ECRONICON OPEN ACCESS

EC PAEDIATRICS
Case Series

Cases of Neuroborreliosis in Children of the Ternopil Region

Svitlana Nykytyuk[1]*, SI Klymnyuk[1] and MM Kostyk[2]

[1]*Ternopil National Medical University I. Horbachevskyi, Ukraine*

[2]*Ternopil Regional Children's Clinical Hospital, Ukraine*

***Corresponding Author**: Svitlana Nykytyuk, Ternopil National Medical University I. Horbachevskyi, Ukraine.

Received: April 12, 2020; **Published:** May 20, 2020

Abstract

Background: Neuroborreliosis is the most common manifestation of the disseminated form of Lyme disease features of central and peripheral nervous system involvement.

Materials and Methods: We reviewed charts of 95 patients with diagnosis of encephalitis. Among them we identified 7 of patients with neuroborreliosis (NB). Diagnosis of NB was made based on history, physical examination, laboratory data (positive anti-borrelia IgM on ELISA with immunoblot confirmation as well as abnormalities on MRI of the brain that were attributed to infectious process (Neuro-Lyme). A case of neuroborreliosis in a children is presented.

Results: The peculiarity of the presented case is in 3 children was diagnosed co-infection with tick-born encephalitis, granulocytic anaplasmosis and herpes virus infection. At an early stage, neurological symptoms occur up to 6 months after the tick bite and in a late stage of borreliosis - after more than 6 months.

Conclusion: 1. For differential diagnosis of neuroinfections and Lyme neuroborreliosis, it is necessary to observe two-stage serological investigation of blood, especially use of antibody screening tests by ELISA with subsequent confirmation by the Western blot assay. 2. Taking into account the ambiguity of approaches in the treatment of the examined group of children in Ukraine, treatment of neuroinfection requires standardization of treatment protocols in accordance with the requirements of the World Health Organization. 3. The course of the disease may different from the classical triad and includes only cerebrospinal syndrome or cervical myalgia. 4. Possibility of co-infections with herpes virus, anaplasma can be present in the patients, proper care must be taken to recognize and treat them.

Keywords: *Child; Borrelia burgdorferi; Lyme Disease; Neuroborreliosis; Human Granulocytic Anaplasmosis; ELISA; Western-blot; IgM; IgG*

Background

Neuroborreliosis is the most common manifestation of the disseminated form of Lyme disease features of central and peripheral nervous system involvement. In Europe, this disease is caused by three types of bacteria including *B. burgdorferi* and more often, *B. garinii* or *B. afzelii*. In North America, the pathogen causing Lyme's disease is almost exclusively *B. burgdorferi*. Transmission to humans usually occurs via an infected tick bite. In endemic areas, the incidence exceeds 100 cases per 100,000 population [1,5]. In the recent years in Europe, there is an increase in the incidence of Lyme's neuroborreliosis with a most common clinical presentation, which occurs in 10 - 15% of cases, the second most common presentation being aseptic meningitis.

Materials and Methods

Histories of the disease of in 95 patients with encephalitis were analyzed. Among them 7 of persons were patients with neuroborreliosis (NB). This diagnosis was confirmed by the patients complaints, anamnesis, laboratory data (increase of anti-borrelia IgM in ELISA and further immunoblot assay response, changes in brain which were revealed by MRI and corresponding infectious changes (Neuro-Lyme). The diagnosis of herpes viral infection in combination with granulocytic anaplasmosis, the was determined by herpes virus and anaplasm DNA examination in based real-time PCR assay. One of the patient had mixed herpes viral infection, which was confirmed by PCR. Our investigations showed that the etiological diagnosis of mixed infection should be confirmed by the data of an immunological examination of blood and the results of investigation of the cerebrospinal fluid (CSF).

Research objective of our study is to analyze the frequency of occurrence, causes and prognosis of tick born neuroinfections in children.

Patients and Methods

We performed a retrospective analysis of 95 patient's charts who were treated in the neurological and infectious-diagnostic departments at Ternopil Regional Children's Hospital (Western Ukraine) during last 6 years (2012 - 2018). This investigation is a part of a joint Ukrainian-Polish project "Research on the epidemiology, pathogenesis, clinical presentation and prevention of Borreliosis" within the framework of research projects of the European Union. We identified 7 (7.4%) of neuroborreliosis in children aged 4 to 16 years.

The diagnosis was confirmed by a two-step laboratory testing: the first one is based on the European ELISA; all positive results were confirmed by a second step testing using more specific Western Blot test.

DNA of anaplasma was identified by PCR in real-time (using Real Best DNA test system Anaplasma phagocytophilum). In 3 children was diagnosed co-infection with tick-born encephalitis, granulocytic anaplasmosis and herpes virus infection.

Results

We reviewed charts of 95 patients with diagnosis of encephalitis. Among them we identified 7 of patients with neuroborreliosis (NB). Diagnosis of NB was made based on history, physical examination, laboratory data (positive anti-borrelia IgM on ELISA with immunoblot confirmation as well as abnormalities on MRI of the brain that were attributed to infectious process (Neuro-Lyme).

Clinical case 1: 15 years girl was admitted to neurological department with complaints of right sided facial muscle weakness and facial asymmetry.

History of present illness (HPI): Developed neck pain 2 weeks prior to presentation, a week later her mother noticed facial asymmetry. Both patient and her parents deny a tick bite.

Past medical history (PMH): None. A child from the first full term uncomplicated pregnancy. She timely met all developmental milestones.

Pertinent physical examination (PE): Right-sided facial droop with muscle weakness at the level of the forehead, cheeks, lips, diminished blink.

Labs: CBC with differential as well as CMP were normal, ESR 7 mm/hr, C-reactive protein 1.18 g/l (< 5.0). ASO 31 (< 150), rheumatoid factor negative. Borrelia antibody IFA as well as confirmatory IgG and IgM Western Blot were positive: IgG 2 RU/ml (n - 1.1), Ig M - 200 RU/ml (n - 22).

Blood biochemistry test: Glucose - 4 mmol/L, total protein - 60 g/l, urea n 3.5 mmol/L, creatinine - 0.052 mmol/L, bilirubin - 11,1 mmol/L, Ca - 2.2 mmol/L, P - 1.2 mmol/L, AST - 30 u/l, ALT - 20 u/l (norm (n) till 40 u/l.); Rheumatoid tests (RT) - Asl-O - 31 (negative - n 150), C-reactive protein - 1.18 g/l (5.0), RF - 2.2 (n 14); results of serological test in she presented 2 weeks after "beginning of disease" according to history of present illness became positive according to anti- borrelia Ig M - 200 RU/ml (n - 22), anti- borrelia Ig G - 2 RU/ml (n - 1.1). Values for Western Blot were Ig M to OspC *B. afzelii*, antigens P41 and Ig G to OspC *B. afzelii*, P41 21.

Patient was diagnosed with Lyme's disease, early disseminated stage with right sided facial nerve palsy.

Case 2: 12-year-old boy was hospitalized with complaints of drowsiness, neck stiffness, intermittent diplopia, occipital headache.

HPI: Acute onset of disease. On presentation chicken pox was diagnosed and the child was transferred to emergency department at TRCH (Ternopil region children hospital).

Epidemiological anamnesis: Tick's bite was not noticed.

PE: General condition of moderate severity due to intoxication syndrome and neurological symptoms. Normal respiratory sounds. Cardiac revealed regular rate and rhythm, no murmurs. Abdomen is soft, non-tender.

Neurological status: AAAx3, PERRLA.

Kernig and Brudzinsky's signs were negative, deep tendon reflexes symmetric 2+ (normal), normal corneal reflex.

Labs: CBC: Hb 125 g/l, RBC 3.96 x 10^{12}/l, (WBC) 5.1 x 10^{9}/l, bands - 15%, segmented neutrophils - 19%, eosinophils - 1%, lymphocytes - 57%, monocytes - 8%. ESR 7 mm/hr.

CMP: Glucose - 3.7 mmol/L, total protein -72 g/l, BUN-5.79 mmol/L, creatinine - 53.8 mmol/L, bilirubin total -9.0 mmol/L, K - 4.6 mmol/L, Na - 130.3 mmol/L, Ca - 2.31 mmol/L, AST - 20 u/l, ALT - 41 u/l, alpha- amylase - 80 u/l, alkaline phosphatase (AP) - 274 u/l.

Ophthalmological exam: Angiopathy of retina vessels.

Electrocardiograpy (ECG): Sinus arrhythmia with a tendency to bradycardia, intraventricular conduction disorder, left ventricular overload.

Preliminary diagnosis on admission: Brainstem encephalitis of unknown etiology. Chicken pox, typical of medium severity, recovery period.

The child was tested according to a two-stage algorithm [6]. Serum samples were checked for Lyme antibodies using ELISA. Confirmation testing was made by Western blot assay. European IgM Western blot was positive in 2 weeks (17 days after the onset of symptoms and 7 days after starting the treatment). ELISA revealed anti-*B. burgdorferi* IgM of 2.29 RU/ml (0.71 - 3.00 is positive), anti- *B. burgdorferi* IgG 0.08 RU/ml (negative 0.0 - 0.50).

Immunoblot assay identified surface proteins OspC (*B. afzelii*), OspC Bb (*B. burgdorferi*), OspC Bg (*B. garinii*). Lipid Bb (*B. burgdorferi*) was borderline proteins P41, OspC (*B. afzelii*) were positive.

Fluid analysis: Total proteins was increased at 1.25 g/l (normal 0.15 - 0.40 g/l), concentration of glucose was decreased at 1.6 mmol/L (normal 2.1 - 3.6 mmol/L). Cytological analysis was negative for malignancy.

Diagnosis: Lyme disease, disseminated form. Neuroborreliosis.

Clinical case 3: 12 years girl presented with complains of generalized weakness, low grade fever.

HPI: Symptoms started 6 days prior. She was given detox therapy but low grade fever persisted, she developed paresthesia of left arm and leg, headache.

Epidemiological anamnesis: Endorses tick bite in abdominal region 5 months prior to presentation. There was a bull's eye rash at the site of tick bite. The child did not get antibacterial therapy previously.

PE: AAO x 3, answers questions appropriately, emotional. Signs of meningeal irritation negative. BMI is low, secondary female sexual characteristics present.

Deep tendon reflexes normal, symmetric. Skin was pale color, clear. Moderate pharyngeal erythema.

Tongue was covered with white plaques. Submandibular lymph nodes were mildly enlarged.

Diminished breath sounds at bases on lung auscultation. The borders of the heart corresponds to the asthenic type of the body structure. On heart examination: regular rate and rhythm, muffled heart sounds.

Neurological exam: CN II-XII grossly intact, normal muscle tone and strength. Deep tendon reflexes normal, symmetric in upper and lower extremities, toes are down going bilaterally.

Considering presence of febrile reaction, presence of moderate catarrhal symptoms, intoxication syndrome and intermittent left sided paresthesia, additional testing, the child was diagnosed acute respiratory viral infection and sensory simple partial seizures.

ECG: Heart rate (hr) 72 per 1 minute, sinus arrythmia, disorder of intraventricular conduction. Myocardial hypoxia.

Immunoblot: Surface proteins OspC (*B. afzelii*) and P41 IgM were identified, VLsE (*B. afzelii*) Ig G, VLsE (*B. garinii*) Ig G, OspC (*B. afzelii*) Ig G were detected.

MRI of the brain: Changes of MR signal in the right fronto-temporal lobe with abnormal grey-white differentiation left temporal lobe, to some degree in the basal ganglia. Differential diagnosis include cysts, tumor.

Echoencephalogram (EEG): Signal frequency was diminished, zonal differentiation is absent, there are outbreaks of low-wavelength activity more in the frontal-parietal region, the appearance of hypnotic high-amplitude hypersynchronization on the background of hyperventilation. Epileptiform episodes were not detected.

CBC: Hb 116 g/l, (RBC) 3.57 x 10^{12}/l, CI 0.9, WBC 6.6 x 10^{9} /l, bands - 5%, segmented neutrophils - 71%, eosinophils - 1%, lymphocytes - 20%, monocytes - 3%, erythrocyte sedimentation rate 5 mm/hr (normal 2 - 10 mm/hr).

Spinal fluid analysis: Glucose 3.2 mmol/L, chloride 116 mmol/L, cell count 70/1 mm^3, neutrophils - 70%, lymphocytes - 30%.

Serology: Positive HSV 1 and 2, HSV-6 DNA by PCR.

CMP: Glucose 5.2 mmol/L, total protein 71.3 g/l, BUN 2.8 mmol/L, creatinine 47.5 mmol/L, bilirubin total 8.9 mmol/l, K 3.63 mmol/L, Na 133 mmol/L, Ca 0.94 mmol/L, AST 17.5 U/L, ALT 8.5 U/L (normal < 40 U/L), amylase 35 U/L.

Diagnosis: Acute mixed infection HSV type 1/2 encephalitis, Lyme borreliosis, manifestation form, disseminated stage, subacute course of moderate severity. Treatment ceftriaxone, acyclovir.

Clinical case 4: 12 years girl was admitted to the hospital with complains of left sided facial weakness facial droop, neck pain mainly on the left.

HPI: Noticed neck pain for before presentation, a week later noticed facial droop.

Epidemiological anamnesis: Neither child nor her parents noticed.

Physical examination: Gait is normal. AAO X 3. PERRLA. Left sided ptosis. Left sided facial droop, tongue is midline. Normal muscle tone. No pathological reflexes. No cerebellar signs.

During the hospital stay ring-shaped erythematous rash with clearing in the center appeared on the side of her trunk.

Laboratory values: Serum Lyme antibody ELISA obtained 10 days after onset of symptoms was positive and showed a presence of anti-borrelia IgM - 5.5 RU/ml, and IgG - 1.1 RU/ml.

CBC: Hb 121 g/l, CI 0.9, red blood cell count (RBC) 3.96 x 10^{12}/l, leucocyte l count (WBC) 5.3 x 10^{9}/l, bands - 4%, segmented neutrophils - 50%) 1%, lymphocytes 42%, monocytes 3%, eosinophils - 0%. ESR - 21 mm/hr.

Blood biochemistry tests: Glucose 4.6 mmol/L, total protein 60 g/l, urea nitrogen 3.5 mmol/L, creatinine 0.052 mmol/L, bilirubin total 11,1 mmol/L, Ca 2.2 mmol/L, P 1.2 mmol/L, AST 30.0 U/l, ALT 20.0 U/l. ASL-O 31 (normal 150), CRP 1.18 (normal 5,0); Urinalysis normal.

MRI of the brain: No focal changes were observed.

ECG: Atrial-ectopic rhythm, signs of myocardial hypoxia.

Diagnosis: Lyme disease, early disseminated phase, with erythema chronicum migrans and left facial palsy.

Clinical case 5: 9-year-old girl, presented with complaints of left sided facial weakness, facial asymmetry.

HPI: Mother noticed facial asymmetry 4-5 days prior to hospitalization

PMH a child from the first uncomplicated, full-term pregnancy, timely met all developmental milestones.

Epidemiological anamnesis: Six months ago she noticed a tick bite. Mother noted erythema at the site of a bite. They did not seek a treatment.

Physical examination: Gait is normal. AAO X 3. PERRLA. Left sided ptosis. Left sided facial droop. Tongue is midline. Normal muscle tone. No pathological reflexes. No cerebellar signs.

CBC: Hb 123 g/l, CI 0.9, RBC4.87 x 10^{12}/l, WBC 12.5 x 10^{9}/l, bands 2%, segmented neutrophils 68%, eosinophils 2%, lymphocytes 27%, monocytes 1%. ECR 4 mm/hr.

Blood biochemistry tests: Glucose 5.5 mmol/L, total protein 58 g/l, urea nitrogen 3.4 mmol/L, creatinine 0.048 mmol/L, bilirubin 10.0 mmol/L, Ca 2.0 mmol/L, P 1.2 mmol/L, AST 30 U/L, ALT 20 U/L (normal before 40 U/L), ASL-O normal (normal 150), C-reactive protein (CRP) 0,23 (normal 5.0), Rheumatoid factor (RF) - negative (normal 14), serum glycosides - 3.2.

Immunogram: By Elisa method there were anti- *B. burgdorferi* IgG - 98.98 RU/ml (pos. 22), IgM 75.29 RU/ml (pos. 22). By Immunoblot method: P41 OspC Ba (*B. afzelii*), OspC Bb (*B. burgdorferi*), Ig M, VLsE (*B. garinii*) Ig G, OspC (*B. afzelii*), P41 Ig G were found.

Urinalysis: Normal.

ECG: There are intraventricular conduction disturbances.

Transthoracic echocardiography of the heart valves, the mitral valve prolapse of the 1 degree with minimal regurgitation.

Diagnosis: Lyme disease, early disseminated phase, left facial palsy.

Clinical case 6: 4-year-old girl presented with complains of difficult swallowing, nasal congestion and general weakness.

HPI: Mother noticed lethargy, poor appetite.

Anamnesis vitae: A child is from first uncomplicated, full term pregnancy. Timely met developmental milestones.

Epidemiological anamnesis: Parents deny history of a tick bite.

Neurological status: Awake, lethargic, fed through the gastric tube. PERRLA. No facial droop.

Gag reflex is absent, movement of soft palate is absent, active movements in the limbs are not limited, Muscle tonus is preserved; tendon and periosteal reflexes - knee ones are alive, D = S, an abdominal reflexes are absent. Vibration sensitivity is not affected. Gait is not tested. Pathological reflexes are absent. The functions of pelvis organs are not violated.

Complete blood count (CBC): Hb 136 g/l, CI 1,0, RBC 4.18 x 10^{12}/l, WBC 10.3 x 10^{9}/l, bands 5%, segmented neutrophils 69%, eosinophils 2%, leucocyte count (WBC) 21%, monocytes 3%, ESR 6 mm/hr.

A month after treatment: CBC: Hb 86 g/l, КП 0,8, red blood cell count (RBC) 3.10 x 10^{12}/L, WBC 4.0 x 10^{9}/L, bands 2%, s 66%, e 2%, I 30%, m 2%, ESR 5 mm/hr/.

Blood biochemistry tests: Glucose 4.5 mmol/L, total protein 72 g/l, urea 6.5 mmol/L, creatinine 48 mmol/L, bilirubin 12.1 mmol/L, Ca1.18, mmol/L, AST 31u/l, ALT 0.487 u/l, LDG 259 U/L.

Spinal fluid analysis: General cell count - 3/1 mm^3, total protein 0,091 g/l, glucose 2,4 mmol/L, C1 121 mmol/L.

Immunological examination: Anti-Borrelia IgM 1.57 RU/ml (no 3. 1.1), IgG 0.33 RU/ml (pos 1.1).

Immunoblot method P41, OspC Ba (*B. afzelii*), OspC Bb (*B. burgdorferi*), OspC Bg (*B. garinii*) were detected.

Tick-borne viral encephalitis IgG 0.36 RU/ml (negative), IgM 0.96 RU/ml (equivocal 0.8 - 1.1).

PCR of blood, liquor HSV 1, 2, 6 were not detected, CMV, WEB- were not detected.

Urinalysis: Normal.

On MRI of the brain, no focal changes are observed.

ECG: Sinus arrhythmia, shortening of the interval P-Q to 0.10, violation of the processes of repolarization, echocardiography of the heart valves - transverse chord in the left ventricle; Ultrasound examination of blood vessels of the head and neck: angiospasm of the vertebral artery, hypoplasia of the left posterior cerebral artery.

Diagnosis: Lyme disease, acute course, severe form, early disseminated stage with the presence of brain stem-encephalitis with bulbar and cerebral syndromes. Normochromic anemia of a moderate severity.

Clinical case 7: 11 years boy, consulted with a neurologist in July 2018 with complaints of a pressure-like headache after a sleep, fatigue.

HPI: The disease ran out with severe cephalalgia without raising the temperature in the debut of the disease acute onset of the disease.

Epidemiological anamnesis: Noticed a tick's bite 4 weeks before the onset of the disease. The child described erythema migrans at the site of the tick's bite.

Neurological exam non focal.

Serologies: Presence of anti-*B. burgdorferi* IgM - 76.89 RU/ml (Normal 16 - 22 RU/ml), IgG- 0.18 RU/ml. By Western Blot: surface proteins, OspBa of *B. Afzelii*, OspBa of B. garinii and anti-borrelia IgM were detected, Ig G p41.

Spinal fluid analysis: WBC count - 5 cells/mm^3 total protein 0.091 g/l, glucose 2.4 mmol/L.

Cytomegalovirus DNA by PCR - negative. Anaplasma DNA by PCR positive.

Brain MRI revealed two non-specific periventricular lesions.

Patient was diagnosed with *B. burgdorferi* and Anaplasma co-infection.

Only in two cases out of seven patients or parents reported history of a tick bite. Four patients that did not recall a tick bite but observed erythema migrans.

Erythema migrans is a typical sign of Lyme's disease is a circular red rash with central clearing that slowly expands. It may be accompanied by fly-like symptoms.

On average 50% of patients with NB indicate a contact with ticks in their history, and only 20 - 30% of patients report erythema migrans [3,13]. Two children had Bell's palsy. According to literature [7], Bell's palsy (unilateral or bilateral) can be seen in 3 - 5% of cases of NB and can be the only disease, manifestation. Recognition of Lyme's Borreliosis symptoms is extremely important for the rapid diagnosis and treatment of this disease. Lyme borreliosis, as a rule, manifests itself by in three different clinical stages (early localized, early disseminated, and late stage).

According to the classification of Neuroborreliosis (EFNS) [3] there are early and late neuroborreliosis. At an early stage, neurological symptoms occur up to 6 months after the tick bite, and in a late stage of borreliosis - after more than 6 months.

It includes manifestations of central and peripheral nervous system involvement (myoclonus, ataxia, dizziness, cranial polyneuritis, transversal myelitis with hemiparesis or idiopathic intracranial hypertension [13]. The most common neurological symptoms typical for lymphocytic meningitis with painful cranial neuritis, polyradiculitis or encephalomyelitis [7].

According to Nau R, Christen HJ, Eiffert H, 2009 [3], neurological manifestations include Bell's palsy, other cranial nerve palsies, aseptic meningitis and radiculopathy Lymphocytic (Bannwarth syndrome) is the second most common presentation of early Lyme disease in Europe. Its clinical features include involvement of the cranial nerves (for example, facial paralysis), paresis, radicular root pain, as well as lymphomonocytic meningitis with a relatively high concentration of lymphocytes in the CSF.

Proposed are following criteria for diagnosis of NB: presence of neurological symptoms, anti - *B. burgdorferi* antibodies positive in CSF, pleocytosis in cerebrospinal fluid (CSF). NB may be diagnosed if two out of three criteria are present.

Anti-Borrelia IgM can be detected serologically in 50 - 90% of patients. However, serological testing frequently can be false negative.

Meningitis, encephalitis, paresis of the cranial nerves, Bannwarth lymphocytic meningitis can develop in a few weeks or months after a tick bite. Most common symptom for children with borreliosis is peripheral paralysis of the face, usually one-sided. Neurological manifestations include the facial (cranial nerve VII) and other paralysis of the cranial nerves, aseptic meningitis and radiculopathy. Clinical manifestations of meningoradiculoneuritis (Bannwarth syndrome) are the second most common presentation of early Lyme disease in Europe. Clinical features include cranial nerve palsies (e.g. facial paralysis), paresis, radiculitis and radiculitis, as well as lymphomonocytic meningitis with a relatively high concentration in the CSF [5].

Criteria of diagnosis of central nervous system Lyme borreliosis (with the exception of late Lyme disease with polyneuropathy) are neurological symptoms of Lyme disease and exclusion of other causes.

For definitive diagnosis of neuro Borreliosis all three criteria must be met. Possible diagnosis of neuro Borreliosis require two out of three criteria.

Diagnostic criteria of late identified Lyme disease of CNS requires all 3 criteria. Possible Lyme disease of CNS requires 2 of 3 criteria, which were present above. If the third criterion is not available, the repeated examination, which is carried out in 6 weeks, should be positive. To establish the diagnosis of late Lyme disease of CNS with polyneuropathy, the following 3 criteria must be used: Peripheral neuropathy, Clinical diagnosis of chronic atrophy, Presence of specific anti- *B. burgdorferi* antibodies.

The most common feature of the European Lyme neuroborreliosis is the triad of Bannwarth syndrome (lymphocytic meningitis, craniocerebral neuropathy and painful radiculitis), but not aseptic meningitis, which is more common in the North American continent. According to international recommendations, serologic diagnosis should be made in two stages. The first stage - ELISA or indirect immunofluorescence, the positive result mast be confirmed by Western blot assay. To determine IgM the most susceptible test is use of borrelia antigen OspC, for IgG - vlsE. Levels of specific IgM can be maintained in the patients' serum for a long time. Additional testing for antibodies to vlsE antigen increases serological percentage of diagnosis by 20 - 30%.

European patient's serums were as a rule more reactive to blots derived from *B. garinii* or *B. afzelii* strains, particularly *B. garinii* 20047 and s VS461. North American patients' sera were more reactive with strains *B. burgdorferi* sensu stricto.

The authors point out that involvement with Lyme's disease is more common in Europe and mostly caused by *B. garinii*, 4th serotype of which determined based on surface protein OspA is known for it's significant neurotropism, which causes NB [12] and *B. afzelii* - reason of dermatoborelliosis appearance [7,8,13].

Despite the research commonly agreed criteria for the diagnosis of neuroborreliosis have not been developed yet. According to A.J. Henningsson, M. Christiansson, I. Tjernberg, 2014 [1], the intrathecal index (AI) of anti-borrelia antibodies must be necessary criterions for diagnosis of neuroborreliosis in Europe. The researchers evaluate the diagnostic value of AI and revealed its specificity and sensitivity in the range 86% - 97%. Our data coincide with the studies of Belarusian researchers [11], which used clinical and immunological examinations revealed an associated infection (borreliosis and anaplasmosis). There may be a co-infection with babesiosis or ehrlichiosis (anaplasmosis). It can be explained by the fact that the Ixodes scapularis ticks may also transfer *Babesia microti* and *Anaplasma phagocytophila*. The literature data confirm that patients with Lyme disease approximately in 2% were infected with both *Babesia* spp and *Anaplasma phagocytophilum* [14]. According to the some authors' observations [15,16], anaplasma can be co-infection agent in a small percentage of cases.

We encountered one case of mixed infection of NB with herpes encephalitis and granulocytic anaplasmosis. Diagnosis of herpes infection in conjunction with granulocytic anaplasmosis was made by identifying herpes virus and anaplasma DNA via Polymerase chain reaction (PCR) in real time.

Based on our research, mixed infection of borreliosis and herpes should be confirmed by serological testing as well as spinal fluid analysis.

Conclusion

1. For differential diagnosis of neuroinfections and Lyme neuroborreliosis, it is necessary to observe two-stage serological investigation of blood, especially use of antibody screening tests by ELISA with subsequent confirmation by the Western blot assay.

2. Taking into account the ambiguity of approaches in the treatment of the examined group of children in Ukraine, treatment of neuroinfection requires standardization of treatment protocols in accordance with the requirements of the World Health Organization.

3. The course of the disease may different from the classical triad and includes only cerebrospinal syndrome or cervical myalgia.

4. Possibility of co-infections with herpes virus, anaplasma can be present in the patients, proper care must be taken to recognize and treat them.

Conflict of Interest

The authors have no conflict of interest to declare.

Bibliography

1. Volokha AP. "Lyme disease (tick borelliosis)". Infectious diseases in children, edition. L. I. Chernyshova, K., VSV "Medicine" (2016): 703-712.

2. Henningsson AJ., *et al.* "Laboratory diagnosis of Lyme neuroborreliosis: a comparison of three CSF anti-Borrelia antibody assays". *European Journal of Clinical Microbiology and Infectious Diseases* 33 (2014): 797-803.

3. Nau R., *et al.* "Lyme Disease: current state of knowledge". *Deutsches Ärzteblatt International* 106 (2009): 72-81.

4. BMJ Best practice Lyme borreliosis (2018).

5. A Mygland., *et al.* "EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis". *European Journal of Neurology* 17 (2010): 8-16.

6. VS Karavaev. "Immunochemical analysis of the recombinant chimeric polypeptide OspC [gar + afz] isolates *Borrelia garini* and *B. afzelli*". *Journal of Microbiology, Epidemiology and Immunobiology* 3 (2016): 37-44.

7. NA Penevskaya., *et al.* "Penevskaya NA Clinical and epidemiological analysis of the results of detection of antibodies to various types of rickettsia in patients with suspicion of tick-borne neuroinfection in the northern regions of the Omsk Region". *Siberian Medical Journal* 8 (2009): 48-53.

8. Halperin JJ. "Nervous system Lyme disease". *The Journal of the Royal College of Physicians of Edinburgh* 40 (2010): 248-255.

9. Dressler F., *et al.* "Antibody responses to the three genomic groups of Borrelia burgdorferi in European Lyme borreliosis". *The Journal of Infectious Diseases* 169.2 (1994): 313-318.

10. GL Norman., *et al.* "Serodiagnosis of Lyme borreliosis by Borrelia burgdorferi sensu stricto, *B. garinii*, and *B. afzelii* western blots (immunoblots)". *Journal of Clinical Microbiology* 34.7 (1996): 1732-1738.

11. AG Euroimmun., *et al.* "Dimerisation of recombinan osp C leads toan antigen with enhanced potential for active vaccination.12. International Conference on Lyme Borreliosis and other Tick-Bome Diseases". Slovenien : Ljubljana (2010).

12. SA Drakina., *et al.* "Mixed infection: tick-borne encephalitis and granulocytic human anaplasmosis". *Clinical Infectology and Parasitology* 1 (2018): 21-26.

13. Lobzin Yu V., *et al.* "Recommendations for doctors". St. Petersburg (2000): 33.

14. S Esposito., *et al*. "Borrelia burgdorferi infection and Lyme disease in children". *International Journal of Infectious Diseases* 17.3 (2013): e153-e158.

15. Nykytyuk SO., *et al.* "Case of acute neuroborehoid disease in a boy of school age". *Actual Infectology* 6.4 (2018): 53- 54.

16. Klymniuk SI., *et al.* "Modern concepts of human granulocytic anaplasmosis". *Infectious Diseases* 3 (2017): 4-9.

17. Steere AC., *et al*. "Prospective study of coinfection in patients with erythema migrans". *Clinical Infectious Diseases* 36 (2003): 1078-1081.

Volume 9 Issue 6 June 2020