Long-term impairment attributable to congenital cytomegalovirus infection: a retrospective cohort study

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ABBREVIATION

cCMV	Congenital cytomegalovirus infection
CROCUS	Consequences and Risk factors Of Congenital cytomegalovirus infection

AIM This study aimed to estimate long-term impairment attributable to congenital cytomegalovirus infection (cCMV).
METHOD This nationwide cohort study retrospectively assessed cCMV in children born in 2008 in the Netherlands, testing 31 484 stored neonatal dried blood spots. Extensive medical data of cCMV-positive children (n=133) and matched cCMV-negative comparison children (n=274) up to 6 years of age were analysed.
RESULTS Moderate to severe long-term impairment was diagnosed in 24.8% (33 out of 133) of all cCMV-positive children (53.8% in symptomatic, 17.8% in asymptomatic), compared with 12.0% (33 out of 274) of cCMV-negative children. Sensorineural hearing loss was seen only in five cCMV-positive children (3.8%). Developmental delays were diagnosed more often in cCMV-positive children than cCMV-negative children: motor (12.0% vs 1.5%), cognitive (6.0% vs 1.1%), and speech–language (16.5% vs 7.3%). Long-term impairment in multiple domains was more frequent in symptomatic (19.2%) and asymptomatic (8.4%) cCMV-positive children than cCMV-negative children (1.8%).
INTERPRETATION Children with cCMV were twice as likely to have long-term impairment up to the age of 6 years, especially developmental delays and sensorineural hearing loss, than cCMV-negative comparison children, with a risk difference of 12.8%. These insights into the risk of cCMV-associated impairment can help optimize care and stimulate preventive measures.

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection worldwide, with a birth prevalence of around 0.6% in industrialized countries.[1] The only systematic review on the prevalence of permanent sequelae of cCMV was published by Dollard et al. in 2007.[2] They found that 12.7% of children with cCMV had signs or symptoms at birth, including hepatosplenomegaly, jaundice, thrombocytopenia, microcephaly, and intracranial calcification, and that 40% to 58% of these children developed permanent sequelae, such as hearing loss and developmental delay. Moreover, 13.5% of children who were asymptomatic at birth were estimated to develop long-term sequelae.[2] They concluded that, overall, 17% to 20% of infected children suffer from permanent neurological or sensory sequelae. These figures are frequently cited as representing the disease burden of cCMV. This systematic review was based on prospective cohort studies with universal neonatal cCMV screening. Often, these prospective studies merely report data on cCMV-positive children, with small or even no comparison groups. This may have led to information bias and an overestimation of the morbidity attributable to cCMV.

The aim of the Consequences and Risk factors Of Congenital cytomegalovirus infection (CROCUS) study was to estimate the long-term consequences of cCMV up to the age of 6 years in the Netherlands. In this large, nationwide retrospective cohort study, the diagnosis of cCMV was established at the age of 5 years; therefore practically all collected data had been recorded before a diagnosis of cCMV was made. The medical data, from birth to the age of 6 years, of children with cCMV and a matched group of children without cCMV were collected and analysed. The comparison between these groups provides insight into the disease burden attributable to cCMV.

METHOD

Study design

Details of the CROCUS study's design have been published previously.[3] In short, children with and without cCMV were retrospectively identified. Subsequently, medical data of all participating children with cCMV and a twice as large matched comparison group of children without cCMV were collected and analysed.

Children living in the Netherlands and born between 1 January and 30 September 2008 were eligible for inclusion. After informed parental consent was obtained, between October 2012 and January 2013, cCMV was diagnosed retrospectively in stored neonatal dried blood spots using polymerase chain reactions between November 2012 and June 2014. The comparison group comprised randomly selected children with negative results from cytomegalovirus polymerase chain reactions, matched to the children with cCMV for sex, birth month, and postal code. First, a screening test was performed on two CMV target genes. When this was positive, a second, different, internally controlled quantitative polymerase chain reaction performed in triplicate was used for confirmation in cCMV-positive children. This was also done in the selected cCMV-negative comparison group.[3] cCMV-positive was defined as a positive result in both the screening and confirmation test. The polymerase chain reactions had an assumed sensitivity of 84%, which was the pooled sensitivity in a recently published systematic review,[4] since the analytical sensitivity of the used polymerase chain reactions of one to five copies per reaction and the input of 15 μL or 50 μL was comparable to the best performing assays in this review.

Medical data of participating cCMV-positive and cCMV-negative children were collected, with informed consent of parents, between May 2014 and January 2015. Complete medical records were requested from their general practitioners. Information about hospital admissions, outpatient clinic visits, and provided care was also requested from all medical specialists and other health care providers who were mentioned by the parents. All records were entered anonymously into the study database before linking the information to the cCMV status.

The primary outcome of the study was sensorineural hearing loss up to the age of 6 years. Secondary outcomes included cognitive and motor developmental delay, and visual impairment. The sample size calculation was based on an expected prevalence of sensorineural hearing loss of 10% in cCMV-positive and 0.1% in cCMV-negative children, with a 90% power and a 5% two-sided alpha. Using a continuity correction, the sample size was estimated at 83 cCMV-positive and 166 cCMV-negative children.

The study was approved by the medical ethics committee of the Leiden University Medical Center in Leiden and is registered in the Dutch Trial Register (number NTR 3582).

What this paper adds

- Congenital cytomegalovirus infection (cCMV) leads to impairment in 25% of cases.
- Fifty per cent of children with cCMV symptoms at birth have long-term impairment.
- The risk difference of moderate to severe long-term impairment between children with and without cCMV is 13%, attributable to cCMV.
- cCMV leads to motor, cognitive, and speech–language developmental delay in children.

Definitions

Symptoms at birth

Clinically apparent abnormalities were defined as one or more clinically evident signs potentially related to cCMV that were recorded in the first 4 weeks of life, comprising prematurity, being small for gestational age, microcephaly, hepatomegaly, or splenomegaly, generalized petechiae or purpura, seizures, and hypotonia.

The z-scores for birthweight and head circumference were calculated using the Dutch reference charts with Growth Analyser Research Calculation Tools (version 4.0, Growth Analyser B.V., Rotterdam, the Netherlands), taking ethnicity and gestational age into account.

Children with aberrant laboratory values, cranial ultrasound or ophthalmological abnormalities, or neonatal sensorineural hearing loss, in addition to clinically apparent abnormalities in the neonatal period, were defined as being symptomatic at birth. Children without any of the above-mentioned symptoms or signs were considered asymptomatic at birth.

Long-term impairment

Sensorineural hearing loss was defined as greater than or equal to 40 decibels (dB) unilateral sensorineural hearing loss or bilateral hearing loss of greater than or equal to 40dB in the better ear. Severity of hearing loss was categorized as moderate (41–70dB), severe (71–90dB), or profound (>90dB).

Visual acuity and diagnoses of ophthalmological disorders were obtained from reports of the ophthalmologist or optometrist. Visual impairment was defined as a visual acuity below 0.3.

The diagnoses of neurological impairment were obtained from reports of medical specialists.

Microcephaly was defined as a head circumference below −2SD for age at the last recorded measurement.

Cognitive developmental delay was defined as an intelligence quotient less than or equal to 70 if this was tested, or it was based on a diagnosis by a medical specialist.

If results of a Movement Assessment Battery for Children[5] were available, a score below the fifth centile was considered indicative of developmental delay. Otherwise, the physical therapist's report was used to determine the diagnosis and severity of motor developmental delay.

Problems in speech and language development, including severity, were determined on the basis of reports from a speech therapist or speech and hearing centre. The

Schlichting Test for Language Production and the Reynell Test for Language Comprehension were used if recorded. A score below −1.5SD was considered indicative of moderate to severe delay.

The frequency of long-term impairment for each domain of impairment (hearing, visual, neurological, cognitive, motor, and speech–language) was estimated by combining disorders considered moderate to severe that were diagnosed up to the age of 6 years. Overall long-term impairment was defined as the presence of one or more disorders in one or more domains. Children with disorders in two or more domains were considered to be more severely impaired. All diagnoses provided by specialists and other health care providers were registered and categorized by MJK and checked by AMO-M.

Missing data handling

The Netherlands has a well-organized health care system that is cost-free and easily accessible for children, with regular checks by the preventive youth health care.[6] All newborn infants are regularly checked in the first weeks of life by a physician or midwife. When specific problems are detected then, or later, by the general practitioner or the youth health care physician, children are referred to a medical specialist or other health care providers. It was assumed that very few relevant outcomes were missed. Therefore the prevalence of long-term impairment was expressed as a percentage of the entire study population. The same is true for the prevalence of neonatal findings. Additionally we displayed the number of children whose neonatal clinical features were available for this study.

Statistical analysis

Data are reported as number and percentage or mean and SD. Data on signs and symptoms at birth of children with and without cCMV were compared. For long-term impairment, data are presented for cCMV-positive and cCMV-negative children and, within these groups, for those who were symptomatic or asymptomatic at birth. The cCMV-positive and cCMV-negative groups were compared for the prevalence of impairment in each of the six domains (hearing, visual, neurological, cognitive, motor, and speech–language), for the prevalence of any impairment, and for the prevalence of impairment in more than one domain. The risk differences and the relative risk with 95% confidence intervals (95% CI) were calculated to compare groups. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline data

In this study, 31 484 neonatal dried blood spots were retrospectively tested, resulting in 156 (0.5%) children diagnosed with cCMV (Fig. 1).[3] Medical data of 407 children were collected, comprising 133 with cCMV and 274 without cCMV. The mean age on 1 January 2014 was similar in both groups (5y 6mo, SD 2mo). In cCMV-positive and cCMV-negative children, 56.4% and 54.4% respectively were males.

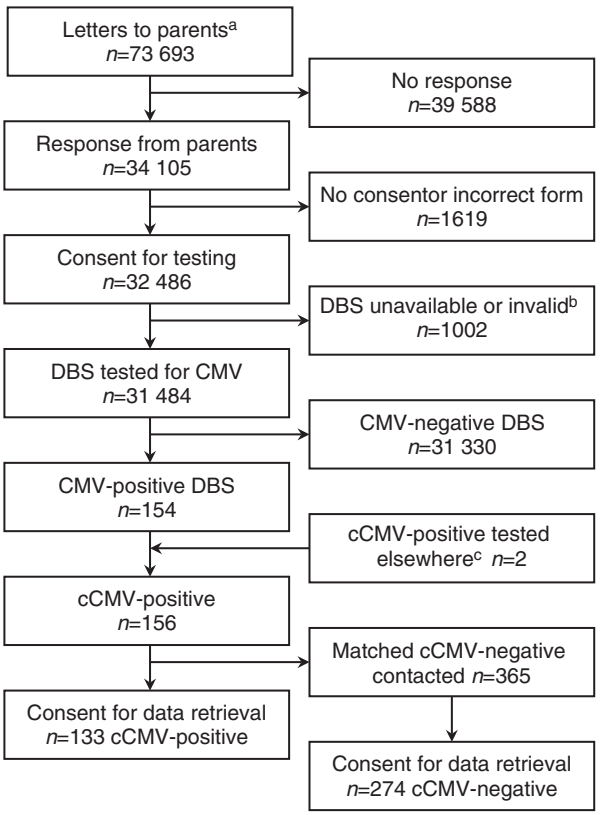

Figure 1: Flow chart of the CROCUS (Consequences and Risk factors Of Congenital cytomegalovirus infection) study (adapted from Korndewal et al.[3]). [a]In 2008, the number of live births in the Netherlands was 184 634 for the entire year and 139 543 between 1 January and 30 September. [b]Dried blood spot (DBS) was considered invalid if it was collected at 21 days and later after birth or if there was not enough material left for testing. [c]DBS of two congenital cytomegalovirus infection (cCMV)-positive children were unavailable for testing, but they had previously been tested elsewhere for cCMV.

Three of the participating children had been diagnosed with cCMV before inclusion in this study: one had been diagnosed with cCMV antenatally and was treated postnatally with valganciclovir because of cranial ultrasound abnormalities; one with cerebral palsy and hearing loss was diagnosed at 20 months of age; and one child identified with hearing loss in the neonatal period was diagnosed at 2 years of age.

Symptoms at birth

Of the children with cCMV, 18.1% had clinically apparent abnormalities in the neonatal period. In the group of children without cCMV, 12.0% had clinically apparent abnormalities (Table I). When additional laboratory, cranial ultrasound or ophthalmological abnormalities, and sensorineural hearing loss were taken into account, 19.6% of children with cCMV and 12.4% of those without cCMV were classified as being symptomatic at birth.

Table I: Symptoms and signs in the neonatal period

Prevalence	cCMV-positive (*n*=133)			cCMV-negative (*n*=274)			cCMV+vs cCMV−risk difference
	n[a]	%[b]	Reported[c]	*n*[a]	%[b]	Reported[c]	% (95% CI)[d]
Preterm birth (<37wks)[e]	13	9.8	132	18	6.6	273	
Small for gestational age[f]	5	3.8	130	10	3.7	271	
Microcephaly (< −2SD)[g]	7	5.3	61	7	2.6	130	
Hepatomegaly/splenomegaly	0		31	0		55	
Petechiae/purpura[h]	0		31	0		55	
Hypotonia/seizures[i]	0		31	0		55	
Clinically apparent abnormality[j]	24	18.1	132	33	12.0	273	6.0 (−1.6 to 13.6)
Thrombocytopenia (<100×10^9/l)[k]	0		8	0		15	
Neutropenia (<0.5×10^9/l)[l]	0		2	0		2	
Elevated ALAT (>80U/l)[m]	0		1	0		1	
Conjugated hyperbili (>2mg/dl)[n]	0		2	0		1	
Neonatal hearing loss[o]	2[p]	1.5	98	0[q]		217	
Cranial ultrasound abnormalities[r]	1[s]	0.8	3	5[t]	1.8	10	
Ophthalmological abnormalities[u]	0		1	0		–	
Symptomatic at birth[v]	26	19.6	133	34	12.4	273	6.9 (−0.7 to 14.9)

[a]Number of children (*n*) with signs or symptoms. [b]Percentage (%) compared with the whole group. [c]Number of children in whom the clinical feature was assessed and available for this study. [d]Risk difference presented as percentage and 95% confidence interval (CI). [e]Gestational age less than 37wks. [f]Weight less than −2SD for gestational age. [g]Head circumference less than −2SD for gestational age. [h]Generalized petechiae or purpura. [i]Hypotonia persisting more than 1h after birth or seizures. [j]One or more clinically evident signs or symptoms potentially related to congenital cytomegalovirus infection (cCMV) in the first 4wks of life. [k]Thrombocytes <100×10^9/l. [l]Neutrophil granulocytes <0.5×10^9/l. [m]Alanine-amino transferase (ALAT) >80 units/l. [n]Conjugated bilirubin >2mg/dl. [o]Sensorineural hearing loss ≥40dB, detected by neonatal hearing screening. [p]Severe unilateral sensorineural hearing loss (SNHL) (*n*=1), moderate bilateral SNHL (*n*=1). [q]Conductive unilateral hearing loss <40dB (*n*=1). [r]Any abnormalities on cranial ultrasound. [s]Germinal matrix cystic lesions (*n*=1). [t]Choroid plexus cyst (*n*=2), subependymal cyst (*n*=1), echodensities grade 1 (*n*=1), subependymal haemorrhage grade 1 (*n*=1). [u]Any permanent ophthalmological abnormalities. [v]One or more signs or symptoms potentially related to cCMV in the first 4wks of life.

Among the 20% of children with available data on physical examination after birth, no hepato- or splenomegaly, hypotonia, or generalized petechiae or purpura were recorded. No abnormalities were reported from the few children who had undergone blood tests. Three children were referred to a speech and hearing centre for further testing after failing the neonatal hearing screening. Of these, two children with cCMV were diagnosed with sensorineural hearing loss; another child without cCMV had unilateral conductive hearing loss.

Long-term impairment

Hearing impairment

Sensorineural hearing loss was present only in cCMV-positive children (3.8%) (Table II). Profound unilateral hearing loss was seen in three children and bilateral hearing loss in two. Hearing loss was present both in symptomatic (*n*=2) and in asymptomatic children (*n*=3). In two children, hearing loss was detected at the neonatal hearing screening. The other three children had late-onset hearing loss, which became apparent at the age of 2 (*n*=1) or 5 years (*n*=2).

Visual impairment

Unilateral visual impairment was present in two children: one cCMV-positive child had optic nerve atrophy and one cCMV-negative child had congenital cataracts (Table II). In addition, two cCMV-positive children had cortical visual impairment. All children with visual impairment were classified as asymptomatic at birth. Other correctable visual disorders, such as refractive errors, strabismus, and amblyopia, were more frequent in the cCMV-negative group.

Neurological impairment

Cerebral palsy with polymicrogyria was present in two cCMV-positive children (Table II). Epilepsy, microcephaly, autism spectrum disorders, and attention-deficit–hyperactivity disorder were diagnosed both in cCMV-positive and in cCMV-negative children. Autism spectrum disorders were diagnosed somewhat more often in cCMV-positive children, whereas attention-deficit–hyperactivity disorder was more frequent in cCMV-negative children.

Developmental delay

Cognitive impairment was more frequent in children with cCMV, especially in the symptomatic group (Table II).

Fine and gross motor impairment and balance impairment were more frequently seen in cCMV-positive children than the cCMV-negative group. In addition, sensory processing disorder and developmental coordination disorder occurred mostly in the cCMV-positive group.

Speech and language problems were common both in cCMV-positive and in cCMV-negative children; nevertheless, they were more prevalent in the cCMV-positive children.

More details of the long-term consequences of children with and without cCMV are provided in Table SI (online supporting information).

Long-term impairment per domain

When all outcome measures were combined, 24.8% of the cCMV-positive children had one or more long-term impairments, compared with 12.0% in the cCMV-negative group (Table III). Within the cCMV-positive group, the

Table II: Long-term impairment, diagnosed in the first 6 years of life, of congenital cytomegalovirus infection (cCMV)-positive and cCMV-negative children with or without symptoms at birth, per condition

	cCMV-positive			cCMV-negative		
Prevalence	All (*n*=133) *n* (%)	Symptomatic[a] (*n*=26) *n* (%)	Asymptomatic[b] (*n*=107) *n* (%)	All (*n*=274) *n* (%)	Symptomatic[a] (*n*=34) *n* (%)	Asymptomatic[b] (*n*=240) *n* (%)
Hearing impairment						
Sensorineural hearing loss[c]	5 (3.8)	2 (7.7)	3 (2.8)	0	0	0
Unilateral	3 (2.3)	1 (3.9)	2 (1.9)	0	0	0
Bilateral	2 (1.5)	1 (3.9)	1 (0.9)	0	0	0
Moderate (40–70dB)	2 ears	1 ear	1 ear			
Severe (71–90dB)	1 ear	1 ear				
Profound (>90dB)	4 ears	1 ear	3 ears			
Visual impairment						
Optic nerve atrophy	1 (0.8)	0	1 (0.9)	0	0	0
Congenital cataract	0	0	0	1 (0.4)	0	1 (0.4)
Cortical visual impairment	2 (1.5)	0	2 (1.9)	0	0	0
Refractive error[d]	13 (9.8)	4 (15.4)	9 (8.4)	42 (15.3)	8 (23.5)	33 (13.8)
Strabismus[d]	2 (1.5)	0	2 (1.9)	9 (3.3)	4 (11.8)	5 (2.1)
Amblyopia[d]	3 (2.3)	0	3 (2.8)	10 (3.7)	2 (5.9)	8 (3.4)
Neurological impairment						
Cerebral palsy	2 (1.5)	1 (3.9)	1 (0 9)	0	0	0
Epilepsy	2 (1.5)	2 (7.7)	0	3 (1.1)	0	3 (1.3)
Microcephaly	2 (1.5)	2 (7.7)	0	3 (1.1)	0	3 (1.3)
Autism spectrum disorder	4 (3.0)	2 (7.7)	2 (1.9)	5 (1.8)	1 (2.9)	4 (1.7)
ADHD[e]	1 (0.8)	1 (3.9)	0	7 (2.6)	0	7 (2.9)
Cognitive impairment						
Cognitive impairment[f]	8 (6.0)	4 (15.4)	4 (3.7)	3 (1.1)	1 (2.9)	2 (0.8)
Motor impairment						
Fine motor impairment[g]	13 (9.8)	5 (19.2)	8 (7.5)	2 (0.7)	0	2 (0.8)
Gross motor impairment[g]	13 (9.8)	4 (15.4)	9 (8.4)	3 (1.1)	1 (2.9)	2 (0.8)
Balance impairment[g]	8 (6.0)	1 (3.9)	7 (6.5)	1 (0.4)	1 (2.9)	0
Sensory processing disorder[h]	4 (3.0)	2 (7.7)	2 (1.9)	1 (0.4)	0	1 (0.4)
Speech–language impairment						
Language disorder[i]	14 (10.5)	6 (23.1)	8 (7.5)	10 (3.7)	1 (2.9)	9 (3.8)
Speech disorder[j]	16 (12.0)	6 (23.1)	10 (9.4)	15 (5.5)	3 (8.8)	12 (5.0)
Oral motor skill difficulties[k]	6 (4.5)	2 (7.7)	4 (3.7)	9 (3.3)	1 (2.9)	8 (3.4)
Auditory processing disorder	2 (1.5)	2 (7.7)	0	1 (0.4)	0	1 (0.4)

The figures in the table represent numbers and percentages unless stated otherwise. [a]Symptomatic at birth. [b]Asymptomatic at birth. [c]Sensorineural hearing loss ≥40dB. [d]Reversible impairment that was not included in the summary outcome measure for long-term impairment. [e]Attention-deficit–hyperactivity disorder. [f]Cognitive impairment according to the medical specialist or an IQ≤70 on the basis of the Snijders-Oomen Nonverbal Intelligence Test or the Wechsler Preschool and Primary Scale of Intelligence. [g]Motor impairment according to the physical therapist or a score below the fifth centile on the Movement Assessment Battery for Children. [h]Sensory processing disorder or developmental coordination disorder. [i]Any moderate to severe problem in language development according to the speech therapist or a score ≤1.5SD on the Reynell Test for Language Comprehension or Schlichting Test for Language Production. [j]Any moderate to severe problem in speech development according to the speech therapist, including articulation disorder, phonological disorder, voice disorders, and lisping. [k]Any moderate to severe problem in oral motor skills, including stuttering, low muscle tone, open mouth posture, and problems with swallowing.

percentage was much higher among symptomatic children (53.8%) than those without symptoms at birth (17.8%). No clear difference was observed between symptomatic and asymptomatic cCMV-negative children (Table III).

The difference between cCMV-positive and cCMV-negative children became more pronounced when the presence of impairment in two or more domains was assessed. The differences between cCMV-positive and cCMV-negative children were statistically significant within the developmental domains (cognitive, motor, and speech–language) and for hearing impairment (Table III).

DISCUSSION

In this nationwide cohort study, based on the screening of 31 484 dried blood spots for cCMV, moderate to severe long-term impairment, particularly sensorineural hearing loss and cognitive, motor, and speech–language impairment, was seen in 24.8% of all children with cCMV compared with 12.0% of children without it. Of the symptomatic cCMV-positive children, 53.8% developed one or more long-term impairments, compared with 17.8% of the asymptomatic cCMV-positive children. Moderate to severe long-term impairment in multiple domains was seen in 19.2% and 8.4% of the symptomatic and asymptomatic cCMV-positive children respectively, compared with 1.8% in the total cCMV-negative group.

Including a large matched cCMV-negative comparison group in this study provided insight into the long-term impairment attributable to cCMV. In other studies, comparison groups were often small or absent, and frequently the prevalence of long-term impairment was described in detail in only the cCMV-positive group.[7–9] The

Table III: Long-term impairment, diagnosed in the first 6y of life, of congenital cytomegalovirus infection (cCMV)-positive and cCMV-negative children with or without symptoms at birth per domain

	cCMV-positive			cCMV-negative			cCMV$^+$ vs cCMV$^-$		cCMV$^+$ vs cCMV$^-$	
	All (*n*=133)	Symptomatic[a] (*n*=26)	Asymptomatic[b] (*n*=107)	All (*n*=274)	Symptomatic[a] (*n*=34)	Asymptomatic[b] (*n*=240)	Risk difference		Relative risk	
Prevalence	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	%	95% CI	RR	95% CI
Hearing impairment[c]	5 (3.8)	2 (7.7)	3 (2.8)	–	–	–	3.8[d]	0.5–7.0	-	-
Visual impairment[e]	3 (2.3)	–	3 (2.8)	1 (0.4)	–	1 (0.4)	1.9	−0.7 to 4.5	6.18	0.65–58.9
Neurological impairment[f]	8 (6.0)	5 (19.2)	3 (2.8)	14 (5.1)	1 (2.9)	13 (5.4)	0.9	−3.9 to 5.7	1.18	0.51–2.74
Cognitive impairment[g]	8 (6.0)	4 (15.4)	4 (3.7)	3 (1.1)	1 (2.9)	2 (0.8)	4.9[d]	0.7–9.1	5.49[d]	1.48–20.4
Motor impairment[h]	16 (12.0)	5 (19.2)	11 (10.3)	4 (1.5)	1 (2.9)	3 (1.3)	10.6[d]	4.9–16.3	8.24[d]	2.81–24.2
Speech–language impairment[i]	22 (16.5)	9 (34.6)	13 (12.1)	20 (7.3)	3 (8.8)	17 (7.1)	9.2[d]	2.2–16.3	2.27[d]	1.28–4.00
≥1 domains of impairment[j]	33 (24.8)	14 (53.8)	19 (17.8)	33 (12.0)	3 (8.8)	30 (12.5)	12.8[d]	4.5–21.1	2.06[d]	1.33–3.19
≥2 domains of impairment[k]	14 (10.5)	5 (19.2)	9 (8.4)	5 (1.8)	1 (2.9)	4 (1.7)	8.7[d]	3.3–14.2	5.77[d]	2.12–15.7

The figures in the table represent the prevalence of impairment per domain in numbers (*n*) and percentages (%), and the risk differences in percentages and relative risk (RR) with their 95% confidence intervals (95% CI). [a]Symptomatic at birth. [b]Asymptomatic at birth. [c]Sensorineural hearing loss. [d]Statistically significant risk difference or relative risk. [e]Optic nerve atrophy, congenital cataract, cortical visual impairment. [f]Cerebral palsy, epilepsy, microcephaly, autism, attention-deficit–hyperactivity disorder. [g]Cognitive impairment based on test or diagnosis. [h]Motor impairment (fine, gross, or balance) based on test or diagnosis, sensory processing disorder, or developmental coordination disorder. [i]Language impairment based on test or diagnosis, speech impairment, oral motor skill difficulties, or auditory processing disorder. [j]Any long-term impairment, in one or more domains. [k]Impairment in two or more domains.

retrospective design of this study ensured that the vast majority of collected data were not affected by awareness of the diagnosis, therefore limiting information bias. This approach also gave a realistic perspective of the disease burden, as outcomes were based on the actual health care that was sought and provided. Furthermore, by collecting a broad range of medical data, this study illustrates in detail the specific medical problems faced by children with and without cCMV during the first 6 years of life.

It is important to note that the retrospective design of this study, while limiting information bias, entails a lack of uniformity in examinations and registration. In particular, only 20% of children had data available on physical examination after birth. On the other hand, it is unlikely that major signs or symptoms were missed, as all newborn infants in the Netherlands are regularly checked in the first weeks of life by a physician or midwife and referred to a paediatrician in the case of abnormalities. Still, some data could be missing or care may not have been sought for specific problems. This could have led to an underestimation of symptoms at birth and long-term impairment both in cCMV-positive and in cCMV-negative children. Moreover, it is not unlikely that, especially in some cCMV-positive children, more long-term impairment, such as sensorineural hearing loss, may become apparent at a later age, which could increase the risk difference between the two groups. A prospective follow-up of this cohort is therefore essential.

Selection bias could have occurred in this study, although it is difficult to assess the potential effect of this bias.[3] Parents of children with an impairment could have been more willing to participate, because they tried to find an explanation for their child's problems, or less willing because they were so busy caring for their child. Children who died in the first 5 years of life were not included; this may have led to an underestimation of the burden of disease. In addition, with a sensitivity of 84% for dried blood spot testing, some children with cCMV remained undetected, most probably those with low viral loads. As high viral loads are possibly related to a poorer outcome than low viral loads, the detected children in this cohort, with their higher viral loads, may have led to an overestimation of the burden of disease.

The percentage of children with impairments in the group without cCMV seems relatively high; however, the prevalence of, for example, speech and language problems and attention-deficit–hyperactivity disorder, which were the most prevalent conditions in this group, are comparable to children of a similar age in the general population.[10,11] This supports our assumption that few relevant problems were missed and confirms the value of our comparison group.

Sensorineural hearing loss occurred in five children with cCMV (3.8%), which is lower than previously reported in other studies.[12] A systematic review concluded that hearing loss occurred in 12.6% of all children with cCMV, in 32.8% of symptomatic children and 9.9% of asymptomatic children.[13] Underreporting of hearing loss could have occurred in our study, for example because of a diagnosis

being made after the collection of medical data. Unilateral sensorineural hearing loss especially can be difficult to recognize, and the average age at diagnosis is 5 years 6 months.[14] Longer follow-up of this cohort could reveal a higher prevalence of sensorineural hearing loss.

Impairments affecting various developmental domains (cognitive, motor, and speech–language) were frequently seen in children with cCMV. In particular, fine and gross motor impairment was eight times more frequent both in symptomatic and in asymptomatic children with cCMV (12.0%) compared with cCMV-negative children (1.5%). Furthermore, cognitive impairment was seen both in symptomatic (15.4%) and in asymptomatic (3.7%) children with cCMV, while very few children in the comparison group had cognitive problems (1.1%). Although speech and language problems are also frequently seen in the general population,[15] these problems occurred twice as often in the cCMV-positive group (16.5%) compared with the cCMV-negative comparison children (7.3%).

These observed cCMV attributable impairments indicate that, in addition to audiological follow-up and support, it is also necessary to be aware of the risk of speech and language problems, and motor impairment.

The broad range of collected data provides insight into the prevalence of specific conditions. This information can be used to confirm or generate new hypotheses. For example, this study supports the potential link between cCMV and balance problems,[16,17] and suggests a conceivable link between cCMV and autism spectrum disorder,[18–20] conditions that are not commonly recognized as being associated with cCMV. It may also be relevant to evaluate the presence of sensory processing disorder and developmental coordination disorder in other cCMV cohorts.

This study reaffirms the significant long-term disease burden of cCMV.[21] More specifically, by including a comparison group, it has demonstrated which kinds of impairment are attributable to cCMV. Consequently, in addition to frequent audiological follow-up, extra awareness of motor, cognitive, and speech–language problems is indicated for children with cCMV. Moreover, this study demonstrates the current lack of awareness of cCMV as, at the age of 5 years, only three of the 133 cCMV-positive children had previously been diagnosed. It is clear that much needs to be done to increase awareness and prevent cCMV. These findings can serve as a basis for modelling scenarios for preventive measures, such as hygienic advice,[22] maternal vaccination,[23] neonatal screening programmes,[24] or antiviral therapy.[25]

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Prevalence of long-term impairment, diagnosed in the first 6 years of life, of cCMV-positive and cCMV-negative children with or without symptoms at birth, per condition

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