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BRIEF COMMUNICATION

Preventable infections in children with leukodystrophy

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Abstract

Children with inherited leukodystrophies have high hospitalization rates, often associated with infection. We studied whether potentially modifiable risk factors (preexisting indwelling central intravenous access, urinary catheter, hardware, or mechanical ventilation; and influenza vaccine) were associated with infection-related hospitalization in children with leukodystrophy. Central intravenous access was associated with sepsis (odds ratio [OR] 9.8); urinary catheter was associated with urinary tract infections (OR 9.0); lack of seasonal vaccination was associated with influenza (OR 6.4); and mechanical ventilation was associated with pneumonia (OR 2.7). We conclude that potentially modifiable risk factors are significantly associated with infection and hospitalization in children with leukodystrophies.

Introduction

Children with inherited leukodystrophies[1–3] and their families face complex health challenges. The incidence of leukodystrophies is almost 1 in 7500 live births with a 34% risk of death by age 8 years.[4] Hospitalization rates and costs of care are high for children with leukodystrophy. The majority of costs come from inpatient hospitalizations, often related to infection.[5]

Treatment for leukodystrophies is largely supportive and there is a lack of evidence-driven guidelines. Bone marrow transplantation (hematopoietic cell transplantation), umbilical cord blood transplantation, and enzymatic therapies are currently used for a subset of diseases, and only benefit a minority of patients.[6–8] Variability in costs and hospitalizations across institutions[9] suggest that care-process models could impact leukodystrophy patient care even in the absence of new therapies. In a previous study we found that infection is significantly associated with hospitalization in leukodystrophy patients,[5] therefore, strategies to reduce rates of infection could have an important clinical impact.

Our objective was to characterize infections in leukodystrophy patients, as a cause or complication of hospitalization. We then sought to identify potentially modifiable risk factors associated with infection-related hospitalization in these patients.

Methods

We performed a retrospective cohort study of children less than 18 years of age with an inherited leukodystrophy

between 1 January 1999 and 30 June 2013. This study was performed at a children's hospital which serves as a tertiary pediatric center as well as the primary children's hospital for an estimated pediatric population of >1.5 million children.[10,11] The study was approved by the Institutional Review Boards of the University of Utah and Intermountain Healthcare (IH).

Patients with inherited leukodystrophies were identified by prospective enrollment of patients presenting to a specialist leukodystrophy clinic; and by a computerized search of the IH database using a previously validated algorithm based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes.[9] A total of 702 unique possible patients were identified; 20 charts could not be located. Two authors (H. M. A., J. L. B.) reviewed all 682 charts to determine whether a patient met inclusion and exclusion criteria. Inclusion and exclusion criteria were based on previous studies:[4,5] brain magnetic resonance imaging (MRI) findings consistent with the diagnosis of a leukodystrophy; patients were excluded from the study if they had a known (past medical history) or likely alternative diagnosis to explain a noninherited leukodystrophy.

Criteria for diagnosis of infection were: admission or discharge diagnosis of infection combined with supporting lab or microbiological data. Infection was defined as urinary tract infection (UTI), sepsis, pneumonia, bronchiolitis, cellulitis or soft tissue infection, influenza, meningitis, infection involving implantable hardware, (e.g., ventriculoperitoneal [VP] shunt infection); and/or a positive bacterial, viral, or fungal culture from a normally sterile site. Nosocomial infection (hospital-acquired infection) was defined as an infection diagnosed during hospitalization, more than 48 h after admission. Bone marrow transplant (BMT)/hematopoietic stem cell treatment status was defined as patients who were within 6 months of the date of their start of ablation for chemotherapy.

For each hospitalization, we evaluated if potential modifiable risk factors for infection were present *prior to the hospitalization*, by determining if the patient had the presence of a gastrostomy-tube, central line, peripherally-inserted central catheter (PICC) line, tracheostomy, and/or mechanical ventilation, indwelling hardware, indwelling urinary catheter, VP shunt, and whether the patient received a flu vaccine during the season year of an hospital admission for influenza (see full description of criteria in Data S1).

Data were collected through manual chart review. Descriptive statistics were used to characterize the study cohort. Odds ratios (ORs) were calculated for the presence or absence of the risk factor at the time of infection-associated hospitalization, and the infection type. ORs were calculated for the entire cohort, as well as separately for BMT and non-BMT patients. In some cases there were not sufficient patients or infections for some categories for ORs calculations for BMT patients. Two-tailed *P*-values were calculated using Fisher's exact test. Each hospitalization with infection was counted as a separate event.

Results

We identified 160 patients with an inherited leukodystrophy (Table S1). Table 1 shows the characteristics of the 232 infection-associated hospitalizations. The most common infections associated with hospitalization were pneumonia (64 hospitalizations, 28%); sepsis (64 hospitalizations, 28%); and bronchiolitis (45 hospitalizations, 19%).

We evaluated for the presence of potentially modifiable risk factors for infection in each of the 232 hospitalizations. We found that a central and/or PICC line was present in 121 hospitalizations (52%); a tracheostomy and/or ventilator was present in 47 hospitalizations (20%); indwelling hardware was present in 41 hospitalizations (18%); and an indwelling urinary catheter was present in 7 hospitalizations (3%) (Table 2).

To determine whether these potentially modifiable risk factors were significantly associated with certain infections and hospitalization, we determined ORs for modifiable risk factors for each infection type (Fig. 1; Table S2). Central and/or PICC lines were significantly associated

Table 1. Characteristics of infections associated with hospitalization.

Outcome	Overall	BMT (n = 46)	Non-BMT (n = 186)	P
Treatment with antimicrobial/-viral	182 (78%)	36 (78%)	146 (78%)	1.0
Positive bacterial or fungal culture	117 (50%)	26 (57%)	91 (49%)	0.4
Positive viral identification	53 (23%)	10 (22%)	43 (23%)	1.0
Abnormal chest X-ray	58 (25%)	3 (7%)	55 (30%)	0.001
Pneumonia	64 (28%)	0 (0%)	64 (34%)	0.0001
Sepsis	64 (28%)	25 (54%)	39 (21%)	0.0001
Bronchiolitis	45 (19%)	9 (20%)	36 (19%)	1.0
Urinary tract infection	33 (14%)	2 (4%)	31 (17%)	0.03
Influenza	20 (9%)	1 (2%)	19 (10%)	0.14
Cellulitis or soft tissue infection	19 (8%)	3 (7%)	16 (11%)	0.77
Hardware infection	15 (6%)	0 (0%)	15 (10%)	0.05
Nosocomial infection	6 (3%)	1 (2%)	5 (3%)	1.0
Meningitis	3 (1%)	0 (0%)	3 (2%)	1.0

Total number of hospitalizations with infections was 232 (from total number of patients = 75). Two-tailed *P*-value was calculated for the difference between BMT and non-BMT patients.

with sepsis (OR 9.8 [95% confidence interval 4.5–21.1], $P = 0.0001$); indwelling urinary catheters were associated with UTI (9.0 [1.9–42.3] $P = 0.0008$); tracheostomy and/or ventilators were associated with pneumonia (2.7 [1.4–5.2] $P = 0.0032$); and lack of seasonal influenza vaccination was associated with influenza (6.4 [1.6–25.6] $P = 0.002$).

To evaluate whether immunosuppression associated with BMT affected the associations with modifiable risk factors, we compared infections and risk factors in BMT and non-BMT patients. For some categories there were insufficient number of BMT patients for analysis. A central line was significantly associated with sepsis for both BMT and non-BMT patients (OR 13.7 [3.0–62.7]; and 8.3 [3.3–21.0]) (Fig. 1). In separate subgroup analysis without BMT patients, the associations of modifiable risk factors with infections were still present (Fig. 1; Table S3).

To determine whether identification of risk factors reflected a more medically fragile subgroup, we evaluated the proportion of patients with bulbar insufficiency. We compared the number of hospitalizations in patients with or without bulbar insufficiency: for patients who had a UTI and an indwelling urinary catheter; and patients with sepsis and a central/PICC line. We found that of the 68 patients with bulbar insufficiency, there were 185 hospitalization events associated with infection. One hospitalization had a UTI and an indwelling urinary catheter (0.5%); 10 patients had hospitalization with sepsis and a central/PICC line (5.4%). In contrast, of the 92 nonbulbar insufficiency patients with 47 hospitalizations, three had hospitalizations with UTI and a urinary catheter (6.4%); and 41 patients had hospitalization with sepsis and a central/PICC line (87%).

Table 2. Prevalence of modifiable risk factors for infections in hospitalization events ($n = 232$).

Characteristic	Overall	BMT ($n = 46$)	Non-BMT ($n = 186$)	P
Central and/or PICC Line	121 (52%)	31 (67%)	90 (48%)	0.89
Tracheostomy or ventilator	47 (20%)	9 (20%)	38 (20%)	1.0
Hardware	41 (18%)	0 (0%)	41 (22%)	0.0001
Urinary catheter	7 (3%)	3 (7%)	4 (2%)	0.14

Number reported is the number of hospitalization events. Two-tailed *P*-value was calculated for the difference between BMT and non-BMT patients.

Discussion

We found that potentially modifiable risk factors are significantly associated with infection in hospitalized children with leukodystrophy. Children with leukodystrophies were

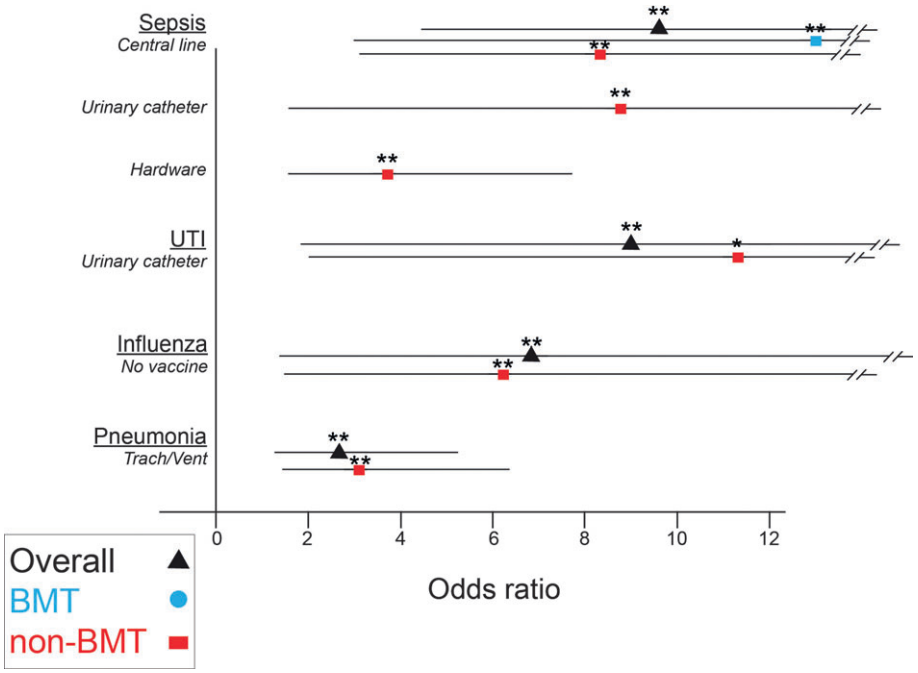

Figure 1. Odds ratios of modifiable risk factors for hospitalizations with infection. Odds ratios and 95% confidence intervals are shown. *$P < 0.05$; **$P < 0.001$. Along the *y*-axis, infection outcome is listed in bold with the risk factor in italics below.

hospitalized with infections at higher rates if they had the presence of one of several risk factors (indwelling central intravenous access, hardware, or indwelling urinary catheters; tracheostomy or need for mechanical ventilation; and failure to receive a seasonal influenza vaccine).

The most common infections were pneumonia, sepsis, bronchiolitis, UTI, and influenza. Nosocomial (hospital-acquired) infections were rare, accounting for only six (3%) hospitalization events. We did observe differences in the types of infections between BMT and non-BMT patients. For example, non-BMT patients more often had pneumonia; whereas twice as many BMT patients had sepsis. Interestingly, since more BMT patients had central lines (67% vs. 48%), this suggests that sepsis rates could be lowered in BMT patients by reducing the duration or frequency; or care for; central lines.

Limitations of this study include that data were collected retrospectively at a single center. We did not analyze the reason for the presence of the modifiable risk factor (e.g., why a patient had an indwelling urinary catheter). Certain risk factors may not be modifiable. For example, some patients require tracheostomies or mechanical ventilation. BMT involves immunosuppression and raises the risk for infection, and could have skewed the results. However, we found that the modifiable risk for infection was still present in non-BMT patients. It is possible that patients with modifiable risk factors for infection are more medically fragile patients, and hence as part of their disease course will have more infections and hospitalizations. We found, though, that at least as represented by bulbar insufficiency, as an indicator of more severe neurological dysfunction, that patients with bulbar insufficiency were not more likely to have the modifiable risk factors associated with their hospitalizations. This suggests that a simple metric for medical fragility may not account for our findings.

However, care for risk factors could be modified. Pulmonary care standardized strategies have been shown to reduce infections and mortality in patients with spinal muscular atrophy or cystic fibrosis.[12,13] Protocols for central lines care can reduce infection rates.[14] Routine catheter care or shortening of catheterization time can reduce UTI rates.[15] Patients with bulbar dysfunction accounted for a larger proportion of infection-associated hospitalizations, ~3 hospitalizations/patient compared to 0.5/nonbulbar dysfunction patient. This suggests that a more significant effect on reducing hospitalizations would result from working with this subgroup.

We expect that our findings on potentially modifiable risk factors for infection in children with leukodystrophies will also be true in other neurologically impaired, medically complex children. Adherence or improvements in prevention strategies could reduce the burden of hospitalization rates or duration of hospital stay and the impact on patients and their families.

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Conflict of Interest

None declared.

References

1. Berger J, Moser HW, Forss-Petter S. Leukodystrophies: recent developments in genetics, molecular biology, pathogenesis and treatment. Curr Opin Neurol 2001;14:305–312.
2. Kaye EM. Update on genetic disorders affecting white matter. Pediatr Neurol 2001;24:11–24.
3. Raymond G, Eichler F, Fatemi A, Naidu S. Leukodystrophies. 1st ed. London: Mac Keith Press, 2011.
4. Bonkowsky JL, Nelson C, Kingston JL, et al. The burden of inherited leukodystrophies in children. Neurology 2010;75:718–725.
5. Nelson C, Mundorff MB, Korgenski EK, et al. Determinants of health care use in a population-based leukodystrophy cohort. J Pediatr 2013;162:624–628.
6. Krivit W, Aubourg P, Shapiro E, Peters C. Bone marrow transplantation for globoid cell leukodystrophy, adrenoleukodystrophy, metachromatic leukodystrophy, and Hurler syndrome. Curr Opin Hematol 1999;6:377–382.
7. Orchard PJ, Tolar J. Transplant outcomes in leukodystrophies. Semin Hematol 2010;47:70–78.
8. de Ru MH, Boelens JJ, Das AM, et al. Enzyme replacement therapy and/or hematopoietic stem cell transplantation at diagnosis in patients with mucopolysaccharidosis type I: results of a European consensus procedure. Orphanet J Rare Dis 2011;6:55.
9. Brimley CJ, Lopez J, van Haren K, et al. National variation in costs and mortality for leukodystrophy patients in US children's hospitals. Pediatr Neurol 2013;49:156–162.e1.

10. Norlin C, Osborn LM. Organizational responses to managed care: issues for academic health centers and implications for pediatric programs. Pediatrics 1998;101:805–811.
11. Age distribution in Utah. Available at: http://governor.utah.gov/dea/Publications/05CensusBriefs2010/2AgeDistribution.pdf. Accessed 23 July 2013.
12. Lemoine TJ, Swoboda KJ, Bratton SL, et al. Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? Pediatr Crit Care Med 2012;13:e161–e165.
13. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. Am J Respir Crit Care Med 2011;183:1463–1471.
14. Gastmeier P, Geffers C. Prevention of catheter-related bloodstream infections: analysis of studies published between 2002 and 2005. J Hosp Infect 2006;64:326–335.
15. Tenke P, Kovacs B, Bjerklund Johansen TE, et al. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents 2008;31:S68–S78.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplemental methods.
Table S1. Selected Demographic and Clinical Characteristics of Leukodystrophy Patients.
Table S2. Odds ratios of modifiable risk factors for hospitalizations with infection. OR, 95% confidence intervals, and *P*-values are given. Risk factor is listed in bold font and the infection outcome is listed below.
Table S3. Odds ratios of modifiable risk factors for hospitalizations with infection in BMT compared to non-BMT patients. ORs (95% confidence intervals; *P*-values) are given. Risk factor is listed in bold font and the infection outcome is listed below. In some categories there were no or insufficient patients for analysis and are listed as "n/a."

