Blastomycosis in children: An analysis of the clinical, epidemiologic, and genetic features.

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Abstract

Background: *Blastomyces sp*. is endemic in regions of the United States and results in blastomycosis, a serious and potentially fatal infection. Little is known about the presentation, clinic course, epidemiology, and genetics of blastomycosis in children.

Methods: A retrospective review of children with culture or cytopathology confirmed blastomycosis from 1999-2014 was completed. *Blastomyces sp*. isolates were genotyped using microsatellite typing and species typed by sequencing of internal-transcribed-spacer2(its2).

Results: Of 114 children with blastomycosis identified; 79% had isolated pulmonary involvement and 21% had extra-pulmonary disease. Children with isolated pulmonary disease had more systemic findings including fever (p=0.01), poor intake (p=0.01), elevated WBC (p<0.01), and elevated CRP (p<0.01) than children with extra-pulmonary disease. Children with extra-pulmonary disease had increased surgeries (p=0.01) and delays in diagnosis (p<0.01) compared to those with isolated pulmonary infection. Of 52 samples genotyped, 48 (92%) children had *B. gilchristii* infections and 4 (8%) had *B.dermatitidis*.

Conclusion: This is the first large scale study of the clinical, epidemiologic, and genetic features of blastomycosis in children. The majority of children had isolated pulmonary disease with systemic findings. Patients with extra-pulmonary disease were less likely to have systemic symptoms or additional laboratory evidence of infection making delays in diagnosis more common. Over 90% of pediatric cases were caused by *B. gilchristii*, which differs from previously reported adult cohorts.

Background

- Blastomycosis, caused by the dimorphic fungus *Blastomyces spp*., is a serious and potentially fatal infection endemic to regions of the United States.
- Little is known about the clinical characteristics or exposure risks in the pediatric population.
- Though adult studies have shown that both *B.gilchristii* and *B.dermatitidis* cause distinct infections it is unclear which is more prevalent in the pediatric population or how this affects phenotype in children.

Methods

• Retrospective chart review of 114 children with culture or cytopathology confirmed blastomycosis over a 10 year period in Wisconsin was performed.
• State epidemiological data for children with confirmed blastomycosis during this time period was analyzed.
• Genotyping of 53 *Blastomyces* isolates from pediatric patients by 27 microsatellite typing and its2 sequencing was completed and phylogenetic analysis was completed.
• Statistical significance was defined as p <0.05.

Table 1: Diagnostic and genetic testing of patients with blastomycosis.

Location of Infection	N=114
Isolated Pulmonary Only	90 (78.9)
Extra-Pulmonary + Pulmonary	14 (12.3)
Isolated Extra-Pulmonary	10 (8.8)
Bone	11 (9.6)
Skin	15 (13.2)
[a]Other	4 (3.5)
[b]Diagnostic Testing for Blastomycosis	
Fungal Culture	95 (83.3)
Smear	92 (80.7)
Serology	16 (14.0)
[c] Urine Antigen Positive	26 (12.8)
Urine Antigen Negative	5 (4.4)
Isolates Genotyped	N=52
Blastomyces dermatitidis	4 (7.7)
Isolated Pulmonary	1 (25.0)
Extra-pulmonary	3 (75.0)
Blastomyces gilchristii	48 (92.3)
Isolated Pulmonary	42 (87.5)
Extra-pulmonary	6 (12.5)

[a] Other locations include 2 CNS, 1 spleen, and 1 abdomen.[b] All patients had Blastomycosis confirmed by fungal culture or smear. Patients may have had additional diagnostic testing completed. [c] Urine antigen testing was completed in 31 patients

Table 2: Demographics and underlying medical conditions of children with blastomycosis.

Demographics	Total n=114	Isolated Pulmonary N=90	[d]Extra-pulmonary n=24	p-value
[b]Age, y	12.9 ± 4.6	12.7 ± 4.5	13.7 ± 4.8	0.34
Male	76 (59.3)	52 (58.4)	15 (62.5)	0.72
Race				
White	73 (64.0)	58 (64.4)	15 (62.5)	0.19
Asian	14 (12.3)	14 (15.6)	0 (0)	0.03
Other/Unknown	23 (20.2)	15 (16.7)	8 (33.3)	0.05
Hispanic	3 (2.6)	3 (3.3)	0 (0)	0.49
African American	1 (0.9)	0 (0)	1 (4.2)	0.21
[c]Underlying Medical Problems	28(24.6)	23 (25.6)	5 (20.8)	0.63
Pulmonary	17 (14.9)	15 (16.9)	2 (8.3)	0.23
Neurologic	5 (4.4)	4 (4.5)	1(4.2)	0.45
Immunocompromised	2 (1.8)	1 (1.1)	1 (4.1)	0.30
[d] Other	8 (7.0)	6 (6.7)	2 (8.3)	0.31

[a] Includes isolated extra pulmonary and combined pulmonary and extra-pulmonary infection.[b] Mean ± standard deviation. [c] Some patients had more than one underlying medical problem. [d] Includes 3 patients with endocrinopathies, 2 with gastrointestinal disorders, 1 with congenital heart disease, one with chronic renal disease, and one with juvenile idiopathic arthritis not on immunosuppressant medication.

Table 3: Clinical, laboratory, and radiographic findings of children with blastomycosis.

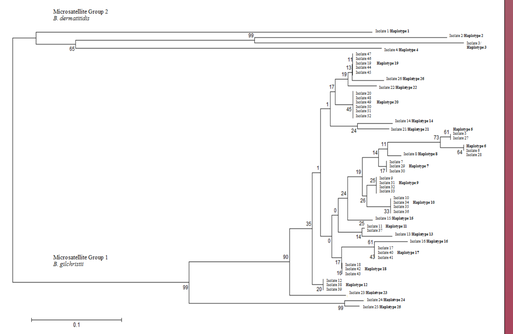
Signs and Symptoms	Total n=114	Isolated Pulmonary N=90	[d]Extra-pulmonary n=24	p-value
Fever	90 (79.0)	76 (84.4)	14 (58.3)	0.01
Weight Loss	47 (41.2)	39 (43.3)	8 (33.3)	0.38
Cough	93 (81.6)	81 (90.0)	12 (50.0)	<0.01
Difficulty Breathing	45 (39.5)	41 (45.6)	4 (16.7)	0.01
Hemoptysis	11 (9.7)	10 (11.1)	1 (4.2)	0.21
Bone or Joint Pain	43 (37.7)	26 (28.9)	17 (70.8)	<0.01
Fracture	4 (3.5)	0 (0)	4 (16.7)	<0.01
Chest Pain	74 (64.9)	66 (73.3)	8 (33.3)	<0.01
Poor Oral Intake	66 (57.9)	58 (64.4)	8 (33.3)	0.01
Pharyngitis	18 (15.8)	17 (18.9)	1 (4.2)	0.05
Lymphadenopathy	14 (12.3)	11 (12.2)	3 (12.5)	0.27
Crackles	37 (32.5)	34 (37.8)	3 (12.5)	0.02
Decreased Breath Sounds	43 (37.7)	39 (43.3)	4 (16.7)	0.02
Abnormal Neurologic Exam	4 (3.5)	1 (1.1)	3 (12.5)	0.03
Hypoxia	13 (11.4)	12 (13.3)	1 (4.2)	0.16
Laboratory Studies (median)	81 (71.1)	65 (72.2)	16 (66.7)	0.59
[a]Initial White Blood Cell Count (WBC), per 1000/µL	13.7	15.1	10.2	<0.01
Highest WBC, per 1000/µL	17.6	19.6	10.7	<0.01
Highest CRP, mg/dL	10.5	18.3	2.2	<0.01
Chest X-ray Obtained	103 (90.4)	84 (93.3)	19 (79.2)	0.04
Infiltrate	94 (82.5)	82 (91.1)	12 (50.0)	<0.01
Effusion or empyema	30 (26.3)	29 (32.2)	1 (4.2)	0.01
Mass	15 (13.2)	12 (13.3)	3 (12.5)	0.27
[b]Hospitalized	76 (66.7)	58 (64.4)	18 (75.0)	0.33
Length of Hospitalization, d	9.0	7.0	10.0	0.74
ICU Care	23 (20.2)	20 (22.2)	3 (12.5)	0.14
Intubated	7 (6.1)	6 (6.7)	1 (4.2)	0.38
Required Oxygen	24 (21.1)	22 (24.4)	2 (8.3)	0.09
[c]Required Surgery	46 (40.4)	27 (30.0)	19 (79.2)	0.01
Length of Illness, d	153.0	140.0	184.0	0.05
Symptom Onset to Start of Antifungal Treatment, d	19.0	15.0	46.5	<0.01
Medications Received				
Itraconazole	92 (80.7)	72 (80.0)	20 (83.3)	0.22
Amphotericin B	39 (34.2)	31 (34.4)	8 (33.3)	0.92
Fluconazole	16 (14.0)	14 (15.6)	2 (8.3)	0.37
Voriconazole	11 (9.7)	8 (8.9)	3 (12.5)	0.24
Ketoconazole	6 (5.3)	3 (3.3)	3 (12.5)	0.09
Length of Treatment, d	140.0	140.0	140.0	0.91
Mortality	5 (4.4)	5 (5.6)	0 (0)	0.30

[a] Includes isolated extra pulmonary and combined pulmonary and extra-pulmonary infection.[b] Continuous variables represented as median values. [c] Patients may have required more than one surgery.

Table 4: Exposure and epidemiologic data for children from state follow up forms.

Demographics	(n=111)
Age (mean in years)	13.0 ± 4.2
Male	67 (60.4)
Season of Diagnosis	
Fall (Sept 23-Dec 20)	38 (34.2)
Winter (Dec 21-Mar 19)	26 (23.4)
Spring (Mar 20-Jun 20)	24 (21.6)
Summer (Jun 21-Sept 22)	23 (20.7)
Known Exposures Within 3 Months of Diagnosis	
Hunting	13 (11.7)
Cabin	13 (11.7)
Camping, Fishing, or Hiking	50 (45.0)
ATV	21 (18.9)
Clearing Brush	29 (26.1)
Excavation	16 (14.4)
Gardening	25 (22.5)
Beaver Dam	9 (8.1)
Occupational	3 (2.7)
Travel	28 (25.2)
Dog Owner	33 (29.7)
Ever Had a Dog with Blastomycosis	9 (8.1)
Household Member with Blastomycosis	10 (9.0)
Lives Near Water	68 (61.3)

Figure 1: Unrooted neighbor-joining tree of 26 *Blastomyces* haplotypes (representing 52 isolates) based on allele sharing distance. Node support (indicated at each branch) represents percent resolution of node across 10,000 bootstrap replicates.



Isolates from patients with extrapulmonary infection are indicated by *. Genetically identical haplotypes were analyzed as one unique haplotype.

Conclusions

- The majority of children had isolated pulmonary disease with systemic findings.
- Patients with extra-pulmonary disease were unlikely to have systemic findings making delays in diagnosis more common.
- Over 90% of infections in children were caused by *B. gilchristii*, which differs from adult cohorts.
- Exposure history and seasonality were similar to what has been previously reported in adults.

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