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Case Report

Evaluation of an Algorithm for the Diagnosis and Therapy of Lyme Neuroborreliosis: A Follow-up Study

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Abstract

Background: Although Lyme Neuroborreliosis (LNB) is often seen in paediatric practice, diagnostic criteria for LNB in children are not clearly defined. The guidelines for LNB in adults are based on a combination of clinical picture, CSF pleocytosis and the detection of specific antibodies against *Borrelia burgdorferi* in CSF and serum. Diagnostic procedure takes several days, thus it isn´t useful in deciding for the need of prompt antibiotic treatment. Aim of study was a retrospective evaluation of an algorithm for the diagnosis and therapy of lyme's disease, which is used since 2005 at the paediatric department of Innsbruck.

Patients and Methods: All patients presenting with acute peripheral facial palsy from January 2006 to December 2014 were reviewed. The patients were diagnosed according to the algorithm, based on the criteria of the German Society of Neurology. The focus lay on evaluation of diagnosis and therapy according to the algorithm and whether overtreatment and underdiagnosis could therefore be avoided.

Results: 120 patients were enrolled with peripheral facial palsy. 65 (54%) were handled as bell´s palsy and 55 (46 %) as *B. burgdorferi* s.l. infection. 19 cases were classified as confirmed LNB, 10 as probable and 26 as possible LNB. A total of 69 patients (58 %) were treated correctly according to the algorithm, 16 (13%) were over treated and 14 (11%) under treated with antibiotics. 21 (18%) could not be classified, according to the algorithm, due to the lack of CSF results. Although receiving proper treatment, 3 cases had a persistent defect after recovery.

Conclusions: The algorithm is an appropriate diagnostic tool for the diagnosis and therapy of LNB, particularly with regard to the necessity of a prompt antibiotic treatment, and therefore helpful to avoid underdiagnosis and overtreatment.

Introduction

Lyme borreliosis is the most common cause of tick-borne infection and Lyme Neuroborreliosis (LNB) is the second most common manifestation of infection with *Borrelia burgdorferi* sensu lato (*B. burgdorferi* s.l.) in Europe [1,2]. It`s an inflammatory multisystemic disease, which is endemic in the temperate zones of the northern hemisphere [3]. In Tyrol the incidence was calculated 5.2/100000 children/year [2]. The disease evolves in different presentations (Tabelle einfügen) [4]. Although Lyme Neuroborreliosis (LNB) is often seen in paediatric practice, diagnostic criteria for LNB in children have not been established yet. The diagnostic criteria for LNB in adults are based on a combination of clinical picture, Cerebrospinal Fluid (CSF), pleocytosis and the detection of specific antibodies against *Borrelia burgdorferi* in CSF and serum. Because the diagnostic procedures take several days, they are not helpful in deciding about the necessity of a prompt antibiotic treatment.

Aim of the study was a retrospective evaluation of an algorithm for the diagnosis and therapy of lyme´s disease, which is used since 2005 at the Department of Paediatrics, medical University Innsbruck. This algorithm is based on the diagnostic criteria of LNB by the German Society of Neurology [3].

Patients and Methods

Paediatric patients, diagnosed with acute peripheral facial palsy in the period between 1st of January 2006 and December 31st 2014, were included. As a unique tertiary hospital in tyrol, all paediatric patients with neurologic symptoms are expected to be referred to the Department of Paediatrics in Innsbruck. In addition to the research at Medical University of Innsbruck, our patients were matched to those whose sera and CSF were sent to the Department of Hygiene, Medical Microbiology and Social Medicine. 120 cases of acute peripheral facial palsy were treated at the Department of Pediatrics of the Medical University Innsbruck between January 2006 and December 2014. The mean patient age was 11.16 years (SD 4.17, range 0.10-18) with a slight predominance of male patients (64 to 56 female patients). All cases were evaluated for demographic data, presenting symptoms, clinical examination, CSF-, serological analysis, use of algorithm, antibiotic treatment and clinical outcome. Pleocytosis in the CSF analysis was defined as the appearance of ≥5/µl mononuclear cells. Specific antibodies to *B. burgdorferi* s.l. (IgG, IgM) in CSF and blood were detected by ELISA, in case of positive or borderline results, samples

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were confirmed by Western immunoblotting. Restitutio ad integrum means a complete cure, patients with reparatio suffer from persistent defect after healing. Antibiotic treatment is defined as an intravenous single dose of ceftriaxone (Rocephin®) 50mg per kg per day, for 14 days. In cases of overtreatment patients received antibiotics, although watch and wait according to the algorithm was recommended, or the antibiotic treatment lasted longer than 14 days. Undertreatment was detected, if another antibiotic agent or drug than recommended in the guideline was prescribed, or the right one was prescribed for a too short term or at the wrong dosage. The study was authorized by the Ethics Committee of Medical University Innsbruck.

Results

120 patients with acute peripheral facial palsy were diagnosed and treated at the Department of Pediatrics of the Medical University Innsbruck. A tick bite was noticed, by the patient or their parents, in 26 cases and erythema migrans was seen in 3 cases. Peripheral facial palsy due to an infection with *Borrelia burgdorferi* was seen in 55 patients (46%). Most of them occurred during the summer: 54% from May to August, 30% from September to December and 16% between January and April. In 112 of 120 cases lumbar puncture was performed (93%), the CSF of 42 children showed a pleocytosis with cell counts between 5 to 355 mononuclear cells/µl. Protein content was elevated in 22 patients with a maximum of 5230 mg/L, whereas glucose content was normal in all samples. In 19 cases IgG antibodies against *B. burdorferi* s.l. were detected by ELISA in the CSF, immunoblotting confirmed this result in 9 patients. 5 samples were tested positive for IgM antibodies and confirmed by immunoblotting in 1 case. The antibody specific index was examined in 11 patients and the median was 4,48 (range 0-35). A PCR for *B. burdorferi* s.l. was performed 23 patients, (2 positive, and 17 negative). In four patients too less CSF was sent to the laboratory. Blood samples were taken from all 120 children with facial palsy. IgG antibodies against *B. burdorferi* s.l. were tested positive in 30 samples by elisa and 31 samples by immunoblot. IgM antibodies were detected in 31 blood samples and confirmed in 24 *via* immunoblot. 8 of 114 children suffered from headache and vomiting after lumbar puncture and received symptomatic treatment with paracetamol, ibuprofen or naproxen, considering the age. A total of 69 patients (58 %) were treated correctly according to the algorithm, 16 (13%) were over treated and 14 (11%) under treated with antibiotics. 21 couldn´t be assigned to the algorithm, for lack of lumbar puncture or CSF results, because too less material was sent.

Application of the diagnostic criteria of the DGN classified 19 patients as confirmed, 10 as probable and 26 as possible neuroborreliosis. Of the 19 confirmed, 15 were treated correctly according to the algorithm, 3 patients were undertreated and 1 patient was over treated with ceftriaxone i.v. for 21 days. Half of 10 probable neuroborreliosis cases were treated with i.v. ceftriaxone for 14 days, whereas the other half was undertreated according to algorithm. 9 of 16, who were classified as possible neuroborreliosis were treated correctly, the rest was over-, undertreated or couldn`t be classified according to the algorithm. Despite correct treatment according to the algorithm, this retrospective study showed persistent defects after recovery in 3 of 120 cases (2,5%). 1 male patient at the age of 16 was diagnosed as probable LNB and received 2g ceftriaxone per day for 14 days. Another male patient at the age of 7 was diagnosed as confirmed LNB and was treated with 1500mg ceftriaxone per day for 14 days. And the last one, a male patient at the age of 8 months, was diagnosed as bell´s palsy and received only symptomatic therapy.

Discussion

This is the first study which evaluates a diagnostic and therapeutic algorithm for practical use in LNB. This study is a consecutive follow up study regarding an investigation dealed with LNB in Tyrol, where an algorithm for paediatric LNB was discussed [2]. Consecutively, this algorithm was established at the Department of Paediatrics in Innsbruck 2005.

Stadium 1 (local infection) had rare findings, only 26 of 120 patients or their parents recognised a tick bite and only 3 (2,5 %) an erythema migrans. In contrast, other studies claim erythema migrans to occur at a frequency of >80% as the first manifestation of borrelia infection [1]. So either early manifestations are less common in paediatric patients, or frequency specifications are overestimated. More than half of all cases (53%) presented between may and august, therefore an increased attention and body inspections on children during these months seem reasonable. However, cases of borrelia infection presented throughout the year, so paediatricians should consider infection with *Borrelia burgdorferi* in any season if patients presented with appropriate symptoms. In 93% of all cases, lumbar puncture was performed, it seems to be one of the most important steps in confirming the diagnosis. In 5 of 8 patients who did not undergo CSF investigation, antibiotic therapy was prescribed on suspicion. Retrospective there was no need for it in all 5 cases. Although over therapy remained without consequences in those 5 cases, the decision-making aid of CSF findings for the need of prompt antibiotic treatment seem to be essential for a structured treatment plan. The ASI is considered to be the most sensitive method for detecting intrathecal antibodies [2]. It was determined in 11 samples and was >2.0 in most cases of confirmed neuroborreliosis. In many other cases ASI could not be tested by the laboratory, because not enough CSF was sent in and ELISA as well as Immunoblot were prioritized. It should be considered to determine ASI in each case of CSF analysis, in order to be able to classify patients according to the algorithm in case of borderline serology results. PCR from liquor samples was only carried out in 23 samples, with 1 positive, 1 weak positive and 17 negative findings. In 4 cases too less liquor was submitted. In addition, in the preliminary study Borrelia DNA could not be detected in any case [2]. The prevalence of positive DNA is reported to be 20%, although it is only recommended to be tested at an early stage, if no antibodies have been produced. Hence, PCR examination should only be considered, if antibodies cannot be detected in early stage of lyme's disease, but there still remains clinical suspicion [3].

Although only 62 out of 120 patients with facial palsy received an eye patch, this is always recommended for incomplete eyelid closure in terms of prophylaxis for keratoconjuncitivits.

A total of 3 patients were undertreated because i.v. ceftriaxone was switched to oral antibiotics prematurely, only oral antibiotics were given or ceftriaxone was given for too short a time. In all those cases, this didn't have any consequences in the follow up, but that´s no reason not to stick to the recommendations: of 50 mg/kg/day

Table 1: Investigated patients.

Patient	Age	Sex	Diagnosis	CSF cells	CSF protein	Intrathecal antibodies	PB ELISA	PB Blot	ASI	Antibiotic therapy	Days	Algorithm restitutio ad integrum	ad
1	9	f	Bp	1	155	Neg	Neg	Neg	0	None		pos	
2	12	f	pro LNB	5	233	Neg	Neg	IgG, IgM		Cef until results		neg, UT(Grosheva, #19) (Grosheva, #19)	
3	9	f	con LNB	0	145	IgG	IgG, IgM	neg	4,9	cef	21	pos	
4	15	f	Bp	3	231	neg	IgM	neg		none		pos	
5	14	m	Bp				neg	neg		cef	14	nc	
6	12	m	Bp	4	192	neg	neg	neg		cef	2	neg OT	
7	13	f	Bp	1	146	neg	neg	neg		none		pos	
8	15	m	pos LNB	9	238	neg	neg	neg	0	none		neg, UT (Grosheva, #19)	
9	11	f	Bp	0	188	neg	neg	neg		none		pos	
10	11	f	Bp	2	188	neg	neg	neg		none		pos	
11	11	f	pos LNB	2	841	neg	neg	IgG		none		pos	
12	8	f	pro LNB	9	212	neg	IgM	IgG, IgM		none		neg, UT(Grosheva, #19) (Grosheva, #19)	
13	4	f	con LNB	149	438	IgG	IgG	IgG		cef	14	pos	
14	11	m	Bp	1	150	neg	neg	neg		none		pos	
15	9	f	Bp	0	270		neg	neg		none		pos	
16	17	m	Bp	2	506	neg	neg	neg		none		pos	
17	17	f	Bp	1	303	neg	neg	neg		none		pos	
18	9	f	Bp		386	neg	neg	neg		cef	14	nc	
19	12	f	Bp		703	neg	neg	neg		cef until results		nc	
20	15	f	pos LNB	58	355	neg	neg	neg		none		neg, UT	
21	15	m	Bp	3	290	neg	neg	neg		none		pos	
22	14	m	pos LNB	17	269		neg	neg		none		nc	
23	5	f	pro LNB	7	160	neg	IgG, IgM	IgM		cef	21	pos	
24	11	m	Bp	3	260	neg	neg	neg		none		pos	
25	4	f	Bp	1	129	neg	neg	neg		none		pos	
26	10	f	con LNB	218	443	IgG	IgG, IgM	IgG	3,1	cef	14	pos	
27	14	m	pro LNB	5	274	neg	neg	neg		cef until results	9	pos	
28	16	m	Bp	0	323	neg	neg	neg		none		pos	
29	15	m	Bp	3	159	neg	neg	neg		cef until results		neg, OT	
30	1	m	con LNB	351	360	IgG	IgG, IgM	neg		cef	14	pos	
31	15	f	pos LNB	6	254	neg	neg	neg		cef until results		pos	
32	11	f	Bp	0	203	neg	neg	neg		clavamox due to peritonsilarabscess		pos	
33	16	m	pos LNB	5	444	neg	IgM	neg		cefuroxim	28	neg, OT	
34	18	f	Bp				neg	neg		none		nc	
35	13	f	Bp		217	neg	neg	neg		cef until results		nc	
36	14	m	Bp	3	174	neg	neg	neg		none		pos	
37	16	f	Bp	1	142	neg	neg	neg		none		pos	
38	11	m	Bp	1	247	neg	neg	neg		cef until results		neg, OT	
39	8	m	Bp	3	148	neg	neg	neg		none		pos	
40	14	f	Bp	1	750	neg	neg	neg		cef until results		neg, OT	
41	15	f	Bp	0	171	neg	neg	neg		none		pos	
42	14	m	pos LNB	14	391	neg	neg	neg		cef	3	pos	
43	8	m	pro LNB	290	439	neg	IgG, IgM	IgG, IgM		cef	14	pos	

44	15	f	pos LNB	10	363	neg	neg			cef	7	neg, OT	
45	4	m	con LNB	175	508	IgG, IgM	IgG, IgM	IgG, IgM		cef	14	pos	
46	13	f	Bp	0	199	neg	neg	neg		none		pos	
47	14	m	Bp			neg	neg	neg		none		nc	
48	10	f	Bp	1	127	neg	neg	neg		none		pos	
49	15	f	Bp	1	272	neg	neg	neg		cef until results		neg, OT	
50	10	f	Bp	2	223	neg	neg	neg		none		pos	
51	11	m	Bp	4	240	neg	neg	neg		none		pos	
52	9	m	Bp				neg			cef and ospamox		nc	
53	11	f	pos LNB				neg	IgG		cef	14	nc	
54	0,8	m	Bp				neg	neg		none		nc	reparatio
55	15	m	Bp	0	874	neg	neg	neg		none		pos	
56	17	f	Bp	1		neg	neg	neg		none		pos	
57	4	f	pos LNB	6		neg	neg	neg		none		neg, UT	
58	9	f	pos LNB	0	137	neg	IgM	IgM		none		pos	
59	3	m	pos LNB	21	335	neg	neg	neg		cef until results		pos	
60	13	m	pos LNB		1800		IgG, IgM	IgG, IgM		cef	21	nc	
61	11	m	pro LNB	5	250	neg	IgG, IgM	IgM	0	doxycycline		neg, UT	
62	14	f	Bp	4	268	neg	neg	neg		none		pos	
63	11	m	Bp	3	157	neg	neg	neg		none		pos	
64	2	m	con LNB	238	756	IgG, IgM	IgG, IgM	IgG, IgM		cef	14	pos	
65	11	m	Bp				neg	neg		none		nc	
66	9	m	pro LNB	75	278	neg	neg	IgM		cef	14	pos	
67	16	f	Bp	1	372	neg	neg	neg		none		pos	
68	17	m	Bp	2	222	neg	neg	neg		none		pos	
69	14	m	pos LNB	3	259	neg	IgG	IgG		none		pos	
70	15	f	Bp	0	211	neg	neg	neg		none		pos	
71	15	m	Bp			neg	neg			none		nc	
72	6	f	con LNB	57	1284	IgG	IgG, IgM	IgG, IgM		claforan, cef	3, 14	neg, UT	
73	14	m	pos LNB				IgG, IgM	IgG, IgM		cef	14	nc	
74	15	m	pos LNB		930	neg	IgM	IgG, IgM		clavamox		nc	
75	16	f	Bp	3	197	neg	neg	neg		none		pos	
76	2	m	Bp	1	195	neg	neg	neg		none		pos	
77	6	f	pos LNB	2	167	neg	IgM	IgG		amoxicillin	14	neg, OT	
78	12	f	Bp	1	217	neg	neg	neg		none		pos	
79	11	f	Bp	2		neg	neg	neg		none		pos	
80	7	f	pos LNB	18	390	neg	neg	neg		cef until results		pos	
81	15	m	pos LNB	8	402	neg	neg	neg		none		neg, UT	
82	9	m	pos LNB				IgG, IgM	IgG, IgM		cef	14	nc	
83	16	m	pos LNB	6	408	neg	neg	neg		none		neg, UT	
84	14	m	con LNB	16	195	IgG	IgG, IgM	IgG	13,7	cef	14	pos	
85	8	m	Bp		523000	neg	neg	neg		cef until results		nc	
86	16	m	pos LNB	101	378	neg	neg	neg		cef until results		pos	
87	6	f	con LNB	110	461	IgG, IgM	IgG, IgM	IgG, IgM		cef	14	pos	

88	15	m	Bp	2	476	neg	neg	neg		cef until results		neg, OT	
89	7	m	con LNB	355	870	IgG, IgM	IgG, IgM	IgG, IgM		cef	14	pos	reparatio
90	16	m	Bp	1	377	neg	IgG	neg		none		pos	
91	10	m	pro LNB	8	270	neg	IgG, IgM	IgG, IgM	0,6	cef after results	14	neg, UT	
92	16	m	pro LNB	98	772	neg	IgM	IgG, IgM		cef	14	pos	reparatio
93	13	m	Bp	0	142	neg	neg	neg		none		pos	
94	6	m	con LNB	53	169	IgG	IgG, IgM	IgG, IgM		cef	14	pos	
95	10	m	pos LNB	5	172		neg			cef	14	nc	
96	10	f	con LNB	64	667	IgG	IgG, IgM	IgG, IgM		cef	14	pos	
97	6	f	Bp	0	592	neg	neg	neg		none		pos	
98	18	m	Bp	1	466	neg	neg	neg		cef until results		neg, OT	
99	8	f	Bp	2	138	neg	neg	neg		none		pos	
100	11	m	con LNB	1	214	IgG	IgG, IgM	IgG		none		neg, UT	
101	9	m	Bp	3	293	neg	neg	neg		cef until results		neg, OT	
102	5	f	pos LNB	35	203	neg	neg	neg		cef	10	neg, OT	
103	16	m	Bp	0	1009	neg	neg	neg		cef until results		neg, OT	
104	11	m	Bp		264	neg	neg	neg		cef	14	nc	
105	7	m	con LNB	264	550	IgG	IgG, IgM	IgG, IgM	35	cef	14	pos	
106	16	f	Bp	1	101	neg	neg	neg		none		pos	
107	15	m	con LNB	330	757	IgG, IgM	IgG, IgM	IgG, IgM	1,8	cef	14	pos	
108	7	f	Bp	0		neg	neg	neg		none		pos	
109	14	f	pos LNB	13	271	neg	neg	neg		none		neg, UT	
110	7	m	Bp	1	209	neg	neg	neg		cef	14	neg, OT	
111	16	f	Bp	2	681	neg	neg	neg		none		pos	
112	6	m	pro LNB	133	382	neg	IgG, IgM	IgG, IgM		cef and amoxicillin	21	neg, UT	
113	15	m	pos LNB	2	275	neg	IgG	IgG		none		pos	
114	6	f	con LNB	113	228	IgG	IgG, IgM	IgG, IgM	2,4	cef	14	pos	
115	6	m	Bp	0		neg	neg	neg		none		nc	
116	7	f	Bp	3	266	neg	neg	neg		cef until results		neg, OT	
117	6	m	Bp	1	153		neg	neg		none		nc	
118	15	f	con LNB	118		IgG	IgG, IgM			cef	21	neg, OT	
119	5	f	con LNB	72		IgG	IgG, IgM	IgG, IgM		cef	14	pos	
120	12	m	con LNB	56		IgG	IgG	IgG	1,5	cef and doxycycline	14	neg, UT	

ceftriaxone intravenously over 14 days [3]. In the medical reports, the reason to change from i.v. to oral regime often was an urge of the children's parents. It seems to be important to point out the importance of a 14-day intravenous antibiotic therapy.

Based on the algorithm, 19 patients could be classified as confirmed, 10 as probable, 26 as possible cases of neuroborreliosis and 65 patients were hospitalized for bell´s palsy. In comparison to the preliminary study 7 confirmed, 16 probable and 7 possible LNB cases were detected. The remaining facial palsy cases were due to an idiopathic cause. At that time, 4 (6%) of the total 30 seropositive cases were undertreated, without use of a diagnostic algorithm. While 5 (8%) of the 36 cases with Bell`s palsy were antibiotically over treated [2]. In the present study, overtreatment was shown in 16 cases (13%), under therapy in 14 patients (11%) and therapy according to the algorithm in 69 cases (58%). 21 (18%) could not be classified according to the algorithm. In retrospective 13 patients received overtreatment with antibiotics up to 21 days. Contrary our expectations, the number of over- or undertreated patients has not changed significantly with use of the algorithm. However, since the case numbers were relatively low in both studies, especially in the preliminary study, this could also be statistical error. Anyway, many cases were not handled according to the algorithm and probably because of that, some patients were over- or undertreated retrospective.

However, 3 patients who were adequately treated suffered from a

defect healing in long-term follow up.

In conclusion, it can be argued that the algorithm for the diagnosis and treatment of Lyme neuroborreliosis represents a suitable diagnostic and therapeutic tool. By taking clear parameters into consideration, the need for a prompt antibiotic treatment can be easily determined. In all cases where the algorithm was taken into account, a comprehensible therapeutic concept was seen which, except in 3 cases, was always curative.

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