Legionella pneumophila Pneumonia in Two Infants Treated with Adrenocorticotropic Hormone

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Patients with infantile spasms, an intractable epileptic disorder, often are treated with adrenocorticotropic hormone. *Legionella pneumophila* is a rare cause of pneumonia in children. We describe 2 infants with *Legionella* pneumonia whose infection occurred within 1 month after starting adrenocorticotropic hormone. *(J Pediatr 2017;186:186-8).*

Infantile spasms (West syndrome) represent an age-specific epileptic disorder of infancy with unique clinical and electroencephalographic (hypsarrhythmia) features and a poor prognosis, including intractable epilepsy and psychomotor retardation.[1] Adrenocorticotropic hormone (ACTH) has been shown to be effective treatment for infantile spasms since 1958, resulting in seizure control and improvement in behavior and electroencephalographic findings.[2] Treatment with either corticosteroids or ACTH can pose substantial risks, including severe infection.[3] *Legionella pneumophila* is a rare cause of pneumonia in children, and cases are reported predominantly among patients with immunodeficiency and neonates.[4,5] ACTH therapy has been reported rarely to be associated with *L pneumophila* infection.[6,7] We describe 2 infants with *L pneumophila* pneumonia.

Case 1

A 9-month-old female infant was diagnosed with cryptogenic infantile spasms. She was given ACTH 100 U/m^2 for 2 weeks, followed by a 4-week taper. One month after initiation of treatment, she was admitted to hospital with the acute onset of high fever, diarrhea, restlessness, and dyspnea. Findings of the physical examination revealed weakness, hypotonia, and tachypnea (50 breaths/min). Oxygen saturation was normal without supplementary oxygen. Auscultation revealed bilateral wheezing and diffuse crackles. Complete blood count showed white blood cells of 4200/mm^3 (47% immature neutrophils) and elevated serum C-reactive protein of 86 mg/L. Chest radiograph demonstrated right upper lobe infiltrate (**Figure**, A; available at www.jpeds.com).

She was treated with piperacillin/tazobactam and oral azithromycin. During the first 3 days of treatment she deteriorated, and pulmonary infiltrates became bilateral with effusion (**Figure**, B). Nasal secretion for viral respiratory panel (for influenza, parainfluenza, adenovirus, human metapneumovirus, and respiratory syncytial virus by nucleic acid testing), blood for culture, and urine for Legionella antigen test taken at the time of hospitalization were negative except for Legionella antigen, which was positive. Azithromycin was changed to levofloxacin intravenously.

ACTH Adrenocorticotropic hormone

Treatment with levofloxacin was continued for 2 weeks. Mild parapneumonic effusion was drained and tested for Legionella as well as for other pathogens by culture and polymerase chain reaction testing. All results were negative. Her general condition and respiratory effort stabilized. The patient had another episode of respiratory decline attributed to aspiration during the same hospitalization. She required mechanical ventilation for 1 week, after which time she returned to her baseline condition and was discharged.

Case 2

A 14-month-old male infant with symptomatic infantile spasms was started on treatment with ACTH 100 U/m^2 for 2 weeks, followed by a 6-week taper. He was hospitalized 2 weeks into therapy due to hypertension. Six days later, he developed high fever, dyspnea, and diarrhea. White blood cell count was 34 000/mm^3. Serum C-reactive protein level was within normal range and chest radiograph showed right upper lobe consolidation (**Figure**, C). The patient was treated with piperacillin/tazobactam for suspected nosocomial or aspiration pneumonia and improved after 2-3 days, with a decrease in white blood cell count to 22 800 cells/mm^3, but his fever did not resolve. Blood culture and viral respiratory polymerase chain reaction panel were negative. A urine test for Legionella antigen was positive, and intravenous levofloxacin was added to antibiotic regimen. He slowly improved, his fever resolved, he returned to his baseline condition, and he was discharged after 2 weeks of antibiotic therapy. Because pneumonia had become manifest 6 days after previous hospital discharge, nosocomial Legionella infection was suspected, and active surveillance for Legionella in water sources in the hospital was performed, which was negative. No other case was detected within 1 month before and after this case. Both patients were receiving nebulizer treatment and oxygen at home. Water and devices were not tested for Legionella contamination.

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The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.02.063

Discussion

We report 2 infants with infantile spasms treated with ACTH who developed *Legionella* pneumonia 1 month after starting treatment. In the current cases, identification was based on urine antigen test, which is specific for *L pneumophila* serogroup 1, but there are some case reports of cross-reaction. Our patients were treated with levofloxacin after diagnosis, in recognition with reports of the superiority of the drug, especially among immunocompromised patients, although macrolides have been considered the first choice for pediatric patients.[8,9]

L pneumophila has been recognized as a cause of severe pneumonia for more than 40 years, and the overwhelming majority of patients are adults. Over decades, Legionella pneumonia has been reported increasingly in children, mainly among immunocompromised patients and as acquired nosocomially.[4,10] In 2006, Greenberg et al[4] reviewed 76 cases of pediatric legionellosis published in the literature; most of the patient had an underling condition or were younger than the age of 1 year. Corticosteroid therapy was a risk factor in 39% of the cases, but specific regimens were not reported. Mortality rate was high (33%) and notably higher in immunosuppressed patients and in children younger than 1 year of age.

The patients described in the current report were 8 and 14 months old. Because infantile spasms represent an age-specific epileptic disorder, with symptoms starting during the first year of life, ACTH treatment makes this specific population prone to such infections.

Short-term ACTH treatment is one of the favored first-line options for the treatment of infantile spasms.[11] Riikonen and Donner[3] published a summary of 162 cases of children treated with ACTH for infantile spasm 35 years ago. Eight children died, 7 from infection. Five children had bacteremia, and 20 had pneumonia. This study was published 4 years after the discovery of *L pneumophila* and included cases up to 1976; if *L pneumophila* was the cause of some infections, it would have been missed. Infection was more common when larger doses or when synthetic analogues were used.[3] In a later study, Shamir et al[12] reviewed febrile episodes in pediatric patients with infantile spasms treated with ACTH during the years 1987-1990. They observed 75 episodes in 27 patients. Serious infection was observed in 7 cases, 3 of whom died. The main diagnoses were bacteremia and pneumonia. Eight of 66 chest radiographs showed pneumonia. The frequency of bacteremia was 5.3%, as described in the general population, but there was a high rate of fatality among their patients, especially among children with bacteremia.[12]

L pneumophila pneumonia among infants with infantile spasms treated with ACTH is reported rarely. Two cases were reported previously.[6,7] One case was an 8-month-old girl who died from *L pneumophila* and *Pneumocystis jirovecii* pneumonia coinfection 1 month after ACTH was started. The other was an 8-month-old boy treated with high-dose ACTH who developed a fatal systemic infection with *L pneumophila* type 1.[7] Rare cases of *L pneumophila* pneumonia have been reported among children treated with corticosteroids for autoimmune thrombocytopenia, severe croup, or asthma.[13-15] Treatment with ACTH is considered not to carry a significant risk for infection, probably because of the short duration of the treatment. Yet, Ohya et al,[16] investigating immunologic function after ACTH therapy, found that the lymphocyte count and $CD4^+$ T-lymphocyte count were significantly depressed immediately, 1 and 3 months after therapy, and did not return to normal even 6-12 months after cessation of treatment. ACTH leads to increased endogenous cortisol secretion, similar to exogenous administration of glucocorticoids.[6]

In another study, Stuck et al[17] calculated the risk for infection among patients taking corticosteroids and demonstrated an increased risk for infection, especially among patients with neurologic diseases, and a greater risk among those who received parenteral or greater doses of corticosteroids.

The increased risk of *P jirovecii* pneumonia has been recognized in several reports, one of which confirmed coinfection with Legionella.[6] The American Academy of Pediatrics currently recommends prophylaxis against pneumocystis for patients with infantile spasms receiving ACTH.[18]

Our patients were treated with nebulizers and oxygen at home. The aerosol of water generated by these instruments may be the source of Legionella, especially because tap water is used. It is prudent to be cautious with the use of steam generators and to use sterile water for respiratory support for these patients.

Standard treatment for pneumonia in children may not include antibiotics active against *L pneumophila*, especially levofloxacin. Legionella must be considered in patients receiving ACTH (or high-dose corticosteroids) who develop pneumonia. The risk for severe and fatal infection is considerable. Precautions to prevent this infection are warranted. Even with a short course of ACTH treatment, these patients may be prone to severe infections and should be followed carefully, with the anticipation of unusual pathogens and severe course should infection occur. ■

Submitted for publication Nov 23, 2016; last revision received Feb 17, 2017; accepted Feb 23, 2017

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References

1. Appleton RE. Infantile spasms. Arch Dis Child 1993;69:614-8.
2. Gupta R, Appleton R. Corticosteroids in the management of the paediatric epilepsies. Arch Dis Child 2005;90:379-84.
3. Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. Arch Dis Child 1980;55:664-72.
4. Greenberg D, Chiou CC, Famigilleti R, Lee TC, Yu VL. Problem pathogens: paediatric legionellosis-implications for improved diagnosis. Lancet Infect Dis 2006;6:529-35.
5. Shachor-Meyouhas Y, Kassis I, Bamberger E, Nativ T, Sprecher H, Levy I, et al. Fatal hospital-acquired *Legionella pneumonia* in a neonate. Pediatr Infect Dis J 2010;29:280-1.
6. Musallam N, Bamberger E, Srugo I, Dabbah H, Glikman D, Zonis Z, et al. *Legionella pneumophila* and *Pneumocystis jirovecii* coinfection in an infant treated with adrenocorticotropic hormone for infantile spasm: case report and literature review. J Child Neurol 2014;29:240-2.