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Cytomegalovirus encephalitis in immunocompetent infants: A 15-year retrospective study at a single center

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ABSTRACT

Objective: Cytomegalovirus (CMV) encephalitis is a disease that primarily affects immunocompromised hosts. Only a few cases have been reported in immunocompetent individuals, especially in children. The aim of this study was to investigate the clinical characteristics of immunocompetent children with CMV encephalitis attending a single medical center in southwest China over a 15-year period.
Methods: The medical records of children with confirmed CMV encephalitis who were hospitalized in the Children's Hospital of Chongqing Medical University during the years 2002–2017 were reviewed. An analysis of the clinical features, laboratory data, and the treatment response to antiviral therapy was performed.
Results: The median age of the patients ($n = 18$) was 5.1 months. 'Seizures' was the earliest and most common neurological symptom, while fever and poor feeding were also present in most patients. Elevated cerebrospinal fluid (CSF) protein was the most noticeable biochemical finding. After treatment with two-stage ganciclovir, all patients showed a steady clinical improvement. The total adverse drug reaction (ADR) rate was 27.3%, mainly presenting as effects on the hematopoietic system and liver. During follow-up ranging from 3 to 36 months, nine patients showed a complete recovery. At the stage of diagnosis, CMV PCR of CSF was positive in all patients, while anti-CMV IgM was positive in 77.8% of patients. After treatment with two-stage ganciclovir, all patients showed a negative result for CMV genome in the CSF and a clear decrease in the urine.
Conclusions: The possibility of CMV encephalitis in the immunocompetent child should be kept in mind, especially in those younger than 6 months of age. Suspicion for a diagnosis of CMV encephalitis is needed in the presence of unexplained prominent seizure, fever, poor feeding, and a marked elevation of protein level in the CSF. CMV PCR assays of CSF are necessary to determine the etiology. Furthermore, measurement of the CMV load in CSF and urine may be useful for evaluating the response to treatment and the outcome. Ganciclovir may lead to clinical improvement with limited ADR. CMV encephalitis in the immunocompetent infant does not necessarily indicate a poor short-term prognosis.

Introduction

Cytomegalovirus (CMV) is endemic in most areas of the world. The seroprevalence of CMV varies in different geographical areas and ranges from 30% to 100% (Hibberd, 1995). In China, the seroprevalence of CMV is approximately 0.6–8.5% in the newborn, 58–84% in infants, and around 95.6–98.7% in fertile women (Zhang et al., 2014). CMV causes end-organ disease in various body organs and tissues. The most common is CMV pneumonitis, followed by hepatitis and nephritis; central nervous system (CNS) involvement is rare (Plosa et al., 2012). CMV infection of the CNS may affect the brain (i.e., diffuse encephalitis, ventriculoencephalitis, cerebral mass lesion) or the spinal cord (i.e., transverse myelitis, polyradiculomyelitis).

CMV encephalitis primarily affects immunocompromised patients, such as those with HIV/AIDS, transplant recipients on immunosuppressive therapy, and those with a malignant hematological disease. In the past, only a few cases of CMV encephalitis have been described in patients not belonging to these groups (Arribas et al., 1996; Salamano et al., 2001; Saliba et al., 2004; Belo et al., 2012; Micallef and Galea, 2018). The incidence of CMV encephalitis in immunocompetent children remains unclear. In a

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review of 676 patients with CMV encephalitis, Arribas et al. (Arribas et al., 1996) found that 85% of the patients were infected with HIV, 12% had other causes of immunosuppression (usually organ transplantation), and only 3% (21 patients) were not immunocompromised. In immunocompetent children aged less than 14 years with a CNS infection, enterovirus is the leading virus, followed by human herpes virus (HHV); infections with CMV and varicella zoster virus (VZV) are relatively rare (Parisi et al., 2016).

The detection of CMV in the CSF, or of CMV antibodies produced intrathecally, is now considered the confirmed standard for establishing a diagnosis of CMV encephalitis; these methods are widely accepted for routine clinical decision-making (Maschio et al., 1999; Drew, 2007). During the past 30 years, techniques based on the amplification of CMV genomes by PCR have provided the most sensitive tools for the diagnosis of CMV encephalitis, and their recent generalized use has widened the previous clinical spectrum of the disease.

The treatment of CMV infection with ganciclovir is indicated in certain situations, but the guidelines for treatment, especially in immunocompetent patients, are not yet established (Iannetti et al., 1991; Stockmann et al., 2015; Baghban and Malinis, 2018).

This article reports the cases of 18 infants from the southwest region of China who presented with a clinical picture of CMV encephalitis but who lacked evidence of an immunocompromising disease. The natural history, laboratory data, and response to ganciclovir therapy of these infants were assessed.

Materials and methods

Patients were traced from records kept by the Children's Hospital of Chongqing Medical University. This is a government hospital in the municipality of Chongqing and the largest children's hospital in southwestern China. Between January 2002 and December 2017, 18 patients who presented with clinical symptoms of a CNS infection received a diagnosis of CMV encephalitis. The diagnosis was confirmed by the presence of a CMV genome load of over 500 copies/ml in at least one CSF sample, as detected by quantitative real-time PCR assay. The CMV primers were selected from the highly conserved UL83 gene, which has been described in detail in a previous work by Gouarin et al. (Gouarin et al., 2004).

Immunological competence was defined by the absence of the following: a congenital or acquired immunodeficiency syndrome; a history of allogeneic transplantation; a history of immunosuppressive treatment (including antineoplastic chemotherapy and long-term glucocorticoid therapy). The evaluation of IgM antibody titers against CMV was performed using a chemiluminescence microparticle immunoassay. Similarly, IgM antibody titers against other viruses were utilized to exclude other viral CNS infections.

Confirmed cases were given the regular therapy of ganciclovir. In the inducement phase, injections of ganciclovir 5 mg/kg were given twice a day for 2 weeks. In the maintenance phase, ganciclovir 5 mg/kg was applied once a day for 2 weeks. Real-time PCR quantification was also performed at the end of ganciclovir therapy, in order to investigate whether the CMV genome load in CSF, blood, and urine samples could be related to the clinical condition and outcome of the infected children.

All patients were followed up for a period ranging from 3 to 36 months, and a neurological examination was performed and psychomotor development evaluated thoroughly at the last evaluation. Day 0 was considered to be the day of the first reported neurological symptoms.

Results

Epidemiological characteristics (Table 1)

Patients included 10 boys and eight girls (male-to-female sex ratio 1.25:1) aged 37–790 days. Among these, three (16.7%) were aged 1–3 months, 10 (55.6%) were aged 4–6 months, three (16.7%) were aged 7–12 months, and two (11.1%) were aged 1–2 years. The median age of the patients was 5.3 months.

Clinical signs and symptoms (Table 1)

All patients had an acute or subacute onset. Seventeen (94.4%) had seizures, of whom 14 had generalized seizures, three had partial seizures, and three had seizure status; seizures mostly occurred within 1–3 days of disease onset. Fourteen (77.8%) had fever, 14 (77.8%) had poor feeding, and four (22.2%) had vomiting. Furthermore, eight patients had an altered state of consciousness

Table 1
Clinical features, CMV genome load, and CMV-IgM of 18 cases at the stage of CMV encephalitis diagnosis.

Patient No.	Age (days)	Sex	Clinical findings[a]	CMV genome load							
				CSF		Serum		Urine		CSF	
				DNA load (GE/ml)	Collection date (days of onset)	DNA load (GE/ml)	Collection date (days of onset)	DNA load (GE/ml)	Collection date (days of onset)	IgM	Collection date (days of onset)
1	112	F	F, S, PF	1.5×10^3	5	3.2×10^3	4	ND	ND	+	5
2	128	M	F, S, PF, V	4.6×10^3	5	5.4×10^3	7	7.9×10^3	7	+	5
3	315	M	S, C	6.3×10^2	7	8.6×10^3	11	1.4×10^4	13	+	7
4	132	M	F, S, PF	2.7×10^3	3	4.8×10^3	6	9.1×10^3	6	+	3
5	146	F	S, PF	9.9×10^2	4	ND	ND	4.6×10^3	7	+	4
6	167	F	F, S, V, C	8.5×10^2	4	6.8×10^3	9	ND	ND	+	4
7	37	M	F, S, PF, C	1.2×10^3	6	ND	ND	3.2×10^4	9	–	6
8	243	F	F, S, C	7.8×10^3	10	1.1×10^3	11	6.7×10^4	12	+	10
9	184	F	F, S, PF	1.6×10^3	6	2.7×10^3	7	ND	ND	+	6
10	180	M	F, S, PF	2.4×10^3	5	3.5×10^3	12	1.5×10^4	14	+	5
11	213	F	S, PF, V	3.3×10^3	4	ND	ND	ND	ND	+	4
12	144	M	S, PF	2.6×10^3	11	ND	ND	ND	ND	+	11
13	196	M	F, PF, C	8×10^2	8	ND	ND	ND	ND	+	8
14	64	M	F, S, PF, V, C	7.2×10^3	7	2.1×10^4	9	3.5×10^4	9	–	7
15	175	M	F, S, PF	3.1×10^3	9	6.3×10^3	10	1.1×10^4	10	+	9
16	159	F	F, S, PF, C	6.5×10^2	10	2.4×10^3	10	ND	ND	+	10
17	148	F	F, S, PF, C	3.4×10^3	6	5.2×10^3	10	8.3×10^4	10	+	6
18	790	M	F, S	7.3×10^2	3	9.2×10^3	8	2.7×10^4	8	+	3

CMV, cytomegalovirus; CSF, cerebrospinal fluid; GE, genome equivalents; F, female; M, male; ND, not done.
[a] S, seizures; F, fever; PF, poor feeding; V, vomiting; C, confusion.

(44.4%), with meningeal irritation in three (16.7%) and altered tonus in two. There was no case of limb or cranial paralysis.

Investigations (Tables 1 and 2)

All patients underwent cerebral imaging during the first week of the disease. Magnetic resonance imaging (MRI) was done for 15 patients and a cerebral computed tomography (CT) scan was done for three patients. Brain lesions were observed in six patients: frontoparietal ($n = 2$) and enlarged ventricle ($n = 4$). All 18 children had an electroencephalogram (EEG) recording taken during the early phase of the disease; this was done between days 0 and 3 in 80% of cases. EEG anomalies were present in 16 patients (88.9%) and consisted of non-specific diffuse slow waves in 13 patients and focal slow waves in five patients; in five cases, these were strictly focal in the frontal area.

Liver function was abnormal in seven patients. A lumbar puncture was performed in all patients. The protein level in the CSF on first assessment after admission was elevated (>0.45 g/l) in 14 patients. In 10 of the 14 patients, the protein level in CSF exceeded 1.2 g/l (range 1.24–1.90 g/l). The white blood cell count in the CSF was elevated in seven patients; the median CSF leukocyte count was 68×10^6 cells/l (most were lymphocytes). All patients had a normal glucose level. A brainstem auditory evoked potential (BAEP) examination was performed for all 18 patients. Five of them (27.8%) showed peripheral auditory pathway impairment.

All patients underwent testing for other viral antibodies in the CSF to exclude the corresponding infections, including human immunodeficiency virus (HIV), Toxoplasma (TOX), rubella virus (RV), herpes simplex virus (HSV), Epstein–Barr virus (EBV), enterovirus (EV), and morbillivirus (MV); all tests were negative.

Treatment (Table 3)

The parents/guardians of seven patients refused ganciclovir treatment and discharged them for economic reasons or fear of drug side effects. Eleven patients (61.1%) had ganciclovir treatment, of whom only eight finished the entire 4 weeks of ganciclovir treatment. The clinical signs and symptoms, including seizure, vomiting, poor feeding, and confusion, improved. This improvement occurred around 3–10 days after treatment initiation, with complete recovery occurring shortly thereafter. Three patients did not complete the ganciclovir treatment. The total adverse drug reaction (ADR) rate was 27.3%. All ADR occurred in the induction phase of treatment, with two patients showing mild neutropenia ($1.2–1.4 \times 10^9$/l) and one patient showing liver damage (alanine aminotransferase (ALT) 135 U/l, aspartate aminotransferase (AST) 217 U/l). The ADR remitted after symptomatic treatment.

CMV. genome load and antibody testing (Tables 1 and 3)

The laboratory tests used for the diagnosis of CMV CNS and systemic infections are CMV PCR and anti-CMV IgM. CMV genome load testing and anti-CMV IgM testing on CSF and/or blood and/or urine was performed for all patients during the 1–2 weeks of the disease. Fifteen patients had CMV PCR testing of at least two samples. At the stage of diagnosis, the CSF CMV PCR was positive in all patients, while anti-CMV IgM was positive in 14 patients (77.8%). Among the three sample types, urine harbored the highest viral load, followed by blood and CSF. The CMV genome load was detected again in the various samples at the end of the treatment course. All patients who completed the entire 4 weeks of ganciclovir treatment showed CSF CMV genome conversion to negative and decreased CMV genome in urine. Of note, an increase in viral load in the blood was observed in two patients after the completion of ganciclovir therapy, although clinical findings of exacerbation were not observed.

Follow-up (Table 3)

The follow-up period ranged from 3 to 36 months. Four patients withdrew from the study. At the final evaluation, the results of neurological and psychomotor development examinations were normal for nine children. Only five of the patients experienced sequelae. Three of the five patients suffered from recurrence of seizures and hearing loss and two patients presented with delayed psychomotor development during follow-up. The reduction in CMV genome load in the CSF and urine appeared to be correlated with a favorable outcome.

Discussion

While the manifestations of CMV encephalitis in immunocompromised patients have been reported extensively, only a few

Table 2
Laboratory data of 18 cases of CMV encephalitis.

Patient No.	Other virus IgM CSF[a]	CSF values			Altered investigation[b]	Multi-organ involvement
		Leukocytes ($\times 10^6$/L)	Glucose mmol/l	Protein g/l		
1	TOX/RV/HSV/HIV (−)	88	–	1.24	EEG, MRI	None
2	TOX/RV/HSV/HIV (−)	–	–	0.65	EEG, BAEP	None
3	HSV/EBV/EV/MV/HIV (−)	–	–	–	EEG	None
4	TOX/RV/HSV/HIV (−)	–	–	–	EEG	None
5	TOX/RV/HSV/HIV (−)	44	–	1.37	EEG	None
6	TOX/RV/HSV/HIV (−)	–	–	1.64	EEG, MRI, BAEP	Liver
7	TOX/RV/HSV/HIV (−)	–	–	1.9	EEG	None
8	HSV/EBV/EV/MV/HIV (−)	53	–	0.77	EEG	None
9	HSV/EBV/EV/MV/HIV (−)	–	–	1.33	EEG	None
10	HSV/EBV/EV/MV/TOX/RV/HSV/HIV (−)	–	–	1.52	None	None
11	HSV/EBV/EV/MV/HIV (−)	60	–	–	EEG, BAEP	None
12	TOX/RV/HSV/HIV (−)	72	–	0.58	EEG	Liver
13	HSV/EBV/EV/MV/HIV (−)	–	–	1.78	EEG, BAEP	None
14	TOX/RV/HSV/HIV (−)	–	–	1.56	EEG	None
15	TOX/RV/HSV/HIV (−)	–	–	1.34	EEG, MRI	None
16	TOX/RV/HSV/HIV (−)	136	–	–	EEG, MRI, BAEP	Liver
17	TOX/RV/HSV/HIV (−)	–	–	1.25	EEG, CT	None
18	HSV/EBV/EV/MV/HIV (−)	35	–	0.73	MRI	None

CMV, cytomegalovirus; CSF, cerebrospinal fluid; ND, not detected; U, undone.
[a] HIV, human immunodeficiency virus; TOX, Toxoplasma; RV, rubella virus; HSV, herpes simplex virus; EBV, Epstein–Barr virus; EV, enterovirus; MV, morbillivirus.
[b] BAEP, brainstem evoked auditory potential; EEG, electroencephalogram; MRI, magnetic resonance imaging; CT, computed tomography.

Table 3
Treatment, adverse drug reactions, outcomes, and CMV genome load after treatment with ganciclovir in 18 cases with CMV encephalitis.

Patient No.	Antiviral treatment			Outcome	CMV genome load					
	Drug	Time	Adverse drug reaction		CSF		Serum		Urine	
					DNA load (GE/ml)	Collection date (days of onset)	DNA load (GE/ml)	Collection date (days of onset)	DNA load (GE/ml)	Collection date (days of onset)
1	ND	ND	ND	Withdrawn	ND	ND	ND	ND	ND	ND
2	Ganciclovir	4 weeks	None	CR	<500	51	ND	ND	8.6×10^2	51
3	Ganciclovir	4 weeks	None	CR	<500	47	9.1×10^3	47	<500	52
4	Ganciclovir	8 days	Granulocytopenia	Withdrawn	ND	ND	ND	ND	ND	ND
5	ND	ND	ND	CR	ND	ND	ND	ND	7.9×10^2	60
6	Ganciclovir	4 weeks	None	CR	<500	45	7.2×10^2	45	<500	45
7	ND	ND	ND	CR	ND	ND	ND	ND	ND	ND
8	Ganciclovir	6 days	Granulocytopenia	CR	ND	ND	ND	ND	5.4×10^2	55
9	Ganciclovir	20 days	Liver damage	S	ND	ND	5.3×10^2	45	ND	ND
10	Ganciclovir	4 weeks	None	S	<500	38	6.5×10^2	38	1.1×10^3	38
11	Ganciclovir	4 weeks	None	CR	<500	40	ND	ND	ND	ND
12	Ganciclovir	4 weeks	None	CR	<500	61	ND	ND	ND	ND
13	ND	ND	ND	PMD, HL	ND	ND	ND	ND	6.9×10^3	63
14	ND	ND	ND	Withdrawn	ND	ND	ND	ND	ND	ND
15	ND	ND	ND	CR	ND	ND	ND	ND	2.5×10^3	60
16	ND	ND	ND	Withdrawn	ND	ND	ND	ND	ND	ND
17	Ganciclovir	4 weeks	None	PMD	<500	36	1.8×10^3	82	1.3×10^3	82
18	Ganciclovir	4 weeks	None	PMD	<500	43	1.6×10^4	57	9.2×10^2	57

CMV, cytomegalovirus; CSF, cerebrospinal fluid; GE, genome equivalents; ND, not done; CR, complete recovery; S, seizures; PMD, psychomotor development delay; HL, hearing loss.

studies have described the clinical course in immunocompetent patients, especially in immunocompetent children. Darin et al. concluded that CMV may be an overlooked infectious agent of the CNS in immunocompetent children (Darin et al., 1994). The present retrospective study describes 18 previously healthy children with proven CMV, shown through the use of PCR on CSF as a confirmed standard for diagnosis. The study found that CMV encephalitis was predominantly observed in infants aged 4–6 months. A high proportion of symptomatic CMV infections during this period of life could be related to the disappearance of passive immunity from maternally acquired CMV-specific antibodies. However, the immune memory for CMV in infants during this period of life has not yet been established.

With regard to the clinical manifestations of CMV encephalitis in immunocompetent adults, the presentation is reported to be a febrile illness with non-specific clinical manifestations, including coma, aphasia or dysphasia, and cranial nerve palsies. The CSF of immunocompetent adults with CMV encephalitis usually exhibits pleocytosis (predominantly lymphocytic) and hypoglycorrhachia. Characteristic periventricular enhancement on MRI provides a clue to diagnosis (Arribas et al., 1996; Rafailidis et al., 2008). Compared with the immunocompetent adult, the present study showed that CMV encephalitis in previously healthy children has its own clinical features, that is, apparent seizures, prominent elevated CSF protein, and non-specific neuroradiological and EEG changes.

Indeed, seizures were observed as the first and most common neurological symptom in most of the case patients (94.4%). There could be two reasons for this. The first supports a pathogenic role for CMV, with associated alterations in neuronal calcium metabolism as the cause of epileptic discharges (Maschio et al., 1999). The second is the possibility that the immature brain is more susceptible to seizures. In the study patients, fever and poor feeding were other common symptoms. Moreover, confusion and focal neurological signs, which are common in adult patients, are not as obvious in infants. In the present study, 10 of the 18 initial CSF samples drawn at the stage of disease onset showed a marked elevation in protein levels, which returned to normal after 2–4 weeks. In the majority of cases, neuroradiological examinations showed normal results or non-specific increases in the ventricle, while EEG showed a general broad slowdown in rhythm, often with focal points of irritation, and also showed non-specific alterations.

Ganciclovir and foscarnet are recommended for the treatment of CMV encephalitis in immunocompromised patients (Iannetti et al., 1991). The treatment of CMV encephalitis in immunocompetent patients is based only on a few case reports. Jacobson et al. recommend antiviral therapy with ganciclovir for immunocompetent patients with CMV encephalitis (Markham and Faulds, 1994; Jacobson, 1997). Ganciclovir is an acyclic deoxyguanosine nucleoside analog and has a mechanism similar to acyclovir, in that it must undergo phosphorylation prior to eliciting antiviral activity. It is reported that this drug may lead to severe ADR, including reversible bone marrow suppression, especially granulocytopenia (Kimberlin et al., 2015). In the study cohort, half of the patients were treated with ganciclovir and a clinical improvement was seen on day 3–10, with recovery occurring shortly thereafter. The successful outcome following early instigation of antiviral therapy in patients 2, 3, 6, 8, 11, 12, and 17 and the comparatively poorer outcome in patients 13 and 16, who did not use ganciclovir, suggests that the treatment may be of benefit. However, due to the lack of randomized, controlled, double-blind studies, it is not clear whether the improvement in the patients' conditions was part of the natural course of the disease in immunocompetent patients or whether it could be attributed to the effect of ganciclovir. Furthermore, of the patients who used ganciclovir, only three (27.3%) experienced transient mild granulocytopenia or liver function damage and these ADR remitted

after symptomatic treatment, showing that ganciclovir treatment in immunocompetent patients with CMV encephalitis is safe.

Previous studies have shown that the prognosis of immunocompromised patients with CMV encephalitis is not favorable. Most cases have been fatal, in spite of specific antiviral therapy (Arribas et al., 1996; Baghban and Malinis, 2018). Interestingly, with follow-up of 3–36 months, most of the study patients presented normal results for neurological and psychomotor development examinations. Therefore, the clinical outcome of CMV encephalitis in these children is considered favorable. Larger series are required to confirm this result.

Some recent studies have suggested the use of CMV genome load as an indicator of the response to antiviral therapy and clinical outcome of patients with CMV infection (Gouarin et al., 2002; Suganuma et al., 2018). In the present study, there was no apparent relationship between the baseline viral load level and the severity of the disease. However, after the administration of antiviral therapy, the CMV genome load in CSF and urine decreased, and this reduction appeared to be correlated with the improvement in neurological function. An increase in CMV DNAemia was observed in two patients after the ganciclovir therapy. This rebound increase in CMV DNAemia has been reported previously and the significance of reappearance remains incompletely understood (Lee-Yoshimoto et al., 2018). In the early onset stage, CMV PCR on the CSF was positive for all patients, while anti-CMV IgM was positive for 77.8% of the patients. The anti-CMV IgM-negative patients were mostly under 3 months old. This may be because young infants have an immature immune system, which may fail to produce antibodies during acute infections. Therefore, the present authors' consider that the detection of CMV genome in CSF aids in the rapid diagnosis of CMV encephalitis, and a decline in CMV viral load in the CSF and urine reflects a favorable response to treatment and a good clinical outcome.

In conclusion, the possibility of CMV encephalitis in the immunocompetent child should be kept in mind, especially in those younger than 6 months of age. During diagnosis, a suspicion for CMV encephalitis should be maintained in the presence of unexplained prominent seizure, fever, poor feeding, and a marked elevation of protein level in the CSF. CMV PCR assays on CSF are necessary to investigate the etiology. Furthermore, measurement of the CMV genome load in CSF and urine may be useful for evaluating the response to treatment and the outcome. Ganciclovir may improve clinical symptoms with limited ADR, and treatment with ganciclovir showed a favorable outcome in most immunocompetent infants with CMV encephalitis.

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Ethical approval

This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University. Consent was obtained from the patients' legal guardians. In this study, personal identifiers, such as name, address, and telephone number, were not disclosed to maintain patient confidentiality. All of the patients' medical information was analyzed anonymously.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Yi Guo contributed to the study design, data collection, data analysis, and writing. Li Jiang contributed to providing the patients. Both of the authors read and approved the final manuscript.

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