after FY 2012 support this explanation.

Sensorineural hearing loss was the most commonly observed cCMV-related symptom at birth, which was consistent with the estimates of a systematic review[28] and the hospital-based study in Japan.[7] Although we assumed that most cases were clinically diagnosed, only two-thirds had at least 1 symptom at birth. Symptoms not directly related to medical treatment, such as petechiae and hepatosplenomegaly, may not have been documented on the claims even though physicians recognized them.[17]

Concerning the sequelae, sensorineural hearing loss and developmental problems were commonly identified like in many other previous studies.[1,10,24] A majority of sensorineural

Table 4

The numbers and proportions of congenital cytomegalovirus patients developed the related sequalae and the timing of first diagnosis of each sequelae.

Sequela	Total n (%)	Months to diagnosis median (range)	With related symptom(s) n (%)	Without related symptom n (%)	P value*
Total	53 (100)		36 (100)	17 (100)	
Observation months, median (range)	33 (8–88)		35 (8–88)	28 (15–65)	
Sensorineural hearing loss	26 (49)	2 (1–14)	24 (67)	2 (12)	<0.001
Diagnosed later†	10 (27)	5 (3–14)	8 (40)	2 (12)	0.06
Impaired vision	2 (3.8)	32 (11–53)	1 (2.8)	1 (5.9)	0.66
Seizure/Epilepsy	7 (13)	9 (1–35)	7 (19)	0	0.01
Cerebral palsy	6 (11)	13.5 (5–45)	6 (17)	0	0.09
Developmental problems	16 (28)	14.5 (6–29)	14 (36)	2 (12)	0.08
Speech problems	8 (15)	18 (7–69)	7 (19)	1 (5.9)	0.37
Motor problems	6 (11)	17 (6–27)	4 (11)	2 (12)	0.78
Mental retardation	5 (9.4)	22 (6–31)	4 (11)	1 (5.9)	0.68

* Log-rank test.
† The patients with sensorineural hearing loss within first 1 month were excluded: the denominators of total patients and the patients with related symptom(s) were 37 and 20, respectively.

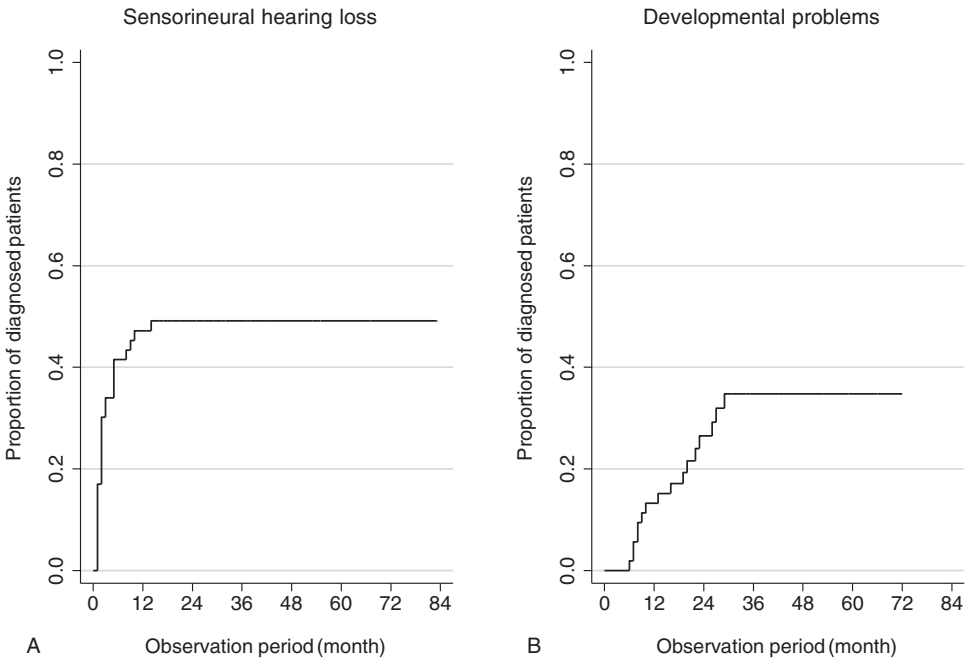

Figure 1. Kaplan–Meier curves of (A) development of sensorineural hearing loss and (B) developmental problems among overall patients.

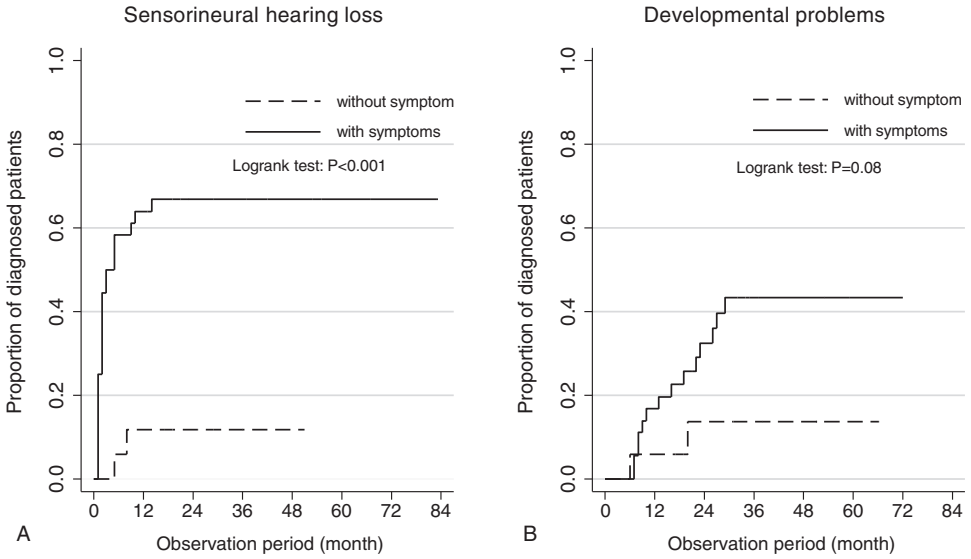

Figure 2. Kaplan–Meier curves of (A) development of sensorineural hearing loss and (B) developmental problems according to the presence of symptom(s) at birth. Solid line: the patients without congenital cytomegalovirus infection-related symptom at birth. Dashed line: the patients with congenital cytomegalovirus infection-related symptom(s) at birth.

Table 5

The medical follow-up with objective hearing tests for total and antiviral-treated congenital cytomegalovirus patients.

Period	Total			Antiviral-treated		
	Observed n	Tested* n (%)	Follow-up† n (%)	Observed n	Tested* n (%)	Follow-up† n (%)
≤ 6 months	53	32 (60)	32 (60)	14	12 (86)	12 (86)
7–12 months	52	21 (40)	15 (19)	14	11 (79)	9 (64)
13–24 months	42	24 (57)	12 (29)	13	11 (85)	8 (62)
25–36 months	23	12 (52)	7 (30)	9	6 (67)	5 (56)

* Number of the patients tested within each period.

† Number of the patients continuously tested up to each period.

hearing loss were diagnosed ≤6 months after birth. In contrast, the developmental problems were gradually identified after 6 months; the median months of diagnosis of speech problems, motor problems, and mental retardation all fell within the second year of life, and most of the cases were identified by the end of the third year. Long-term monitoring should be needed focusing on different types of sequelae, especially after the first 6 months. Sequelae were more commonly observed in patients with symptoms at birth than in those patients without symptoms in line with the previous findings.[7,10,29,30] Developmental problems, however, were less observed in the present study, even among the symptomatic cases, compared with a hospital-based study with similar observation period in Japan.[10] We should also note that the majority of those diagnosed as having cCMV after 6 months developed sequelae before their diagnosis of cCMV, indicating that some of the patients had not been identified as having cCMV until they developed common sequela (e) and might have lost the opportunity for early intervention. The implementation of the universal newborn screening program may reduce the risk of such delayed diagnosis.[2,18]

The essential examinations, such as objective hearing test and fundus examinations, were not necessarily done for cCMV patients. The very low proportions and the large gap of proportions between the groups with and without symptoms in fundus examinations imply the potential risk of under detections of the eye symptoms and could have been associated with the low prevalence of chorioretinitis in the present study.

More than one-fourth of the patients received antiviral treatment, which was at a similar level of those reported in the United States.[17] The antivirals were prescribed predominantly for those with symptoms at birth, but we should note that even such patients may not have been followed up continuously with periodical objective hearing tests, especially after the first year of life. Although long-term monitoring and follow-up of cCMV patients have been recommended repeatedly by different authors,[2,18,28,31] further efforts would be needed to raise disease awareness among healthcare providers.

We should acknowledge several limitations mostly related to the claims data. First, we could not estimate the true cases of cCMV as we identified the cases only using the claims data. Some symptoms and sequelae that may not require medical care might also have been underestimated. Second, the accuracy of our case identification method using diagnostic codes was not validated. The claims-based diagnoses might not be accurate enough.[16,17] However, relatively high accuracy of diagnostic codes of common chronic conditions in the JMDC Claims Database[32] may support our case identification strategy. Third, some relevant information, including maternal data, test results, disease severity, brain imaging, and laterality of symptoms and/or sequelae, as well as the examinations and treatments not covered by the insurance, were not available through the claims data. Fourth, we could not trace the individuals if they changed the insurance plan due to job changing or retirement. However, this effect is limited because those who were not traced for 6 months accounted for only 1.8% (3792/211,339) of the beneficiaries. Fifth, the median follow-up period of 33 months may be still short for fully detecting late-onset sequelae. Finally, the claims data obtained in this study were limited to specific insurance plans for the employees of large companies with relatively higher socioeconomic status than that of the general population; therefore, the generalizability of our results may be restricted.

The expected benefit of universal or targeted newborn screening for cCMV would be maximized through continuous follow-up and appropriate treatment of detected infants. Our findings, however, indicate these are not necessarily attained in usual clinical practice. The universal screening program, if implemented, should be accompanied by strategic monitoring and follow-up plans to support timely interventions. Continuous efforts are also needed to boost healthcare providers disease awareness and to monitor medical care for cCMV patients.

Author contributions

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References

[1] Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17:253–76.
[2] Cannon MJ, Griffiths PD, Aston V, et al. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? Rev Med Virol 2014;24:291–307.
[3] Boppana SB, Ross SA, Shimamura M, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. N Engl J Med 2011;364:2111–8.
[4] Fowler KB, Ross SA, Shimamura M, et al. Racial and ethnic differences in the prevalence of congenital cytomegalovirus infection. J Pediatr 2018;200:196–201.
[5] Vaudry W, Lee B, Rosychuk R. Congenital cytomegalovirus infection in Canada: active surveillance for cases diagnosed by pediatricians. Paediatr Child Health 2014;19:e1–5.
[6] Townsend CL, Forsgren M, Ahlfors K, et al. Long-term Outcomes of Congenital Cytomegalovirus Infection in Sweden and the United Kingdom. Clin Infect Dis 2013;56:1232–9.
[7] Koyano S, Inoue N, Oka A, et al. Screening for congenital cytomegalovirus infection using newborn urine samples collected on filter paper: feasibility and outcomes from a multicentre study. BMJ Open 2011;1:e000118.
[8] Yamaguchi A, Oh-Ishi T, Arai T, et al. Screening for seemingly healthy newborns with congenital cytomegalovirus infection by quantitative real-time polymerase chain reaction using newborn urine: An observational study. BMJ Open 2017;7:
[9] Puhakka L, Lappalainen M, Lönnqvist T, et al. The burden of congenital cytomegalovirus infection: a prospective cohort study of 20 000 infants in Finland. J Pediatric Infect Dis Soc XXX;doi: 10.1093/jpids/piy027.
[10] Koyano S, Morioka I, Oka A, et al. Congenital cytomegalovirus in Japan: more than 2 year follow up of infected newborns. Pediatr Int 2018;60:57–62.
[11] Townsend CL, Peckham CS, Tookey PA. Surveillance of congenital cytomegalovirus in the UK and Ireland. Arch Dis Child Fetal Neonatal Ed 2011;96:F398–403.
[12] Bartlett AW, Hall BM, Palasanthiran P, et al. Recognition, treatment, and sequelae of congenital cytomegalovirus in Australia: an observational study. J Clin Virol 2018;108:121–5.
[13] Sorichetti B, Goshen O, Pauwels J, et al. Symptomatic congenital cytomegalovirus infection is underdiagnosed in British Columbia. J Pediatr 2016;169:316–7.

[14] Torii Y, Kimura H, Ito Y, et al. Clinicoepidemiologic Status Of Mother-To-Child Infections. Pediatr Infect Dis J 2013;32:699–701.
[15] Yamada H, Tairaku S, Morioka I, et al. Nationwide survey of mother-to-child infections in Japan. J Infect Chemother 2015;21:161–4.
[16] Leung J, Cannon MJ, Grosse SD, et al. Laboratory testing and diagnostic coding for cytomegalovirus among privately insured infants in the United States: a retrospective study using administrative claims data. BMC Pediatr 2013;13:90.
[17] Leung J, Dollard SC, Grosse SD, et al. Valganciclovir use among commercially and medicaid-insured infants with congenital CMV Infection in the United States, 2009–2015. Clin Ther 2018;40:430–9.
[18] Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017;17:e177–88.
[19] Gantt S, Dionne F, Kozak FK, et al. Cost-effectiveness of universal and targeted newborn screening for congenital cytomegalovirus infection. JAMA Pediatr 2016;170:1173–80.
[20] Ikegami N, Yoo BK, Hashimoto H, et al. Japanese universal health coverage: Evolution, achievements, and challenges. Lancet 2011;378:1106–15.
[21] Kimura S, Sato T, Ikeda S, et al. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. J Epidemiol 2010;20:413–9.
[22] Ministry of Health, Labour and Welfare. Notification No. 52 (2016) Annex Table 1: Medical Fee Schedule (in Japanese). [updated 2016 Mar 4; cited 2018 July 4] Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000106421.html.
[23] Health Insurance Claims Review and Reimbursement Services. Medical Procedures Master (in Japanese). [updated 2018 Feb 21; cited 2018 July 4]. Available from: http://www.ssk.or.jp/seikyushiharai/tensuhyo/kihonmasta/h28/kihonmasta_01.html
[24] Dreher AM, Arora N, Fowler KB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. J Pediatr 2014;164:855–9.
[25] Maternal and Child Health Division Chief, Equal Employment, Children and Families Bureau, Ministry of Health, Labour and Welfare. Implimentation of Newborn Hearing Test (No.0329-2) (in Japanese). [updated 2016 Mar 29; cited 2018 Nov 8]; Available from: https://www.mhlw.go.jp/file/04-Houdouhappyou-11908000-Koyoukintoujidoukateikyoku-Boshihokenka/tyoukaku2.pdf
[26] Numazaki K, Fujikama T. Chronological changes of incidence and prognosis of children with asymptomatic congenital cytomegalovirus infection in Sapporo, Japan. BMC Infect Dis 2004;4:1–5.
[27] Sugishita Y, Shimatani N, Katow S, et al. Epidemiological characteristics of rubella and congenital rubella syndrome in the 2012-2013 epidemics in Tokyo, Japan. Jpn J Infect Dis 2015;68:159–65.
[28] Goderis J, De Leenheer E, Smets K, et al. Hearing loss and congenital CMV infection: a systematic review. Pediatrics 2014;134:972–82.
[29] Goderis J, Keymeulen A, Smets K, et al. Hearing in children with congenital cytomegalovirus infection: results of a longitudinal study. J Pediatr 2016;172:110–5e2.
[30] Capretti MG, Marsico C, Guidelli Guidi S, et al. Neonatal and long-term ophthalmological findings in infants with symptomatic and asymptomatic congenital cytomegalovirus infection. J Clin Virol 2017;97:59–63.
[31] Lim Y, Lyall H. Congenital cytomegalovirus – who, when, what-with and why to treat? J Infect 2017;74:S89–94.
[32] Hara K, Tomio J, Svensson T, et al. Association measures of claims-based algorithms for common chronic conditions were assessed using regularly collected data in Japan. J Clin Epidemiol 2018;99:84–95.