Congenital Cytomegalovirus infection in Flanders: demography, management and outcome

PhD thesis presented on 16/2/2022 at Ghent University, Ghent, Belgium.

Annelies Keymeulen

Promotor: Koenraad Smets **Co-promoter:** Els De Leenheer

Department of Neonatology, Ghent University Hospital , Ghent, Belgium

Abstract

Congenital CMV is the most frequent congenital infection worldwide. Because of the major disease burden of cCMV, it is important to obtain data on congenital CMV infection as precisely as possible in order to optimize pre- and postnatal management and therapy. The Flemish cCMV registry collects data on diagnosis, management, treatment and follow-up of children with congenital CMV. It is, to our knowledge, the first time that outcome data are presented in such a large cohort of children with congenital CMV. Many of our data correspond well with what is known in literature or described in other cohorts.

Background

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). In the United States (US), Canada, Western Europe, and Australia, cCMV occurs in about 5–7 per 1000 live births overall. In other parts of the world, such as Latin America, Africa, and most Asian countries, cCMV rates are higher at approximately 10–30 per 1000 live births (3).

Congenital CMV has a significant long-term impact on affected children, being the major cause of non-hereditary sensorineural hearing loss and the major infectious cause of neurodevelopmental abnormalities in infants born in developed countries. Despite this important disease burden, cCMV remains largely unrecognized and there is limited evidence on which to base management and therapy of children with cCMV infection. Since large-scale screening programs are not available to this point, we can only base our knowledge on data obtained by registries.

This PhD work is based on the Flemish CMV registry containing data on 1059 children with cCMV infection. In 2007 the registration of patients that presented with cCMV in the collaborating hospitals (Ghent University hospital, University hospital Leuven, University Hospital Antwerp, Middelheim Antwerp, Hospital Network Antwerp and AZ Sint Jan Bruges) was started.

Results

Conducting a registry for 14 years has shown us the possible limitations and shortcomings of a clinical registry and over the years we succeeded in addressing some of these shortcomings.

The development and introduction of the electronic version of the database was an important milestone which improved data gathering in a substantial way. In the electronic database, all data are reported in a uniform manner which makes it easier to describe the results. And, by making the database available online, more patients can be recruited, including from non-tertiary hospitals. To reduce the amount of missing data on neurological follow-up a patient-reported questionnaire was developed, based upon validated scoring systems for neurodevelopmental outcome, to evaluate the neurological development of children of 5-6 years of age. We have found that the use of questionnaires was most valuable and helped in filling the data gaps on long-term neurodevelopmental outcome. However, interventions to increase the response rate may enhance our data gathering even more (4).

During these 14 years of registration, data were collected on prenatal/neonatal management, treatment and follow-up of 1059 children with cCMV in Flanders. It is, to our knowledge, the first time that data are presented in such a large cohort of children with cCMV. Symptomatic disease was diagnosed in 319/1059 (30,5 %) children. Of those 13,5 % were classified as mild, 16 % as moderate and 70,5 % as severe infections. Antiviral therapy was given in 63,9 % of patients eligible for therapy. As for long-term follow-up, data show that both symptomatic and asymptomatic children can develop long-term sequelae, independent of the timing of seroconversion (5).

Hearing outcome in this population was described for the first time in 2016. Results from 123 children with a symptomatic and 256 children with an asymptomatic cCMV infection were analyzed. In children with symptomatic cCMV, 63% had hearing loss, in the group with asymptomatic cCMV this was only 8%. Delayed-onset hearing loss occurred in 10.6% of symptomatic cCMV children compared to 7.8% of children with asymptomatic cCMV. In symptomatic children 29.3% used some kind of hearing amplification, this was the case in 1.6% of asymptomatic children (6).

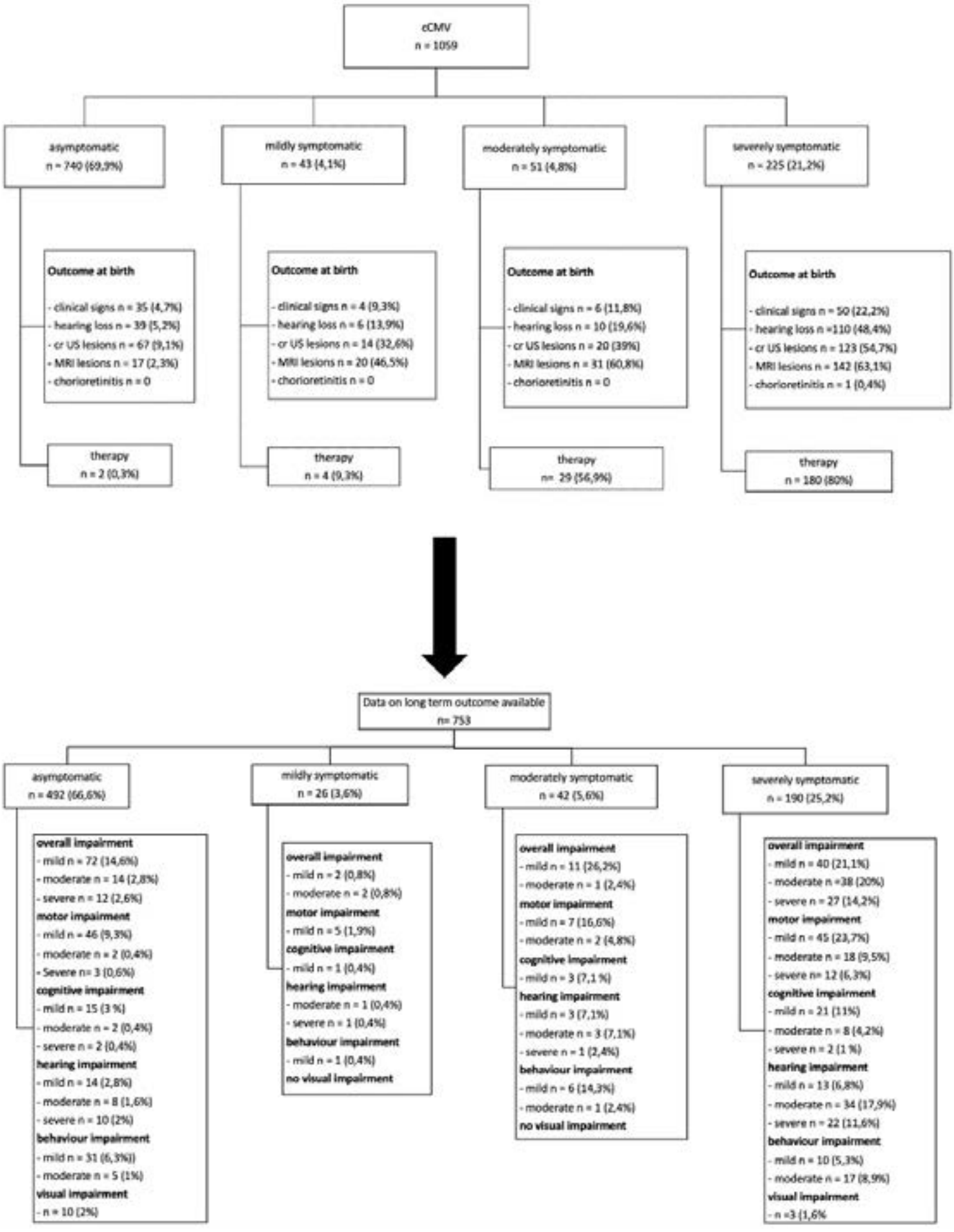
Our results show that, during follow-up of children with cCMV infection, special attention should be given to audiological follow-up, to the detection of hypotonia at young age which might impact motor development, to the possible higher risk of autism spectral disorder and to the risk of speech and language impairment even in absence of hearing loss.

Figure 1 presents an overview of the cCMV-population in Flanders between 2007 and 2020.

When comparing our data with what is described in literature, our data seem to confirm some hypotheses regarding cCMV or support the current recommendations for counselling and management. However, some data, although sometimes acquired in small groups, add to the discussion between experts on some topics on cCMV. One of those is whether or not cranial ultrasound (crUS) and cerebral magnetic resonance imaging (MRI) have both a place in the assessment of children with congenital cytomegalovirus infection. In our study, one in five children with normal crUS showed abnormal findings on MRI which suggests that both are complementary in the assessment of CNS involvement in children with cCMV (7).

During the 14 years of data collection, an additional study was set up to evaluate the potential of dried blood spots (DBS) as a congenital cytomegalovirus (cCMV) testing specimen. For this purpose, the laboratory diagnostic accuracy of polymerase chain reaction (PCR) on DBS was compared to viral urine cultures from neonates suspected for cCMV. The results of this study have shown that CMV-PCR on DBS could be valuable as screening tool but not for diagnostic purposes (8).

Figure 1: General overview of our cCMV-population in Flanders



Conclusion

The importance of registries is well established: the provided data can help develop clinical research, improve patient care and can be a valuable source of data on patient outcomes. This is one of the most important goals of the Flemish registry, founded in 2007.

Conducting this registry enabled us to describe both the perinatal characteristics and the long-term neurodevelopmental outcome of children with cCMV, included in the registry between 2007 and 2020. It is, to our knowledge, the first time that outcome data are presented in such a large cohort of children with congenital CMV. The fact that many of our data correspond well with what is known in literature or described in other cohorts, shows that our results could be representative of the (primary) cCMV population in Flanders. Our research also underscores the need for a thorough follow-up in all cCMV infected children, in order to estimate the true disease burden of this most common congenital infection worldwide.

Some data add to ongoing discussions on topics of cCMV and some preliminary findings raised interesting research questions that will require further studies. There are still many gaps in our understanding on cCMV. Hence, there is an ongoing need of collecting data on perinatal management and 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. With the Flemish registry, an important step is taken to achieve this goal.

REFERENCES:

1. Luck SE, Wieringa JW, Blázquez-Gamero D, Henneke P, Schuster K, Butler K et al. ESPID Congenital CMV Group Meeting, Leipzig 2015. Congenital Cytomegalovirus: A European Expert Consensus Statement on Diagnosis and Management. Pediatr Infect Dis J. 2017 Dec;36(12):1205-1213. doi: 10.1097/INF.0000000000001763. PMID: 29140947.
2. Casteels A, Naessens A, Gordts F, De Catte L, Bougatef A, Foulon W. Neonatal screening for congenital cytomegalovirus infections. J Perinat Med. 1999;27(2):116-21. doi: 10.1515/JPM.1999.015. PMID: 10379501.
3. Fowler KB, Boppana SB. Congenital cytomegalovirus infection. Semin Perinatol. 2018 Apr;42(3):149-154. doi: 10.1053/j.semperi.2018.02.002. Epub 2018 Mar 2. PMID: 29503048.
4. Keymeulen A, De Leenheer E, Goderis J, Dhooge I, Smets K. Congenital cytomegalovirus infection registry in Flanders: opportunities and pitfalls. Acta Clin Belg 2921 Jun; 76(3): 169-176. doi: 10.1080/17843286.2019.1683262. Epub 2019 Oct 23.
5. Keymeulen A, De Leenheer E, Casaer A, Cossey V, Laroche S, Mahieu L et al. Results of a multicenter registry for congenital cytomegalovirus infection in Flanders, Belgium: from prenatal diagnosis over neonatal management to therapy. Early Hum Dev. 2021 Dec;163:105499. doi: 10.1016/j.earlhumdev.2021.105499. Epub 2021 Oct 26. PMID: 34743933.
6. Goderis J, Keymeulen A, Smets K, Van Hoecke H, De Leenheer,E, Boudewyns A et al. Hearing in Children with Congenital Cytomegalovirus Infection: Results of a Longitudinal Study J Pediatr. 2016 May; 172:110-115. https://doi: 10.1016/j.jpeds.2016.01.024. Epub 2016 Feb 5.
7. Keymeulen A, De Leenheer E, Casaer A, Cossey V, Herregods N, Laroche S et al. Cranial ultrasound and MRI: complementary or not in the diagnostic assessment of children with congenital CMV infection? Eur J Pediatr. 2021 Oct 12. doi: 10.1007/s00431-021-04273-y. Online ahead of print. PMID: 34636957
8. (8) Vercauteren K, Keymeulen A, Mahieu L, Cossey V, Casaer A, Van Mol C et al. Prospective multicenter comparison of urine culture with PCR on driedblood spots using 2 different extraction and PCR methods in neonates suspected for congenital cytomegalovirus infection.
9. Diagn Microbiol Infect Dis. 2020 Jul;97(3):115051. doi: 10.1016/j.diagmicrobio.2020.115051. Epub 2020 Mar 26. PMID: 32408061.