Evaluation of clinically asymptomatic high risk infants with congenital cytomegalovirus infection

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Abstract
Objective  To determine the frequency of abnormal findings on evaluation of neonates with congenital CMV infection who have a normal physical examination
Study design  Retrospective, 2-center study (1996–2017) that reviewed results of complete blood cell count and platelets, serum alanine aminotransferase (ALT) and bilirubin concentrations, eye examination, cranial ultrasonography or other neuroimaging, and brainstem evoked responses performed on neonates with congenital CMV infection and a normal physical examination
Results  Of 34 infants with congenital CMV infection and a normal physical examination, 56% (19/34) had ≥1 abnormality: 39%, elevated ALT concentration; 45%, abnormal neuroimaging (five, lenticulostriate vasculopathy; six, intraventricular hemorrhage; four, calcifications); 12%, anemia; 16%, thrombocytopenia; and 3%, chorioretinitis. Seven (21%) infants had sensorineural hearing loss, and 18 infants received antiviral therapy.
Conclusion  Some infants with congenital CMV infection and a normal physical examination had abnormalities on laboratory or neuroimaging evaluation, which in some cases prompted antiviral treatment.

Introduction

Congenital cytomegalovirus (CMV) infection occurs in 0.2–2.4% of all live births and is a leading nongenetic cause of sensorineural hearing loss and neurodevelopmental impairment in childhood [1–6]. Approximately 90% of neonates with congenital CMV infection are “asymptomatic,” meaning that they are well-appearing and have no clinically apparent signs of disease detected at birth. Since these infants have a normal physical examination, they often are not evaluated with laboratory or neuroimaging studies. In some cases, abnormalities detected on such tests, if performed, may reclassify them as “symptomatic,” thereby increasing the risk of hearing loss and disabilities from the 5 to 10% seen in asymptomatic infants [7, 8].
Moreover, recognition of abnormalities may identify neonates who could benefit from antiviral therapy. However, it remains unknown how often neonates with clinically inapparent CMV infection have subtle abnormalities detected on more complete evaluation. Therefore, the objective of this study was to determine the frequency of abnormal findings on laboratory, ophthalmologic, neuroimaging, and audiologic evaluation performed on neonates who had a normal physical examination and were diagnosed with congenital CMV infection, the majority of which occurred in the setting of recognized primary maternal infection.

Materials and methods

This was a retrospective cohort study of prospectively collected data on infants with congenital CMV infection who were referred to and evaluated by the authors at Parkland Memorial Hospital and Children’s Medical Center, Dallas, TX from 1996 to 2011 (PJS) and at Clínica y Maternidad Suizo Argentina, Sanatorio Otamendi, Stamboulian Center, and Sanatorio de la Trinidad Ramos Mejía, Buenos Aires, Argentina from 2008 to 2017 (FG and LNV). Congenital CMV infection was defined as a positive culture or polymerase chain reaction (PCR) test of urine performed in the first 21 days of life [9, 10]. The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center with written or verbal consent obtained from parents of infants enrolled at the participating centers in Buenos Aires, Argentina.

Infants with congenital CMV infection who had a normal physical examination and growth parameters constituted the study population. They were identified by targeted CMV screening when born to mothers who seroconverted for CMV during pregnancy or were infected with the human immunodeficiency virus (HIV), there was a sibling with congenital CMV infection, or they failed the newborn hearing screen [11–13]. The infants’ medical records were reviewed and pertinent demographic, clinical, laboratory, and radiographic data were recorded. Specifically, the results of the complete blood cell count (CBC) and platelets, serum alanine aminotransferase (ALT) concentration, serum bilirubin (total/direct) concentration, eye examination, cranial ultrasonography or other neuroimaging, and brainstem evoked responses (BSER) from the initial presentation or evaluation were reviewed.

Definitions

For term newborns born at ≥37 weeks’ gestation and preterm newborns born at <37 weeks’ gestation, serum ALT ≥40 U/mL and direct bilirubin >2 mg/dL were considered abnormal. Anemia was defined as hematocrit <40% at 0–7 days of age, <35% at 8–14 days, and <30% at 15–28 days, and thrombocytopenia as a platelet count <150,000/mm³ [14]. BSER threshold of 0–20 dB was considered normal hearing, while thresholds of 21–30, 31–60, and 61–90 dB constituted mild, moderate, and severe hearing loss, respectively [15].

Statistical analysis

Statistical analysis was performed using Sigma Plot 11.0 (SPPSS, Chicago, IL) and GraphPad Software (San Diego, CA). Descriptive analyses were performed using frequency distributions and rates. Means with standard deviation (SD) and medians were used to summarize patient demographics and characteristics, where appropriate.

Results

During the study period, there were 34 infants who had a normal physical examination and were diagnosed with CMV infection by culture (n = 14, Dallas) or PCR testing (n = 20, Buenos Aires) of urine performed in the first 3 weeks of age. The majority (82%) of the mothers were Hispanic and delivered vaginally (68%); 15% (5/34) of the infants were preterm and 63% were male (Table 1). Infants were diagnosed with CMV infection for the following reasons: 3 (9%) had mothers with HIV infection although none of the infants were infected, 21 (62%) had mothers diagnosed with CMV infection during the pregnancy, 6 (18%) referred on the newborn hearing screen, 1 (3%) had a sibling with congenital CMV infection, and 3 (9%) were preterm who had abnormalities detected as part of standard medical care. Of the latter three preterm infants, one born at 29 weeks’ gestation had thrombocytopenia and abnormal cerebral ultrasound, one born at 33 weeks’ gestation had thrombocytopenia, and one born at 27 weeks’ gestation had abnormal cerebral ultrasound (Table 1).

Of the 21 mothers diagnosed with CMV infection during the pregnancy, two mothers of infants at Parkland Hospital and Children’s Medical Center, Dallas, had fever and upper respiratory tract infection and both had serum CMV IgM and IgG antibodies detected in the second or third trimester, with one having a negative blood CMV DNA PCR test. Neither mother received any CMV-specific treatment. The other 19 mothers were from Buenos Aires and had serum CMV IgM and IgG antibodies detected during pregnancy as part of standard prenatal care, with one of them also having a positive blood CMV PCR test, and 12 had an amniocentesis that resulted in a positive amniotic fluid CMV DNA PCR test. Nine of the women had flu-like symptoms during pregnancy, and 12 received hyperimmune CMV immune globulin intravenous therapy in Buenos Aires.
Table 1 Characteristics of the mothers and their infants who had congenital CMV infection and a normal physical examination

| No. of mothers | Dallas   | Buenos Aires | Total |
|----------------|---------|--------------|-------|
| Age (year, mean ± SD, range)       | 25.8 ± 5.7 (17–33) | 33.1 ± 8 (22–52) | 29.9 ± 6.9 (17–52) |
| Ethnicity                         |         |              |       |
| Hispanic                          | 8 (57%) | 20 (100%)    | 28 (82%) |
| Non-Hispanic white                | 5 (36%) | 0            | 5 (15%)  |
| Non-Hispanic black                | 1 (7%)  | 0            | 1 (3%)   |
| Type of delivery (n = 28)         |         |              |       |
| Vaginal                           | 9 (64%) | 10/14 (71%)a | 19 (68%) |
| Cesarean                          | 5 (36%) | 4/14 (29%)a  | 9 (32%)  |
| CMV infection during pregnancy (positive serum CMV IgM and IgG; see text) | 2 | 17 | 19 |
| HIV-infection                     | 3 (21%)b | 0 | 3/31 (10%)a |

No. of infants

| Age at diagnosis (days, mean ± SD; range) | 4.5 ± 5.3 (1–21) | 5.6 ± 5.7 (1–21) | 5.1 ± 5.4 (1–21) |
| Gestational age (weeks, mean ± SD; range) | 37 ± 3.4 (29–41) | 37.9 ± 3.1 (27–40) | 37.4 ± 3.2 (27–41) |
| Weight (gram, mean ± SD; range)           | 2964 ± 850 (860–1430) | 2861 ± 755 (1216–4045) | 2900 ± 792 (860–1430) |
| Head circumference (cm, mean ± SD; range)  | 33.7 ± 3.3 (25.5–39.5) | 33.6 ± 2.7 (27.5–38) | 33.6 ± 2.9 (25.5–39.5) |
| Male gender                               | 6 (43%) | 16 (80%)  | 22 (63%) |

CMV cytomegalovirus, SD standard deviation, PCR polymerase chain reaction, HIV human immunodeficiency virus, cm centimeter

aNumber positive/number tested or known
bInfants not HIV-infected

Among the 34 CMV-infected neonates who had a normal physical examination, 19 (56%) had at least one abnormality on laboratory, radiographic, or ophthalmologic evaluation (Table 2) and eight (24%; 4, preterm) infants had ≥2 abnormalities. Laboratory testing performed on 25 (71%) infants revealed an elevated ALT concentration in 39% (9/23) of infants, two of whom also had lenticulostriate vasculopathy on cranial ultrasound with normal hearing, one had a grade I intraventricular hemorrhage and severe unilateral sensorineural hearing loss, one had periventricular and temporal lobe hyperlucency on brain magnetic resonance imaging (MRI) and normal hearing testing, while the remainder only had isolated elevation of ALT (Table 2). Anemia was detected in 12% (3/25) of infants, one of whom also had thrombocytopenia, one had lenticulostriate vasculopathy detected by cranial ultrasonography that was confirmed by MRI, and one had grade III–IV intraventricular hemorrhage detected by cranial ultrasonography.

Twenty-four (71%) neonates had neuroimaging performed that consisted of cranial ultrasonography (n = 22), computerized tomography (n = 2), or MRI (n = 7) (Table 2), with only four infants having more than one neuroimaging study (Table 3). Of the 22 infants who had a cranial ultrasound performed, ten (45%) had at least one abnormality, with lenticulostriate vasculopathy detected in five (23%) and grade I intraventricular hemorrhage in five (23%) infants (Tables 2, 3). One (5%) infant had both lenticulostriate vasculopathy and grade I intraventricular hemorrhage and another one (5%) had three abnormalities consisting of ventriculomegaly, diffuse calcifications, and grade I intraventricular hemorrhage.

Cranial computerized tomography was performed in two infants and was abnormal in one that showed thalamic calcifications. The cranial ultrasound performed on the latter infant showed lenticulostriate vasculopathy (Table 3, infant #3). Brain MRI was performed in seven infants and was abnormal in three infants, with one having periventricular calcifications and temporal lobe hyperlucency (Table 3; patient #4, cranial ultrasound normal), one hadthalamic calcifications (Table 3; patient #2; cranial ultrasound showed lenticulostriate vasculopathy), and another had germinal matrix hemorrhage (Table 3; patient #1, cranial ultrasound showed grade I intraventricular hemorrhage).

Ophthalmologic evaluation was performed in 33 (94%) infants and was abnormal in one infant who had choroiditis. All infants had newborn hearing screen performed and when abnormal, subsequent diagnostic testing showed sensorineural hearing loss in 21% (7/34) of infants with the majority of the hearing loss unilateral (4/7, 57%) and moderate-to-severe in severity (6/7, 86%). Five of the seven infants with hearing loss had neuroimaging abnormalities.

Antiviral therapy consisting of ganciclovir (n = 2), valganciclovir (n = 12), or both (n = 4) was provided to 53% (18/34) of infants (Table 4). The associated abnormalities that prompted antiviral therapy are provided in Table 4, although three infants in Buenos Aires who had normal evaluations received valganciclovir treatment based on detection of CMV by PCR in amniotic fluid.
Discussion

The optimal evaluation of the well-appearing neonate with congenital CMV infection is not known, and beyond hearing screening and possibly ophthalmologic examination, no recommendations exist [16]. This study sought to determine how frequently these “asymptomatic” infants have laboratory, ophthalmologic, and neuroimaging abnormalities that may predict risk for hearing loss and developmental delay. We found that as many as 56% of infants have laboratory, radiographic, ophthalmologic, and audiologic evaluation in 34 infants with congenital CMV infection and a normal physical examination at birth.

Table 2

|                  | Dallas   | Buenos Aires | Total  |
|------------------|----------|--------------|--------|
| No. of infants   | 14 (41%) | 20 (59%)     | 34     |
| No. of infants with at least 1 abnormality | 7 (50%)  | 12 (60%)     | 19 (56%) |
| Laboratory evaluation | 10 (71%) | 15 (75%)     | 25 (71%) |
| Any abnormality  | 4 (40%)  | 11 (73%)     | 15 (60%) |
| Complete blood cell count | 10 (40%) | 15 (60%)     | 25 (100%) |
| Anemia           | 0        | 3 (20%)      | 3 (12%) |
| (hematocrit; mean, range) |          | (35%, 30–39%) | (35%, 30–39%) |
| Thrombocytopenia | 2 (20%)  | 2 (13%)      | 4 (16%) |
| (#/ml; mean, range) | (33,500; 10,000–57,000) | (126,000; 114,000–132,000) | (78,250; 10,000–132,000) |
| Hepatic assessment | 8 (57%)  | 15 (75%)     | 23 (92%) |
| Elevated alanine aminotransferase (U/mL; mean, range) | 2 (22%)  | 7 (78%)      | 9 (39%) |
| Direct hyperbilirubinemia | 0        | 0            | 0      |
| Neuroimaging     | 14 (100%)| 10 (50%)     | 24 (71%) |
| Any abnormality  | 6 (43%)  | 5 (57%)      | 11 (46%) |
| Cranial ultrasonography | 13 (93%) | 9 (90%)      | 22 (92%) |
| Any abnormality  | 6 (46%)  | 4 (44%)      | 10 (45%) |
| Diffuse calcifications | 1 (8%)   | 0            | 1 (55%) |
| Lenticulostriate vasculopathy | 2 (14%)  | 3 (30%)      | 5 (23%) |
| Ventriculomegaly | 1 (8%)   | 0            | 1 (5%)  |
| Any Grade of IVH | 5 (39%)  | 1 (11%)      | 6 (27%) |
| Grade I IVH      | 5 (100%) | 0            | 5 (83%) |
| Grade II–III IVH* | 0        | 1 (100%)     | 1 (17%) |
| Cranial computerized tomography | 1 (7%)   | 1 (10%)      | 2/24 (8%) |
| Thalamic calcifications | 0        | 1 (100%)     | 1 (50%) |
| Brain magnetic resonance imaging | 2 (14%)  | 5 (50%)      | 7/24 (29%) |
| Periventricular calcifications and temporal lobe hyperlucency | 0        | 1 (20%)      | 1 (14%) |
| Calcifications of thalami | 0        | 1 (20%)      | 1 (14%) |
| Germinal matrix hemorrhage | 1 (50%)  | 0            | 1 (14%) |
| Ophthalmological evaluation | 13 (93%) | 20 (100%)    | 33 (97%) |
| Chorioretinitis  | 0        | 1 (5%)       | 1 (3%)  |
| Audiologic evaluation (brainstem evoked responses) | 14 (100%) | 20 (100%)    | 34 (100%) |
| Sensorineural hearing loss | 6 (43%)  | 1 (5%)       | 7 (21%) |
| Unilateral       | 3 (50%)  | 1 (100%)     | 4 (57%) |
| Bilateral        | 3 (50%)  | 0            | 3 (43%) |
| Mild             | 1 (17%)  | 0            | 1 (14%) |
| Moderate         | 2 (33%)  | 0            | 2 (29%) |
| Severe-profound  | 3 (50%)  | 1 (100%)     | 4 (57%) |

*Neonate born at 27 weeks’ gestation
neonates with congenital CMV infection and a normal physical examination had abnormalities that would reclassify them as "symptomatic."

Among the laboratory tests performed, the most frequent finding was a mildly elevated serum ALT concentration even though no infant had signs of hepatitis including hepatomegaly. Only one infant had chorioretinitis, although the importance of such a finding and its response to antiviral therapy likely makes ophthalmologic evaluation warranted in all neonates with congenital CMV infection [17–19].

Cranial ultrasound detected abnormalities in 45% of infants in whom the test was performed. Although

### Table 3 Results of neuroimaging studies in the four CMV-infected neonates who had more than one study performed

| No. of patient | Site       | Gestational age (week) | Weight (gram) | Sex | Cranial ultrasonography | Cranial computerized tomography | Brain magnetic resonance imaging |
|----------------|------------|------------------------|---------------|-----|--------------------------|---------------------------------|---------------------------------|
| 1              | Dallas     | 37                     | 2464          | F   | IVH grade I              | Not done                        | Germinal matrix hemorrhage      |
| 2              | Buenos Aires | 38                    | 2950          | M   | Lenticulostriate vasculopathy | Not done                        | Thalamic calcifications         |
| 3              | Buenos Aires | 34                    | 1760          | M   | Lenticulostriate vasculopathy | Thalamic calcifications         | Not done                        |
| 4              | Buenos Aires | 38                    | 3310          | M   | Normal                   | Not done                        | Periventricular calcifications and temporal lobe hyperlucency |

**IVH** intraventricular hemorrhage

### Table 4 Neonates with clinically inapparent congenital CMV infection who received antiviral therapy

| No. of patient | Site       | Gestational age (week) | Weight (gram) | Sex | Abnormality                                      | Therapy, duration                      |
|----------------|------------|------------------------|---------------|-----|-------------------------------------------------|----------------------------------------|
| 1              | Dallas     | 37                     | 2770          | M   | Lenticulostriate vasculopathy, elevated ALT     | Ganciclovir, 6 weeks                   |
| 2              | Dallas     | 29                     | 860           | M   | Thrombocytopenia, ventriculomegaly, diffuse cerebral calcifications, IVH grade I | Ganciclovir, 6 weeks                   |
| 3              | Dallas     | 41                     | 3295          | M   | Elevated ALT, IVH grade I, hearing loss         | Valganciclovir, 6 weeks                |
| 4              | Dallas     | 37                     | 2464          | F   | IVH grade I, hearing loss                       | Valganciclovir, 6 weeks                |
| 5              | Buenos Aires | 34                    | 1910          | F   | Anemia and thrombocytopenia                     | Ganciclovir, 14 days, Valganciclovir, 6 months |
| 6              | Buenos Aires | 40                    | 3150          | F   | None                                            | Valganciclovir, 6 months               |
| 7              | Buenos Aires | 40                    | 3977          | F   | None                                            | Valganciclovir, 6 months               |
| 8              | Buenos Aires | 40                    | 3475          | F   | None                                            | Valganciclovir, 6 months               |
| 9              | Buenos Aires | 38                    | 2950          | M   | Anemia, lenticulostriate vasculopathy, thalamic calcifications | Valganciclovir, 6 months               |
| 10             | Buenos Aires | 40                    | 3300          | M   | Thrombocytopenia                                | Valganciclovir, 6 months               |
| 11             | Buenos Aires | 38                    | 2820          | M   | Elevated ALT                                   | Valganciclovir, 6 months               |
| 12             | Buenos Aires | 30                    | 1500          | M   | Lenticulostriate vasculopathy                   | Ganciclovir, 14 days, Valganciclovir, 6 months |
| 13             | Buenos Aires | 34                    | 1760          | M   | Elevated ALT, lenticulostriate vasculopathy, thalamic calcifications | Ganciclovir, 14 days, Valganciclovir, 6 months |
| 14             | Buenos Aires | 38                    | 3400          | M   | Elevated ALT                                   | Valganciclovir, 6 months               |
| 15             | Buenos Aires | 38                    | 2865          | M   | Elevated ALT                                   | Valganciclovir, 6 months               |
| 16             | Buenos Aires | 38                    | 2530          | M   | Elevated ALT                                   | Valganciclovir, 6 months               |
| 17             | Buenos Aires | 38                    | 3310          | M   | Elevated ALT, periventricular calcifications and temporal lobe hyperechogenicity | Valganciclovir, 6 months               |
| 18             | Buenos Aires | 27                    | 1216          | M   | Anemia, IVH grade II–III, hearing loss          | Ganciclovir, 14 days, Valganciclovir, 6 months |

**ALT** alanine aminotransferase, **IVH** intraventricular hemorrhage
lenticulostriate vasculopathy is a nonspecific finding associated with a variety of conditions, it has been associated with congenital CMV infection and sensorineural hearing loss [20–24]. Grade I intraventricular hemorrhage also was a frequent finding, although its significance and possible relationship to congenital CMV infection remains unknown. Only four infants who had more than one neuroimaging test performed had abnormalities on at least one of them (Table 3). Cranial computerized tomography was abnormal in one of two infants, in which it was performed, and it demonstrated thalamic calcifications when the cranial ultrasound showed lenticulostriate vasculopathy (Table 3, patient #3). Similarly, MRI showed thalamic calcifications on one infant whose cranial ultrasound demonstrated lenticulostriate vasculopathy (Table 3, patient #3), while in a second infant (Table 3, patient #2), it showed periventricular calcifications and temporal lobe hyperlucency even though the ultrasound was normal.

Sensorineural hearing loss occurred in 21% of evaluated patients, higher than the 5–10% that has been reported previously among asymptomatic infants [25]. This likely represented selection bias as targeted CMV screening for referred hearing screen was performed during the study period. The fact that the hearing loss was moderate to severe in six (86%) infants and bilateral in three (43%) infants highlights the importance of targeted CMV screening of infants who refer on the newborn hearing screen [11, 26–28]. Unfortunately, this study did not include data on late-onset hearing loss which can occur in an additional 15–25% of CMV-infected infants [7].

The results of this study argue for a more complete evaluation of well-appearing neonates with congenital CMV infection. Using the disease classification of Rawlinson et al. [16], further evaluation of the study infants who had a normal physical examination and growth parameters classified seven infants with moderate-severe infection, ten with mild symptomatic infection, three with asymptomatic infection and isolated sensorineural hearing loss, and fourteen infants with asymptomatic infection. As universal screening for congenital CMV infection is being discussed and anticipated in the near future [29, 30], the need for such evaluation needs to be assessed and included as part of potential health benefits and cost analyses [31]. From this study, the performance of a complete evaluation (Table 5) may lead to institution of antiviral therapy to improve hearing and possibly neurodevelopmental outcomes in some infants [32–34].

Limitations of this study include the small sample size and its retrospective nature, and thus not all infants received comprehensive and consistent laboratory and radiological evaluation to know the actual incidence of specific abnormalities. Since the study included infants born since 1996, there may be a time bias with respect to management of these infants, as antiviral therapy has become more accepted with convenient oral administration. The latter may be a likely reason for the valganciclovir treatment of three infants in Buenos Aires who had a normal evaluation. In addition, 62% of the mothers in this convenience sample of CMV-infected infants were diagnosed with CMV during the pregnancy, and therefore the infants may have been more likely to have abnormalities than if they had been born to mothers with CMV reactivation. Nevertheless, 90% of these infants would have been expected to be “asymptomatic” as their physical examination and growth parameters suggested. Regardless, abnormalities detected on evaluation were not infrequent, suggesting that optimal classification of CMV-infected neonates to predict risk of sensorineural hearing loss will require such testing. In addition, infants did not have blood CMV DNA PCR testing that may help predict hearing outcomes [35]. Finally, the lack of an uninfected control group of infants may have resulted in an overestimate of the abnormalities attributable to congenital CMV infection, especially among the five preterm infants whose abnormal findings could have been related to prematurity. However, none of the term infants were diagnosed with other conditions that could have explained the abnormalities noted on laboratory, ophthalmologic, and neuroimaging evaluation.

In conclusion, well-appearing neonates with congenital CMV infection and a normal physical examination frequently have laboratory or neuroimaging abnormalities. This finding argues for performance of a more complete evaluation on these “asymptomatic” infants as suggested in Table 5 since some may benefit from antiviral treatment. Finally, these findings have important public health implications if universal CMV screening is adopted as standard care.

**Table 5** Evaluation of clinically “asymptomatic” neonates with congenital cytomegalovirus (CMV) infection who have a normal physical examination and growth parameters

| (1) Complete blood cell and platelet counts |
| (2) Serum alanine aminotransferase (ALT) concentration |
| (3) Serum total and direct bilirubin concentration |
| (4) Serum creatinine concentration (if antiviral therapy initiated) |
| (5) Blood quantitative CMV viral load |
| (6) Cranial ultrasound<sup>a</sup> |
| (7) Ophthalmologic evaluation |
| (8) Audiologic evaluation<sup>b</sup> |

<sup>a</sup>Magnetic resonance imaging if further brain evaluation desired
<sup>b</sup>Newborn hearing screen, and if not passed, then diagnostic auditory brainstem evoked responses

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Author contributions AR, had full access to all study data and is responsible for the data integrity and accuracy of the data analysis. He participated in the study concept and design, acquisition of data, analysis and interpretation of data, initial and subsequent drafts of the paper, and approved the final paper as submitted. FZ, participated in the study concept and design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. L.E.L, participated in the study concept and design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. KE.O, participated in the study design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. AG.S, participated in the study concept and design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. 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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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