CORRESPONDENCE

Lyme Neuroborreliosis

by Prof. Dr. med. Sebastian Rauer, PD Dr. med. Stefan Kastenbauer, Dr. med. Volker Fingerle, Prof. Dr. med. Klaus-Peter Hunfeld, Prof. Dr. med. Hans-Iko Huppertz, and Dr. med. Rick Dersch in issue 45/2018

Critical Comments

The guideline of the German Society of Neurology (DGN) (1) and the corresponding publication in the *Deutsches Ärzteblatt* (2) contain a number of serious errors, resulting in misguidance in the medical and forensic fields. Especially with regard to the late stage of the disease, the DGN guideline is not based on the evidence-based literature, but on a structured consensus. Thus, it represents an S2k guideline and not an S3 guideline, as it is wrongly labelled. In contrast to the DGN, the German Society of Dermatology (DDG) has described its 2017 guideline on Lyme borreliosis correctly as an S2k guideline.

As prerequisites for the diagnosis of late-stage Lyme neuroborreliosis, typical clinical features, inflammatory CSF syndrome, intrathecal antibodies, and Lyme *Borrelia*-positive serology in the blood are demanded. However, while these requirements are backed by strong evidence in the early stage of the disease, this is not the case in the late stage. In addition, in 30% of cases with late-stage disease, *Borrelia* antibodies are missing (3).

In contradiction to the statement in the DGN guideline, the high diagnostic significance of the lymphocyte transformation tests is supported by numerous articles in the literature (3).

The post-treatment Lyme disease syndrome (PTLDS) is a hypothesis. The claim that PTLDS is a sign of defect healing cannot be supported by the literature. It is incomprehensible that the DGN guideline negates a causal relationship between an initial Lyme borreliosis and the (hypothetical) PTLDS.

The DGN guideline explicitly states that the available literature on the antimicrobial therapy of late-stage Lyme neuroborreliosis is insufficient. Nevertheless, the guideline recommends a treatment similar to that for early-stage disease. The article does not mention that the persistence of *Borrelia* infection after antimicrobial therapy is comprehensively described in the literature (4). Similarly, the assertion that 4-week antimicrobial therapy guarantees the elimination of Lyme borreliosis is unfounded (4).

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Conflict of interest statement

The authors declare that no conflict of interest exists.

Additions

From a dermatological perspective, some points can be added to this very clearly structured article by Rauer et al. (1). In endemic areas, erythema migrans—the clinical marker of early Lyme disease—has such a high specificity that a laboratory diagnosis is generally not required, in contrast to Lyme neuroborreliosis. However, the histopathological evaluation of lesional skin is of diagnostic value as it helps to rule out important conditions in the differential diagnosis, such as unspecific arthropod reactions, erysipelas, granuloma annulare, or localized scleroderma. The biopsy is best obtained from the edge of the erythema. Histological findings include an inflammatory infiltrate with lymphocytes and histiocytes in the superficial dermis as well as dilated blood vessels as the pathologic correlate of the erythema, in the presence of normal epidermis.

Despite the mostly clinically self-limiting nature of erythema migrans, antimicrobial therapy is always required to prevent pathogen persistence and thus potential later *Borrelia*-induced diseases, such as Lyme neuroborreliosis, among others. Unlike some other courses of Lyme neuroborreliosis, erythema migrans can be successfully treated with oral antimicrobial therapy. The antibiotics used are doxycycline (2 × 100 mg or 1 × 200 mg daily orally for 10–14 days) or amoxicillin, in pediatric patients aged less than 9 years amoxicillin or cefuroxime axetil, and during pregnancy and breastfeeding amoxicillin, each for 14 days (2). If (oral) antimicrobial therapy is planned, treatment adherence can be significantly improved if the patient is

thoroughly informed about the importance of the treatment as well as potential side effects and drug interactions prior to start of treatment. DOI: 10.3238/arztebl.2019.0344b

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In Reply:

The classification of guidelines according to the rules of the Association of the Scientific Medical Societies in Germany (AWMF) defines the system of the guideline development process with regard to the methodological approach (therefore: “S classes”), not with regard to the quality of the available data (evidence from clinical studies). Thus, a guideline of the S3 class must fulfill the following requirements, which are fulfilled by the S3 guideline on Lyme neuroborreliosis (1):

- Representative panel: Involved were mandate holders of 19 medical scientific societies, the Robert Koch Institute, the Paul Ehrlich Society, three patient organizations, and the German Borreliosis Society (DBG, Deutsche Borreliose Gesellschaft).
- Systematic literature search, selection and evaluation of the literature: This was carried out at the German Cochrane Center over a period of one year. The results have been published in four systematic reviews.
- Structured consensus process: The structured consensus process involved five consensus conferences, independently hosted by the AWMF.
- Declaration of interests and handling of conflicts of interest: These are documented in detail in the guideline report.

The hypothetical assumption that CSF testing could be unremarkable in patients with late-stage Lyme neuroborreliosis and that approximately 30% of cases with Lyme borreliosis are found to be seronegative in the late stage of the disease, is not supported by evidence. Furthermore, this assumption contradicts the infection-pathophysiological rationale. During a supplementary conference held on 17 January 2017, the related literature cited by the

DBG members was evaluated and discussed in detail by the signees—also in the presence of a mandate holder of the DBG. The above mentioned assumptions could not be substantiated by any of the cited studies.

The lymphocyte transformation test (LTT) for *Borrelia* is not suitable for routine testing as it lacks sensitivity and specificity. For the available of evidence from studies, please refer to the microbiological guideline on the laboratory diagnosis of Lyme borreliosis (2).

The post-treatment Lyme disease syndrome (PTLDS) is defined as persisting unspecific symptoms which can occur after treatment of Lyme borreliosis. In patients with PTLDS, typically no chronic infection with *Borrelia burgdorferi* is detected. Consequently, no benefit is to be expected from repeated or long-term microbial therapy; to the contrary, this strategy is associated with a risk of serious side effects. To address this problem, three studies offering class I evidence are comprehensively delineated in the guideline (3–5).

Controlled treatment studies and case series on Lyme neuroborreliosis have found no indication of pathogen persistence after two to three weeks of antimicrobial therapy. In the guideline, a pragmatic approach to potential exemptions is proposed. The publication of Middelveen et al. cited by the DBG members does not contribute to a better understanding of this question at all, because none of the twelve patients in this study suffered from Lyme neuroborreliosis which was confirmed clinically and by CSF testing. DOI: 10.3238/arztebl.2019.0345

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Prof. Rauer owns stock in the ravo Diagnostik company (Freiburg), which manufactures serologic tests for the diagnosis of Lyme borreliosis. He received payment for medical evaluations relating to the topic of the article from various judicial bodies and insurance companies. He received lecture fees from Biogen.