DIAGNOSTIC PROBLEMS OF (NEURO)BORRELIOSIS IN CHILDREN

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ABSTRACT

The clinical picture of infections by *Borrelia burgdorferi* spirochetes differs in some respects. The Bannwarth syndrome (painful radiculoneuritis) occurs only in adults and acrodermatitis chronica atrophicans in children is observed very rare.

The most typical neurological manifestation of Lyme Borreliosis in childhood is the cranial nerve palsy, especially the peripheral facial nerve palsy. This palsy presents as „isolated" in the majority of cases, i.e. without any clinical signs or symptoms of meningitis. However, in nearly all children with cranial nerve palsy caused by *Borrelia burgdorferi* there is evidence of simultaneous aseptic meningitis in cerebrospinal fluid. Thus, a lumbar puncture is mandatory in every case of facial palsy to confirm or exclude the diagnosis of a neuroborreliosis.

The clinical spectrum of neuroborreliosis in children and supportive diagnostic parameters in clinically inconclusive cases are discussed.

KEY WORDS

neuroborreliosis, children, meningitis, facial nerve palsy, cerebrospinal fluid, neopterin

INTRODUCTION

The correct diagnosis of Lyme Borreliosis (LB) is easy if clinical symptoms are typical and conform with specific laboratory findings. In some cases the constellation of symptoms and serological results is inconclusive. In these cases a careful synopsis of clinical and laboratory diagnostic criteria available has to be done. In case of neuroborreliosis (NB) neopterin was demonstrated to be elevated in cerebrospinal fluid (CSF) of adults (1). This early marker for activation of cellular immunity reflects clinical activity of a diagnosed disease (2-5). While many studies have dealt with neopterin measurements in peripheral blood and urine (6) few investigators have determined the concentration of this immune activation marker in CSF. Since NB is an inflammatory disease neopterin concentrations may give additional information in case of clinically/laboratory inconclusive cases.

Table I. Specific and nonspecific parameters for the diagnosis of Lyme Borreliosis in children.

specific serum parameters	specific CSF parameters
serum *Bb* ELISA IgG	CSF/serum *Bb* IgG ratio *Bb* ELISA IgG *Bb* culture *Bb* polymerase chain reaction
nonspecific serum parameters	**nonspecific CSF parameters**
creatinin phosphokinase electrophoresis C-reactive protein white blood count neopterin	cells glucose content protein protein electrophoresis (9) neopterin

Legends:
Bb = *Borrelia burgdorferi*, CSF = cerebrospinal fluid

SEROLOGIC DIAGNOSIS

The catchment area of the Pediatric Department of Graz is known to be endemic for LB (7, 8). It is known that enzyme-linked immunosorbent assay (ELISA) specific for *Borrelia burgdorferi* (*Bb*) sometimes give false positive or false negative results. Therefore, in case of a clinical suspected diagnosis of LB in our patients a set of laboratory tests was done as shown in Table 1.

NEOPTERIN MEASUREMENTS

Paired CSF/serum specimens were determined for neopterin employing a commercially available radioimmunoassay (Immuno Biological Laboratories, Hamburg, Germany). Specimens in which all specific and nonspecific parameters remained negative/normal and an inflammatory disease was excluded served as control samples. In 25 children with definite NB (8.3 ± 2.9 yrs, m:f = 14:11) and in 46 controls (8.2 ± 3.5 yrs, m:f = 25:21) out of paired CSF/serum samples neopterin was measured. For results see Table 2.

The data demonstrate CSF and serum neopterin levels from children without any inflammatory disease to be invariably low but in children suffering from definite NB CSF neopterin values to be about 6 fold higher while serum values remain normal.

CLINICAL DIAGNOSIS

The spectrum of clinical picture of LB in children is well described (7). It includes dermatological pictures like erythema migrans, borrelial lymphocytoma, and very rare cases of acrodermatitis chronica atrophicans (10,11) as well as arthritis, and (severe) neurological forms of the disease.

Depending on the specific laboratory findings the diagnosis of a definite NB can be made in case of an acute neurological disease plus evidence of intrathecal production of *Bb* antibodies (12) and/or *Bb* cultivation in CSF and/or polymerase chain reaction positive for *Bb* in CSF. In 62% of

Table II. Neopterin levels in cerebrospinal fluid and serum of children with neuroborreliosis compared with controls.

	CSF (nmol/l)	**serum** (nmol/l)
controls (n=46)	5.0 ± 1.8	7.6 ± 1.4
neuroborreliosis (n=25)	28.2 ± 11.0	8.4 ± 2.1

Legend:
CSF = cerebrospinal fluid

NB anamnestic tick or insect bites and in 32% untreated single erythema migrans-like lesions were seen at the Department of Pediatrics in Graz. Time period between a tick or insect bite - if observed - and onset of neurological disease ranged between 11 days (supporting recent observations of an early dissemination of *Bb* in LB(13)) and several months.

CRANIAL NERVE PALSY AND NEUROBORRELIOSIS

The clinical spectrum observed in our children was aseptic meningitis, aseptic meningitis plus cranial nerve palsy (mainly VII, VI), and two cases of acute cerebellar ataxia.

The majority of children (77%) with facial palsy by *Bb* infection did not show any clinical sign or symptom to suffer from aseptic meningitis (stiff neck, cephalea) but investigation of CSF afterwards gave clear evidence of aseptic meningitis.

In all children intravenous treatment with penicillin G sodium (4 x 80,000 to 120,000 I.U./kg/day) or ceftriaxone (1 x 60 to 90 mg/kg/day) for 14 days was performed. Pharmacokinetics of both antibiotics in case of intact blood brain barrier was recently described (14,15).

DISCUSSION

In general, LB is a well treatable inflammatory disease which in some cases is self-limited. But dissemination of the infectious agent may be followed by progression and chronification later on. In these cases a restitutio ad integrum is no more guaranteed by late antibiotic treatment. For that reason, antibiotic treatment is recommended in all cases of confirmed LB as early as possible.

From a clinical point of view the spectrum of LB in children differs from that in adults. Beneath the very rare acrodermatitis chronica atrophicans (10,11) the Bannwarth syndrome (painful radiculoneuritis) is not observed in children. The typical neurologic manifestation of NB in childhood is the peripheral paresis of cranial nerve VII, mostly in combination with CSF pleocytosis. Additionally, in about 60% CSF protein is increased (16).

For the physician a borreliogenic cranial nerve palsy does not express any clinical signs or symptoms of a meningitis in the majority of cases. However, obligate lumbar puncture could demonstrate the existence of aseptic meningitis in all cases of borreliogenic facial palsy. Therefore, in every case of an "isolated" peripheral facial palsy an obligate lumbar puncture is recommended to confirm or exclude *Bb* as causative agent. Additionally, it has to be stressed that in some cases of CSF proven definite NB laboratory findings in serum may be normal. Thus, diagnosis or exclusion of a neurologic manifestation is insufficient by serum parameters alone.

In most cases a careful synopsis of clinical and laboratory parameters available allows a definite diagnosis. But when clinical symptoms and specific laboratory results are divergent diagnosis is not easy. In these cases neopterin - a nonspecific but sensitive marker of inflammation - may help to support or exclude the diagnosis of a recent NB.

Further studies of these topics could give additional information whether and how rapid neopterin increases in dermatoborreliosis to support therapeutic decisions.

REFERENCES

1. Dotevall L, Fuchs D, Reibnegger G et al. Cerebrospinal fluid and serum neopterin levels in patients with Lyme neuroborreliosis. Infection 1990; 18: 210-14.

2. Fredrikson S, Link H, Eneroth P. CSF neopterin as marker of disease activity in multiple sclerosis. Acta Neurol Scand 1987; 75: 352-55.

3. Hausen A, Fuchs D, Reibnegger G et al. Application of neopterin - a marker for activation of cellular immunity - in clinical chemistry. Sci Pharm 1989; 57: 249-64.

4. Fuchs D, Chiodi F, Albert J et al. Neopterin concentrations in cerebrospinal fluid and serum of individuals infected with HIV-1. AIDS 1989; 3: 285-88.

5. Wachter H, Fuchs D, Hausen A et al. Neopterin as marker for activation of cellular immunity: immunologic basis and clinical application. Adv Clin Chem 1989; 27: 81 -141.

6. Werner ER, Bichler A, Daxenbichler G et al. Determination of neopterin in serum and urine. Clin Chem 1987; 33: 62-66.

7. Millner MM, Müllegger RR, Spork KD, Stanek G. Lyme borreliosis of central nervous system (CNS) in children: a diagnostic challenge. Infection 1991; 19: 273-78.

8. Millner MM, Spork KD, Müllegger RR. Die Neuroborreliose im Kindesalter. Päd Prax 1993; 46: 23-36.

9. Reiber H. The discrimination between different blood-CSF barrier dysfunctions and inflammatory reactions of the central nervous system by a recent evaluation graph for the protein profile of cerebrospinal fluid. J Neurol 1980; 224: 89-99.

10. Nadal D, Gundelfinger R, Flueler U, Boltshauser E. Acrodermatitis chronica atrophicans. Arch Dis Child 1988; 63: 72-74.

11. Müllegger RR, Schlüpen EM, Millner MM et al. Acrodermatitis chronica atrophicans in an 11-year old girl. Br J Derm 1996; 135: 609-12.

12. Stanek G. Laboratory diagnosis and seroepidemiology of Lyme borreliosis. Infection 1991; 19: 263-67.

13. Luft BJ, Steinman CR, Neimark HC et al. Invasion of the central nervous system by *Borrelia burgdorferi* in acute disseminated infection. JAMA 1992; 267: 1364-67.

14. Millner MM, Thalhammer GH, Dittrich P et al. Beta-lactam antibiotics in the treatment of neuroborreliosis in children: preliminary results. Infection 1996; 24: 174-77.

15. Thalhammer GH. Neuroborreliosis in childhood: treatment with penicillin G sodium and ceftriaxone. Accepted by Acta Dermatovenerologica Alpina Pannonica et Adriatica 1996.

16. Millner MM. Die Lyme-Borreliose im Kindesalter. Päd Pädol 1992; 27: 81- 93.

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