Neurodevelopmental outcome in children with congenital cytomegalovirus infection : a prospective multicenter cohort study

Long-term neurodevelopmental outcome in children with congenital cytomegalovirus infection: a prospective multicenter cohort study.

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Short title

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Keywords

congenital infection / outcome / neurodevelopmental outcome / congenital cytomegalovirus infection

Abstract

Background
Congenital cytomegalovirus infection (cCMV) is the most common congenital infection worldwide and is a major cause of neurodevelopmental impairment in children. At this point there are insufficient data on neurodevelopmental outcome of children with cCMV, both symptomatic and asymptomatic.

Aim
This study aimed to describe the neurodevelopmental outcome in a large prospective cohort of children with cCMV.

Methods
All children with cCMV, included in the Flemish cCMV register, were eligible for this study. Data on neurodevelopmental outcome was available in 753 children. Data on neuromotor, cognitive, behavioral, audiological and ophthalmological outcome were analyzed.

Results
Neurodevelopmental outcome was normal in 530/753 (70,4 %) at any age of last follow-up. Mild, moderate and severe neurodevelopmental impairment was found in 128/753 (16,9%), 56/753 (7,4%) and 39/753 (5,2%), respectively. Adverse outcome is found both in the symptomatic and asymptomatic children (53,5% versus 17,8%). Autism spectrum disorder (ASD) was diagnosed more often than in the general population in Flanders (2,5% versus 0,7%). Speech and language impairment was found in 2%, even in absence of hearing loss.

Conclusion
Both symptomatic and asymptomatic cCMV children are at risk of sequelae, with higher risk in case of first trimester infection. During follow-up of this population, special attention should be given to the audiological follow-up, the presence of hypotonia at young age, the possible higher risk of ASD and the risk of speech and language impairment even in absence of hearing loss. Our results emphasize the need for multidisciplinary neurodevelopmental follow-up of all cCMV infected children.

List of abbreviations

ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorder
AST	aspartaat-aminotransferase
ALT	alanine-aminotransferase
cCMV	congenital cytomegalovirus infection
crUS	cranial ultrasound
CNS	central nervous system
CT	computed tomography
DNA	desoxyribonucleic acid
IUGR	intra-uterine growth restriction
LSV	lenticulostriatal vasculopathy
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
SNHL	sensorineural hearing loss

Introduction

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection affecting about 0,15-2% of all live births worldwide and 0,5% in Europe [1,2,3]. Congenital CMV infection can occur as the result of a primary CMV infection during pregnancy, a reinfection with a new strain or reactivation of a latent infection [2,3]. Of all infected children, 15-20 % will be symptomatic at birth [2,4]. These symptomatic children are at high risk (4060%) of developing serious neurological sequelae such as sensorineural hearing loss, cerebral palsy, mental retardation and visual impairment [1,2,5,6]. Although most asymptomatic children develop normally, still 15-20% of them will develop sequelae, particularly sensorineural hearing loss [1,2,3,5,6].

It is important to have a better understanding of the natural history of cCMV infection and of the long-term outcome of the infected children to counsel parents and guide follow-up programs and treatment. At this point there are insufficient data on long-term neurodevelopmental outcomes of children with cCMV, particularly for the asymptomatic group. [7] It is challenging to perform long-term follow-up and only a few studies of cCMV have data on neurodevelopmental outcome beyond 1-2 years of age. [5,6,7]

In 2007, a multicenter register was set up to document diagnosis, treatment and follow-up of patients that presented with cCMV in the collaborating hospitals in the Flanders region of Belgium. This longitudinal study describes the neurodevelopmental outcome of children with confirmed congenital CMV which are included in the Flemish register between 2007 and 2020. Both asymptomatic and symptomatic children are entered in the register and follow-up is offered to all children as suggested by the Flemish consensus. In this report we describe the results on neurodevelopmental outcome of the patients included in this register, with emphasis on neuromotor, cognitive and neurobehavioral outcome.

Patients and methods

Patients

Patients were recruited from six centers in Flanders, Belgium who initially participated in the register. This registration was approved by the Ethics Committee and was enlisted at the Privacy Commission. Inclusion in the register was performed after written informed consent of a parent or a legal guardian. All data were collected on paper and sent to the database manager until 2013 when an electronic database [8] was developed, enabling entry of all data in a uniform manner by each physician with access to the database.

Patients are included in the register only after diagnosis of cCMV is confirmed by viral isolation and/or CMV-DNA positive PCR on urine/saliva sampled within the first 3 weeks of life or by retrospective diagnosis (> 21 days of age), made by CMV-DNA positive PCR on dried blood spot (DBS). Current testing strategy for cCMV in Flanders consists of testing in case of known maternal seroconversion. In Flanders, screening for seroconversion is performed at 12-13 weeks and afterwards in case of suspicion of seroconversion. If a baby presents with clinical signs suggestive for CMV-infection, they are tested at birth. Universal neonatal screening is not performed.

At enrolment of the patient, data are collected concerning the timing of seroconversion, fetal ultrasound, amniocentesis, prenatal MRI, indication for diagnostic testing at birth, age at diagnosis, diagnostic techniques, demographic features, clinical features at birth, laboratory results, results of central nervous system imaging (crUS, MRI), audiological testing, ophthalmologic investigation and antiviral therapy. All recommended investigations to evaluate involvement of central nervous system, hearing and vision, are preferably performed within 1 month after birth to identify children eligible for antiviral treatment.

Classification at birth

Classification of the children as (a)symptomatic is made after all additional investigations at birth are performed and is based on the combination of presence of clinical features, laboratory results, results central nervous system imaging by crUS and/or MRI and the results of audiological and ophthalmologic investigation. Recently, following the international recommendation that symptomatic children should be classified as mildly, moderately or severely symptomatic [1], all children were re-classified in this way based upon the results of the first investigations at birth. [9] Figure 1 shows the definition of the classification as used in Flanders, Belgium. Patients with late diagnosis of cCMV (beyond age of 28 days) are classified asymptomatic at birth, since there was no reason to test them for cCMV at birth. This group is analyzed separately.

Therapy

Indication for treatment has changed over the years and is in agreement with the most recent consensus of the Flemish society of Paediatrics', Neonatology and Perinatal Epidemiology Working Group (2018). Treatment is offered to severely symptomatic neonates and can be considered in moderately symptomatic children based on expert opinion. After being informed on the possible benefits and short- and long-term side-effects of antiviral therapy, parents are involved in the decision making.

Initially, treatment consisted of intravenous ganciclovir during 6 weeks at a regimen of 6 mg/kg, twice daily. Since 2012, oral treatment with valganciclovir for 6 weeks, 16 mg/kg twice daily, has been introduced. Since end of 2017, valganciclovir therapy duration has been prolonged to 6 months.

Follow up

Every participating center is responsible for organizing the follow-up of the children from

8 their center included in the register. Results of this follow-up are entered in a uniform manner in the electronic database which is available online. There are separate forms for audiological and neurodevelopmental follow-up.

The neurodevelopmental assessment consisted of evaluation of physical, motor and cognitive development, as well as behavior and is performed by a multidisciplinary team (pediatric neurologist, neonatologist, physiotherapist, speech therapist and psychologist)

namely, the centers of developmental disorders (COS) in Flanders. Initially, follow-up was recommended at 4 months, 12 months, 18 months, 24 months and yearly after that until 72 months. Due to the high workload in the centers for developmental disorders, follow-up was altered with a first consultation at 4 months in case of symptomatic disease and at 12 months in case of asymptomatic disease. Thereafter, follow-up is planned as deemed necessary by the specialists of the COS based on the findings of their examination. Neurodevelopmental evaluation is performed using following tests according to the age of the child: Alberta Infant Motor Scale (AIMS), Bayley Scales of Infant Development (second/third edition), Wechsler Intelligence scales for children (third edition).

Over the years, an important loss to follow-up was noticed for neurodevelopmental evaluation. To address this problem, a patient-reported questionnaire was developed to evaluate the neurological development of children of 5-6 years of age. Different domains are questioned: motor and cognitive development, behavior and social-affective development. It is based upon validated scoring systems for neurodevelopmental outcome and was tested for its ease of use by parents of healthy (non-cCMV) children in a kindergarten. [9] Since 2013 we send this questionnaire to the parents of every child in our registry when they reach the age of 5-6 years. The results of this questionnaire were also entered in the database and are integrated in the overall results presented here. Table 1 shows the classification of cognitive outcome per subdomain.

As for audiologic assessment, generally diagnostic ABR during natural sleep is used in children younger than 6 months. Older children are tested by age-appropriate tone audiometry, as described by Goderis et al. [10] All asymptomatic children are followed yearly; the asymptomatic children are followed every six months until 3 years of age and yearly after that. In this report we describe hearing outcome as normal, mildly, moderately or severely impaired.

At this time, all children in Flanders with congenital hearing loss (of all etiology) have a vestibular screening at 6 months. It was decided that also in all children with cCMV (with or without hearing loss) vestibular screening should be performed at age 6 months. Follow-up of vestibular function is planned if first results are abnormal. Ophthalmological follow-up is performed by fundoscopy, should be performed yearly and is scored as normal/abnormal.

Table 1 gives an overview of the classification and scoring in every domain separately.

At the end, based on results of the subdomains, all patients were classified as having a normal development or a mild, moderate or severe impairment. Development was normal in case of normal neurodevelopmental outcome (cognitive, neuromotor, behavior), normal hearing and normal vision. If in any subdomain, development was impaired, the overall development was classified as impaired based upon the ‘worst’ classification. For example, if a child is bilaterally deaf but wears a cochlear implant and has normal motor, cognitive and behavioral development, the overall development is classified as severe because of the severe hearing impairment.

The primary study objective is to describe the neuromotor, cognitive, behavioral, visual and audiological development. Secondary objective is to assess the association between overall

development and trimester of infection and the association between development and classification as symptomatic/asymptomatic at birth.

Results

Demographic features

In December 2020, 527/1059 (49,7%) children in the register reached the age of 6 years and older and 99/1059 (9,3%) are 12 months or younger. On December 31st , 2020, neurodevelopmental data of 753 children of 1059 children with cCMV infection were available. Male/female ratio in this group is 1,1 (395 males/358 females). The median gestational age at birth was 39 weeks (IQR = 2) and prematurity (< 37 weeks) was present in 7,9%.

In this study population 492/753 (65,5%) is classified as asymptomatic at birth. Two hundred sixty children are classified as symptomatic (34,5%) of which 28/260 (10,7%) mildly, 42/260 (16,3%) moderately and 190/261 (73%) severely symptomatic. Treatment with (val)ganciclovir was given in 180 of 261 symptomatic children (69,2%).

The number of children in which outcome data are available in the database decline with advanced age of follow-up. The percentage of children with abnormal development is higher in children with last follow-up at later age. Median age of last follow-up in the study population is 12 months (IQ 12-13 months).

Perinatal characteristics

Imaging of the central nervous system was performed in 717/753 (95,2%) by cranial ultrasound (crUS), computed tomography scan (CT), magnetic resonance imaging (MRI) or a combination of those. Abnormal crUS was described in 175/660 (26,5%), abnormal CT in 8/41 (19,5%) and abnormal MRI in 188/531 (35,4%). The recommended management of children with cCMV in Flanders has changed over the years and MRI was not mandatory for a long period during this registration while crUS was. Hence, in children where no MRI was performed, only crUS was used to evaluate CNS involvement.

Hearing and ophthalmological evaluation at birth are available in 749/753 (99,5%) and 729/753 (96,8%), respectively. Hearing loss was detected at birth in 114/749 (15,2%) and ophthalmological evaluation was abnormal in 4/729 (0,5%). Clinical features (e.g. microcephaly, growth restriction, petechiae, hepatosplenomegaly and jaundice) were present at birth in 66/753 (8,8%) of the children.

Neurodevelopmental outcome

Normal development at last evaluation was found in 530/753 (70,4 %). Mild, moderate and severe impairment is found in 128/753 (16,9%), 56/753 (7,4%) and 39/753 (5,2%), respectively. Among those 223 patients with abnormal outcome 87 (39%) presented with isolated neuromotor impairment, 5 (2,2%) with isolated intellectual disability, 55 (24,7%) with isolated hearing loss, 8 (3,5%) with isolated behavioural problems and 15 (6,7%) with

combined motor, intellectual, behavioural and hearing disability. The other 53 children presented with impairments in different combinations of the subdomains.

Neuromotor impairment

Of 753 children, 581 (77,1%) had a normal motor development. Mild neuromotor impairment was found in 131/753 (17,4%); moderate impairment in 23/753 (3,1%) and severe neuromotor impairment in 18/753 (2,4%). One baby had Down syndrome.

Marked hypotonia was among the most reported findings in this population. Eighty-one of the 172 impaired children (47%) presented with hypotonia that impaired their motor development. Among all neuromotor impaired children, 10 (5,8%) are diagnosed with cerebral palsy (table 3). In 78 of 172 (45,3%) impaired children therapy was initiated (e.g., Bobath therapy, physiotherapy, home guidance, revalidation center, …). Five of the children are in need of a sitting or walking aid. Six children developed epilepsy.

Cognitive impairment

Normal cognitive development is present in 675/753 (89,6%). We find a mild impairment in 44/753 (5,7%), moderate impairment in 8/753 (1,1%) and severe impairment in 7/753 (0,9%) (table 2). Results on cognitive outcome were not available in 20/753 (2,6%) children. Delayed speech development was described in 16 of 58 cognitive impaired children (27,6%), in 7 of them without hearing loss. Occupational therapy, speech therapy or need for special education was initiated in 22/58 (37,9%) of the impaired children.

Neuro-behavioral impairment

In 140/753 (18,6%) no information on behavior was found in the database. In 536 of the remaining 613 children (87%) behavior was reported to be normal. Mild impairment is found in 57/613 (9,3%), moderate impairment in 19/613 (3,1%) and severe impairment only in 1 (0,2%). There is a wide variety in behavioral problems that is not always specified in the database. Autism spectrum disorder (ASD) was diagnosed in 19 of 77 children (24,6%) with impaired behavior and attention deficit hyperactivity disorder (ADHD) was found in 7/77 (9%). Other problems are listed in table 2.

Hearing impairment

Follow-up of hearing was available in 739 children. Normal hearing was found in 623 (84,3%). Hearing loss defined as ≥ 40dB in the best ear was present in 37/739 (5%), hearing loss between 40 and 55 dB in the best ear with or without hearing aid in 40/739 (5,4%) and hearing loss > 55 dB in the best ear with or without hearing aid in 39/739 (5,3%). Hearing loss was present in 29,2% of the asymptomatic children and in 70,8% of the symptomatic group. Twenty-one children were in need of hearing aids/cochlear implants (table 2).

Vision

No visual problems at last age of follow-up were found in 725/753 (96,3%) of all children.

There were no data on vision in 14/753 (1,8%). Only a minority (1,9%) reported correctable visual problems such as refractive disorders or amblyopia. There were no cases of late onset chorioretinitis among the 739 children with ophthalmological follow-up.

Relation between neurological outcome and classification at birth

Table 3 shows the distribution of overall developmental outcome in relation to classification at birth. In 7 of 465 (1,5 %) asymptomatic children, overall development outcome was defined as severely impaired. All of them were classified as severely impaired because of isolated severe hearing loss. No severe impairment was reported in the mildly and moderately symptomatic children. In the severely symptomatic group, severe impairment was found in 27/190 children (14,2 %). There was a significant higher proportion of children with severe impairment in the severe symptomatic group compared to the mildly, moderately and asymptomatic children. (P = 0,00) The group of children with delayed diagnosis and classified as asymptomatic in our registry are described separately in this table. In this group, 12/27 (44,5%) of the children have a normal overall development outcome. Mild, moderate and severe impairment is seen in 18,5% in each subgroup.

Relation with trimester of infection

In 495/753 (65,7%) children in the study population, data on timing of seroconversion are available. There are 233 (47%) first trimester infections, 166 (33,5%) second trimester infections and 96 (19,5%) of the infections occurred in the third trimester. Table 3 shows the numbers of mild, moderate and severe impairment in the population in relation to trimester of infection. There is a statistically significant lower proportion of children with normal development after first trimester infections compared to second or third trimester infections first trimester infections. (P = 0,00)

Discussion

To our knowledge, this is the largest cohort of children with cCMV in which neurodevelopmental outcome is described. For this study, all children in which data on outcome are entered in the database were included, regardless of age at last follow-up. Hence, the age at last follow-up differs in the study population: in the majority (66,9%) of the children, last age at follow-up is 4 to 12 months and in 79/753 (10,5%), it was 72 months. Since 43,6% of the study population is younger than 60-72 months at this moment, this was to be expected. However, we noticed a decline in the number of children with follow-up at later age, even in the children who have reached the age of 6 years. Several explanations can be found for this observation. First, the follow-up as recommended by the Flemish consensus, is not mandatory. Parents may prefer their own pediatrician, who may organize the follow-up at a different pace according to the findings during follow-up. Secondly, neurological sequelae are mostly expected in the group of children with abnormal CNS imaging. Hence, parents are reassured about the development in case of normal CNS imaging at birth which may result in not attending neurological follow-up consultations. Last, due to the high workload in the COS in Flanders, follow-up in every child until 6 years of age is not feasible. In all children with cCMV a first consultation is planned within the first year of

age, depending on their classification at birth. Consultations beyond that age are planned mostly in case of abnormal findings or if problems should occur and that also may contribute to the lack of follow-up data at later age in some patients and may be an explanation for the fact that there is a decline in the percentage of children with normal development with older age, as table 3 shows.

Mild to severe impairment was diagnosed in 223/753 (29,6%) of all CMV-infected children, 54,7% in the symptomatic group and 20% in the asymptomatic children. A review by Dollard et al. on the prevalence of long-term sequelae reported permanent impairment in 40-58% of the symptomatic children and 13,5% in the asymptomatic group. [4] Although there are methodological differences between various studies on long-term outcome results, we compared our results with more recent studies and found similar results in the study by Korndewal et al. [11] They found moderate to severe long-term impairment in 24,8% of their population (53,8% in symptomatic, 17,8% in asymptomatic children). In the study by Townsend et al. sequelae were found in 42% of symptomatic children, versus 14% in asymptomatic children. [6] In both studies, the population of CMV-infected children was the result of screening for cCMV, either at birth [6] or retrospectively by dried blood spot [11] and all children were matched with cCMV-negative children. In this way, the authors were able to describe the true disease burden of cCMV in their population. The fact that the results in our population (which is not the result of routine screening) are similar to theirs, suggests that our data can be considered representative for the disease burden of cCMV in Flanders.

Severe neuromotor impairment was found in 18/753 (2,4%) children, of which 10 (1,3%) are diagnosed with any type of cerebral palsy. The majority of these children (9/10) had abnormal CNS imaging at birth. All of these 9 children showed lesions on MRI. A review by Himpens et al. reported a prevalence for cerebral palsy for term infants of 0,1%, putting children with cCMV infection at a tenfold higher risk of developing cerebral palsy. [12]

We found a remarkably high number of children with hypotonia (46%). In all children, hypotonia had an impact on motor development, sometimes necessitating physiotherapy in case of motor milestones delay. Hypotonia may be associated with different conditions, such as neuromuscular, genetic, central nervous system, connective tissue, and/or metabolic problems but it may also be the only impairment in a child without any distinct etiology. [13] Depending on the population and the criteria used, prevalence of hypotonia ranges from 6,7% to 39,6%. [14] Whether or not hypotonia may be responsible for delayed motor development is still a matter of debate. [13] In our cCMV-positive population, the percentage of children with hypotonia is higher than what is described for other conditions. A possible explanation for this finding is the correlation between vestibular dysfunction and motor development. A study by Dhondt et al. showed that congenital CMV can also impair the vestibular function which may have a functional impact on motor development in children. Children with hearing loss seem to be the most at risk. However, even normal-hearing and/or asymptomatic cCMV children can present with vestibular dysfunction. [15] This new finding merits further attention in future follow-up studies. In this population, hypotonia is mostly found in children < 24 months of age and seems to improve with age (even in untreated children). Given the fact that in 471/753 (62,5%) children most recent outcome data are at age 4 or 12 months, hypotonia accounts for a large part of the mild to

moderate motor impairment in our population and hence explains the high use for physiotherapy in this group. However, it is reassuring that in most children hypotonia improves with age and physical therapy with minimal residual impact on the motor abilities of the child, and parents can be counselled this way. In children with bilateral vestibular dysfunction (often in combination with deafness), it is shown that both fine and gross motor function can remain impaired throughout the years. [15]

As for cognitive impairment, we see mild to severe impairment in 10,4% of our population. Again, these percentages are in line with was in found in literature. Korndewal et al. reported cognitive impairment in 6% of their population, which was higher than in their control group (1,1%). [11] Townsend et al. described abnormal development in 19%. [6] The high number of children with speech-language impairment (20,8%) in the group of cognitive impaired children, is consistent with what is described in literature. In the population of Korndewal et al. speech and language problems occurred twice as often compared to the control group (16,5% versus 7,3%).[11] Obviously, hearing loss can lead to speech and language impairment and one would expect that associated hearing loss is the main reason for this finding. However, in our population, 7 children with speech impairment showed no hearing loss. As the DECIBEL study by Korver et al. demonstrated, children with hearing loss due to cCMV show lower developmental quotients than children with hearing loss without cCMV and the difference in language development is significant. [16] Another study described speech impairment in 32% while hearing loss was present in only 5% of their population [17]. The need for timely initiation of speech therapy remains important. Abnormal speech development is the most frequent cognitive developmental disorder, with many variations. Next to impaired hearing, also mental development disorder, emotionalbehavioural problems (ADHD) and autism spectrum disorders can be associated with speech impairment. [17] The latter three are more frequently found in children with cCMV. Moreover, it has been described that children with injury in the frontal and temporal regions may show delays in the early phases of language development. [18] Notably, those are regions in the brain where white matter hyperintensity is often found in children with cCMV. So, perhaps these findings might partly explain the higher occurrence of speech impairment in our population. Further studies to identify mechanisms underlying these observations are necessary.

A wide variety of behavioral problems have been found in our population. Part of the population is very young (< 18 months) at last follow-up. So, some ‘problems’ encountered (headstrong, self-determining, impulsive behavior) might be temporary and no longer a problem at later age. Some children of younger age show some characteristics of autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (AD(H)D). For the children with difficult social contact or attention problems at age 12-18 months, follow-up at later age would be interesting to see whether these problems are predictive for the development of ASD or ADHD. In the study population, 19/753 (2,6%) of the children were diagnosed with autism spectrum disorder whereas the prevalence of ASD in Flanders is estimated 1 in 150 (0,6-0,7%). The diagnosis in these children was made by neurologists using the standardized testing methods. No diagnosis of ASD was made based on parental answers in the questionnaires. Korndewal et al. also found a slightly higher percentage of ASD in the CMV-positive population (3%) compared to the control group (1,8%). [11] An association between cCMV and ASD has been suggested in literature. Case reports of children with cCMV and

autism have been published for more than 40 years. [20,21,22] Over the years, studies have found a relation between cCMV and ASD. In children with confirmed diagnosis of ASD a higher incidence of cCMV is found. [23,24,25] A meta-analysis by Maeyama et al. suggested a statistically significant association between cCMV and ASD. However, the small sample size in the studies limits the conclusions of this meta-analysis. [26] The role of cCMV in the occurrence of ASD is yet to be elucidated but some authors recommend systematical screening for cCMV in autistic disorders. [24]

Sensorineural hearing loss is the most common neurodevelopmental deficit in children with cCMV. It is widely known that cCMV is the leading nonhereditary cause of sensorineural hearing loss. A review by Goderis et al. reported hearing loss in 12.6% (range 10,2%-16,5%) of children with cCMV, being 3 times more frequent in symptomatic children than in asymptomatic children. [27] In this cohort 17,2 % developed SNHL necessitating some form of hearing aid in 16,1% of them. It is important to note that these are findings at various ages between 4 months and 72 months. Since SNHL due to cCMV can be fluctuating over time, the audiological outcome at age 4-6 years might be different from the current reported hearing in some of these children. The results in the cohort of Salomé et al. where SHNL in the asymptomatic group was only fluctuating and transient, underscore this hypothesis. [29] These findings emphasise the need for a thorough longitudinal audiological follow-up in all CMV-infected children, both symptomatic and asymptomatic, in order to optimize counselling.

Ophthalmological follow-up occurred mostly once at age 12 months without further follow-up, unless visual problems occur. A recent report on long-term visual and ocular outcome in children with cCMV found progressive chorioretinitis to be rare and found no evidence that cCMV can lead to late onset or reactivation of chorioretinitis. The authors recommend an annual follow-up in case of abnormal ophthalmological examination at birth. When normal, children may be re-examined as clinically indicated by signs or symptoms. [28] We did not find any ophthalmological abnormalities, such as chorioretinitis, optic atrophy, strabismus or cortical visual impairment in our cohort.

More than half of the severely symptomatic children show any form of mild to severe impairment, while only 17,8 % of asymptomatic children are diagnosed with some form of impairment. Dollard et al. estimated the risk of sequelae in asymptomatic children to be between 5 and 15%, and between 17 to 60% in symptomatic children. [5] Eleven of 12 asymptomatic children (i.e., both children asymptomatic at birth and children with delayed diagnosis) with severe impairment in this cohort presented with isolated hearing loss. This finding in our population illustrates that asymptomatic children are at risk of developing hearing loss as well. The one asymptomatic child diagnosed with severe impairment, both neuromotor and cognitive, next to hearing loss, was diagnosed with cCMV retrospectively at later age. In table 3, a separate group is described with the children who were diagnosed at later age with ccMV (in our registry, classified as being asymptomatic). In this group we find an impaired overall development in 55,5%. These children were not diagnosed at birth which implies that they showed no clinical signs suggestive of cCMV at birth and passed the newborn hearing screening test. Hence, no additional examinations were performed, and we have no idea whether or not there were lesions on central imaging. This finding, although in a small group, suggests that a universal neonatal screening would be beneficial to detect all

children with cCMV since the absence of clinical signs or hearing loss at birth seems insufficient to rule out cCMV completely.

We found a higher risk of adverse neurodevelopmental outcome after infections acquired in the first trimester, compared to second and third trimester infections. This corresponds well with findings in literature. [30] However, even after second or third trimester infections, children are still at risk of long-term sequelae, even with severe impairments. The association between outcome and trimester of infection/classification at birth is of importance when counselling parents on the outcome of cCMV. Parents can be counselled that the highest risk of long-term sequelae is related to first trimester infections or severe symptomatic presentation at birth. It is important, however, that they are made aware that long-term sequelae can occur in every child with cCMV. This fact emphasises the need for long-term follow-up in every child with cCMV.

Our study has some limitations. First, since our population is not the result of universal screening of all newborns, we may encounter selection bias. This might result in an overrepresentation of symptomatic children and hence, higher percentages of neurodevelopmental sequelae. However, when comparing our results with what is already reported on neurodevelopmental outcome in literature, we find similar findings. Secondly, we do not have a control group of CMV-negative children to estimate what proportion of the sequelae may be attributed to cCMV. However, our results do correspond well with findings in studies with control group [6,11] so our cohort is likely to be representative for cCMV in Flanders. Thirdly, the length of follow-up with median age of 12 months poses a limitation. This might result in an overrepresentation of mild to moderate impairment (due to the high number of hypotonia reported in this age), an underestimation of behavioral problems (since it might be too early to detect ASD or ADHD) and it may also lead to an underestimation of SNHL (since late-onset SNHL may appear beyond this age). Last, results on hearing and vison are not described in detail. The aim of this report was to document neurodevelopmental outcome with emphasis on neuromotor, cognitive and behavioral outcome. Since the presence of SNHL can have an impact on the overall development, we found it important to report basic results here. A more detailed description of SNHL and the evolution over time in patients in the Flemish registry, has been published in 2016 [9] and an update in the most recent larger population is in progress.

Conclusion

We described the neurodevelopmental outcome of children with cCMV, included in the Flemish CMV registry between 2007 and 2020. It is, to our knowledge, the first time that outcome data are presented in such a large cohort. Many of our data correspond well with what is known in literature. Our study shows that both symptomatic and asymptomatic children can develop sequelae, independent of the timing of seroconversion. During follow-up of children with cCMV infection, special attention should be given to audiological follow-up, to the detection of hypotonia at young age which might impact motor development, to the possible higher risk of ASD and to the risk of speech and language impairment even in absence of hearing loss. Our findings underscore the need for thorough neurodevelopmental follow-up in all cCMV infected children. There is an ongoing need of reports on long-term

follow-up of children with cCMV, in order to estimate the true long-term disease burden of this most common congenital infection worldwide.

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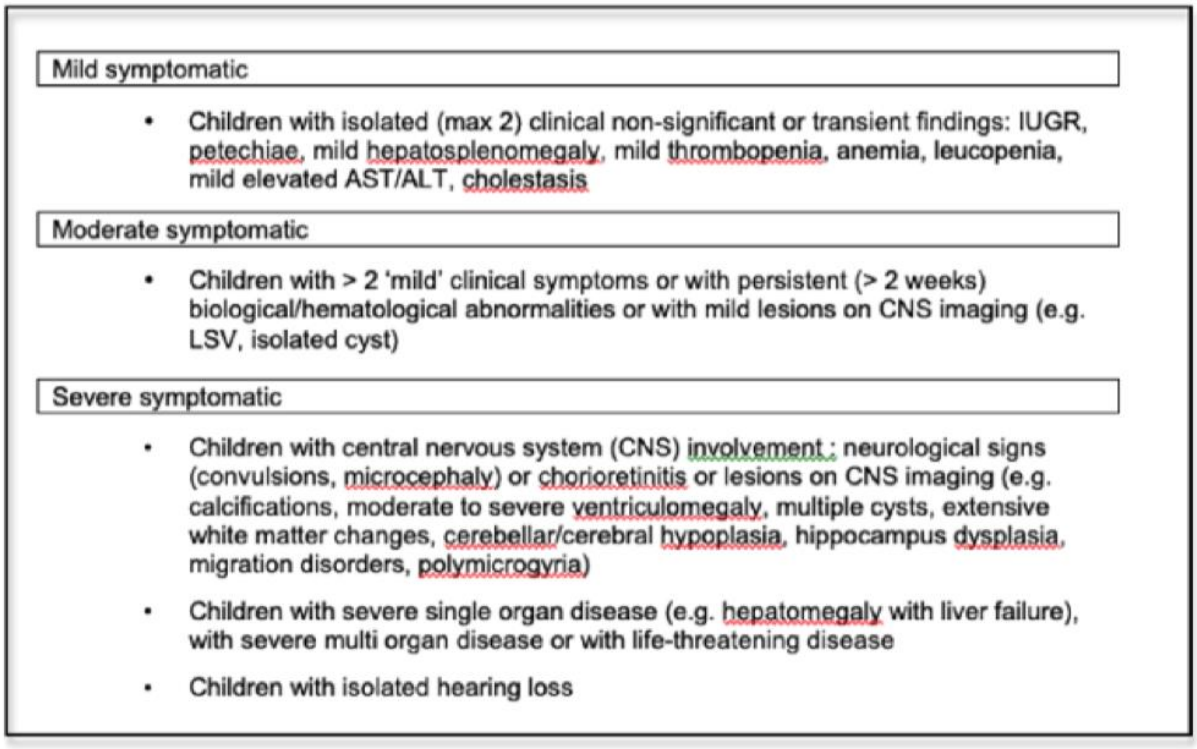
FIGURES

Figure 1. Definition of classification mild/moderate/severe symptomatic.



TABLES

Table 1. Classification into normal/mild/moderate/severe impairment in every subdomain.

Neuromotor development		
Alberta Infant Motor Scale (AIMS)	>25	normal
	10 < AIMS < 25	mild
	5 < AIMS < 10	moderate
	< 5	severe
Bayley Scales of Infant and Toddler Development second or third edition (BSID-II or BSID -III)	Motor score (PDI) > 85 on BSID-II or > 90 on BSID-III	normal
	Motor score (PDI) of 70-84 on BSID-II OR motor score of 80-89 on BSID-III	mild
	Motor score (PDI) of 55-69 on BSID-II OR motor score of 70-79 on BSID-III	moderate
	Motor score (PDI) of < 55 on BSID-II OR motor score of <69 on BSID-III	severe
Gross Motor Function Classification System (GMFCS)	cerebral palsy GMFCS I	mild
	cerbral palsy GMFCS II	moderate
	cerbral palsy GMFCS III-IV	severe
Neurocognitive development		
Bayley Scales of Infant and Toddler Development second or third edition (BSID-II or BSID -III)	Cognitive score (MDI) of > 85 on BSID-II OR cognitive score of >90 on BSID-III	normal
	Cognitive score (MDI) of 70-84 on BSID-II OR cognitive score of 80-89 on BSID-III	mild
	Cognitive score (MDI) of 55-69 on BSID-II OR cognitive score of 70-79 on BSID-III	moderate
	Cognitive score (MDI) <55 on BSID-II OR cognitive score of <69 on BSID-III	severe
Wechsler intelligence scales	IQ > 85	normal
	70 < IQ < 84	mild
	55 < IQ < 69	moderate
	< 55	severe
Behavior		
	no problems	normal
	Behavioral and/or social-emotional problems with no more than minor impairments in social functionin	mild
	Behavioral and/or social-emotional problem with moderate functional impairment	moderate
	Behavioral and/or social-emotional problems with marked impairment in social functioning	severe
Hearing		
auditory brainstem response / audiometry	< 20 dB	normal
	21 - 40 dB in the best ear with/without hearing aid	mild
	Hearing loss corrected with aids (40-70dBHL) or hearing loss but not corrected by aids (70-90dBHL)	moderate
	> 55 dB in the best ear with/without hearing aid	severe
Vision		
	no retinopathy/normal vision	normal
	Vision impaired but appears to have useful vision	mild
	Moderately reduced vision or blind in one eye with good vision in the contralateral eye	moderate
	Blind or can only perceive light or light reflecting objects	severe

Table 1. Classification of outcome per subdomain.

Table 2. Reported impairments per domain

motor impairment	n	mental impairment	n	behaviour	n	hearing	n
hypotonia	81	speech delay	16	ASD	19	unilateral CI	8
cerebral palsy bilateral				self-determining, headstrong	10	bilateral CI	11
atactic CP	2	disharmonic IQ profile	6	emotion regulation problem	9	hearing aid	2
dyskinetic	1			ADHD	7		
spastic	5	severe cognitive delay	3	difficult social contact	7		
cerebral palsy unilateral				attention problems	7		
spastic	2	Down syndrome	1	impulsive behaviour	5		
delayed walking	2			feeding difficulties	3		
fine motor problems				sleeping disorders	2		
writing	3						
DCD	6						
epilepsy	3						

Table 3. Distribution of normal/mild/moderate/severe impairment in relation to trimester of infection and classification at birth.

Classification at birth	normal	mild impairment	moderate impairment	severe impairment
asymptomatic (n = 465)	382 (82,2%)	67 (14,4%)	9 (1,9%)	7 (1,5%)
mildly symptomatic (n =26)	22 (84,6%)	2 (7,7%%)	2 (7,7%)	0
moderately symptomatic (n = 42)	30 (71,4%)	11 (26,2%)	1 (2,4%)	0
severely symptomatic (n = 190)	86 (45,2%)	40 (21,1%)	38 (20%)	27 (14,2%)
delayed diagnosis (n = 27)	12 (44,5%)	5 (18,5%)	5 (18,5%)	5 (18,5%)
trimester of infection	**normal**	**mild impairment**	**moderate impairment**	**severe impairment**
< 13 weeks (n = 233)	138 (59,2%)	50 (21,5%)	27 (11,6%)	18 (7,7%)
14-27 weeks (n = 166)	137 (82,5%)	22 (13,3%)	4 (2,4%)	3 (1,8%)
> 27 weeks (n = 96)	81 (84,4%)	9 (9,4%)	3 (3,1%)	3 (3,1%)