Received: 18 January 2020 | Revised: 3 April 2020 | Accepted: 6 April 2020

DOI: 10.1111/apa.15305

REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Retrospectively diagnosing congenital cytomegalovirus infections in symptomatic infants is challenging

Natalia Lüsebrink[1] | Matthias Kieslich[1] | Holger F. Rabenau[2] | Rolf L. Schlößer[3] | Horst Buxmann[3]

[1]Department of Neurology, Neurometabolics and Prevention, Clinic for Children and Adolescents, University Hospital Frankfurt/Main, Frankfurt/Main, Germany

[2]Department of Hygiene, Institute for Medical Virology, University Hospital Frankfurt/Main, Frankfurt/Main, Germany

[3]Department of Neonatology, Clinic for Children and Adolescents, University Hospital Frankfurt/Main, Frankfurt/Main, Germany

Correspondence
Horst Buxmann, Department of Neonatology, Clinic for Children and Adolescents, University Hospital Frankfurt/Main, Theodor Stern Kai 7, 60590 Frankfurt/Main, Germany.
Email: horst.buxmann@kgu.de

Abstract

Aim: Our aim was to analyse the diagnostic workup of hospitalised infants with symptoms of congenital cytomegalovirus (CMV) infections.

Methods: This retrospective study was carried out at the University Hospital Frankfurt, Germany, from 2008 to 2017 on infants aged 4 weeks to 12 months presenting with neurological symptoms consistent with congenital CMV infections.

Results: We studied 117 infants, and workup data for CMV infections were available for 84%. Of these, 54% were immunoglobulin G- and immunoglobulin M-seronegative for CMV or immunoglobulin G-seropositive with no viral shedding. Congenital CMV infection was excluded in these cases. In 16%, the CMV workup was incomplete, precluding a definitive diagnosis. Dried blood spots (DBS) were requested from 30%. CMV polymerase chain reaction was negative in 19 of these 29 infants, and CMV deoxyribonucleic acid detection confirmed congenital CMV infections in six patients. DBS had been destroyed in line with German law in four cases. Congenital CMV infections were diagnosed (5%) or excluded (62%) in 67% of patients and unanswered in the remaining 33%.

Conclusion: Diagnoses of congenital CMV infections were widely considered and found in 5%. CMV was not stringently investigated in all patients or remained elusive due to German law on destroying DBS.

KEYWORDS

cytomegalovirus, infectious diseases, neurological impairment, neonatology, newborn screening

1 | INTRODUCTION

Congenital cytomegalovirus (CMV) infections are estimated to occur in 0.2%-0.5% of all live births in Germany.[1] They are the most frequent non-genetic cause of developmental delays[2] and sensorineural hearing loss[3] in the Western world. Congenital CMV infections are clinically silent in approximately 90% of affected newborn infants.[4,5] Therefore, suspicion often only arises later in infancy or childhood. An estimated 13.5% of primarily asymptomatic congenital CMV-infected newborns will suffer neurodevelopmental sequelae.[5] Some

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; CSF, cerebrospinal fluid; DBS, dried blood spots; DNA, deoxyribonucleic acid; Ig, immunoglobulin; PCR, polymerase chain reaction.

of the possible presenting symptoms include microcephaly,[6] developmental delays,[7] epilepsy and sensorineural hearing loss,[3,8,9] all of which prompt neuropaediatric evaluations.

Distinguishing between congenital CMV and postnatal CMV infections is critical, as the long-term complications and treatment recommendations differ significantly.[10-12] Proving a congenital CMV infection requires the detection of viral shedding or the presence of viral deoxyribonucleic acid (DNA) in the newborn infant within 3 weeks of birth.[10,11] If CMV is detected later in life, it could be the result of either congenital CMV or postnatal CMV infections.[10,11] Congenital CMV is not included in the nationwide newborn screening programmes. Therefore, diagnosis of congenital CMV beyond the newborn period can be challenging. A diagnosis is possible if a dried blood spot (DBS), the only remaining routine sample from this critical time period, is available and CMV DNA is detected by polymerase chain reaction (PCR) analysis.[13,14] German data protection laws require the destruction of DBS after 3 months,[15] which can make the retrospective diagnosis of congenital CMV infections impossible.

The differential diagnoses of children presenting with developmental delays, epilepsy and other typical signs and symptoms of congenital CMV infections are broad, often resulting in extensive workups to determine the genetic, metabolic and perinatal causes. Analyses for congenital infections are usually included in the laboratory investigations. However, the correct interpretation of the results and initiation of follow-up investigations, if indicated, require time, financial and personal resources, as well as background knowledge. We sought to evaluate the current diagnostic workup for possible congenital CMV infections in infants older than 3 weeks of age in clinical practice at our institution. We aimed to assess the comprehensiveness of the laboratory investigations and the success rate in terms of making or excluding a congenital CMV infection diagnosis.

Key notes

- This study analysed the retrospective diagnosis of congenital cytomegalovirus (CMV) infections in 117 hospitalised infants aged 4 weeks to 12 months with neurological symptoms.
- Workup data for CMV infections were available for 84%, and congenital CMV infections were found in 5% of the study cohort, underlining the clinical relevance of this differential diagnosis.
- However, it was not possible to reach a congenital CMV diagnosis in one-third of the cases.

2 | PATIENTS AND METHODS

Inpatients aged 4 weeks to 12 months who presented to our Clinic for Children and Adolescents at the University Hospital Frankfurt, Main, Germany, were included in this retrospective study. The period from 2008 to 2017 was covered. The patient charts were retrieved from our electronic hospital information system by searching for a number of keywords describing potential signs and symptoms of congenital CMV infections. These were as follows: calcifications,[16] cerebral palsy,[16,17] cholestasis,[7,18] congenital CMV,[18,19] cystic lesions,[16] delayed myelination,[16,20] elevated transaminases,[7,18] epilepsy,[7] hearing loss,[3,9] hepatopathy,[7,18,19] leukoencephalopathy,[16,20] microcephaly,[6,7] polymicrogyria,[16,20] psychomotor retardation,[7,21] pyramidal signs,[16,20] retinitis,[22] speech delay[6,21] and visual impairment.[22] Various German words, spellings and abbreviations were used to ensure that all patients were identified. The charts were reviewed individually to ascertain their pertinence to the question posed. Infants were excluded if there was a clear diagnosis other than congenital CMV infection to explain their symptoms. For example, cholestasis in a child with biliary atresia was disregarded. Subsequent virological diagnostic tests were reviewed and evaluated for eligible patients. Anti-CMV immunoglobulin (Ig) G and M antibody testing was performed with the Enzygnost CMV IgG and IgM assay (Siemens) according to the manufacturer's instructions, using the Behring ELISA Processor BEP 2000 (now Siemens Healthcare Diagnostics). The results were recorded semi-quantitatively as arbitrary units per millilitre (AU/mL).

To assess CMV DNA load, internally controlled CMV real-time polymerase chain reaction (PCR) using the TaqMan Gen Ex Master Mix (Life Technologies) and the ABI7900 sequence detection system (Life Technologies) [23] was performed. For internal control, we added a defined number of cell culture supernatant-derived murine CMV, namely Smith strain ATCC VR-1399 virions (American Type Culture Collection).[23] Detection of CMV DNA using dried blood spots (DBS) as the sample material and real-time PCR as the analytic method was performed according to previously described methods.[24] CMV isolation from urine samples in cells was performed as previously described using human foreskin fibroblasts as indicator cells.[25,26]

The statistical analysis was performed by calculating the exact Clopper-Pearson 95% confidence intervals (CIs) for patient group proportions, according to the diagnostic workup they received and the final results regarding their congenital CMV infection status.

This study was approved by the Ethics Committee of the Department Medicine at the University Hospital Frankfurt, Goethe University, Germany (reference number: 158/18).

3 | RESULTS

A total of 117 patients were included from 2008 to 2017. Congenital CMV infections were not considered as a differential diagnosis in 19 of the infants (16%, 95% CI 10%-24%), but they were for the remaining 98 (84%, 95% CI 76%-90%) patients (Figure 1). The virological investigations included CMV serology of the blood or cerebrospinal fluid (CSF), PCR analysis for CMV DNA of the blood or urine or CSF and CMV cultures of the urine. Only four of the mothers of the infants had known

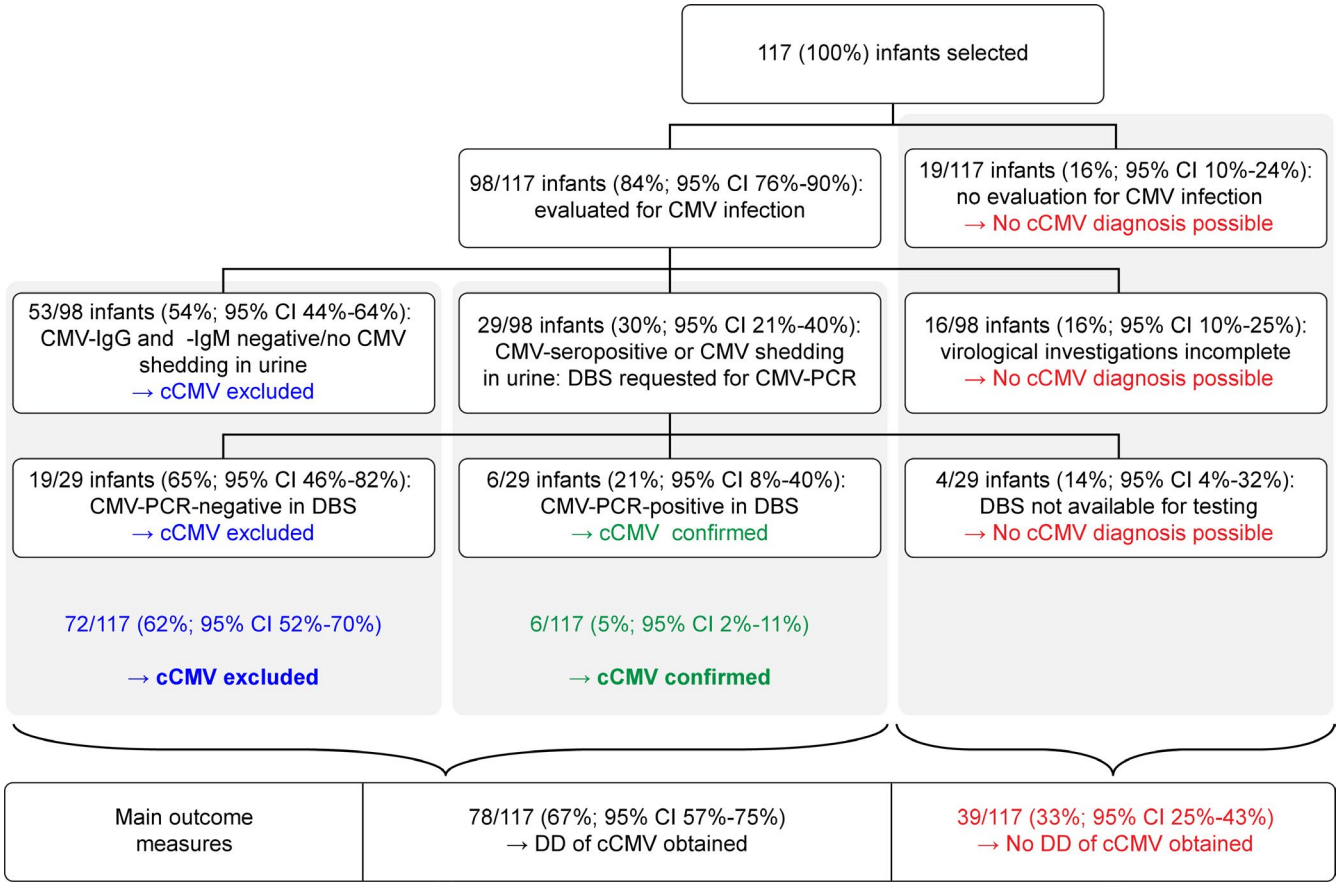

FIGURE 1 Depiction of the diagnostic workup process for the 117 selected infants with possible congenital CMV (cCMV) infections (percentages, which refer to the whole cohort, and 95% confidence intervals are reported). A definitive diagnosis, meaning confirmed or excluded congenital CMV infection at best, could be made with virtual certainty in 67% (95% CI 57%-75%) of infants. In 33% (95% CI 25%-43%) of the patients, no definitive congenital CMV infection diagnoses could be made

CMV serology results, and two of these mothers were seronegative. This excluded a congenital CMV infection in the child.

In total, 53/98 (54%, 95% CI 44%-64%) infants were seronegative for CMV IgG and IgM or were seropositive for CMV IgG without viral shedding. Hence, congenital CMV infections were excluded. DBS were requested from 29/98 patients (30%, 95% CI 21%-40%) with positive CMV serology and/or virus shedding in the urine. These were compatible with congenital CMV infections, postnatal CMV infections or maternal CMV IgG transfer *in utero*. The CMV PCR analysis was negative in 19/29 (65%, 95% CI 46%-82%) of the infants. Congenital CMV infections were confirmed by detecting CMV DNA in the DBS of 6/29 (21%, 95% CI 8%-40%) patients (Figure 1). All of them showed hearing loss as one clinical symptom (Table 1). Three out of these six subsequently received antiviral therapy. In 4/29 (14%, 95% CI 4%-32%) cases, DBS were not available for testing.

In 16/98 infants (16%, 95% CI 10%-25%), the CMV workups were incomplete, for example only CMV PCR in cerebrospinal fluid, precluding a definitive diagnosis.

Workups for any CMV infections were not performed in 19/117 (16%, 95% CI 10%-24%) patients.

Regarding the entire cohort of 117 infants, 78 (67%, 95% CI 57%-75%) patients had a reliable diagnosis: 6/117 (5%, 95% CI 2%-11%) were confirmed to have congenital CMV infections and 72/117 (62%, 95% CI 52%-70%) were excluded, at best, from having one. In 39/117 (33%, 95% CI 25%-43%) patients, the differential diagnosis of a congenital CMV infection remained unanswered.

4 | DISCUSSION

Congenital CMV infections can manifest clinically at birth with symptoms such as petechiae (55%-76%),[7,18] jaundice (40%-81%),[7] hepatosplenomegaly (17%-76%)[7,18,19] and microcephaly (30%-53%).[7,18] Alternatively, they can present with delayed detected sequelae, which mainly consist of sensorineural hearing loss (7%-56%),[7,9,18] and neurodevelopmental impairment (16%-27%).[7] If the symptoms appear beyond 3 weeks of life, targeted investigations are necessary to retrospectively verify or exclude the differential diagnosis of congenital CMV infection. We hypothesised that this question would often be incompletely addressed in clinical practice. Therefore, we aimed to analyse the diagnostic workups of infants with symptoms

TABLE 1 Number of selected patients by symptom(s) of our screening and final diagnosis (multiple selections possible), aged 1.4-11.5 mo, mean: 5.2 mo. In total, 49 patients were female, and 68 were male

Symptoms	No. of selected patients	cCMV confirmed	cCMV excluded	No cCMV diagnosis possible
Epilepsy	28	0	15	13
Hearing loss	21	**6**	9	6
Psychomotor retardation	17	1	14	2
Cholestasis	16	0	10	6
Microcephaly	14	1	7	6
Speech delay	14	0	10	4
Elevated transaminases	12	0	6	6
Hepatopathy	8	0	5	3
CNS cystic lesions	2	0	2	0
Retinitis	2	0	2	0
CNS calcifications	1	0	1	0
Cerebral palsy	1	1	0	0
Migration disorders	1	0	1	0
Polymicrogyria	1	0	1	0
Pyramidal sings	1	0	1	0
Delayed myelination	0	0	0	0
Leukoencephalopathy	0	0	0	0
Visual impairment	0	0	0	0

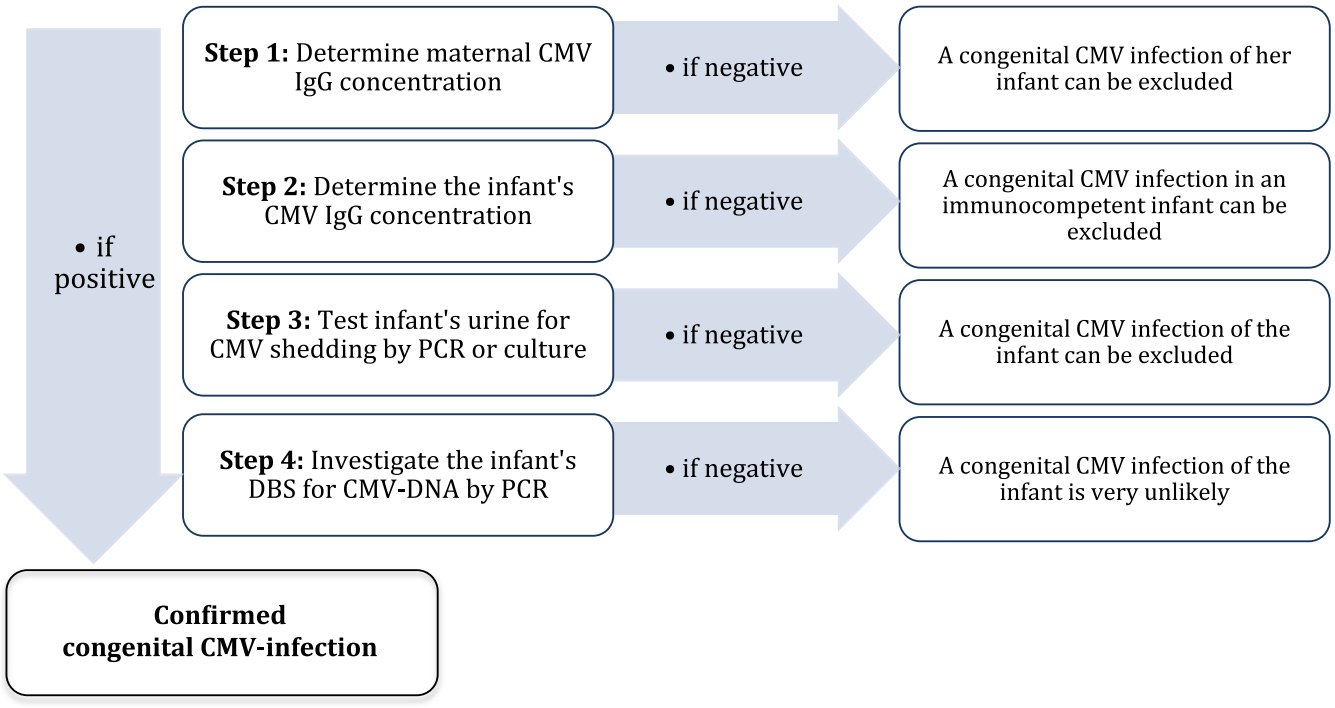

FIGURE 2 Graduated diagnostic workup plan for the retrospective diagnosis or exclusion of congenital CMV infections in patients aged 4 wk to 12 mo

consistent with congenital CMV infections in the clinical daily routine at our institution.

The response to the primary outcome parameter was that congenital CMV infections were diagnosed (5%) or excluded (62%) in 67% of patients. This rate was higher than expected. To the best of our knowledge, no comparable data have been published so far. Therefore, further studies are needed to analyse the retrospective congenital CMV detection rates in other clinical settings.

In our cohort, congenital CMV infections were considered in the vast majority (98/117, 84%) of patients older than 3 weeks of age with consistent clinical symptoms. Comprehensive investigations were performed in 82/98 (84%) of these infants. Using broad virological diagnostic methods with the available materials, congenital CMV infections could essentially be excluded in 72/82 patients (87%) and confirmed in 6/82 infants (7%) by detecting CMV DNA through PCR of the DBS. This represented a relevant subgroup of the cohort investigated. In addition, three families opted for off-label antiviral therapy with valganciclovir in the light of the potential benefits, even if it is started beyond the newborn period.[27,28]

It must be considered that the sensitivity of CMV PCR from DBS varies according to the chosen method[13,14] and this can result in a potential underdiagnosis of congenital CMV infections. Therefore, the number of patients with congenital CMV infections in our cohort could have been even higher. This uncertainty will persist as long as congenital CMV screening is not established. It was very important for the patients and parents described in our cohort for us to find a diagnosis that explained the presenting symptoms, because that diagnosis could lead to a causal or at least symptomatic therapeutic approach. Having a diagnosis can help to set up a tailored follow-up programme for patients and avoid unnecessary, potentially painful diagnostic procedures.

In 4/82 cases (5%) of broad CMV investigations, the diagnosis remained elusive because DBSs were unavailable for testing since they were destroyed after 3 months according to the strict German data protection laws.[15] To the best of our knowledge, there is no other country in Europe or Northern America where the elimination of residual blood samples from DBS is so restrictively regulated as in Germany.[15]

Investigations for suspected congenital CMV infections are available within the routine diagnostics of hospitals in industrialised countries. However, our data showed that in daily practice without a specific standard operating procedure (SOP), clinicians did not always stringently follow the diagnostic workup until a congenital CMV infection was retrospectively verified or confidently excluded.

Therefore, we propose the following graduated diagnostic workup plan for infants from 4 weeks to 12 months of age, which should be feasible in daily clinical or even outpatient practice (Figure 2).

As the first step, the CMV IgG serology of the mother should be analysed. If there are no detectable CMV IgG antibodies in the healthy mother, a congenital CMV infection in her child can be excluded.

If the mother is CMV IgG-positive, the serology of the infant should be evaluated for CMV IgG. In the event that no CMV IgG antibodies are detected in the infant, a congenital CMV infection can be excluded if the child is clinically non-immunocompromised.

If the child is CMV IgG-seropositive, the urine should be checked for CMV shedding by PCR or short-term culture as the next diagnostic step. In the event that CMV is not detectable in the infant's urine, a congenital CMV infection can be excluded because untreated children shed CMV for longer than 1 year.[29] If CMV is found in the child's urine, this could be the result of a congenitally or postnatally acquired CMV infection.

Therefore, the DBS of the infant should be evaluated for CMV DNA by PCR, which is the key examination for the retrospective congenital CMV diagnosis. If CMV is detected in the DBS; then, a congenital CMV infection in the child is verified. In light of the current limited detection rates for this method, and the variable presence and degree of CMV viraemia in an affected newborn infant at the time of DBS sampling, a negative CMV PCR result from the DBS does not reliably exclude a congenital CMV infection. Nevertheless, a negative CMV PCR result makes this diagnosis highly unlikely, especially if optimised diagnostic options and elution techniques are used[24,30] and the detection rate limitation of approximately 200-400 copies/mL[24,30] is reached.

Our study had limitations, which mainly consisted of its retrospective design and its reliance on the data acquired and noted by clinicians and the coded patient symptoms in our electronic hospital information system during the study period. In addition, the results of our cohort were influenced by the heterogeneity of the chosen diagnostic methods. Prospective studies are urgently needed to verify the results of this analysis, the first one published to date, on the challenges of retrospectively diagnosing congenital CMV infections in symptomatic infants.

5 | CONCLUSION

In infants beyond the newborn period up to 1 year of age, clinical symptoms consistent with congenital CMV infection are numerous. The important distinctions between congenital CMV and postnatal CMV infections were not stringently investigated in all cases. This was probably due to the lack of guidelines or tests remained incomplete because DBS were destroyed after 3 months according to German law.

ACKNOWLEDGEMENTS

We are grateful to Professor Eva Herrmann, from the Institute of Biostatistics and Mathematical Modelling, Goethe University, Frankfurt and Farsad-Assadi Mahin-Dokht, from the Division of Software and Information Systems, University Hospital Frankfurt for their assistance and also to the clinicians who coded the patients' symptoms in our electronic hospital information system during the study period.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Holger F. Rabenau https://orcid.org/0000-0001-9394-2176
Horst Buxmann https://orcid.org/0000-0001-6196-9171

REFERENCES

1. Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K. Primary human cytomegalovirus (HCMV) infection in pregnancy. *Dtsch Arztebl Int*. 2017;114:45-52.

2. Cannon MJ, Davis KF. Washing our hands of the congenital cytomegalovirus disease epidemic. *BMC Public Health*. 2005;5:70.
3. Fowler KB, McCollister FP, Sabo DL, et al. A targeted approach for congenital cytomegalovirus screening within newborn hearing screening. *Pediatrics*. 2017;139:e20162128.
4. Swanson EC, Schleiss MR. Congenital cytomegalovirus infection: new prospects for prevention and therapy. *Pediatr Clin North Am*. 2013;60:335-349.
5. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. 2007;17:355-363.
6. Kimberlin DW, Jester PM, Sanchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med*. 2015;372:933-943.
7. Dreher AM, Arora N, Fowler KB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. *J Pediatr*. 2014;164:855-859.
8. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. *Pediatrics*. 2014;134:972-982.
9. Foulon I, Brucker YD, Buyl R, et al. Hearing loss with congenital cytomegalovirus infection. *Pediatrics*. 2019;144:e20183095.
10. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis*. 2017;17:e177-e188.
11. Luck SE, Wieringa JW, Blazquez-Gamero D, et al. Congenital cytomegalovirus: a European expert consensus statement on diagnosis and management. *Pediatr Infect Dis J*. 2017;36:1205-1213.
12. Kadambari S, Whittaker E, Lyall H. Postnatally acquired cytomegalovirus infection in extremely premature infants: how best to manage? *Arch Dis Child Fetal Neonatal Ed*. 2019. https://doi.org/10.1136/archdischild-2019-317650. [Epub ahead of print].
13. Wang L, Xu X, Zhang H, Qian J, Zhu J. Dried blood spots PCR assays to screen congenital cytomegalovirus infection: a meta-analysis. *Virol J*. 2015;12:60.
14. Ross SA, Ahmed A, Palmer AL, et al. Newborn dried blood spot polymerase chain reaction to identify infants with congenital cytomegalovirus-associated sensorineural hearing loss. *J Pediatr*. 2017;184:57–61 e1.
15. Bundesausschuss G, Hess JR. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinien des Bundesausschusses der Ärzte und Krankenkassen über die Früherkennung von Krankheiten bei Kindern bis zur Vollendung des 6. Lebensjahres (Kinder-Richtlinien) zur Einführung des Erweiterten Neugeborenen-Screenings. BAnz. Nr. 60 (S. 4833). 2005 [cited 2020 Mar 21]: [A-1158]. Available from: URL: https://www.g-ba.de/downloads/39-261-170/2004-12-21-Kinder-TMS.pdf
16. Alarcon A, Martinez-Biarge M, Cabanas F, Quero J, Garcia-Alix A. A prognostic neonatal neuroimaging scale for symptomatic congenital cytomegalovirus infection. *Neonatology*. 2016;110:277-285.
17. Shepherd E, Salam RA, Middleton P, et al. Neonatal interventions for preventing cerebral palsy: an overview of cochrane systematic reviews. *Cochrane Database Syst Rev*. 2018;6:CD012409.
18. Ross SA, Boppana SB. Congenital cytomegalovirus infection: outcome and diagnosis. *Semin Pediatr Infect Dis*. 2005;16:44-49.
19. Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143:16-25.
20. Averill LW, Kandula VV, Akyol Y, Epelman M. Fetal brain magnetic resonance imaging findings in congenital cytomegalovirus infection with postnatal imaging correlation. *Semin Ultrasound CT MR*. 2015;36:476-486.
21. Oliver SE, Cloud GA, Sanchez PJ, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol*. 2009;46:S22-S26.
22. Jin HD, Demmler-Harrison GJ, Coats DK, et al. Long-term visual and ocular sequelae in patients with congenital cytomegalovirus infection. *Pediatr Infect Dis J*. 2017;36:877-882.
23. Preiser W, Buxbaum S, Fleckenstein C, Doerr HW. Measurement of CMV DNA levels and CMV-specific CD4-lymphocyte counts in patient specimens: requirements for test quality and practicability in a routine diagnostic service. In: Proesch S, Cinatl J, Scholz M, eds. *New Aspects of CMV-Related Immunopathology*, vol. 24. Basel, Switzerland: Karger; 2003:133-148.
24. Göhring K, Dietz K, Hartleif S, Jahn G, Hamprecht K. Influence of different extraction methods and PCR techniques on the sensitivity of HCMV-DNA detection in dried blood spot (DBS) filter cards. *J Clin Virol*. 2010;48:278-281.
25. Buxmann H, Miljak A, Fischer D, Rabenau HF, Doerr HW, Schloesser RL. Incidence and clinical outcome of cytomegalovirus transmission via breast milk in preterm infants ≤31 weeks. *Acta Paediatr*. 2009;98:270-276.
26. Weber B, Hamann A, Ritt B, Rabenau H, Braun W, Doerr HW. Comparison of shell viral culture and serology for the diagnosis of human cytomegalovirus infection in neonates and immunocompromised subjects. *Clin Investig*. 1992;70:503-507.
27. del Rosal T, Baquero-Artigao F, Blazquez D, et al. Treatment of symptomatic congenital cytomegalovirus infection beyond the neonatal period. *J Clin Virol*. 2012;55:72-74.
28. Amir J, Attias J, Pardo J. Treatment of late-onset hearing loss in infants with congenital cytomegalovirus infection. *Clin Pediatr (Phila)*. 2014;53:444-448.
29. Cannon MJ, Hyde TB, Schmid DS. Review of cytomegalovirus shedding in bodily fluids and relevance to congenital cytomegalovirus infection. *Rev Med Virol*. 2011;21:240-255.
30. Berg C, Friis MB, Rosenkilde MM. Development of highly efficient protocols for extraction and amplification of cytomegalovirus DNA from dried blood spots for detection and genotyping of polymorphic immunomodulatory genes. *PLoS ONE*. 2019;14:e0222053.
31. Pellegrinelli L, Galli C, Primache V, et al. Diagnosis of congenital CMV infection via DBS samples testing and neonatal hearing screening: an observational study in Italy. *BMC Infect Dis*. 2019;19:652.

How to cite this article: Lüsebrink N, Kieslich M, Rabenau HF, Schlößer RL, Buxmann H. Retrospectively diagnosing congenital cytomegalovirus infections in symptomatic infants is challenging. *Acta Paediatr*. 2020;00:1–6. https://doi.org/10.1111/apa.15305