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CASE REPORT

Controversies in the therapeutic approach to congenital cytomegalovirus infection

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Abstract

Treatment of congenital cytomegalovirus infection is mandatory in cases with severe systemic and/or neurological involvement. However, some patients are paucisymptomatic, with very subtle systemic manifestations and/or minimal brain alterations. Current international guidelines do not clearly state whether these children should be treated, and this decision is not straightforward for clinicians. Of a small series of six infants with congenital cytomegalovirus infection admitted to our neonatal unit between 2015 and 2019, half showed paucisymptomatic neurological manifestations. In these cases, the determination of ß2-microglobulin in cerebrospinal fluid and magnetic resonance imaging aided in the decision-making concerning the therapeutic approach to follow.

Keywords Congenital cytomegalovirus · Infant · Guidelines · Decision-making

Introduction

Congenital cytomegalovirus (cCMV) infection is currently the leading cause of sensorineural deafness and a major cause of permanent neurodevelopmental alterations in newborns from developed countries [1]. Antiviral treatment has been shown to be effective in reducing both, although it has a long duration, and side effects have been observed in experimental studies (neutropenia, carcinogenicity, and gonadotoxicity). This is why clinical trials have been geared only to patients with symptomatic cCMV infection; current guidelines do not recommend treating when congenital infection is asymptomatic or symptoms are mild or transient [2–4].

However, some patients are paucisymptomatic, with very subtle systemic manifestations and/or minimal brain alterations. Although the proportion of these patients in the total population of neonates with cCMV infection is unknown, it is probably not negligible, and these cases constitute a real challenge as to whether or not to indicate treatment based on the risk–benefit balance.

Case reports

We present three infants with paucisymptomatic neurological manifestations out of six consecutive patients with cCMV infection admitted in a tertiary hospital in the period 2015–2019. Difficulties in indicating antiviral treatment based on current guidelines and international recommendations are discussed. This study was approved by the local ethics committee and parents authorized to use their children´s medical records and MRI scans.

Five of the six patients were diagnosed within the first week of life through the determination of the CMV DNA in urine; one infant was a 28-week-preterm newborn whose diagnosis was established through analysis of Guthrie card from newborn biochemical screening following the ultrasound finding of late-onset lenticulostriated vasculopathy (LSV) at 36 postmenstrual weeks. The characteristics of the six neonates are listed in Table 1. Two of them (cases 1 and 2) had LSV as the only finding, one of them with intrauterine growth retardation. The remaining four (cases 3, 4, 5, and 6) had various alterations in brain magnetic resonance imaging (MRI), though infant six had only very subtle white matter (WM) changes and MRI was performed at 37 weeks gestational age (GA), which

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Table 1 Characteristics of the six neonates with congenital cytomegalovirus infection

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
GA, weeks	28	37	39	32	38	37
Sex	Male	Female	Female	Male	Male	Male
Weight, grams	1280	1735	1980	2000	2840	2330
Systemic manifestations	No	IUGR	Thrombopenia, petechiae	No	No	Thrombopenia, IUGR
Diagnostic method	PCR CMV (Gouthrie card)	PCR CMV (urine)	PCR CMV (urine)	PCR CMV (urine)	PCR CMV (urine)	PCR CMV (urine)
Age at diagnosis	8 weeks (36 weeks PMA)	< 2 weeks of life	< 2 weeks of life	< 2 weeks of life	< 2 weeks of life	< 2 weeks of life
DNA CMV in blood (copies/ml)	5980	92	23,048	600	32,560	396
Treatment	No	Yes	Yes	Yes	Yes	Yes
Duration of treatment	-	6 months	6 months	6 months	6 months	6 months
Side effects of treatment	-	No	Neutropenia	No	No	No
Outcome (latest revision)	Autism spectrum disorder; no hearing loss (49 months)[a]	Normal (15 months); no hearing loss	Normal and mild-moderate bilateral hearing loss (11 months)	Normal and no hearing loss (5 months)	Neurodevelopmental delay; worsening of hearing loss (right deafness) (13 months)	Normal and no hearing loss (4 months)
Hearing loss (age at diagnosis)	No	No	Yes, mild-moderate bilateral (neonate)	No	Yes, severe bilateral (neonate)	No

CMV cytomegalovirus, *GA* gestational age, *IUGR* intrauterine growth restriction, *PCR* polymerase chain reaction, *PMA* postmenstrual age

[a]This infant has familiar antecedents of autism spectrum disorder

means that those WM changes could be due to an early-term age (Fig. 1) (Table 2).

Following the recommendations of the current guidelines (Fig. 2), patients with significant alterations on MRI (patients 3, 4, and 5) were treated with valganciclovir for 6 months. However, there was no clear criterion on what to do for the child with minimal WM changes (and mild LSV—patient 6) and for the two patients with LSV (patients 1 and 2). Based on B2microglobulin (β2-m) levels in CSF, we decided to treat patient 6 but not the two patients with LSV exclusively, although at the express wish of the parents one of them was ultimately treated. Of the five patients receiving treatment, one had side effects to treatment (neutropenia) forcing temporary discontinuation of treatment on two occasions. Two of the six patients (patients 3 and 5) did not pass auditory screening at birth, showing different degrees of deafness in auditory studies. The others have not developed any degree of hearing loss to date (Table 1).

Discussion

Kimberlin et al.'s [3] trial published in 2015 showed that treatment with valganciclovir aimed at newborns over 32 weeks of gestational age and started in the first 30 days and for 6 months reduced the risk of deafness at 12 and 24 months and improved Bayley III neurodevelopment test in the area of language in infants with cCMV infection at the age of 24 months.

This clinical trial included a very heterogeneous population of neonates with cCMV infection as they included as symptomatic any infant presenting one or more of the following manifestations: thrombopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis, and neurological involvement (microcephaly, calcifications, chorioretinitis, hearing impairment, and CMV DNA in cerebrospinal fluid). Inevitably this clinical

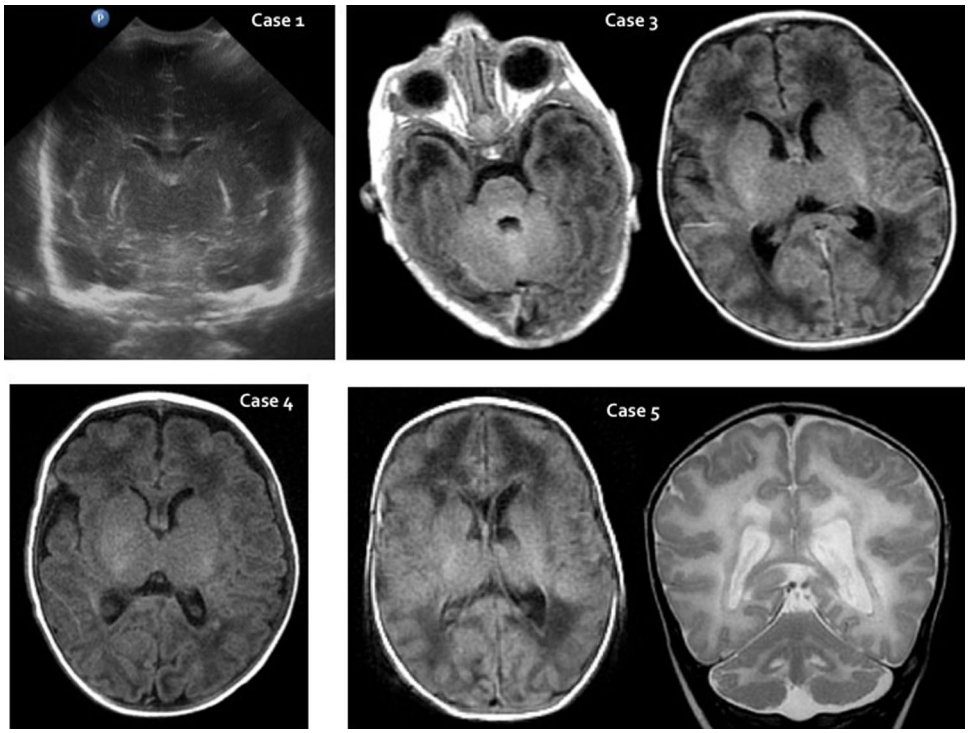

Fig. 1 Neuroimaging findings of some of the infants of our series with congenital cytomegalovirus infection. Cranial ultrasound coronal scans showing bilateral lenticulostriated vasculopathy. MRI in cases 3, 4 and 5 demonstrating white matter changes as hypointensity in axial T1-weighted sequence. Perisylvian polimigrogyria in seen in coronal T2-weighted imaging in case 5

trial did not shed light on what the benefit of treatment for infants with each of these manifestations separately was, or what the benefit was for those children with other types of manifestations, especially those with mild neurological symptoms. Following the Kimberlin trial, two clinical management guides were developed that are listed in the algorithm shown in Figs. 1 and 2 [2, 4]. Both sets of guidelines indicate treatment in cCMV infection when there is moderate-severe systemic and/or central nervous system involvement, based on the increased risk of alterations in neurodevelopment, especially in the sensory (hearing loss) and cognitive areas [5, 6]. On the other hand, they differ as to whether or not paucisymptomatic cases should be treated.

In our series, the decision to treat was consistent in three patients (infants 3, 4, and 5) with moderate-severe neurological abnormalities, but the decision was challenging in patient 6 with subtle WM changes (and mild LSV), and in the two cases with isolated LSV (infants 1 and 2).

Neuroimaging is an essential tool for the evaluation of neurological involvement in cCMV infection. It has demonstrated high sensitivity in predicting motor and cognitive alterations. Several studies have graded the severity of the damage; although they were heterogeneous in terms of the imaging tools used, they all consistently consider the same serious criteria including alterations of neural migration, calcifications, ventriculomegaly, and WM changes [7–9]. However, the criterion of WM changes in the referred guidelines is not uniform as Rawlinson et al.'s describe it as periventricular echogenicity and Luck et al.'s as WM abnormalities. Furthermore, the severity of the alteration is not referenced [2, 4]. This aspect is relevant, as cases with multifocal or diffuse alteration are clearer and suggest symptomatic forms of infection [8], while mild cases with focal involvement of the WM may cast doubts, and more so when the analysis is qualitative and the judgement is established by visual inspection.

Another neurologically difficult finding to consider in susceptibility to treatment is the LSV. LSV is an echogenicity observed on ultrasound of the lenticulostriated branches of the middle cerebral artery located in the region of the thalamus and the basal ganglia [10]. Patients 1 and 2 had only isolated LSV in cerebral ultrasound without alteration of the WM in the MRI and without any other associated clinical-analytical manifestations. The indication of treatment in these cases is challenging due to the non-specific nature of this finding and the lack of consensus as to whether it is a relevant finding for CMV infection [10]. One study found a reduction in the risk of hearing loss with antiviral treatment in these children with cCMV infection [11], while another recent study found no link between LSV and hearing loss [12]. Isolated LSV are not included among the treatment indications in the Rawlinson et al.´s guidelines while it is included by Luck et al.'s although for them it is not a sufficient treatment criterion in case of an isolated finding [2, 4].

Due to the lack of consistent evidence, we use other biomarkers in the decision-making concerning the indication of treatment in these paucisymptomatic cases with focal WM

Table 2 Neurological involvement of the 6 patients with congenital cytomegalovirus infection and indication of treatment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Cranial ultrasound	Moderate LSV	Mild LSV	Moderate LSV Caudothalamic cysts Increased periventricular echogenicity	Mild LSV Moderate periventricular echogenicity	Severe LSV Ventriculomegaly Increased periventricular echogenicity Caudothalamic cysts Abnormal perisylvian area	Mild LSV
MRI	Normal	Normal	Caudothalamic cyst WM changes (diffuse and temporal involvement)	Calcifications Periventricular cyst WM changes (diffuse)	Ventriculomegaly Polymicrogyria Periventricular cysts WM changes (diffuse and temporal involvement)	Very subtle WM changes
Ophthalmologic examination	Normal	Normal	Normal	Normal	Chorioretinitis	Normal
Hearing test	Normal	Normal	Hearing loss	Normal	Hearing loss	Normal
Proteins in CSF (mg/dl)	-	83	100	191	66	139.4
β2-microglobulin in CSF (mg/l)	3.99	2.50	10.34	5.75	10.04	7.20
DNA CMV in CSF (copies/ml)	0	0	340	0	48	0
Indication of treatment according to Rawlinson et al.´s guidelines (criterion)	Not to treat	Not to treat	Treat (WM changes and CMV in CSF)	Treat (calcifications, WM changes; and abnormal CSF proteins for age)	Treat (ventriculomegaly, neuronal migration abnormalities, WM changes, hearing loss and chorioretinitis)	Not to treat
Indication of treatment according to Luck et al.´s guidelines (criterion)	Not to treat	Not to treat	Treat (cysts, WM changes)	Treat (cysts, calcifications, and WM changes)	Treat (ventriculomegaly, cysts, WM changes, neuronal migration abnormalities, hearing loss and chorioretinitis)	Not to treat
Staff and parental decision	Not to treat	Treat	Treat	Treat	Treat	Treat

CMV cytomegalovirus, *CSF* cerebrospinal fluid, *LSV* lenticulostriated vasculopathy, *MRI* magnetic resonance imaging, *WM* white matter

injury and/or LSV. Evidence for the value of the number of copies of CMV in blood [13, 14], urine [15], Guthrie card [16], and CSF [17, 18] is low and/or controversial. Therefore, they are of little use at the present time as outcome tools.

β2-m has been shown to be very useful in predicting neuroevolutive sequelae in this congenital infection. It is a low molecular weight protein present on the surface of all nucleated cells and is elevated in the CSF of the newborn in case of infection [19]. A 7.9 mg/L cut-off point has been identified as the best individual biomarker to identify children at high risk of adverse neurodevelopmental outcome (assessing motor, cognitive, behavioral, epileptic, visual, and auditory areas), and in combination with MRI findings there is a high predictive value of neurodevelopmental alterations with a positive predictive value of 100% [8, 20]. The two patients with isolated LSV (infants 1 and 2) had low values of β2-m. Based on this we decided not to treat with valganciclovir, though one of the patients received treatment at the express request of the parents. The patient with subtle WM changes and mild LSV (patient 6) had 7.20 mg/L, a value very close to the cut-off point for adverse neurodevelopment, and therefore treatment was initiated.

Summary

The difficulty in paucisymptomatic patients is, first establishing whether the manifestations they present are specifically attributable to CMV infection and not to other conditions.

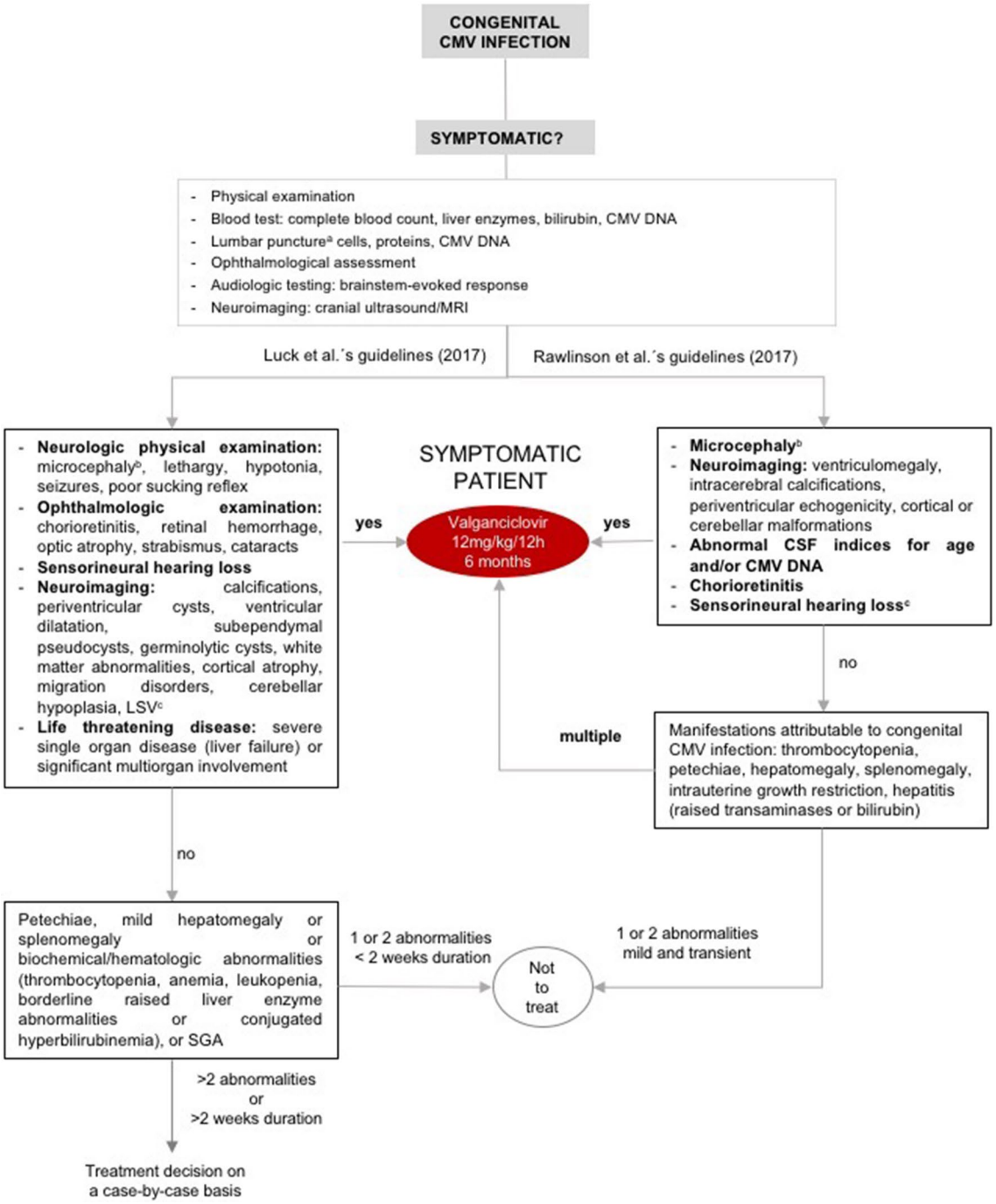

Fig. 2 Treatment algorithm according to Luck et al.'s and Rawlinson et al.'s guidelines. *CSF* cerebrospinal fluid, *CMV* cytomegalovirus, *LSV* lenticulostriated vasculopathy, *SGA* small for gestational age. [a]In the Luck et al.'s guidelines, lumbar puncture is not recommended to be performed routinely in babies with cCMV infection. [b]Defined as head circumference < 2 standard deviations for gestational age. [c]If there are no other symptoms, treatment is not recommended

Second, it needs to be determined whether these paucisymptomatic or oligosymptomatic manifestations may lead to an increased risk of changes in neurodevelopment in the medium and long term. Finally, it must be decided whether the benefits of treatment in these patients will outweigh adverse effects since antiviral treatment is not risk-free (neutropenia being its most feared side effect), requires close follow up and its costs are not negligible; moreover, ganciclovir has shown gonadal toxicity and carcinogenic effects in animal testings. The lack of information regarding these

three points conditions the lack of consensus on the guidelines for the indication of treatment.

Additionally, the proportion of paucisymptomatic cases in the total population of neonates with cCMV infection is unknown, but there were three infants in our short consecutive series of six patients. It may be that, at present, with voluntary interruption of gestation in severe cases, the proportion of these mild cases is higher with the decision whether to indicate treatment based on the poor knowledge of the risk–benefit balance, which constitutes a real challenge.

Therefore, studies are needed on this congenital infection that will include and individualize these cases, and place them in therapeutic efficacy studies, to better define the target population that would benefit from antiviral treatment and determine its optimal duration.

The guidelines we have referred to in this study represent an important effort toward unifying the treatment criteria, especially in infants with moderate-severe symptomatology. While we have other validated scores for disease severity at presentation and risk of sequelae that include paucisymptomatic infants, we suggest that patients with mild neurological findings and cCMV infection should be included in follow-up programs to detect neurodevelopmental disorders, especially deafness.

In addition, we also believe that all patients with cCMV infection should undergo an MRI as was suggested in the Luck et al.'s guidelines (although this recommendation did not achieve full consensus), as well as lumbar puncture, as specified in the Rawlinson et al.'s guidelines, but not in those Luck et al.'s, which did, however, include β2-m determination.

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Compliance with ethical standards

Conflict of interest There are no conflict of interests.

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