Identification of congenital cytomegalovirus infection using real-world healthcare data

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Introduction

- Infants with congenital cytomegalovirus infection (cCMVi) may present with symptoms such as sensorineural hearing loss (SNHL) during the neonatal period and/or develop permanent disability, and may require valgancivlovir treatment (Tx).
- This study aims to identify infants with cCMVi using information available in an electronic healthcare database in Israel, and to assess the validity of the cCMVi database definition in a sample of infants.

Methods

Design & Database: Retrospective cohort study using electronic healthcare data (1998-2018) from Maccabi Healthcare Services (MHS), a 2.4-million-member healthcare system in Israel.

Study population: Infants enrolled ≥30 days since birth; linked maternal data of women aged 18-44 years at start of pregnancy (SoP, 2013-2017).

cCMVi identification using structured data ≤90 days after birth:

- CMV Dx = diagnosis codes (ICD-9-CM 771.1, 078.5)
- Tx = dispensed valgancivlovir
- SNHL = diagnosis codes (ICD-9-CM 389.1-389.2)
- Maternal CMV testing history – to help inform the timing of the CMVi (congenital vs. postnatal) among infants whose earliest CMV Dx was at age 22-90 days.

→ cCMVi database definition = CMV Dx and/or Tx ≤90 days after birth

Validation of cCMVi database definition by expert chart review:

- Infants randomly sampled within subgroups based on CMV coding practices (timing, codes), presence of Tx and/or SNHL → Positive predictive value: PPV = N_{true} / N_{total}
- Infants randomly sampled based on maternal data = primary CMVi in pregnancy, with no CMV Dx code in infant's records → investigate coding practices that may impact sensitivity

Results

Study population = 182,582 infants linked to 133,481 mothers

- Pregnancies = 178,277; multiple pregnancies = 2.4%
- Median age at SoP=30 years (interquartile range [IQR]=26-34).
- Infants born prematurely = 11,242 (6.2%; **Table 1**)
- Infants born to mothers CMV-seronegative at SoP = 34,153 (18.7%)

cCMVi identification = 452 infants with CMV Dx/Tx ≤90 days

- CMV Dx codes: ICD-9 771.1 = 24.3%; 078.5 = 75.7%
- Median age at CMV Dx = 9 days (IQR=5-19); ≤21 days = 75.9%
- Tx at age ≤90 days = 111 (24.6%); 91-365 days = 12 (2.7%)
  - Median age at Tx = 26 days (IQR=17-41)
  - All infants with Tx ≤90 days also had CMV Dx ≤90 days
- SNHL Dx at age ≤90 days = 17 (3.8%); 91-365 days = 16 (3.5%)
  - Median age at SNHL Dx = 103 days (IQR=36-438)
- Infants with first CMV Dx at age 22-90 days + no Tx or SNHL ≤90 days = 86 (19.0%); breakdown by maternal CMV testing results:
  - Primary CMVi in pregnancy (n=26)
  - Seronegative at SoP + no evidence of primary CMVi (n=8)
  - Seropositive at SoP (n=44)
  - Unknown (n=8)
- Maternal CMV testing for 452 infants identified with cCMVi → **Table 1**

Table 1: Characteristics and cCMVi identification

Characteristics		Total N (col. %)	cCMVi*, n (row %)
Total N		182,582 (100.0%)	452 (0.2%)
Sex	Male	93,726 (51.3%)	219 (0.2%)
	Female	88,856 (48.7%)	233 (0.3%)
SES	Low	51,247 (28.1%)	107 (0.2%)
	Medium	58,747 (32.2%)	164 (0.3%)
	High	72,378 (39.6%)	181 (0.3%)
SoP year	2013	35,339 (19.4%)	76 (0.2%)
	2014	35,508 (19.4%)	87 (0.2%)
	2015	36,448 (20.0%)	90 (0.2%)
	2016	37,241 (20.4%)	86 (0.2%)
	2017	38,046 (20.8%)	113 (0.3%)
Premature	GA <37 weeks	11,242 (6.2%)	43 (0.4%)
Maternal age, years	18-24	30,729 (16.8%)	92 (0.3%)
	25-34	108,868 (59.6%)	289 (0.3%)
	35-44	42,985 (23.3%)	71 (0.2%)
Maternal CMV seroprevalence at SoP	Seropositive	125,903 (69.0%)	193 (0.2%)
	Seronegative	34,153 (18.7%)	206 (0.6%)
	Unknown	22,526 (12.3%)	53 (0.2%)

*cCMVi identified in database; GA, gestational age; SES, socioeconomic status; SoP, start of pregnancy

Validation of cCMVi database definition

- Sample of infants with CMV Dx/Tx ≤90 days (n=38); PPV→ **Table 2**
  - PPV was highest for CMV Dx combined with Tx and/or SNHL
  - In absence of Tx and/or SNHL (≤90 days):
    - PPV for early Dx (≤21 days) was not higher than for later Dx (22-90 days); ruled out cases that had negative CMV urine test results after the early Dx code
    - PPV for later Dx with 771.1 vs. 078.5 codes were similar; with both codes, ruled out cases including infants born to mothers who were CMV-seronegative at SoP.
- No cCMVi identified by chart review in sample of 9 infants without CMV Dx ≤90 days whose mothers had primary CMVi in pregnancy.

Table 2: Validation of cCMVi definition (sample)

Group, definition (time window, days since birth)		cCMVi*, N (col %)	Sample: N_{true} / N_{total}	PPV (95% CI)
#1	Dx + Tx (90)	111 (24.6)	12/12	100.0% (73.5%-100.0%)
#2 (not in #1)	SNHL (90)	4 (0.9)	3/4	75.0% (19.4%-99.4%)
#3 (not in #1-2)	Dx (21)	251 (55.5)	4/12	33.3% (9.9%-65.1%)
#4 (not in #1-3)	Dx 771.1 (22-90)	10 (2.2)	3/5	60.0% (14.7%-94.7%)
#5 (not in #1-4)	Dx 078.5 (22-90)	76 (16.8)	4/6	66.7% (35.9%-99.6%)

*cCMVi identified in database

Conclusions

- In a large Israeli healthcare system, 0.2% of infants had a CMV Dx/Tx in their electronic health records suggestive of potential cCMVi.
- Preliminary case review suggests that while the validity of CMV Dx may be limited by cases of suspected cCMVi before screening test results are obtained, differences in diagnosis practices within 90 days (timing, codes) appear to be minimal and allow for capture of asymptomatic as well as symptomatic cCMVi.
- This study will help inform analyses on the clinical and economic burden of cCMVi in this population where awareness of CMV is high but newborn screening is not universal.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA contracted with Maccabi Healthcare Services to conduct the study.