SWISS SOCIETY OF NEONATOLOGY

Congenital cytomegalovirus infection

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Early pregnancy of this 31-year-old 3G/3P mother was uneventful. At 22 weeks of gestation, reduced amniotic fluid, hyperechogenic bowel and scaphocephaly were seen on antenatal ultrasound. The mother was referred to the fetal medicine unit at our hospital for further evaluation. Amniocentesis revealed a normal female karyotype. Maternal TORCH screening showed primary cytomegalovirus (CMV) infection with positive IgG and IgM titers, and a viral load of 1.2 million DNA copies per ml. Amniotic fluid testing confirmed fetal infection with positive culture, antigen testing and polymerase chain reaction (PCR).

At 24 weeks of gestation, antenatal ultrasound revealed periventricular calcifications in the left cerebrum. Fetal MRI at that time showed mild ventriculomegaly with septa in the posterior lateral horns (Fig. 1) and cysts in the caudothalamic groove.

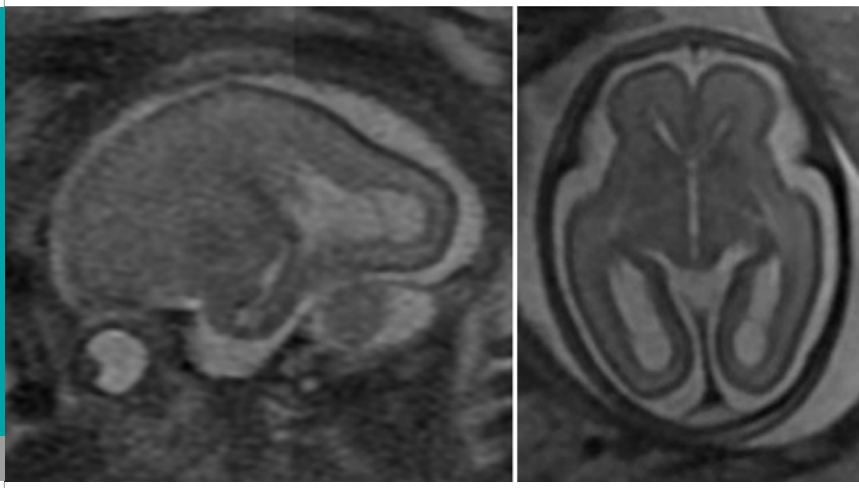

Fig. 1

Sagittal and axial T2-weighted MR images at 24 weeks of gestation showing septa in the posterior lateral horns.

At 34 weeks of gestation, fetal MRI was repeated and revealed progressive ventriculomegaly and a small cerebellum in addition to the previously described lesions. No signs of migration abnormalities were seen at that point (Fig. 2).

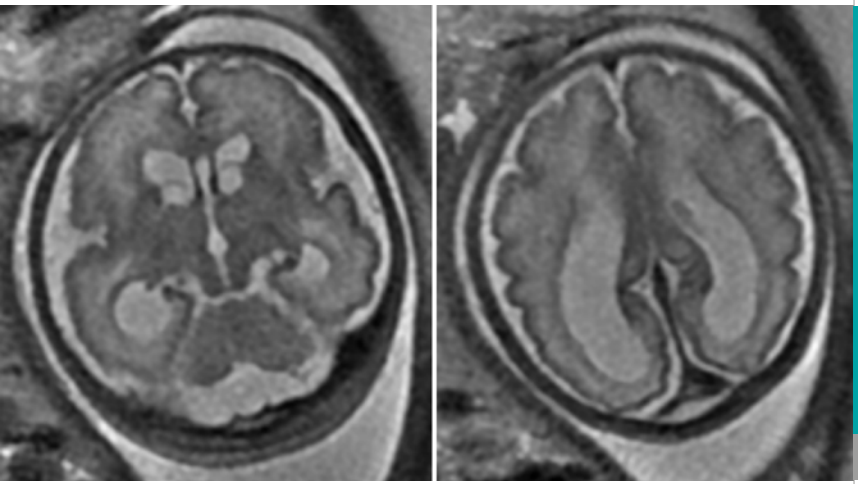

Fig. 2

Axial T2-weighted images at 34 weeks of gestation showing progressive ventriculomegaly and cysts in the caudothalamic groove.

The further course of pregnancy was unremarkable, fetal weight and head circumferences were normal. The mother showed no clinical signs of infection during pregnancy.

At 37 5/7 weeks, a female infant was born by uncomplicated spontaneous vaginal delivery following prolonged rupture of membranes of 48 hours. Postnatal adaptation was uneventful apart from additional oxygen administration up to an FiO_2 0.4 between 5 to 10 minutes after birth. Apgar scores were 8, 8 and 9 at 1, 5 and 10 minutes, respectively, and arterial cord pH was 7.23. Body weight was 2900 g (P25-50), body length was 48 cm (P10-25) and head circumference was 33 cm (P10-25). Physical examination showed multiple petechiae and hepatosplenomegaly with the liver edge felt 3 cm and spleen edge 2.5 cm below the costal margin. Neurological examination on admission revealed no gross abnormalities.

Urine was positive for CMV PCR, CMV culture and antigen testing. On admission, there was a platelet count of 65 G/l and a neutrophil count of 3.25 G/l. Cerebral US on day one of life showed dilatation of the lateral ventricles close to the 97th percentile, bilateral pseudocysts in the caudothalamic groove, lenticulostriate vasculopathy and a frontal connatal cyst on the left side (Fig. 3). Dilatation of the lateral ventricles and the size of the pseudocysts were slightly increasing over the course of the first 23 days of hospitalization.

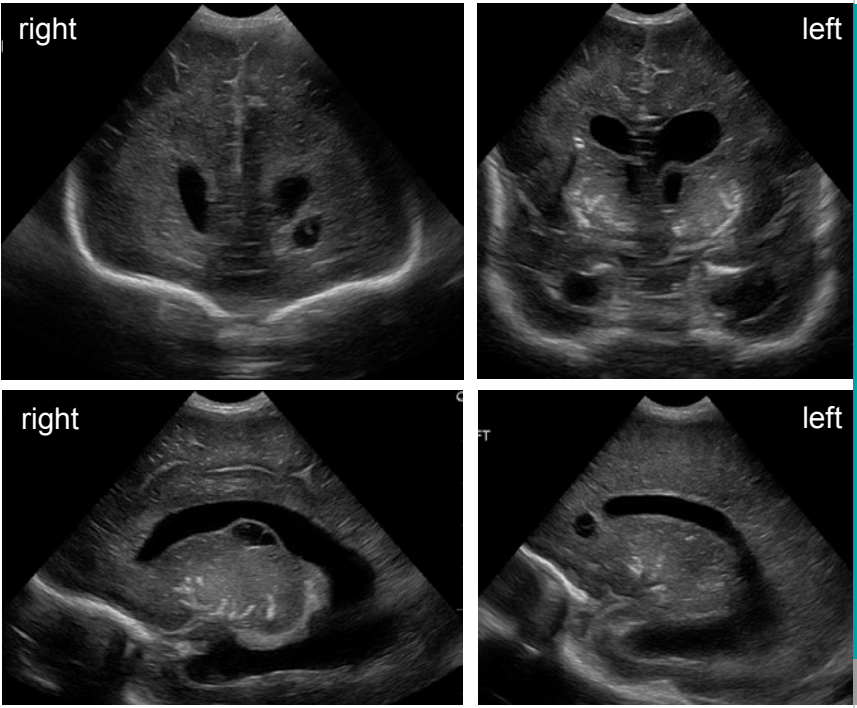

Fig. 3

Coronal and parasagittal cranial ultrasound images showing ventriculomegaly, a left-sided frontal cyst in the white matter, bilateral cysts in the caudothalamic groove, as well as lenticulostriate vasculopathy and calcifications.

MRI on day 21 of life showed extensive bilateral perisylvian and cerebral polymicrogyria (Fig. 4), reduced brain volume, marked ventriculomegaly, multiple cerebral and cerebellar calcifications and cysts in the caudothalamic groove and in the frontal white matter (Fig. 5).

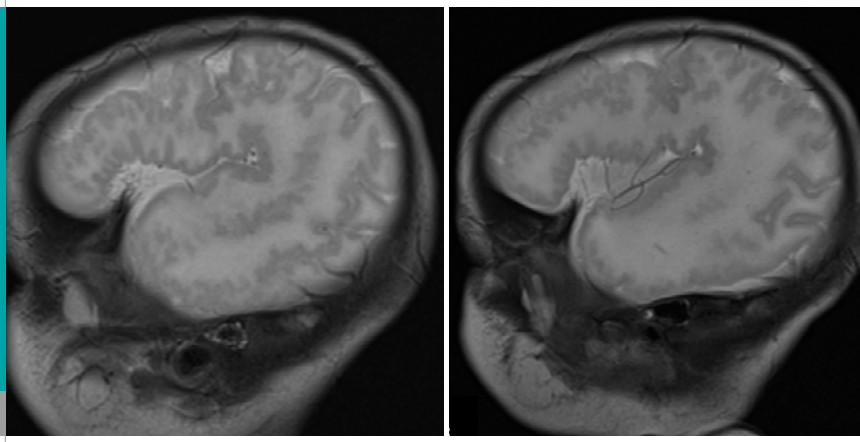

Fig. 4

Sagittal axial T2-weighted MR images showing extensive polymicrogyria (day of life 21).

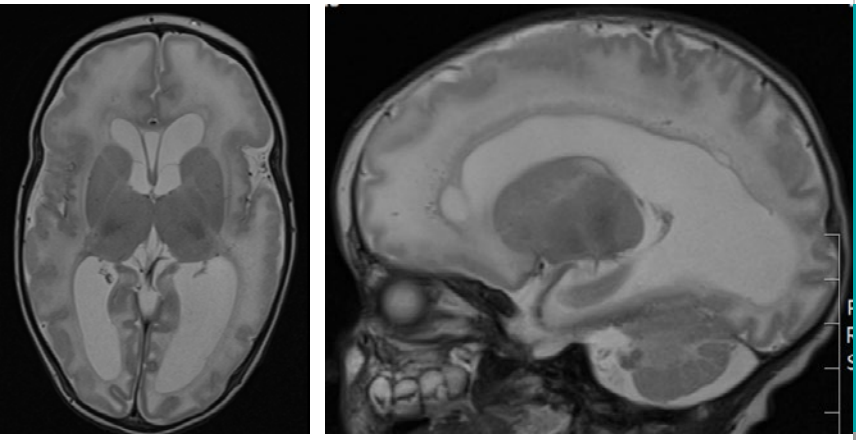

Fig. 5

Axial and sagittal T2-weighted MR images showing ventriculomegaly, cysts in the caudothalamic groove and frontal cysts on the left side (day of life 21).

Otoacoustic emissions failed bilaterally on day of life four. In addition, brainstem evoked response audiometry (BERA) failed to show response up to sound levels of 90 dB, and auditory steady-state response (ASSR) testing at 500, 1000, 2000 and 4000 Hz also showed no response up to sound levels of 80 dB. Thus, severe sensorineural hearing loss (SNHL) was confirmed. Ophthalmologic consultation on day three did not show any signs of chorioretinitis. Placental histology revealed chronic, lymphoplasmatic villitis with immunohistochemical confirmation of CMV bodies.

Antiviral therapy with ganciclovir was started on day of life 7 with a dose of 6 mg/kg body weight two times a day for 14 days intravenously and then orally until day of life 23 (I.e., a corrected gestational age of 40 6/7 weeks). Platelet count decreased to 44 G/l on day of life 10, and therefore, treatment with ganciclovir was paused for two days until platelet counts reached > 100 G/l. Another potential side effect of the treatment was neutropenia. Liver and renal blood tests, on the other hand, remained normal during the antiviral treatment. CMV DNA counts in the blood only decreased from 6346 to 5243 copies/ml after 10 days of treatment. Antigen testing and CMV culture in the urine remained positive during the entire hospital stay.

Apart from the failed hearing tests, neurological assessment was normal for her corrected gestational

age. Head growth was normal with head circumference of 34.5 cm (P25-50) at discharge.

Antiviral therapy was continued for another 4 weeks with oral valganciclovir 16 mg/kg body weight two times a day. Over this course of therapy, platelet and neutrophil counts were stable and CMV DNA counts dropped further to 294 copies/ml. At two months of age, BERA and ASSR testing revealed no response up to sound levels of 100 dB, confirming the diagnosis of severe bilateral SNHL. Support with bilateral hearing aids was started and evaluation for possible cochlear implants at the age of 6 month is ongoing. Neurologic follow-up at four months of age revealed global developmental delay (corresponding to an age of about two months). In addition, muscular hypotonia, visual dysmaturity with intermittent nystagmus and strabismus convergens was present.

DISCUSSION

Congenital CMV infection is the most common congenital infection with a birth prevalence of 0.6 – 0.7% in the developed countries, posing a major global burden which exceeds most routinely screened diseases. CMV is a neurotropic virus, which establishes lifelong latency in infected humans like other herpes viruses. The seroprevalence in women of childbearing age in Germany is estimated to be 40 to 50%, and the rate of CMV acquisition is 1 to 7% per year. The main risk factor contributing to CMV acquisition is prolonged contact with young children. Maternal infection is mostly asymptomatic and fetal transmission can occur transplacentally at any gestational age (1, 2).

Primary infection in seronegative mothers occurs in 1 to 4% of all pregnancies with a high risk for transmission of 30 to 40%. Fortunately, in early pregnancy, when infection of the fetus leads to more severe neurologic damage as in our case, intrauterine transmission rates in maternal primary infection are lower than in late pregnancy. In contrast to the presented case, more than two-thirds of congenital CMV infections occur in seropositive women with secondary infections (prevalence of reactivation or reinfection with a different viral strain estimated at 10 – 30%). The risk for transmission in these cases is lower with 1 to 3% (1, 2). Approximately 12.7% of all newborn infants with congenital CMV infection are symptomatic at birth (Table 1).

Congenital CMV infection: symptoms and laboratory findings

Petechia	**Thrombocytopenia**
Hepatosplenomegaly	**Elevated liver enzymes**
Jaundice	**Conjugated hyperbilirubinaemia**
Neurological symptoms Microcephaly Seizures Lethargy, poor suck	
Chorioretinitis	
Blueberry muffin rash	**Anaemia**
Intrauterine growth restriction (IUGR)	
Hydrops fetalis	

Patients with congenital CMV infection are at major risk for long-term sequelae. It is the leading cause of nonhereditary deafness in children in developed countries. Hearing loss and motor/cognitive deficits occur in about 50% of symptomatic children, whereas vision impairment is present in about 22% of the children, and 4% of symptomatic children die. Asymptomatic newborn infants develop long-term sequelae in 13.5% of cases and mortality is close to 0%. However, two-thirds of infants with long-term sequelae due to congenital CMV infection were asymptomatic at birth. SNHL, in particular, is known to be progressive (1, 2).

CMV can be found in a wide range of brain cells, hence

many structures like the cortex, white matter, germinal matrix, basal ganglia, thalamus, brain stem and cerebellum can be affected (3, 4). Fetal brain and cortical development can grossly be grouped into three different stages: neural proliferation in the ventricular zone and neuroblast migration from week 8 to 15, and 20, respectively, and neuronal differentiation and organization which goes on during pregnancy and beyond (Fig. 6) (4).

The timing of fetal infection in terms of cerebral involvement is crucial. Early fetal infection generally leads to more extensive injuries and clinical sequelae. Depending of the stage of brain development when CMV infection happens, different types of developmental brain malformations occur: infection before 18 weeks of gestation typically leads to lissencephaly, microcephaly, cerebellar hypoplasia and ventriculomegaly, whereas infection from 18 to 24 weeks leads to migrational abnormalities such as polymicrogyria and schizencephaly. Periventricular pseudocysts and intraventricular synechiae, cerebellar hypoplasia and moderate ventriculomegaly are common lesions. Finally, infections in the third trimester are associated with delayed myelination, dysmyelination and white matter disease. In all stages, calcifications are frequently observed (3).

Positive and negative predictive values of cerebral US for poor neurological outcome are 66% and 91%,

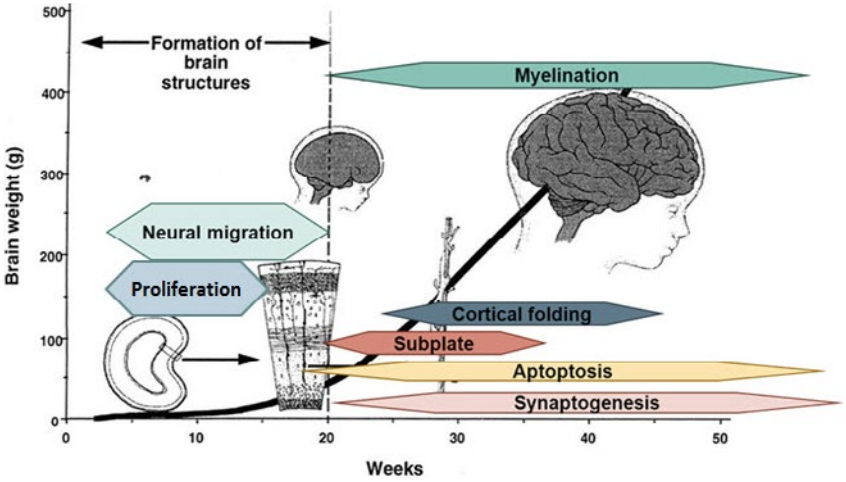

Fig. 6

Fetal brain and cortical development showing the three main stages: neural proliferation, neuroblast migration and differentiation and organization. (adapted from Stanley E, Clinics Dev Medicine, 2010).

respectively. The weakness of this imaging modality lies in its limited ability to visualize the posterior fossa, cortical abnormalities, the cerebellum, the subtentorial space, sulcation and gyral abnormalities, subtle white matter injury and delayed myelination. MRI in addition to cerebral US reveals new abnormalities in up to 20% of cases and reaches positive and negative predictive values of 77% and near 100%, respectively. Thus each symptomatic or asymptomatic newborn infant with pathologic findings on cerebral US should undergo MRI scanning. However normal cerebral US imaging and MRI still do not completely rule out long-term sequelae such as SNHL (3, 5).

Early diagnosis and identification of CNS involvement is important for accurate prognosis and decision-making regarding postnatal antiviral treatment. A definitive diagnosis of congenital infection should be established within three weeks after birth, as later diagnosis can no longer clearly differentiate between congenital and postnatal infection. Detection of CMV in urine or saliva is considered the gold standard. CMV PCR has displaced „older" methods such as CMV culture, it is, however, much more expensive. Antigen testing has a high sensitivity (> 99%) and gives very fast results. After confirmation of congenital CMV infection, further early evaluation includes full blood count, liver function tests and coagulation studies, ophthalmological and audiological assessment (6).

After full evaluation, patients should be allocated to one of the following groups: asymptomatic, symptomatic, symptomatic with severe focal organ disease, or symptomatic with CNS involvement. Severe focal disease is defined as severe hepatitis, severe bone marrow suppression, colitis or pneumonia. CNS involvement includes pathological findings on neuroimaging, microcephaly, SNHL and chorioretinitis (6).

Antiviral treatment should be started within the first 30 days of life and is clearly recommended in symptomatic newborn infants with CNS involvement; additionally, it can be considered in symptomatic newborn infants with severe focal disease. In symptomatic newborn infants with CNS involvement, ganciclovir therapy seems to reduce long-term sequelae: SHNL progression and neurodevelopement delay were both reduced by 60% within the first year of life (6). Up to 79% of treated patients were able to maintain normal hearing, whereas only 31% of non-treated patients did. Only 10 versus 17 developmental milestones were not met with therapy versus no therapy. However, there is no clear benefit with regards to hepatitis, and ganciclovir cannot undo brain lesions, which exist at the start of treatment (7).

Current guidelines suggest intravenous treatment with ganciclovir for two to three weeks followed by oral therapy with valganciclovir to complete 6 weeks of therapy in total (6). However, there is emerging

evidence that prolonged antiviral treatment up to 6 months can improve long-term outcomes (7). During treatment, weekly full blood count and renal function tests should be followed to monitor for adverse effects (thrombocytopenia, neutropenia, anemia) and because ganciclovir is excreted renally. Viral load usually drops one or two logs during treatment, rises again drastically after treatment termination and children may excrete CMV in urine for over a year. Long-term follow-up includes regular audiology, ophthalmologic and neurodevelopment assessments since long-term sequelae can worsen or develop de novo over time. Current guidelines are summarized in Fig. 7 (6).

Fetal abnormalities in cerebral US, fetal thrombocytopenia and IUGR are associated with poor neurodevelopmental outcome. Odds ratio for poor outcome in the presence of fetal cerebral US abnormalities is reported as high as 25.5 (8). After birth, microcephaly, neuroimaging abnormalities and elevated beta2-microglobulin levels in cerebrospinal fluid samples have been identified as risk factors for poor neurodevelopmental outcome (9).

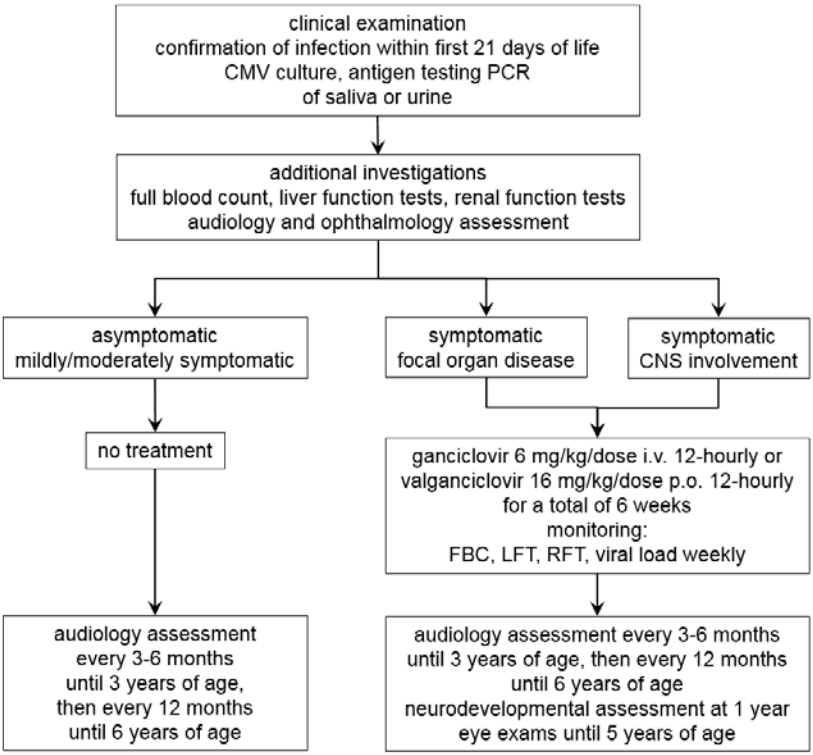

Fig. 7

Summary of current guidelines on management in congenital CMV infection (adapted from Kadambari S, Williams EJ, Luck S, et al. Early Human Development 2011).

REFERENCES

1. Manicklal S, Emery VC, Lazzarotto T, et al. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev 2013;26:86-102 *(Abstract)*

2. Kenneson A, Cannon M. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17:253–276 *(Abstract)*

3. Lanari M, Capretti MG, Lazzarotto T, et al. Neuroimaging in CMV congenital infected neonates: how and when. Early Hum Develop 2012;8852:53-55 *(Abstract)*

4. Lian G, Sheen V. Cerebral developmental disorders. Curr Opin Pediatr 2006;18:614-620 *(Abstract)*

5. Capretti MG, Lanari M, Tani G, et al. Role of cerebral ultrasound and magnetic resonance imaging in newborns with congenital cytomegalovirus infection. Brain Dev 2014;36:203-211 *(Abstract)*

6. Kadambari S, Williams EJ, Luck S, et al. Evidence based management guidelines for the detection and treatment of congenital CMV. Early Hum Develop 2011;87:723-728 *(Abstract)*

7. Gwee A, Curtis N, Garland SM, et al. Question: which infants with congenital cytomegalovirus infection benefit from antiviral therapy? Arch Dis Child 2014;99:597-601 (no abstract available)

8. Benoist G, Salomon LJ, Jacquemard F, et al. The prognostic value of ultrasound abnormalities and biological parameters in blood of fetuses infected with cytomegalovirus. BJOG 2008;115:823–829 *(Abstract)*

9. Alarcon A, Martinez-Biarge M, Cabañas F, et al. Clinical, biochemical, and neuroimaging findings predict long-term neurodevelopmental outcome in symptomatic congenital cytomegalovirus Infection. J Pediatr 2013;163:828-834 *(Abstract)*

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