Lyme disease in a neonate complicated by the Jarisch–Herxheimer reaction

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Lyme disease in a neonate complicated by the Jarisch–Herxheimer reaction

Michael Prodanuk MD, Helen Groves MB BCh BAO PhD, Danielle Arje MD MSc, Ari Bitnun MD MSc

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For the parents' first-hand account of this experience, see www.cmaj.ca/lookup/doi/10.1503/cmaj.220945

A 21-day-old girl presented to the emergency department of an Ontario children's hospital in early summer with a 1-day history of rash on the left arm and 3 days of decreased activity, poor feeding (not waking to feed, decreased volumes) and abdominal distension. She had no fever, weight loss, irritability, recent travel or known infectious contacts.

The neonate was a dichorionic diamniotic twin whose mother had been treated for hyperthyroidism during the pregnancy. Labour was induced at 37 weeks' gestation for intrauterine growth restriction, and the twins were born by vaginal delivery. The patient's mother had screened positive for *Streptococcus agalactiae* (group B streptococcus) on perineal swab culture and had received intrapartum prophylaxis with intravenous (IV) penicillin; however, no maternal fever or prolonged rupture of membranes were noted. The patient and her twin had not required resuscitation at birth; however, both had been admitted to the neonatal intensive care unit for nasogastric tube feeding. Both infants had been discharged at 4 days of life after bottle feeding was successfully established.

On presentation to the emergency department, the patient's vital signs were normal for age (temperature 37.1°C, heart rate 180 beats/min, respiratory rate 40 breaths/min, blood pressure 86/51 mm Hg, mean arterial pressure 63 mm Hg, oxygen saturation 100% on room air). Examination showed mottled skin with preserved capillary refill at 2–3 seconds, a distended but soft abdomen, and a large, blanchable erythematous patch with partial central clearing on the left forearm (Figure 1). We found no abnormalties on cardiovascular, respiratory and neurologic examination.

Bloodwork showed an elevated C-reactive protein level of 33.1 (normal 0.1–1.0) mg/L with normal complete blood count (leukocytes 6.2 × 10^9/L, neutrophils 2.24 × 10^9/L, platelets 298 × 10^9/L, hemoglobin 132 × 10^9/L), electrolytes, venous blood gas, creatinine and transaminases. We collected blood and urine samples for cultures. An electrocardiogram showed sinus tachycardia. An abdominal radiograph showed nonspecific, mildly dilated loops of bowel.

The neonate's family lived on a farm and had regularly found ticks on their dog over the preceding weeks. The parents reported finding an engorged tick on the infant's left forearm 5 days before presentation, attached for no more than 24 hours

Key points

- In Canada, the incidence of Lyme disease among children is increasing, and the disease may be seen in neonates.
- Early localized Lyme disease is a clinical diagnosis; serology at this stage of disease has poor sensitivity and is not routinely recommended.
- Neonates with Lyme disease may be at higher risk for disseminated infection; health care providers should consider a full septic workup and intravenous antibiotics when managing these patients.
- Initial antibiotic treatment of Lyme disease (and other spirochetal infections) may result in the Jarisch–Herxheimer reaction.

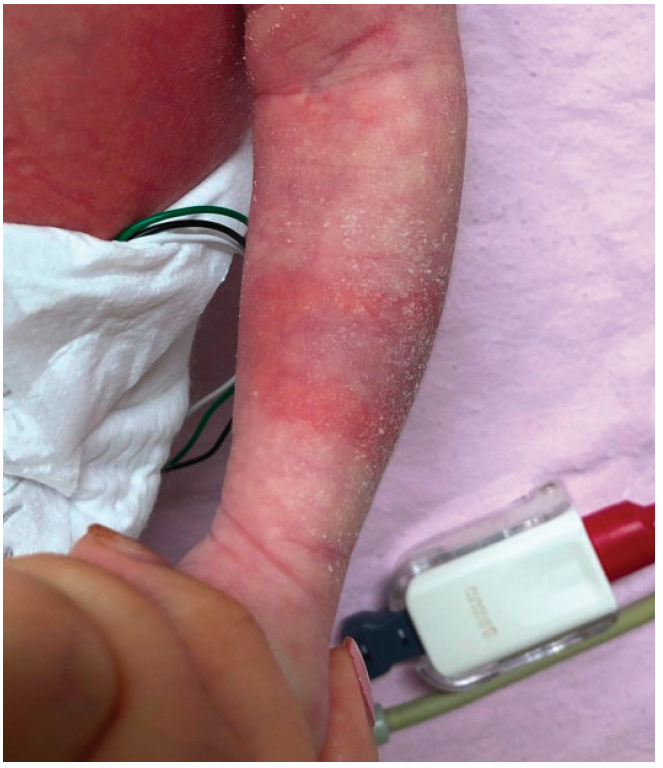

Figure 1: Photograph of an infant with Lyme disease, showing an erythematous patch with partial central clearing on the left forearm.

before removal. Before presenting to hospital, the parents had submitted the specimen to a private commercial laboratory, where it had been identified as an *Ixodes scapularis* tick. Using polymerase chain reaction (PCR), the lab had also identified that it was positive for *Borrelia burgdorferi*. We could not confirm the validity of this assay, however.

Given the erythema migrans lesion at the site from which the engorged tick was removed, we made a presumptive diagnosis of Lyme disease and administered IV ceftriaxone. About 2 hours after the first dose of ceftriaxone, the infant developed a fever of 38.3°C, an increased heart rate of 196 beats/min and a delayed capillary refill of 5 seconds. This deterioration raised our concern for both neonatal sepsis and the Jarisch–Herxheimer reaction — a transient but potentially serious clinical phenomenon, characterized by fever and other systemic symptoms, that develops within hours of starting antibiotic treatment for spirochetal infections. We administered ampicillin for possible late-onset neonatal sepsis, and IV fluids; several hours later, the patient's perfusion, vital signs and temperature normalized.

After clinical stabilization, we performed a lumbar puncture as part of a full septic workup for neonatal sepsis. Analysis of cerebrospinal fluid (CSF) showed a leukocyte count of 4 (reference range < 19) × 10^6/L, an erythrocyte count of 216 (reference 0) × 10^6/L, a protein level of 0.96 (reference range 0.2–0.7) g/L and a glucose level of 2.2 (reference range 2.1–3.6) mmol/L. Cultures from CSF, blood and urine samples showed no growth. Serum Lyme immunoglobulin (Ig) M/IgG enzyme immunoassay was nonreactive. Lyme antibody testing of the CSF was not performed.

The erythema migrans rash resolved after 2 days of ceftriaxone, and the patient subsequently completed a 14-day course of this antibiotic. On follow-up at 8 weeks of age, the infant had no symptoms of Lyme disease and was showing normal growth and development.

Discussion

We present an uncommon case of probable Lyme disease in a neonate who developed the Jarisch–Herxheimer reaction after starting antibiotics. Lyme disease is a tick-borne bacterial infection endemic to regions of Canada, the United States, Europe and Asia. In North America, it is caused by the spirochete *Borrelia burgdorferi*, which is transmitted primarily by *Ixodes scapularis* in eastern and central Canada and *Ixodes pacificus* in British Columbia.[1] The incidence of Lyme disease is increasing in Canada.[2] The annual number of cases reported by the Public Health Agency of Canada increased from 144 in 2009 to 2851 cases in 2021.[3] This increase has been concurrent with a northward expansion of *Ixodes* species, possibly mediated by increasing temperatures related to climate change.[2]

Few cases of Lyme disease have been reported among neonates. Miller and colleagues reported a case of a 2-week-old neonate with isolated erythema migrans and a reactive IgM Western blot, initially treated with cefotaxime.[4] Cerebrospinal fluid studies were not supportive of meningitis, so the patient was transitioned to oral amoxicillin to complete a 21-day treatment course, with a good outcome. Handel and colleagues described a case of a 5-week-old infant who presented with fever and several erythema migrans lesions, and whose serology was nonreactive.[5] This patient received a 14-day course of ceftriaxone, with resolution of symptoms. Based on these reports, newborns with findings consistent with early localized disease may also be at higher risk for disseminated disease.[4,5] Given our patient's very young age, systemic symptoms (poor feeding and decreased activity) and mottled skin, we considered both disseminated Lyme disease and late onset neonatal sepsis (caused by group B streptococcus, *Escherichia coli* or other pathogens). Consequently, we performed a full septic workup and administered broad-spectrum IV antibiotics. Once we excluded bacterial sepsis, treatment for disseminated Lyme disease was completed; antibiotic selection and duration were adapted from the Canadian Paediatric Society's recommendations for Lyme meningitis.[1]

The diagnosis of early localized Lyme disease is a clinical one and does not require serologic confirmation.[1] A history of tick bite or travel to a region where Lyme disease is endemic is a prerequisite to the diagnosis.[1] Serology has poor sensitivity at this stage of the disease, and fewer than 50% of patients with isolated erythema migrans are seropositive.[6] In later disease stages, serologic confirmation is reliable and is recommended for diagnosis.[1] Serologic diagnosis involves a 2-tiered approach to minimize false-positive results, with a screening enzyme immunoassay, followed by more specific tests, such as an immunoblot, if the screening test is positive. The Infectious Disease Society of America (IDSA) does not recommend cultures or PCR testing of blood samples for *Borrelia burgdorferi* owing to low diagnostic accuracy.[7] For suspected infection of the central nervous system, antibody testing of CSF is highly specific for Lyme neuroborreliosis when the CSF-to-serum antibody index is elevated. Testing of CSF by PCR is not advised owing to very low sensitivity. For the diagnosis of Lyme arthritis, PCR testing of synovial fluid may be considered to guide treatment decisions, but culture is not recommended.[7]

For this patient, the diagnosis of Lyme disease was based on the presence of erythema migrans and history of an engorged tick attached to the neonate's skin. Alternate diagnoses of cellulitis or late-onset neonatal sepsis were less likely given the central clearing of the rash (classic appearance of erythema migrans) and the negative results from cultures. Of note, nonreactive Lyme serology is expected at this early disease stage. The identification of the tick as *Ixodes scapularis* and the detection of *Borrelia burgdorferi* by PCR in the removed tick by a private laboratory was additionally supportive. The IDSA guideline recommends identification of the tick species as this may affect counselling and treatment, but recommends against testing the ticks for *Borrelia burgdorferi* as the results do not reliably predict risk of infection.[7]

Within hours of the first dose of ceftriaxone, our patient developed fever, tachycardia and other symptoms consistent with the Jarisch–Herxheimer reaction. This reaction is a recognized response to the treatment of spirochetal infections such as Lyme disease, syphilis, relapsing fever and leptospirosis.[8] It is characterized by fever, rigors and intensification of rashes within 24 hours of starting antibiotics. Clinical instability is uncommon but acute

respiratory distress syndrome, seizures and hypotension may occur. The proposed pathophysiology involves accelerated phagocytosis during rapid bacterial death, which induces cytokine release by monocytes, producing a systemic inflammatory response. The reaction is typically self-limiting and resolves in several hours with supportive care; antibiotics may be continued. The Jarisch–Herxheimer reaction in neonates is best described in the treatment of congenital syphilis; a case series reported the occurrence of this reaction in 18% of 60 neonates.[9] Death is very uncommon, but has been described in a small number of neonates treated with penicillin for relapsing fever.[10]

The incidence of Lyme disease is increasing among children in Canada, including neonates who have been exposed to ticks. Serology is nonreactive in most patients with early localized disease and is therefore not recommended for diagnosis. Given the limited data for neonates and the possible predisposition of this population to disseminated Lyme disease, clinicians should strongly consider administering IV antibiotics to target Lyme disease, as well as regular neonatal pathogens, pending the results of a full sepsis workup. Health care providers should also be aware of the possibility of the Jarisch–Herxheimer reaction during the initial phase of treatment.

References

1. Onyett H; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Lyme disease in Canada: focus on children. *Paediatr Child Health* 2014;19:379-88.
2. Ogden NH, Koffi JK, Pelcat Y, et al. Environmental risk from Lyme disease in central and eastern Canada: a summary of recent surveillance information. *Can Commun Dis Rep* 2014;40:74-82.
3. Lyme disease: monitoring. Ottawa: Public Health Agency of Canada; modified 2022 Apr. 1. Available: https://www.canada.ca/en/public-health/services/diseases/lyme-disease/surveillance-lyme-disease.html#a1 (accessed 2022 Apr. 24).
4. Miller JD, Higgins GL III. Images in emergency medicine. Infant with rash. Neonatal Lyme disease. *Ann Emerg Med* 2014;64:559, 574.
5. Handel AS, Hellman H, Hymes SR. Two neonates with postnatally acquired tickborne infections. *Pediatrics* 2019;144:e20191937.
6. Summaries of infectious diseases: Lyme disease (Lyme Borreliosis, *Borrelia burgdorferi* sensu lato Infection). In: *Red Book: 2021–2024 Report of the Committee on Infectious Diseases.* 32nd ed. Itasca (IL): American Academy of Pediatrics; 2021;482-9.
7. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis and treatment of Lyme disease. *Clin Infect Dis* 2021;72:e1-48.
8. Butler T. The Jarisch–Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *Am J Trop Med Hyg* 2017;96:46-52.
9. Wang C, He S, Yang H, et al. Unique manifestations and risk factors of Jarisch–Herxheimer reaction during treatment of child congenital syphilis. *Sex Transm Infect* 2018;94:562-4.
10. Melkert PW, Stel HV. Neonatal *Borrelia* infections (relapsing fever): report of 5 cases and review of the literature. *East Afr Med J* 1991;68:999-1005.

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Affiliations: Department of Paediatrics (Prodanuk, Arje, Bitnun), Faculty of Medicine, University of Toronto; Division of Infectious Diseases (Groves, Bitnun), The Hospital for Sick Children, Toronto, Ont.

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Correspondence to: Michael Prodanuk, michael.prodanuk@sickkids.ca

The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.