CONTINUING MEDICAL EDUCATION

Lyme Disease—Current State of Knowledge

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SUMMARY

Background: Lyme disease is the most frequent tick-borne infectious disease in Europe. The discovery of the causative pathogen Borrelia burgdorferi in 1982 opened the way for the firm diagnosis of diseases in several clinical disciplines and for causal antibiotic therapy. At the same time, speculation regarding links between Borrelia infection and a variety of nonspecific symptoms and disorders resulted in overdiagnosis and overtreatment of suspected Lyme disease.

Method: The authors conducted a selective review of the literature, including various national and international guidelines.

Results: The spirochete Borrelia burgdorferi sensu lato is present in approximately 5% to 35% of sheep ticks (Ixodes ricinus) in Germany, depending on the region. In contrast to North America, different genospecies are found in Europe. The most frequent clinical manifestation of Borrelia infection is erythema migrans, followed by neuroborreliosis, arthritis, acrodermatitis chronica atrophicans, and lymphocytosis benigna cutis. Diagnosis is made on the basis of the clinical symptoms, and in stages II and III by detection of Borrelia-specific antibodies. In adults erythema migrans is treated with doxycycline, in children with amoxicillin. The standard treatment of neuroborreliosis is third-generation cephalosporins.

Conclusions: After appropriate antibiotic therapy, the outcome is favorable. In approximately 95% of cases neuroborreliosis is cured without long-term sequelae. When chronic borreliosis is suspected, other potential causes of the clinical syndrome must be painstakingly excluded.

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Key words: tick bite, antibiotic, borreliosis, laboratory diagnosis, Lyme disease

Lyme disease is the most common tick-borne infectious disease in Europe (1). The responsible pathogen, Borrelia burgdorferi, was discovered 26 years ago. This organism was found to be the cause of erythema chronicum migrans and of other disease manifestations as well, and the overarching entity of Lyme borreliosis was thereby defined. After the manifestations of neuroborreliosis had been wrongly ascribed, for decades, to an unknown virus, this discovery was a milestone in modern infectious disease medicine. The identification of the pathogen also opened up new possibilities for the etiological diagnosis of a variety of conditions due to Borrelia burgdorferi sensu lato (of which the main types are Borrelia burgdorferi sensu stricto, B. garinii, B. afzelii, and B. spielmanii), as well as new possibilities for pathogen-directed antibiotic therapy aimed at the cause of the disease.

Borrelia burgdorferi sensu lato, like Treponema pallidum and other pathogenic organisms, can cause chronic as well as acute infection (1). In persistent infections of the central nervous system (CNS), the bacterial count in the CNS is often low; bacterial constituents are released in small quantities over an extended period of time. Current research therefore addresses the question whether this might lead to stimulation of both the innate immune response (predominantly through the family of toll-like receptors) and the acquired immune response (by stimulating antigen-specific B and T cells), thereby maintaining a state of chronic inflammation. Furthermore, autoimmune processes are suspected to play a role in the development of chronic disease manifestations (2).

In parallel with the marked improvement of knowledge about the causative organism, clinical features, diagnosis, and treatment of Lyme disease in recent years, this disease entity has also become a collecting basin for speculations and fears about a possible link

Causative organisms

Acute and chronic infection in human beings can be caused by Borrelia burgdorferi sensu lato, of which the main types are Borrelia burgdorferi sensu stricto, B. garinii, and B. afzelii.

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between tick-borne pathogens and a multiplicity of nonspecific complaints and conditions. One reason for this is the relatively high prevalence of antibodies against Borrelia burgdorferi (5% to 25%) even in healthy persons, depending on their prior exposure to tick bites in their occupational and leisure-time activities (1). The persistence of antibodies is not uncommonly misconstrued as evidence of florid infection, and thus the overdiagnosis and overtreatment of Lyme disease have become a significant problem. It is not surprising that worried physicians and patients often insist on treatment with antibiotics even in the absence of a clear indication.

Learning objectives: After reading this article, the reader should

- be acquainted with preventive measures against Borrelia infections,
- know when disease due to Borrelia burgdorferi is to be diagnosed, and
- know what kind of antibiotic treatment is appropriate, according to current knowledge.

Microbiology

The Gram-negative spirochetal bacterium Borrelia burgdorferi sensu lato is transmitted by the bite of an infected tick; in Germany, depending on the region, it is found in about 5% to 35% of ticks (e.g., in 25% of the ticks studied in southern Lower Saxony in the spring of 2007). The disease that it causes, Lyme borreliosis, has highly variable and often complex clinical manifestations and therefore must be included in the differential diagnosis of conditions belonging to many different medical specialties. Unlike the pathogen causing early summer meningoencephalitis, Borrelia burgdorferi is present throughout central Europe, in the same geographical area as its vector, the ixodid tick (Ixodes ricinus).

In Europe, unlike North America, there are several clinically relevant species of Borrelia burgdorferi causing human disease, which can be distinguished from each other genotypically (Borrelia burgdorferi sensu stricto, B. afzelii, B. garinii, B. spielmanii). Borrelia spielmanii has been described to date only as a cause of erythema migrans. Borrelia afzelii is the only known pathogen causing the chronic skin condition acrodermatitis chronica atrophicans (3). The other species can apparently give rise to all of the clinical manifestations of borreliosis (3). Borrelia garinii is found more often in cases of neuroborreliosis (4).

In view of the different spectrum of pathogens (the only pathogen causing Lyme disease in the USA is Borrelia burgdorferi sensu stricto), the findings of North American clinical studies are not automatically applicable to the situation in Europe.

The probability of transmission to a human being by a tick bite is low in the first 24 hours of adhesion and then increases markedly. It is only after contact with blood that the borrelia in the gut of the tick migrate to its salivary gland, so that they can be transmitted to the human victim through the puncture wound (1, 5).

Preventive measures against infection include the following:

- Wearing appropriate protective clothing
- Carefully inspecting the skin for ticks
- Removing the ticks rapidly.

In children, ticks are often found at the hairline. Forceps (tweezers) are a suitable instrument for removing them. Any superfluous manipulation of ticks, e.g., crushing them or covering them with oils or ointments, should be avoided, as these maneuvers may promote the regurgitation of blood and thereby increase the likelihood of borrelial transmission. Once the tick has been removed, the puncture site should be meticulously disinfected (5).

The prophylactic administration of antibiotics is not recommended as a routine measure (5). There is debate about whether this might be of benefit in certain exceptional cases, e.g., multiple tick bites in a highly endemic area for the disease, but the necessary duration of antibiotic treatment in such cases has not been adequately documented in clinical trials. The treatments that are sometimes given range from a single dose to a three-week course of antibiotics. The mere demonstration of borrelia in the tick does not constitute an indication for antibiotic treatment (5, 6).

After a tick bite, the rate of seroconversion—i.e., the probability that specific antibodies to Borrelia burgdorferi will be produced—is in the range of 3% to 6%. Clinically silent infection is common: clinically overt disease arises after only 0.3% to 1.4% of tick bites. In several prospective, regionally representative studies, the annual incidence of overt borreliosis in Germany was found to be 100 to 150 cases per 100 000 persons per year (7). In a study based in Würzburg (Bavaria) involving 313 cases over a period of 12 months, Borrelia burgdorferi infection manifested itself as erythema migrans in 89% of cases, as stage II neuroborreliosis in 3%, as borrelial lymphocytoma in 2%, as

Probability of transmission

The probability of transmission to a person bitten by a tick is low in the first 24 hours of tick adhesion and then becomes markedly higher.

Antibiotics

The routine administration of antibiotics is not recommended after tick bites. It is currently debated whether antibiotics should be given under certain exceptional circumstances, e.g., multiple bites in a highly endemic area, but the necessary duration of antibiotic treatment has not yet been adequately studied in clinical trials.

carditis in less than 1%, as arthritis in 5%, and as acrodermatitis chronica atrophicans in 1%. There was not a single case of chronic (Stage III) neuroborreliosis (7). Most cases arose between June and August; only 15% arose between November and April (7).

Clinical features

Lyme borreliosis can affect many different organs. The stage of the disease is classified as early or late, and the manifestations are classified as local or generalized. The frequency of the individual clinical manifestations is highly variable, depending on the age of the patient, the species of the pathogen, and other factors (1, 8).

Stage I (days to weeks after the tick bite): erythema migrans around the site of infection.

Stage II (weeks to six months after the tick bite): meningoradiculitis (inflammation of the meninges and nerve roots; Bannwarth syndrome), meningitis, peripheral facial palsy, encephalitis, myelitis, cerebral arteritis, multiple erythemas, arthritis, myalgia, borrelial lymphocytoma, myositis, myo- or pericarditis, iritis.

Stage III (longer than six months after the tick bite, perhaps years after it): encephalitis or encephalomyelitis, cerebral arteritis, polyneuropathy, mono- or oligoarthritis, acrodermatitis chronica atrophicans.

The course of the disease may skip any individual stage, e.g., a patient with neuroborreliosis need not have had erythema migrans in the past. Spontaneous recovery is the rule mainly in stages I and II. Stage III is differentiated from Stage II rather arbitrarily by a cut-off interval of six months from the day of the tick bite.

Stage I (early, localized): The typical, and by far the most common (> 80%), manifestation of early Borrelia infection is erythema migrans, which is usually seen one to two weeks after the tick bite (range, 3 to 30 days) (e1). The erythema spreads locally around the site of the puncture wound in a circular or oval configuration, and it may become quite large. The rash is painless but may itch. Two or more skin lesions appear in some cases, indicating early systemic dissemination of the bacteria. If left untreated, erythema migrans usually resolves spontaneously in a few days to weeks (median, 4 weeks).

In 10% to 30% of cases, erythema migrans is accompanied by nonspecific constitutional symptoms such as malaise, a subfebrile temperature, short-lasting migratory pains in the small joints, bursae, and tendons, and fatigability (1).

Stage II (weeks to six months after the tick bite, generalized): Meningoradiculoneuritis (Bannwarth syndrome) is the leading manifestation of this stage in adult patients. After erythema migrans, this is the second most common manifestation of acute Lyme disease in adults. Its main clinical features are lymphomonocytic meningitis, radiculitis (inflammation of the spinal nerve roots), cranial nerve deficits (most commonly a uni- or bilateral peripheral facial palsy), radicular pain, and paresis (1). The protein concentration in the cerebrospinal fluid (CSF) is often relatively high, a finding that distinguishes this condition from a viral infection of the central nervous system.

In children, the major finding is usually an acute peripheral facial palsy, usually associated with CSF pleocytosis, or else a lymphocytic meningitis without focal neurological manifestations (8, 9).

Borrelial carditis is a relatively rare complication in Europe (in contrast to North America), occurring in about 1% of all cases of illness due to Borrelia burgdorferi (7). It reportedly arises with a latency of four days to seven months after the tick bite (median, 21 days). It is often accompanied by other manifestations, such as erythema migrans or neurological deficits. Its symptoms are dizziness, palpitations, or syncope, caused by disturbances of intracardiac impulse generation or impulse conduction. The typical finding is an atrioventricular block of variable severity, which usually resolves within six weeks. Rarely, ST- and T-wave changes indicate the presence of myocarditis.

Borrelial lymphocytoma (also called lymphadenosis cutis benigna of Bäfverstedt) is the typical cutaneous manifestation of stage II disease, usually arising within 2 months of the tick bite. Its frequency is approximately 2%; it is often accompanied by erythema migrans (7). The lesion is a benign reddish-purple tumor that tends to appear on the earlobe in children, and on the nipples, scrotum, nose, or arms in adults *(figure 1)*.

Stage III (late or persistent disease): The typical manifestations are acrodermatitis chronica atrophicans of Herxheimer (ACA) and chronic Borrelia-induced arthritis.

Six months to several years after the tick bite, inflammatory skin lesions may arise that undergo a transition to an atrophic stage of ACA. These lesions tend to appear on the extensor surfaces of the limbs but are occasionally located on the face or trunk. They consist of parchment-like thinning of the skin with prominent venous markings and, sometimes, altered

Clinical entity

Lyme disease can affect many organs. The frequency of the individual clinical manifestations varies depending on the age of the patient, the infecting species, and other factors.

Acrodermatitis chronica atrophicans of Herxheimer (ACA)

Six months to several years after the tick bite, inflammatory skin lesions can develop, primarily on the extensor surfaces of the limbs, which undergo a transition to an atrophic stage of ACA.

pigmentation. The patients complain of pain, pruritus, and hyperesthesia or paresthesia. ACA is occasionally associated with polyneuropathy.

In stage III, chronically progressive meningoencephalitis and multifocal cerebral vasculitis can arise (1). The term "chronically progressive meningoencephalitis" is used when irreversible neurological damage is present and the course of the illness is not self-limited, as it is in acute Borrelia-induced meningoencephalitis.

In a series of 18 patients (10), the following clinical manifestations were found:

- in 16 patients, spastic quadric- or paraparesis;
- in 11, cranial nerve deficits *(figure 2)*;
- in 9, bladder dysfunction;
- in 7, sensory disturbances;
- in 6, ataxia;
- in 4, altered personality;
- in 2, flaccid paresis;
- in 2, dysarthria.

Fewer than 5% of all patients with neuroborreliosis suffer from chronic progressive meningoencephalitis. Cerebral borrelial vasculitis, a rare condition, is an obliterating vasculitis with thickening of the vascular intima and adventitia and perivascular lymphocytic infiltrates (11, 12). Rare cases of extrapyramidal motor disease associated with Borrelia infection have been described (e2), but there is some question as to the causal relationship.

In untreated Lyme disease, joint manifestations can arise months to years after the tick bite, usually in the form of a chronic mono- or asymmetrical oligoarthritis. The knee and elbow joints are most commonly affected. A not very painful arthritis occurring in episodic attacks is typical, often associated with a voluminous effusion but only mild signs of inflammation. Each episode lasts for several days to weeks. In children, borrelial arthritis has a good prognosis and rarely becomes chronic, even when untreated (7, 8) *(figure 3)*.

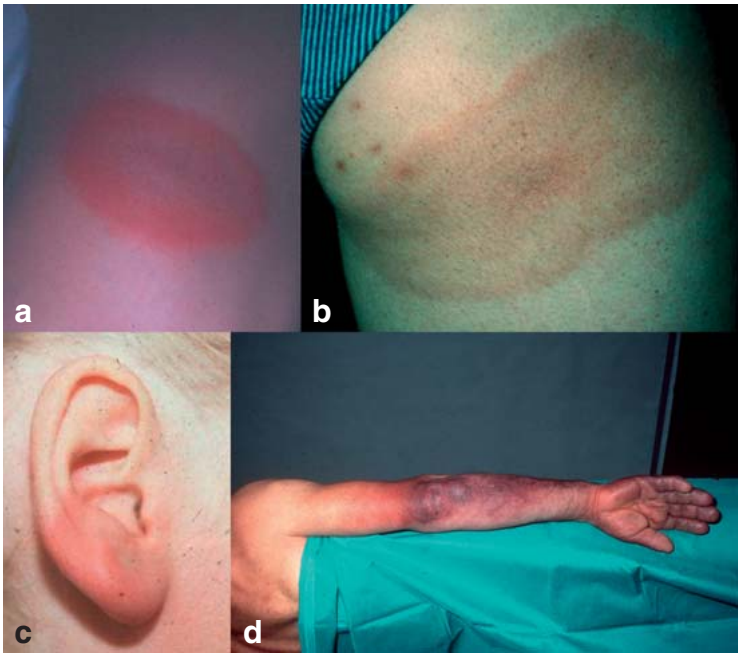

Figure 1: Cutaneous manifestations of Lyme disease:
(a) Macular erythema migrans. (b) Annular erythema migrans with a red margin and central pallor. (c) Borrelial lymphocytoma on an earlobe. (d) Acrodermatitis chronica atrophicans of the right arm (photographs kindly supplied by Prof. Dr. H. Prange of the Neurology Department, Göttingen University Hospital).

Diagnostic evaluation

Borrelia burgdorferi sensu lato can be cultured from body fluids only in highly specialized laboratories, and, because of the low bacterial count in the fluids that are tested, the polymerase chain reaction (PCR) is of limited diagnostic sensitivity. Routine microbiological diagnostic testing therefore generally consists of an assay for Borrelia-specific antibodies. Lyme disease is a clinical diagnosis, i.e., clinical criteria (the history, symptoms, and signs) are decisive for the assignment of the diagnosis and the interpretation of the serological findings. The more typical the clinical features, the less important the serological findings. Serological examination should be performed immediately whenever an infection with Borrelia burgdorferi sensu lato is suspected on clinical grounds. If the findings are negative or ambiguous and the clinical suspicion remains, then the serological examination should be repeated in three weeks. If clinically evident erythema migrans is present, no serology need be obtained, because antibiotic treatment is indicated regardless of the laboratory findings.

The clinical findings and laboratory parameters are accordingly considered in the published case-definition criteria ([13, 14]; *see also the box "Internet Addresses"*).

In Europe, microbiological testing for Lyme disease must take the heterogeneity of the causative organisms into account. The guidelines recommend a stratified serological diagnostic evaluation: first, a sensitive

Establishing the diagnosis

Lyme disease is a clinical diagnosis, i.e., clinical criteria (the history, symptoms, and physical findings) play the decisive role in the establishment of the diagnosis and the interpretation of serological findings.

The interpretation of serological findings

The less specific the patient's symptoms, the lower the predictive value of a positive serological finding.

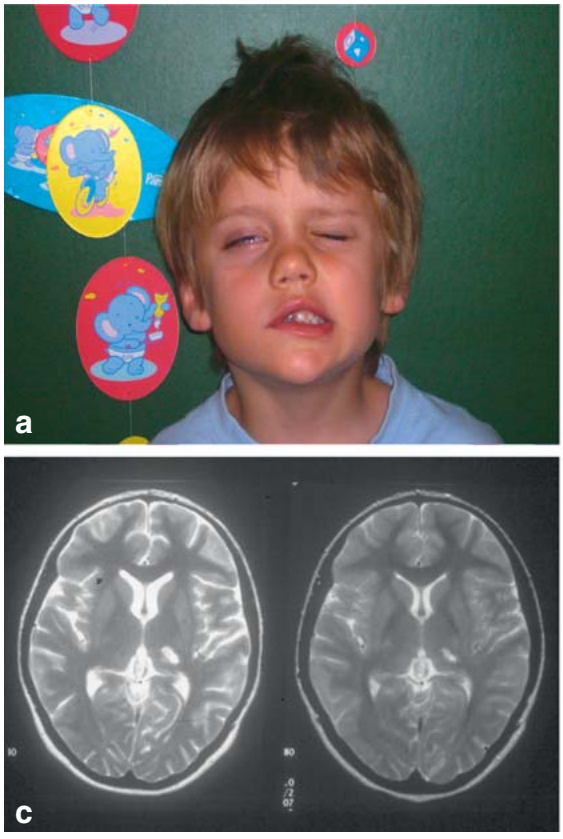

Figure 2: Manifestations of Lyme disease in the nervous system.

(a) Peripheral facial palsy, a common manifestation of neuroborreliosis in childhood and adolescence.

(b) CSF pleocytosis in neuroborreliosis: predominantly activated lymphocytes, monocytes, plasma cells, and rare neutrophilic granulocytes (kindly supplied by I. Nagel, Neurochemical Laboratory, Göttingen University Hospital).

(c) Borrelia vasculitis: T2-weighted axial MRI scans of the brain of a 14-year-old girl with subacute right hemiparesis predominantly affecting the upper limb, CSF pleocytosis, and synthesis of antibodies against Borrelia burgdorferi in the CNS; complete clinical resolution after parenteral antibiotic treatment; MRI in the acute phase (right) and four months later (left).

ELISA that differentiates IgG and IgM antibodies should be used as a screening test. Positive or borderline results should then be confirmed with an immunoblot, the interpretation of which is described in the guidelines (13). In case of doubt, a reference laboratory should check the specificity of the finding (14).

Antibodies against Borrelia are found in fewer than 50% of patients with erythema migrans (1). In contrast, when neurological manifestations arise, Borrelia-specific IgM or IgG antibodies are found in the serum of more than 90% of patients (9, 13). "Borrelia serology may be negative in the early phase of a borrelial infection, particularly if antibiotic treatment has been started early" (14). Serology together with the corresponding clinical manifestations has a high diagnostic specificity.

In neuroborreliosis, the CSF examination reveals pleocytosis, usually with a leukocyte concentration well below 1000/µL, in which lymphocytes predominate. The CSF protein concentration is often elevated to 1 g/L or higher. The clinical suspicion of neuroborreliosis is confirmed by the demonstration of CSF pleocytosis and intrathecally formed specific antibodies against Borrelia (antibody index, AI). The Borrelia-specific AI is determined for both IgG and IgM *(box)*.

A pathological Borrelia-specific AI is conclusive evidence of a current or previous episode of neuroborreliosis. In early stages of the disease, the Borrelia-specific AI can still be negative. CSF pleocytosis reflects the degree of activity of the inflammatory process in the central nervous system. Repeated determinations of the specific antibody titer in the serum and of the CSF/serum AI provide no valid information about the degree of activity of the disease or the response to treatment.

In summary, the detection of specific antibodies in the serum in the early phase of a Borrelia infection is

Neuroborreliosis

Clinically suspected neuroborreliosis is confirmed by the demonstration of CSF pleocytosis and of intrathecally formed specific antibodies (antibody index). The Borrelia-specific antibody index (AI) is determined for both IgG and IgM.

The inflammatory process in the central nervous system

The Borrelia-specific antibody index (AI) can still be negative in early stages of the disease. The criterion for the activity of the inflammatory process in the central nervous system is CSF pleocytosis.

neither a necessary criterion for the diagnosis (e.g., the sensitivity of this test in the early phase of erythema migrans is 50% at most) nor a sufficient criterion for it (as shown by the high prevalence of specific antibodies [<5% to more than 25%] in the general population). The less specific the patient's symptoms, the lower the predictive value of a positive serological finding. Conversely, if a borrelial infection has persisted for longer than eight weeks, Borrelia-specific antibodies must be detectable in the serum. An elevated Borrelia-specific AI is not proof of a fresh episode of neuroborreliosis; even when neuroborreliosis has been successfully treated, an elevated Borrelia-specific AI can be found for years afterward, long after the CSF leukocyte count has become normal again.

The direct demonstration of the infectious agent by laboratory culture or PCR should be attempted only when there are special indications for this, such as inconclusive clinical or serological findings. Direct demonstration requires especially careful preparation of the sample to be tested (skin biopsy, CSF, joint puncture or biopsy; sensitivity for skin, 50% to 70%; for joint puncture, 50% to 70% [PCR only]; for CSF, 10% to 30%). PCR is preferred because it can be performed much more rapidly than culture.

Neither antigen testing of body fluids nor PCR on urine samples is recommended, as these techniques have not been clinically validated. The same holds for the lymphocyte transformation test, which, in principle, should be able to detect very early Lyme disease and to distinguish active from no longer active infection. This method is particularly subject to false-positive results and is therefore not suitable for diagnostic use in its current stage of development (6, 15).

Treatment

Lyme disease has a good prognosis (14, 16, 17). Most of its clinical manifestations are self-limiting. Even in the pre-antibiotic era, and also afterward, for as long as neuroborreliosis was mistakenly considered to be a viral infection (i.e., until 1982), spontaneous cures were often observed. Antibiotic treatment shortens the clinical course and prevents complications and rare chronic infections (16, e3–e5). The long-term results of antibiotic treatment are very good (14, 16–18). When the disease is treated in accordance with published guidelines, recurrences are very rare. On the other hand, reinfection is possible after another tick bite. The development of antibiotic resistance of the pathogenic organism has not been demonstrated to date. Even after the pathogen has been eliminated, the clinical manifestations may take weeks to resolve. The effect of treatment should be judged from the clinical manifestations rather than the laboratory findings. Antibiotic treatment rapidly relieves pain in Bannwarth syndrome (14). 95% of patients with spinal radiculitis had severe pain at the beginning of treatment; after 14 days of treatment with ceftriaxone, the intensity of pain was markedly reduced in all patients. Stage II neuroborreliosis resolved completely, without any residual symptoms, in 90% of patients after 3 months and in 95% after 12 months; 5% still had a mild facial palsy. The neurological deficits resolve more slowly after antibiotic treatment of stage III neuroborreliosis, and the frequency of residual damage is higher: after 12 months, the pareses, ataxia, and bladder dysfunction had completely resolved in 10 of 15 patients (66%) (16). In neuroborreliosis, normalization of the CSF pleocytosis can be used as an additional measure of the response to treatment, alongside the clinical findings.

Because the serological findings can vary markedly, and because antibodies, including those formed in the central nervous system, can persist for a long time, serological follow-up testing is not a suitable means of monitoring the success of treatment.

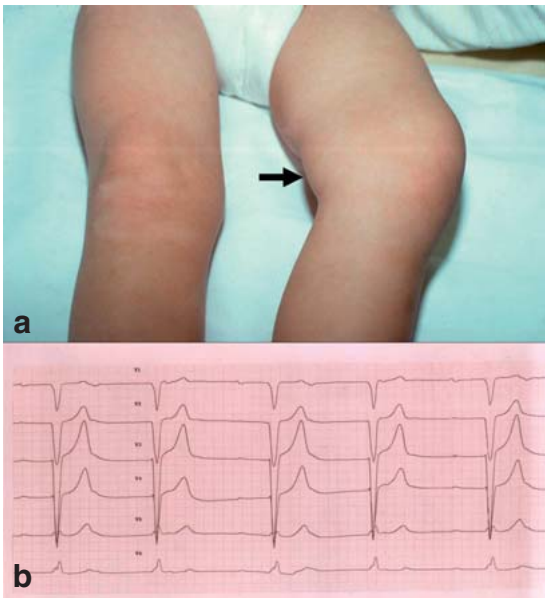

Figure 3:
Manifestations of Lyme disease in other organs:
(a) Lyme arthritis of the left knee;
(b) type III atrioventricular block, a rare complication of cardiac Borrelia infection.

Treatment

Lyme disease has a good prognosis. Most of its clinical manifestations are self-limited.

Serology

Because the serological findings vary widely, and because antibodies (including those formed in the central nervous system) persist for a long time, serological follow-up testing is not a suitable method for judging the adequacy of treatment.

TABLE

The treatment of Borrelia infection (daily doses for adults)

	Antibiotic	Duration of treatment	Reference
Erythema migrans (Stage I)	Doxycycline 100 mg po bid Amoxicillin 500 mg po tid Cefuroximaxetil 500 mg po bid	14 days	17
Acute neuroborreliosis (Stage II)	Ceftriaxone 2 g IV qd Cefotaxime 2 g IV tid Doxycycline 100 mg po bid–tid Penicillin 6×10^6 U IV tid–qid	14 days	14,17
Chronic neuroborreliosis (Stage III)	Ceftriaxone 2 g IV qd Cefotaxime 2 g IV tid Doxycycline 100 mg po bid–tid	14 to 21 (up to 28) days	14,17
Lyme arthritis	Doxycycline 100 mg po bid Amoxicillin 500 mg po tid Cefuroximaxetil 500 mg po bid	28 days	17
Acrodermatitis chronica atrophicans	Doxycycline 100 mg po bid Amoxicillin 500 mg po tid Cefuroximaxetil 500 mg po bid	21 days	17
Lyme carditis	Symptomatic carditis: Ceftriaxone 2 g IV qd Asymptomatic carditis: "oral or parenteral antibiotic treatment"	14 days	17
Borrelial lymphocytoma	Doxycycline 100 mg po bid Amoxicillin 500 mg po tid Cefuroximaxetil 500 mg po bid	14 days	17

Median recommended durations of treatment are given in the table; some authors and guidelines recommend shorter or longer durations (for details, cf. Reference 17). Doses must be adjusted for children. Doxycycline is not given to children under 9 years old to treat borreliosis because of its side effects.

An infection with Borrelia burgdorferi sensu lato is not followed by any lasting immunity.

The choice of antibiotic, its mode of administration, and the duration of treatment depend on the stage of the disease, the clinical manifestations, and the age of the patient *(table)*. The recommendations given here are based on treatment studies, on in vitro data regarding pathogen sensitivity, and on the pharmacokinetic parameters of the antibiotics that are used.

The pathogenic organisms causing borreliosis are highly sensitive in vitro to cefotaxime, ceftriaxone, and macrolides (minimal inhibitory concentration for the growth of 90% of strains [MIC_{90}], 0.06 to 0.12 mg/L) and somewhat less sensitive to amoxicillin, other aminopenicillins, and tetracyclines (MIC_{90}, 0.5 mg/L). The MIC_{90} of penicillin is relatively high (4 mg/L).

The current standard of treatment in stage I in adult patients is doxycycline 100 mg po bid or amoxicillin 500 mg po tid for two weeks (evidence level A) (17). While taking doxycycline, patients should avoid exposure to the sun, because phototoxic side effects are otherwise common. Children under 9 years old should not take tetracyclines, because these can cause yellowish discoloration of the teeth; amoxicillin is usually given instead. Alternatively, cefuroximaxetil or (in case of allergy to beta-lactam antibiotics) macrolides can be given instead, but the effectiveness of these drugs seems to be less reliable (17).

In randomized studies involving patients with stage II neuroborreliosis, the following treatment regimes were found to be effective: penicillin 6×10^6 U IV tid-qid (evidence level A), cefotaxime 2 g tid (A), ceftriaxone 2 g IV qd for 14 days (A), and doxycycline 100 mg po bid–tid for 2 weeks (B) (14, e6). The third-generation cephalosporins are recommended despite their higher daily treatment costs because of their low

Immunity

An infection with B. burgdorferi sensu lato is not followed by permanent immunity. Conclusively documented cases of clinically manifest reinfection have been described.

The choice of antibiotic

The choice of the antibiotic drug, its mode of administration, and the duration of treatment depend on the stage of the disease, the clinical manifestations, and the age of the patient.

BOX

Formula for the Borrelia-specific antibody index (AI)

$$\frac{\dfrac{\text{Borrelia-specific Ig in CSF}}{\text{Borrelia-specific Ig in serum}}}{\dfrac{\text{total Ig in CSF}}{\text{total Ig in serum}}} = \text{AI}$$

MIC_{90} values. After the intravenous administration of 2 g of drug, equally high CSF concentrations of cefotaxime and ceftriaxone are achieved (19). Ceftriaxone 2 g IV qd for 14 days is the standard treatment because it needs to be given only once daily.

In stage III, ceftriaxone 2 g IV qd is given for 14 to 21 days (or for 14 to 28 days; for alternative treatments, see the *table*).

Prolongation of the treatment to more than 28 days is not indicated. On the contrary, this carries a high risk of side effects, including pseudomembranous colitis and the accumulation of ceftriaxone calcium salts in the gall bladder, which can also become symptomatic.

Chronic, nonspecific symptoms accompanied by a positive Borrelia serology

In addition to the clinical and laboratory findings described above that clearly fulfill the case-definition criteria, chronic, nonspecific symptoms accompanied by a positive Borrelia serology are sometimes thought to represent a form of Lyme disease. There is concern in such situations that chronic Lyme disease has arisen without the clinical signs of an acute infection ever having been observed previously. The authors consider this to be possible, in view of the fact that typical neuroborreliosis or borrelial arthritis can develop in the absence of prior erythema migrans. Nonetheless, an especially meticulous process of differential diagnosis is mandatory in such cases. In the guidelines of the German Neurological Society, the following is stated: "If Borrelia antibody tests are positive (...) and have been confirmed as positive by a reference laboratory (...), and if other causes have been excluded, then a single course of antibiotic treatment can be considered in individual cases (...). Failure of this empirical course of antibiotic treatment to relieve the patient's symptoms lastingly is evidence against the presence of chronic Lyme disease" (14).

Patients who have been through an episode of borreliosis that has resolved after adequate antibiotic treatment may have symptoms thereafter, most commonly impaired performance, fatigability, impaired concentration, or chronic pain (20). This symptom complex is often designated by the as yet inadequately defined terms "chronic Lyme disease" or "post-Lyme syndrome," implying the pathogenetic conception of a persistent infection or of a persistent secondary disease after eradication of the causative organism (18). In many studies that have been performed on such patients, the bacterium could no longer be demonstrated, and a reintroduction or prolongation of antibiotic therapy had the same effect as placebo treatment (21). In one study involving 55 patients who were still suffering from severe fatigability and exhaustion 6 months (or more) after adequate antibiotic treatment for borreliosis, a new 28-day course of ceftriaxone (2 g/day) improved their fatigability and exhaustion, but not the cognitive impairment that was simultaneously present (22). Moreover, controlled studies have shown that symptoms of this kind do not seem to arise any more often in patients who have had definitively documented Lyme disease than they do in normal control individuals (23). Nonetheless, prolonged antibiotic treatment is still postulated by some to be beneficial, mainly on the basis of case reports and nonrandomized studies. Such treatment generally lies within the sphere of "alternative medicine" (24).

New experimental data suggest that T-cell clones activated in a borrelial infection can react not only with Borrelia antigens, but also with endogenous proteins such as heat shock protein 90 (HSP90). This cross-reaction to exogenous and endogenous antigens might induce an autoimmune illness, which might in turn explain cases of antibiotic-resistant, chronic illness after borrelial infection (2, 25). Research is currently addressing the question whether a borrelial infection can induce an autoimmune reaction of rheumatic type that persists after the pathogen has been eliminated. There is much controversy over another question, i.e., whether borrelial infection can cause psychiatric disease.

The demystification of this infectious disease is urgently needed and can only be brought about by further,

Antibiotic treatment in children

Tetracyclines are contraindicated for children under 9 years old, because they can cause yellow discoloration of the teeth. Children in this age group with skin or joint manifestations are usually treated with amoxicillin.

"Post-Lyme borreliosis"

According to the findings of controlled studies, symptoms such as impaired performance, fatigability, impaired concentration, or chronic pain apparently do not arise any more frequently in persons who have had unambiguously documented Lyme disease than they do in normal control individuals.

Internet addresses for further information

- Quality Standards for the Microbiological Diagnosis of Infectious Diseases (MIQ) from the German Society for Hygiene and Microbiology: http://pollux.mpk.med.uni-muenchen.de/alpha1/nrz-borrelia/miq-lyme/frame-miq-lyme.html
- Guidelines of the German Neurological Society: http://www.leitlinien.net

unambiguous scientific documentation of its long-term consequences.

Residual manifestations in the aftermath of Borrelia burgdorferi infections must be treated symptomatically, e.g., with anti-inflammatory drugs or antidepressants. On the other hand, in the authors' judgment, the administration of repeated cycles of antibiotic treatment is not indicated.

Conflict of interest statement
Professor Nau and Professor Eiffert have received support for their work on neuroborreliosis from the Else Kröner Fresenius Foundation. Professor Christen states that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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REFERENCES

1. Satz N: Klinik der Lyme-Borreliose. Verlag Hans Huber, Bern, 2. Auflage, 2002.
2. Lünemann JD, Gelderblom H, Sospedra M, Quandt JA, Pinilla C, Marques A, Martin R: Cerebrospinal fluid-infiltrating CD4+ T cells recognize Borrelia burgdorferi lysine-enriched protein domains and central nervous system autoantigens in early Lyme encephalitis. Infect Immun 2007; 75: 243–51.
3. Ohlenbusch A, Matuschka F-R, Richter D, Christen H-J, Thomssen R, Spielman A, Eiffert H: Etiology of the Acrodermatitis chronica atrophicans lesion in Lyme disease. J Infect Dis 1996; 174: 421–3.
4. Wilske B, Busch U, Eiffert H, Fingerle V, Pfister HW, Rössler D, Preac-Mursic V: Diversitiy of OspA and OspC among cerebrospinal fluid isolates of Borrelia burgdorferi sensu lato from patients with neuroborreliosis in Germany. Med Microbiol Immunol 1996; 184: 195–201.
5. Robert-Koch-Institut. RKI Ratgeber Infektionskrankheiten „Lyme-Borreliose“ 2007. http://www.rki.de/nn_466802/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber__Mbl__LymeBorreliose.html
6. Wilske B, Fingerle V: Lyme-Borreliose Diagnostik. Mikrobiologe 2005; 15: 209–20.
7. Huppertz HI, Böhme M, Standaert SM, Karch H, Plotkin SA: Incidence of Lyme borreliosis in the Würzburg region of Germany. Eur J Clin Microbiol Infect Dis 1999; 18: 697–703.
8. Christen H-J, Eiffert H: Lyme-Borreliose: Haut- und Nervensystem. Monatschr Kinderheilk 2003; 151: 1146–55.
9. Christen HJ, Hanefeld F, Eiffert H, Thomssen R: Epidemiology and clinical manifestations of Lyme borreliosis in childhood. A prospective multicentre study with special regard to neuroborreliosis. Acta Paediatr Suppl 1993; 386: 1–75.
10. Ackermann R, Golmer E, Rehse-Küpper B: Progressive Borrelien-Enzephalomyelitis. Dtsch Med Wochenschr 1985; 110: 1039–42.
11. Miklossy J, Kuntzer T, Bogousslavsky J, Regli F, Janzer RC: Meningovascular form of neuroborreliosis: similarities between neuropathological findings in a case of Lyme disease and those occurring in tertiary neurosyphilis. Acta Neuropathol 1990; 80: 568–72.
12. Eiffert H, Karsten A, Schlott T, Ohlenbusch A, Laskawi R, Hoppert M, Christen HJ: Acute peripheral facial palsy in Lyme disease—a distal neuritis at the infection site. Neuropediatrics 2004; 35: 267–73.
13. Wilske B, Zöller L, Brade V, Eiffert H, Göbel UB, Stanek G, Pfister HW: MiQ12 2000 Lyme-Borreliosis http://www.dghm.org/red/index.html?cname=MIQ
14. Kaiser R, Kölmel HW, Pfister HW, Rauer S, Wilske B: Neuroborreliose (Leitlinie der Deutschen Gesellschaft für Neurologie). In Diener HC et al. (eds.): Leitlinien für Diagnostik und Therapie in der Neurologie, 3. Aufl, Thieme, Stuttgart 2005.
15. Aguero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP: Diagnosis of Lyme borreliosis. Clin Microbiol Rev 2005; 18: 484–509.
16. Kaiser R: Verlauf der akuten und chronischen Neuroborreliose nach Behandlung mit Ceftriaxon. Nervenarzt 2004; 75: 553–7.
17. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC 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. IDSA Giudelines 2006; 43: 1089–134.
18. Feder HM, Johnson BJB, O´Connell et al.: A critical appraisal of „chronic lyme disease“. N Engl J Med 2007; 357: 1422–30.
19. Nau R, Prange HW, Muth P, Mahr G, Menck S, Kolenda H, Sörgel F: Passage of cefotaxime and ceftriaxone into cerebrospinal fluid of patients with uninflamed meninges. Antimicrob Agents Chemother 1993; 37: 1518–24.
20. Krupp LB, Masur D, Schwartz J, Coyle PK, Langenbach LJ, Fernquist SK, Jandorf L, Halperin JJ: Cognitive function in late Lyme borreliosis. Arch Neurol 1991; 48: 1125–9.
21. Auwaerter PG: Point: antibiotic therapy is not the answer for patients with persisting symptoms attributable to lyme disease. Clin Infect Dis 2007; 45: 143–8.
22. Krupp LB, Hyman LG, Grimson R et al.: Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology 2003; 60: 1923–30.

Borrelia as a cause of rheumatic disease?

Current research is addressing the question whether a Borrelia infection can induce an autoimmune reaction of rheumatic type that persists after the elimination of the causative organism.

Sequelae

Persisting symptoms in the aftermath of Borrelia burgdorferi infection must be treated symptomatically (e.g., with anti-inflammatory agents or antidepressants).

23. Seltzer EG, Gerber MA, Cartter ML, Freudigman K, Shapiro ED: Long-term outcomes of persons with Lyme disease. J Am Med Assoc 2000; 283: 609–16.

24. Stricker RB. Counterpoint: Long-term antibiotic therapy improves persistent symptoms associated with lyme disease. Clin Infect Dis 2007; 45: 149–57.

25. Eiffert H, Karsten A, Ritter K, Ohlenbusch A, Schlott T, Laskawi R, Christen HJ: Autoantibodies to human manganese superoxide dismutase (MnSOD) in children with facial palsy due to neuroborreliosis. Neuropediatrics 2005; 36: 386–8.

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Stuck B et al.: Tonsillectomy in Children:
1d, 2b, 3e, 4c, 5a, 6d, 7e, 8e, 9a, 10c.

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Approximately how high is the annual incidence of clinically evident borreliosis in Germany?

a) 10 000 to 15 000 cases per 100 000 inhabitants per year
b) 1000 to 1500 cases per 100 000 inhabitants per year
c) 100 to 150 cases per 100 000 inhabitants per year
d) 10 to 15 cases per 100 000 inhabitants per year
e) 1 to 5 cases per 100 000 inhabitants per year

Question 2

What is the most common clinical manifestation of Borrelia infection?

a) Acrodermatitis chronica atrophicans
b) Bannwarth syndrome
c) Erythema migrans
d) Lymphocytoma
e) Neuroborreliosis

Question 3

What is the drug of choice for the treatment of erythema migrans in children?

a) Amoxicillin
b) Doxycycline
c) Erythromycin
d) Fosfomycin
e) Rifampicin

Question 4

What is the drug of choice for the treatment of erythema migrans in adults?

a) Amoxicillin
b) Doxycycline
c) Erythromycin
d) Fosfomycin
e) Rifampicin

Question 5

Which of the following medications is used in the standard treatment of both acute and chronic neuroborreliosis?

a) Amoxicillin
b) Erythromycin
c) Penicillin
d) Ceftriaxone
e) Vancomycin

Question 6

How is Borrelia infection generally diagnosed?

a) By culture of the causative organism in normally sterile body fluids
b) By demonstration of the genome of the causative organism in normally sterile body fluids with PCR
c) From the history and physical findings, with the aid of serology
d) From the physical findings and imaging studies
e) From the microscopic demonstration of the causative organism in a biopsy specimen

Question 7

What are the main features of Bannwarth syndrome (the most common mode of presentation of neuroborreliosis in adulthood)?

a) Cranial nerve deficits, radiculitis, lymphomonocytic meningitis
b) Cranial nerve deficits, abdominal pain, granulocytic CSF pleocytosis
c) Urinary incontinence, unilateral pareses, granulocytic CSF pleocytosis
d) Intense meningism, headache, granulocytic CSF pleocytosis
e) Urinary incontinence, constipation, weight loss

Question 8

What are the typical CSF findings in untreated neuroborreliosis?

a) A granulocytic pleocytosis, elevated protein, and the demonstration of many spirochetes
b) A granulocytic pleocytosis, elevated protein, and the demonstration of Borrelia-specific antibody synthesis in the central nervous system
c) Normal CSF leukocyte count, elevated protein, and the demonstration of Borrelia-specific antibody synthesis in the central nervous system
d) A lymphomonocytic pleocytosis, normal total protein, and a markedly elevated CSF lactate concentration
e) A lymphomonocytic pleocytosis, elevated protein, and the demonstration of Borrelia-specific antibody synthesis in the central nervous system

Question 9

How can a tick be safely removed?

a) As soon as possible after attachment, with a forceps
b) As soon as possible after attachment, by scalpel excision with a wide margin
c) If possible, 12 hours after coating the tick with a special ointment
d) Under sterile conditions by a board-certified surgeon
e) No sooner than 24 hours after attachment, in order to avoid irritating the hungry tick

Question 10

Which of the following tests is used routinely in clinical practice to document a suspected Borrelia infection?

a) IgG- and IgM-ELISA
b) Immune blot
c) Culture
d) Polymerase chain reaction (PCR)
e) Microscopy

CONTINUING MEDICAL EDUCATION

Lyme Disease—Current State of Knowledge

Roland Nau, Hans-Jürgen Christen, Helmut Eiffert

E-REFERENCES

e1. Van Dijk JG, Pondaag W, Malessy MJA: Obstetric lesions of the brachial plexus. Muscle Nerve 2001; 24: 1451–61.

e2. Waters PM: Update on management of pediatric brachial plexus palsy. J Pediat Orthop 2005; 14A: 233–44.

e3. Bahm J, Becker M, Disselhorst-Klug C et al.: Surgical strategy in obstetric brachial plexus palsy: the Aachen Experience. Semin Plast Surg 2004; 18: 285–99.

e4. Bahm J, Noaman H, Becker M: The dorsal approach to the suprascapular nerve in neuromuscular reanimation for obstetric brachial plexus lesions. Plast Reconstr Surg 2005; 115: 240–4.

e5. Pondaag W, de Boer R, van Wijlen-Hempel MS, Hofstede-Buitenhuis SM, Malessy MJA: External rotation as a result of suprascapular nerve neurotization in obstetric brachial plexus lesions. Neurosurgery 2005; 57: 530–7.

e6. Bisinella GL,Birch R, Smith SJM: Neurophysiological predicition of outcome in obstetric lesions of the brachial plexus. J Hand Surg 2003; 28B: 148–52.

e7. Vredeveld JW, Blaauw H, Sloof BACJ, Rozeman CAM: The findings in paediatric obstetric brachial plexus palsy differ from those in older patients: a suggested explanation. Dev Med Child Neurol 2000; 42: 158–61.

e8. Horii E, Nakamura R, Koh S, Inagaki H, Yajima H, Nakao E: Surgical treatment for chronic radial head dislocation. J Bone Joint Surg 2002; 84A: 1183–8.

e9. Ozkan T, Aydin A, Ozer K, Ozturk K, Durmaz H, Ozkan S: A surgical technique for pediatric forearm pronation: brachioradialis rerouting with interosseous membrane release. J Hand Surg 2004; 29A: 22–7.

e10. Bahm J, Gilbert A: Surgical correction of supination deformity in children with obstetric brachial plexus palsy. J Hand Surg 2002; 27B: 20–3.

e11. El Gammal TA, Saleh WR, El Sayed A, Kotb MM, Imam HM, Fathi NA: Tendon transfer around the shoulder in obstetric brachial plexus paralysis: clinical and computed tomographic study. J Pediatr Orthop 2006; 26: 641–6.

e12. Nath RK, Paizi M: Improvement in abduction of the shoulder after reconstructive soft-tissue procedures in obstetric brachial plexus palsy. J Bone Joint Surg 2007; 89B: 620–6.

e13. Bahm J, Ocampo-Pavez C: Free functional gracilis muscle transfer in obstetric brachial plexus palsy. J brachial Plex Peripher Nerve Inj 2008 (submitted).

e14. Chuang DCC: Neurotization and free muscle transfer for brachial plexus avulsion injury. Hand Clin 2007; 23: 91–104.

e15. Bahm J, Meinecke L, Brandenbusch V, Rau G, Disselhorst-Klug C: High spatial resolution electromyography and video-assisted movement analysis in children with obstetric brachial plexus palsy. Hand Clin 2003; 19: 393–9.

e16. Krumlinde-Sundholm L: Development of the Assisting Hand Assessment: a rasch-built measure intended for children with unilateral upper limb impairments. Scand J Occupational Therapy 2003; 10: 16–26.

e17. Kirkos JM, Kyrkos MJ, Kapetanos GA, Haritidis JH: Brachial plexus palsy secondary to birth injuries: long-term results of anterior release and tendon transfers around the shoulder. J Bone Joint Surg 2005 ; 87B: 231–5.

e18. Ho ES, Curtis CG, Clarke HM: Pediatric evaluation of disability inventory: its application to children with obstetric brachial plexus palsy. J Hand Surg 2006; 31A: 197–202.

e19. Krumlinde-Sundholm L, Holmefur M, Kottorp A, Eliasson AC: The Assisting Hand Assessment: current evidence of validity, reliability, and responsiveness to change. Dev Med Child Neurol 2007; 49: 259–64.

e20. Noetzel MJ, Wolpaw JR: Emerging concepts in the pathophysiology of recovery from neonatal brachial plexus injury. Neurology 2000; 55: 5–6.

e21. Brown T, Cupido C, Scarfone H, Pape K, Galea V, McComas A: Developmental apraxia arising from neonatal brachial plexus palsy. Neurology 2000; 55: 24–30.

e22. Strömbeck C, Remahl S, Krumlinde-Sundholm L, Sejersen T: Long-term follow-up of children with obstetric brachial plexus palsy II: neurophysiological aspects. Dev Med Child Neurol 2007; 49: 204–9.

e23. PalmgrenT, Peltonen J, Linder T, Rautakorpi S, Nietosvaara Y: Sensory evaluation of the hands in children with brachial plexus birth injury. Dev Med Child Neurol 2007; 49: 582–6.

e24. Pondaag W, Malessy MJA: Recovery of hand function following nerve grafting and transfer in obstetric brachial plexus lesions. J Neurosurg Pediatr 2006; 105: 33–40.

e25. Hattori Y, Doi K, Dhawan V, Ikeda K, Kaneko K, Ohi R: Choline acetyltransferase activity and evoked spinal cord potentials for the diagnosis of brachial plexus injury. J Bone Joint Surg 2004; 86B: 70–3.

e26. Allen RH: On the mechanical aspects of shoulder dystocia and birth injury. Clinical Obstet Gynecol 2007; 50: 607–23.

e27. Gonik B, Walker A, Grimm M: Mathematic modeling of forces associated with shoulder dystocia: a comparison of endogenous and exogenous sources. Am J Obstet Gynecol 2000; 182: 689–91.

e28. Gurewitsch ED: Optimizing shoulder dystocia management to prevent birth injury. Clinical Obstet Gynecol 2007; 50: 592–606.

e29. Becker MHJ, Lassner F, Bahm J, Ingianni G, Pallua N: The cervical rib. a predisposing factor for obstetric brachial plexus lesions. J Bone Joint Surg 2002; 84B: 740–3.

e30. Clarke HM, Curtis CG: An approach to obstetrical brachial plexus injuries. Hand Clin 1995; 11: 563–80.

e31. Gilbert A, Tasson JL: Obstetrical palsy: a clinical, pathologic and surgical review. In: Terzis JK: Microreconstruction of nerve injuries. Philadelphia: Saunders 1987.