To the editor:

**Epstein-Barr virus infection in Western European pediatric non-Hodgkin lymphomas**

The Epstein-Barr virus (EBV) is strongly associated with endemic Burkitt lymphoma (BL) and can also be found in a subset of other non-Hodgkin lymphomas (NHLs). At the present time, only very limited information is available regarding the prevalence of EBV in pediatric NHL in Western Europe and the United States. Concurrently, little data exists in regard to EBV gene expression patterns in pediatric lymphoma patients. Of note, prior data from a large series of mainly adult lymphoma cases suggested that EBV positivity may be a poor prognostic factor in a subgroup of NHL.  We determined the incidence of EBV infection as well as EBV protein expression in the entire spectrum of pediatric NHL in a large, nonselected Western population. In addition, we correlated EBV status with patient characteristics, clinical presentation, and treatment outcome.

All pediatric patients from Germany, Austria, and part of Switzerland with a diagnosis of NHL who had been registered at the NHL-BFM (Berlin-Frankfurt-Münster) data center during the period from April 1990 to December 1998 were identified (n = 1415). There were 50 patients with NHL as a secondary malignancy or evidence of significant immunodeficiency excluded from our study. Of the remaining patients (n = 1365), those with adequate paraffin-embedded biopsy specimens available were evaluated for EBV infection (n = 429, 31%). The distribution of NHL subtypes, as well as the clinical characteristics of the cases available for in situ hybridization for EBV-encoded small RNAs (EBER-ISH), was similar to the remainder of the patient population (data not shown). The patients were treated according to the protocols of the therapeutic trials NHL-BFM 90 and NHL-BFM 95.

We performed EBER-ISH on all 429 patients, as previously described. EBER-ISH revealed EBV infection of tumor cells in 25 (11.3%) of 222 cases of BL. All other entities were EBV-negative. In most of the EBER-positive BL cases (19 of 26, 73%), EBER-positive cells comprised the majority of tumor cells. Of the 26 cases, 7 (27%), however, had an EBER-positive tumor cell population of less than 50%. Also identified were 5 cases with single, nonmalignant EBV-positive cells (bystander cells). These cases included one peripheral T-cell lymphoma and 4 anaplastic large-cell lymphomas. Immunohistochemistry for EBV-encoded antigens EBNA-2 (EBV-encoded nuclear antigen 2), LMP-1 (latent membrane protein 1), and ZEBRA (BamHI fragment Z EBV replication activator) was performed on all EBER-positive cases. The results were consistently negative, with the exception of one BL case expressing LMP-1 in single tumor cells.

The clinical characteristics of the EBER-positive BL patients were similar to the EBER-negative BL patients (data not shown) except for the age at diagnosis. The age at diagnosis was significantly younger in EBV-positive compared with EBV-negative BL patients, with a mean of 6.6 versus 9.1 years, respectively (Figure 1A). The probability of event-free survival was 0.96 in EBER-positive versus 0.90 in EBER-negative cases, and statistically not significantly different with P (log-rank) = 0.33 (Figure 1B).

We show that in Western European pediatric NHL, EBV is present in 11.3% of BL cases and invariably absent from all other entities. This suggests that, in industrialized countries, EBV is not involved in the pathogenesis of pediatric non-Burkitt NHL. In BL, there was no statistically significant difference in survival between EBV-negative versus EBV-positive patients, but the latter presented at a significantly younger age. This finding, together with prior epidemiologic observations and the known oncogenic potential of EBV in vitro, suggests that EBV plays a role in the pathogenesis of a subset of sporadic BL. We hypothesize that infection with EBV early in life increases the risk of developing this malignancy.

**References**

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