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CLINICAL FEATURES OF CEREBRAL PALSY IN CHILDREN WITH SYMPTOMATIC CONGENITAL CYTOMEGALOVIRUS INFECTION

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Original article

Running head: Cerebral palsy and symptomatic congenital CMV infection
ABSTRACT

Background: Human cytomegalovirus is the most common cause of vertically transmitted viral infection, affecting around 1% of liveborns. Infection is symptomatic in nearly 10% of infected children who are at higher risk of development of severe neurological disorders, including cerebral palsy.

Aims: To study the clinical profile of children with cerebral palsy caused by symptomatic congenital cytomegalovirus infection in a multicenter study involving six countries from the Surveillance of Cerebral Palsy in Europe (SCPE) Network.

Methods: Data on 35 children (13 males, 22 females; mean age at last assessment 12y 6mo, age range 14y 6mo, min 4y, max 18y 6mo) on pre/perinatal history and last clinical assessment were collected. Classification of cerebral palsy and associated impairments was performed according to SCPE criteria.

Results: The majority of children had bilateral spastic cerebral palsy, 85.7%, with a confidence interval (CI) [69.7-95.2], and 71.4% [CI 53.7-85.4] were unable to walk (GMFCS levels IV-V) while fine motor function was severely affected in 62.8% [CI 44.9-78.5] (BFMF levels IV and V). Most of the children with severe CP had severe associated impairments. 11.4% of children had severe visual and 42.8% severe hearing impairment, 77.1% [CI 59.9-89.6] suffered from epilepsy, also 77.1% had severe intellectual impairment, and speech was undeveloped in 71.4%. Female:male ratio was 1.69:1 and 80% of children were term born.

Conclusions: Cerebral palsy following symptomatic congenital cytomegalovirus infection seems to be in most cases a severe condition and associated impairments are overrepresented. Furthermore, it occurred more often in females and term born children.

Keywords: symptomatic congenital cytomegalovirus infection, cerebral palsy, children, neurological impairment
INTRODUCTION

Human cytomegalovirus (CMV), one of the herpes viruses, is the most common cause of vertically transmitted viral infection and affects around 1% of liveborns.\textsuperscript{1,2} Infection is symptomatic in nearly 10% of infected children and commonly presents with symptoms of neonatal sepsis, microcephaly, intrauterine growth retardation, prematurity and/or neonatal hepatitis.\textsuperscript{1,2} The vast majority of infected children are asymptomatic at birth.\textsuperscript{1,2}

As antenatal and postnatal diagnostic assessment has progressed, detailed knowledge on the outcome of congenital CMV infection becomes even more important. Besides conventional laboratory methods of human CMV detection such as isolation of virus from urine/blood/saliva or specific serology (IgM, IgG, avidity), PCR (polymerase chain reaction) for CMV DNA enables fast detection of active infection and assessment of its dynamics.\textsuperscript{3,4} Especially the use of Guthrie cards so far routinely collected for metabolic screening of newborns enables retrospective diagnosis in children suspected of congenital CMV infection.\textsuperscript{5}

Both symptomatic and asymptomatic congenital CMV infections are common cause of neurodevelopmental impairments. It has been generally assumed that first born and symptomatic children are at a higher risk for severe impairments, as well as children infected as a consequence of first trimester maternal infection.\textsuperscript{2,6} Microcephaly at birth in children with symptomatic congenital CMV infection is a predictor of poor cognitive outcome, reflecting the negative effect of CMV on early neurogenesis.\textsuperscript{7,8} Sensorineural hearing loss, intellectual impairment, microcephaly, visual impairments and cerebral palsy are most often listed as severe sequelae of congenital CMV infection.\textsuperscript{2,9} Although one study of Australian group of authors describes the clinical types of CP in children with perinatal exposure to neurotropic viruses, this is the first study, to the best of our knowledge, that describes clinical features of cerebral palsy (CP) in children with symptomatic congenital CMV infection by classifying the severity of CP and its associated impairments.\textsuperscript{10}

MATERIALS AND METHODS

Data on children with symptomatic congenital CMV infection was collected through a multicenter study of countries involved in the SCPE-NET (Surveillance of Cerebral Palsy in Europe Network) which declared to have registered data on CMV as one of the causes of CP: Portugal, Germany, Hungary, Austria (Tyrol), Slovenia and Croatia. From initially reported 45 children with symptomatic congenital CMV infection, 10 had to be excluded due to inappropriate laboratory proof of infection. Finally, 35 children (7 from Portugal, 1 from Germany, 4 from Hungary, 4 from Austria, 4 from Slovenia and 15 from Croatia) were included.

Ethical approval for the study was given by the Ethical committee of University of Zagreb, School of Medicine, as a part of the project of Croatian Ministry of Science “Neurodevelopmental outcome of children with intrauterine growth retardation and/or hypoxia (072-1081870-0025) “. Patients or their caregivers have given informed consent to the research and publication of results.

Children were born from 1994 until 2009. In all children congenital CMV infection was confirmed by specific serology, PCR for CMV DNA in blood/urine/Guthrie card and/or isolation of the virus from urine. Follow-up included repeated neurodevelopmental assessments, examination of hearing and vision, assessment of cognitive development and communication. Last assessment was performed at the age of 4 years and 18 years 6 months, respectively. Classification of cerebral palsy and associated impairments was performed according to SCPE criteria.\textsuperscript{11} Cerebral palsy was classified into three types: spastic (with bilateral and unilateral subtypes), dyskinetic (with choreo-athetotic and dystonic subtype) and ataxic CP. Functional classification was performed separately for lower and upper limbs: Gross Motor Function Classification System (GMFCS) and Bimanual Fine Motor Function
Vision impairment according to SCPE was classified into three categories, none, mild and severe impairment (blind or no useful vision, after correction, in the better eye; the level of vision loss is $<6/60$ (Snellen scale) or $<0.1$ (Decimal scale) in both eyes). Hearing impairment was similarly divided: none, mild and severe (severe or profound hearing loss, before correction, in the better ear; the level of hearing loss is $>70$db in both ears). Intellectual impairment was classified in 3 categories of IQ or estimation of IQ according to SCPE: IQ $\geq 85$ (normal intellect, normal schooling), IQ 50-84 (mild to moderate intellectual impairment; reading, calculating and writing abilities but modified school curriculum) and IQ $< 50$ (severe intellectual impairment, e.g. no reading, writing and calculation abilities). Epilepsy was defined as two or more unprovoked seizures, excluding febrile or neonatal seizures; data on active epilepsy (child receiving antiepileptic treatment at last follow up) were collected. Communication impairment was assessed according to the Viking Speech Scale for expressive speech of children with CP into four levels. Communication impairment was assessed according to the Viking Speech Scale for expressive speech of children with CP into four levels. 

Data upon head circumference (HC) was collected at birth and at the last assessment; microcephaly was defined as HC below 3rd percentile according to Fenton chart for prematures and World Health Organization charts for children until five years. For children above that age microcephaly was defined as HC below -2 standard deviations (SD) according to Nellhaus. To give a better grasp of statistics over our population sample, and cover for sampling errors, we present confidence intervals with our results, where appropriate. We calculated these confidence intervals using the Clopper-Paerson exact binomial proportion method, with a chosen 95% confidence level.

**RESULTS**

A total of 35 children (13 males, 22 females; mean age at last assessment 12y 6mo, age range 14y 6mo, min 4y, max 18y 6mo) were included in this study. Symptoms of congenital CMV infection were available for totally 23/35 children, reported from Croatia, Hungary and Slovenia. Most often the newborns presented with a sepsis-like syndrome (3), isolated jaundice (8), hepatitis (4), microcephaly (13), intrauterine growth retardation (6), convulsions (3), hypertonus (4) or petechiae (3); as isolated or combined symptoms. Eighteen children of 35 (51.4%) were born from a first pregnancy, 9/35 (25.7%) from a second and 6/35 (17.1%) from a third or more, while for two children mother’s parity was unknown. 28/35 children were term born (80.0%) and one child was born after term (2.8%). Six of 35 children were born preterm (17.1%), of which only one (2.8%) was very preterm (born at 31st week of gestational age (GA)) while other five (14.2%) were moderately preterm born children (34-36 week GA). Microcephaly at birth was observed in 13/35 (37.1%) children, and 6/35 (17.1%) had a HC between the 3rd and 15th percentile (10th for preterm born) while only 9/35 (25.7%) had a HC above -1 SD. For the remaining seven children data on HC at birth was unavailable.

In Table 1 type and subtype of cerebral palsy are presented. The vast majority, 30/35 (85.7%, with a confidence interval (CI) [69.7- 95.2]) of children had bilateral spastic cerebral palsy. Only one child (2.8%) had unilateral spastic cerebral palsy, three (8.5%) had dyskinetic and one (2.8%) ataxic CP. Figure 1 and Table 2 show results of gross and fine motor function according to GMFCS and BFMF respectively. Seven children (20.0%) had mild cerebral palsy with ability to walk (GMFCS levels I-II), three children (8.6%) were able to walk with assistive device (GMFCS level III), while 25/35 children (71.4% [CI 53.7-85.4]) had a severe CP without ability to walk (GMFCS levels IV-V). Results of functional classification for the upper limbs (BFMF scale) were very similar, showing ten (28.5%) children in levels I-II, three (8.6%) in level III and 22/35 (62.8%[CI 44.9-78.5]) in levels IV-V.
Table 3 shows results of visual and hearing assessments, epilepsy, cognitive and speech development and head circumference at the last assessment. Ten (28.5%) children had normal vision, 20 (57.1%) mild impairment and four (11.4%) severe visual impairment; 14 (40.0%) children had normal hearing, four (11.4%) mild impairment and 15/35 (42.8%) severe hearing impairment, of whom three had to receive a cochlear implant. 27/35 (77.1% [CI 59.9-89.6]) children had epilepsy, 26/35 (76.4%) received an antiepileptic therapy at their last assessment. Only one child (2.8%) had normal cognitive development, five (14.2%) had mild to moderate delay, while 27/35 (77.1%) of children were diagnosed with severe intellectual impairment. Similarly, normal to almost normal speech development was reported in only three (8.5%) children, while speech was poorly understandable in 5 (14.2%) children and absent in 25/35 (71.4% [CI 53.7-85.4]) children. Head circumference at the last assessment was available for 32/35 children: 20 (57.1%) had microcephaly, in six (17.1%) children HC was between the 3rd and 15th percentile and also in six (16%) children HC was above -1 SD.

DISCUSSION

Cerebral palsy following symptomatic congenital CMV infection according to our study is mostly a severe condition, associated impairments are frequent, often seen not only in children with severe, but also in those with mild motor impairment.

The main subtype of cerebral palsy caused by symptomatic congenital CMV infection in this multicenter study involving countries from the SCPE-NET, was bilateral spastic with 85.7% [CI 69.7-95.2], much more frequent than in the general CP population (the SCPE database gives 54.9%). Severe forms without any ability to walk, e.g. GMFCS levels IV and V, were seen in 71.4% [CI 53.7-85.4] which is again much higher than the 31% reported for CP in general in a recent survey of CP in Western Sweden. Accordingly, fine motor function was severely affected in 62.8% [CI 44.9-78.5] (BFMF levels IV and V), which was reported only in 26% of the general Swedish population. Associated impairments, usually severe, were also often reported. Around 77% [CI 59.9-89.6] of children had severe intellectual impairment which is much higher than the 33% reported in the SCPE database or the 40% in the recent Swedish study. Epilepsy also occurred much more frequently, e.g. in 77% [CI 59.9-89.6] versus 21% or 33% in recent studies. The high rate of children in our cohort (71.4%) who did not develop speech also reflects the severity of the disease. In comparison to data from general populations of children with CP, significant severe associated impairments were more common even in children with mild motor impairment (GMFCS I-II). This severe outcome data indicates that brain lesions due to the infection must often be severe and bilateral in children with symptomatic congenital CMV infection.

Further evidence for severe and early affection of the brain is the primary microcephaly seen in 37.1% of the children, and HC between 3rd and 15th percentile in another 17.1%. Microcephaly at birth has been reported as predictor of poor outcome. Head circumference at last assessment showed that even more children developed microcephaly (57.1%), which is in concordance with the poor neurodevelopmental outcome, and indicates the negative effect of the early viral disease on brain growth and development.

In contrast to CP in general with a reported male:female ratio of 1.33:1 female patients were more frequent than males in this symptomatic congenital CMV group with CP (F:M ratio 1.69:1). Prematurity was seen in 17.1%, most were moderately preterm (14.2%) – in comparison to the general CP population where almost half of children are born prematurely (approximately 20% are born moderately and 27% very preterm).

All of the children had one or more symptoms of CMV infection during newborn period, which is in accordance with the evidence from the literature, that symptomatic infection is a prognostic sign of more severe outcome. However, although children from
mother’s first pregnancy are also often considered as having a higher risk for a poor neurodevelopmental outcome due to a higher rate of maternal primo-infection, recent studies show that children born from subsequent pregnancies are also at high risk due to exposure of a mother to her own CMV-infected children. In this study, numbers were not different of children who were born from a first or subsequent pregnancies. Another evidence supporting early intrauterine infection is the high percentage (42.8%) of severe hearing impairment in our patients, even higher than the previously reported sensorineural hearing loss in 24% children after first trimester infection, in contrast to only 2.5% in group infected later in pregnancy. Our study shows a high prevalence of epilepsy among CMV-CP patients (77.1%) which also required continuous antiepileptic therapy in most of them. Suzuki et al found a strong correlation between the prevalence of epilepsy among children with congenital CMV infection and development of CP, as all of the CMV children suffering from epilepsy developed CP, while only 25% of the CMV children without epilepsy had CP. Results from SCPE-NET registers show that 35% of children with CP in the general population had a history of epilepsy and among them 72% received antiepileptic therapy.

Cerebral palsy is often listed among the most severe sequelae of congenital CMV infection, but seldom reported separately in the same context. In the last few years, an Australian group tried to determine the association between genetic predisposition, viral exposure and cerebral palsy. In the study on stored dried neonatal blood spots from Caucasian newborns that were subsequently diagnosed as having CP and from control newborns showed high prevalence of neurotropic viruses. Of the 414 CP cases, 131 were diagnosed with diplegia, 119 with hemiplegia, 112 with quadriplegia and 52 with other or unspecified subtypes. Results of analysis showed significant association between any viral exposure and cerebral palsy at all gestational ages. Although existence of CMV was not related to development of CP, the prevalence of CMV was significantly higher in control newborns born before 37th week of gestation than in term borns, implying association of intrauterine infection and preterm delivery. “Double jeopardy” hypothesis was introduced 2009, signifying interaction of genetic susceptibility and viral infection in causation of CP.

In one of their most recent studies McMichael et al. performed a highly specific PCR-based search for herpes simplex viruses 1 and 2, varicella zoster virus, Epstein–Barr virus (EBV), CMV, human herpes viruses 6, 7 and 8, and parvovirus B19 on DNA extracted from dried blood spots of 339 Caucasian children with cerebral palsy and 594 controls. CMV and EBV were detected in 5 (1.5%) and 3 (0.9%) of the children with CP, respectively, but not in the control group, indicating that these two viruses are significantly associated with cerebral palsy. However, except of the data that all examined children from both groups were asymptomatic, there are no other clinical data on severity of cerebral palsy caused by infection. Most recent results from an Australian CP Register were published in abstract attributing 1.6% of CP cases to a CMV infection. In comparison to other children with CP in the register, the CMV group had more often spastic quadriplegia (75%), wheel-chair dependency (76%), epilepsy (68%), severe hearing (56%) and visual (16%) impairments and communication impairment (64%) (Smithers-Sheedy H, Badawi N, Raynes-Greenow C, Jones C and the ACPR Group. Cerebral palsy and congenital cytomegalovirus infection: a population based cohort study. Abstract book of 4th Congenital Cytomegalovirus Congress, San Francisco 2012; p62; “personal communication”).

Taken together, our results point out that CP caused by symptomatic congenital CMV infection is predominantly bilateral spastic. Disability is more severe in terms of gross and fine motor function than in BS-CP in the general CP population, and associated impairments are also more common and severe. Severe affection of the brain in its development is also
reflected by a high rate of microcephaly. In addition, CP caused by symptomatic congenital CMV infection is more often affecting females.

This study comprises data from six European countries involved in SCPE-NET, but limitation of this study is that data are not derived from national registers and are not population based. i.e. from initially reported 16 children symptomatic congenital CMV infection from Portuguese national register, 9 had to be excluded to inappropriate proof infection. Other children were included from countries involved in SCPE-NET which declared to have registered data on CMV as one of the causes of CP. Data on four Croatian children were obtained from national register while others were recruited from national scientific project on follow-up of children with intrauterine growth retardation. Data on four Croatian children were obtained from national register while others were recruited from national scientific project on follow-up of children with intrauterine growth retardation. Other limitations are small number of children included in this study and lack of control group. Study gathered CMV infected children with CP from countries involved in European cerebral palsy register, so it was not possible to obtain data on group of CMV infected children without CP.

Despite large number of congenitally CMV infected children, universal screening for CMV is not routinely performed, so many of those children are undiagnosed. We based our study on children with clear laboratory proof of infection which also contributed to reduction of number of studied patients.

Hence, our results can be indicative, but further research needs to be done, especially by integrating diagnostic data on congenital CMV infection in the database of national CP registers, so that the accurate prevalence of CP due to CMV infection, its severity and associated impairments could be determined in SCPE register.

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LITERATURE:

Table 1. Types and subtypes of cerebral palsy according to SCPE classification in children with cerebral palsy caused by CMV infection.

<table>
<thead>
<tr>
<th>CP type</th>
<th>Subtype</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>spastic</td>
<td>bilateral</td>
<td>30 (85.7%)</td>
</tr>
<tr>
<td></td>
<td>unilateral</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>dyskinetic</td>
<td>dystonic</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td></td>
<td>choreo-athetotic</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>ataxic</td>
<td></td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td>35 (100%)</td>
</tr>
</tbody>
</table>
Figure 1. Functional classification of motor impairment in children with cerebral palsy caused by CMV infection, *Gross Motor Function Classification System (GMFCS)*, indicating that higher scores of disability are frequent.
Table 2. Functional classification of motor impairment in children with cerebral palsy caused by CMV infection, *Bimanual Fine Motor Function (BFMF)*

<table>
<thead>
<tr>
<th>BFMF level</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
<td>a</td>
<td>b</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>1 (5.7%)</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>8 (22.8%)</td>
<td>9</td>
<td>25.7%</td>
<td>13</td>
<td>37.1%</td>
<td>35 (100%)</td>
</tr>
</tbody>
</table>
Table 3. Results of visual and hearing impairments, head circumference, epilepsy, cognitive and speech development at last assessment in children with cerebral palsy caused by cytomegalovirus infection. (NA – not available, AET – anti-epileptic therapy)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild impairment</th>
<th>Severe impairment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vision</strong></td>
<td>10 (28.5%)</td>
<td>20 (57.1%)</td>
<td>4 (11.4%)</td>
<td>34+1NA</td>
</tr>
<tr>
<td><strong>Hearing</strong></td>
<td>14 (40.0%)</td>
<td>4 (11.4%)</td>
<td>15 (42.8%)</td>
<td>33+2NA</td>
</tr>
<tr>
<td><strong>Microcephaly</strong></td>
<td>No</td>
<td>3-15 percentile</td>
<td>Yes (&lt;3 percentile)</td>
<td>Total</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>6 (17.1%)</td>
<td>6 (17.1%)</td>
<td>20 (57.1%)</td>
<td>32+3NA</td>
</tr>
<tr>
<td><strong>Epilepsy</strong></td>
<td>No</td>
<td>Yes</td>
<td>AET</td>
<td>Total</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>8 (22.8%)</td>
<td>27 (77.1%)</td>
<td>26 (76.4%)</td>
<td>35</td>
</tr>
<tr>
<td><strong>Intellectual impairment</strong></td>
<td>Normal</td>
<td>Mild/Moderate</td>
<td>Severe</td>
<td>Total</td>
</tr>
<tr>
<td>Intellectual impairment</td>
<td>1 (2.8%)</td>
<td>5 (14.2%)</td>
<td>27 (77.1%)</td>
<td>33+2NA</td>
</tr>
<tr>
<td><strong>Speech</strong></td>
<td>Viking I</td>
<td>Viking II</td>
<td>Viking III</td>
<td>Viking IV</td>
</tr>
<tr>
<td>Speech</td>
<td>1 (2.8%)</td>
<td>2 (5.7%)</td>
<td>5 (14.2%)</td>
<td>25 (71.4%)</td>
</tr>
</tbody>
</table>