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The landscape of primary mismatch repair deficient gliomas in children, adolescents, and young adults: a multi-cohort study

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Abstract

Background: Gliomas are a major cause of cancer-related death among children, adolescents, and young adults (age 0-40 years). Primary mismatch repair deficiency (MMRD) is a pan-cancer mechanism with unique biology and therapeutic opportunities. We aimed to determine the extent and impact of primary MMRD in gliomas among children, adolescents, and young adults.

Methods: Clinical and molecular data were collected from a population-based cohort of children, adolescents, and young adults with gliomas from Toronto (TOR-Ped, age 0-18 years, collected Jan 1, 2000, to Dec 31, 2021; and TOR-AYA, age 18-40 years, collected Jan 1, 2000, to June 30, 2019). Additional validation paediatric cohorts from St Jude Children's Research Hospital (0-18 years, 2015-21) and the Children's Brain Tumor Network (0-18 years, 1981-2021) were used. Functional genomic tools were applied with the primary aim of assessing primary MMRD prevalence among glioma subgroups and germline impact. To evaluate the effect of primary MMRD on therapy and overall survival, Kaplan-Meier estimates were used on an additional cohort of patients with primary MMRD gliomas treated with immunotherapy.

Findings: 1389 gliomas were included in the study. The prevalence of primary MMRD ranged between 3·7% and 12·4% in high-grade gliomas (overall 30 of 483; 6·2%, 95% CI 4·2-8·7) and less than 1% in low-grade gliomas (four of 899; 0·4%, 0·1-1·1; p<0·0001 by χ^2 test). Specific molecular analysis for all gliomas showed that primary MMRD was absent among oligodendrogliomas (none of 67) and uncommon in $BRAF^{V600E}$ gliomas (one of 110) and histone mutant-driven gliomas (one of 150). In the paediatric age group (<18 years), primary MMRD was common in IDH^{WT} and $H3^{WT}$ gliomas harbouring pathogenic TP53 variants (21 of 61; 34·4%, 22·7-47·7) and in malignant IDH^{mut} gliomas

(five of eight; 62·5%, 24·5-91·5). Germline aetiology accounted for 33 (94·3%) of 35 primary MMRD gliomas, including children, adolescents, and young adults with previously unrecognised Lynch syndrome. Survival was poor for patients with primary MMRD gliomas. Particularly poor survival was observed for those with IDH^{mut} astrocytomas with primary MMRD when compared with those with mismatch repair-proficient gliomas (HR 12·6, 95% CI 2·8-57·5; p=0·0011 by multivariable Cox regression). Immune checkpoint blockade was associated with improved survival for patients with primary MMRD gliomas compared with conventional chemoradiotherapy regimens (HR 0·4, 0·3-0·7; p=0·0017 by multivariable Cox regression), regardless of age or germline status.

Interpretation: Primary MMRD is more common than previously reported in gliomas in children, adolescents, and young adults, is enriched in specific molecular subgroups, and is associated with poor outcomes. Accurate detection, genetic testing, early diagnosis through surveillance, and implementation of immunotherapy might improve survival for these patients.

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