Prognostic Significance of Chromosome 17p Deletions in Childhood Primitive Neuroectodermal Tumors (Medulloblastomas) of the Central Nervous System

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ABSTRACT

Deletions in the short arm of chromosome 17 (17p) are the most common genetic abnormality in primitive neuroectodermal tumors of the posterior fossa/medulloblastoma (PNET/Mb). The biological consequences of these deletions are not known for children with PNET/Mb; however, the presence of a tumor suppressor gene located in 17p, distinct from p53, has been implicated in tumorigenesis. Two recent studies suggest that 17p deletions in PNET/Mb are associated with a poor prognosis. To address this question, we identified deletions of chromosome 17p by cytogenetic and/or molecular biology methods in tumor biopsy samples from 56 patients with PNET/Mb. Associations between clinical characteristics or survival outcomes and 17p status were examined by multivariate analysis. Forty-one percent of PNET/Mb cases had a deletion of 17p. No significant association was found between 17p deletion and shorter survival duration or higher metastatic stage. Multivariate analysis did not find independent prognostic significance for 17p deletions after accounting for the effects of significant clinical variables. A larger study of the prognostic value of 17p deletion should be considered; however, clinical use of this factor to distinguish high-risk from standard-risk PNET/Mb populations is not warranted at this time.

INTRODUCTION

Clinical prognostic factors play a major role in therapeutic decisions for children with PNET/Mb. Single-institution and collaborative group studies have identified clinical factors such as metastatic stage, patient age, and extent of tumor resection as characteristics that have independent prognostic significance for PNET/Mb survival outcomes (1-4). These factors are currently used to distinguish children with a high risk of PNET/Mb recurrence (e.g., age < 4 years, large postoperative residual tumor, or leptomeningeal metastasis) from those with a standard risk. Based on this classification, patients with high-risk PNET/Mb receive more intensive treatment than those with standard-risk disease. Because the quality of life for long-term survivors of PNET/Mb is often severely impaired by cognitive deficits and other late effects of treatment, recent therapeutic trials designed to reduce late treatment effects rely on clinical prognostic factors for appropriate patient selection (5).

In contrast to clinical prognostic factors, most efforts to identify biological prognostic factors for PNET/Mb have been inconclusive. In other childhood malignancies, tumor biology characteristics add to the prognostic power of established clinical factors, identify clinically relevant subsets of high-, intermediate-, or low-risk patients, or may provide insight into patterns of treatment response, resistance, or metastatic potential. Neuroblastoma biological factors such as N-myc amplification or deletion of chromosome 1p have independent prognostic significance that equals or exceeds any of the clinical prognostic factors for this tumor (6, 7). For PNET/Mb, various tumor characteristics have been evaluated for potential clinical significance including ploidy, mitotic index, differentiation lineage, and Trk expression (8-15). The conclusions from many of these studies are either contradictory or based on an insufficiently large sample size to establish the independent prognostic significance of the candidate biological factor when the effects of other known prognostic variables are controlled. Several recent studies report that deletions of chromosome 17p, which are found in up to 50% of all cases of PNET/Mb, predict a poor survival outcome (16-19). However, conclusions from these studies are based on unspecified tumor sample selection criteria, and potentially relevant clinical characteristics of the patient populations were not described. At present, no published study

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3 The abbreviations used are: PNET, primitive neuroectodermal tumor; Mb, medulloblastoma; FISH, fluorescence in situ hybridization; RFS, recurrence-free survival.
has established the independent prognostic significance of 17p deletions in PNET/Mb.

We evaluated PNET/Mb biopsy samples from 56 children by use of cytogenetic methods, FISH, and molecular genetic techniques to determine loss of heterozygosity and detect deletions in chromosome 17p. The results of cytogenetic and molecular studies of chromosome 17 were then compared with patient survival outcomes and with clinical factors of independent prognostic significance. In this study, the largest evaluation of the prognostic significance of 17p deletion in PNET/Mb, we did not find significant differences in survival between patients with or without 17p deletions. Furthermore, when corrected for the effects of independent clinical prognostic factors by multivariate analysis, 17p deletion status did not have independent prognostic significance.

PATIENTS AND METHODS

Clinical and Laboratory Studies. The following inclusionary criteria defined the patient population for this study: (a) diagnosis of a posterior fossa PNET/Mb; (b) evaluation of 17p in the initial diagnosis primary tumor specimen; (c) complete clinical information that identified the patient’s gender, date of birth, date of diagnosis, tumor location, and treatment; (d) complete evaluation for metastatic disease by cerebral spinal fluid cytological studies and myelography or magnetic resonance imaging of the entire spine; and (e) clinical and neuroimaging follow-up of nonrelapsed patients for at least 2 years after completion of therapy. Fifty-six patients with posterior fossa PNET/Mb met all of the above inclusion criteria and were included in this study.

For all patients, the diagnosis of posterior fossa PNET/Mb was determined by histological assessment of tumors obtained at surgery at the Children’s Hospital of Philadelphia (43 patients) or the Children’s Hospital of Los Angeles (13 patients). Immunohistochemical studies with antibodies to neurofilament protein and glial fibrillary acidic protein were used as an adjunct to the routine histological examination of the surgical specimen. Clinical information was obtained from tumor registries, surgical reports, and clinic records. Two patients were diagnosed in 1978, and the remaining 54 patients were diagnosed between 1985 and 1993. The extent of surgical resection was determined by postoperative neuro-imaging, with the exception of one patient who was classified according to the surgeon’s assessment given in the operative report. Patients were classified according to the following groups: (a) gross total resection (≥90% removal of tumor); (b) partial resection (<90% but ≥50% removal of tumor); and (c) biopsy (<50% removal of tumor). Metastatic staging was reported according to the Chang classification scheme (20) and grouped for the purpose of statistical analysis into two categories, MO versus M1–3. Clinical outcome measures included RFS (i.e., time from initial diagnosis to tumor recurrence) and total survival (i.e., time from initial diagnosis to death from progressive tumor).

A combination of cytogenetic and molecular methods was used to identify chromosome 17p deletions in these patients. The 13 cases from the Children’s Hospital of Los Angeles were evaluated by RFLP analysis (21). Sixteen of the 43 cases from the Children’s Hospital of Philadelphia were evaluated by standard cytogenetic analysis alone (22, 23). The remaining 27 cases were analyzed by FISH (24) and/or loss of heterozygosity analysis by RFLP (25) or single-strand conformation polymorphism analysis (26). All of the results of the 17p deletion analysis for the 56 patients have been described in detail in previous publications (21–26).

Statistical Methods. In this analysis, the results of the cytogenetic and molecular genetic studies were determined without knowledge of the recurrence or survival status of the children. Tests of differences between percentages were performed using the Pearson χ2 test or, if the sample size was too small, Fisher’s exact test (27). All estimates of RFS and total survival times were calculated using the Kaplan-Meier method, which adjusts for the fact that some patients did not experience the event of interest during the study (28). A forward stepwise with elimination Cox regression procedure (29) was used to identify clinical prognostic variables, exclusive of chromosome 17p deletion, that were associated (P ≤ 0.1) with time to recurrence of PNET/Mb. The prognostic significance of chromosome 17p deletion was assessed with a Cox regression model that included the above-identified clinical prognostic variables. Cox regression analysis thereby provided an accurate estimate of adjusting for the effects of clinical prognostic variables. Sample size and power were calculated using the method described by Lachin (30). All descriptive statistics, Kaplan-Meier estimates, Cox regression, power, and sample size results were calculated using SAS version 6.09 (SAS Institute, Cary, NC). The Wald χ2 test statistic was used to determine the P value for all Cox regression results. A two-sided P value of 0.05 or less was considered significant for all tests.

RESULTS

Clinical Parameters. Table 1 summarizes the demographic characteristics of all 56 patients in this study. The median age at diagnosis was 6.5 years (range, 0.8–21.8 years). For subsequent age-related statistical analyses, patients were grouped by age ≤3 years versus >3 years at initial diagnosis. Forty patients (71%) had a gross total resection, and 16 (29%) had a partial resection. No patient had a biopsy only. The predominance of males (63%) is consistent with previous reports (2, 4). Twelve patients (21%) had evidence of metastatic disease (M1–3), and 44 (79%) patients were M0 at initial presentation. For subsequent statistical analyses, patients were grouped by metastatic stage M0 versus M1–3. Median follow-up time for all patients was 4.4 years (range, 0.4–12.9 years), whereas the median follow-up time for surviving patients was 5.5 years (range, 2.0–9.3 years).

Postoperative therapy included radiation and/or chemotherapy. Of the 56 patients in the study, 52 (93%) were treated with radiation therapy; all received combined local and craniospinal radiation according to previously described protocols (4, 5, 31). For nine patients (16%), treatment was limited to radiation only. The posterior fossa radiation dose was less than 5000 cGy in one patient due to chemotherapy for Wilms’ tumor 8 years before the diagnosis of a posterior fossa PNET/Mb. Craniospinal radiation cumulative doses ranged from 1800–3600 cGy. Whereas 41 patients received craniospinal radiation at conventional doses
Chemotherapy was administered to 47 patients (84% of the study population). Thirty-seven patients were treated with radiation therapy and a chemotherapy regimen that included cisplatinum, 1-(2-chloroethyl)-3-cyclohexyl-l-nitrosourea, and vincristine (4). Four young children received an infant brain tumor chemotherapy regimen (31), three with and one without subsequent radiation therapy. One young child received a chemotherapy regimen including Cytoxan, carboplatin, and vincristine, followed by radiation therapy (St. Jude Children’s Hospital institutional study). Two patients received a regimen of eight chemotherapeutic agents in 1 day (32) but no radiation therapy. Three patients received other chemotherapeutic regimens, two with and one without craniospinal irradiation.

**Evaluation of Chromosome 17p Deletion.** The 56 patient samples were obtained at the time of the initial surgical resection. To identify chromosome 17p deletions, specimens were evaluated by standard cytogenetic analysis (35 cases; Refs. 22-25), interphase FISH analysis (11 cases; Ref. 24), and/or loss of heterozygosity assays (34 cases; Refs. 21, 25, and 26). Sixteen of the 56 cases were successfully analyzed by standard cytogenetic methods alone. Fifteen of the 16 cases (94%) demonstrated tumor-specific abnormalities. One tumor, which had been directly harvested after surgery, had a normal karyotype. The 15 tumors with abnormal karyotypes demonstrated a variety of numerical and structural chromosome abnormalities, including 5 cases with an i(17q). No tumor had a primary deletion of chromosome 22 or monosomy 22, which is characteristic of atypical teratoid or rhabdoid tumor (33). Twenty-one cases were successfully evaluated by two or more methods and showed concordant results. Deletion of chromosome 17p was seen in 23 (41%) of the 56 tumors included in this study (21-26).

The results of cytogenetic and molecular genetic 17p deletion studies were analyzed with respect to patient age at diagnosis, metastatic stage, and histology, each of which has been previously reported to be associated with prognosis (2, 4, 8, 12, 34-37). As shown in Table 1, although the percentage of patients with deletions of 17p who were older than 3 years of age at diagnosis was more than double that of infants younger than 3 years of age at diagnosis, this difference was not statistically significant ($P < 0.17$, Fisher’s exact test). Metastatic stage was not significantly associated with 17p deletion status either ($P < 0.52$, Fisher’s exact test). The percentage of tumors with a chromosome 17p deletion among PNETs/Mb without evidence of differentiation was similar to those with glial and/or neuronal differentiation. However, because different immunohistochemical methods may have been used during the period of the initial patient accrual to evaluate tumors for evidence of differentiation, the statistical comparisons of 17p deletion and histology are not presented, and differentiation status was not included in the survival analysis.

**Survival Outcomes.** Table 2 indicates the Kaplan-Meier RFS rates for all patients at 5 years and summarizes survival outcomes when grouped according to the following characteristics: age at diagnosis, metastatic stage (M0 versus M1-3), extent of resection (partial versus gross total resection), and treatment (radiation alone, chemotherapy alone, or radiation and chemotherapy). The 5-year RFS rates and 5-year total survival rates were identical and thus are not shown. XRT, radiation therapy; chemo, chemotherapy.

(e.g., 3600 cGy), craniospinal doses were reduced in 11 younger patients.

<table>
<thead>
<tr>
<th>Clinical characteristics of PNET/Mb patients</th>
<th>17p deletion</th>
<th>No deletion</th>
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<tbody>
<tr>
<td>Total no.</td>
<td>23 (41)</td>
<td>33 (59)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (21)</td>
<td>14 (67)</td>
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<tr>
<td>Age at diagnosis</td>
<td>≤3 yrs</td>
<td>2 (20)</td>
</tr>
<tr>
<td>&gt;3 yrs</td>
<td>21 (46)</td>
<td>25 (54)</td>
</tr>
<tr>
<td>Metastatic stage</td>
<td>M0</td>
<td>17 (39)</td>
</tr>
<tr>
<td>M1-3</td>
<td>6 (50)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>Gross total</td>
<td>19 (48)</td>
</tr>
<tr>
<td>Partial</td>
<td>4 (25)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Therapy</td>
<td>XRT + chemo</td>
<td>18 (42)</td>
</tr>
<tr>
<td>Chemo alone</td>
<td>0 (0)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>XRT alone</td>
<td>5 (56)</td>
<td>4 (44)</td>
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<th>Five-year RFS for PNET/Mb study patients</th>
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<tr>
<td>All patients</td>
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<tr>
<td>Age at presentation</td>
</tr>
<tr>
<td>≤3 yrs</td>
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<tr>
<td>&gt;3 yrs</td>
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<tr>
<td>Metastatic stage</td>
</tr>
<tr>
<td>M0</td>
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<tr>
<td>M1-3</td>
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<tr>
<td>Surgical resection</td>
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<tr>
<td>Gross total</td>
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<td>Partial</td>
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<tr>
<td>Therapy</td>
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<td>XRT + chemo</td>
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<tr>
<td>Chemo alone</td>
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<tr>
<td>XRT alone</td>
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<tr>
<td>Chromosome 17p</td>
</tr>
<tr>
<td>Deletion of 17p</td>
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<tr>
<td>No deletion</td>
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</table>

**Table 2**Five-year RFS for PNET/Mb study patients

$^{*}$ Kaplan-Meier RFS rate at 5 years. Total survival rates were identical and thus are not shown. XRT, radiation therapy; chemo, chemotherapy.
Chromosome 17p Deletions and Clinical Outcome in PNET/Mb

476 Chromosome 1p Deletions and Clinical Outcome in PNET/Mb

... out 17p deletion, this difference was not statistically significant (P = 0.25, Cox regression).

Multivariate Analysis of Chromosome 17p Deletion and Prognosis. The prognostic value of chromosome 17p deletion was examined using multivariate Cox regression analysis. First, we evaluated the predictive significance of clinical variables including age at diagnosis, extent of resection, metastatic stage, and treatment in predicting RFS time. In our study population, only treatment modalities (P = 0.046) and metastatic stage (P = 0.090) showed levels of significance P < 0.1, the threshold that we prospectively established for inclusion in subsequent Cox regression models (see “Patients and Methods”). Second, to evaluate the independent prognostic value of chromosome 17p deletion, we adjusted for the effect of prognostically significant clinical variables (i.e., treatment and metastasis) on RFS rates by use of the Cox regression model. When the effects of significant clinical factors on RFS are accounted for, the difference in disease-free survival rates between patients with or without chromosome 17p deletion was not statistically significant (P = 0.213). Results of multivariate Cox regression analyses on total survival were virtually identical. The clinical variables, metastasis and treatment modalities, were independently associated with total survival at P < 0.1 levels of significance. Again, when adjusted for the effect of the clinical variables, the difference in total survival rates between patients with or without chromosome 17p deletion were not statistically significant (P < 0.299, Cox regression analysis).

Post Hoc Sample Size Considerations. Because no statistically significant difference in RFS was detected between patients with and without 17p deletions, we retrospectively examined two considerations related to the sample size required for conducting another study. A difference in RFS of 37% or greater between the patients with and without 17p deletions could have been detected in a study with 56 patients (5% α-error, 80% power; Ref. 30). Conversely, to detect a clinically meaningful difference in RFS (e.g., 25%) between patients with and without 17p deletion, a sample size of 122 patients would be required (30).

DISCUSSION

The deletion of chromosome 17p sequences that results from the formation of an i(17q) has been implicated as a primary genetic event in PNET/Mb tumorigenesis, based on the finding of an i(17q) as the only structural change in several tumors (23) and the loss of this chromosomal region in up to 50% of PNETs/Mb (24). These findings implicate an as yet unidentified tumor suppressor gene distinct from p53 (25, 38, 39) that maps to 17p. For neuroblastoma, a neural tumor of the peripheral nervous system, deletion of chromosome 1p is found in 25–30% of all cases and is associated with poor prognosis (6, 7). The clinical significance of the loss of 17p in PNETs/Mb, however, is not yet understood.

The objective of the present study was to determine if deletion of chromosome 17p is an independent prognostic factor in children with PNETs. Our study was limited to patients with posterior fossa PNET/Mb because, in most reports, the clinical outcome for supratentorial PNETs versus posterior fossa PNET/Mb is different (1, 34). Furthermore, the only cases included were those in which we obtained unambiguous results from the cytogenetic or molecular analyses. Because the laboratory studies were conducted over an 8-year period, a number of different cytogenetic and molecular genetic techniques were used to evaluate the tumors for deletions of 17p. Although interphase FISH analysis is currently the most sensitive and specific means of detecting deletions (24), the cytogenetic studies and loss of heterozygosity assays were equally successful due to the highly informative nature of the loci examined and the fact that deletions of 17p in central nervous system PNET/Mb encompass almost all of 17p (21, 24, 25). Clearly, once the locus on chromosome 17 that is involved in the development of PNET/Mb has been identified, much more detailed genotype-phenotype correlations will be possible.

In contrast to reports suggesting that deletion of 17p is associated with poor prognosis in PNET/Mb (16, 17), we found that this deletion was not an independent predictor of clinical outcome in the largest reported group of genetically characterized primary posterior fossa PNETs evaluated by means of multivariate analysis. After adjusting for the effects of metastatic stage and treatment, the independent value of 17p deletion status for the prediction of RFS or total survival is not statistically significant or clinically useful in our study group. Furthermore, we did not find significant associations between 17p deletion and patient age at initial diagnosis, metastatic stage, or tumor differentiation.

In 1991, Cogen (17) concluded that childhood Mb patients with loss of heterozygosity for 17p had a higher incidence of tumor recurrence than those without 17p deletions. After stratifying 22 patients into “good-risk” (n = 11) or poor-risk (n = 11) groups according to the extent of resection and metastatic stage, they observed that 4 good-risk patients had distal and

Fig. 1 Kaplan-Meier curve of RFS for 56 patients with PNET/Mb stratified by chromosome 17p deletion status. The probability of RFS stratified by chromosome 17p deletion were not statistically significant (P = 0.213). Results of multivariate Cox regression analyses on total examined two considerations related to the sample size required for conducting another study. A difference in RFS of 37% or...
proximal deletions of chromosome 17p, and all of these patients had tumor recurrence. No good-risk patient without 17p deletion had tumor recurrence. For poor-risk patients, the number of relapsed patients with or without 17p deletions was nearly identical. However, it is difficult to interpret this data in any other way than hypothesis-generating because the number of patients is small, statistical analysis was not used, relevant clinical data was not described, and the average follow-up time was short (24 months). Despite comparable rates of 17p deletion for the present study and that of Cogen (41 and 45%, respectively; Ref. 17), our different conclusions for the prognostic value of 17p deletions may be due to significant differences in patient characteristics and data analysis methods.

Batra et al. (16) reported lower survivals for Mb patients with deletions of 17p. They suggested that the association between this deletion and shorter survival “represents a potentially significant trend.” In their retrospective analysis, 28 patients with Mb were selected for evaluation of loss of heterozygosity for markers on 17p. The clinical characteristics at initial diagnosis, tumor staging results, and treatment information were not reported. It is therefore difficult to compare our study population with that of Batra et al. (16) or to explain the apparent difference in our results.

Even if one disregards the possible differences in clinical characteristics (e.g., patient age, extent of resection, metastatic stage, or treatment) between the patient populations in our study and that of Batra et al. (16), differences in statistical analysis may explain the different conclusions. To identify the independent prognostic value of 17p deletions, we used multivariate analysis to control for the effect of clinical variables whose independent prognostic significance has been confirmed in other large studies (2, 4, 8, 12, 34–37). This approach is often not feasible in studies with small patient numbers. Accordingly, Batra et al. (16) analyzed their survival data by the univariate log-rank χ² statistic. However, these authors used a one-tailed test to determine if chromosome 17p deletion was associated with a worse prognosis and concluded that patients with loss of heterozygosity for 17p showed significantly different survival (P = 0.045). We know of no reason to conclude a priori that deletion of 17p is only clinically relevant if it predicts a worse clinical outcome or that this deletion cannot be associated with a better outcome. Therefore, we used a two-tailed test of significance to examine the hypothesis that 17p deletions in children with PNET/Mb are associated with a different survival outcome than the absence of 17p deletions. If one reevaluates the data of Batra et al. (16) using a two-tailed test of significance, loss of heterozygosity for 17p would not have prognostic significance (P = 0.09), and our conclusions would be in agreement.

More recently, Emadian et al. (40) analyzed a cohort of 21 Mb patients for 17p deletion status and clinical outcome. The patients were stratified into good-risk (13 patients) or poor-risk (8 patients) groups based on the extent of surgical resection and metastatic disease. There was no association found between loss of heterozygosity for 17p and poor clinical risk (Fisher’s exact test, P = 0.66). Furthermore, there was no difference in survival between patients with and without 17p deletions (log-rank test, P = 0.77). However, based on the limited sample size in their study, the authors indicated that they had only moderate power to detect a 10-fold or greater risk of recurrence associated with 17p deletion status.

We have demonstrated in a large study of primary PNET/Mb patients that deletion of 17p is not an independent predictor of survival outcomes. The median follow-up time for the present study was 5.5 years. Although this brings us to a relatively stable region of the survival curve for posterior fossa PNET/Mb (4), we cannot exclude the possibility that with longer follow-up, we will see additional tumor recurrence and deaths in our patient groups that may change the results of our multivariate analyses. Nevertheless, potentially interesting trends seen here and in previous studies (21, 40), such as a difference in the incidence of 17p deletions in younger and older patients, warrant further investigation. This may be best accomplished as part of a multi-institution effort that will generate the large number of patients needed to determine the prognostic value of this chromosomal deletion with a high degree of confidence. Until such a study is completed and independently confirmed, the use of 17p deletion status together with established clinical prognostic factors to classify PNET/Mb patients according to their risk of relapse or for other clinical decision-making purposes is not warranted.

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