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Immunoglobulin fetal therapy and neonatal therapy with antiviral drugs improve neurological outcome of infants with symptomatic congenital cytomegalovirus infection

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Abstract

Infants with symptomatic congenital cytomegalovirus infection (cCMV) suffer from long-term sequelae. This study aimed at evaluating the efficacy of combining immunoglobulin (Ig) fetal therapy (FT) and neonatal therapy (NT) with antiviral drugs to improve neurological outcomes of affected infants.

Women whose fetuses had symptomatic cCMV received Ig injection into the fetal peritoneal cavity and/or maternal blood as FT, while affected newborns received oral valganciclovir or intravenous ganciclovir as NT. We compared the neurological outcomes at ≥18 months old between infants receiving FT with or without NT (FT group) and those receiving NT only (NT group).

From 2009 to 2019, 15 women whose fetuses had symptomatic cCMV received FT, while 19 newborns received NT only. In FT group, two newborns died, and two were <18 months old. Neurological outcomes of the remaining 11 infants in FT group were as follows: normal 45.5%, mild impairments 36.4%, and severe impairments 18.2%. In NT group, one newborn died, one's parents refused the follow-up, one was <18 months old, and two had only chorioretinitis as symptoms. Neurological outcomes of the remaining 14 infants in NT group were as follows: normal 21.4%, mild impairments 14.3%, and severe impairments 64.3%. The proportion of infants with severe impairments in FT group was significantly lower than that in NT group (18.2% vs 64.3%, $p<0.05$).

This is the first trial demonstrating that the combination of Ig FT and NT with antiviral drugs may be more effective in improving neurological outcomes of newborns with symptomatic cCMV as compared to NT only.

Keywords: Antiviral drugs, congenital cytomegalovirus infection, fetal therapy, immunoglobulin, neonatal therapy

Abbreviations:

CMV, cytomegalovirus; cCMV, congenital cytomegalovirus infection; Ig, immunoglobulin; FT, fetal therapy; NT, neonatal therapy; FGR, fetal growth restriction; GCV, ganciclovir; VGCV, valganciclovir; US, ultrasound; EFBW, estimated fetal body weight; SD, standard deviation; GW, gestational weeks; MRI, magnetic resonance imaging; Fip, Ig injection into the peritoneal cavity of fetuses; Miv, intravenous Ig injection through mothers; ABR, auditory brain-stem response; DQ, developmental quotient; NRFS, non-reassuring fetal status; SGA, small for gestational age.

1. Introduction

Human cytomegalovirus (CMV) is the most common cause of congenital infection and can lead to severe long-term sequelae in affected infants. The prevalence of congenital CMV infection (cCMV) is 0.2%–2.4% in newborns in developed countries (Alford *et al.* 1990, Peckham 1991, Revello and Gerna 2002) and 10%–15% of infected fetuses have symptomatic infection at birth. The clinical manifestations of cCMV include fetal growth restriction (FGR), low birth weight, and multiple organ involvement with petechiae, hepatosplenomegaly, and encephalitis. These are very severe and can cause perinatal death and major neurological long-term sequelae in approximately 90% of surviving infants with symptomatic cCMV (Stagno and Whitley 1985).

Recent reports show that early antiviral therapies with intravenous ganciclovir (GCV) or oral valganciclovir (VGCV) for newborns with symptomatic cCMV do not only improve audiologic outcomes but also reduce the degree of developmental delays in affected infants (Kimberlin *et al.* 2003, Oliver *et al.* 2009, Kimberlin *et al.* 2015, Nishida *et al.* 2016).

Conversely, it is expected that newborns who are already diagnosed with symptomatic cCMV prenatally will have poorer outcomes than those who cannot be diagnosed in utero. However, there are no evidence-based therapeutic guidelines for symptomatic cCMV fetuses diagnosed prenatally. Investigators have reported that symptoms of cCMV identified by fetal ultrasound (US) examinations disappear at birth following fetal therapy (FT) with immunoglobulin (Ig) injection into maternal blood, amniotic fluid, or umbilical cord blood (Nigro *et al.* 2005), and following high-dose oral valacyclovir therapy for pregnant women (Leruez-Ville *et al.* 2016). In contrast, FT with injection of Ig with a high titer of anti-CMV antibody into the peritoneal cavity of an affected fetus with ascites and hepatomegaly has been performed for the first time in 1995 (Negishi *et al.* 1998). A multi-center study for 12 pregnancies with fetuses with

symptomatic cCMV has demonstrated that FT with Ig injection into the peritoneal cavity of affected fetuses or into the maternal blood reduce the incidence and severity of sequelae in surviving infants (Japanese Congenital Cytomegalovirus Infection Immunoglobulin Fetal Therapy Study 2012).

However, no studies have assessed the efficacy of the combination of Ig FT and NT with antiviral drugs in improving long-term outcomes of newborns with symptomatic cCMV. Therefore, this clinical study assessed the neurological outcomes at 1.5 or 3 years of adjusted-age in infants with symptomatic cCMV who received Ig FT with or without NT as compared with those who received NT with VGCV or GCV only.

2. Materials and Methods

2.1. Patients enrollment

The Institutional Review Board of Kobe University Hospital approved the single-center trials of Ig FT (reference number 928) and NT (reference number 923) for symptomatic cCMV. Written informed consent was obtained from all mothers and partners. From October 2009, women whose fetuses had symptomatic cCMV received Ig FT, while newborns with symptomatic cCMV received NT with oral VGCV or intravenous GCV. Newborns with other diseases leading to delay of neurological development, hearing difficulties, or epilepsy were excluded from this study.

2.2. Diagnosis of symptomatic congenital CMV infection of the fetuses

Symptomatic cCMV of fetuses was diagnosed by the presence of imaging findings associated with cCMV together with the positive CMV-DNA in the amniotic fluid obtained by the prenatal amniocentesis. A real-time CMV-DNA PCR analysis for the amniotic fluid was performed according to a previous report (Tanaka *et al.* 2000).

Ultrasound (US) examinations were performed by perinatologists (K.T. and H.Y.) using the Voluson E8 or E10 (GE Healthcare, Milwaukee, WI, USA) or the ARIETTA 60 (Hitachi Aloka Medical, Tokyo, Japan). The following parameters were considered as fetal US findings associated with cCMV: FGR, ventriculomegaly, microcephaly, intracranial calcification, pleural effusion, ascites, and hepatosplenomegaly. FGR was defined as an estimated fetal body weight (EFBW) less than the mean −1.5 standard deviation (SD) for gestational weeks (GW). Microcephaly was defined as a head circumference less than the mean −3.0 SD for GW (Chervenak *et al.* 1984). Ventriculomegaly was defined as a diameter of the atrium of the lateral ventricle greater than 10mm, and classified into three categories: mild (10–12 mm), moderate (12–15 mm), and severe (> 15 mm) (Gaglioti *et al.* 2005). Hepatosplenomegaly

was defined as a biometric measurement of the fetal liver and spleen beyond 95% confidence interval of reference values for that of GW (Schmidt *et al.* 1985, Murao *et al.* 1987). Magnetic resonance imaging (MRI) examinations were performed if necessary.

2.3. Immunoglobulin fetal therapy

The routes of Ig administration for FT were composed of injection into the peritoneal cavity of fetuses (Fip) and intravenous injection to mothers (Miv) (Figure 1). Fetuses with ascites received Fip after draining the ascites as much as possible, at a dose of 2.5–5.0 g Ig once every 1–2 weeks. Fetuses with no ascites received Fip at 1.0–2.0 g Ig once, or their mothers received Miv per week every 1–2 weeks. If Fip was impossible due to the presence of threatened labor, refusal, or unfavorable fetal position for centeses, mothers received Miv at a dose of 7.5–15.0 g (2.5–5.0 g/day × 3 days) Ig per week every 1–2 weeks. Ig with a highest neutralizing antibody titer against CMV (titers of 1:238 to 1:270) available among Venoglobulin-IH (Japan Blood Products Organization, Tokyo, Japan), Kenketsu venilon-I (Teijin Pharma, Tokyo, Japan), and Kenketsu glovenin-I (Nihon Pharmaceutical, Tokyo, Japan) were used.

Fetuses with FT were carefully monitored using ultrasonography and cardiotocogram. Viral loads in the amniotic fluid or maternal/fetal/neonatal blood were repeatedly measured using real-time PCR method if possible. If no improvements in the imaging findings or viral loads were found, termination of pregnancy to start early neonatal antiviral therapy was considered for fetuses with GW ≥ 32 GW and EFBW ≥1200 g (Figure 1).

2.4. Diagnosis and treatment of symptomatic congenital CMV infection of the newborns

Symptomatic cCMV of newborns was diagnosed by positive PCR results for CMV-DNA in the urine together with the presence of at least one clinical symptom of

cCMV. The clinical symptoms indicating cCMV were as follows: microcephaly, hepatosplenomegaly/hepatitis, thrombocytopenia, brain image abnormality, CMV-associated retinopathy, or abnormal auditory brain-stem response (ABR). The definitions of each clinical symptom were described previously (Nishida *et al.* 2016).

Newborns with symptomatic cCMV received NT with oral administration of VGCV 16–32 mg/kg/day for 6 weeks until June 2015 (Kimberlin *et al.* 2008, Lombardi *et al.* 2009) or 32 mg/kg/day for 6 months since July 2015 (Kimberlin *et al.* 2015). If they could not receive oral VGCV, but received intravenous administration of GCV (Kimberlin *et al.* 2003, Oliver *et al.* 2009).

2.5. The assessment of neurological outcomes in treated infants

Infants with FT or NT underwent physical and ABR examinations every 3 months until 1 year of adjusted-age, and every 3–12 months thereafter. Neurological outcomes at 1.5 and 3 years of adjusted-age were assessed by physical examinations and a developmental quotient (DQ) using the Kyoto Scale of Psychological Development (Kono *et al.* 2008). Normal development was defined as no sequelae and an overall DQ ≥80; a mild impairment as unilateral hearing difficulty or mild developmental delay (an overall DQ of 70–79); and a severe impairment as bilateral hearing difficulty requiring hearing aids, epilepsy requiring antiepileptic drugs, or severe developmental delay (an overall DQ <70).

2.6. Statistics

Differences in clinical characteristics and neurological outcomes between children with cCMV who received FT with or without NT (FT group) and those who received NT only (NT only group) were analyzed using the Mann–Whitney *U* test, Fisher exact test, and the chi-square test. Statistical significance was set at p-value <0.05. SPSS

software, version 19 (SPSS Inc, Chicago, Illinois) was used.

Cases with <18 months old of adjusted-age, neonatal death, or refusal of the follow-up were excluded from analyses for comparison between two groups. Newborns who had only chorioretinitis at birth as a symptom of cCMV in NT group were also excluded from comparison with FT group, because the chorioretinitis could not be diagnosed prenatally.

3. Results

3.1. Clinical features of pregnancies with symptomatic congenital CMV infection treated by Ig fetal therapy

From October 2009 to December 2019, 15 women with fetuses with symptomatic cCMV received Ig FT. Table 1 shows the clinical courses of pregnancies and outcomes of infants. The prevalence of US findings associated with cCMV observed prior to FT were as follows: ventriculomegaly 73.3% (11/15), fetal ascites 53.3% (8/15), hepatomegaly 53.3% (8/15), and FGR 40.0% (6/15). Two fetuses had ventriculomegaly only (Cases 1 and 11 in Table 1), two had FGR only (Cases 3 and 4 in Table 1), and the remaining 11 had multiple abnormal US findings associated with cCMV.

The median GW at initiation of FT was 29 GW (range, 20–35 GW). Three cases received Fip only, five received Miv only, and the remaining seven did both Fip and Miv. The median number of FT courses and total doses of Ig per case were 4 courses (range, 1–9 courses) and 30 g (range, 2.5–75 g), respectively. The median GW at delivery and birth weight were 33 GW (range, 30–38 GW) and 2,192 g (1,378–2,996 g), respectively. Twelve of the 15 pregnancies (80.0%) resulted in preterm delivery with cesarean section. The indications for cesarean deliveries were as follows: presence of refractory ascites, n=4 (Cases 9, 12, 13, and 15 in Table 1); growth arrest in FGR, n=2 (Cases 3 and 4 in Table 1); non-reassuring fetal status (NRFS), n=2 (Cases 7 and 8 in Table 1); tocolysis failure, n=2 (Cases 2 and 14 in Table 1); breech presentation, n=2 (Cases 6 and 10 in Table 1); thrombocytopenia in a fetus, n=1 (Case 5 in Table 1).

The prevalence of clinical findings at birth in the newborns who received FT were as follows: abnormalities in head (ventriculomegaly, intracranial calcification, or subependymal cyst, etc.), 86.7% (13/15); abnormalities in liver (hepatomegaly or liver dysfunction), 66.7% (10/15); hematological disorders (thrombocytopenia, anemia, or neutropenia), 66.7% (10/15); ABR abnormalities, 60.0% (9/15); ascites, 40.0% (6/15);

small for gestational age (SGA), 20.0% (3/15); chorioretinitis, 13.3% (2/15). One newborn had abnormalities in head only (Case 11 in Table 1), one had liver dysfunction only (Case 10 in Table 1), and the remaining thirteen had multiple disorders associated with cCMV.

Two newborns with FT died at an early neonatal period. One case (Case 2 in Table 1) had massive and refractory fetal ascites, received FT (3 Miv and 6 Fip), and was delivered by cesarean section due to tocolysis failure at 31 GW. This case died because of respiratory failure caused by hypoplastic lungs. The other case (Case 7 in Table 1) had fetal pericardial effusion, cardiomegaly, and hepatosplenomegaly, received FT (4 Miv and 1 Fip), and was delivered by cesarean section due to NRFS at 31 GW. This newborn also died because of respiratory failure caused by hypoplastic lungs. The procedures of FT were not associated with these neonatal deaths.

In the remaining 13 newborns whose mothers received FT, 12 received both FT and NT, and one received FT only because this case had only a mild liver dysfunction at birth (Case 10 in Table 1).

3.2. Short-term effects of fetal therapy in pregnancies with symptomatic congenital CMV infection

In four of the six pregnancies with FGR, fetal growth increased after FT (Cases 2, 5, 6, and 8 in Table 1). One case experienced the disappearance of both ventriculomegaly and hepatomegaly after FT (Case 10 in Table 1), and another experienced temporary disappearance of ascites (Case 7 in Table 1).

Table 2 shows serological and virological findings in mothers and newborns who received FT. A decrease or disappearance of CMV-DNA after FT in the amniotic fluid in seven cases (Cases 1, 4, 5, 6, 7, 9, and 13 in Table 2) and in fetal ascites in two cases (Cases 2 and 15 in Table 2) was observed.

3.3. Effects of fetal therapy with or without neonatal therapy

We observed a disappearance of CMV-DNA in the urine or blood of all twelve newborns who underwent both FT and NT (Table 2). Because two infants (Cases 14 and 15 in Table 1) were less than 1.5 years of adjusted-age, we evaluated the neurological outcomes of eleven infants with symptomatic cCMV in the 1.5 or 3 years of adjusted-age (Table 1 and Figure 2). Five of the eleven infants (45.5%) had normal development without sequela, four (36.4%) had mild impairments, and the remaining two (18.2%) had severe impairments (Table 1 and Figure 3).

3.4. Clinical features and neurological outcomes of newborns who received neonatal therapy alone

From October 2009 to December 2019, nineteen symptomatic cCMV-infected newborns received NT only (VGCV, n=17; GCV, n=1; GCV and VGCV, n=1). Table 3 shows clinical courses and outcomes. Ten of the 19 newborns in NT group were transferred to the neonatal intensive care unit in Kobe University Hospital for suspicion of cCMV, and were diagnosed by CMV-DNA PCR in the urine (Cases 6, 8, 9, 10, 11, 12, 14, 15, 17, and 19 in Table 3). Five newborns were diagnosed using urinary CMV screening by a PCR assay, and were later confirmed with clinical symptoms of cCMV (Cases 1, 3, 4, 5, and 13 in Table 3). Four newborns with symptomatic cCMV who were prenatally diagnosed had no FT. In two of the four, the parents of fetuses refused FT (Cases 2 and 18 in Table 3). The other two pregnant women could not receive FT due to premature delivery (Cases 7 and 16 in Table 3). The median GW at delivery and birth weight of the 19 newborns who received NT only were 38 GW (range, 24–40 GW) and 2,326 g (715–3,312 g), respectively.

The prevalence of clinical findings at birth in the 19 newborns who received NT

only were as follows: abnormalities in head, 84.2% (16/19); ABR abnormalities, 52.6% (10/19); abnormalities in liver, 47.4% (9/19); SGA, 47.4% (9/19); haematological disorders, 42.1% (8/19); chorioretinitis, 15.8% (3/19); ascites, 5.3% (1/19). Two infants had abnormalities in head alone (Cases 8 and 19 in Table 3), two with chorioretinitis alone (Cases 1 and 5 in Table 3), and the remaining fifteen had multiple disorders associated with cCMV. One newborn was delivered at 24 GW by cesarean section because of NRFS following a premature rupture of the membranes. He died at 29 days old due to diffuse peritonitis; therefore, NT was not completed (Case 16 in Table 3). In this case, GCV therapy was not associated with the neonatal death. Except this case, a disappearance of CMV-DNA in the urine or blood of the newborns was seen in the remaining 18 newborns.

One infant died before completing NT (Case 16 in Table 3); one's parents refused the follow-up after NT (Case 18 in Table 3); and another was less than 1.5 years of adjusted-age (Case 19 in Table 3). These 3 infants did not undergo neurological evaluations (Figure 4). Two newborns who had only chorioretinitis (Cases 1 and 5 in Table 3) were excluded from comparison with FT group (Figure 4). Neurological outcomes at 1.5 or 3 years of adjusted-age in the 14 children in NT group were included in the final analysis (Table 3 and Figure 4). Three of the 14 infants in NT group (21.4%) had normal development without sequela, 2 (14.3%) had mild impairments, and the remaining 9 (64.3%) had severe impairments (Table 3 and Figure 3).

3.5. Comparison of neurological outcomes between infants who received fetal therapy and those received neonatal therapy only

Table 4 shows the clinical characteristics of the 11 cases in FT group (10 with NT and 1 without NT) and the 14 cases in NT group. GW at birth in FT group (median 36 GW, range 31–38 GW) was earlier than that in NT group (38 GW, 32–40 GW;

$p<0.05$). The proportion of SGA in NT group was higher than that in FT group (64.3% vs 18.2%, $p<0.05$).

There was no difference in the proportion of normal development without sequela between 11 infants in FT and 14 in NT group (45.5% vs 21.4%, $p=0.39$) (Figure 3). However, the proportion of infants with severe impairments in FT group was significantly lower than that in NT group (18.2% vs 64.3%, $p<0.05$) (Figure 3).

4. Discussion

In this single-center study, fifteen pregnant women whose fetuses had symptomatic cCMV received Ig FT. Two pregnancies ended in early neonatal death, and the survival rate was 86.7% (13/15). Twelve of the 13 alive newborns received NT with VGCV, but one did not because the prenatal US findings of ventriculomegaly and hepatomegaly disappeared after FT in this case. Consequently, in FT group, twelve newborns with symptomatic cCMV received a combination of FT and NT, and one newborn received FT only. Two infants were less than 1.5 years of adjusted-age in FT group. Five of the remaining 11 (45.5%) infants with FT (10 with NT, and 1 without NT) had normal development without sequelae at 1.5 or 3 years of adjusted-age.

On the other hand, 19 newborns with symptomatic cCMV received NT only. In this NT group, one newborn died, one's parents refused the follow-up, one was less than 1.5 years, and two had only chorioretinitis as symptoms. Neurological outcomes in 14 of the 19 infants in NT group were evaluated, and 3 of the 14 (21.4%) infants had normal development without sequelae.

Investigators have shown that approximately 90% of surviving infants with symptomatic cCMV suffer from major neurological long-term sequelae (Stagno and Whitley 1985). The present study found that the proportion of infants with severe impairments in FT group was lower than that in NT group (18.2% vs 64.3%, $p<0.05$). To the best of our knowledge, this is the first study demonstrating that the combination of Ig FT and NT with VGCV may be more effective for decreasing incidence of severe impairments in infants with symptomatic cCMV detectable in utero than NT only.

Two newborns died early after birth despite FT (Cases 2 and 7 in Table 1). Both died of respiratory failure due to hypoplastic lungs. Hypoplastic lungs with diaphragmatic eventration was caused by massive ascites in one (Case 2 in Table 1), and by lung compression due to cardiomegaly, pericardial effusion, and hepatomegaly in

another (Case 7 in Table 1). The prognosis of fetuses with hypoplastic lungs despite FT may be extremely poor. One newborn in NT group died at 29 days old due to diffuse peritonitis (Case 16 in Table 3). This death was not due to NT-related adverse events but due to gastrointestinal disorders caused by extremely premature birth. Thus, newborn death in the present study was not directly associated with the procedures of FT and NT. The Ig FT and NT with VGCV/GCV may be safe for both mothers and newborns, because no adverse events occurred.

Previous studies showed the efficacies of FT for cCMV using maternal intravenous, intra-umbilical-cord, or intra-amniotic administration of CMV hyperimmune globulin (Nigro *et al.* 2005), and using maternal oral administration of high-dosage valacyclovir (Leruez-Ville *et al.* 2016). However, these studies enrolled many women whose fetuses had a single abnormal US finding, including only abnormal echodensities in fetal intestine or liver. The latter study used high-dose oral valacyclovir for some women whose fetuses had no abnormal US findings but had only blood CMV-DNA load of > 3000 copies/ml. Additionally, they showed 93.9% (14/15) (Nigro *et al.* 2005) and 82.9% (34/41) (Leruez-Ville *et al.* 2016) of newborns had no morphological abnormalities associated with cCMV. Conversely, in the present study, 73.3% (11/15) of fetuses with FT showed multiple abnormal US findings and no fetuses with only abnormal echodensities in the organs were included; 93.9% (14/15) of newborns with FT had symptomatic cCMV. The present study enrolled more severe cases than the previous studies (Nigro *et al.* 2005, Leruez-Ville *et al.* 2016), and also assessed neurological outcome at 1.5 or 3 years of adjusted-age.

Regarding the short-term effects of Ig FT, the rates of disappearance of abnormal US findings were as follows: FGR, 50% (3/6); hepatosplenomegaly, 37.5% (3/8); ascites, 25.0% (2/8); ventriculomegaly, 18.2% (2/11). In addition, CMV-DNA of fetuses disappeared or decreased in 53.8% (7/13) for the amniotic fluid and 66.7% (2/3)

for the ascites. However, favorable short-term effects of FT did not always cause good long-term neurological outcomes, such as in Cases 1, 2, 4, 5, 7, 8, 9, and 13 in Table 1 and 2.

Twelve of the 19 newborns (63.2%) with NT only were delivered at term, and eleven of the 12 newborns were not diagnosed of cCMV prenatally. In contrast, 6 of 15 newborns (40.0%) with FT were prematurely born by cesarean sections to start early neonatal antiviral treatment against refractory fetal ascites or FGR (Cases 3, 4, 9, 12, 13, and 15). Therefore, GW at birth in FT group was earlier than that in NT group ($p<0.05$). Despite the differences in GW at birth between the two groups, the proportion of infants with severe neurological impairments in FT group was lower than that of NT only group. These results suggest that early intervention for symptomatic cCMV with FT followed by NT are more effective for improving long-term neurological outcomes compared to NT only.

In the present, all five fetuses who received FT of Miv only, did not have ascites. Two of the five fetuses had mild impairments, and 3 had normal development without sequelae. Conversely, all eight fetuses with ascites received FT of Fip (3 Fip only and 5 Fip+Miv). After excluding two dead newborns and 2 children who were less than 1.5 years of adjusted-age, 2 had severe impairments, 1 had mild impairment, and 1 had normal development without sequelae. We could not determine which was more effective, Miv or Fip, for improving neurological outcomes in children with cCMV.

This study is not a randomized controlled trial. Therefore, we did not prove the efficacy of Ig FT. However, it is very difficult ethically to conduct a randomized controlled trial in pregnant women whose fetuses have symptomatic cCMV. This is because it is evident that their infants will have poor neurological prognosis and mortality, if they receive no medical treatments. Further studies are needed to confirm the results and to evaluate whether FT are more effective in improving neurological

outcomes of newborns with symptomatic cCMV.

Declaration of Competing Interest

The authors have no conflicting interests to declare.

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Table 1. The clinical course of symptomatic congenital cytomegalovirus infection and outcome of infant after fetal therapy with or without neonatal therapy.

Case	Age, gravidity /paritiy	Fetal ultrasound findings (GW)	GW at diagnosis	Doses of maternal iv Ig (GW)	Doses of fetal ip Ig (GW)	Changes in fetal findings		Birth weight, delivery mode, (GW)	Clinical findings at birth	Antiviral therapy for the newborn	Outcome of infant (age at evaluation)
						Ultrasound findings	Laboratory finding				
1	35 y, 2/1	Severe ventriculomegaly (30)	34	7.5 g (34)	—	None	None	2956 g, VD, (38)	Ventriculomegaly, subependymal cyst, unilateral ABR abnormality	Ig + VGCV	Unilateral hearing difficulty (3 y)
2	27 y, 2/1	FGR (19), ascites (19), cardiomegaly (22)	20	7.5 g (22), 7.5 g (24) 7.5 g (25)	2.5 g (20), 1.5 g (21), 2.4 g (23), 1.8 g (26), 2.1g (27), 2.5g (29)	Increase in growth	Disappearance of CMV-DNA in ascites	1824 g, CS, (31)	Ventriculomegaly, intracranial calcification, hypoplastic lung, ascites, thrombocytopenia, anemia	None	Death at 1 day old
3	28 y, 4/1	FGR (25), oligohydramnios (31)	29	6.5 g (31), 1.5 g (32)	1.0 g (31), 1.0 g (32)	None	None	1396 g, CS, (32)	SGA, bilateral ABR abnormality	Ig + VGCV	Normal development without sequela (3 y)
4	19 y, 3/0	FGR (26)	27	7.5 g (29)	1.0 g (30), 1.0 g (31)	None	None	1378 g, CS, (31)	SGA, ventriculomegaly, intracranial calcification, hepatosplenomegaly, liver dysfunction, pancytopenia, petechia, unilateral ABR abnormality	Ig + VGCV	Unilateral hearing difficulty (3 y)
5	36 y, 1/0	Ascites (21), FGR (23), severe ventriculomegaly (23), schizencephaly (31)	27	7.5 g (30), 5.75 g (31), 15 g (32), 11.15 g (33), 1.45 g (34)	1.25 g (31), 1.35 g (33), 1.05 g (34)	Increase in growth	None	2184 g, CS, (36)	Schizencephaly, ventriculomegaly, intracranial calcification, hepatosplenomegaly, liver dysfunction, chorioretinitis, bilateral ABR abnormality	Ig + VGCV	Severe developmental delay, epilepsy, bilateral hearing difficulty (3 y)
6	23 y, 2/1	FGR (19), hyperechoic bowel (21), moderate ventriculomegaly (25), hepatomegaly (25), cardiomegaly (22)	26	15 g (27), 15 g (29), 15 g (31), 15 g (33), 15 g (35)	—	Increase in growth	None	2192 g, CS, (36)	Ventriculomegaly, hepatomegaly,cholestasis, thrombocytopenia, petechia, bilateral ABR abnormality	Ig + VGCV	Normal development without sequela (3 y)
7	30 y, 3/1	Ascites (22), mild ventriculomegaly (24), hepatosplenomegaly (24), cardiomegaly (24), pericardial effusion (24), oligohydramnios (30)	24	15 g (24), 15 g (25), 15 g (26), 15 g (30)	2.5 g (28)	Temporary disappearance of ascites	None	2236 g, CS, (31)	Ventriculomegaly, intracranial calcification, hypoplastic lung, hepatomegaly, thrombocytopenia, liver dysfunction, petechia	None	Death at 1 hour after birth
8	32 y, 8/2	FGR (29), moderate ventriculomegaly (33)	33	15 g (34), 15 g (35)	—	Increase in growth	None	2030 g, CS, (36)	SGA, PV calcification, subependymal cyst, liver dysfunction, petechia, unilateral ABR abnormality	Ig + VGCV	Mild developmental delay (3 y)
9	21 y, 1/0	Moderate ventriculomegaly (28), hepatomegaly (28), ascites (28), hyperechoic bowel (28)	31	—	2.5 g (31)	None	None	2688 g, CS, (33)	Ventriculomegaly, intracranial calcification, subependymal cyst, hepatosplenomegaly, ascites, thrombocytopenia, anemia, petechia, chorioretinitis, bilateral ABR abnormality	VGCV	Bilateral hearing difficulty (1.5 y)
10	29 y, 1/0	Mild ventriculomegaly (28), hepatomegaly (35)	30	15 g (32), 15 g (33), 15 g (35)	—	None	None	2996 g, CS, (37)	Mild liver dysfunction	None	Normal development without sequela (1.5 y)
11	37 y, 2/1	Severe ventriculomegaly (30)	34	15 g (35), 15 g (36)	—	None	None	2646 g, VD, (38)	Ventriculomegaly, subependymal cyst	VGCV	Normal development without sequela (1.5 y)
12	29 y, 2/0	Ascites (20), moderate ventriculomegaly (24), PV calcification (24), hepatomegaly (24)	25	15 g (27), 15 g (29), 15 g (32)	2.5 g (25), 5.0 g (26), 5.0 g (28), 5.0 g (31), 5.0 g (33)	None	None	2848 g, CS, (34)	Ventriculomegaly, intracranial calcification, subependymal cyst, hepatomegaly, ascites, thrombocytopenia, petechia	VGCV	Normal development without sequela (1.5 y)
13	29 y, 1/0	Ascites (21), hepatomegaly (22), mild ventriculomegaly (24)	24	15 g (28)	2.5 g (24), 5.0 g (25), 2.5 g (26), 5.0 g (27), 5.0 g (29), 2.5 g (31)	None	None	2312 g, CS, (33)	Ventriculomegaly, subependymal cyst, hepatomegaly, ascites, thrombocytopenia, petechia, unilateral ABR abnormality	Ig + VGCV	Unilateral hearing difficulty (1.5 y)
14	19 y, 1/0	Ascites (23), microcephaly (24), mild ventrimulomegary (24) hepatomegaly (24), hyperechoic bowel (24)	25	—	2.5 g (26), 2.5 g (27), 2.5 g (28), 2.5 g (29)	None	None	1860 g, CS, (30)	Ventriculomegaly, intracranial calcification, ascites, liver dysfunction, thrombocytopenia, anemia, petechia, bilateral ABR abnormality	VGCV	N.D.
15	32 y, 2/1	Ascites (20), hyperechoic bowel (20), hepatomegaly (27)	22	—	5.0 g (25), 5.0 g (26), 2.5 g (27), 5.0 g (30)	None	None	1660 g, CS, (32)	Ventriculomegaly, intracranial calcification, ascites, thrombocytopenia, neutropenia, petechia	VGCV	N.D.

Abbreviations: GW, gestational weeks; FGR, fetal growth restriction; iv, intravenous; ip, intraperitoneal; CMV, cytomegalovirus; VD, vaginal delivery; CS, cesarean section; ABR, auditory brain-stem response; SGA, small for gestational age; PV, periventricular; Ig, immunoglobulin; VGCV, valganciclovir; N.D., not determined.

Table 2. Serological and virological fingings in the 15 pregnancies in which immunoglobulin fetal thrapies for symptomatic CMV infection were performed

Case	Maternal CMV IgM/ IgG avidity index (GW)	Viral loads prior to fetal therapy (GW)	Viral loads after fetal therapy (GW)	Neonatal CMV IgM (days old)	Viral loads in the newborn (days old)
1	2.1 (33) / 72.3 % (35)	Maternal blood <20 (34) Amniotic fluid 3.9 $\times 10^7$ (34)	Amniotic fluid 2.1$\times 10^7$ (38) Umbilical cord blood 2.1 $\times 10^2$ (38)	1.0 (1)	Blood 5.1 $\times 10^2$ (1) Blood antigenemia - (1) Urine 4.7 $\times 10^7$ (1) / - (44)
2	2.5 (19) / 16.6 % (19)	Maternal blood <20 (19) Amniotic fluid 1.6 $\times 10^5$ (19) Fetal ascites 3.4 $\times 10^5$ (20)	Fetal ascites 1.0$\times 10^2$ (22) / - (23, 25, 28, 30) Amniotic fluid 6.7$\times 10^7$ (27) Umbilical cord blood 92 (30)	0.2 (0)	Blood 66 (1) Blood antigenemia - (1) Urine 1.2 $\times 10^7$ (1)
3	3.8 (27) / 3.6 % (27)	Maternal blood <20 (28) Amniotic fluid 4.1 $\times 10^4$ (28) UmB antigenemia + (31)	N.D.	0.6 (1)	Blood 2.2 $\times 10^2$ (2) / - (17) Blood antigenemia + (1) / - (8) Urine 8.2 $\times 10^6$ (0) / - (29)
4	4.3 (22) / 10.9 % (22)	Maternal blood <20 (22) Amniotic fluid 3.4 $\times 10^7$ (22)	Amniotic fluid 6.4$\times 10^5$ (31) Umbilical cord blood 4.5$\times 10^7$ (31)	2.2 (0)	Blood 1.8 $\times 10^2$ (0) / - (117) Blood antigenemia + (1) / - (42) Urine 1.1 $\times 10^7$ (1) / - (61)
5	4.2 (29) / 63.8 % (29)	Amniotic fluid 6.5 $\times 10^6$ (27) Maternal blood <20 (29)	Amniotic fluid 4.5$\times 10^6$ (35) Umbilical cord blood 20 (35)	1.4 (0)	Blood 6.0 $\times 10^2$ (0) Blood antigenemia + (0) / - (20) Urine 4.0 $\times 10^5$ (0) / - (176)
6	11.4 (25) / 38.3 % (29)	Maternal blood <20 (25) Amniotic fluid 4.5 $\times 10^4$ (26)	Amniotic fluid 1.3$\times 10^4$ (36)	12.7 (0)	Blood 3.2 $\times 10^2$ (0) / - (85) Blood antigenemia + (0) / - (35) Urine 5.6 $\times 10^7$ (0)
7	3.6 (25) / 32.7 % (24)	Maternal blood <20 (24) Amniotic fluid 3.4 $\times 10^6$ (24)	Amniotic fluid 1.8$\times 10^6$ (29) Fetal ascites 2.0$\times 10^3$ (28) / 1.6$\times 10^3$ (29) Umbilical cord blood 9.9$\times 10^3$ (31) Umbilical cord blood antigenemia + (31)	12.3 (0)	Blood antigenemia + (0)
8	13.6 (34) / 63.1 % (34)	Amniotic fluid 3.2 $\times 10^7$ (33) Maternal blood <20 (34)	Amniotic fluid 4.0$\times 10^7$ (36)	6.9 (1)	Blood 8.1 $\times 10^4$ (0) / - (211) Blood antigenemia + (1) Urine 2.1 $\times 10^8$ (0)
9	10.3 (31) / 62.4 % (31)	Maternal blood <20 (31) Amniotic fluid 1.6 $\times 10^7$ (31) Fetal ascites 4.2 $\times 10^2$ (31)	Amniotic fluid 9.7$\times 10^6$ (33) Umbilical cord blood 2.3$\times 10^3$ (33)	4.0 (0)	Blood 5.6 $\times 10^2$ (0) / - (28) Blood antigenemia + (1) / - (42) Urine 1.2 $\times 10^8$ (0)
10	5.1 (21) / 1.1 % (23)	Maternal blood <20 (23) Amniotic fluid 1.2 $\times 10^6$ (30)	Amniotic fluid 2.0$\times 10^7$ (37) Umbilical cord blood 2.4$\times 10^4$ (37)	1.4 (0)	Blood 2.5 $\times 10^4$ (0) Blood antigenemia + (0) Urine 1.8 $\times 10^8$ (1)
11	4.2 (31) / 52.8 % (33)	Maternal blood <20 (33) Amniotic fluid 2.6 $\times 10^7$ (34)	N.D.	12.4 (0)	Blood 8.4 $\times 10^4$ (0) / - (16) Blood antigenemia + (0) / - (23) Urine 2.5 $\times 10^8$ (0)
12	4.7 (20) / 19 % (21)	Maternal blood <20 (24) Amniotic fluid 6.5 $\times 10^6$ (24)	Amniotic fluid 9.7$\times 10^6$ (34) Umbilical cord blood 1.0$\times 10^5$ (34)	8.2 (0)	Blood 7.8 $\times 10^4$ (0) / - (141) Blood antigenemia + (0) Urine 1.2 $\times 10^8$ (0) / - (141)
13	4.5 (21) / 23.3 % (23)	Maternal blood <20 (23) Amniotic fluid 2.6 $\times 10^6$ (23) Fetal ascites <1.0 $\times 10^2$ (24)	Fetal ascites <1.0 $\times 10^2$ (31) Amniotic fluid 1.4 $\times 10^6$ (33) Umbilical cord blood 6.7 $\times 10^2$ (33)	9.5 (0)	Blood 1.6 $\times 10^4$ (0) / - (33) Blood antigenemia - (0) Urine 2.6 $\times 10^7$ (0) / - (61)
14	11.2 (23) / 31.0 % (24)	Maternal blood <20 (24) Amniotic fluid 3.2 $\times 10^6$ (25) Fetal ascites <1.0 $\times 10^2$ (26)	Amniotic fluid 6.4 $\times 10^6$ (29) Umbilical cord blood 5.1 $\times 10^5$ (30)	0.9 (3)	Blood 2.9 $\times 10^5$ (0) / - (29) Blood antigenemia + (0) / - (29) Urine 4.1 $\times 10^8$ (0) / - (50)
15	2.5 (20) / 34.7 % (22)	Maternal blood <20 (22) Amniotic fluid 4.0 $\times 10^6$ (22) Fetal ascites 1.5 $\times 10^2$ (25)	Fetal ascites <1.0 $\times 10^2$ (26) Amniotic fluid 5.2 $\times 10^6$ (32) Umbilical cord blood 1.2 $\times 10^3$ (32)	3.0 (0)	Blood 2.9 $\times 10^4$ (0) / - (41) Blood antigenemia - (0) Urine 1.3 $\times 10^8$ (0) / - (66)

Cases in Table 1 are the same as those in Tabel 2.
Abbreviations: CMV, cytomegalovirus; IgM, immunoglobulin M; IgG, immunoglobulin G; GW, gestational weeks; N.D., not determined.

Table 3. The clinical courses, findings, and outcomes of 21 infants with symptomatic CMV infection who received neonatal therapy alone

Case	Age, gravidity/parity	Fetal ultrasound findings (GW)	Birth weight, delivery mode, (GW)	Clinical findings at birth	Antiviral therapy for the newborn	Neonatal CMV IgM (days old)	Viral loads in the newborn (days old)	Outcome of infant (age at evaluation)
1	38 y, 1/0	N.D.	2868 g, VD, (38)	Chorioretinitis	Ig + VGCV	0.9 (1)	Blood 5.6 $\times 10^3$ (1) / - (290) Blood antigenemia + (1) / - (122) Urine 1.9 $\times 10^4$ (1)	Normal development without sequela (3 y)
2	22 y, 2/0	FGR, microcephaly, ventriculomegaly, intracranial calcification (30)	1860 g, CS, (36)	SGA, microcephaly, ventriculomegaly, intracranial calcification, hepatosplenomegaly, thrombocytopenia, liver dysfunction, petechia, bilateral ABR abnormality, retinal vascular malformation	Ig + VGCV	2.7 (0)	Blood 3.1 $\times 10^2$ (0) / - (148) Blood antigenemia - (1) Urine 6.2 $\times 10^7$ (1)	Severe developmental delay, epilepsy, bilateral hearing difficulty (3 y)
3	28 y, 6/3	N.D.	3160 g, VD, (38)	Intracranial calcification, unilateral ABR abnormality	Ig + VGCV	0.7 (27)	Blood 2.2 $\times 10^2$ (27) / - (53) Blood antigenemia - (27) Urine 1.4 $\times 10^5$ (27) / - (67)	Normal development without sequela (3 y)
4	28 y, 3/1	FGR (31)	940 g, CS, (32)	SGA, ventriculomegaly, thrombocytopenia, neutropenia, bilateral ABR abnormality	Ig + VGCV	3.6 (70)	Blood 1.2 $\times 10^2$ (43) / - (252) Blood antigenemia + (43) / - (252) Urine 2.8 $\times 10^7$ (43)	Severe developmental delay (3 y)
5	19 y, 1/0	N.D.	2450 g, VD, (36)	Chorioretinitis	Ig + VGCV	2.6 (5)	Blood 2.6 $\times 10^3$ (7) / - (59) Blood antigenemia + (5) / - (59) Urine 1.4 $\times 10^6$ (1) / - (222)	Normal development without sequela (1.5 y)
6	40 y, 2/1	FGR (34)	2210 g, CS, (39)	SGA, ventriculomegaly, cerebral atrophy, cystic lesions in the brain white matter, unilateral ABR abnormality	Ig + VGCV	0.7 (14)	Blood 1.1 $\times 10^4$ (28) / - (57) Blood antigenemia - (42) Urine 4.0 $\times 10^6$ (28) / - (71)	Severe developmental delay, unilateral hearing difficulty (3 y)
7	28 y, 1/0	FGR, microchephaly, ventriculomegaly, (23)	1255 g, CS, (35)	SGA, microcephaly, ventriculomegaly, cerebral atrophy, cystic lesions in the brain white matter, hepatomegaly, cholestasis, liver dysfunction	Ig + VGCV	6.8 (0)	Blood 4.4 $\times 10^4$ (0) / - (42) Blood antigenemia + (0) / - (42) Urine 5.4 $\times 10^7$ (0) / - (42)	Severe developmental delay, bilateral hearing difficulty (3 y)
8	31 y, 2/1	N.D.	3312 g, VD, (38)	Ventriculomegaly	Ig + VGCV	1.9 (1)	Blood 3.4 $\times 10^4$ (1) / - (65) Blood antigenemia + (17) / - (65) Urine 5.6 $\times 10^7$ (1)	Unilateral hearing difficulty (3 y)
9	30 y, 2/1	N.D.	2152 g, VD, (38)	Microcephaly, ventriculomegaly, intracranial calcification, hypoplasia of the brain, liver dysfunction, jaundice, thrombocytopenia, pneumonia, cataract, unilateral ABR abnormality	Ig + VGCV	4.6 (16)	Blood 4.7 $\times 10^6$ (23) / - (295) Blood antigenemia + (23) / - (379) Urine 2.9 $\times 10^8$ (23)	Severe developmental delay, epilepsy, bilateral hearing difficulty (3 y)
10	34 y, 3/1	N.D.	2054 g, VD, (39)	SGA, microcephaly, ventriculomegaly, intracranial calcification, subependymal cyst, hepatosplenomegaly, liver dysfunction, thrombocytopenia, petechia, chorioretinitis, unilateral ABR abnormality	Ig + VGCV	3.8 (1)	Blood 1.2 $\times 10^5$ (1) / - (100) Blood antigenemia + (1) / - (136) Urine 1.0 $\times 10^8$ (2) / - (100)	Normal development with autism spectrum disorder (3 y)
11	32 y, 2/0	Ventriculomegaly (29)	2548 g, VD, (39)	SGA, ventriculomegaly, intracranial calcification, subependymal cyst, bilateral ABR abnormality	Ig + VGCV	3.9 (7)	Blood 4.6 $\times 10^2$ (5) / - (17) Blood antigenemia + (7) / - (46) Urine 4.9 $\times 10^7$ (5) / - (53)	Severe developmental delay, autism spectrum disorder, bilateral hearing difficulty (1.5 y)
12	29 y, 3/2	N.D.	2362 g, VD, (38)	SGA, microcephaly, ventriculomegaly, intracranial calcification, subependymal cyst, hepatosplenomegaly, liver dysfunction, jaundice, thrombocytopenia, petechia	Ig + VGCV	3.5 (5)	Blood 2.1 $\times 10^4$ (5) / - (217) Blood antigenemia + (5) / - (72) Urine 2.6 $\times 10^8$ (3)	Severe developmental delay (3 y)
13	35 y, 2/1	FGR (25)	1948 g, VD, (40)	SGA, microcephaly, ventriculomegaly, intracranial calcification, hepatomegaly, liver dysfunction, thrombocytopenia, petechia, bilateral ABR abnormality	VGCV	2.2 (0)	Blood 1.2 $\times 10^4$ (0) / - (55) Blood antigenemia - (0) Urine 1.1 $\times 10^7$ (0) / - (55)	Bilateral hearing difficulty (3 y)
14	23 y, 1/0	Pericardial effusion (32), hydrops (34)	2326 g, CS, (35)	Hydrops, ventriculomegaly, dysplasia of the brain white matter, bilateral ABR abnormality	Ig + VGCV	2.2 (0)	Blood 8.2 $\times 10^3$ (0) / - (69) Blood antigenemia - (0) Urine 4.2 $\times 10^8$ (0) / - (93)	Severe developmental delay, bilateral hearing difficulty (1.5 y)
15	27 y, 3/0	Ventriculomegaly (33)	2880 g, VD, (39)	Ventriculomegaly, intracranial calcification, subependymal cyst, liver dysfunction	GCV→ VGCV	7.1 (71)	Blood 3.0 $\times 10^4$ (0) / - (112) Blood antigenemia - (71) Urine 3.1 $\times 10^7$ (0) / - (112)	Mild developmental delay (3 y)
16	33 y, 2/0	Ascites , hepatomegaly (23)	715 g, CS, (24)	Ascites, hepatosplenomegaly, liver dysfunction, thrombocytopenia	GCV	10.2 (0)	Blood 1.6 $\times 10^6$ (0) / 1.2 $\times 10^4$ (22) Blood antigenemia + (0) / + (17) Urine 2.4 $\times 10^5$ (0) / 2.6 $\times 10^7$ (22)	Death at 29 days old due to diffuse peritonitis
17	31 y, 1/0	FGR (35)	1870 g, CS, (35)	SGA, ventriculomegalym, intracranial calcification, subependymal cyst, polymicrogyria pancytopenia, petechia	VGCV	7.9 (5)	Blood 3.7 $\times 10^5$ (5) / - (74) Blood antigenemia + (1) / - (74) Urine 1.7 $\times 10^9$ (5) / - (60)	Normal development without sequela (1.5 y)
18	30 y, 3/2	Ascites (20), ventriculomegaly (23), hepatomegaly (34)	3216 g, VD, (38)	Ventriculomegaly, subependymal cyst, hepatomegaly, unilateral ABR abnormality	VGCV	<0.8 (1)	Blood 1.8 $\times 10^5$ (1) / - (99) Blood antigenemia + (1) / - (28) Urine 2.9 $\times 10^8$ (1) / - (99)	N.D.
19	31 y, 1/0	Ventriculomegaly (32)	2784 g CS, (40)	Subependymal cyst, dysplasia of the brain white matter	VGCV	1.5 (1)	Blood 10.0 $\times 10^5$ (15) / - (51) Blood antigenemia + (1) / - (30) Urine 7.4 $\times 10^8$ (15) / - (51)	N.D.

Abbreviations: GW, gestational weeks; CMV, cytomegalovirus; IgM, immunoglobulin M; N.D., not determined; FGR, fetal growth restriction; VD, vaginal delivery; CS, cesarean section; SGA, small for gestational age; ABR, auditory brain-stem response; Ig, immunoglobulin; VGCV, valganciclovir; GCV, gancilovir.

Table 4. Clinical characteristics of mothers and newborns included in the final analysis

	Fetal therapy group n =11	Neonatal therapy only group n =14	*p* -value
Age, years	29 (19–37)	30 (22–40)	0.9
Gravidity	2 (1–8)	2 (1–6)	0.6
Parity	0 (0–2)	1 (0–3)	0.6
GW at birth	36 (31–38)	38 (32–40)	< 0.05
Birth weight, g	2,312 (1,378–2,996)	2,181 (940–3,312)	0.6
Abnormalities in newborns at birth			
Abnormal findings in head	81.8%	100%	0.2
Abnormal findings in liver	72.7%	50.0%	0.4
Haematological disorders	54.5%	50.0%	1.0
ABR abnormalities	72.7%	64.3%	1.0
Ascites	27.3%	0%	0.07
SGA	18.2%	64.3%	< 0.05
Chorioretinitis	18.2%	7.1%	0.6
Multiple abnormalities	81.8%	92.9%	0.6

Data are expressed as the median (range).
Abbreviations: GW, gestational weeks; ABR, auditory brain-stem response; SGA, small for gestational age.

Figure legends

Figure 1. Flow diagram of fetal and neonatal therapies for symptomatic congenital CMV infection performed at Kobe University Hospital.

Abbreviations: CMV, cytomegalovirus; PCR, polymerase chain reaction; Ig, immunoglobulin; US, ultrasound; EFBW, estimated fetal body weight; GW, gestational weeks; ABR, auditory brain-stem response; CT, computed tomography; MRI, magnetic resonance imaging; VGCV, valganciclovir; GCV, ganciclovir.

Figure 2. Flow diagram of the subjects in the fetal therapy group included in the final analysis.

Abbreviations: Ig, immunoglobulin; CMV, cytomegalovirus; VGCV, valganciclovir.

Figure 3. A comparison of neurological outcomes at 1.5 and 3 years of adjusted-age between the FT group (n=11) and the NT only group (n=14).

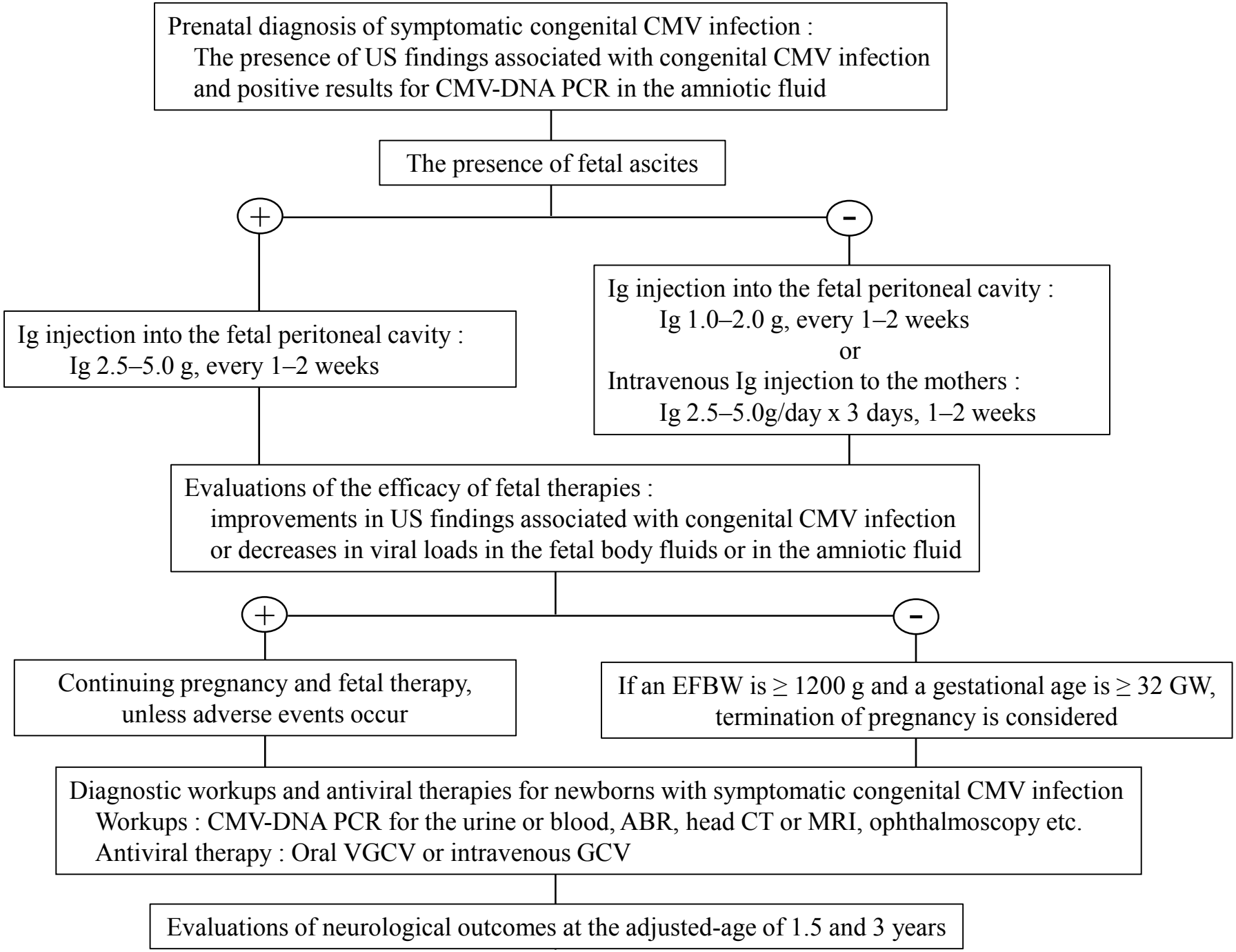
The white column indicates children with normal development without sequelae, the gray column indicates those with mild impairment, and the black column indicates those with severe impairment.

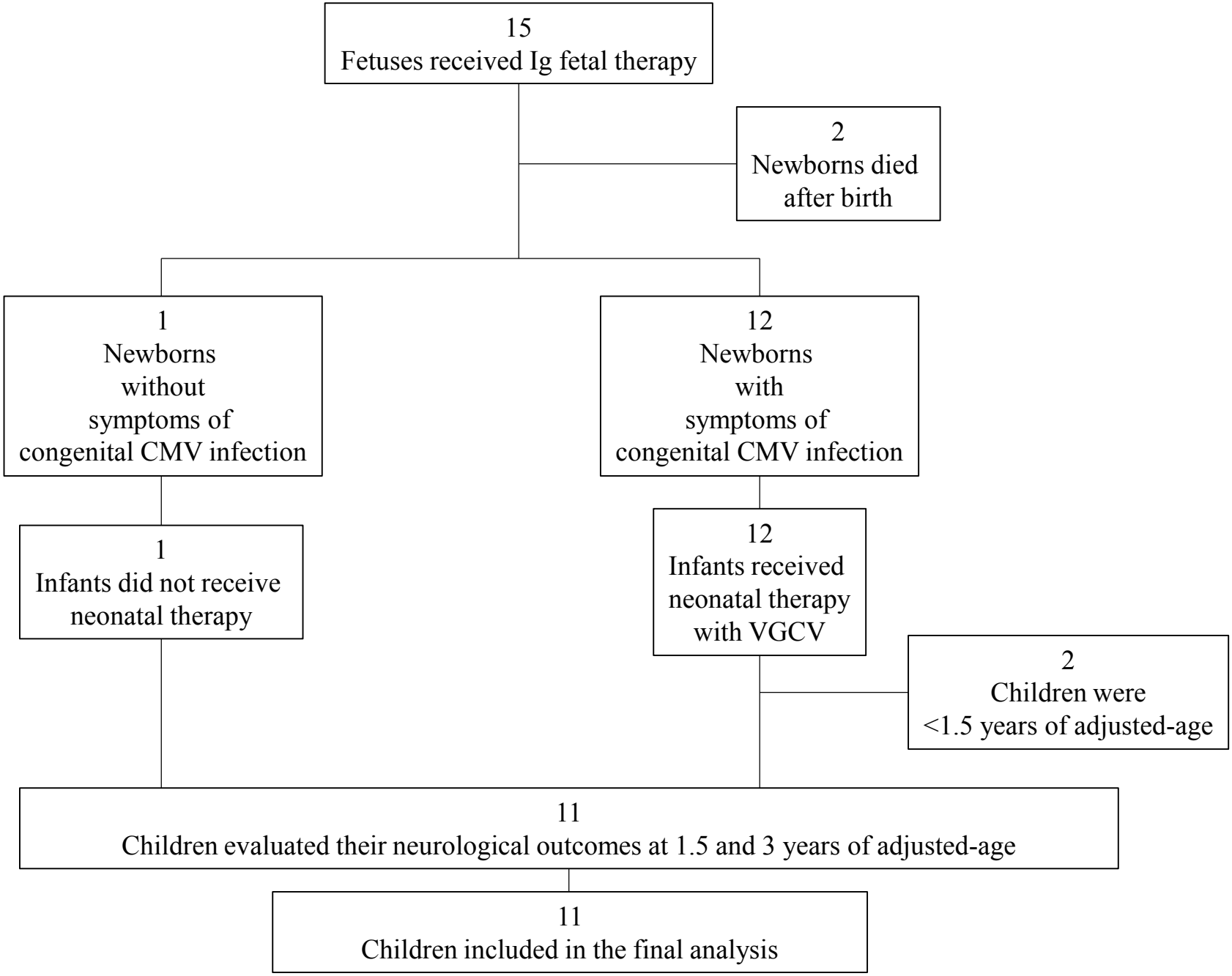
In the FT group, 5 children (45.5%) had normal development without sequelae, 4 (36.4%) had mild impairment, and 2 (18.2%) had severe impairment. In the NT only group, 3 children (21.4%) had normal development without sequelae, 2 (14.3%) had mild impairment, and 9 (64.3%) had severe impairment.

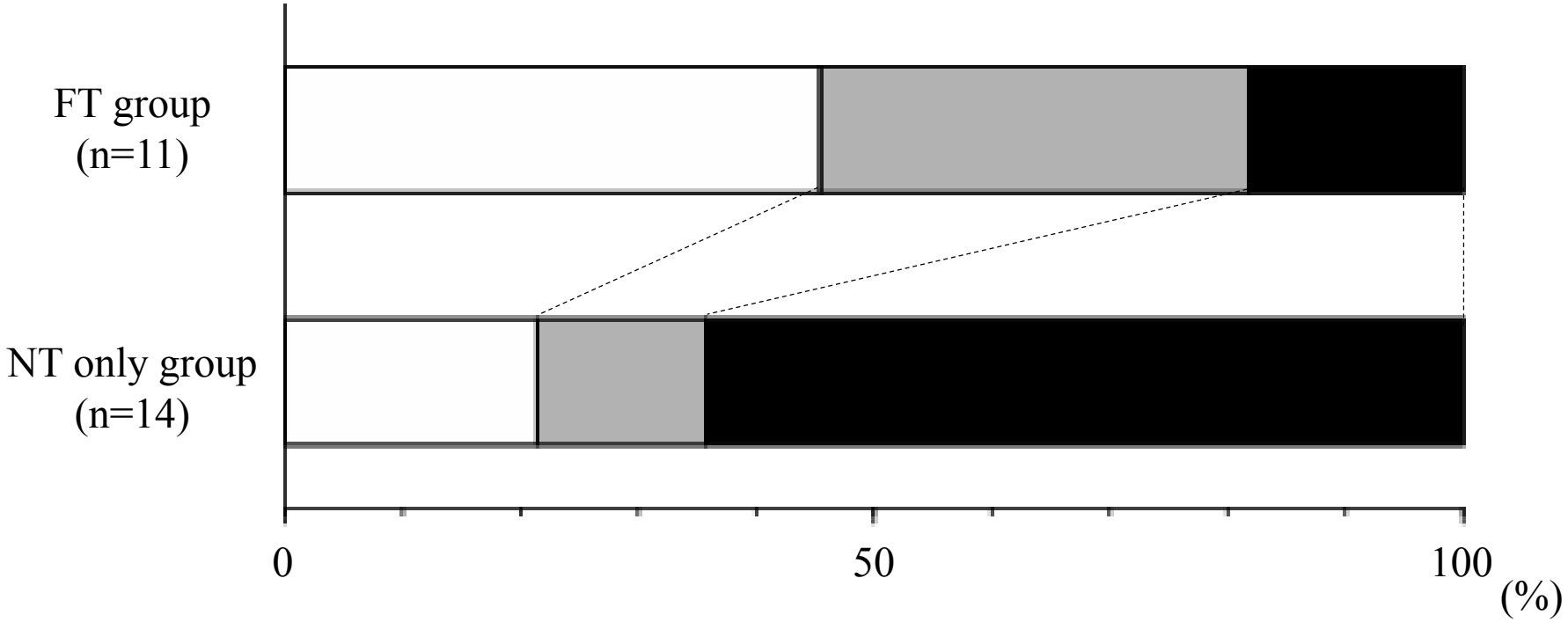
Abbreviations: FT, fetal therapy; NT, neonatal therapy.

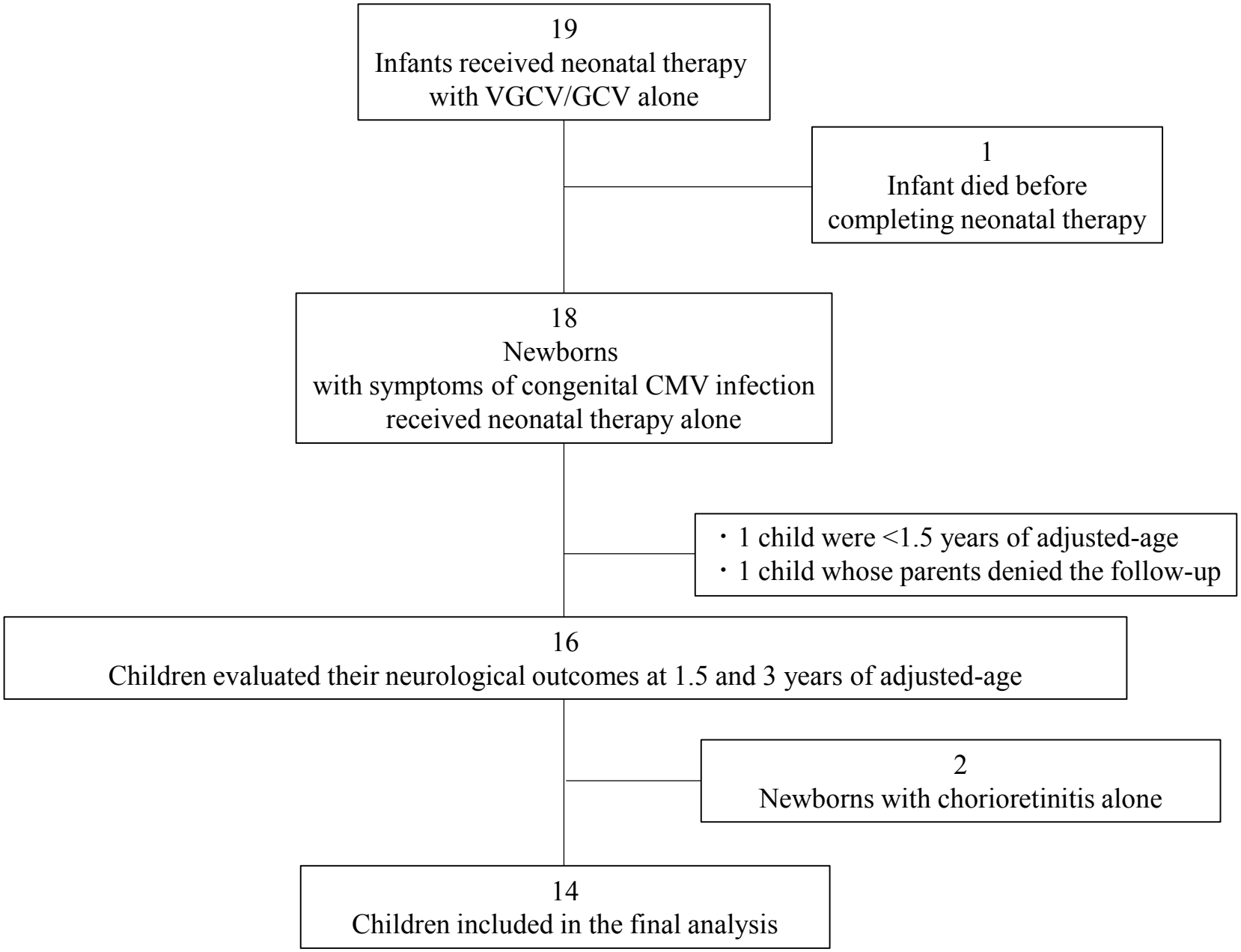
Figure 4. Flow diagram of the subjects in the neonatal therapy only group included in the final analysis.

Abbreviations: VGCV, valganciclovir; GCV, ganciclovir; CMV, cytomegalovirus.


Prenatal diagnosis of symptomatic congenital CMV infection :
The presence of US findings associated with congenital CMV infection and positive results for CMV-DNA PCR in the amniotic fluid
The presence of fetal ascites
+
-
Ig injection into the fetal peritoneal cavity :
Ig 2.5–5.0 g, every 1–2 weeks
Ig injection into the fetal peritoneal cavity :
Ig 1.0–2.0 g, every 1–2 weeks
or
Intravenous Ig injection to the mothers :
Ig 2.5–5.0g/day x 3 days, 1–2 weeks
Evaluations of the efficacy of fetal therapies :
improvements in US findings associated with congenital CMV infection or decreases in viral loads in the fetal body fluids or in the amniotic fluid
+
-
Continuing pregnancy and fetal therapy, unless adverse events occur
If an EFBW is ≥ 1200 g and a gestational age is ≥ 32 GW, termination of pregnancy is considered
Diagnostic workups and antiviral therapies for newborns with symptomatic congenital CMV infection
Workups : CMV-DNA PCR for the urine or blood, ABR, head CT or MRI, ophthalmoscopy etc.
Antiviral therapy : Oral VGCV or intravenous GCV
Evaluations of neurological outcomes at the adjusted-age of 1.5 and 3 years


15
Fetuses received Ig fetal therapy
2
Newborns died after birth
1
Newborns without symptoms of congenital CMV infection
12
Newborns with symptoms of congenital CMV infection
1
Infants did not receive neonatal therapy
12
Infants received neonatal therapy with VGCV
2
Children were <1.5 years of adjusted-age
11
Children evaluated their neurological outcomes at 1.5 and 3 years of adjusted-age
11
Children included in the final analysis


FT group
(n=11)
NT only group
(n=14)
0
50
100
(%)


19
Infants received neonatal therapy with VGCV/GCV alone
1
Infant died before completing neonatal therapy
18
Newborns with symptoms of congenital CMV infection received neonatal therapy alone
・1 child were <1.5 years of adjusted-age
・1 child whose parents denied the follow-up
16
Children evaluated their neurological outcomes at 1.5 and 3 years of adjusted-age
2
Newborns with chorioretinitis alone
14
Children included in the final analysis