Ophthalmic Outcomes of Congenital Toxoplasmosis Followed Until Adolescence

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KEY WORDS: congenital toxoplasmosis, long-term prognosis, ocular lesions, retinochoroiditis, burden of disease

ABBREVIATIONS
AF—amniotic fluid
AIC—Akaike information criterion
CI—confidence interval
CT—congenital toxoplasmosis
Ig—immunoglobulin
IQR—interquartile range
LL—log-linearity
PCR—polymerase chain reaction
PH—proportional hazards

WHAT’S KNOWN ON THIS SUBJECT: In children with congenital toxoplasmosis, ocular lesions can be detected and may relapse after birth despite pre- and postnatal treatment. Long-term ocular outcome beyond puberty and associated prognostic factors are unknown due to limited follow-up.

WHAT THIS STUDY ADDS: Our study in 477 patients with treated congenital toxoplasmosis who were followed up to 22 years indicated that new ocular lesions can be detected well into adolescence (with a cumulative probability at 18 years of almost 50%), but they rarely cause severe visual impairment.

abstract

BACKGROUND: Congenital toxoplasmosis (CT) can elicit severe damage to several organs, especially the eye, and may be manifested at birth or later. We assessed the long-term ocular prognosis in a cohort of congenitally infected children treated according to a standardized protocol and monitored for up to 22 years.

METHODS: This prospective study included confirmed cases of CT, which were identified by obligatory antenatal screening at the Lyon (France) reference center between 1987 and 2008. Data obtained through ocular examinations were recorded on a standardized form and confirmed by an independent external committee. Risk factors for retinochoroiditis were identified by using a multivariable Cox model and a flexible model that accounted for changes in the factor effects during follow-up.

RESULTS: A total of 477 of 485 infected live-born children were followed for a median of 10.5 years (75th percentile: 15.0 years). During the follow-up, 142 patients (29.8%) manifested at least 1 ocular lesion. Lesions were unilateral in 98 individuals (69.0%) and caused no vision loss in 80.6%. Lesions were first manifested at a median age of 3.1 (0.0–20.7) years. In 48 (33.8%) of the children, recurrences or new ocular lesions occurred up to 12 years after the appearance of the first lesion. Early maternal infection and confirmation of CT in children, prematurity, and nonocular CT lesions at baseline were associated with a higher risk of retinochoroiditis.

CONCLUSIONS: Although the consequences of CT are rarely severe in treated children, regular postnatal monitoring is nevertheless justified because of the lifelong persisting risk of new ocular manifestations. Pediatrics 2014;133:e601–e608

(Continued on last page)
Toxoplasmosis is a severe congenital infection, which can precipitate hydrocephalus, neurologic disorders, and ocular damage. Although most children are asymptomatic at birth, clinical manifestations can appear at any time. Reactivated infection is common and probably the most frequent cause of retinochoroiditis. When the macula is involved, the loss of visual function can be disabling.

Screening for Toxoplasma infection during pregnancy permits the early treatment of fetal infection. Indirect evidence indicates that this measure can reduce the short-term severity of toxoplasmosis. Whether the long-term outcome is thereby affected is unknown because no prospective data on the evolution beyond the sixth year of age in treated children are available. Such data would be invaluable in making follow-up and treatment decisions.

We assessed the long-term ocular prognosis and the associated prognostic factors in a cohort of patients identified by systematic prenatal screening, subjected to a standardized treatment before and after birth and monitored on a regular basis for up to 22 years.

**METHODS**

This prospective study included all first-born children with serologically confirmed congenital toxoplasmosis (CT). The disease was detected by maternal antenatal screening at the Croix-Rousse University Hospital, Lyon, France, between April 1987 and March 2008. Children in whom retinochoroiditis was detected before the serological confirmation of CT were excluded (Fig 1). The study included only individuals who had been followed for at least 6 months.

**Definition and Monitoring of Maternal Infection**

Maternal infection was identified by the universal antenatal screening of susceptible women, which is mandatory in France on a monthly basis since 1992 and has been performed in the Lyon area every 1 to 3 months since 1985. Maternal infection was defined as the change from a negative to a positive result for specific immunoglobulin (Ig) G antibodies or as a significant increase in IgG, occurring concomitantly with high IgM titers (see Supplemental Material). Gestational age at the time of maternal infection was estimated prospectively and thus was blinded with respect to the outcome.

**Definition and Monitoring of Congenital Infection**

Children were considered to be infected if at least 1 of the following criteria was satisfied: (1) a positive result in mice that had been inoculated with fetal blood or amniotic fluid (AF) or a positive polymerase chain reaction (PCR) in AF, (2) a positive result for specific IgM and/or IgA in fetal blood or peripheral blood after birth, (3) an increase in specific IgG during the first year of life or persistence of specific IgG (>5 IU/mL) detected by indirect immunofluorescence (Toxospot IF; bioMérieux, Marcy l’Étoile, France) after the first year of life.

Children were treated according to a standard protocol. Assessments at birth included cerebral ultrasonography, an ocular examination, and testing of neonatal blood for IgM, IgA, and IgG. All children underwent a pediatric check-up and an assessment of neurologic development, as well as serological testing for IgG and IgM, every 3 months for at least 1 year. Individuals with proven infection were treated for 12 months with pyrimethamine, first combined with sulfadiazine for 2 months, and then combined with sulfadoxine for 10 months. Neurologic, ophthalmologic, and serological examinations were repeated every trimester for the first 2 years, every semester during the third year, and annually thereafter without age limit. In the event of an active retinochoroiditis being detected at the end of the treatment period, a combination of pyrimethamine + sulfadoxine was administered for 3 months.

**Data Collection**

Information pertaining to each child was prospectively collected in a dedicated database during the routine visits. It included the estimated date of maternal infection, the results of the antenatal tests (ultrasonography, analyses of fetal blood and AF) and of the neonatal test (analysis of peripheral blood; neurologic, radiologic, and ophthalmologic evaluations), and details regarding the ante- and postnatal treatment regimens (date, type, and dosages). Missing data were supplied on request by the responsible consultant.

Ocular examinations were performed by ophthalmologists experienced in identifying ocular manifestations of toxoplasmosis and in examining children, and their findings were recorded on a standardized form. For children up to 3 years of age, Parinaud charts were implemented to assess visual acuity, which was age-matched according to standard norms. Best-corrected distance vision was assessed by using Snellen charts. The findings from both eyes assessed in mydriasis were confirmed at the end of the study period by an external data-monitoring committee. Blindness was defined according to the *International Classification of Diseases, 10th Revision*, as a corrected visual acuity of <1/20 (or corresponding visual field loss) in the better eye, and low vision corresponded to a best-corrected visual acuity of <3/10 but ≥1/20 in the better eye. In accordance with French legislation, parents were informed that data pertaining to their child may be used in research studies unless their consent is withheld. No refusal was registered. The study was...
Statistical Analyses

Descriptive statistics included means (±SD), medians (interquartile range [IQR]), and frequency distributions. Main analyses assessed the association between the risk of developing retinochoroiditis during the follow-up and the following factors: mother’s age at the time of delivery, gestational age (in weeks) and clinical signs at the time of maternal infection, duration of in utero treatment with pyrimethamine + sulfadiazine (in days), child’s gender, gestational age at birth, period of diagnostic (<1995 before PCR availability on AF versus ≥1995 when it became standard), age of the child at the time of CT diagnosis (assigned as “0” if CT was diagnosed at the time of or before birth), nonocular CT clinical signs at baseline, and specific IgM and IgA at birth. Time-to-event methods were used to account for variation in follow-up durations and timing of retinochoroiditis detection. In all analyses, baseline was either the date of birth, if CT had been diagnosed before or at birth, or the date of the postnatal diagnosis. The outcome was defined as the time interval between baseline and the first retinochoroiditis occurrence. Subjects who remained free of retinochoroiditis until the end of follow-up were censored at the end of the study (December 2010) or at the time of their last ophthalmologic examination. The cumulative probability for the retinochoroiditis occurrence was estimated by using the Kaplan-Meier method.

A series of separate univariate Cox proportional hazards (PH) models were used to select factors having at least marginally nonsignificant (P < .25) associations with the retinochoroiditis occurrence. All selected factors were then included in a Cox model to identify independent risk factors for the retinochoroiditis occurrence. The Cox model imposes a priori the assumption that the effects of prognostic factors do not change during the entire follow-up (PH assumption) and that the risk (the logarithm of the hazard) increases linearly with increasing value of a continuous covariate (log-linearity [LL] hypothesis). A flexible extension of the Cox model, validated in simulations, was also applied to account for possible departures from these assumptions that could cause the Cox model estimates to be biased and to miss important risk factors. This flexible model uses regression splines to jointly estimate time-dependent and nonlinear effects of continuous covariates, as well as time-dependent effects of categorical factors (see Supplemental Material for details). Likelihood ratio tests were used to assess the statistical significance of possible violations of the PH and/or the LL hypotheses for each covariate included in the multivariable model. To account for possible inflation type I errors, only P values <.04 were considered to be significant. The flexible model was also used to recheck for potential significant effects of those covariates that were initially excluded from the final analyses. The fit of the flexible model was compared with the
fit of the Cox model by using the Akaike information criterion (AIC)\(^8\) with an AIC reduction of \(\geq 4\) points indicating an important improvement of the model's predictive ability\(^9,16\).

Most analyses were performed by using Stata version 7.0 (StataCorp, College Station, TX), and the flexible models were estimated by using a customized program\(^8\). A 2-tailed \(P\) value \(< .05\) was considered to be significant.

RESULTS

Study Population

A total of 2361 consecutive pregnancies were monitored for primary toxoplasma infection between April 1987 and March 2008 at the Croix-Rousse Hospital, Lyon, France. Among the 485 infected live-born children, 477 (female-to-male ratio: 1:07) were followed for \(\geq 6\) months after the diagnosis of CT (Fig 1).

Most of the children were infected during the third trimester (Table 1). CT was diagnosed before birth in 27.9% of the infants and at birth in 48.4%. In the remaining 23.7%, the diagnosis was based on an increase in the levels of specific IgG during the first year of life (median: 5 months; IQR: 3–8 months). Most of the pregnant women (81.6%) had been treated with spiramycin alone (41.7%) or with spiramycin followed by pyrimethamine + sulfadoxine (32.3%; Table 1). The proportion of women treated with spiramycin alone decreased in more recent years as the practice of conducting PCR analyses on AF has increased. In the 88 untreated women, infection was diagnosed at delivery. Pyrimethamine and sulphonamides were administered postnatally for a median of 15 months (IQR: 12–19 months) in all but 7 of the 477 children.

Follow-up

At their last examination, the patients' ages ranged from 6 months to 22 years (median: 10.5 years; 75th percentile: 15.0 years). At this time, 65.2% (\(n = 311\)) were free of CT clinical manifestations, including 13 (median [IQR] follow-up time: 8.9 [1.7–11.4] years) of the 20 patients who had undergone treatment for \(\leq 3\) months. Most of those with subclinical infection had been infected after 1995 (63.3%) and had been born to mothers who had undergone seroconversion during the third trimester (74.8%).

Nonocular Lesions

Among the 166 children (34.8%) with at least 1 sign of CT at their last examination, nonocular lesions were detected in the first month of their life in 49 (10.3%) of the whole cohort; 59.2% born to mothers who seroconverted before 1996 and 51.0% infected in the second trimester, including the following: intracranial calcifications (\(n = 45\)); hydrocephalus (\(n = 5\)), with moderate psychomotor retardation in 3; splenomegaly (\(n = 4\)); hepatomegaly (\(n = 2\)); microphthalmia (\(n = 3\)); and microcephalus (\(n = 1\)). Seven of these children were treated for \(< 3\) months (including 2 with intracranial calcifications and 1 with hydrocephalus).

| TABLE 1 Characteristics of Mothers and Children (Lyon Cohort Study 1987–2010) |
|---------------------------------|----------|-----------------|-----------------|----------|
| Overall (\(n = 477\))          | 1995 or Earlier (\(n = 214\)) | Later Than 1995 (\(n = 263\)) | \(P\) |
| Mothers of children with congenital infection | | | |
| Age at time of paternal infection, mean ± SD, y | 28.8 ± 5.2 | 28.0 ± 5.6 | 28.5 ± 4.8 | < .0001 |
| Trimester of paternal infection, n (%) | | | |
| First | 24 (5.0) | 9 (4.2) | 15 (5.7) | .684 |
| Second | 130 (27.3) | 61 (28.5) | 69 (26.2) | |
| Third | 323 (67.7) | 144 (67.3) | 179 (68.1) | |
| Treatment during pregnancy, n (%) | | | |
| No treatment (diagnosis made at the time of delivery) | 88 (18.5%) | 32 (15.0%) | 56 (21.3%) | .076 |
| Treatment according to a standard protocol | | | |
| Spiramycin alone | 198 (51.2%) | 107 (58.8%) | 92 (44.4%) | .005 |
| Pyrimethamine + sulfadiazine | 31 (8.0%) | 7 (3.9%) | 24 (11.6%) | |
| Spiramycin, then pyrimethamine + sulfadiazine | 154 (38.6%) | 65 (33.7%) | 89 (43.0%) | |
| Pyrimethamine + sulfadiazine, then spiramycin | 5 (1.3%) | 3 (1.7%) | 2 (1.0%) | |
| Time after estimated date of seroconversion at which prenatal treatment was initiated, median (IQR), wk | | | |
| Infected children, n (gender ratio, female:male) | 477 (1.97) | 214 (0.91) | 263 (1.23) | .104 |
| Length of follow-up, median (IQR), y | 10.5 (5.0–15.0) | 15.4 (13.1–18.1) | 6.5 (3.0–10.0) | |
| Time at which congenital infection was diagnosed, median (IQR), months | 5 (3–8) | 5 (3–7) | 5 (2–8) | .670 |
| Before birth, n (%) | 133 (27.9) | 48 (22.4) | 85 (32.3) | .037 |
| At birth, n (%) | 231 (48.4) | 107 (51.7) | 124 (47.2) | |
| After birth, n (%) | 113 (23.7) | 59 (27.6) | 54 (20.5) | |
| Postnatal treatment, n (%) | | | |
| No treatment | 1 (0.2) | 1 (0.5) | 0 (0.0) | .449 |
| Treatment according to a standard protocol | | | |
| Pyrimethamine + sulfadiazine immediately after birth | 288 (60.4) | 87 (40.7) | 201 (76.4) | < .001 |
| Pyrimethamine-sulfadoxine after a body weight of 5 kg was attained | 435 (91.2) | 206 (96.3) | 229 (87.1) | .001 |
| Treatment with spiramycin alone | 6 (1.2) | 1 (0.5) | 5 (1.9) | .231 |
During follow-up, new neurologic manifestations were detected in 9 children: hydrocephalus (n = 3), with moderate psychomotor retardation in 1 child; isolated seizures in children with calcifications (n = 2); microphthalmia (n = 2); encephalopathy (n = 1); cortical atrophy (n = 1); and aphasia (n = 1). Most of these 9 children had been born to mothers who had undergone seroconversion before 1996 (n = 8) and in the second trimester of pregnancy (n = 6).

Ocular Lesions

In 142 (29.8%) of the patients, at least 1 retinochoroiditis was detected (Table 2). The lesions were monocular in 98 (69.0%) and caused no loss of vision in 80.6% of those 88 children in whom visual acuity was extant. Visual acuity was extant in 43 of the 44 patients with bilateral lesions and was bilaterally normal in 34 of the patients (72.7%) (Fig 2). Severe bilateral visual impairments were not encountered.

The initial lesion was detected during the first 2 weeks of life in 8 children (5.6%) only. These lesions were monocular in 2 cases and inactive at the time of detection in all but 1 instance. In the remaining 134 children with retinochoroiditis (94.4%), the first lesion was detected later after birth, at a median age of 4.2 years (range: 35 days to 20.7 years). When considering the 142 children with retinochoroiditis, the initial retinal lesions were detected after 7 months of age in 75% of the cases, after 3 years in 50%, after 8 years in 25%, after 10 years in 20%, and after 12.5 years in 10%. The cumulative probability for the development of retinochoroiditis with increasing time, accounting for the losses to follow-up, is presented in Fig 3. Two peaks in incidence were observed, at ∼7 years of age and between 11 and 13 years (see Supplemental Fig 4). Among the 20 children who were treated for <3 months, 5 experienced at least 1 retinochoroiditis (at 11.6 months, 1.7 years, 4.5 years, 5.6 years, and 6.7 years of age, respectively). The location was peripheral in all but 1 case. Initial lesions involving the macula were detected earlier (median: 17 months; IQR: 5.3 months to 7.3 years) than those located in the peripapillary region (median: 5.2 years; IQR: 6.8 months to 8.9 years; P = .0001). At their last examination (up to 12 years after the detection of the first lesion), 48 (33.8%) children had either experienced at least 1 recurrence of retinochoroiditis (n = 5), developed a new ocular lesion (n = 34), or experienced both conditions (n = 9).

**Prognostic Factors**

The multivariable Cox regression indicated that the risk of retinochoroiditis decreased significantly with higher gestational age at the time of maternal

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**Table 2: Prognostic Factors Associated With Ocular Lesions in Children With CT (Lyon Cohort Study 1987–2010)**

<table>
<thead>
<tr>
<th>Overall (%)</th>
<th>Ocular Lesion (%)</th>
<th>Univariate Analysis</th>
<th>Cox Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>477</td>
<td>29.8</td>
<td></td>
</tr>
<tr>
<td>Mothers of children with congenital infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1995</td>
<td>214</td>
<td>42.1</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;1995</td>
<td>263</td>
<td>19.8</td>
<td>0.78</td>
</tr>
<tr>
<td>Gestational age at the time of infection, median (IQR), wk</td>
<td>28 (23–32)</td>
<td>26 (20–32)</td>
<td>0.97</td>
</tr>
<tr>
<td>Infected children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>230</td>
<td>29.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>247</td>
<td>30.4</td>
<td>1.08</td>
</tr>
<tr>
<td>Gestational age at birth, median (IQR), wk</td>
<td>38 (37–39)</td>
<td>38 (36–39)</td>
<td>0.85</td>
</tr>
<tr>
<td>≤34 weeks of gestation</td>
<td>26</td>
<td>30.8</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;34 weeks of gestation</td>
<td>451</td>
<td>28.7</td>
<td>0.90</td>
</tr>
<tr>
<td>Time at which congenital infection was diagnosed (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before or at birth</td>
<td>364</td>
<td>30.2</td>
<td>1.00</td>
</tr>
<tr>
<td>≤5 months of age</td>
<td>62</td>
<td>35.5</td>
<td>1.89</td>
</tr>
<tr>
<td>&gt;5 months of age</td>
<td>51</td>
<td>19.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Presence of at least 1 other symptom of CT at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>428</td>
<td>27.4</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>49</td>
<td>53.1</td>
<td>2.72</td>
</tr>
</tbody>
</table>

RR, relative risk.

* Data are n unless otherwise indicated.

* Data are percentages unless otherwise indicated.

AIC = 1556.11.
infection and with older age at the time of CT diagnosis (Table 2). No significant violations of the linearity hypothesis were detected for either variable ($P = .442$ and .057, respectively), confirming a risk reduction for retinochoroiditis of 3% for each additional week of gestational age at the time of maternal infection (95% confidence interval [CI]: 1%–5%) and of 6% for each additional month until CT postnatal diagnosis (95% CI: 0%–12%). For other prognostic factors, however, the flexible model detected significant violations of the LL and PH assumptions and improved the prediction of the outcomes ($\text{AIC} = 1551.0$) compared with the Cox model ($\text{AIC} = 1556.1$). Significant nonlinear ($P < 10^{-3}$) and time-dependent effects were detected for gestational age at birth, with children born at term having a reduced risk of retinochoroiditis, which only lasted between 2 and 10 years (data not shown). Furthermore, the risk increase associated with nonocular CT lesions at baseline lasted only until the age of $\sim 6$ years ($P = .020$ for the test of nonproportionality; data not shown).

**DISCUSSION**

To date, the long-term prognosis of CT has remained a matter of speculation. In the available publications related to patients who had been treated after birth, the follow-up periods were short, and the reported data do not provide answers to many of the questions that arise during the management of CT.

After a follow-up of up to 22 years, retinochoroiditis developed in nearly 30% of CT patients despite pre- and postnatal treatment. Lesions were often detected late, with 2 peaks in incidence at 7 and 13 years of age. They were mostly unilateral and caused little or no visual impairment, despite the occurrence of secondary events in every third individual up to 12 years after the first manifestation. Another reassuring
circumstance was that the neurologic lesions were rare and seldom gave rise to severe handicaps in children born after 1995. Hence, our data afford no indications for a termination of pregnancy in the absence of severe fetal abnormalities. Recently, we reported that the improvements in antenatal diagnosis and treatment that were effected in 1995 led to a decrease in the severity of CT at 3 years of age. Although no such period effect was observed for the long-term risk of developing retinochoroiditis, a possible impact of the treatment cannot be excluded. Indeed, a comparison of the incidences of ocular manifestations in the current study with previously published data related to untreated patients confirms the beneficial influence of CT management. It is noteworthy that in such a large cohort of patients, neither severe bilateral visual impairment nor severe neurologic damage was encountered. However, neither a prenor a postnatal course of treatment completely suppressed the ocular evolutive process. It now appears that lesions are encountered in almost 30% of cases up to a median age of 12 years, with a cumulative probability at 18 years of close to 50%. Only a few lesions were detected at birth. Half (50%) of the initial lesions were detected after 3 years of age and as late as 20 years. Similar findings have been reported by Berrebi et al: 28 of the 107 children followed for >1 year manifested at least 1 ocular lesion after a median follow-up of 7.8 years.

The shorter monitoring periods probably account for the findings of Faucher et al who reported the occurrence of retinal lesions in only 19% of the 127 children after a median follow-up of 4 years, as well as for those of Tan et al who found a 17% incidence of retinal lesions in 284 children after a follow-up of 4.8 years. In addition, the use of real-time data and the limited cooperation capabilities of younger children could have led to a delay in the detection of some lesions, particularly those located peripherally, which would be ultimately revealed in 1 of the numerous follow-up examinations. However, a confirmation of this circumstance would serve only to reinforce our belief that the risk of the development of retinochoroiditis tends to be underestimated.

The prolonged and higher risk of developing retinochoroiditis needs to be taken into account in any assessment of prenatal screening efficiency. It should also encourage an extension of the follow-up time beyond the traditionally recommended age limit of 5 to 12 years, because our data provide evidence that the risk of ocular affection persists throughout life, even in treated children. In our experience, this extended follow-up is perceived by adult patients as reassuring and beneficial.

In the current study, the longer follow-up times allowed us to assess the long-term impact of several prognostic factors that were identified in the same cohort of patients at an earlier stage and that have been likewise recognized by other investigators. Gender had no significant impact. The decreasing risk of developing retinochoroiditis with increasing gestational age at the time of maternal infection and with each additional month until CT postnatal diagnosis in children was confirmed. However, the negative impact of birth before the 39th week of pregnancy and of nonocular signs of infection at baseline appear to wane after the sixth to tenth year of life.

CONCLUSIONS

Our data based on representative and unselected cases indicate that the consequences of CT are rarely severe in French early-treated patients, but that annual postnatal check-ups should be continued throughout puberty to identify new lesions. The findings thereby gleaned would moreover help to improve our understanding of the complications of CT, of temporal peaks in its incidence, and thus generally of the long term evolution the disease.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of Faiza Senni in the management of data and the statistical advice of Dr Amel Mahboubi.

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Pediatrics 2014;133;e601; originally published online February 17, 2014; DOI: 10.1542/peds.2013-2153

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