Article

Approach of pediatric neuroborreliosis.

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Abstract

Diagnosing Lyme neuroborreliosis in the pediatric population can be challenging, especially in absence of erythema chronicum migrans or explicit neurological symptoms. Consensus on the diagnostic process in children is lacking. This retrospective study gives an overview of most frequent presenting symptoms, work up and management at the University Hospitals Leuven, Belgium.

A retrospective analysis was performed of 20 pediatric patients with Lyme neuroborreliosis treated at the University Hospitals of Leuven from 2014 until 2019. Medical records were reviewed and data, including peripheral blood and cerebrospinal fluid results, imaging reports and treatment methods were collected.

All patients presented during spring or summer time. In only a minority of patients (25%) a history of a tick bite was reported, and erythema chronicum migrans lesions were never even noted. Clinical presentation varied but facial nerve palsy was the main presenting symptom (75%). Only fifty percent of these children had a positive immunoblot in peripheral blood, while eighty percent had intrathecal synthesis of *Borrelia* antibodies. All patients were treated with intravenous antibiotics, of which seventy percent had complete clinical resolution. Fifteen percent of the patients had only minimal sequelae, other data were lacking.

Pediatric Lyme neuroborreliosis can be difficult to diagnose. Serological testing alone is not sufficient for the diagnosis. A lumbar puncture, although invasive, is necessary for confirmation of the diagnosis by detection of intrathecal synthesis of *Borrelia* antibodies. Overall, prognosis is good after adequate antibiotic treatment.

Introduction

Lyme disease is the most common tick-borne disease in Europe and the United States, and is caused by the spirochete *Borrelia burgdorferi* sensu lato. In Europe *B. burgdorferi* sensu stricto, *B. afzelii* and *B. garinii* are the most frequent species, whereas the latter two are not to be found in America. Lyme borreliosis usually occurs in summer time and can be divided in 3 stages, depending on the clinical manifestations. Early localized disease occurs within 2-3 weeks after the tick bite and classically presents with an erythema chronicum migrans (ECM) lesion, often without other symptoms. Without adequate therapy, early or late disseminated Lyme disease may emerge after several weeks or even months. By that time the spirochete has entered the blood stream or invaded other tissues. Lyme neuroborreliosis (LNB) occurs when there is invasion of het central nervous system, which is in up to 15% of the affected children. The most typical presentation of LNB in children is facial nerve palsy or meningitis, but also more nonspecific symptoms may occur. Children can, for example, present with headache, loss of appetite, behavioral change , vertigo, … The diagnosis of LNB is based on the combination of a history of tick bite, neurological signs, anti-*Borrelia* antibodies in serum and cerebrospinal fluid (CSF), often associated with CSF pleiocytosis. Therapy consists of antibiotic treatment and is successful in the majority of cases (1-4).

Diagnosis and work up of pediatric LNB can be challenging, since clinical presentation can be variable. This retrospective study aims to highlight the different neurological manifestations of LNB in children, and tries to give a clear overview of work up and management.

Methods

A retrospective analysis of all pediatric (<18 years old) patients treated for LNB at the University Hospitals of Leuven from 2014 to 2019, was performed. Diagnosis of definite LNB was made after fulfilling following criteria: presence of neurological symptoms suggestive for LNB, CSF pleiocytosis and intrathecal synthesis of *Borrelia* antibodies. If only 2 of these criteria were met, it was considered a case of possible LNB. Both definite and possible LNB patients were included in this study. Children with pre-existing neurological conditions were excluded. Medical records of all patients were reviewed. Information about the presenting symptoms and clinical signs (general and neurological, presence of prior tick bite or ECM,…) were gathered. The timing (month of the year) and duration of symptoms were also taken into account. Data, including peripheral blood and CSF results, imaging reports and treatment methods were collected. If both available, an immunoblot was performed on serum as well as CSF, after which their intensity was compared. Intrathecal synthesis was suspected in case of higher intensity of the CSF blot.

Approval of the ethics committee was granted (reference number: MP016134).

Results

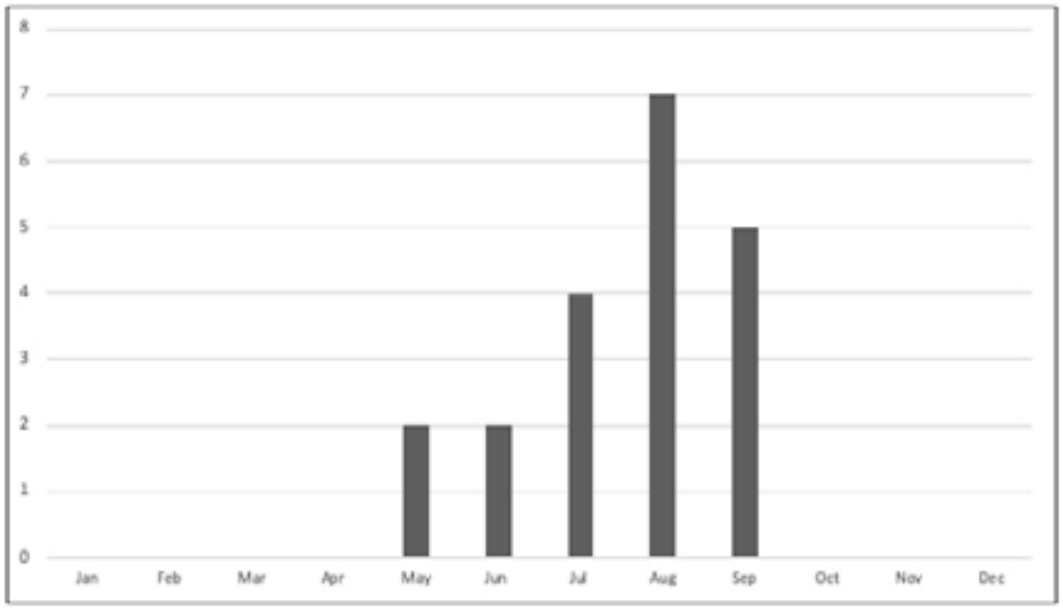
Patient characteristics

During the study period, 20 patients were treated at our hospital for LNB and included in the analysis. The majority of the children were female (75%). The median age was 8 years, with an average age of 7.9 years. The youngest child was 3 years old, the oldest 12 years. None of the patients had a history of neurological comorbidities. Only 5 patients mentioned the occurrence of a tick bite, none of these children's parents noticed an ECM prior to presentation. All patients presented during spring or summer (May to September, Figure 1).

Clinical manifestations

The main presenting symptom was cranial nerve palsy (Table 1). Seventy-five percent of these children developed a facial nerve palsy, only one an oculomotor nerve palsy with ptosis and anisocoria. One girl presented with diplopia, without clear ophthalmological or cranial nerve abnormalities. Only one boy developed bilateral facial nerve palsy, after first presenting with typical symptoms of meningitis. Of all patients only one child presented with fever. Pain was another common symptom, with 9 patients (45%) complaining of acute neck/back pain or headache. One girl suffered from generalized pain and developed a Guillain-Barre syndrome. Three patients (15%) presented with typical signs of meningitis. The majority of children was diagnosed with LNB within the first week of symptoms. Three patients had symptoms for more than 1 month.

Figure 1: *CTiming of presentation. Y axis = number of patients, x-axis = months*



Laboratory results

A blood test and lumbar puncture was performed in all patients (table 2). None of the children had an elevated C-reactive protein (CRP) in peripheral blood, two patients had a slightly elevated white blood cell (WBC) count. Mean WBC count in CSF was 258/µL (normal value WBC <5/µL), with a minimum of 0.4/µL and maximum of 2391/µL (table 2). In all patients WBC differentiation showed a preponderance of lymphocytes. In 3 cases WBC count was below 5/µL. Mean CSF glucose and protein levels were respectively 53 mg/dL and 591 mg/L.

Borrelia enzyme linked immunosorbent assay (ELISA) and immunoblot were performed on serum samples. ELISA tested positive in 16 of the cases, negative in 4. Of those 16 patients 5 eventually had a negative immunoblot. In total 50 percent of the children tested positive after immunoblotting. Eighty percent of the patients had obvious intrathecal synthesis of *Borrelia* antibodies. In 2 cases the immunoblot on CSF was not performed. In 2 other cases results were indecisive: both immunoblots detected only small amounts of *Borrelia* antibodies in CSF, insufficient for evident intrathecal synthesis. CSF samples tested positive in 3 patients with negative ELISA and 7 patients with negative immunoblot on serum samples. In 7 patients *Borrelia* PCR (polymerase chain reaction) was tested on CSF. All but one came back negative, despite positive immunoblot. Of all children treated at our hospital, 14 patients were diagnosed with definite LNB, in 6 patients diagnosis was suspected but only 2 diagnostic criteria were met (possible LNB).

Table 1: *Overview of presenting symptoms of patients with LNB*

Presenting symptom	Number of patients
Cranial nerve palsy	16 (80%)
Facial nerve palsy	15 (75%)
- Unilateral	14 (70%)
- Bilateral	1 (5%)
Oculomotor nerve palsy	1 (5%)
Diplopia	1 (5%)
Meningitis	3 (15%)
Guillain Barré syndrome	1 (5%)
Fever	1 (5%)
Vomiting	1 (5%)
Weight Loss	1 (5%)
Limb pain	3 (15%)
Headache	7 (35%)
Neck/back pain	7 (35%)

Imaging

Thirteen patients (65%) underwent central imaging. A brain computed tomography (CT) scan was performed in 9 cases, magnetic resonance imaging (MRI) of the brain was also executed 9 times. Five patients underwent both MRI and CT of the brain. The majority of the patients had imaging while being hospitalized (n=7), five already had imaging before admission. In one case brain MRI was performed 2 months after therapy, because of persisting facial nerve palsy. MRI confirmed facial neuritis. Central imaging of all other children did not show any abnormalities. Two patients underwent electromyography (EMG) for a persistent facial nerve palsy, both showed signs of regeneration.

Treatment

All patients were treated with intravenous (IV) ceftriaxone, most of them (n=16) for 3 weeks. In three cases IV treatment had to be ceased because of sudden skin rash, two of them (10 and 12 years of age) switched to doxycyclin, a younger child (5 years old) to amoxicillin. Two patients were treated for only 2 weeks. Six patients received alternative treatment before changing to ceftriaxone, because of uncertain diagnosis at that time (table 3).

Outcome

Complete clinical resolution was noted in the majority of the patients (n=13). In two patients a discrete facial asymmetry persisted, while one patient continued having mild anisocoria. There was full motoric remission of the child with Guillain-Barré syndrome. One girl had to be readmitted because of post viral asthenia, but eventually fully recovered. Three children were lost to follow up.

Table 2: *Serology results of peripheral blood and CSF samples*

Patient	Peripheral blood			Cerebrospinal fluid			Conclusion LNB
No	ELISA	IgM	IgG	IgM	IgG	WBC	
1	+	+	+	+	+	192	Definite
2	+	+	UC	+	+	186,8	Definite
3	+	-	UC	+	+	145,6	Definite
4	+	+	UC	NA	NA	22,8	Possible
5	+	+	UC	+	+	41	Definite
6	+	-	UC	+	+	127,7	Definite
7	-	UC	-	UC	UC	1,4	Possible
8	+	-	UC	+	+	48,4	Definite
9	+	+	UC	+	UC	24	Definite
10	-	-	-	+	+	135	Definite
11	+	+	-	+	UC	137	Definite
12	+	+	UC	+	+	0,4	Possible
13	+	+	-	NA	NA	625	Possible
14	+	-	+	+	+	110	Definite
15	-	-	-	+	+	900	Definite
16	+	-	UC	+	+	2391	Definite
17	+	UC	UC	UC	UC	26,8	Possible
18	-	UC	-	+	-	10	Definite
19	+	-	+	+	+	40	Definite
20	+	-	-	+	+	3	Possible

Abbreviations: *UC unclear ; NA not available; WBC white blood cell (normal amount in CSF <5WBC/µL)*

Table 3: *Serology results of peripheral blood and CSF samples*

Treatment	No of patients
IV ceftriaxone	16
Before ceftriaxone treatment	
IV cefotaxime	1
IV cefotaxime + Acyclovir	2
PO cefuroxime	1
IV pulse steroids (3 days)	2
IV steroids (7 days)	1
PO methylprednisolon	1
Switch after skin reaction	
PO doxycyclin	2
PO amoxicillin	2

Abbreviations: *PO perorally ; IV intravenous*

Discussion

Cranial nerve palsy, more specifically facial nerve palsy, is the most common clinical manifestation of LNB in the pediatric population (1-4). Of our group of patients 75% presented with facial nerve palsy. In the last decades, the occurrence of Lyme disease in children presenting with facial nerve palsy has increased. Still, numbers can strongly differ between endemic areas, with mainly a European preponderance. A recent Northern American study confirmed LNB in up to 34% of the children with facial nerve palsy, which made it the most frequently diagnosed etiology. In the majority of patients (66%) no clear cause was found (Bell's palsy or idiopathic facial nerve) (5). In a different Norwegian study LNB was mentioned to be the cause of facial nerve palsy in up to 75% of the children (6).

Besides cranial nerve palsy 15% of our patients showed clinical signs of meningitis. However, less specific symptoms, as for example headache, fatigue or fever, did also occur (Table 1). Therefore, in combination with the absence of erythema chronicum migrans or noticed tick bites, correct diagnosis of LNB can be difficult. Studies showed a delay of LNB diagnosis in children with more nonspecific symptoms or absence of cranial nerve palsy. Compared to adults, painful meningoradiculitis, radiculoneuritis and encephalopathy are less common presenting symptoms in children (3-4).

Serological testing of Lyme disease is most often performed by the 'two step procedure' (7,8). This method combines a sensitive enzyme immunoassay with an additional immunoblot. While ELISA is a very sensitive and cost-effective method for detecting *Borrelia* antibodies, immunoblotting is a more qualitative, time consuming and high-cost procedure with higher specificity. Therefore, immunoblotting is generally preserved for positive ELISA samples.

By itself, the two-tier procedure is insufficient for diagnosis of LNB. For example, in patients with acute neuroborreliosis, antibody testing can be negative in serum, while already being positive in CSF (7-9). Thus, because of this seronegative window negative serology cannot exclude diagnosis of LNB. Of all our study patients only 50% (n=10) tested positive after the two-tier procedure, while 80% (n=16) showed intrathecal *Borrelia* antibodies. Serological follow-up can be useful to detect seroconversion in case of early negative serological testing but in case of long lasting symptoms (>6 weeks) a negative two step procedure helps to rule out Lyme infection (4,11).

Besides difficulties with diagnosing early manifestations of Lyme disease, also the possibility of false-positivity has to be taken into account (5,7). In 2016 an American study found that only 71% of the children with a positive IgM but negative IgG immunoblot had Lyme disease (10). A positive IgM immunoblot is thus not always a sign of active infection and can lead to important over-diagnosis. This IgM false-positivity is mostly caused by cross-reactivity or previous infection. IgM immunoblot is known to remain positive for a long time after infection. We therefore advise to only perform testing when there is real clinical suspicion of Lyme disease. This increase in pre-test probability will lead to a better positive predictive value of the two-tier procedure.

In literature international consensus about diagnostic evaluation of LNB in children is still lacking. In 2012 the European Federation of Neurological Societies (EFNS) published renewed guidelines concerning diagnosis and management of European LNB. Mygland and colleagues applied following diagnostic criteria: presence of neurological symptoms suggestive for LNB without other clear causes, CSF pleiocytosis and presence of intrathecal synthesis of *Borrelia* antibodies. They spoke of 'definite' LNB when all 3 criteria were met, and of 'possible' LNB when only 2 criteria were fulfilled. This implies performing lumbar punctures with every suspicion of LNB. The EFNS also mentioned that when intrathecal antibody production is lacking, *Borrelia* antibodies have to be found in serum after a duration of 6 weeks to confirm diagnosis (12,13). The Infectious Disease Society of America (IDSA) on the other hand suggested that a lumbar puncture solely is indicated when clinical signs of meningitis are present (ie nuchal rigidity, headache). They stated that, for children with isolated facial nerve palsy, lumbar puncture was not needed (14). Current Belgian guidelines (BAPCOC) are similar to those of the IDSA and EFNS. In their opinion a lumbar puncture is not always needed in case of a child presenting with facial nerve palsy and positive *Borrelia* serology. In all other cases (ie. adults or children without facial nerve palsy), they advise to do CSF testing (15).

Since clinical presentation of LNB in children is not always clear cut and diagnostic testing takes time, other neurological conditions have to be taken into account. This is why all our patients underwent a lumbar puncture and in 65 percent of the cases central imaging was performed (brain MRI and/or CT). The majority of our patients had a lymphocyte-predominant pleiocytosis in CSF. In 80% there was evident intrathecal synthesis of *Borrelia* antibodies, confirming the diagnosis of LNB. Viral PCRs (including for example *Herpes simplex virus, Cytomegalovirus, Enterovirus,…*) and cultures were performed on CSF in almost all patients, in order to rule out other possible viral and bacterial causes. Central imaging came back negative in all of our patients.

During the last decade, studies have suggested CXCL13 (CXC motif ligand 13) to be an early diagnostic marker for LNB (11, 16-19). This chemokine is produced in non-lymphoid tissues during inflammation and attracts B cells to the central nervous system, resulting in intrathecal synthesis of *Borrelia* antibodies. Henningsson et al demonstrated a statistically significant difference in CXCL13

concentrations between LNB and non-LNB patients, along with a rapid decrease after adequate therapy. A meta-analysis in 2018 evaluated the accuracy of CXCL13 as a diagnostic tool for LNB (20). They found an acceptable pooled sensitivity and specificity of 89% and 96% respectively, using a cut-off value of 162 pg/mL. Rupprecht and colleagues also stated that intrathecal *Borrelia* antibody index tested negative in 10-30% of the patients with symptom duration less than 6 weeks. CSF CXCL13 measurement could thus be a supplemental early marker in diagnosing acute LNB. However, consensus about the right cut-off value has still to be reached. CXCL13 was not tested in our study patients but should be considered as a possible valuable addition to our diagnostic approach. CXCL13 testing can be done in our hospital's laboratory, since it functions as national reference center for *Borrelia spp.* No additional costs are charged.

Borrelia PCR is another diagnostic method for LNB. Specificity is acceptable but sensitivity is low (10-30%). Therefore PCR is less useful in diagnosing LNB (8,11,16). In our patients PCR of CSF was performed 7 times, of which only one tested positive. A positive PCR of CSF appears to be more frequent in patients with a shorter duration of symptoms (<2 weeks) (8). Isolating *Borrelia* by culture is no standard procedure either, since it is expensive and results are only available after more than 2 weeks. The sensitivity of a culture is only 3 – 17% in CSF samples. Therefore a negative culture cannot exclude LNB (21).

Consensus is not only lacking in diagnosing LNB, also regarding to LNB treatment opinions differ. The EFNS advised parenteral antibiotic treatment (IV ceftriaxone) of LNB with CNS manifestations (myelitis, encephalitis, vasculitis) (12). In absence of CNS manifestations (meningitis, cranial nerve palsy, radiculopathy, peripheral neuropathy) European studies showed that oral doxycycline and intravenous ceftriaxone, penicillin or cefotaxime were equally effective and safe (22). Although it has excellent central nervous system penetration, doxycycline is not used in children under the age of 8 years because of the risk of irreversible tooth discoloration. These children were generally treated with amoxicillin or cefuroxime axetil. The American guidelines, for example of IDSA and the American Academy of Neurology (AAN), also approved oral treatment of cranial nerve palsy, but didn't agree on other subjects (14,21,23). The IDSA guidelines for example recommended IV treatment in case of meningitis, radiculopathy or late LNB. The AAN on the other hand accepted oral therapy in patients with meningitis or neurological syndromes with CSF pleiocytosis, but suggested IV treatment in those patients with more severe symptoms. All aforementioned studies advised a total duration of treatment of 14 days (10-28 days).

The majority of our patients was treated with parenteral antibiotics (ceftriaxone monotherapy) once correctly diagnosed with LNB. Thirty percent of the children received other therapy prior to diagnosis, because LNB was not yet confirmed. Only four patients switched to oral treatment, all of them because of an allergic skin reaction after IV administration of ceftriaxone. Based on current guidelines, oral treatment could also have been considered in our patients.

Prognosis after treatment for LNB is generally good. The majority of our children with LNB had complete resolution of their symptoms. A recent review mentioned complete recovery in 70-85% of the LNB patients within 6-12 months (21). Even over 90% of their children with cranial nerve palsy fully recovered. Previous studies showed the importance of early treatment. Treatment delay seemed to increase the chance of residual symptoms (1). Besides fast and adequate treatment, preventive measurements (such as tick repellents, protective clothing) are of course equally important, since the majority of children who developed LNB were not aware of a previous tick bite (24-27).

Conclusion

Facial nerve palsy is the most common presenting symptom of LNB in the pediatric population, though more nonspecific presentation is possible. LNB needs to be considered if a child presents with neurological symptoms, especially in spring or summertime. The majority of patients will have no clear notion of a previous tick bite or erythema migrans lesion. The diagnostic process of LNB in children is often challenging, and consensus concerning diagnostic work up is lacking. Although invasive for children, we suggest performing lumbar punctures in order to look for pleiocytosis, suggestive for LNB, and to confirm intrathecal synthesis of *Borrelia* antibodies. If necessary other investigations are indicated to rule out other possible causes. Treatment consists of adequate antibiotic therapy, after which there is a good resolution of symptoms. In absence of CNS manifestations or without an ill appearing child, antibiotics could be administered orally, although in reality, based on the presence of pleiocytosis, IV treatment is often more frequently preferred.

REFERENCES:

1. Murray T, Shapiro E. Lyme disease. Clin Lab Med. 2010;30(1):311–328.
2. Cardenas-de la Garza JA, De la Cruz-Valadez E, Ocampo-Candiani J, Welsh O. Clinical spectrum of Lyme disease. Eur J Clin Microbiol Infect Dis. 2019;38(2):201–208.
3. Södermark L, Sigurdsson V, Näs W, Wall P, Trollfors B. Neuroborreliosis in Swedisch Children: A population-based study on incidence and clinical characteristics. Pediatr Infect Dis J. 2017;36(11):1052-1056.
4. Halperin JJ. Neuroborreliosis. Neurol Clin. 2018;36(4):821-830.
5. Nigrovic L, Thompson AD, Fine AM et al. Clinical predictors of Lyme disease among children with a peripheral facial palsy at an emergency department in a Lyme disease-endemic area. Pediatrics. 2008 Nov;122(5):e1080-5.
6. Tveitnes D, Øymar K, Natås O. Acute facial nerve palsy in children: how often is it lyme borreliosis? Scand J Infect Dis. 2007;39(5):425-431.
7. Talagrand-Reboul E, Raffetin A, Zachary P, Jaulhac B, Eldin C. Immunoserological Diagnosis of Human Borrelioses: Current Knowledge and Perspectives. Front. Cell. Infect. Microbiol. 2020; 10:241.
8. Wilske B, Fingerle V, Schulte-Spechtel U. Microbiological and serological diagnosis of Lyme borreliosis. FEMS Immunol Med Microbiol. 2007;49(1): 13–21.
9. Ljostad U, Skarpaas T, Mygland A. Clinical usefulness of intrathecal antibody testing in acute Lyme neuroborreliosis. Eur J Neurol. 2007;14(8):873–876.
10. Lantos PM, Lipsett SC, Nigrovic LE. False Positive Lyme Disease IgM Immunoblots in Children. J Pediatr. 2016;174:267-269.e1.
11. Dessau RB, van Dam AP, Fingerle V, Gray J, Hovius JW, Hunfeld KP, et al. To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis: a position paper of ESGBOR, the ESCMID study group for Lyme borreliosis. Clin Microbiol Infect. 2018;24(2):118-124.
12. Mygland A, Ljostad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol. 2010,17(1):8–16.
13. Knudtzen FC, Andersen NS, Jensen TG, Skarphédinsson S. Characteristics and Clinical Outcome of Lyme Neuroborreliosis in a High Endemic Area, 1995-2014: A retrospective Cohort Study in Denmark. Clin Infect Dis. 2017; 65(9): 1489-1495.
14. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(9):1089-1134.
15. Belgian Antibiotic Policy Coordination Committee (BAPCOC). LYME-BORRELIOSE (Infectie met Borrelia) [Internet]. 2016. Available from: https://overlegorganen.gezondheid.belgie.be/sites/ default/files/documents/gids_lyme_borreliose_nl_march2017.pdf
16. Pöyhönen H, Lähdesmäki T, Hytönen J, Peltola V. Cerebrospinal Fluid Pleocytosis and Elevated C-X-C Motif Chemokine Ligand 13 Value Predict Lyme Borreliosis in Children With Facial Palsy. Pediatr Infect Dis J. 2019;38(12):1195–1198.
17. Henningsson AJ, Lager M, Brännström R, Tjernberg I, Skogman BH. The chemokine CXCL13 in cerebrospinal fluid in children with Lyme neuroborreliosis. Eur J Clin Microbiol Infect Dis. 2018; 37(10):1983–1991.
18. Barstad B, Tveitnes D, Dalen I, Noraas S, Ask IS, Bosse FJ, et al. The B-lymfocyte chemokine CXCL13 in the cerebrospinal fluid of children with Lyme neuroborreliosis: associations with clinical and laboratory variables. Infect Dis. 2019; 51(11-12): 856-863.
19. Eckman EA, Pacheco-Quinto J, Herdt AR, Halperin JJ. Neuroimmunomodulators in Neuroborreliosis and Lyme Encephalopathy. Clin Infect Dis. 2018;67(1):80-88.
20. Rupprecht TA, Manz KM, Fingerle V, Lechner C, Klein M, Pfirrmann M, et al. Diagnostic value of cerebrospinal fluid CXCL13 for acute Lyme neuroborreliosis. A systematic review and meta-analysis. Clin Microbiol Infect. 2018;24(12):1234-1240.
21. Borchers AT, Keen CL, Huntley AC, Gershwin ME. Lyme disease: A rigorous review of diagnostic criteria and treatment. J Autoimmun. 2015; 57: 82-115.
22. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012;379:461-473.
23. Halperin JJ, Shapiro ED, Logigian E, Belman AL, Dotevall L, Wormser GP, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2007; 69(1):91-102.
24. Skogman BH, Croner S, Nordwall M, Eknefelt M, Ernerudh J, Forsberg P. Lyme Neuroborreliosis in Children. A Prospective Study of Clinical features, Prognosis, and Outcome. Pediatr Infect Dis J. 2008;27(12):1089-1094.
25. Thorstrand C, Belfrage E, Bennet R, Malmborg P, Eriksson M. Successful treatment of neuroborreliosis with ten day regimens. Pediatr Infect Dis J. 2002;21(12):1142–1145.
26. Chason ME, Monaghan M, Wang J, Cheng Y, DeBaisi RL. Symptom Resolution in Pediatric Patients with Lyme Disease. J Pediatr Infect Dis. 2019; 8(2):170-173.
27. Nigrovic LE, Neville DN, Balamuth F, Bennett JE, Levas MN, Garro AC. A minority of children diagnosed with Lyme disease recall a preceding tick bite. Ticks Tick Borne Dis. 2019;10(3):694–696.