Consequences of congenital cytomegalovirus infection in early childhood

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Chapter 5

Congenital cytomegalovirus infection: child development, quality of life and impact on daily life

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Abstract

Background
Congenital cytomegalovirus infection (cCMV) is the most common congenital infection worldwide and can lead to long-term impairments such as developmental delay. It is currently unknown how this affects the daily life of children and their parents.

Methods
Children with cCMV were identified by testing stored dried blood spots of 31.484 five-year-old children born in 2008 in the Netherlands. Parents of 133 children with cCMV and 274 children without cCMV participated and filled in questionnaires on the child's development, the child's and parents' quality of life, care provided for the children, and consequences of cCMV on daily life. School performance reports at six years of age were also investigated.

Results
Children with cCMV had delays in general and expressive language development more often and they attended physical therapists more frequently than children without cCMV. School performance of children with cCMV and symptoms at birth was poorer than that of cCMV-negative children with similar symptoms at birth. The quality of life of children with long-term impairment was lower in children with cCMV than those without cCMV. Parents of children with cCMV and long-term impairments reported more physical and concentration problems than parents of children without cCMV.

Conclusions
These findings indicate that cCMV has a considerable impact, not only on the child's development and school performance, but also on the daily life of children and their parents. The care for children with cCMV should therefore include support for motor and speech-language development as well as family-centered care.

Introduction

A congenital cytomegalovirus infection (cCMV) ensues when cytomegalovirus (CMV) is transmitted from the mother to the fetus during pregnancy. cCMV is the most common congenital infection, with an overall birth prevalence of 0.6 to 0.7% in industrialized countries. [1, 2] In 2007, a key review on sequelae of cCMV estimated that approximately 10 to 15% of children born with cCMV were symptomatic at birth, showing clinical features such as hepatosplenomegaly, thrombocytopenia, petechiae, microcephaly and intracranial calcifications. [1] About half of these symptomatic children develop long term sequelae, including hearing loss, motor deficits and mental retardation. Moreover, about 10 to 15% of children who are asymptomatic at birth develop long term sequelae. [1]

Knowledge concerning the full range of long-term consequences of cCMV is still incomplete. [3] Besides, most studies on long-term consequences of cCMV included no, or only small control groups, and they often had a prospective study design, which may have led to information bias. Some studies were based on a population of referred patients, rather than on a screening program, and thus included a selected population.
We performed a nationwide retrospective screening based cohort study in the Netherlands on the disease burden of cCMV up to the age of six years among congenitally infected children and a cCMV-negative control group. [4] The birth prevalence of 0.5% in this study was comparable to that in other European countries. [5] It is noteworthy that only 2.6% of the cCMV positive children had been previously diagnosed. [4] We found that long-term impairments were twice as prevalent in children with cCMV (24.8%) compared to the cCMV-negative control group (12.0%). [6]
We expected that these impairments will affect the quality of life and daily life activities of these children and their parents. To our knowledge, these consequences have been given no, or only limited attention, in previous studies.

This paper presents the outcomes of the CROCUS-study (**C**onsequences and **R**isk factors **O**f congenital **C**ytomegalovir**US** infection) concerning the child's development, school achievements, the quality of life of the child and parents and the impact on daily life. These data can be used for assessing the full impact of cCMV and can provide input for optimization of care.

Patients and Methods

Study design

The design of the CROCUS-study has been previously described. [4] In short, the first part of this study consisted of identification of children with and without cCMV at the age of five years. Subsequently data of participating children with cCMV and a selected cCMV-negative control group were collected. Children born in the Netherlands between January 1 and September 30 2008 were eligible for this study. Children with cCMV were identified by testing stored neonatal dried blood spots for CMV DNA using two separate polymerase chain reaction tests, with an assumed sensitivity of 84.4%. [7] A twice as large group of cCMV-negative children, matched to the cCMV-positive children for age, sex and postal-code region, was selected as a control group. All parents gave written informed consent and the study was approved by the medical ethics committee of the Leiden University Medical Center.

Data collection

Parents of children with cCMV were informed of the diagnosis of cCMV shortly after this was made. When the parents of the cCMV-positive children and the selected cCMV-negative control group were willing to participate in the second part of the study, they gave informed consent to collect data from the school and from healthcare providers who were involved in the care of their child. Additionally, four questionnaires were sent to the parents. The Child Development Inventory (CDI) [8, 9] translated into Dutch [10] was used to assess the development of the children. The parental proxy report (age 5-7) of the Pediatric Quality of Life Inventory™ (PedsQL™) [11-15] was used to assess the quality of life of the children. The 12-Item Short Form Health Survey (SF-12®) [16, 17] was used to assess the quality of life of the parents. In addition, a questionnaire was included concerning the medical history of the child, the family composition and characteristics, the amount of care needed by the child and the influence of the child's problems on the life of parents. These parental questionnaires were sent when the child was five years of age, a few months after the diagnosis of cCMV was known.

Definitions

The cCMV-positive and cCMV-negative children were divided into groups of children with symptoms at birth (symptomatic) and those without symptoms at birth (asymptomatic). Additionally they were grouped according to the presence or absence of long term impairments.

Being symptomatic at birth was defined as having one or more of the following signs or symptoms in the first four weeks of life: preterm birth (<37 weeks gestational age), being small for gestational age (birthweight <-2 standard deviations (SD) for gestational age), microcephaly (head circumference <-2 SD for gestational age), abnormal physical examination (hepato- or splenomegaly, petechiae or purpura, hypotonia or seizures), abnormal laboratory findings (thrombocytopenia <100*10^9/L, neutropenia <0.5*10^9/L, alanine aminotransferase >80 IU/L, conjugated hyperbilirubinemia > 2 mg/dL), cranial ultrasound abnormalities, ophthalmological abnormalities or neonatal sensorineural hearing loss (≥ 40 decibel).

Long-term impairment was defined as any moderate-to-severe impairment in one or more of the following domains: hearing (sensorineural hearing loss), visual (optic atrophy, congenital cataract, cortical visual impairment), neurologic (cerebral palsy, epilepsy, microcephaly, autism spectrum disorder, attention deficit-hyperactivity disorder), cognitive (mental retardation), motor (fine or gross motor skill or balance problems, development coordination disorder or sensory processing disorder) and speech-language (speech, language or oral motor skill problems or auditory processing disorder).

The Child Development Inventory gives an estimation of developmental age per domain. In this study, a developmental age of -2 standard deviations below calendar age or lower was classified as developmental delay.

The school performance results were based on a widely used pupil tracking system in the Netherlands. During the first two years of education, from the age of four years, a child is generally tested four times. The test results are divided into either quintiles (I, II, III, IV or V) or quartiles (A, B, C or D/E). A separate category is used for children with the lowest 10% score (V minus or E). When a child was in the lowest 10% scoring range in more than 50% of the tests or if it received special needs education this was considered a poor school performance.

The PedsQL™ consists of a Psychosocial and Physical Health Summary Score and a Total Scale Score. The scores can range from 0 to 100, where higher scores indicate better functioning. The SF-12® results in a Mental and Physical Health Composite Score. These composite scores are standardized to a mean of 50 with a standard deviation of 10 using QualityMetric Scoring Software 4.5 (QualityMetric Inc., Lincoln, RI, USA). Higher composite scores indicate a better health status.

Statistical analysis

The prevalence of developmental delay and poor school results were given as percentages. The health related quality of life scores were presented as means. The proportion of children receiving care and support and the amount of parents experiencing negative consequences in daily life were shown as percentages. The cCMV-positive children were compared to the cCMV-negative children. Mean differences or risk differences between these groups and their 95% confidence intervals (95% CI) were calculated.

For the child development inventory and school results, data were presented primarily for the children with or without symptoms at birth, as these developmental outcomes were considered a potential consequence of cCMV itself. For the quality of life, the amount of provided care and the consequences for the daily life of parents, data were presented for the groups with and without long-term impairment, in order to evaluate the effect of cCMV-associated impairments on these different outcome measures.

Subgroup analyses were performed comparing symptomatic children with and without cCMV and comparing cCMV-positive and cCMV-negative children with long-term impairment.

Additionally, for the children who had cCMV and long-term impairment, the groups with and without symptoms at birth were compared.

All statistical analyses were performed in SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Baseline data (Table 5.1)
A total of 31,484 dried blood spots were retrospectively tested and 156 children with cCMV were identified. Parents of 407 children, including 133 cCMV-positive and 274 cCMV-negative children, consented to data collection for this part of the study. Only three of the participating children with cCMV had been diagnosed with cCMV prior to this study. The baseline data of the children in this study are displayed in Table 5.1. The parent questionnaire revealed no significant differences in family characteristics such as family size and educational level of the parents, between the cCMV-positive and cCMV-negative children.

Table 5.1 - Patient and family characteristics and response rates of children with and without cCMV

	cCMV+ n = 133	**cCMV-** n = 274	p-value (chi-square)
Patient characteristic			
Mean age on 1 January, 2014 (years)	5.6 ± 0.2	5.6 ± 0.2	0.799
Male sex	75 (56.4)	149 (54.4)	0.702
Symptomatic at birth ¥	26 (19.6)	34 (12.4)	0.059
Long-term impairment ¥	33 (24.8)	33 (12.0)	0.001
Family characteristics	**n = 119**	**n = 242**	
Number of family members ‡			
Total	4.3 ± 0.8	4.3 ± 0.9	0.799
Siblings	1.5 ± 0.7	1.5 ± 0.7	0.776
Older siblings	1.3 ± 0.6	1.4 ± 0.7	0.216
Educational level mother ‡			
Low	10 (8.5)	17 (7.2)	
Middle	42 (35.9)	89 (37.9)	
High	65 (55.6)	129 (54.9)	0.935
Origin mother ‡			
the Netherlands	115 (94.3)	225 (90.4)	
Foreign	7 (5.7)	24 (9.6)	0.202
Educational level father ‡			
Low	17 (14.5)	34 (14.2)	
Middle	36 (30.8)	86 (35.8)	
High	64 (54.7)	120 (50.0)	0.784
Origin father ‡			
the Netherlands	111 (91.0)	226 (90.8)	
Foreign	11 (9.0)	23 (9.2)	0.945

Table 5.1 - Patient and family characteristics and response rates of children with and without cCMV

	cCMV+ n = 133	**cCMV-** n = 274	p-value (chi-square)
Response rate	**n = 133**	**n = 274**	
Child Development Inventory	123 (92.5)	242 (88.3)	0.196
PedsQL™	123 (92.5)	241 (88.0)	0.164
SF-12®	122 (91.7)	242 (88.3)	0.294
Parental questionnaire	119 (89.5)	242 (88.3)	0.731
Test results from schools	117 (88.0)	243 (88.7)	0.832

The figures represent mean ± standard deviation (SD) or number (n) and percentage (between brackets) for children with (cCMV+) and without (cCMV-) congenital CMV infection.
¥ including children with preterm birth, small for gestational age, microcephaly, cranial ultrasound abnormalities and neonatal sensorineural hearing loss. ¥ including any moderate-to-severe impairment in one or more of the following domains: hearing, visual, neurologic, cognitive, motor and speech-language. ‡ based on parental questionnaire

Child development and school results

Child Development Inventory (Table 5.2, Figure 5.1)
On most domains of the Child Development Inventory, the development of children with cCMV was comparable to children without cCMV. However, a delay in expressive language and general development was reported more often in children with cCMV compared to those without cCMV, with risk differences of 8.0% (95% CI 1.3-14.8) for expressive language and 6.9% (95% CI 0.9-12.8) for general development. (Table 5.2)
In children with symptoms at birth, problems in self-help were seen more often in cCMV positive than in cCMV negative children, with a risk difference of 22.9% (95% CI 3.9-41.8).
In children with cCMV who had long-term impairment, a delay in general development was more common than in children with long-term impairment without cCMV: 44.4% versus 16.0%, risk difference: 28.4%, 95% CI: 4.8-52.1. (Figure 5.1)
There was no difference in the prevalence of developmental delay between the symptomatic (n = 14) and asymptomatic (n = 19) children with cCMV who developed long-term impairment (data not shown).

Table 5.2 - Prevalence (%) of developmental delay for various domains of the Child Development Inventory for children with and without cCMV.

	cCMV-positive			cCMV-negative		
	Overall (n = 123)	**Sympt.** (n = 23)	**Asympt.** (n = 100)	**Overall** (n = 242)	**Sympt.** (n = 31)	**Asympt.** (n = 211)
Expressive language	13.8*	26.1	11.0	5.8*	12.9	4.7
Language comprehension	12.2	21.7	10.0	6.6	12.9	5.7
Fine motor	6.5	17.4	4.0	3.7	12.9	2.4
Gross motor	21.1	26.1	20.0	13.2	22.6	11.8
Self help	13.8	26.1*	11.0	14.5	3.2*	16.1
Social	41.5	47.8	40.0	42.1	41.9	42.2
Letters	6.5	13.0	5.0	5.8	6.5	5.7
Numbers	4.1	4.3	4.0	4.1	6.5	3.8
General development	10.6*	21.7	8.0	3.7*	6.5	3.3

Percentage of children with developmental delay (developmental age below -2 standard deviations for calendar age) for cCMV-positive and cCMV-negative children who were symptomatic (sympt.) or asymptomatic (asympt.) at birth. * statistically significant difference between cCMV-positive and cCMV-negative children ($p < 0.05$)

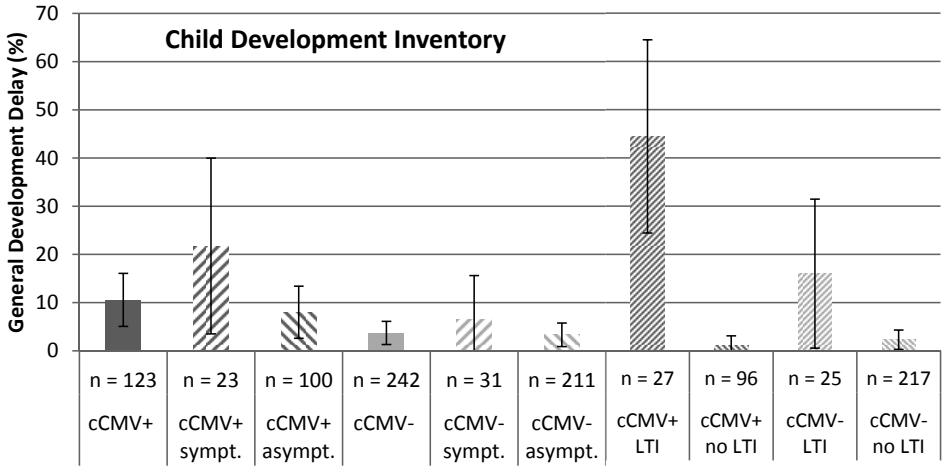


Figure 5.1 - Percentage and 95% CI of children with general developmental delay based on the Child Development Inventory for cCMV-positive (cCMV+) and cCMV-negative (cCMV-) children who were symptomatic (sympt.) or asymptomatic (asympt.) at birth or those with (LTI) or without long-term impairment(no LTI).

School performance (Figure 5.2)
Six children (5.3%) in the cCMV-positive group and seven children (2.9%) in the cCMV-negative group attended special needs education.
The percentage of children with a poor school performance was higher in children with cCMV and symptoms at birth (26.1%) compared to cCMV-negative children with symptoms at birth (3.3%), giving a risk difference of 22.8% (95% CI: 3.7-41.8).
The difference in poor school performance between cCMV-positive (26.9%) and cCMV-negative (17.9%) children with long-term impairment was much smaller and statistically not significant (risk difference: 9.1%, 95% CI: -13.1-31.3). Children with cCMV and long-term impairment who were symptomatic at birth had poor school results more often (41.7%) compared to those without symptoms at birth (14.3%), however the risk difference (27.4%, 95% CI: -6.0-60.8) was not statistically significant (data not shown).

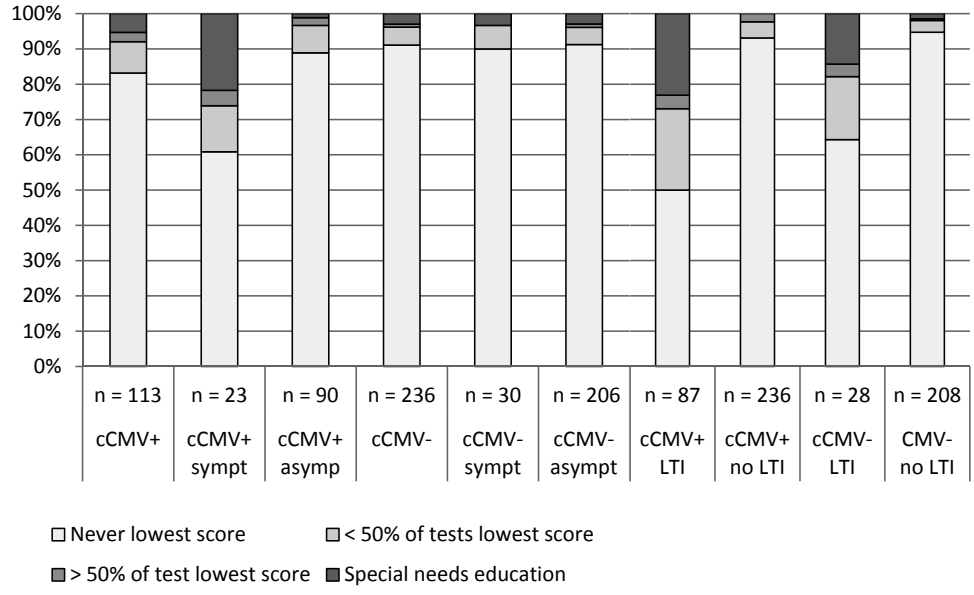


Figure 5.2 - School performance of children with and without cCMV, during the first two years of primary regular education.
Frequency of mathematic and language tests in the lowest score range (under the tenth percentile) and the prevalence of children attending special needs education. For children with (cCMV+) and without cCMV (cCMV-) and the symptomatic (sympt) and asymptomatic (asympt) subgroups as well as for the children with (LTI) and without long-term impairment (no LTI).

Consequences for children

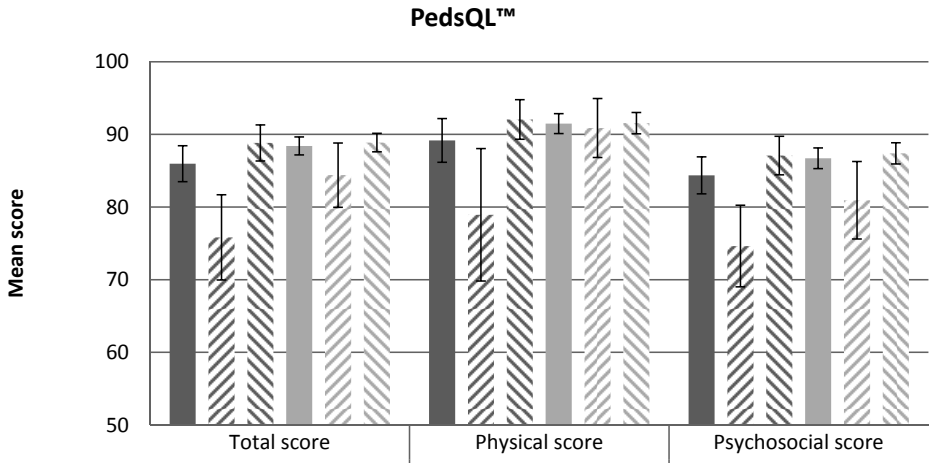
Care and support (Table 5.3)
Children with cCMV attended a physical therapist more often (12.6%) than the cCMV-negative (3.3%) with a risk difference of 9.3% (95% CI: 2.9-15.7). This difference between children with and without cCMV was higher for children with long-term impairment, with a risk difference of 36.0% (95% CI: 15.3-56.7). There was no difference between symptomatic and asymptomatic children with cCMV who developed long-term impairment (data not shown).
Between children with and without cCMV who were symptomatic at birth a difference of 21.8% (95% CI: 1.8-41.8) was seen for physical therapy attendance (data not shown).
There were no statistically significant differences between children with and without cCMV for consultations by medical specialists or other healthcare providers.

Table 5.3 - The percentage of children who received care and support, for the children with and without cCMV who did or did not develop long-term impairment (LTI).

	cCMV-positive			**cCMV-negative**		
	Overall	**LTI**	**no LTI**	**Overall**	**LTI**	**no LTI**
	(n = 119)	(n = 25)	(n = 94)	(n = 242)	(n = 25)	(n = 217)
Medical day care	1.7	8.0	0.0	0.8	8.0	0.0
Medical specialist [A]	16.8	44.0	9.6	12.8	24.0	11.5
Physical therapist	12.6*	40.0*	5.3	3.3*	4.0*	3.2
Speech therapist	11.8	52.0	1.1	6.6	32.0	3.7
Occupational therapist	3.4	12.0	1.1	0.4	4.0	0.0
Support at school	8.4	32.0	2.1	3.7	12.0	2.8
Additional support [B]	3.4	12.0	1.1	1.7	4.0	1.4
Psychological support	2.5	8.0	1.1	2.1	8.0	1.4
Any support	28.6	76.0	16.0	24.4	52.0	21.2

A including pediatrician, otorhinolaryngologist, ophthalmologist and other medical specialist
B including welfare support worker, remedial educationalist, pedagogical staff member and play therapist * statistically significant difference between cCMV+ and cCMV- children ($p < 0.05$)

Quality of life: PedsQL™ (Figure 5.3)
The average of the total scale score and physical and psychosocial health summary scores were generally comparable between children with and without cCMV. However, children with cCMV and long-term impairment had lower scores than their cCMV-negative counterparts, with a mean difference of 8.6 (95% CI: 1.3-15.8) for the total scale score and 11.9 (95% CI: 2.1 - 21.8) for the physical health summary score. For children who had cCMV and long-term impairment no differences were seen between those with and those without symptoms at birth (data not shown).



	Total score	Physical score	Psychosocial score
cCMV+	86,0	89,2	84,4
cCMV+ LTI+	75,8 *	78,9 *	74,6
cCMV+ LTI-	88,8	92,1	87,1
cCMV-	88,4	91,5	86,7
cCMV- LTI+	84,4 *	90,9 *	80,9
cCMV- LTI-	88,9	91,6	87,4

Figure 5.3 - Quality of life of children with and without congenital CMV infection.
The quality of life is measured using the PedsQL™ parent proxy report (age 5-7) and presented as mean scores for cCMV-positive (cCMV+) and cCMV-negative (cCMV-) children with (LTI+) or without (LTI-) any long-term impairment. * Statistically significant difference between cCMV+ and cCMV- ($p < 0.05$). Total score: Total scale score; Physical score: Physical health summary score; Psychosocial score: Psychosocial health summary score

Consequences for parents

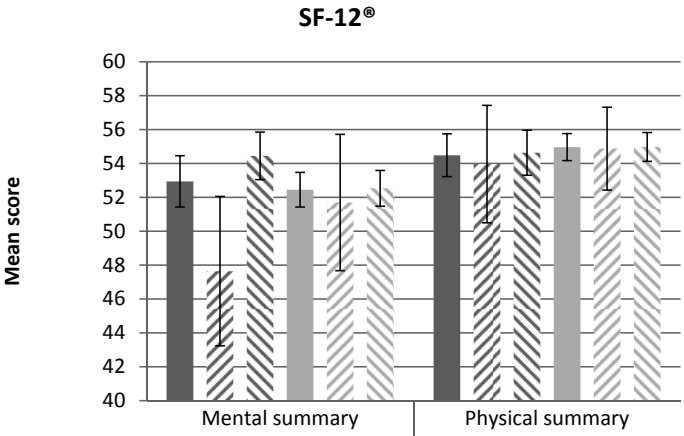
Daily life consequences (Table 5.4)
In the parent questionnaire, we asked about the consequences of their child's problems for various aspects of the parents' life. Parents of children with cCMV and long-term impairment reported having more physical and concentration problems than parents of children with long-term impairment without cCMV. The risk difference between cCMV-positive and cCMV-negative was 28.0% (95% CI 3.8-52.2) for physical problems and 24% (95% CI 0.1-48.0) for concentration problems. Even though the differences between cCMV-positive and cCMV-negative children with long-term impairment were not statistically significant for the other aspects of daily life, they were consistently more common in the parents of cCMV-positive children.
Similar results were found for cCMV-positive children with long-term impairment who were symptomatic at birth and those who were asymptomatic at birth (data not shown).

Table 5.4 - Impact on various aspects of daily life of parents, due to their child's problems, shown for parents of children with and without cCMV.

	cCMV-positive			**cCMV-negative**		
	Overall	**LTI**	**no LTI**	**Overall**	**LTI**	**no LTI**
Aspects of daily life	(n = 119)	(n = 25)	(n = 94)	(n = 242)	(n = 25)	(n = 217)
Physical	13.4	44.0*	5.3	7.4	16.0*	6.5
Sleep	10.1	24.0	6.4	7.4	16.0	6.5
Concentration	11.8	40.0*	4.3	5.4	16.0*	4.1
Work / daily activities	5.9	28.0	0.0	5.8	16.0	4.6
Housekeeping	5.9	24.0	1.1	3.3	12.0	2.3
Leisure time	7.6	32.0	1.1	5.0	24.0	2.8
Social	8.4	32.0	2.1	7.4	28.0	5.1
Financial	5.0	24.0	0.0	3.3	16.0	1.8
Emotional	16.8	44.0	9.6	12.8	32.0	10.6
Any consequence	25.2	68.0	13.8	21.5	44.0	18.9
Any severe consequence	7.6	24.0	3.2	6.6	24.0	4.6

Data are presented as number and percentage for children with (cCMV+) and without cCMV (cCMV-) and the subgroups with (LTI+) and without long-term impairments (LTI-).

Quality of life: SF-12® (Figure 5.4)
In general, there were no differences in mean health-related quality of life scores between parents of children with and without cCMV. The largest difference in quality of life was seen between parents of children with cCMV and long-term impairment and parents of children with long-term impairment without cCMV. The mean difference between these groups was 4.1, however this difference was not statistically significant (95% CI: -1.8-9.9).
No differences were seen between parents of symptomatic and asymptomatic children with cCMV who developed long-term impairment (data not shown).



	Mental summary	Physical summary
cCMV+	52,9	54,5
cCMV+ LTI+	47,6	54,0
cCMV+ LTI-	54,4	54,6
cCMV-	52,4	55,0
cCMV- LTI+	51,7	54,9
cCMV- LTI-	52,5	55,0

Figure 5.4 - Mean mental and physical component summary scores, measured using the SF-12®, for parents of cCMV-positive (cCMV+) and cCMV-negative (cCMV-) children, with (LTI+) or without (LTI-) any long-term impairment.

Discussion

This study demonstrated that a delay in general development and in expressive language is more common in children with cCMV than in children without cCMV. Children with cCMV and symptoms at birth have poorer school performances compared to cCMV-negative children with symptoms at birth. These consequences of cCMV are reflected in the overall and physical quality of life, which is lower for cCMV-positive children with long-term impairment compared to their cCMV-negative counterparts. Moreover, the parents of children with cCMV and long-term impairment reported significantly more physical and concentration problems than parents of cCMV-negative children with long-term impairment.

Although it is known that congenital CMV infection is related to developmental delay, especially in those with symptoms at birth, [1, 5, 18] this study reveals new insights by looking at various domains of development. The delay in expressive language in children with cCMV is interesting since only 5 cCMV-positive children in this study (3 in the asymptomatic group) had been diagnosed with sensorineural hearing loss before the age of five or six years. This means that language development is impaired in cCMV-positive children even in the absence of hearing loss. Only a few studies looked at language development in asymptomatic children with cCMV of whom only a few had hearing loss. [5, 19] They found language impairment in 6.8 to 31.6% of these children.

In line with the problems in expressive language reported in the child development inventory, speech therapy was more frequently needed by children with cCMV, than by cCMV-negative children, although this difference was not statistically significant.
The need of children with cCMV for physical therapy, both in the symptomatic and asymptomatic groups, was significantly higher than in children without cCMV. Although other authors reported that motor developmental delay occurs in children with cCMV, [6, 20] this area has received little attention up to now.

Furthermore, this is the first study to assess the quality of life of children and parents and the consequences for the daily life of parents in relation to their child's cCMV. The slightly, but statistically significant, lower quality of life in the cCMV-positive children in comparison to the cCMV-negative children with long-term impairment is certainly relevant, especially considering that the quality of life is usually subject to adaptation. [21, 22] Patients experiencing a disability generally give themselves higher quality of life ratings, presumably due to physical and psychological adaptation, compared to people imagining having such a disability. [23] Moreover, in another study parents of children with disabilities rated the quality of life of their children significantly higher than the physicians did. [24]

In addition to physical and concentration problems, parents of children with cCMV and long-term impairment reported a markedly lower mental quality of life compared to parents of cCMV-negative children with long-term impairment. The lack of statistical significance of this difference is probably due the relatively small number. However, in view of the abovementioned suggestion that the quality of life in studies is often overestimated due to adaptation, [21, 22] this difference is a relevant finding.

It is interesting to see that there is no difference within the group of children with cCMV and long-term impairment between those who were symptomatic at birth and those who were asymptomatic. This suggests that if children develop long-term impairment the developmental and daily life problems in symptomatic and asymptomatic children are equally severe. It is important to realize that, although the risk of long-term impairment is higher in the symptomatic children, the majority of children with cCMV and long-term impairment are asymptomatic at birth.

The design of this study has both advantages and disadvantages. Due to the inclusion of a cCMV-negative control group, this study can estimate the consequences attributable to cCMV. The retrospective design of this study enabled evaluation of the actual care that was provided, mostly without previous knowledge of the cCMV diagnosis, since only three parents were aware of the diagnosis prior to this study. On the other hand, there is a risk of recall and information bias, because the parental questionnaires were administered after the diagnosis of cCMV was communicated. This may have led to an overestimation of negative consequences in the cCMV-positive group and subsequently to an overestimation of the risk difference between the groups.

Conclusion

Children with congenital CMV face general developmental delay and expressive language delay more often than children without cCMV. Children with cCMV and long-term impairment, comprising 25% of all children with cCMV, have a lower quality of life. The parents of cCMV-positive children with long-term impairment experience more physical and concentration problems and their mental quality of life is lower, than parents of cCMV-negative children.
Overall, these findings indicate that a congenital CMV infection leads to a considerable burden of care for children and has an impact on the quality of life of both children and their parents. This study demonstrates that, besides the current regular medical care for children with cCMV, support for language and motor development is required and that family-centered care is essential. Moreover, these data can be used in discussions on the necessity of measures to attempt to prevent cCMV.

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Conflict of interest
All authors reported having no disclosures.

References

1. Dollard, S.C., S.D. Grosse, and D.S. Ross, New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol, 2007. 17(5): p. 355-63.
2. Kenneson, A. and M.J. Cannon, Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol, 2007. 17(4): p. 253-76.
3. Manicklal, S., et al., The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev, 2013. 26(1): p. 86-102.
4. Korndewal, M.J., et al., Disease burden of congenital cytomegalovirus infection at school entry age: study design, participation rate and birth prevalence. Epidemiol Infect, 2016. 144(7): p. 1520-7.
5. Ahlfors, K., S.A. Ivarsson, and S. Harris, Report on a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. Scand J Infect Dis, 1999. 31(5): p. 443-57.
6. Korndewal, M.J., et al., Long-term impairment attributable to congenital cytomegalovirus infection. Manuscript submitted for publication. 2016.
7. Wang, L., et al., Dried blood spots PCR assays to screen congenital cytomegalovirus infection: a meta-analysis. Virol J, 2015. 12: p. 60-70.
8. Ireton, H. and F.P. Glascoe, Assessing children's development using parents' reports. The Child Development Inventory. Clin Pediatr (Phila), 1995. 34(5): p. 248-55.
9. Doig, K.B., et al., The Child Development Inventory: A developmental outcome measure for follow-up of the high-risk infant. J Pediatr, 1999. 135(3): p. 358-62.
10. Korver, A.M., et al., DECIBEL study: Congenital cytomegalovirus infection in young children with permanent bilateral hearing impairment in the Netherlands. J Clin Virol, 2009. 46(Suppl 4): p. S27-31.
11. Chan, K.S., et al., The PedsQL: reliability and validity of the short-form generic core scales and Asthma Module. Med Care, 2005. 43(3): p. 256-65.
12. Varni, J.W. and C.A. Limbers, The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr Clin North Am, 2009. 56(4): p. 843-63.
13. Varni, J.W., et al., The PedsQL 4.0 Generic Core Scales: sensitivity, responsiveness, and impact on clinical decision-making. J Behav Med, 2002. 25(2): p. 175-93.
14. Varni, J.W., M. Seid, and P.S. Kurtin, PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care, 2001. 39(8): p. 800-12.
15. Varni, J.W., M. Seid, and C.A. Rode, The PedsQL: measurement model for the pediatric quality of life inventory. Med Care, 1999. 37(2): p. 126-39.
16. Gandek, B., et al., Tests of data quality, scaling assumptions, and reliability of the SF-36 in eleven countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol, 1998. 51(11): p. 1149-58.
17. Gandek, B., et al., Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol, 1998. 51(11): p. 1171-8.
18. Boppana, S.B., S.A. Ross, and K.B. Fowler, Congenital cytomegalovirus infection: clinical outcome. Clin Infect Dis, 2013. 57(Suppl 4): p. S178-81.

19. Milewska-Bobula, B., et al., Evaluation of intellectual development of children following congenital, mildly symptomatic cytomegalovirus (CMV) infection. A prospective study. Med Wieku Rozwoj, 2010. 14(4): p. 370-3.
20. De Kegel, A., et al., Early motor development of children with a congenital cytomegalovirus infection. Res Dev Disabil, 2015. 48: p. 253-261.
21. Peeters, Y., T.P. Vliet Vlieland, and A.M. Stiggelbout, Focusing illusion, adaptation and EQ-5D health state descriptions: the difference between patients and public. Health Expect, 2012. 15(4): p. 367-78.
22. Ubel, P.A., G. Loewenstein, and C. Jepson, Whose quality of life? A commentary exploring discrepancies between health state evaluations of patients and the general public. Qual Life Res, 2003. 12(6): p. 599-607.
23. Peeters, Y. and A.M. Stiggelbout, Health state valuations of patients and the general public analytically compared: a meta-analytical comparison of patient and population health state utilities. Value Health, 2010. 13(2): p. 306-9.
24. Nolan, R., et al., Differing perceptions regarding quality of life and inpatient treatment goals for children with severe disabilities. Acad Pediatr, 2014. 14(6): p. 574-80.