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Association of Anesthesia Care and Cognitive Outcomes in Survivors of Childhood Acute Lymphoblastic Leukemia

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We read with interest Banerjee et al's work describing the long term neurocognitive outcomes of childhood acute lymphoblastic leukemia.[1] The adult sequelae of pediatric major illness is a subject of substantial interest as short-term therapeutic outcomes continue to improve and the number of adult survivors of major illness increase.

As observational researchers within the field of anesthesiology, in reading the manuscript we were left with three questions::

Firstly, does the cohort, after adjustment, vary only by anesthesia exposure? As the authors note, anesthesia care was commonly provided for a full range of procedures. Thus it seems likely that anesthesia exposure is highly co-linear with extent of treatment. While the authors adjusted for methotrexate exposure and intrathecal administration as recommended by current guidelines[2], the number and nature of the treatment exposures described in this study appear highly variable. There likely are non-oncologic factors which also impact these outcomes. Taken collectively, factors which may influence long-term cognitive trajectories appear incompletely accounted for.

Secondly, why is the incidence of significant cognitive deficit so high? A robust debate exists on the long term outcomes of children who have been exposed to anesthesia care at a young age.[3] The described 42% incidence of 3 or more psychometric tests at 2 standard deviations below expected values appears to be beyond what contemporary anesthetic literature describes.[4]

Thirdly, what is the biological plausibility of the relationship? The authors conclude that exposure to propofol and volatile anesthetic agents are associated with the described outcome. Pre-clinical work has linked these agents, alongside ketamine to histological changes in animal models. However, animal models have not clearly translated into clinical practice.[3,5] The authors' discussion of this phenomena appears incomplete. Limited consideration has been offered to the possibility of direct or mediated neurotoxicity of the cytotoxic agents routinely and variably employed in the treatment protocols described in this study.

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Conflicts of Interest: None

While we agree that it is desirable to seek non-pharmacologic methods of achieving patient comfort, in light of the questions noted above, we believe the study findings should be considered as hypothesis-generating, and authors' stated conclusions to limit anesthetic exposures in order to reduce neurocognitive impairment and neuroimaging abnormalities are premature. We look forward to further work which validates the hypotheses emerging from this study.

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