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A genetically distinct pediatric subtype of primary CNS large B-cell lymphoma is associated with favorable clinical outcome

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Primary central nervous system (CNS) lymphoma (PCNSL) is an aggressive non-Hodgkin lymphoma with CNS confinement; large B-cell lymphoma (LBCL) accounts for most PCNSL. The median age for PCNS-LBCL is 66 years, with occurrence in younger adults and pediatric cases being uncommon.1 Although immunodeficient children have an increased risk of developing PCNSL, most cases of pediatric PCNSL in the past few decades have been reported in immunocompetent individuals. Previous studies have reported that the prognosis for PCNS-LBCL is better in pediatric and younger adults than in older adults who have a median survival of <3 years.2,3 Aberrant constitutive activation of the NF-κB signaling pathway is a hallmark of PCNS-LBCL in adults and is characterized by frequent MYD88 mutation, CD79B mutation, PRDM1 mutation/deletion, CDKN2A biallelic deletion, and HLA gene cluster deletion.4-9 However, the molecular pathogenesis of PCNS-LBCL in children and young adults is largely unknown and may be different from that in older adults, helping to explain the divergent clinical outcomes.

This multi-institutional study was conducted to investigate the molecular characteristics of pediatric and young-adult PCNS-LBCL and define associations with clinical outcomes and pathologic features. The cohort consisted of 12 patients <40 years of age without known immunodeficiency, including 6 males and 6 females with median age at diagnosis of 17 years (range, 7-38 years). All patients were confirmed to have primary CNS confinement without systemic involvement based on staging positron-emission tomography/computed tomography and bone marrow biopsy. All patients were treated with a combination of dexamethasone, methotrexate, and rituximab, together with various accompanying agents (supplemental Tables 1-2). Tumors were uniformly composed of dense aggregates of large lymphoid cells with perivascular and parenchymal involvement, were Epstein-Barr virus (EBV) negative, and had diffuse strong immunoreactivity for B-cell markers (CD20 and PAX5). No BCL2 rearrangement and no MYC amplification or rearrangement were present (supplemental Tables 3-4). No appreciable differences in cytology or growth pattern were identifiable between these pediatric and young-adult patients with PCNS-LBCL compared with their older adult counterparts. The Institutional Review Board, Human Research Protection Program Committee at the University of California San Francisco approved this study (CHR 18-25787), which was conducted in accordance with the Declaration of Helsinki.
Targeted next-generation DNA sequencing and genome-wide copy number analysis were performed on the 12 tumors, as well as 6 conventional PCNS-LBCL from older adult patients (supplemental Methods). Based on the molecular signatures, 2 distinct groups were identified: "pediatric type, MYD88-wildtype" and "adult type, MYD88-mutant" (Figure 1). The pediatric type, MYD88-wildtype group consisted of 8 patients (5 males, 3 females) with a median age of 14 years (range, 7-25 years). No patients were immunocompromised or HIV positive, and none had a known tumor predisposition syndrome. Two tumors were supratentorial, 1 was infratentorial, and 2 were both supratentorial and infratentorial. Four cases were of the germinal center phenotype, according to Hans criteria. All tumors had a non–double-protein expressor phenotype, and none showed a double- or triple-hit genotype for MYC/BCL2/BCL6. The median Ki-67 labeling index was 90% (range, 40% to 95%). Genetic alterations commonly occurring in adults with PCNS-LBCL (MYD88 mutation, CDKN2A/B homozygous deletion, HLA gene cluster deletion, and PRDM1 mutation/deletion) were rare or absent (supplemental Figure 1; supplemental Tables 5-7). Instead, mutations in GNA13 (50%), NFKBIE (50%), and TP53 (75%) were recurrently identified. Although this group was highly enriched for pediatric age (88%), 25-year-old patient 4 was included based on the lack of MYD88 mutation and presence of NFKBIE and TP53 mutations. A single tumor in patient 15 showed GATA2 homozygous deletion, which has not been reported in systemic or PCNS-LBCL. Interestingly, alterations in GATA2 are recurrent in pediatric myeloid malignancies such as leukemia and myelodysplastic syndrome.11-14 Other likely oncogenic alterations in individual tumors included focal high-level amplification of JAK2 and CD227 (PD-L1) and EZH2 p.Y646N hotspot mutation that is a recurrent variant found in systemic LBCL and follicular lymphoma. Four tumors in this group exhibited a small number of chromosomal gains or losses (<5 per tumor), whereas the quantity of chromosomal aberrations was high (≥5) in the remaining 4 tumors. No differences in radiologic or histologic features between these pediatric-type PCNS-LBCL and their adult type counterparts was appreciated (Figure 2A-F).

The adult type, MYD88-mutant group consisted of 4 young-adult patients (25-38 years of age) and the 6 cases of conventional PCNS-LBCL that occurred in older adults. All tumors harbored activating hotspot missense mutations in MYD88. In addition, 80% demonstrated homozygous deletion of CDKN2A/B, 60% demonstrated inactivating mutations or deletion of PRDM1, 60% demonstrated focal homozygous deletions of the HLA gene cluster on chromosome 6p22.1, and 40% demonstrated CD79B mutations. Only single tumors contained TP53, GNA13, or NFKBIE mutations (10% frequency each), in contrast to their frequent occurrence in the pediatric type tumors. Most adult-type, MYD88-mutant tumors
Pediatric type, \textit{MYD88}-wildtype - patient #15, 11-yo M patient

Adult type, \textit{MYD88}-mutant - patient #5, 33-yo F patient

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Pediatric \textit{MYD88}-wildtype PCNS-LBCL is associated with favorable clinical outcomes compared with its adult-type counterpart. (A-F)}
\end{figure}

Representative radiologic and histopathologic findings in pediatric- and adult-type PCNS-LBCL. Preoperative T1-weighted postcontrast magnetic resonance images of patients with pediatric type, \textit{MYD88}-wildtype (A) or adult type, \textit{MYD88}-mutant (D) PCNS-LBCL, showing overlapping radiologic features, including intraparenchymal mass.
immune evasion.5,9 have frequent deletions of the HLA gene cluster associated with survival, in contrast with the microenvironment and immune status correlating with better overall pediatric-type tumors may be associated with a unique tumor with the prosurvival signals driven by NF-

The effects of the frequent GNA13 and MYD88 mutations are likely to synergize with enrichment for TP53 and PRDM1 mutations. Young adults aged 25 to 40 years had genetic profiles similar to those of conventional PCNS-LBCL in older adults. We speculate that these may represent a tumor type that is biologically equivalent to that most commonly occurring in older adults, and we thus collectively termed this group adult type, MYD88-mutant. Our findings suggest that unlike adult-type tumors, constitutive activation of the NF-κB pathway in pediatric-type PCNS-LBCL is driven by NFKBIE and GNA13 mutations instead of MYD88 hotspot mutations. The effects of the frequent TP53 mutations are likely to synergize with the prosurvival signals driven by NFKBIE and GNA13 mutations in pediatric-type PCNS-LBCL. The intact HLA alleles in the pediatric-type tumors may be associated with a unique tumor microenvironment and immune status correlating with better overall survival, in contrast with the MYD88-mutant tumors in adults that have frequent deletions of the HLA gene cluster associated with immune evasion.5,9

In summary, we have identified a genetically distinct subtype of EBV-negative PCNS-LBCL occurring in immunocompetent pediatric and young-adult patients ≥25 years of age. This MYD88-wildtype group harboring frequent TP53, NFKBIE, and GNA13 mutations has favorable outcomes compared with the MYD88-mutant group occurring in older adults >25 years of age. Prospective next-generation DNA sequencing is advocated for PCNS-LBCL in the pediatric and young-adult population, for clinically distinguishing this unique pediatric-type disease.

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**References**


**Figure 2 (continued)** Lesions with diffuse enhancement and significant edema in the adjacent white matter. Histologic analysis showed sheets of malignant large B-cells diffusely expressing CD20. Hematoxylin and eosin, magnification ×400 (B,E); and CD20, original magnification, ×400 (C,F). (G) Kaplan-Meier survival plot of 7 patients with pediatric type, MYD88-wildtype PCNS-LBCL. (H) Kaplan-Meier meta-analysis of 53 pediatric and young-adult patients with PCNS-LBCL stratified by age ≤ 25 years vs 26 to 40 years.


