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Consequences of congenital cytomegalovirus infection in the first years of life.
Summary

Cytomegalovirus (CMV) belongs to the Herpesviridae family. Like other herpesviruses, it can establish life-long latency after a primary infection. Besides reactivation of the latent virus, reinfection with a different strain of CMV can occur. The term ‘recurrent infection’ is often used to cover both reactivation and reinfection. An infection with CMV is usually asymptomatic, although it can cause a mononucleosis-like syndrome with fever and malaise in some persons. It can cause severe illness in immunocompromised or immunosuppressed patients.

The virus can be transmitted via body fluids (e.g. urine, saliva, breastmilk) through intimate contact. In addition, the virus can be transmitted vertically in the case of a primary or recurrent infection of the mother during pregnancy. The transmission rate is higher with a primary maternal infection (32%) compared to a recurrent maternal infection (1.4%) and the transmission rate increases with the duration of pregnancy.

A congenital cytomegalovirus infection (cCMV) occurs if the virus is transmitted from the mother to the unborn child through the placenta. cCMV is the most common congenital infection worldwide, with a birth prevalence of around 0.6-0.7% in industrialized countries. The birth prevalence increases with the ambient maternal seroprevalence and is higher in developing countries. cCMV can lead to symptoms and signs at birth, such as being small for gestational age, microcephaly, intracranial calcifications, hepatosplenomegaly, petechiae or purpura, chorioretinitis and neurological findings. These findings occur in approximately 10-15% of children born with cCMV. Long-term impairment occurs in about 50% of children with symptoms at birth and in 10-15% of children who are asymptomatic at birth. Long-term consequences related to cCMV include sensorineural hearing loss, cerebral palsy, epilepsy, chorioretinitis, optic atrophy, delayed psychomotor development and mental retardation. Despite the fact that the prevalence of cCMV is relatively high and that the consequences are considerable, awareness of cCMV among the general population as well as healthcare workers, in the Netherlands and in many other countries, is low. There are some preventive measures that could potentially reduce the prevalence and consequences of cCMV. With primary prevention, transmission of the virus from mother to fetus is prevented. This could be achieved by hygienic measures such as avoiding contact with urine and saliva of young children. Women who are or want to become pregnant should not kiss a child on the mouth, share foods or utensils or put anything that has been in the mouth of a young child in her mouth and she should wash her hands after changing diapers. A vaccine would be an alternative way to prevent CMV infections in pregnant women, however there is currently no vaccine available against CMV. Secondary prevention is the prevention or limitation of disease due to cCMV. This could include treating the mother with antiviral drugs or CMV-specific antibodies. Currently there is no evidence that these treatments are beneficial. Prevention of deterioration of disease (tertiary prevention) has been demonstrated in children with neurologic symptoms at birth who were treated with (val)ganciclovir. It is unknown if this treatment would also be beneficial for other groups of children with cCMV.

The CROCS study (Consequences and Risk factors of Congenital cytomegalovirus infection) was designed in order to obtain an estimation of the burden of cCMV. This study aimed to evaluate a broad range of consequences of cCMV in children up to six years of age in the Netherlands. Not only medical conditions, but also personal and financial consequences of cCMV were assessed using this nation-wide retrospective cohort study, which included a large group of children with cCMV and a twice as large control group.
In chapter 2 the seroprevalence of CMV was discussed. This article was based on the PIENTER2 study, which is a cross-sectional population-based serum bank established in 2006-2007 in the Netherlands. Blood samples from 6249 persons, aged 6 months to 79 years, were tested for CMV-specific IgG antibodies and questionnaires were obtained from these participants.

The overall seroprevalence of CMV in the Netherlands was 45.6% and it increased steadily with age. Because the seroprevalence was much higher in non-Western migrants (76.7%) compared to Western migrants (57.3%) and native Dutch persons (40.1%) the analyses were stratified for origin. In the Dutch and Western populations, the seroprevalence was higher in women, persons with a low educational level and those who had contact with young children from outside their own household. In the non-Western population, the risk factors for seropositivity were a lower educational level and being a first-generation migrant. Risk factors for higher antibody levels, which may be related to CMV reactivation or reinfection, could be identified by looking at the geometric mean concentration among seropositive individuals. The geometric mean concentration increased with age and was higher in women than in men and in non-Western migrants compared to native Dutch and Western migrants. It was also higher among Dutch and Western individuals in persons who lived in a household with young children.

The most prominent independent risk factors for CMV seropositivity were age and origin. The high seroprevalence among non-Western migrants, especially among first generation migrants, could be related to a higher infection rate in the country of origin and to differences in lifestyle. The increase in CMV seroprevalence with age could be related to cumulative exposure throughout life, although it could also reflect a higher infection rate during the childhood of persons who are now elderly.

Chapter 3 describes the design of the CROCUS study. This study was designed to estimate the long-term consequences of congenital CMV infection up to the age of six years in the Netherlands. Many studies on the long-term consequences of cCMV are prospective, have a relatively short follow-up, and include small or no control groups. The CROCUS study is a nationwide cohort study in which retrospectively diagnosed children with cCMV and a cCMV-negative control group are included. The study looks at a broad range of consequences of cCMV. The CROCUS study consists of two parts. First, parents of more than 73,000 children were invited to allow their children to be included in this study. Children with a cCMV infection were identified by testing stored dried blood spots of 31,484 children for CMV using a polymerase chain reaction. In total 156 children (0.5%) with cCMV were diagnosed. Surprisingly only four of these children (2.6%) had been diagnosed prior to this study, which indicates that cCMV is currently being underdiagnosed in the Netherlands. Second, medical data and school results of children with cCMV and a twice as large control group were collected. In addition four parental questionnaires; on child development, the quality of life of the children and their parents, and a general questionnaire on medical history, everyday life consequences and demographic features, were sent to participating parents. Parents of 133 cCMV-positive and 274 cCMV-negative children gave informed consent for participation.

This study design limits information bias due to its retrospective nature because parents and professionals looking after the children did not know of the CMV status of the child until the diagnosis was made by the CROCUS study. However, this design can also lead to some
limitations because data was not collected prospectively in a systematic manner and was sometimes incomplete. In addition, selection bias can be caused by for example response rate differences between parents of children with and without health problems, and by a lower sensitivity of the test for cCMV when the viral load is low.

The clinical consequences of congenital CMV infection are presented in chapter 4. In the CROCUS study we found that 19.6% of children with cCMV could retrospectively be classified as having been symptomatic at birth compared to 12.4% of children without cCMV. The risk of developing any moderate-to-severe long-term impairment, including hearing, visual, neurologic, cognitive, motor and speech-language impairment, was higher in children with cCMV (24.8%) compared to children without cCMV (12.5%). Moreover, this risk was higher in cCMV-positive children with symptoms at birth (53.8%), compared to children with cCMV who were asymptomatic at birth (17.8%). In the cCMV-negative group, there was no significant difference in prevalence of long-term impairments between the symptomatic (8.8%) and asymptomatic (12.5%) children. In addition, impairment in multiple domains was seen much more often in children with cCMV (10.5%) than in children without cCMV (1.8%). Again this was more frequent in symptomatic (19.2%) than in asymptomatic (8.8%) children with cCMV.

Even though it is clear that children with cCMV who are symptomatic at birth have the highest risk of long-term impairments, this study demonstrates that asymptomatic children with cCMV have more long-term impairments than children without cCMV. The impairments in these children with cCMV include not only hearing loss, but also cognitive, motor and speech-language impairment. This study justifies increased awareness and prompt initiation of preventive measures against cCMV. Additionally, it shows that more attention and care is needed for the cognitive, motor and speech-language development of children with cCMV.

In chapter 5 other consequences of cCMV are investigated. In the CROCUS study child development, quality of life and daily life consequences for children with and without cCMV and their parents were assessed using parental questionnaires and data from schools. Assessment of child development showed that delays in the general and expressive language development were more frequent in children with cCMV (13.8% and 10.6%) compared to those without cCMV (5.8% and 3.7% respectively). Additionally, more children with cCMV and symptoms at birth attended special needs education or had poorer school performances compared to their cCMV-negative counterparts.

Physical therapy was needed by 10.9% of all children with cCMV and by 40% of those with long-term impairment, but only by 2.9% of children without cCMV. In addition, the overall and physical health-related quality of life of children with cCMV and long-term impairments was lower than children without cCMV even in those with long-term impairment.

Parents of children with cCMV and long-term impairment reported having physical problems (44%) and concentration problems (40%) due to the problems of their child more often than parents of children with long-term impairments without cCMV (16% and 16% respectively). Parents of children with cCMV and long-term impairment also had lower mental health scores for quality of life compared to parents of cCMV-negative children with long-term impairment, although this difference was not statistically significant.

Even though the differences in quality of life between the cCMV-positive and cCMV-negative groups with long-term impairment, for both children and parents, are relatively small it is still a relevant finding. This is especially so when one considers that perception of quality of
life is usually subject to physical and psychological adaptation to disabilities. Furthermore, this study confirms the findings in chapter 4 that children with cCMV have more problems than only hearing loss and neurological disability.

The **financial consequences** of congenital CMV infection are discussed in **chapter 6**. This chapter was also based on the CROCUS study, using the healthcare resources use by children with cCMV and the matched control group and their reference prices. The mean healthcare costs per child in the first six years of life were higher in the cCMV-positive children (€6,113) than in the cCMV-negative children (€3,546). If this mean difference in costs (€2,568) is extrapolated to the whole birth cohort of 2008, then the additional national healthcare costs attributable to cCMV in the Netherlands would be 2.4 million euro. The total healthcare costs of children with cCMV would add up to approximately 5.6 million euro in the first six years of life (3.0 million euro/100,000 children).

Children with symptoms at birth and cCMV had higher average healthcare costs (€15,922) in the first six years of life than children with cCMV who are asymptomatic at birth (€3,730) and than children without cCMV (€10,878 in symptomatic and €2,507 in asymptomatic). A similar picture arises when looking at children with and without long-term impairment. The average costs in children with cCMV and long-term impairment (€17,205) were twice as high as in children with long-term impairment without cCMV (€8,332) and six to seven times higher than children without long-term impairment. The largest differences in costs between children with and without cCMV were seen in costs for physical and speech therapy and visits to a rehabilitation center.

Even though the cost difference between cCMV-positive and cCMV-negative children is not statistically significantly different, the costs attributable to cCMV are substantial. The lack of statistical significance is probably due to the large variance in costs. In addition, if other costs, such as costs for psychosocial care, future healthcare costs, special needs education and decreased productivity would be taken into account, the difference between children with and without cCMV would probably increase further. These considerable costs of cCMV should also be included in the equation when considering preventive measures against cCMV.

**Discussion and conclusion**

The reason to design the CROCUS study was to overcome some limitations that were observed in other studies. These included prospective study designs, small study populations, very small or absent control groups and focus on only a few specific conditions. Although the CROCUS study overcame most of these problems, it had some limitations of its own. For example, differences in response rates in various parts of the study could have led to selection bias. Differences between parents who responded and those who did not respond might have led to an underestimation of the birth prevalence. Due to the test characteristics of the polymerase chain reaction, with an assumed sensitivity of 84.4%, it is likely that the birth prevalence of cCMV has been underestimated in this study. Furthermore, the retrospective design of the study has led to a less systematic manner of recording the data generated during the first years of life. This caused a relatively large amount of missing data for some of the outcomes. However, as many of these biases can both lead to either over- or underestimation of the disease burden, it is impossible to assess the true impact of the limitations in our study design.
Summary

If the results from the CROCUS study are extrapolated to the annual birth cohort of 2008 in the Netherlands, it is estimated that 915 children with cCMV were born that year. Of these children 179 (19.6%) would have been symptomatic and 736 (80.4%) would have been asymptomatic at birth. Long-term impairment in the first six years of life would occur in 227 children, of whom the majority would have been asymptomatic at birth (n = 131).

In addition to these medical consequences, these children will also experience a lower quality of life and their condition will have an impact on the daily life of their parents. It is important to realize that approximately the same number of children with these problems will be born each year with the same substantial burden for the children themselves, their parents and society.

When evaluating the preventive measures that have been mentioned in the introduction, it is clear that measures that are evidence-based and currently available should be implemented directly. This includes the hygienic advice, both for seropositive and seronegative women who are, or want to become pregnant. In addition, all children with clinically apparent cCMV and neurological symptoms at birth should be treated with (val)ganciclovir, in order to prevent (deterioration of) hearing loss. More evidence is needed before other preventive measures can be advised.

This research leads to some recommendations for the care of children with cCMV. Besides the evaluation of hearing loss, the standard care for children with cCMV should include evaluation for motor development and speech-language development and instigation of appropriate care when indicated. Additionally attention should be paid to the quality of life of both children and parents. Future research on cCMV should be focused on obtaining consensus for definitions used in this field, evaluation of the relative contribution of reactivations and reinfecion in seropositive persons and evaluation of prognostic markers preferably in neonates. Additionally, it is essential that the CROCUS study is continued and that the children in this cohort will be followed in a prospective manner. This valuable cohort can supply much information on the consequences of cCMV at later ages. The cooperation and contribution of these children and their parents will provide valuable information in the fight against cCMV.