pediatric stroke

Case Report

Disseminated fungal infection in a 17-month-old boy presenting with cardioembolic stroke

Taryn-Leigh Surtees[1], MD, Sarah A Auerbach[2], DO, Elizabeth C. Lloyd[2], MD, Reilly D. Hobbs[3], MD, Martha D. Carlson[4], MD, PhD

[1]Pediatric Neurology, Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8111, St. Louis, MO 63110-1093, USA; [2]Pediatric Infectious Diseases, University of Michigan, D5101 MPB, 1500 E. Medical Center Dr., Ann Arbor, Michigan, 48109, USA; [3]Department of Surgery, University of Michigan, 2101 Taubman Center, 1500 E. Medical Center Drive. Ann Arbor, MI 48109, USA; [4]Pediatric Neurology, University of Michigan, C.S. Mott Children's Hospital 1500 E. Hospital Dr., SPC 4279, Ann Arbor, Michigan 48109, USA.

Corresponding Author:
Taryn-Leigh Surtees, [a]Pediatric Neurology, Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8111, St. Louis, MO 63110-1093, tsurtees@wustl.edu, 440-318-4324
Or Sarah A Auerbach, Pediatric Infectious Diseases, D5101 MPB, 1500 E. Medical Center Dr., Ann Arbor, Michigan, 48109, saauerba@med.umich.edu, 410-382-8093

Case Report

pediatric stroke

Case Report

Abstract

Abstract

We report the first case, to our knowledge, of pediatric *Lichtheimia* endocarditis in a patient who presented with multifocal arterial ischemic strokes. The unusual organism in an otherwise healthy-appearing child prompted an evaluation for immunodeficiency, and the diagnosis of chronic granulomatous disease was made. This case highlights the need to maintain a high index of suspicion for pediatric stroke in a child with any neurologic complaint and to consider an underlying immunodeficiency especially in well-appearing patients with fungal endocarditis and no known predisposing risk factors. We conclude with a discussion of *Lichtheimia* species infections and their treatment in immunocompromised patients.

Pediatr Stroke. 2022;4: 1-15
www.pediatricstrokejournal.com

pediatric stroke

Case Report

Disseminated fungal infection in a 17-month-old boy presenting with cardioembolic stroke

A 17-month-old boy initially presented to the emergency department with a chief complaint of altered mental status. History was notable only for developmental delay with an inability to take steps unassisted and a four-word vocabulary. The last known well was eight hours prior, when he had abrupt behavioral change with truncal instability and gaze deviation to the left. On presentation, he was afebrile, mildly tachycardic (HR 154) and hypertensive (BP 124/75, >95%ile). Four days prior, hand-foot-and-mouth disease was diagnosed by his pediatrician due to the presence of oral lesions and lesions over the soles of the feet.

A non-contrast head CT demonstrated a large hypodensity in the left middle cerebral artery (MCA) territory with loss of gray-white differentiation (Figure 1), suggestive of an arterial ischemic stroke. Neurologic exam was notable for a right lower facial droop with flattening of the nasolabial fold and right upper extremity plegia; the latter was evident only upon detailed neurologic testing due to the presence of an IV stabilizer board on that extremity. The right lower extremity had less spontaneous movement and a positive Babinski response. A dermatologic exam revealed erythematous papules over the left heel (Figure 2) and no oral lesions. The remainder of the exam, including cardiac, was normal. Brain MRI with MRA head and neck demonstrated a large area of acute ischemia in the left MCA and left anterior cerebral

artery (ACA) distributions, as well as punctate foci of ischemia in the right cerebellum, raising suspicion for a cardioembolic process (Figure 3). Vessel imaging revealed a proximal occlusion in the left MCA (Figure 4). After discussion with neuroradiology, he was deemed to be an unsuitable candidate for endovascular intervention given his age and the extent of completed infarct on head CT and FLAIR change on MRI. He was outside the time window for alteplase (tPA) and was admitted to the pediatric ICU for neuroprotective measures, monitoring, and evaluation.

Laboratory values on admission were notable for anemia with hemoglobin 8.3 g/dL (reference 11-14 g/dL) and an elevated CRP 6.3 mg/dL (reference <0.6 mg/dL). White blood cell count and differential were normal, and a blood culture was negative. A funduscopic exam to evaluate for ocular involvement from an embolic process revealed a yellow-white choroidal lesion in the right eye with adjacent subretinal fluid, hypofluorescent macula, and hyperfluorescent spots on fluorescein angiography (Figure 5). A transthoracic echocardiogram demonstrated a 1.7 cm mobile mass within the left atrium (Figure 6). Given infarct size >2/3 of one cerebral hemisphere, the risk of hemorrhagic transformation with systemic heparinization for surgical excision of the mass was substantial, though the risk for further cardioembolic events was also deemed significant. On day five of admission, he underwent open heart surgery. Operative

findings were notable for a large gelatinous mass originating from the right superior pulmonary vein.

A fungal calcofluor stain of the excised mass showed non-septate hyphae. Intravenous liposomal amphotericin B was started. A mold grew by post-operative day two, identified as *Lichtheimia* species. The choroidal lesion in the right eye was re-evaluated and consistent with fungal infiltrate. He underwent intravitreous amphotericin injections at five days and two weeks after initiation of systemic amphotericin. Thereafter, the lesion improved on serial exams. He ultimately underwent conventional angiography, which revealed no mycotic aneurysms. A full-body PET scan demonstrated a hypermetabolic mesenteric mass and FDG-avid foci in the left frontal lobe, right cerebellum, left deltoid muscle and left quadriceps muscle; the hypermetabolic foci were thought to be consistent with fungal emboli. Benefits of surgical resection of the mesenteric mass were not felt to outweigh the risks, as complete source control was unlikely to be achieved given the widespread foci identified on PET scan. Instead, surveillance imaging was performed to assess response to long-term IV amphotericin.

After three weeks of antifungal therapy, the intramuscular foci resolved, and a trans-esophageal echocardiogram was negative for a residual cardiac mass. The mesenteric lesion was absent on

abdominal ultrasound performed at 6.5 weeks of antifungal therapy. A repeat MRI brain ten weeks into therapy showed evolution of the known infarct and interval developmental of a possible abscess in the left frontal lobe (Figure 7). He eventually underwent brain biopsy and partial abscess wall resection approximately five months after the initial presentation. The biopsy showed necrotic brain tissue with fragmented fungal hyphae; fungal culture was negative, and the infection was thought to be adequately treated given the absence of live fungal elements. He completed approximately seven months of liposomal amphotericin B therapy and continues on treatment dosing of oral posaconazole at approximately one year after initial presentation.

After discovery of the patient's invasive fungal infection, an extensive workup for immunodeficiency was initiated with markedly abnormal dihydrorhodamine (DHR) flow cytometry testing, consistent with chronic granulomatous disease (CGD). Maternal testing was also abnormal in a pattern consistent with a female carrier. Genetic testing revealed a pathogenic mutation in CYBB (c.1244C>4, p.PRO415His), confirming the diagnosis of CGD.

Throughout the prolonged hospital course, he remained constitutionally well, with clinical appearance continuing to belie the severity of disease. Eight months after the stroke, some

neurologic function was regained. He was ambulatory with antigravity strength in the proximal right upper extremity, though distal arm and hand extension remained weak. Expressive language was limited to vocalizations but receptive language was spared.

Discussion:

This case underscores the importance of maintaining a high level of suspicion for pediatric stroke, including the need to perform a neurologic exam in any patient with neurologic complaints. Pediatric stroke is a rare entity, affecting an estimated 2 to 13 per 100,000 children per year.[1] Due in part to its rarity and to the high prevalence of stroke mimics, delayed diagnosis of pediatric stroke is common.[2,3] Timeliness of stroke diagnosis is essential; delayed diagnosis can exclude patients from consideration of hyperacute interventions, including intravenous tPA or endovascular interventions such as intra-arterial tPA and thrombectomy.[2] In this case, the diagnosis of stroke was considered only after neuroimaging was obtained; stroke had not been contemplated at the initial presentation.

Stroke affecting multiple vascular territories and bilateral strokes should raise suspicion for a cardioembolic source and should prompt evaluation with echocardiogram. The absence of fever or other signs of infection does not preclude the possibility of acute endocarditis and

cardioembolic stroke.[4,5] In retrospect, the diagnosis of hand-foot-and-mouth disease was incorrect; the erythematous papules on the heels represented Janeway lesions.

Fungal causes of endocarditis are quite rare, comprising 2-4% of endocarditis cases.[6] The overwhelming majority of cases are due to *Candida* and *Aspergillus* species, encompassing 50% and 25% of cases, respectively. The remaining cases are due to numerous other fungal organisms including Mucorales species.[6] Fungal endocarditis caused by mold has a mortality rate of >80% and is frequently diagnosed postmortem.[7,8]

Lichtheimia species are molds belonging to the Zygomycetes class and Mucorales order, similar to *Mucor* and *Rhizopus* species. They are found in soil.[9] Spores are transmitted most often via inhalation, but also through percutaneous routes or ingestion.[9,10] The manifestation of disease reflects the mode of transmission, with rhinocerebral and pulmonary infection being the most common.[9,10] Infection with these molds rarely occurs in immunocompetent hosts and should therefore prompt an immune evaluation if there is no known predisposing condition. Associated risk factors include implanted foreign material (including cardiovascular devices), diabetes mellitus, prolonged neutropenia, immunosuppression, iron chelation therapy, broad spectrum

antibiotic use, severe malnutrition, and primary breakdown in the integrity of the skin barrier such as from trauma, surgical wounds, or burns.[8,9]

Mucorales and Aspergillus species are associated with higher stroke risk than other fungal pathogens as they cause angioinvasive disease which can lead to thrombosis, infarction, and tissue destruction.[11] Prompt diagnosis is important as delay may allow for dissemination of infection. For Mucorales, therapy should be prompt and aggressive, including a combination of surgical debridement if feasible, systemic antifungal therapy, and reversal of underlying risk factors.[10] Amphotericin is the first line therapeutic option, but oral azoles may be used for step-down therapy, if the organism is susceptible.[12] Optimal duration of antifungal therapy for invasive *Lichtheimia* infections has not been established, though fungal endocarditis is generally treated for at least 6 weeks.[8,12] This case highlights the importance of evaluating for immunodeficiency when faced with an unusual infection in an otherwise healthy host.

Our patient presumably developed this infection due to underlying CGD, an inherited primary immunodeficiency affecting 1 in 200,000 live births.[13] Most cases in the United States are inherited as X-linked recessive.[14] Autosomal recessive inheritance occurs less frequently.[13] X-linked inheritance tends to be more severe with earlier onset of disease, with most children

being diagnosed by five years of age.[13] Diagnosis is made by DHR flow cytometry and should be followed by genetic testing.

Individuals with CGD are more susceptible to bacterial and fungal infections, which can result in development of widespread granulomas. The most common sites of infection are the lungs, liver, skin, and lymph nodes.[13] The most common organisms causing infection in this population in the United States are *Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia*, *Aspergillus*, *Nocardia*, and *Salmonella.*[13] CGD has the highest prevalence of invasive fungal infections among all primary immunodeficiencies, and invasive fungal infections are a significant cause of morbidity and mortality.[13] Mortality due to all infections has likely decreased since lifelong prophylaxis with trimethoprim-sulfamethoxazole and itraconazole became the standard of care.[15] In this case, given infection with *Lichtheimia*, lifelong prophylaxis with posaconazole, rather than itraconazole is required for adequate *Lichtheimia* coverage. The only definitive cure for CGD is hematopoietic stem cell transplant.[13]

This case of a young boy with multifocal ischemic strokes secondary to *Lichtheimia* endocarditis underscores the importance of maintaining a high suspicion for stroke in the pediatric population and of evaluating for immunodeficiency should an unusual pathogen be identified.

Unique challenges in this case included how long to continue antifungal treatment, how frequently to perform surveillance imaging, and how to interpret and act upon neuroimaging when a suspected intracranial fungal abscess was identified.

Acknowledgments

We would like to thank Drs. Richard Ohye and Rachel Gottlieb-Smith for their helpful suggestions and contributions to the review of the manuscript. We would also like to thank our ophthalmology colleagues for the funduscopic images.

References:

1. Beslow LA, Jordan LC. Pediatric Stroke: The Importance of Cerebral Arteriopathy and Vascular Malformations. *Childs Nerv Syst*. 2010;26(10):1263-1273. doi:10.1007/s00381-010-1208-9

2. Mackay MT, Yock-Corrales A, Churilov L, Monagle P, Donnan GA, Babl FE. Accuracy and Reliability of Stroke Diagnosis in the Pediatric Emergency Department. *Stroke*. 2017;48(5):1198-1202. doi:10.1161/STROKEAHA.116.015571

3. Srinivasan J, Miller SP, Phan TG, Mackay MT. Delayed recognition of initial stroke in children: need for increased awareness. *Pediatrics*. 2009;124(2):e227-234. doi:10.1542/peds.2008-3544

4. Raoult D. Afebrile blood culture-negative endocarditis. *Ann Intern Med*. 1999;131(2):144-146. doi:10.7326/0003-4819-131-2-199907200-00012

5. Lamas CC, Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. *Heart*. 2003;89(3):258-262.

6. Gould FK, Denning DW, Elliott TSJ, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2012;67(2):269-289. doi:10.1093/jac/dkr450

7. Yuan SM. Fungal Endocarditis. *Brazilian Journal of Cardiovascular Surgery*. Published online 2016. doi:10.5935/1678-9741.20160026

8. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications. *Circulation*. 2015;132(15):1435-1486. doi:10.1161/CIR.0000000000000296

9. Richardson M. The ecology of the Zygomycetes and its impact on environmental exposure. *Clinical Microbiology and Infection*. 2009;15:2-9. doi:10.1111/j.1469-0691.2009.02972.x

10. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in Human Disease. *Clin Microbiol Rev*. 2000;13(2):236-301. doi:10.1128/CMR.13.2.236

11. Hier DB, Caplan LR. Stroke due to fungal infections. In: Caplan LR, Bogousslavsky J, eds. *Uncommon Causes of Stroke*. 2nd ed. Cambridge University Press; 2008:47-52. doi:10.1017/CBO9780511544897.009

12. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clinical Microbiology and Infection*. 2014;20:5-26. doi:10.1111/1469-0691.12371

13. Arnold DE, Heimall JR. A Review of Chronic Granulomatous Disease. *Adv Ther*. 2017;34(12):2543-2557. doi:10.1007/s12325-017-0636-2

14. Roos D. Chronic granulomatous disease. *Br Med Bull*. 2016;118(1):50-63. doi:10.1093/bmb/ldw009

15. Marciano BE, Spalding C, Fitzgerald A, et al. Common Severe Infections in Chronic Granulomatous Disease. *Clinical Infectious Diseases*. 2015;60(8):1176-1183. doi:10.1093/cid/ciu1154

Figure 1. Axial non-contrast head CT demonstrating a large hypodensity in the distribution of the left middle cerebral artery with loss of gray-white differentiation and mass effect on the left lateral ventricle.
Figure 2. Painless, erythematous papules over the sole of the left foot.
Figure 3. Brain MRI with A) a large area of acute ischemia with restricted diffusion in the left MCA and left ACA distributions with B) ADC correlate as well as C) a punctate focus of ischemia in the right cerebellum with D) ADC correlate.
Figure 4. Magnetic resonance angiogram demonstrating abrupt loss of flow in the proximal left MCA.
Figure 5. A choroidal lesion in the right eye with adjacent subretinal fluid and hypofluorescent macula.
Figure 6. Transthoracic echocardiogram demonstrating the left ventricle (LV) and left atrium (LA) with a mass (arrow) originating from the left atrium.
Figure 7. Brain MRI performed 4 months after the patient's stroke demonstrating a cystic mass with A) heterogenous T2 signal intensity, B) a rim-enhancing pattern with gadolinium contrast, and C) restricted diffusion with D) ADC correlate.