Delirium in Hospitalized Children with Cancer: Incidence and Associated Risk Factors

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Objective To assess the incidence of delirium and its risk factors in hospitalized children with cancer.

Study design In this cohort study, all consecutive admissions to a pediatric cancer service over a 3-month period were prospectively screened for delirium twice daily throughout their hospitalization. Demographic and treatment-related data were collected from the medical record after discharge.

Results A total of 319 consecutive admissions, including 186 patients and 2731 hospital days, were included. Delirium was diagnosed in 35 patients, for an incidence of 18.8%. Risk factors independently associated with the development of delirium included age <5 years (OR = 2.6, $P = .026$), brain tumor (OR = 4.7, $P = .026$); postoperative status (OR = 3.3, $P = .014$), and receipt of benzodiazepines (OR = 3.7, $P < .001$). Delirium was associated with increased hospital length of stay, with median length of stay for delirious patients of 10 days compared with 5 days for patients who were not delirious during their hospitalization ($P < .001$).

Conclusions In this cohort, delirium was a frequent complication during admissions for childhood cancer, and was associated with increased hospital length of stay. Multi-institutional prospective studies are warranted to further characterize delirium in this high-risk population and identify modifiable risk factors to improve the care provided to hospitalized children with cancer. *(J Pediatr 2017;191:212-7).*

Delirium is a critical neurocognitive syndrome that can arise in the context of a serious underlying medical condition. This syndrome represents a neuropsychiatric change from baseline, with fluctuation in awareness and cognition.[1] Delirium occurs as a result of factors related to the primary illness, the treatment of that illness, and the stressful and disorienting environment of the hospital.[2,3] Delirium is strongly linked to poor outcomes, including increased mortality.[4,5] This alteration in mental state is independently associated with longer hospital length of stay, increased hospital costs, and long-term cognitive impairment in survivors.[6-10] Importantly, with early detection and treatment, delirium is often reversible.[11,12]

In hospitalized adults with cancer, delirium is the most common neuropsychiatric complication. It has a reported incidence ranging from 18% to 50%, depending on the population sampled, with delirium rates upward of 80% in palliative care wards.[11,13-16] Risk factors for the development of delirium in adults with cancer have been identified, including specific oncologic diagnoses, cancer stage, stem cell transplantation, geriatric age, medications administered, and pre-existing dementia.[13-16] Delirium in oncology patients has been shown to decrease effectiveness of pain management, and increase psychological distress in patients, families, and medical providers.[17-20] Early recognition of delirium in adults with cancer has been shown to be key to successful treatment.[11,21]

Although delirium in hospitalized adults with cancer is widely recognized, little is known about the incidence of delirium in pediatric oncology.[12,22] The recent development of validated pediatric delirium screening tools allows for early identification of delirium in hospitalized children.[23-25] In a 2015 hospital-wide quality improvement initiative, delirium screening was implemented as standard of care in every patient at Memorial Sloan Kettering Cancer Center (MSKCC). For the Department of Pediatrics, the Cornell Assessment of Pediatric Delirium (CAPD) was chosen as the bedside screening tool.[25] The CAPD is administered by the child's nurse, takes less than 2 minutes to complete, and is validated in children of all ages and stages of development.[26-28] We hypothesized that delirium would occur in >10% of hospitalized children with cancer, with identifiable risk factors (including young age, poor nutrition, and receipt of benzodiazepines), and would be associated with increased length of hospital stay.

CAPD	Cornell Assessment of Pediatric Delirium
MSKCC	Memorial Sloan Kettering Cancer Center
TPN	Total parenteral nutrition

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Methods

This is a retrospective cohort study of every child admitted to the pediatric service at MSKCC between April 1, 2015, and June 30, 2015. Inclusion criteria involved all consecutive admissions between the ages of 0-21 years during the 3-month study period.

All children were prospectively screened for delirium twice daily throughout their hospitalization. Delirium was defined as a positive screen (a CAPD score of 9 or higher),[25] with diagnosis of delirium confirmed by the medical team. Children were assigned a daily status (delirium or no delirium), as well as an overall status for the hospitalization (delirium ever vs delirium never). Delirium duration was defined as the total number of days with delirium during the admission.

The retrospective data collection was based on a review of risk factors for delirium in hospitalized adults with cancer. Clinical information was collected via review of the electronic medical record. Demographic data included sex (male vs female), age (by category), primary oncologic diagnosis, primary reason for admission, history of stem cell transplant (yes/no), and presence of metastatic central nervous system disease. Daily data consisted of: medications administered (by category, including narcotics, benzodiazepines, anticholinergics, steroids, granulocyte colony stimulating factor, and chemotherapeutics), laboratory values (including absolute neutrophil count and albumin level), need for supplemental oxygen (yes/no), provision of total parenteral nutrition (TPN) (yes/no), and do-not-resuscitate order status (yes/no).

Outcome data included length of hospital stay (inclusive of date of admission and date of discharge), and in-hospital mortality.

Statistical Analyses

Demographic and clinical characteristics were reported as N (%) and distribution (mean, median, minimum, maximum, and IQR), as appropriate. Factors associated with delirium development (delirium ever vs never during an admission) were analyzed by χ^2 or Fisher exact tests, as appropriate. Variables determined a priori as risk factors for delirium development were used for multivariable modeling. As some children were admitted more than once during the 3-month study period, a generalized estimating equation model with a binomial distribution and unstructured working correlation matrix was used for the multivariable analysis. Hospital length of stay was compared between admissions (ever vs never delirious) by the Wilcoxon rank-sum test. Daily factors associated with daily delirium status (delirium vs no delirium) were analyzed by χ^2 or Fisher exact tests, as appropriate. Death during the study period was analyzed between ever and never delirious patients by the Fisher exact test. All *P* values were 2-sided with statistical significance evaluated at the .05 alpha level. All analyses were performed in R version 3.3.2 (Vienna, Austria).[29]

The MSKCC Institutional Review Board approved this observational, minimal risk study with waiver of requirement for informed consent.

Results

Sample Characteristics

Consecutive admissions (n = 319), comprising 186 individual patients, were included (**Table I**). These patients ranged in age from 2 months to 21 years; 49% were male. Of the 186 patients, 70 were admitted more than once during the study period. The median number of admissions for these 70 patients was 2. Primary oncologic diagnoses are categorized in **Table I**, with a nearly one-quarter each of patients with neuroblastoma and leukemia/lymphoma. Thirty-five children (19%) had a history of stem cell or bone marrow transplantation; 8 of these children were transplanted during the course of the study. Nine children (5%) had a do-not-resuscitate order placed during the hospitalization. Three children (1.6%) died in the hospital during the 3-month study period.

Of the 319 admissions, the most common reason for hospitalization was fever and neutropenia (n = 85), followed by chemotherapy (n = 61) and surgery (n = 61). A majority of children received narcotics (55%) and anticholinergics (68%) during their admission. A substantial minority received benzodiazepines (40%) and chemotherapeutics (39%). Median hospital length of stay was 5 days, with an IQR of 3-9 days. A total of 2731 patient days were included in analyses. Description of admission characteristics is found in **Table II**.

Delirium was diagnosed in 35 of the 186 patients, for an incidence of 18.8% in this cohort. Duration of delirium ranged from 1 to 18 days, with a median duration of 2 days (IQR 1-4 days). Delirium usually occurred early in the hospitalization, with a median first occurrence of delirium on hospital day 2 (IQR hospital day 1-4). Delirium developed in 3 of the 8 children (37.5%) who received stem cell transplants during the study period. Of note, delirium developed in all 3 children who died during the study period.

When assessed by hospital days, delirium was diagnosed in approximately 5.4% of the 2731 days (n = 148 days with de-

Table I. Selected characteristics of the study sample (n = 186)

		n (%)
Age (y)	0-2	19 (10.22%)
	2-5	44 (23.66%)
	5-13	47 (25.27%)
	>13	76 (40.86%)
Sex	Female	94 (50.54%)
	Male	92 (49.46%)
Primary diagnosis	Brain tumor	20 (10.75%)
	Leukemia/lymphoma	43 (23.12%)
	Neuroblastoma	45 (24.19%)
	Sarcoma	42 (22.58%)
	Other	36 (19.35%)
Transplant history	No	151 (81.20%)
	Yes	35 (18.80%)
DNR status	No	177 (95.16%)
	Yes	9 (4.84%)
CNS disease	No	141 (75.81%)
	Yes	45 (24.19%)

CNS, central nervous system; *DNR*, do-not-resuscitate.