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NEUROBORRELIOSIS IN CHILDREN: REPORT OF CASE AND A REVIEW OF THE LITERATURE

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Abstract. *Introduction.* Neuroborreliosis constitutes a neurological sequelae of Lyme disease, due to the pathogenic activity of the spirochetal agent, Borrelia burgdorferi. Transmission of this microorganism to human hosts occurs through the bite of an infected tick. The persistent intracellular presence of Borrelia burgdorferi gives rise to a primary cutaneous manifestation known as erythema migrans. Later, at advanced stages of the disease, it can lead to central nervous system involve.

The aim is to present a case study of a 15-year-old female patient with neuroborreliosis, a neurological complication of Lyme disease, and to discuss the possible mechanisms of this complication.

Material and methods. Clnical, laboratory, instrumental examination and neurological status assessment of the patient M revealed the Facial muscles palsy on the left side of the face, with no signs of Meningitis. The hospital conducted tests for Borreliosis, a lumbar puncture, and an MRI of the brain.

Results. This clinical report demonstrate the progression of neuroborreliosis, marked by encephalitis and facial nerve palsy, in a 15-year-old female patient. Unfortunately, Lyme borreliosis was detected in the late stages of the disease because the primary symptoms that occur in the early, localized stage - erythema migrans - were omitted. Nonetheless, the identification of neuroborreliosis and the implementation of appropriate therapeutic interventions (Ceftriaxone & Doxycycline, Prednisolone, Acetazolamide prescription) facilitated the patient's recovery. The discussion presents possible mechanisms for the development of this complication.

Conclusions. With this clinical case, we aimed to demonstrate the development of neuroborreliosis with encephalitis and palsy of the facial nerve in an 15-year-old girl, the rare childhood diseases in our regions. Unfortunately, Lyme borreliosis was detected in the late stages of the disease because the primary symptoms that occur in the early, localized stage - erythema migrans - were omitted. However, the diagnosis of neuroborreliosis and adequate treatment contributed to the patient's recovery. The discussion presents possible mechanisms for the development of this complication.

Key words: Neuroborreliosis, Lyme diseases, Encephalitis, Facial nerve palsy, children, treatment.

Нейробореліоз у дітей: клінічний випадок та огляд літератури

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Резюме. *Вступ*. Нейробореліоз є частим проявом хвороби Лайма. Захворювання зумовлене патогенною активністю збудника з родини спірохет – Borrelia burgdorferi. Передача цього мікроорганізму відбувається через укус зараженого кліща, а тривале внутрішньоклітинне персистування Borrelia burgdorferi викликає як первинні симптоми – мігруючу еритему, так і ураження центральної нервової системи.

Мета дослідження: представити випадок нейробореліозу в 15-річної дівчинки та обговорити можливі механізми розвитку цього ускладнення.

Матеріали та методи. Проведено клініко-лабораторне та інструментальне обстеження пацієнтки з хворобою Лайма. У результаті розгляду неврологічного статусу діагностовано параліч лицевих м'язів зліва, без ознак менінгіту. Отримання позитивного тесту з ідентифікації бореліозу, проведення аналізу спинномозкового ліквора, МРТ дослідження головного мозку, діагноз було підтверджено.

Результати досліджень. Даний випадок демонструє прогресування нейробореліозу, що супроводжується енцефалітом і паралічем лицевого нерву. Лайм-бореліоз був виявлений на пізніх стадіях захворювання, тому що первинним симптомам, що виникають на ранній, локалізованій стадії, не було приділено достатньо уваги.

Висновки. Даним клінічним випадком ми мали на меті продемонструвати розвиток нейробореліозу з енцефалітом і паралічем лицевого нерва у 15-річної дівчинки, рідкісних дитячих захворювань у наших краях. На жаль, Лайм-бореліоз був виявлений на пізніх стадіях захворювання, тому що первинні симптоми, які виникають на ранній, локалізованій стадії, – «мігруюча еритема» – були відсутні. Проте діагностика нейробореліозу та адекватне лікування сприяли одужанню пацієнта. Представлено можливі механізми розвитку цього ускладнення.

Ключові слова: нейробореліоз, хвороба Лайма, енцефаліт, параліч лицевого нерва, діти, лікування.

Introduction

The symptoms of Lyme diseases are quite variable, depending on the stage of the disease, develop gradually, and progress from erythema to systemic disorders such as arthritis, carditis, and neurological complications, the latter called neuroborreliosis [1]. According to official data from the Public Health Center of the Ministry of Health of Ukraine, 2,745 cases of Lyme disease were registered in 2020, and 2,442 cases in 2021 (average 7,5 per 100.000), including 450-500 cases in children aged 1 to 18 years; neuroborreliosis is detected with a frequency of 3.5–5%.

The aim of research is to present a case study of a 15-year-old female patient with neuroborreliosis, a neurological complication of Lyme disease, and to discuss the possible mechanisms of this complication

Description of the clinical case

Bioethics approval of Bioethics commission at Danylo Halytsky Lviv National Medical University, the protocol number is 9, dated- 25/09/2023

The 15-year-old girl, Maria, presented to a physician on July 10, 2023, complaining of pain in the muscles of her back in the lumbar region, extending to the thoracic region. The body temperature increased to 37.5º C. The pain appeared suddenly without apparent cause. Two days later, she experienced general weakness, pain in the muscles of her left arm, and numbness in the arm. Similar symptoms developed on the right side the following day. The pain in the back and arms intensified. Within a day, the patient noticed an inability to smile and close her eye.

Upon thorough medical history inquiry, it was established that 25 days prior to the onset of the aforementioned symptoms, an unusual erythema was observed on the skin of the back, in the area of the right scapula. This erythema was circular, approximately 7 cm in diameter, with slight central clearing (Figure 1). It was a painless formation, with the only symptom being mild itching. The patient cannot recall whether there was a tick bite and believes that it is unlikely to have occurred. The patient and the family physician did not attribute due attention to this sign, and no further investigations were conducted. Only observation and the prescription of antihistamines were recommended. This symptom spontaneously regressed within a few days.

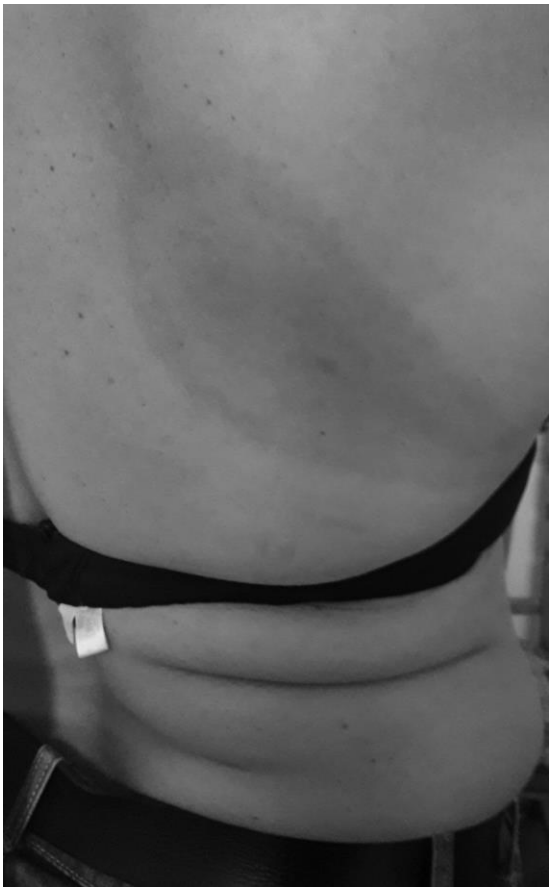

Figure 1. Erythema on the back of a 15-year-old girl M., which was later recognized as erythema migrans. The own photo of the patient. Submitted for publication with the consent of the patient.

On July 15, the child was admitted to one of the clinical hospitals in Lviv. Considering the course of the illness and the presence of neurological signs, Lyme borreliosis with facial nerve palsy was suspected. Neurological examination revealed palsy of the facial muscles on the left side of the face, with no signs of meningitis. The hospital conducted tests for borreliosis, a lumbar puncture, and an MRI of the brain.

On MRI (16.07.2023) the lesion was diffusely hyperintense on T2-weighted images, while T1-weighted images showed peripheral rim-like and nodular enhancement. We also observed small lesions in the white matter of the brain and asymmetry of the lateral ventricles (S > D). Cerebrospinal fluid analysis (15.07.2023) showed colorless, clear fluid with a protein level of 0.33 g/L, cell count of 148/mm^3, and glucose level of 3,0 mmol/L. PCR of the cerebrospinal fluid did not detect herpes viruses 1 and 2, Varicella Zoster virus, or borrelia. Immunofluorescence assay of the cerebrospinal fluid revealed no IgM and IgG antibodies to tick-borne encephalitis virus. Serological blood tests indicated IgG antibodies to Borrelia burgdorferi at 169.5 U/mL (≥22 U/mL considered positive) and IgM antibodies at 1.57 U/mL (above 1.0 U/mL considered positive). CBC (17.07.2023): Hb – 147 g/l, RBC – 5,0*10^{12} /L, WBC – 11,1*10^9 /L, granulocytes – 85,9%, lymphocytes – 12,4%. Proteinogram (17.07.2023): albumin - 66,6 g/l, alpha-1-globulin - 49,1%, alpha-2-globulin -12,4%, beta-globulin – 13,5%, gamma-globulin – 21,8%, ratio – 1,0.

Based on the medical history, clinical presentation, and laboratory findings, the diagnosis of Lyme borreliosis, early disseminated stage, neurological form, meningoencephalitis, and facial nerve palsy was established.

The patient's treatment included prescribing first Ceftriaxone at a dose 2,0 g per day for 7 days than Doxycycline 200 mg/day for 14 days, Prednisolone at 0.5 mg/kg/day for 7 days, and Acetazolamide (ACZ) 500 mg/day. From the 3rd day of treatment the severity of the symptoms of the disease decreased, the signs of paresis of the facial nerve disappeared after the 12th day from the start of therapy. According to the control MRI (20.08.2023), only a slight asymmetric expansion of the lateral ventricles was detected, no lesions in the white matter were visualized

Discussion. Thesymptomsofneuroborreliosis include radiculopathy, meningitis, and facial palsy. Facial palsy and Lyme meningoencephalitis are often seen together, occurring in 63% of patients with Lyme meningitis in European countries and 50% of patients in the USA. The difference in the European and American population is due to different spirochete species [2, 3]. The most serious manifestations of neuroborreliosis is chronic encephalomyelitis. In patients, spastic paraparesis, ataxia, paresis of the cranial nerves (most often facial palsy), deafness, urinary disorders, and various degrees of cognitive impairment develop. The exact time of onset of the infection was difficult to determine, most patients did not remember any manifestations that would indicate Lyme disease, only 10% of patients reported meningoradiculitis 9 mo. to 5 y. before [4].

We diagnosed neuroborreliosis according to the European Federation of Neurologic Societies (EFNS) guidelines. For a definitive diagnosis of neuroborreliosis, three criteria must be met, and two for a possible diagnosis: neurological symptoms, cerebrospinal fluid pleocytosis, and intrathecal production of Bb-specific antibodies [5]. According to the IDSA and AAN guidelines, the diagnosis of Lyme neuroborreliosis can be confirmed if the following conditions are met: the patient has had contact with ticks in an endemic area, they have clinical symptoms that are consistent with neuroborreliosis, and diagnostic testing is positive (positive antibodies to B burgdorferi with or without positive B burgdorferi antibodies in cerebrospinal fluid) [6].

After the initial stage of B. burgdorferi infection, the macroorganism develops antibodies to several bacterial proteins. Despite the presence of neutralizing antibodies, the host's acquired immune response limits spirochete numbers but does not eradicate B. burgdorferi, and most hosts become persistently infected. The ability of the bacteria to survive an antibody response suggests that either the bacteria «hide out» in sites protected from antibodies or that the bacteria evade antibody reactivity by varying antigens or otherwise masking reactive proteins [7].

It has been established that B. burgdorferi can penetrate the central nervous system. This is confirmed by the detection of the pathogen in the cerebrospinal fluid, by bacterial culture of the cerebrospinal fluid or PCR. Indirect methods that indicate the invasion of Borrelia into the CNS are the detection of antibodies in the cerebrospinal fluid, lymphocytic pleocytosis, and the presence of the chemoattractant cxcl13. However, the mechanisms by which B. burgdorferi enters the CNS and the pathophysiology of neuroborreliosis are still poorly understood. There is no evidence that B.

burgdorferi produces any toxins (common to many bacterial pathogens, such as lipopolysaccharide, toxins, and specialized secretion systems) so it is believed that the main factor in the pathogenesis is the inflammatory response of the macroorganism to the influence of the bacterium's antigens. In experimental studies on primary tissue cultures of dorsal root ganglia of rhesus macaques incubated with Borrelia burgdorferi, intense production of inflammatory cytokines ccl2, IL-6, and IL-8, as well as apoptosis of sensory neurons, was established [8].

The development of an inflammatory reaction in response to Borrelia penetration is accompanied by the production of cytokines, including IL-6 and TNF-α, and nitric oxide, leading to vascular lesions, such as vasculitis and hypoxia. This inflammatory and angioparalytic response results in axonal degeneration and, consequently, neuropathy. Immunopathological factors, particularly autoimmune reactions against nervous tissue proteins that cross-react with antibodies to Borrelia antigens, primarily flagellin, play a significant role in the pathogenesis of neuroborreliosis [8]. It has been reported that 80% of patients with confirmed neuroborreliosis exhibit elevated titers of antibodies to cerebral cortex proteins in the cerebrospinal fluid [9]. Sensitization of T lymphocytes to certain neuroproteins is also of considerable importance.

Modern data [10] indicates that the cells of the choroid plexus of the brain's blood vessels, as in many other infectious diseases, may play a key role in the pathogenesis of Lyme neuroborreliosis by inducing inflammatory factors, promoting immune cell migration, and possibly by disrupting the structure and function of the blood-brain barrier.

Conclusions

With this clinical case, we aimed to demonstrate the development of neuroborreliosis with encephalitis and palsy of the facial nerve in an 15-year-old girl, the rare childhood diseases in our regions. Unfortunately, Lyme borreliosis was detected in the late stages of the disease because the primary symptoms that occur in the early, localized stage - erythema migrans - were omitted. However, the diagnosis of neuroborreliosis and adequate treatment contributed to the patient's recovery. The discussion presents possible mechanisms for the development of this complication.

Conflict of interest. The authors declare that there is no conflict of interest in relation to this paper, as well as the published research results, including the financial aspects of conducting the research, obtaining and using its results, as well as any non-financial personal relationships.

REFERENCES

1. Garcia-Monco JC, Benach JL. Lyme Neuroborreliosis: Clinical Outcomes, Controversy, Pathogenesis, and Polymicrobial Infections. Ann Neurol. 2019 Jan;85(1):21-31. doi: 10.1002/ana.25389.
2. Pachner AR, Steere AC. The triad of neurologic manifestations of Lyme disease: meningitis, cranial neuritis, and radiculoneuritis. Neurology. 1985 Jan;35(1):47-53. doi: 10.1212/wnl.35.1.47.
3. Kozak S, Kaminiów K, Kozak K, Paprocka J. Lyme Neuroborreliosis in Children. Brain Sci. 2021 Jun 7;11(6):758. doi: 10.3390/brainsci11060758.
4. Campo-Caballero D, Munoz-Lopetegi A, Fernandez-Garcia de Eulate G, Rodriguez-Antiguedad J, Gabilondo A, Gonzalez F, Villanua J, Lopez de Munain A. Encefalomielitis extensa por Borrelia: una forma atipica de neuroborreliosis [Extensive encephalomyelitis due to Borrelia: an atypical form of neuroborreliosis]. Rev Neurol. 2019 Feb 16;68(4):169-170. Spanish.
5. Mygland A, Ljøstad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I; European Federation of Neurological Societies. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol. 2010 Jan;17(1):8-16, e1-4. doi: 10.1111/j.1468-1331.2009.02862.x.
6. Garkowski A, Łebkowska U, Kubas B, Garkowska E, Rutka K, Gawarecka E, Zajkowska J. Imaging of Lyme Neuroborreliosis: A Pictorial Review. Open Forum Infect Dis. 2020 Aug 19;7(10):ofaa370. doi: 10.1093/ofid/ofaa370.
7. Ramesh G, Santana-Gould L, Inglis FM, England JD, Philipp MT. The Lyme disease spirochete Borrelia burgdorferi induces inflammation and apoptosis in cells from dorsal root ganglia. J Neuroinflammation. 2013 Jul 18;10:88. doi: 10.1186/1742-2094-10-88.
8. Bolz DD, Weis JJ. Molecular mimicry to Borrelia burgdorferi: pathway to autoimmunity? Autoimmunity. 2004 Aug;37(5):387-92. doi: 10.1080/08916930410001713098.
9. Parthasarathy G, Gadila SKG. Neuropathogenicity of non-viable Borrelia burgdorferi ex vivo. Sci Rep. 2022 Jan 13;12(1):688. doi: 10.1038/s41598-021-03837-0. PMID: 35027599;
10. Tilly K, Rosa PA, Stewart PE. Biology of infection with Borrelia burgdorferi. Infect Dis Clin North Am. 2008 Jun;22(2):217-34, v. doi: 10.1016/j.idc.2007.12.013. PMID: 18452798;

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