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Revisiting DLB diagnosis:

A consideration of prodromal DLB and of the diagnostic overlap with Alzheimer's disease.

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Introduction.

In recent years there has been a concerted effort to establish the phenotype of prodromal /pre-dementia Alzheimer's disease (AD).^{1,2} The terminologies used for this state have varied, the current position being that a diagnosis of AD now encompasses both the pre-dementia and dementia phases, and is diagnosed on the basis of the presence of an early and significant episodic memory impairment and in-vivo biomarker evidence of Alzheimer's pathology.³ There have also been initiatives to characterize the pre-dementia phase of Parkinson's Disease (PD), currently referred to as PD-MCI (mild cognitive impairment)^{4,5} and to a lesser extent the prodromal features of PD itself.⁶ The justification for these shifts to earlier diagnosis is that preventative treatment for neurodegenerative disorders will be most effective if given before extensive neurochemical and anatomic pathological changes have occurred in the brain. This argument has gained considerable force from the failure of several amyloid modifying agents to demonstrate clinical benefits in populations with mild to moderate AD. Trials of potential preventative agents in earlier stages of disease will only be possible once reliable methods of prodromal diagnosis have been established. The purpose of this brief paper is to consider the issues surrounding development of a definition and methods for determining a pre-dementia/prodromal diagnosis for patients who later progress to dementia with Lewy bodies (DLB). Before doing so it is helpful first to review the current situation regarding diagnosis of DLB at the dementia stage.

Clinical diagnostic concepts and methods for DLB have evolved over the last three decades to incorporate a variety of different terminologies including diffuse LB disease (DLBD)^{7,8,9}, LB dementia (LBD)¹⁰, dementia associated with cortical Lewy bodies (DCLB)¹¹, the LB variant of Alzheimer's disease (LBVAD)^{12,13}, and senile dementia of LB type (SDLT)¹⁴. Dementia with Lewy bodies (DLB) was eventually agreed as a term to include all of these within operationalised consensus criteria^{15,16}. The latest restatement of these criteria are manifest by their inclusion as neurocognitive disorder with Lewy bodies (NCDLB) in the latest revision of DSM-5¹⁷. This formal recognition of DLB as a diagnostic category equivalent in rank to others such as AD, vascular cognitive impairment and fronto-temporal dementia will inform and empower patients and families in legal and clinical issues

such as advance care planning, treatment of non-cognitive symptoms and sensitivity to antipsychotic prescription . It will also enable clinical and research practice, and has major implications for reimbursement and regulatory authorities. It reflects a general recognition of the importance of non-Alzheimer dementias as common disorders that require a different approach both in the clinic and the laboratory.

Consensus Criteria for DLB.

The consensus clinical diagnostic criteria for DLB have been in widespread use for almost two decades. Such criteria identify probable and possible DLB cases, depending upon the number of core and suggestive features present, both levels requiring the presence of dementia defined as “ a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function”. By definition, therefore, the consensus criteria exclude individuals at a pre-dementia stage. As originally conceived they were shown to have a high specificity for clinical DLB diagnosis compared with autopsy validation ¹⁸, but apparently failed to detect a significant number of eventually proven Lewy body (LB) pathology cases, their sensitivity ranging from 0-83% with a mean of around 40%¹⁹. In order to address this perceived insensitivity the DLB Consortium met again to resolve improving the identification of cases ante-mortem. No major amendments to the previously described core features of DLB were proposed, namely fluctuating cognition with pronounced variations in attention and alertness; recurrent visual hallucinations that are typically well formed and detailed; and spontaneous motor features of parkinsonism, but improved methods for their clinical assessment were recommended. A new category of features “suggestive” of DLB was added comprising REM sleep behaviour disorder (RBD), severe neuroleptic sensitivity, and abnormal dopamine transporter neuro-imaging imaging. It was proposed that if one or more of these suggestive features was present, in addition to one or more core features, a diagnosis of probable DLB could be made. Possible DLB was to be diagnosed if one or more suggestive features were present in a patient with dementia even in the absence of any core features. ¹⁶.

The Lewy body variant of Alzheimer’s disease, or AD with Lewy bodies?

The improved consensus criteria have been suggested to detect 25% more DLB cases than the previous version ²⁰ although a retrospective application of the new criteria to an autopsy verified sample reported that cases with Braak stage 5 and 6 Alzheimer tangle pathology are still unlikely to be correctly clinically diagnosed. Such cases tend to lack core or suggestive DLB features, and clinically resemble AD²¹. It has also been shown that the DLB clinical syndrome is modified by the

severity of Alzheimer neuritic plaque pathology, although total β -amyloid load has no effect.²² This is consistent with the original proposition that the likelihood of a patient having the typical DLB clinical syndrome is “directly related to the severity of Lewy-related pathology and inversely related to the severity of concurrent AD-type pathology.”¹⁶ Given that AD-type pathology is frequently present in DLB, there will therefore always be a significant number of patients who will prove very difficult to identify solely on clinical grounds. This group are best described pathologically as AD with LB or as LBVAD.¹² It is difficult to estimate the proportion that fall into this category but it is probably reasonable to assume that they account for most of the difference in the prevalence of all dementia cases reported to have cortical LB pathology at autopsy (10-15%)²³, and the clinically diagnosed prevalence in secondary care services from which such autopsy series are usually derived (7.5%)²⁴. In other words, only a half of DLB pathology cases look clinically like typical DLB and they are probably accurately diagnosed once the patient reaches a suitably qualified diagnostician. An equal number of cases will however have a different clinical presentation which may be difficult or impossible to distinguish from AD; intermediate between AD and DLB, or atypical in some other way.

From a clinicians' perspective it might be easier to conclude that these cases are not DLB and that an additional diagnostic category such as LBVAD or AD with LB should be reintroduced. DLB would then become a very clearly circumscribed clinico-pathological syndrome, i.e. with both high diagnostic specificity and sensitivity. Identification of the LBVAD/ADLB group would remain problematic, since the anticipated characteristics of the clinical presentation remain uncertain. It would seldom correspond to the recently proposed IWG2 group “mixed-AD” category, since such patients require two of the three DLB core clinical features i.e. also fulfil DLB criteria. More likely they would present as atypical AD or even typical AD, with an additional requirement for the presence of at least one LB biomarker. Engagement with the Alzheimer diagnostic community over these important overlap cases should be a priority.

Prodromal LB disease

The constellation of clinical features that have been suggested as indicative of early LB disease are listed in table 1. These symptom lists have been derived by asking patients at their time of diagnosis with PD and DLB, about their experience of these symptoms in the ten to fifteen year period prior to presentation.^{6,25,26} These earlier symptoms of sleep disturbance and autonomic involvement have long been recognized by researchers as part of the Lewy body spectrum but they are often not enquired about in clinical practice and their non-specific nature may make them not useful as early markers, e.g. constipation and dizziness are very common in the older population whether Lewy

body disease is present or not. Although subject to recall and retrospective biases, such reports are remarkably consistent both in the items mentioned and their relative timings making it evident that the prodromal symptoms of PD and DLB overlap substantially. This suggests that at the very earliest stage of LB disease it may not be possible to predict which phenotypic pathway they will subsequently follow and the only realistic diagnostic label at this early stage is of “symptoms suggestive of prodromal LB disease”. Since most such symptoms can be caused by multiple other causes in older people, their positive predictive value for LB disease is likely to be minimal and a LB biomarker needs be incorporated in order to increase disease specificity for a prodromal LB disease entity. The clinical utility of such a broad diagnostic category as prodromal LB disease is however questionable and requires further consideration which is outside of the scope of this paper. The prognostic implications of a clinical diagnosis of rapid eye movement sleep behaviour disorder (RBD) a diagnosis of which has already been shown to be predictive not just of DLB but also PD and multi-system atrophy (MSA) and highly associated with later progression to autopsy confirmed LB disease^{27,28} particularly requires further elaboration.

Prodromal /pre-dementia DLB. Progression and validation.

Figure 1 offers a simple starting point for a consideration of the introduction of a pre-dementia stage into the DLB diagnostic process and which assumes progression to an eventual dementia state.

FIGURE 1 HERE

The term “typical DLB” has been used in figure 1 to capture all those cases which are recognizable by the clinician by virtue of meeting Consensus criteria for probable or possible DLB. In many such cases a confident diagnosis of DLB will be made on clinical grounds alone and biomarker confirmation may not be required. In other cases when the clinician is less confident, additional biomarker evidence will be required. It is apparent from figure 1 that a patient presenting with prodromal DLB may progress either to typical DLB, or to atypical DLB and the above data suggest that these may be approximately equally likely events. This poses some difficulties for the validation of a prodromal DLB diagnosis, since progression to a more typical state over time is the usual standard. Given that this is the case it is apparent that there will be a need for biomarker confirmation of LB pathology not only at the prodromal stage, but also at the dementia stage for atypical cases. The situation is simplified if DLB-dementia is restricted to typical cases only, i.e. if atypical cases are regarded as LBVAD/ADLB as argued earlier. It is not clear what to call these prodromal cases who eventually progress to atypical DLB, but the reality for many prodromal

dementia cases may be that a mixed pathology diagnosis is more appropriate and will be defined by a non-specific clinical presentation and multiple biomarker abnormalities. Again this is a topic which needs debating with the wider dementia diagnostics community.

Returning to the more straightforward situation of prodromal, progressing to typical DLB, an important question is which biomarker(s) might be most useful to detect it early. An abnormal striatal dopamine transporter uptake scan has been established as useful in DLB-dementia and could be a helpful test in the pre-dementia situation.²⁹ But post-mortem studies have demonstrated that up to 50% of cases with synuclein pathology do not have substantial mid brain involvement even at autopsy³⁰, so it is likely that that many DLB patients presenting with limbic and cortical related symptoms will not have abnormal dopaminergic function, especially at an early stage. More sensitive biomarker alternatives to support the presence of LB disease could include MIBG cardiac scintigraphy³¹, or demonstration of alpha-synuclein in biopsy of sub-mandibular gland³², sigmoid colon³³ or cutaneous nerve³⁴. All of these, however, need robust demonstration of sensitivity and specificity in typical and atypical DLB dementia cases before they can be extended to confirming diagnosis at a pre-dementia stage.

Prodromal DLB subtypes – proposal of a broader classification

It is apparent from the previous discussion that pre-dementia DLB may have one of several broad clinical profiles, a situation which differs from AD in which a mild cognitive impairment is generally considered as the key prodrome. Prodromal DLB should only be suspected when the pattern of early clinical symptoms is suggestive of higher CNS involvement, i.e. is already leading to cognitive or psychiatric features. Three such prodromal DLB subtypes are considered below – see figure 2. Other early symptoms can only be interpreted as indicative of prodromal LB disease in general, or in the case of early motor symptoms, of prodromal PD.

The mild cognitive impairment variant (**DLB-MCI**) is the most obvious of these and there is already good evidence suggesting that this is usually non-amnesic, multi-domain in type and possibly associated with early visuoperceptual and attentional deficits³⁵. Conversion to DLB in such patients may occur even more frequently than conversion to AD in patients with amnesic MCI. DLB-MCI broadly corresponds to the DSM-5 category of mild neurocognitive disorder with Lewy bodies.¹⁷

A **delirium onset DLB (DLB-del)**, with provoked or spontaneous delirium as the presenting features has also been described,^{36 37} often occurring months or years prior to dementia onset and present in up to 25% of DLB cases compared with only 7% of AD³⁸. There have been no systematic studies of the frequency of LB disease in patients presenting with delirium although phosphorylated alpha-synuclein pathology in myenteric plexus was found in 44% of gastrectomy³⁹ patients having a post-operative delirium compared with only 6% in those who did not. The implications for management of delirium with antipsychotic agents are clear. Also described in the literature but not widely recognized is a **psychiatric disorder DLB (DLB-psych)** with its primary presentation as a late-onset affective disorder or psychosis³⁶, typically treatment refractory and with adverse sensitivity to neuroleptic and other psychotropic agents.⁴⁰ Mild cognitive and neurological deficits are often present at an early stage but the underlying basis is unsuspected until revealed by appropriate neuroimaging or disease progression.

Conclusions.

Prodromal DLB criteria will as a minimum, require a person to meet clinical criteria for one of these prototypic syndromes (MCI, delirium-onset or psychiatric onset) accompanied by at least one biomarker supportive of Lewy body disease. The next step is to clarify these concepts before moving to test them in suitable samples of patients and with suitably selected and disease staged biomarkers.

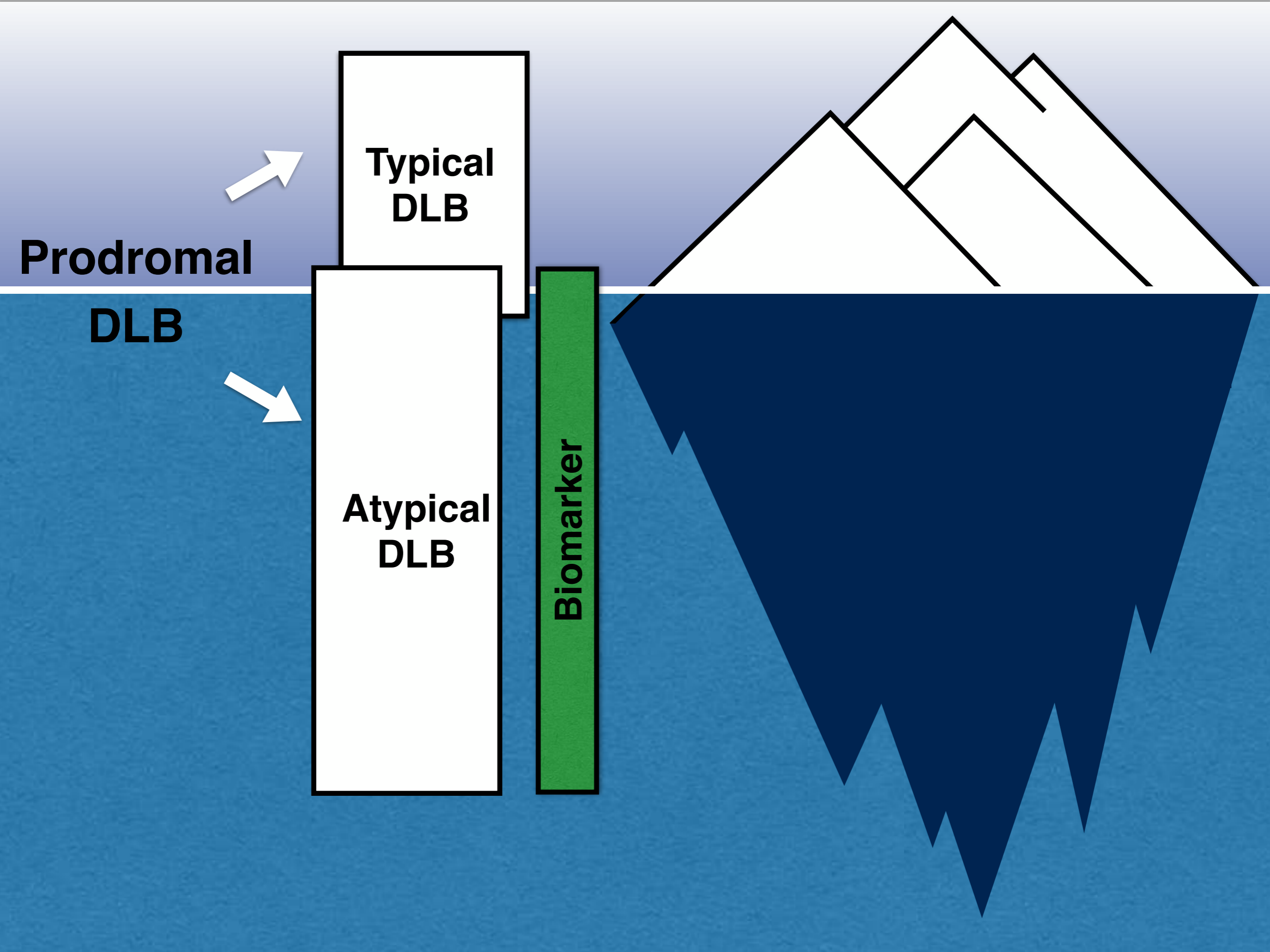
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Prodromal / pre-dementia DLB

may present as

DLB- mild cognitive impairment onset

DLB-mci

DLB-delirium onset

DLB-del

DLB-psychiatric onset

DLB-psych

Early symptoms –typically 5-15 years pre-dementia

Decreased sense of smell

REM sleep behavior disorder

- nightmares
- crying or shouting during sleep
- limb movements during sleep

Constipation

Dizziness on standing

Urinary incontinence

Increased saliva

Increased sweating

Intermediate symptoms

Delirium – provoked or unexplained

Late onset psychiatric disorder

- psychosis
- depression

Later symptoms

Cognitive impairment

Visual hallucinations

Parkinsonism

Table 1

Clinical features that have been suggested as indicative of early LB disease