Clinical research

Familial recurrence of congenital heart disease in patients with ostium secundum atrial septal defect

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Aims Ostium secundum atrial septal defect (osASD) is one of the most common cardiac malformations. Few data are available on the familial recurrence of congenital heart disease (CHD), in particular, in a large group of patients with isolated osASD. The aim is to investigate the familial recurrence of CHD in up to third-degree relatives from a large sample of consecutively enrolled patients with osASD, taking into account the influence of degree of relatedness (as number of relatives).

Methods and results From January 1998 to December 2002, we enrolled 583 patients with osASD and 408 healthy subjects, referred to our tertiary centre. We hypothesized that a positive family history required at least one relative with CHD to constitute a risk factor. In this model of analysis, the null hypothesis is a similar familial history between cases and controls. Among 583 patients with osASD, 109 (19%) had at least one relative with CHD. Among the 408 healthy subjects studied, only 23 (6%) had a family history of CHD. A familial recurrence of CHD was demonstrated in 72 of 312 (23%) patients with isolated osASD and in 37 of 271 (13.6%) patients with non-isolated osASD. Familial recurrence of isolated osASD was demonstrated in 22 of 312 patients (7%) with an isolated osASD and only in six of 271 patients (2.2%) with non-isolated osASD. The familial recurrence risk of isolated osASD in patients with isolated osASD was higher in sibs, especially in sisters (33.3%).

Conclusion This study underscores the role of genetic factors in the determination of CHD, particularly osASD. Our results could represent the basis for further studies to calculate a ‘value of family history’ to adapt the familial recurrence to the real size of each family group. In this way, we could select families with a ‘tendency’ to develop CHD, particularly osASD. In these families, we could analyse the genetic pattern to establish abnormalities and the bases of CHD.

KEYWORDS
Congenital heart disease; Atrial septal defect; Familial recurrence

Introduction

Ostium secundum atrial septal defect (osASD) is one of the most common cardiac malformations,1–8 which occurs as an isolated anomaly in 10% of individuals9 with congenital heart disease (CHD).

Like other CHDs, osASD is caused by the interaction of hereditary and environmental factors.10–25 Moreover, recent studies have demonstrated that isolated or syndrome CHD can be associated with single gene defects.26–29 Potential environmental risk factors for CHD are parity and previous pregnancies, advanced maternal age, miscarriages, maternal alcohol consumption, maternal smoking, rubella virus infection, and maternal exposure to chemicals in the workplace.9,18–20,22

We recently suggested the influence of genetic and environmental factors during pregnancy on the higher rate of recurrence and concordance of CHD in a population of dizygotic twins than in non-twin siblings.30

Several case reports have described the familial distribution of osASD.13,23,31–33 Most of them included patients with karyotype aberrations. Limited data, however, are available on the familial recurrence of CHD in a large group of patients with osASD.

Until now, the main large population study has only investigated the nuclear family (parents and sibs),9 and the recurrence rate of CHD in patients with isolated osASD was 4.9%. The study sample with osASD was small (only 61 cases), and there was no match with a control group of healthy subjects.

The aim of our study was to investigate the familial recurrence of CHD in up to third-degree relatives (parents, siblings, cousins, aunts, uncles, and grandparents) in a large sample of consecutively enrolled patients with osASD.
Methods

From January 1998 to December 2002, 2478 patients with CHD were referred to our tertiary centre. We enrolled 583 patients with osASD (cases) (239 male; 344 female) and 408 healthy subjects (controls) (219 male; 189 female), referred to our tertiary centre for suspected CHD.

All the 991 patients (583 cases and 408 controls) underwent clinical, EKG, and echocardiographic examinations.

The dimensions and the physiopathological value of the osASD and the clinical features of the patients with isolated or non-isolated osASD (cases) were not used as criteria to identify groups. The recurrence of CHD, in particular, of isolated osASD was considered in 583 patients (of 2478 with CHD) with isolated or non-isolated osASD and in 408 healthy subjects.

There was no relationship between cases and controls; cases with a demonstrated blood relationship with other patients in this study were excluded and considered only for evaluation of familial recurrence. The same procedure of inclusion was also applied to the control group. Patients with syndromes were not considered in this study.

To investigate the recurrence of CHD in their first-to-third-degree relatives and to exclude maternal exposure to the known potential risk factors, a structured interview with both the parents of the affected patients and the parents of the control subjects was conducted.

Relatives (of cases and controls) with CHD followed in other cardiological centres were then submitted to clinical, EKG, and echocardiographic examination in our division to confirm the previous diagnosis.

No clinical or instrumental evaluations were performed for relatives (of cases and controls) identified as healthy in the structured interview.

For cases and controls, asymptomatic relatives with unknown functionally normal bicuspid aortic valve, relatives with an unidentified or poorly documented spontaneously closed small interventricular muscular septal defect, and relatives below 1 year of age with a small isolated interatrial defect or patent ductus arteriosus could be missed and, therefore, by mistake, considered healthy subjects.

Cases and controls were compared for maternal age, previous pregnancies, previous miscarriages and previous abortions, gestational age, and relatives’ education. These factors are described as potential risk factors for CHD, but we do not think that they can influence the familial recurrence risk of CHD. Moreover, cases and controls were compared for familial composition as total number of subjects for each degree of relatedness; this is one of the main factors that could affect a different familial recurrence risk of CHD.

The recurrence risk of CHD was considered for each degree of relatedness (first to third) in relatives of patients with isolated or non-isolated osASD, in relatives of patients with isolated osASD, and in relatives of controls.

Moreover, the recurrence risk of isolated osASD was measured for each degree of relatedness (first to third) in patients with isolated osASD.

The echocardiographic evaluation was performed by experienced paediatric cardiologists with Aloka 5500 and Acuson Sequoia C256 using 2.5–7.0 MHz phased-array transducers. Combined two dimensional and M-mode were obtained from multiple tomographic planes. Spectral Doppler and colour Doppler flow imaging were performed on all patients. All images were recorded on a super VHS videotape.

The hypothesis of our study was to consider a positive family history (at least one relative with CHD) as a risk factor for CHD. This model of analysis needs a similar family composition (size and structure) for cases and controls; a group with more relatives has a greater risk of positive family history. In this model of analysis, the null hypothesis is a similar family history.

The familial incidence of CHD was established in cases and controls by comparing the two groups for each degree of relatedness (first to third) using an adjusted logistic regression. This test was selected to evaluate the influence of the degree of relatedness on the familial recurrence of CHD. The same test was applied to measure the familial recurrence of CHD in patients with isolated osASD and in patients with non-isolated osASD and the familial recurrence of isolated osASD in patients with isolated osASD and in patients with non-isolated osASD.

Statistical analysis was carried out by SPSS (Statistical Package for Social Sciences, Rel 10.1; SPSS Inc., 444 North Michigan Avenue, Chicago, IL 60611, USA). Continuous data were expressed as mean (SD). The two-sided Student’s t-test for unpaired data was used to estimate the difference between mean values. Qualitative data were expressed as percentages; statistical analysis was performed with odds ratio (95% confidence limits); the statistical significance was established with $\chi^2$ test (two-tailed).

A $P$-value of $<0.05$ was considered statistically significant.

Results

The general characteristics of the study population are described in Table 1. The defects associated with osASD in patients with non-isolated osASD and the related frequencies are described in Table 2.

There were no significant differences for potential risk factors of CHD between cases and controls (Table 1). The mean age in cases (4.81 years) and in controls (4.62 years) was comparable ($P = 0.469$). All the patients were born and lived in the Campania region. Cases and controls were compared by family composition (such as size and structure); the two groups were similar in composition and total number of subjects for each degree of relationship (Table 1).

<table>
<thead>
<tr>
<th>Table 1 General characteristics and potential risk factors in the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n = 583) Controls (n = 408) P-value</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Family members (n)</td>
</tr>
<tr>
<td>Maternal age (years)</td>
</tr>
<tr>
<td>Mothers with one or fewer pregnancies (n)</td>
</tr>
<tr>
<td>Mothers with more than two previous miscarriages (n)</td>
</tr>
<tr>
<td>Mothers with more than two previous abortions (n)</td>
</tr>
<tr>
<td>Assisted fecundation (%)</td>
</tr>
<tr>
<td>Mothers with primary education (n)</td>
</tr>
<tr>
<td>Fathers with primary education (n)</td>
</tr>
</tbody>
</table>

Cases, subject with isolated or non-isolated osASD; controls, healthy subjects; ne, not evaluable.
From January 1998 to December 2002, among 2478 patients with CHD referred to our tertiary centre for a suspect of CHD, there were 583 with isolated or non-isolated osASD. Of 583, 109 (18.7%) had at least one relative (first to third degree) with CHD.

Among the 408 healthy subjects studied, only 23 (6%) had a family history of CHD. In particular, 6% had the risk of positive familial history of CHD in the control group. In Table 3, we reported the results of the adjusted logistic regression analysis for the evaluation of the incidence of CHD in cases and controls, taking into account the influence of the size of each degree of relatedness on the familial recurrence of CHD. The recurrence of CHD in cases was significantly higher than the incidence of CHD in controls for each degree of relationship (first to third).

We also compared the familial recurrence of CHD between patients with an isolated osASD and patients with a non-isolated osASD: a familial recurrence of CHD was demonstrated in 72 of 312 (23%) patients with isolated osASD and in 37 of 271 (13.6%) patients with non-isolated osASD. The recurrence of CHD for each degree of relatedness was not statistically different between the two groups when adjusted for each degree of relationship (Table 4).

Moreover, we investigated the familial recurrence of isolated osASD in patients with isolated osASD and in those with non-isolated osASD (Table 5): 22 patients (7%) of 312 with an isolated osASD had a family recurrence of isolated osASD; only six patients of 271 (2.2%) with non-isolated osASD had a familial recurrence of isolated osASD. The recurrence of isolated osASD for each degree of relatedness was not statistically different between the two groups when adjusted for each degree of relatedness.

Furthermore, we described the familial recurrence risk of CHD for each degree of relationship (first to third) in patients with isolated or non-isolated osASD and in patients with isolated osASD (Table 6). The familial recurrence risk of CHD in patients with isolated or non-isolated osASD was higher in the first degree of relationship when compared with controls (OR: 3.25; CI 95%: 1.68 < OR < 6.40): it was higher in sibs, particularly in brothers (8.3% in brothers of patients with isolated or non-isolated osASD; 10.8% in brothers of patients with isolated osASD).

In the same table, we also described the familial recurrence risk of isolated osASD for each degree of relatedness (first to third) in patients with isolated osASD. The familial recurrence risk of isolated osASD for each degree of relatedness (first to third) in patients with isolated osASD (Table 6) was higher in sibs, especially in sisters (33.3%). Moreover, a high recurrence risk of isolated osASD in mothers of patients with isolated osASD was observed (22.7%). In addition, as we compared the three groups, the familial recurrence risk of isolated osASD in relatives of patients with isolated osASD was higher than the familial recurrence risk of CHD in patients with isolated or non-isolated osASD and in patients with isolated osASD, for each degree of relatedness (first to third).

**Discussion**

This is the largest published series of patients with osASD and the first study in which a familial recurrence of CHD is demonstrated in patients with osASD. We were unable to demonstrate a significantly higher familial recurrence of isolated osASD in patients with isolated osASD than in patients with non-isolated osASD, but our results were at the limit of significance for the first degree of relatedness ($P = 0.0634$). This was probably due to the relatively low number of
patients in relation to the low frequency of the disease in
the general population.

Until now, the main large population study has investi-
gated the familial recurrence of CHD only in the nuclear
family (parents and sibs);9 the recurrence rate of CHD in
patients with isolated osASD was 4.9%. In the previous
study, the sample with osASD was small (only 61 cases)
and there was no match with a control group of healthy
subjects.

Here, we investigated the familial recurrence of CHD in up
to third-degree relatives (parents, siblings, cousins, aunts,
uncles, and grandparents), taking into account the influence
of the size of each degree of relatedness on the familial
recurrence of CHD. Moreover, we compared our population
of osASD patients with a large sample of consecutively
enrolled healthy subjects.

In a recent report,30 we suggested the role of genetic
and environmental factors during pregnancy in the higher
recurrence and concordance of CHD in a population of
dizygotic twins than in non-twin siblings.

Here, we investigated the familial recurrence of CHD in a
large number of subjects with osASD; the main finding of our
study was the higher recurrence rate of CHD in patients with
osASD than in controls for each degree of relatedness.

The familial recurrence of CHD in patients with non-
isolated osASD was lower than in patients with isolated
osASD. Patients with non-isolated osASD probably represent
a different genetic or genetic–environmental pathophysiolo-
gical mechanism (perhaps different genes coming into play
with environmental factors).

In our study, the familial recurrence risk was more evident
in first-degree relatives. In particular, the familial recur-
cence risk of isolated osASD in patients with isolated osASD
was higher in sibs, especially in sisters (33.3%). Moreover,
a high recurrence risk of isolated osASD in mothers of
patients with isolated osASD was observed (22.7%).

This result was already suggested in previous studies.
Particularly, Nora and Nora34 reported that the recurrence
risk of CHD in offspring, when one parent was affected,
was 3.5%; the recurrence risk of CHD in offspring of
mothers with osASD was 4.6%.25

Cases with isolated osASD could have a major recurrence
of isolated osASD for the same genetic abnormality. Normal embryological events depend on a long sequence
of stages that begins at conception. The frequency of an
occasional mistake depends both on the quality of the
instructions (genetic factors) and on the environmental
factors.

This study highlights the role of genetic factors in the
determination of CHD, particularly osASD.

Little is known about the genetic mechanism underlying
the different cardiac phenotypes.26,27 The linkage analysis

| Table 3 | Familial recurrence of CHD in the study population and in the control group taking into account the size of each degree of
<table>
<thead>
<tr>
<th>Parameters</th>
<th>B</th>
<th>SE</th>
<th>Wald 95% CI</th>
<th>df</th>
<th>$\chi^2$</th>
<th>P-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.3880</td>
<td>0.320</td>
<td>-1.0151</td>
<td>0.2390</td>
<td>1</td>
<td>1.4715</td>
<td>0.2251</td>
</tr>
<tr>
<td>First degree of relatedness</td>
<td>1.0493</td>
<td>0.345</td>
<td>0.3724</td>
<td>1.7262</td>
<td>1</td>
<td>9.2315</td>
<td>0.0024</td>
</tr>
<tr>
<td>Second degree of relatedness</td>
<td>1.1505</td>
<td>0.510</td>
<td>0.1504</td>
<td>2.1506</td>
<td>1</td>
<td>5.0841</td>
<td>0.0241</td>
</tr>
<tr>
<td>Third degree of relatedness</td>
<td>1.2878</td>
<td>0.376</td>
<td>0.5501</td>
<td>2.0254</td>
<td>1</td>
<td>11.7088</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

First degree of relatedness, parents and siblings; second degree of relatedness, aunts, uncles, and grandparents; third degree of relatedness, cousins.

| Table 4 | Familial recurrence of CHD in patients with isolated osASD and in patients with non-isolated osASD, taking into account the size of
each degree of relatedness
<table>
<thead>
<tr>
<th>Parameters</th>
<th>B</th>
<th>SE</th>
<th>Wald 95% CI</th>
<th>df</th>
<th>$\chi^2$</th>
<th>P-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.4735</td>
<td>0.3854</td>
<td>-1.2288</td>
<td>0.2819</td>
<td>1</td>
<td>1.5091</td>
<td>0.2193</td>
</tr>
<tr>
<td>First degree of relatedness</td>
<td>0.4995</td>
<td>0.3149</td>
<td>-0.1177</td>
<td>1.1167</td>
<td>1</td>
<td>2.5163</td>
<td>0.1127</td>
</tr>
<tr>
<td>Second degree of relatedness</td>
<td>0.5572</td>
<td>0.4808</td>
<td>-0.3851</td>
<td>1.4996</td>
<td>1</td>
<td>1.3433</td>
<td>0.2465</td>
</tr>
<tr>
<td>Third degree of relatedness</td>
<td>0.5405</td>
<td>0.3204</td>
<td>-0.0875</td>
<td>1.1684</td>
<td>1</td>
<td>2.8453</td>
<td>0.0916</td>
</tr>
</tbody>
</table>

First degree of relatedness, parents and siblings; second degree of relatedness, aunts, uncles, and grandparents; third degree of relatedness, cousins.

| Table 5 | Familial recurrence of isolated osASD in patients with isolated osASD and in patients with non-isolated osASD, taking into account
the size of each degree of relatedness
<table>
<thead>
<tr>
<th>Parameters</th>
<th>B</th>
<th>SE</th>
<th>Wald 95% CI</th>
<th>df</th>
<th>$\chi^2$</th>
<th>P-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.4053</td>
<td>0.3855</td>
<td>1.1608</td>
<td>0.3502</td>
<td>1</td>
<td>1.1055</td>
<td>2.9131</td>
</tr>
<tr>
<td>First degree of relatedness</td>
<td>1.4761</td>
<td>0.7951</td>
<td>-0.0823</td>
<td>3.0345</td>
<td>1</td>
<td>3.4464</td>
<td>0.0634</td>
</tr>
<tr>
<td>Second degree of relatedness</td>
<td>0.5674</td>
<td>1.3342</td>
<td>-3.1824</td>
<td>2.0477</td>
<td>1</td>
<td>0.1808</td>
<td>0.6707</td>
</tr>
<tr>
<td>Third degree of relatedness</td>
<td>1.0654</td>
<td>0.6267</td>
<td>-0.1628</td>
<td>2.2937</td>
<td>1</td>
<td>2.8906</td>
<td>0.0891</td>
</tr>
</tbody>
</table>

First degree of relatedness, parents and siblings; second degree of relatedness, aunts, uncles, and grandparents; third degree of relatedness, cousins.
and positional cloning have allowed investigators to identify a small number of disease-related genes.35,36

Our results lay the foundation for further studies to calculate the 'value of family history' and to adapt the familial recurrence to the real size of each family group. In this way, we could select the families with a 'tendency' to develop CHD, particularly osASD; in these families, we could analyse the genetic pattern to establish these abnormalities.

The distribution analysis of CHD could provide a useful tool to evaluate the role of genetic and environmental factors in the development of heart disease, thus allowing us to understand the underlying mechanisms for normal and abnormal development of cardiac structures. The analysis of familial and environmental association with CHD could provide more accurate knowledge of the mechanisms responsible for CHD and allow early treatment to modify the natural course of the disease.

Study limitation

The familial recurrence of CHD was established by an 'interview'. A study carried out with an 'interview' could underestimate the familial incidence of both the cases and the controls. This 'mistake' would depend on the missing detection of asymptomatic relatives with CHD and on the possible voluntary slip of affected relatives.

In contrast, a study based on clinical, EKG, and echocardiographic examinations of all members of the 991 families (583 cases and 408 controls, over 20 000 subjects) would be expensive and time consuming.

The control group of healthy subjects could be a selected cohort, referred to our tertiary centre for suspected CHD. Our goal will be to take a stratified sample of the whole population.

Consanguinity cannot be excluded in the cases or controls. This inaccuracy would not weaken the hypothesis of our study: the role of genetic factors in determining CHD, particularly osASD.

References


Table 6 Recurrence risk of CHD in relatives of patients with isolated or non-isolated osASD; in relatives of patients with isolated osASD; in relatives of controls; recurrence risk of isolated osASD in relatives of patients with isolated osASD

<table>
<thead>
<tr>
<th>Family Relationship</th>
<th>PFR of CHD in patients with isolated or non-isolated osASD (n = 583)</th>
<th>Recurrence risk (%)</th>
<th>PFR of CHD in patients with isolated osASD (n = 312)</th>
<th>Recurrence risk (%)</th>
<th>PFR of CHD in patients with isolated osASD (n = 22)</th>
<th>Recurrence risk (%)</th>
<th>PFR of CHD in controls (n = 408)</th>
<th>Recurrence risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers</td>
<td>14/583</td>
<td>2.4</td>
<td>8/312</td>
<td>2.6</td>
<td>5/22</td>
<td>22.7</td>
<td>2/408</td>
<td>0.5</td>
</tr>
<tr>
<td>Fathers</td>
<td>4/583</td>
<td>0.7</td>
<td>2/312</td>
<td>0.6</td>
<td>0/22</td>
<td>0</td>
<td>1/408</td>
<td>0.2</td>
</tr>
<tr>
<td>Brothers</td>
<td>26/315</td>
<td>8.3</td>
<td>19/176</td>
<td>10.8</td>
<td>2/13</td>
<td>15.4</td>
<td>5/183</td>
<td>2.7</td>
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<tr>
<td>Sisters</td>
<td>14/302</td>
<td>4.6</td>
<td>11/178</td>
<td>6.2</td>
<td>6/18</td>
<td>33.3</td>
<td>4/172</td>
<td>2.3</td>
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<tr>
<td>Maternal male</td>
<td>2/583</td>
<td>0.3</td>
<td>2/312</td>
<td>0.6</td>
<td>2/22</td>
<td>9</td>
<td>0/408</td>
<td>0</td>
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<tr>
<td>Grandparents</td>
<td>0/583</td>
<td>0</td>
<td>0/312</td>
<td>0</td>
<td>0/22</td>
<td>0</td>
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<tr>
<td>Paternal male</td>
<td>2/583</td>
<td>0.3</td>
<td>1/312</td>
<td>0.3</td>
<td>0/22</td>
<td>0</td>
<td>0/408</td>
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<tr>
<td>Grandparents</td>
<td>1/583</td>
<td>0.2</td>
<td>0/312</td>
<td>0</td>
<td>0/22</td>
<td>0</td>
<td>1/408</td>
<td>0.2</td>
</tr>
<tr>
<td>Paternal uncles</td>
<td>4/937</td>
<td>0.4</td>
<td>2/583</td>
<td>0.3</td>
<td>0/37</td>
<td>0</td>
<td>2/660</td>
<td>0.3</td>
</tr>
<tr>
<td>Maternal uncles</td>
<td>4/937</td>
<td>0.4</td>
<td>3/495</td>
<td>0.6</td>
<td>1/37</td>
<td>2.7</td>
<td>2/642</td>
<td>0.3</td>
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<td>Paternal uncles</td>
<td>3/1050</td>
<td>0.5</td>
<td>3/564</td>
<td>0.5</td>
<td>0/59</td>
<td>0</td>
<td>3/688</td>
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<tr>
<td>Maternal cousins</td>
<td>25/2797</td>
<td>0.9</td>
<td>17/1628</td>
<td>1</td>
<td>5/124</td>
<td>4</td>
<td>4/1700</td>
<td>0.2</td>
</tr>
<tr>
<td>Paternal cousins</td>
<td>31/3176</td>
<td>1</td>
<td>20/1616</td>
<td>1.2</td>
<td>9/185</td>
<td>4.9</td>
<td>6/2087</td>
<td>0.3</td>
</tr>
<tr>
<td>Total first-degree</td>
<td>58/1783</td>
<td>3.3</td>
<td>40/354</td>
<td>11.3</td>
<td>13/75</td>
<td>17.3</td>
<td>12/1171</td>
<td>1</td>
</tr>
<tr>
<td>relatives</td>
<td>Total second-degree relatives</td>
<td>21/6377</td>
<td>0.3</td>
<td>14/3441</td>
<td>0.4</td>
<td>3/257</td>
<td>1.2</td>
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