that used for permanent waving. Because hair straightening is carried out for customers with naturally curly hair, the lotion must be entirely spread onto hair strands from the proximal end close to the scalp. Furthermore, thermal reconditioning which may accelerate reaction between hair mercury and thiols in the lotion is often applied to straighten hair strands completely. These differences are presumably the causes of the different patterns of decrease in hair mercury concentration.

In an epidemiological study, Dakeishi et al. (2005) reported a 30% lower mercury concentration in hair samples from a group of mothers who had "artificial hair-waving treatments" than in hair samples from a group of mothers who did not. They analyzed full-length hair strands and their "with treatments" group included permanent waving and straightening. When the average mercury concentrations in full-length hair strands of the group in which permanent waving and straightening were combined was calculated in the present study, the 25% mercury concentration reduction was observed after the treatments. This is similar to the reduction observed in the "with treatments" group of Dakeishi et al. (2005).

In this study, no significant difference by permanent waving in average hair mercury concentration was observed for the first 3-cm segments. This is a great advantage of using hair mercury concentration as a biomarker of methylmercury exposure in studies of prenatal methylmercury exposure. Assuming that hair samples are collected from puerperal women around the time of delivery, the proximal segments 3 cm from the scalp reflect the methylmercury concentration in maternal blood and thus represent fetal exposure during the third trimester when fetuses are most vulnerable to methylmercury exposure. Unfortunately, this is not the case for hair straightening, because, as shown in this study, even the segments closest to the scalp showed a slight decrease, which, however, is not statistically significant.

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Changes in mercury concentrations of segmental maternal hair during gestation and their correlations with other biomarkers of fetal exposure to methylmercury in the Japanese population ☆

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Abstract

Methylmercury (MeHg) is one of the most hazardous substances that affects the fetus through fish consumption. The objective of this study was to evaluate the changes in the level of exposure to MeHg by assessing the mercury (Hg) concentrations of the segmental hair at parturition and 3 months after parturition, and to study their correlations with the total Hg concentrations of maternal and cord red blood cells (RBCs) and neonatal hair as biomarkers of fetal exposure to MeHg at parturition. In total, 40 paired samples of maternal hair from the scalp, maternal and cord RBCs, and 21 samples of neonatal hair from the scalp were collected at parturition. In addition, 19 samples of maternal hair from the scalp were collected at 3 months after parturition. The maternal hair samples were cut into 1 cm segments from the scalp end toward the tip. The geometric mean of the Hg concentrations in cord RBCs was approximately 1.6 times higher than that in the maternal RBCs, and a strong correlation coefficient ($r = 0.91$) was found between them. The increase or decrease in the Hg concentrations of the segmental hair during gestation differed largely among individuals. The correlation coefficients between the Hg concentrations of the segmental hair and cord RBCs were the strongest ($r = 0.90$) in the hair segment 1 cm from the scalp and decreased gradually with the distance from the scalp. The correlation coefficients between the Hg concentrations of the segmental hair collected at 3 months after parturition and maternal RBCs were over 0.9 in the hair segments 5 and 6 cm from the scalp, suggesting that the time required for the incorporation of Hg from the blood into a growing hair was very short. The geometric mean of Hg concentrations in the neonatal hair at parturition was similar to that in the maternal hair 1 cm from the scalp at parturition, and they exhibited a strong correlation ($r = 0.95$). The findings of this study indicate that maternal hair close to the scalp at parturition and neonatal hair are useful biomarkers of fetal exposure to MeHg at parturition. In addition, the segmental maternal hair throughout gestation is essential to obtain important information on MeHg exposure during the different sensitive windows or bolus MeHg exposure during gestation.

Keywords: Methylmercury; Exposure; Segmental maternal hair; Cord red blood cells; Maternal red blood cells; Neonatal hair

1. Introduction

Methylmercury (MeHg) is a well-known and widespread environmental neurotoxicant. In general, human exposure to MeHg occurs primarily through the consumption of fish and sea mammals. Fetuses are known to be a high-risk group for MeHg exposure because of the high susceptibility of their developing brains (Björnberg et al., 2003;

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Choi, 1989; Sakamoto et al., 1993; WHO, 1990). Moreover, MeHg easily crosses the blood–placenta barrier and accumulates in higher concentrations in the fetus than in the mother (Choi, 1989; Sakamoto et al., 2004, 2002a, b; Stern and Smith, 2003; WHO, 1990). Therefore, it is important to examine the effect of MeHg exposure on the fetus and assess the exposure levels of pregnant women, particularly in Japanese and certain other populations that consume considerable amounts of fish and sea mammals (Nakai et al., 2004; NRC, 2000; WHO, 1990). The occurrence of an epidemic of fetal-type Minamata disease in Minamata, Japan (Harada, 1978), attracted worldwide attention to the high risk posed by MeHg. Thereafter, large prospective cohort studies were conducted in the Seychelles (Myers et al., 2003, 1995a, b) and Faroe Islands (Grandjean et al., 2005, 1999, 1997), where the consumption of fish or sea mammals is high.

The target organ for MeHg exposure during gestation is the fetal brain. Therefore, biomarkers reflecting the Hg concentrations in the fetal brain during gestation are very important for the prediction of the effects of MeHg on infant development. In the Faroe Islands study, cord blood was the preferred biomarker of exposure to MeHg, although maternal hair was also collected and analyzed. In the Seychelles study, maternal hair was used as a measure of MeHg exposure in fetuses. Each of these biomarkers has its advantages and disadvantages. Cord blood circulates in the fetal body and can directly reflect the MeHg concentration in the organs, including the fetal brain, at birth (Cernichiari et al., 1995; NRC, 2000). Further, an analysis of cord blood may provide measurements of exposure mainly over the third trimester; however, cord blood is only available at parturition and the information cannot necessarily be extrapolated to evaluate the exposure in the target tissue at other times. The developing fetal brain will have sensitive windows (periods) of MeHg exposure during different periods of gestation, and the resulting neurotoxic effect could be more a function of episodic bolus exposure than of average continuous exposure; thus, a time-course evaluation of the exposure throughout the gestation period may be a critical factor. Although hair Hg analysis involves a number of variables such as hair growth rate, density, color, waving, external contamination, and permanent treatment (WHO, 1990), the segmental analysis of the maternal hair that grows during gestation will provide time-course data (Björnberg et al., 2003; Morrissette et al., 2004) since the average hair growth rate is commonly assumed to be approximately 1 cm per month (Boischio and Cernichiari, 1998; Cernichiari et al., 1995; Grandjean et al., 1992). To evaluate the time required for the incorporation of Hg from the blood into a growing hair, we also collected maternal hair at 3 months after parturition, and we studied the correlation between the Hg concentrations in maternal red blood cells (RBCs) at parturition and the Hg concentrations of segmental maternal hair collected at 3 months after parturition.

Neonatal hair may also be a biomarker of fetal exposure to MeHg during the gestation period. Some studies (Lindow et al., 2003; Razagui and Haswell, 2001) demonstrated the relationship between the Hg levels in maternal and neonatal hair. However, the relationships between neonatal hair and other biomarkers of fetal exposure to MeHg at parturition have not been well studied.

The present study was designed to investigate the MeHg exposure at different periods of gestation by assessing the Hg concentrations of the segmental maternal hair throughout gestation; additionally, their correlations with the Hg concentrations of neonatal hair, maternal RBCs, and cord RBCs were studied. Further, the Hg concentrations of the segmental maternal hair collected at 3 months after parturition was compared with those of maternal RBCs at parturition to evaluate the time required for the incorporation of Hg from the blood into a growing hair.

2. Materials and methods

2.1. Subjects and sampling

In total, 40 healthy pregnant Japanese women without any particular exposure to Hg provided informed consent to participate in the present trial approximately 1 week before parturition. These women ranged in age from 22 to 39 years (average age, 29.6±4.1 years) and resided in Munakata City, Fukuoka, Japan. Blood samples from the umbilical cord were collected immediately after birth and maternal blood, 1 day after parturition. Both blood samples were obtained by venipuncture and by using a small amount of heparin sodium; these were centrifuged at 3000 rpm for 10 min to separate the RBCs and the plasma. The RBC samples were stored at −80 °C until the total Hg (THg) analysis. About 50 full-length strands of maternal ($n = 40$) and neonatal ($n = 21$) hair were also collected at parturition by cutting the strands close to the scalp in the occipital area. Approximately 50 full-length strands of maternal hair ($n = 19$) were also collected at 3 months after parturition. The maternal hair strands were cut into 1 cm segments from the scalp end toward the tip and THg was analyzed. In the case of three mothers who underwent permanent treatment during the different gestation periods, the Hg concentration data for the hair segments that grew before the treatment were not used in the analysis since the hair treatment was known to decrease Hg concentrations in hair (Dakeishi et al., 2005; Yamamoto and Suzuki, 1978). Full-length neonatal hair was used for the analysis because of its very low weight. This study was approved by the Ethics Committee of the National Institute for Minamata Disease (NIMD).

2.2. Mercury analysis

THg was determined in 0.5 g of RBCs and approximately 5–6 mg of hair samples by using cold vapor atomic absorption spectrophotometry (CVAAS) according to the method of Akagi et al. (2000). This method involves sample digestion with HNO_3, $HClO_4$, and H_2SO_4 (1:1:5), followed by reduction to elemental Hg vapor by $SnCl_2$. The detection limit was 0.01 ng/g. The accuracy of THg determination was confirmed by using reference whole-blood material level 2, MR9067 (Seronorm201605; Nycomed Co., Oslo, Norway); the average value of the THg was 7.5 μg/L, and the expected range is 6.8–8.5 μg/L as determined by inductively coupled plasma sector field mass spectrometry (ICP-SFMS) and reference NIES CRM No. 13 human hairs (National Institute for Environmental Studies, Environmental Agency of Japan). The average value of THg was 4.32 ng/mg, and the expected range is 4.22–4.62 ng/mg.

2.3. Statistics

The differences in the Hg concentrations of the paired blood samples were analyzed by a paired t test by using logarithmically transferred Hg concentrations. The associations between the Hg concentrations among the samples were studied by Pearson's correlation analysis by using logarithmically transferred Hg concentrations. A P value less than or equal to 0.01 was considered statistically significant.

3. Results

Table 1 shows the geometric means and 25th–75th percentiles of Hg concentrations and coefficients of variation of these concentrations in each centimeter of the segmental maternal hair from the scalp toward the tip, maternal RBCs, cord RBCs, and neonatal hair at parturition. Fig. 1 shows the correlation between the Hg concentrations in the maternal RBCs and cord RBCs. In all 40 cases, the Hg concentrations in cord RBCs were higher than those in maternal RBCs. The geometric mean of the Hg concentrations in cord RBCs was 13.2 ng/g; this was approximately 1.6 times higher ($P<0.01$) than that in maternal RBCs Hg (8.15 ng/g).

The geometric mean of the Hg concentration of maternal hair gradually decreased from the root toward the tip of the hair (Table 1). Fig. 2 shows individual changes in Hg concentrations in each centimeter of the maternal segmental hair from the scalp toward the tip at parturition. The increase and decrease in the Hg concentrations of maternal segmental hair throughout gestation differed considerably among individuals (Fig. 2), and the coefficients of variation increased with the distance from the scalp end (Table 1). Some mothers showed Hg concentrations that were approximately 100–200% and some others showed 50% of Hg concentrations at the middle or tip of the hair when compared with those 1 cm from the scalp (Fig. 2). Five mothers stated that their fish consumption increased during gestation, and five others stated that their fish consumption decreased during this period.

Table 2 shows the correlation coefficients among Hg concentrations in each centimeter of the segmental maternal hair from the scalp toward the tip, maternal RBCs, cord RBCs, and neonatal hair at parturition. The Hg concentrations of the maternal hair 1 cm from the scalp showed the highest correlation coefficients with those in the maternal RBCs (0.86) and cord RBCs (0.90). However, the Hg concentrations in all segmental maternal hairs showed significant and strong correlations ($P<0.01$); these decreased gradually with the distance from the scalp. The Hg concentrations in the neonate hair also showed strong correlations ($P<0.01$) with those in maternal hair 1 cm from the scalp (0.95), maternal RBCs (0.86), and cord RBCs (0.90). Fig. 3 shows the correlation between the Hg concentrations of maternal hair and neonatal hair.

Table 3 shows the geometric means and 25th–75th percentiles of Hg concentrations in each centimeter of the segmental maternal hair from the scalp toward the tip at 3 months after parturition and the correlation coefficients among maternal hair 1 cm from the scalp, maternal RBCs, and cord RBCs at parturition. The segmental hair 5 and 6 cm from the scalp at 3 months after parturition showed strong correlation coefficients (over 0.9) with the maternal RBCs, cord RBCs, and maternal segmental hair 1 cm from the scalp at parturition.

4. Discussion

The Hg concentrations in the cord RBCs were approximately 1.6 times higher than that in maternal RBCs, and there was a significant correlation between them, as was previously reported by us (Sakamoto et al., 2007, 2004, 2002b). This suggests that MeHg is actively transported to the fetus across the placenta via a neutral amino acid carrier, as demonstrated in previous studies (Aschner and

Table 1
Geometric means, 25th–75th percentiles, and coefficients of variation in the Hg concentrations in each centimeter of the segmental maternal hair from the scalp toward the tip, maternal RBCs, cord RBCs, and neonatal hair at parturition

	N	Geometric mean (ng/g)	25% Value	75% Value	Coefficient of variation
Maternal RBCs	40	8.15	6.28	11.17	0.43
Cord RBCs	40	13.20	9.99	17.02	0.44
Each centimeter of maternal hair from the scalp toward the tip (cm)					
1	40	1557	1126	2154	0.47
2	40	1490	1147	1985	0.50
3	39	1471	1105	1964	0.49
4	39	1433	1054	1748	0.52
5	39	1372	990	1883	0.51
6	39	1410	1031	2027	0.54
7	38	1417	1042	2144	0.57
8	37	1444	1054	2324	0.57
9	35	1442	1174	2305	0.61
Neonatal hair	21	1466	1032	1822	0.46

Coefficients of variation were calculated using logarithmically transferred Hg concentrations.
Hg concentrations in cord RBCs were significantly higher than that in the maternal RBCs by paired t test ($P<0.01$).

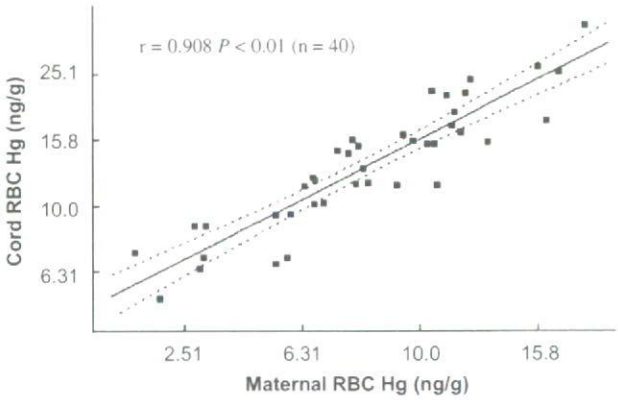

Fig. 1. Correlation between Hg concentrations in maternal RBCs and cord RBCs. Correlation coefficients were calculated by using logarithmically transferred Hg concentrations. The dotted lines represent 95% confidence intervals for the regression line.

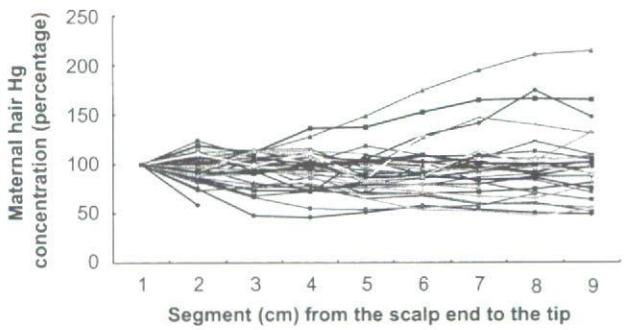

Fig. 2. Individual changes in Hg concentrations in each centimeter of the maternal segmental hair from the scalp toward the tip at parturition. Hg concentration in each maternal hair 1 cm from the scalp is taken as 100%.

Clarkson, 1987; Kajiwara et al., 1996). Human and animal studies have revealed the higher Hg accumulation in the fetuses than in the mothers during gestation when their fetal vulnerability to MeHg exposure is high (Björnberg et al., 2003; Choi, 1989; Pan et al., 2004; Reuhl and Pounds, 1981; Sakamoto et al., 2002a, b, 2007, 2004; WHO, 1990). Therefore, intensive attention must be paid to fetal exposure to MeHg during gestation.

Serum or plasma is known as a good biomarker of elemental or mercuric Hg exposure (WHO, 1991). On the other hand, the Hg concentration in RBCs is the best biomarker of MeHg exposure (Group, 1970; Svensson et al., 1992; WHO, 1990). Additionally, more than 90% of Hg in RBCs is known to be in the methyl form in populations consuming high amounts of fish (Kershaw et al., 1980; Laundy et al., 1984; Liu et al., 1991; Phelps et al., 1980). Further, hematocrit values are low in mothers (hemodilution) and high in fetuses at parturition (Sakamoto et al., 2004), and the degree of the anemia in mothers at parturition differs considerably among individuals. Therefore, in the present study, we use THg concentrations in RBCs, not whole blood, to reveal the MeHg levels in mothers and fetuses.

The hair segments 1 cm from the scalp at parturition showed strong correlation coefficients with the maternal RBCs and cord RBCs. This indicates that the hair proximal to the scalp is a good biomarker of fetal exposure to MeHg during the late gestation period. Björnberg et al. (2003) also used segmental hair samples and reported that the associations between MeHg in cord blood and THg in different segments were highest in hairs 1–2 cm from scalp ($r = 0.67$, $n = 15$). However, the correlation coefficient was lower than our result since their hair samples were collected at gestational week 32–34.

Table 2
Correlation coefficients among Hg concentrations in each centimeter of the segmental maternal hair from the scalp toward the tip, maternal RBCs, cord RBCs, and neonatal hair at parturition

	N	Correlation coefficients		
		Maternal RBCs	Cord RBCs	Maternal hair 1 cm from the scalp
Maternal RBCs	40	1.000		
Cord RBCs	40	0.908	1.000	
Each centimeter of maternal hair from the scalp (cm)				
1	40	0.858	0.899	1.000
2	40	0.841	0.863	0.949
3	39	0.792	0.816	0.914
4	39	0.792	0.812	0.892
5	39	0.822	0.847	0.904
6	39	0.808	0.822	0.878
7	38	0.758	0.798	0.853
8	37	0.727	0.785	0.836
9	35	0.723	0.793	0.849
Neonatal hair	21	0.819	0.868	0.946

Correlation coefficients were calculated using logarithmically transferred Hg concentrations.
All the correlation coefficients were statistically significant ($P < 0.01$).

However, the mean Hg concentrations of the maternal segmental hair from the scalp to the tip were fairly stable in the experiment group ($n = 40$); the increase and decrease in the Hg concentrations of maternal segmental hair throughout gestation differed considerably among individuals. The changes in MeHg exposure during the first or second trimester should be closely related to the amount of MeHg exposure during these periods. Additionally, the coefficient of variation of Hg concentrations in the segmental hair increased from the scalp toward the tip, which indicates the difficulty of estimating the MeHg exposure level in the first or second trimester by using the hair proximal to the scalp. Therefore, in addition to the analysis of Hg concentrations in cord blood or segmental hair proximal to the scalp, an analysis of the segmental maternal hair throughout gestation will be essential to obtain important information on MeHg exposure during the different sensitive windows or bolus MeHg exposure during gestation.

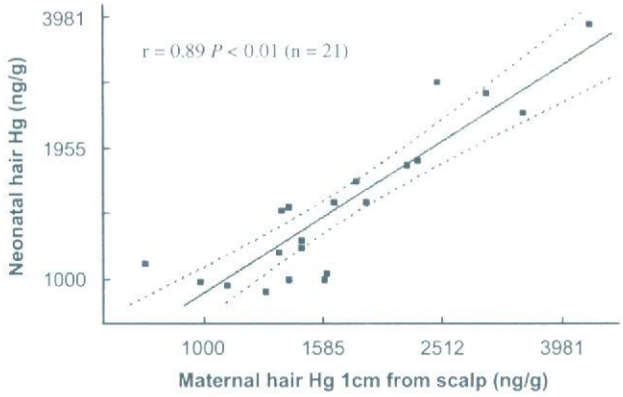

Fig. 3. Correlation between the Hg concentrations in the maternal hair and neonatal hair. Correlation coefficients were calculated by using logarithmically transferred Hg concentrations. The dotted lines represent 95% confidence intervals for the regression line.

Decrease in the mean Hg concentration of segmental maternal hair from the tip toward scalp was observed in populations consuming low amounts of fish in Canada (Morrissette et al., 2004). In this study on a Canadian population, informed consent was obtained at the beginning of gestation. It is reasonable to assume that obtaining informed consent around the time of conception caused a decline in the fish consumption during gestation, as is evidenced by the decreased fish-eating habits during pregnancy (Morrissette et al., 2004). In our experiment, informed consent was obtained immediately before parturition and the increase or decrease in Hg concentration of the hair might have corresponded to the individual changes in the amount or type of fish consumed since five mothers reported an increase and another five reported a decrease in their fish consumption during gestation.

The Hg concentrations in the segmental hair 5 and 6 cm from the scalp at 3 months after parturition showed strong (over 0.9) correlation coefficients with those in maternal RBCs, cord RBCs, and maternal hair 1 cm from the scalp at parturition. This may be explained by the faster hair growth rate (1.37 cm/month) in Japanese women (Saitoh et al., 1969), in comparison with that in English men which is 1.03 cm/month (Hislop et al., 1982). This also suggests that the time required for the incorporation of Hg from the blood into a growing hair and the appearance of hair above the scalp is not so long as the time (60 days) presumed by

Table 3
Geometric means and 25th–75th percentiles of Hg concentrations in each centimeter of the segmental maternal hair from the scalp toward the tip at 3 months after parturition and correlation coefficients among maternal RBCs, cord RBCs, and maternal hair 1 cm from the scalp at parturition

	N	Geometric mean (ng/g)	25% Value	75% Value	Correlation coefficients		
					Maternal RBCs	Cord RBCs	Maternal hair 1 cm from the scalp at parturition
Maternal RBCs	19	8.01			1.000		
Cord RBCs	19	13.03			0.932	1.000	
Maternal hair 1 cm from the scalp at parturition	19	1684	1178	2230	0.915	0.924	1.000
Each centimeter of maternal hair from the scalp at 3 months after parturition (cm)							
1	19	1627	1335	2230	0.6511	0.636	0.740
2	19	1598	1256	2599	0.7878	0.810	0.832
3	19	1518	1178	2396	0.8565	0.841	0.898
4	19	1530	1148	2422	0.8961	0.883	0.927
5	19	1534	1150	2092	0.9122	0.923	0.949
6	19	1564	1188	2091	0.9245	0.922	0.940
7	19	1480	1189	2147	0.8976	0.860	0.892
8	19	1460	1161	2166	0.8610	0.853	0.832
9	18	1460	1059	2059	0.8299	0.777	0.798

Correlation coefficients were calculated using logarithmically transferred Hg concentrations.
All the correlation coefficients were statistically significant ($P<0.01$).
Hg concentrations in cord RBCs were significantly higher than that in the maternal RBCs by paired t test ($P<0.01$).

Grandjean et al. (1992), and the hair proximal to the scalp at parturition is a good biomarker of fetal exposure to MeHg.

The Hg concentrations in neonatal hair also showed strong correlations with those in the maternal RBCs, cord RBCs, and maternal hair 1 cm from the scalp. This indicates that neonatal hair can also be used as a good biomarker of fetal exposure to MeHg. However, not all infants have hair and their hair is fine and light. For the same reasons, segmental analysis is not possible. Nevertheless, the Hg concentration in neonatal hair was similar to that of the maternal hair, unlike the relationship between the Hg concentrations in maternal RBCs and cord RBCs (1:1.6); this indicates a lower MeHg incorporation from fetal blood to fetal hair. Some studies have reported that the hairs of both mothers and neonates have similar Hg concentrations (Lindow et al., 2003; Razagui and Haswell, 2001), but others have reported a higher hair Hg concentration in the hair of neonates (Fujita and Takabatake, 1977; Mohan et al., 2005).

The findings of this study support the use of maternal hair Hg proximal to the scalp at parturition or neonatal hair as equally valuable as biomarkers of fetal exposure to MeHg at parturition. In addition, the segmental analysis of maternal hair during gestation can provide important information regarding the variations in fetal exposure to MeHg throughout various gestational periods.

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