

The Neuropsychiatric Assessment of Lyme Disease

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www.mentalhealthandillness.com/tnaold.html

Objective: A structured clinical interview is proposed to assist in the overall clinical assessment when late stage Lyme disease is suspected.

Method: From a combination of clinical experience, journal review, and discussion with colleagues, a structured interview was developed. Information from patients with late stage neuropsychiatric Lyme disease (NPLD) was entered into a database to serve as a reference point for diagnosis and tracking the patient's status after diagnosis.

Results: An analysis of symptoms acquired from a thorough history and mental status exam can be quite helpful towards the total clinical assessment when suspecting late stage Lyme disease. Details are provided in the text of this article.

Conclusion: When NPLD is a diagnostic possibility, a detailed, well-focused interview and mental status exam is proposed, and a database of symptoms seen in NPLD is established. It is recommended to continue perfecting the assessment as well as expanding the database. If diagnostic accuracy is improved, there would be better consensus regarding treatment strategies.

Objective

There are many unanswered questions regarding chronic Lyme disease. They remain unanswered as a result of our inability to accurately diagnose the presence or absence of the causative agent *B. burgdorferi*. The usual laboratory tests alone are not totally reliable to confirm or refute the diagnosis of Lyme disease (1). When we combine the current laboratory tests with a very thorough history, physical, and mental status exam, the accuracy of diagnosis is greatly increased. If we can improve the accuracy of diagnosing the presence of Lyme disease, there would then be more agreement regarding treatment guidelines. In an effort to improve diagnostic accuracy, I have developed a psychiatric diagnostic and tracking system.

Background

There are an increasing number of patients with chronic Lyme disease (neuroborreliosis) presenting in psychiatric offices. Lyme disease does not begin as a psychiatric illness. Other symptoms occur in early stage disease. Late in the progression of this disease neurological, cognitive, and psychiatric symptoms predominate. If not well understood, these symptoms are sometimes viewed as

non-specific and bizarre. Actually the symptoms can be quite specific with a clear physiological basis, but far too often a routine evaluation is insufficient to adequately evaluate these patients. When the evaluation is not properly targeted, key symptoms can be overlooked and these patients may be mistakenly diagnosed with chronic fatigue syndrome, fibromyalgia, M.S., lupus, Epstein barr, as well as many other medical and psychiatric symptoms. (2) They are considered by some to be "hypochondriacal" or "crazy." As a result, many of these patients feel alienated from the mainstream of the health care system. (3,4,5). The recent work of Drs. Fallon and Nields drew attention to the significance of the psychiatric component of chronic Lyme disease. (2,6,7,8,9,10).

As a psychiatrist practicing in a Lyme endemic area, I have evaluated and treated many of these patients from a psychiatric perspective over a period of years. Most of these patients were previously diagnosed with Lyme disease and many were considered to have been cured by prior adequate antibiotic treatment. I would like to share some of my observations, experience, and impressions from working with this population. Clinical experience is critical to add towards our total understanding of chronic Lyme disease (11).

We can view Lyme disease as a stealth Phoenix - it is difficult to find, and even more difficult to eradicate after it has penetrated deep into body tissue. (1,11) Once late stage disease exists, it is impossible, with current technology, to prove that *B. burgdorferi* has been eradicated. Constant vigilance is, therefore, required. Years of failure to recognize, diagnose, and adequately treat these patients has led to an ever expanding epidemic of chronic Lyme disease. (12,13,14,15,16).

All involved with late state Lyme disease agree there is a large amount of inaccurate information on this subject. This disagreement exists at every level - journals, scientific meetings, clinical practice, media outlets, etc. (17,18,19) Some of this disagreement can best be viewed as the normal difference of opinion seen when scientists approach a very complex problem from a very different perspective. To fuel the intensity of these disputes, some approach these issues with a significant bias. The full recognition of this illness has implications, which could effect tourism, real estate values, disability, insurance company/managed care liability, workman's compensation cases, motor vehicle issues, some criminal cases, and political issues. Bias issues can adversely effect patient care, research funding, and medical regulatory issues. Some of those previously impacted by bias now have difficulty approaching this disease with full-unhampered objectivity.

As physicians, it is our responsibility to protect life and quality of life. A tenacious pro-active stand prevents bias from obstructing access and quality of care.

Lyme disease is clearly a very complex disease. When considering a similar spirochete disease, syphilis, it has been said, "To know syphilis is to know medicine." However, to know Lyme disease is not only to know medicine but also neurology, psychiatry, politics, economics, and law. The complexity of this disease and all that surrounds it challenges our scientific as well as our ethical capabilities. I shall not address every aspect of this disease but I shall focus on diagnosis, in particular from a psychiatric perspective.

The diagnosis of Lyme disease and in particular late stage Lyme disease is a total clinical diagnosis (20). We need to return to basics. In my opinion, a very thorough history, mental status exam, neurological, and physical are the most significant components of the examination. We, in psychiatry, are uniquely trained to perform the type of exam that is needed for these patients. Laboratory tests, which are highly controversial, are also helpful, but the interpretation of the findings is complex and requires clinical correlation.

The commonly used blood, urine, and spinal fluid tests have a significant rate of false negatives in the chronic neuropsychiatric Lyme disease population. (See *addendum - Seronegative Lyme – on page 14.*)

Other tests that may be useful include P.E.T. and SPECT. Brain SPECT scans in Lyme patients sometimes show a swiss cheese pattern of hypoperfusion. (10)

In my experience, the location of the hypoperfusion may correlate with brain areas noted to be dysfunctional on the clinical exam. Although often reliable, not every neuropsychiatric Lyme disease patient demonstrated SPECT findings.

Some patients show findings on MRI's, but more commonly after illness has persisted for a few years. HTL tissue typing may be useful in showing who is more vulnerable to a more severe form of the illness. (21,22,23) Spinal taps (24) and nerve conduction studies can provide additional information. Psychological testing by an examiner who is experienced with evaluating Lyme disease may also be helpful.(2) Lyme urine antigen tests and PCR are being used with more frequency in the assessment of chronic Lyme disease. In addition to B. burgdorferi infections, coinfections with other agents leading to interactive infections are a significant issue. Some of these coinfections are other tick borne diseases, such as babesiosis, human granulocytic ehrlichiosis, human monocytic ehrlichiosis, etc. Other non-tick borne coinfections may also be significant, such as CMV, strep, etc. None of these tests can, however, exclude the diagnosis of Lyme disease. Many of our colleagues in internal medicine find the evaluation of this disease to be highly frustrating since compared to other illnesses there are less so called "objective" findings which are present. In both psychiatry and primary care, we are trained to contend with this gray zone of diagnostic criteria in which a skillful interviewer can recognize that subjective symptoms are valid. We are more accepting of Sir William Osler's quote - "If you listen long enough,

the patient will give you the answer." Effective communication with the patient is critical in considering the diagnosis. For us, Lyme disease presents with more objective symptoms than we commonly see with other mental disorders. There has been a recent trend to incorrectly view so called "objective" signs and symptoms as more valid than those which are "subjective." Often a machine or lab test is perceived as giving validity to these "objective" signs. Many of these "objective" tests are far less valid and are based on questionable techniques, faulty assumptions, and flawed logic. On the other hand, "subjective" complaints are sometimes viewed with excessive suspicion. When a credible patient describes a symptom that challenges our medical capability, it is an error to assume without the proper supporting evidence that they are lying, delusional, or hypochondriacal. In an effort to create predictability, reliance upon cookbook medicine has given us a recipe for disaster. Algorithms should be viewed as teaching tools and very rough guidelines, but should never be given more significance than a detailed thorough exam and sound clinical judgment. We, as physicians, owe it to our patients to always retain our courage and never defer our sound clinical judgment to dictatorial guidelines. When considering a diagnosis of Lyme disease, a distinction is made between the following groups:

1. Never infected by *B. burgdorferi*.
2. Infected by a Lyme like bacteria. (i.e., some other spirochete)
3. Infected by a *B. burgdorferi* and manifesting.
 - Subclinical illness
 - Minimal self-limiting illness
 - Early stage disease
 - Disseminated disease
4. Infected, never manifesting late stage disease, and currently either cured or in remission.
5. Infected, having manifested late stage disease and:
 - Not previously diagnosed with Lyme disease.
 - Previously diagnosed and treated with:
 - a. Possible cure
 - b. Remission
 - c. Subsequent progression of Lyme disease symptoms.
 - d. Current illness unrelated to Lyme disease.

e. Progression of Lyme disease symptoms and comorbid illness (es)

Late stage neuropsychiatric Lyme disease can best be conceptualized as a disseminated and progressive, (predominately sub-cortical), encephalopathy. Animal studies and autopsies have contributed to our understanding of the disease process. (25,26,27,28). As symptoms progress, additional symptoms occur and increase in severity.

These symptoms may be categorized in the following manner:

1. Brain Stem

- Cranial Nerve symptoms
- Autonomic symptoms. Dysautonomia may be the result of involvement of brain stem, involvement of other parts of the autonomic nervous system, or end organ pathology - i.e.: migraine, temperature dysregulation, sexual dysfunction, bright light sensitivity, mitral valve prolapse, irregular pulse, neutrally mediated hypotension, asthma, non-ulcerative dyspepsia, irritable bowel, and irritable bladder
- Hormonal symptoms: From the result of either hypothalamus or end organ involvement, i.e., thyroid disease, HPA axis dysregulation, decline of sex hormone functioning, hypoglycemia
- Long track disconnection syndromes (very late in the progression of the disease)
- Cerebellar symptoms

2. Limbic system, greater limbic system, extended amygdala

- Altered attention, emotional, and behavioral modulation
- Pathological psychiatric syndromes

3. Cortical (May be from either cortical or sub-cortical nuclei involvement)

- Signature syndromes
- Processing difficulties

4. Peripheral Neuropathy

The Structured Interview

When evaluating a patient, I recommend completing the following structured interview. I have found it to be quite helpful and cost effective in evaluating the possibility of neuropsychiatric Lyme disease. I have gradually developed this examination after interviewing many patients with neuropsychiatric Lyme disease. Since these patients have multiple deficits, which impair effective communication, we cannot expect the patient to volunteer the relevant

information. Therefore, we must methodically ask the appropriate questions in order to acquire an accurate history. The thoroughness of this exam combined with sound clinical judgment helps us to differentiate between who may have had Lyme disease, who may be in remission, who is showing active disease, and who may have some closely related condition. When the diagnosis is unclear, I suggest repeating the exam at a later date to consider whether the symptoms are increasing, stable or improving. The exam should also be repeated during and after treatment to further track the patient's status.

On the structured interview, at the left is a database for each item. The first data base column shows the incidence of a given symptom based on history prior to infection to serve as a control. The second column shows the incidence of these symptoms in the same population after infection in cases with significant clinical and laboratory findings. I am still in the process of completing this database. Many of the patients I have seen with LD are children, teenagers, and young adults. As a group, it has been my experience to find their pre-morbid status to be healthier than the average, both mentally and physically. This is a disease that more commonly attacks "lovers of life." (29) - young, healthy active individuals who engage in more outdoor activities, particularly those living in suburban and rural areas. Many report they have never had any significant illness prior to the onset of Lyme disease. After becoming ill, most of the patients report they had previously been diagnosed with Lyme disease and were given, what was considered by some standards, to be an adequate treatment. Subsequently, their symptoms progressed with increasing cognitive, psychiatric, and neurological components. Most of the patients tested positive at some point in the course of their illness. Some were not seropositive until after treatment had progressed. Some were seronegative which resulted in a significant delay in treatment and a progression to a greater number and more severe symptoms. When comparing the symptoms, there appeared to be no significant difference between the strongly seropositive (some of whom sell their blood to be used as a reference for labs), and the patients with more moderate laboratory findings and the seronegative group. The longer the interval between initial infection and effective treatment, the worse the prognosis.

Some symptoms are more specific than others. The control database is useful as a reference point. By looking at the patient's profile and comparing it to the database, we can see that some symptoms are more prevalent than others. Symptoms with an asterisk correlate with high diagnostic significance. Any single symptom may be seen in other illnesses, but the cluster of symptoms combined with our total knowledge of psychiatry, neurology, and medicine helps us to make the appropriate diagnosis. Patients with NPLD show significant number of positive responses. Patients with a different diagnosis do not demonstrate a large number of positive responses.

(See the Neuropsychiatric Assessment of Lyme Disease Form, on page 15.)

A Review of Items in the Interview

To review each item in sequence, refer to the flow sheet. Some of these times are self-explanatory whereas others require clarification. Recurrent erythema migrans rash is sometimes seen in the chronic Lyme population and has diagnostic significance. On rare occasions, chicken pox and other conditions can bring out the bull's eye rash. For example, patients with a chronic Lyme infection who become infected with chickenpox sometimes show the bull's eye rash around the chickenpox lesions.

The cognitive symptoms are particularly noteworthy when NPLD is suspected. When we attempt to correlate SPECT or PET findings with areas of deficit which are demonstrated in a clinical exam, cognitive deficits are easier to localize than emotional ones. Many of these patients give a history of an acquired attention deficit disorder. Auditory hyperacusis is particularly noteworthy.

Memory deficits are more selective for working memory, short-term memory, slowness of retrieval, and sequential memory (2). Long-term memory for information prior to the onset of the encephalopathy is usually relatively preserved until very late in the course of the illness. Memory encoding errors sometimes exist with the creating of some false memories, some of which occur during dissociative episodes. Working spatial memory can be impaired, i.e.: patients may have difficulty with the spatial awareness of where their front and back doors are in their house. One patient had a panic attack when they were lost in their garage and had lost the spatial awareness of the location of the door. The slowness of retrieval is evidenced as these patients grope to retrieve words and names. In the later stage of this disease they also have difficulty recalling motor sequences, (2,30) i.e., a recall of the sequential steps needed to tie their shoelaces. They are able to tie their shoelaces but must think out each sequential step. Many Lyme patients state "I feel like I have become dyslexic."

Impairment of reading comprehension is an earlier sign with the later addition of auditory comprehension difficulties. Acquired left/right confusion is seen with some of these patients displaying what appears to be an acquired Gerstmann's Syndrome or some variant of this syndrome. They have problems with calculations and often complain of errors when trying to calculate their checkbooks. Fluency of speech is a very significant problem. When interviewing these patients, this is a clearly evident symptom. Stuttering is seen in many of these patients, a finding which may correlate with left caudate/striatum involvement. Slurred speech is significant and can lead to the false impression that these patients are intoxicated which has, on occasion, led to motor vehicle charges. Handwriting declines and a comparison of writing samples can be useful to confirm this finding. Optic ataxia (41) is another important finding. Sometimes it can be bilateral or unilateral. This is an upper parietal function involving the contra-lateral side. When this symptom is present, patients have

trouble targeting, and they may bump into doorways, place objects incorrectly, and have problems driving in congested traffic.

Agnosia is a late appearing symptom. One patient was unable to recognize her own car in a parking lot. After receiving IV antibiotic treatment, she could recognize her car but was not able to recognize which key unlocked the car and which one started her car. Some of these patients display intrusive images which are more commonly of an aggressive nature but sometimes can be of a sexual or other nature. Occasionally these images are of a homicidal nature. The hallucinations are quite different from those commonly seen in schizophrenia. NPLD hallucinations are correlated with better reality testing.

Executive function and thought process are severely impaired with Lyme patients. This is very significant in contributing to the disability, which is seen in these patients, especially those accustomed to doing five things at once in their usual professional capacities. A small impairment in a patient who assumes a high level of responsibility can result in severe consequences. Cognitive tracking deficits, commonly called brain fog is a symptom that most of these patients describe. It is very different from the concentration impairment seen in clinical depression. Brain fog is a slowness and sluggishness of internal thought. Patients describe this as though their thought processes are shrouded in a fog.

The emotional and behavioral symptoms caused by Lyme disease are more complex to understand than the cognitive impairments. Let's first review the physiology of emotion. The different emotional functions have a hierarchy of circuitry, which includes stimulatory pathways, opposing inhibitory pathways, and a hierarchy of modulation centers. The basic hierarchy is pre-frontal cortex, para limbic association areas, limbic structures, and brain stems - hypothalamus. Lyme encephalopathy can result in dysfunction of the modulation centers, inhibitory pathways, and stimulatory pathways. Autopsies, animal studies, and brain imaging tests have contributed to this understanding. The presenting symptoms of NPLD are sometimes emotional in nature, and include obsessive-compulsive disorder, depression, and aggression, panic disorder, and other phobic disorders.

In considering the behavioral symptoms, these patients can become suddenly suicidal and there have been completed suicides attributed to Lyme disease. Homicidal ideation, urges, and behavior occur in some of these patients. Some adult patients describe struggling to not act on these urges. When these patients act on a homicidal urge, more commonly it is a child becoming assaultive to a sibling. Dissociative episodes sometimes occur with these patients occasionally accompanied with aggressive behavior and loss of memory.

Compensatory compulsions are common in an effort to compensate for the memory deficits. NPLD can imitate a number of common psychiatric syndromes. It can be difficult to differentiate Lyme disease from rapid cycling Bipolar illness or Posttraumatic Stress Disorder. Eating disorders are common. Invariably these patients either gain or lose weight. Sometimes massive weight gain is also seen.

Neurological symptoms have been previously recognized as a component of Lyme disease (31-46). Cranial nerve findings begin before the cognitive changes are seen and can intensify again late in the course of the illness. There are times when the cranial nerve findings are more evident late in the day when the patient becomes tired and they acquire double vision, choke on food, or lose their ability to talk. Grand mal seizures are more significant with congenital Lyme cases, while complex partial seizures are seen in a notable percent of other NPLD patients. These seizures are effectively controlled with both anticonvulsants and antibiotics.

Some neurological findings are common such as numbness, tingling, sensory loss, burning, weakness, tremors, myoclonic jerks, torticollis, and fainting. Ataxia is common in these patients who are often clumsy, which leads to frequent accidents. Myotonia is uncommon but I have seen this in a few patients, and Parkinson's syndrome caused by Lyme disease can also be seen, although it is uncommon. A number of these patients have herniated discs after having Lyme disease for several years. I suspect, but cannot prove, there is a causal relationship between Lyme disease and herniated discs. Burning is quite specific to NPLD, but is also seen in herpes infections. The patient describes a sensation that a blowtorch is burning the skin. It can affect any part of the body. In some patients the burning migrates, while in others it remains in a given area. Both antibiotics and anticonvulsants relieve this symptom.

Joint pain, swelling, and tightness is an earlier manifestation of Lyme disease and is often more effectively treated than the central nervous system symptoms. Knees are the joints most commonly involved (47). Bone pain as a result of periostitis affects certain bones, such as the tibiae. The periosteum is spongy on examination. Chronic fatigue and fibromyalgia may be seen as part of Lyme disease (48). Of course, these two syndromes can be caused by other conditions as well. Chondritis of the ear and nose and costochondritis are sometimes seen with these patients.

The cardiac symptoms (49-57) are quite prominent early on in the disease although more commonly with alternating episodes of racing pulse and bradycardia. Conduction defects can be fatal in some cases. Other cardiac complications including cardiomyopathy can be a later manifestation of this disease. Irritable bladder is common. Chronic Lyme patients frequently acquire a number of autonomic nervous system problems which were not present prior to the onset of the disease. Alcohol intolerance is common and most patients state

"I don't drink any more." Some other physical manifestations are quite uncommon.

The Jarish Herxheimer reaction is seen when antibiotics are having a therapeutic effect. There can be a worsening in the symptoms, which may include the periostitis, and the psychiatric and cognitive symptoms. Some patients become very impulsive, aggressive, depressed, and suicidal during a Herxheimer reaction and may require close monitoring during these times.

Progression of symptoms is a significant item. After working with these patients, it is clear there are common patterns in which different symptoms appear in a different sequence. This item is checked when the symptoms are appearing in a sequence that is seen in the progression of Lyme disease, i.e.: it begins with a tick bite, then a bull's eye rash associated with a flu like illness, then there may be some of the disseminated symptoms such as the joint pain. The cranial nerve symptoms may be seen. Later there is the development of the cognitive symptoms that gradually increase over time. Then the psychiatric symptoms develop later in the course of the illness with an intensification of the cognitive and neurological symptoms. Not every stage is seen in all patients. Although many similarities exist between patients, no two patients display the exact same symptoms; and there are many variants in the manner in which the disease presents. There is some evidence that different clusters of symptoms are associated with different strains of the bacteria, and there are many variants in the manner in which this disease presents.

After completing the interview and relevant mental status, neurological, and physical exams, we now review the pattern of symptoms that exist. Some of the symptoms may be difficult to localize, i.e., in a given patient is light sensitivity a result of meningeal irritation, cornea involvement, iritis, cranial nerve involvement, brain stem involvement, dysautonomia, or some other pathological process? Similar questions could be raised regarding other symptoms as well. The broad spectrum of symptoms helps to make the diagnosis. Can the symptoms be explained on some other basis? Is there some comorbid illness present?

The Role of the Psychiatrist in Treatment

Although diagnosis is the major focus of this article, I would like to say a few words about the role of psychiatry in the treatment of Neuropsychiatric Lyme Disease. The effective treatment of psychiatric symptoms in these patients helps improve their overall prognosis and reduce their need for antibiotic treatment. Let's review the physiology.

In a state of stress, the body's resources are allocated away from immune and regenerative functions towards stress related functions (58). If we reduce the symptoms related to the state of stress, the body will then allocate more resource

towards immune and regenerative functions. Therefore, the treatment of sleep disorder, depression, anxiety, ADD, etc. associated with neuropsychiatric Lyme disease helps the patient recover. The treatment of sleep disorder is particularly significant. Chronic fatigue and fibromyalgia whether or not caused by Lyme disease are associated with a deficiency of slow wave sleep (62). Improvement of sleep quality, particularly slow wave sleep is strongly correlated with improvement of the chronic fatigue and fibromyalgia components of Lyme disease, which in turn benefits overall prognosis.

In a milder case, this psychiatric treatment may lead to a total remission. In more severe cases this treatment merely buys time and gradually becomes less effective as the infection progresses, and the psychiatric symptoms become increasingly difficult to treat. When this trend exists, antibiotics and other treatments need to be combined with the psychiatric treatment. Some patients clearly need extended and repeated courses of antibiotic treatment (1, 59, 60). Although it is sometimes stated that most patients respond to conservative courses of antibiotic treatment, many of the patients I see have shown inadequate responses to such approaches and some have responded better to more aggressive, well-monitored antibiotic treatments. As with any treatment, the administration of antibiotics is an individualized risk versus benefit clinical decision. For effective treatment often intramuscular and intravenous antibiotics are needed, sometimes for extended period of time. It is well recognized such treatments have potential risks and a methodical risk vs. benefit assessment is needed. This decision should only be made by physicians who have assumed clinical responsibility, have personally examined the patient, and who have adequate knowledge of the illness and the therapeutic agents.

Other treatments include nutritional approaches and physical therapy. Hyperbaric oxygen is a treatment that is showing increasing potential in the treatment of Lyme disease. It is currently speculated that many of the symptoms seen in chronic disease are attributable to an inflammatory process rather than active infection. Although it is clear some inflammatory symptoms exist (61), it is difficult to accept this belief to explain the majority of the progressive symptoms seen in these patients. The Jarish Herxheimer reaction appears to be inflammatory in nature and is of fairly brief duration after antibiotic treatment is discontinued. Many of the symptoms perceived as "inflammatory" improve in response to antibiotic treatment. The inflammatory view is not without risk when steroids are administered which can increase the progression of active infection.

As with any other invisible disability, many of the chronic patients feel demoralized after being exposed to stigma and abuse from those who cannot understand or those who are biased for a variety of reasons. Neuropsychiatric Lyme disease patients are the recipients of double stigmas - that of Lyme disease as well as mental disorder. Some patients are contending with illness while also stating there is a lack of support from family, health care providers,

employers, and/or insurance companies. When such conditions exist, the stress level is magnified and the progression of the illness tends to increase.

We can also assist our patients by helping to understand the nature of this condition, resolving conflict, and offering input towards advocacy efforts. Lyme disease is an illness that has proven managed care to be a catastrophic failure. Early, effective treatment is critical. Managed care short-term cost containment techniques have resulted in very expensive long-term direct and indirect costs. Most of the indirect costs have been shifted to the general public.

To emphasize this point, I have seen too many examples of young people who have been denied needed treatment. Their condition deteriorates, they develop more symptoms, and health care expenditures increase, which in some cases leads to lifetime disability. In addition to the human cost, the extra financial burden for health care and disability expenses are shifted to the general public through various public tax funded programs. A significant amount of advocacy is needed to correct the many system failures seen with this disease.

Future Research Issues

In summary, my experience with Neuropsychiatric Lyme Disease has led me to ask the question - How much of mental disorders are caused by a chronic infectious process? Nervous system tissue is of ectodermal embryological origin and has similarities to skin that are also of ectodermal origin. Herpes simplex lies dormant in skin for extended periods of time and becomes symptomatic during times of stress causing fever blisters.

Might a similar process occur in the central nervous system with this or other infectious agents? Does an expanding bull's eye, erythema migrans process occur in the central nervous system as it does in skin? Why is this a benign disease in some people, while malignant in others?

Microbes evolve faster than people. For this reason, infectious disease will always exist. Many poorly understood diseases were later found to have an infectious disease basis. Infectious agents are continually evolving. New organisms are being recognized, and old ones develop new capabilities. As we develop new therapeutic agents, microbes evolve defenses against this technology. We are seeing increasing problems with infectious disease in humans and animals. Why? Are we losing ground in the "arms war"? Is this due to increased exposure to otherwise remote part of the globe? Is it a natural cycle of infectious disease? Is it a result of a declining global environment? Has the irresponsible use of technology contributed to this problem? Why is Lyme disease more prevalent now? How much of what is called "Lyme disease" is some other infectious disease? Could some of these patients be infected with seronegative syphilis? What can we do to reduce the number of infected ticks in our environment?

The study of this illness yields more questions than answers. It blurs the boundaries between psychiatry and other medical disciplines. It challenges our ethical capability. We need to continue approaching this with an open mind while listening very carefully to our patients.

Conclusion

When neuropsychiatric Lyme disease is a diagnostic possibility, a well-focused interview can assist toward the diagnosis and the evaluation of any change in status over time. Such a tracking system can assist toward clinical decision making and research. Once the reference point database is established, it shall constantly be updated.

SERONEGATIVE LYME DISEASE

1. Recent infection before immune response
2. Antibodies are in immune complexes
3. Spirochete encapsulated by host tissue (i.e.: lymphocytic cell walls)
4. Spirochete is deep in host tissue (i.e.: fibroblasts, neurons, etc.)
5. Blebs in body fluid, no whole organisms needed for PCR
6. No spirochetes in body fluid on day of test
7. Genetic heterogeneity (300 strains, 100 in U.S.)
8. Antigenic variability
9. Surface antigens change with temperature
10. Utilization of host protease instead of microbial protease
11. Spirochete in dormancy phase (L-form) with no cell walls
12. Recent antibiotic treatment
13. Recent anti-inflammatory treatment
14. Concomitant infection with babesia may cause immunosuppression
15. Other causes of immunosuppression
16. Lab with poor technical capability for Lyme disease
17. Lab tests not standardized for late stage disease
18. Lab tests labeled "for investigational use only"
19. CDC criteria is epidemiological not a diagnostic criteria
20. Lack of standardized control
21. Most controls use only a few strains as reference point
22. Few organisms are sometimes present
23. Encapsulated by glycoprotein "S-layer" which impairs immune recognition
24. "S"- layer binds to IgM
25. Immune deficiency
26. Possible down regulation of immune system by cytokines
27. Revised W.B. criteria fails to include most significant antigens

NEUROPSYCHIATRIC LYME ASSESSMENT
 See Article - Neuropsychiatric Assessment of Lyme Disease

+ Symptom/syndrome present	1 st Col. Premorbid Baseline
+/- Sub-syndromal	2 nd Col. Present in course of illness
- Symptoms not present	3 rd Col. Initial Visit
? Unknown	4 th Col. Subsequent visits, etc.
O Not applicable or available	
* High diagnostic significance	
# Uncommon symptoms	
DB1 - Database of NPLD patients pre-infection	
DB2 - Database of NPLD patients post infection	

Patient Name:

Date of Birth:

Current Age:

Date:

Date of Infection:

Date of LD Diagnosis:

Date Treatment Started:

History Exposure to Endemic Area:

History of Tick Bite:

History Erythema Migrans Rash:

With Flu-Like illness

Recurrent Erythema Migrans Rash:

Lab Findings:

Other Diagnoses Considered:

Pre-Existing Psychiatric Illness:

Pre-Existing Physical Illness:

Cognitive Symptoms

Attention Span (Perception)

Sustained Attention

Allocation of attention

Distracted by Frustration

Distracted by Hyperacuity

**Auditory*

Visual

Tactile

Olfactory

Memory

**Working Memory*

**Working Spatial Memory*

Recent Memory

Remote Memory

Encoding Errors

Memory Retrieval

**Slowness of retrieval*

Words

Numbers

Names

Faces

Motor sequences

Geographical/Spatial

**Sequential Memory*

Letter reversals

Spelling errors

Word substitution errors

Number reversals

Processing

**Reading comprehension*

**Auditory comprehension*

Sound localization

Transposition of laterality

**L-R confusion*

Visual imagery

**Calculation*

**Fluency of speech*

**Stuttering*

**Slurred speech*

**Fluency of written language*

**Handwriting*

**Spatial perceptual distortions (microscopia, etc)*

Decreased body awareness

Derealization

**Optic ataxia*

Agnosia

Apraxia

Imagery

Complex imagery

**Intrusive images*

Aggressive

Sexual

Other

Hypnagogic Hallucinations

Vivid nightmares

Illusions

Hallucinations

Thought Processes / Exec function

Unfocused concentration

**Fuzzy/Fog sensation*

**Prioritizing multiple tasks*

**Concentration on multiple tasks*

Racing thoughts

Obsessive thoughts

Mental apathy

Abstract reasoning

Mood Symptoms

Decreased frustration tolerance

Sudden abrupt mood swings

Hypervigilance
Paranoia

Behavioral Symptoms

Disinhibition
Exaggerated startle reflex
Explosive anger
Suicidal
Homicidal
Accident prone
Decreased social functioning
Decreased job/school performance
Marital/family difficulties
Substance abuse
Legal difficulties
Dissociative episodes
Compensatory compulsions
Dropping objects
Crying spells

Psychiatric Syndromes

Depression
**Rapid Cycling Bipolar*
Panic Disorder
Obsessive-Compulsive disorder
Social phobia
Generalized anxiety
PTSD

Oscillating Rhythms

Impaired sleep wakefulness cycle
Not well rested in the a.m.
Insomnia
Initial
Mid
Late
Hypersomnia
Loss of 24 hour cycle
Narcolepsy

Eating Disorder

Anorexia
Weight loss
Non-appetite motivated
Over-eating
Weight gain w/o increased food intake
Weight gain with increased food intake

Sexual

**Decreased libido*

Menstrual irregularity
Decreased capacity for pleasure
Other

Temperature Control

Body Temperature Fluctuations
Flushing
Intolerance to heat
Intolerance to cold
Decreased body temperature
Low grade fevers
Night sweats
Chills

Neurological

Headaches
**Cervical Radioculopathy*
Migraine
Orgasm Migraine
TMJ
Tension
Cluster
Sinus

Cranial Nerves

I. Olfactory, loss of smell, altered taste

II. Ophthalmologic

Blurred vision
**Photophobia*
Bright Light
Fluorescent and flicker
Floater
Flashes
**Conjunctivitis*
Eye pain
Dry eyes
Papilledema
Blind spots
Night blindness
Peripheral shadows
Other

III, IV, VI double vision or eye drifts when tired

Ptosis

V. Sensory loss

****VII. Bell's Palsy***

***VIII. Tinnitus**

Hearing loss
Dizziness
Vertigo
Motion sickness
Tullio's

IX, X Episodic loss of speech

Choking on food, difficulty swallowing

XI. SCM and trap pain and paresis

XII.

Seizures

Grand Mal
*Complex partial

Other Neurological

Numbness
Tingling
Sensory loss
Burning
Static electric sensation
Crawling sensation under the skin
Stabbing sensation
Paresis
Tremor
Twitching
Muscle tightness
Muscle discomfort
Myoclonic jerks
Torticollis
#Myotonia
#EPS
Ataxia
Fainting
Herniated disks
Spasticity
Rhombert
Other

Other Physical Symptoms

Joint
Pain, swelling, tightness (specify joints)
Bone thinning/fractures
*Bone pain (tibia, ribs, iliac crest, sternum, clavicle, elbow etc)
Plantar fasciitis
Chronic fatigue syndrome
Fibromyalgia
Myalgia

Chondritis (ear, nose, costochondral)
Tendonitis
Carpal Tunnel

Cardiac

Heart block
MVP
Racing pulse
Episodes of rapid and slow HR
Pericarditis
Cardiomyopathy
Murmur
Hypertension
Hypertensive crisis

Pulmonary / Upper Respiratory

Shortness of breath
Cough
Sore throats
Swollen glands
Asthma

Gastrointestinal (GI)

Upper GI distress
Non ulcerative dyspepsia
Irritable bowel
#Hepatitis
#Pancreatitis
#Inflammatory bowel
#Cholecystitis
#Gall stones

Genitourinary (GU)

Genital pain
Breast pain, tenderness
Lactation
Irritable bladder
#Atrophy of genitalia
Anesthesia of genitalia

Autoimmune symptoms

Other

Alcohol intolerance
Hair loss
Thyroid dysfunction
Wilson's Syndrome
Adrenal insufficiency
Hypoglycemia

Vasculitis
Ankle edema
Tooth pain
Nose bleeds
MCS
Allergies
Splenomegaly
Ecchymosis
Chronic pain
ACA
Lymphocytoma

Fluctuations of Symptoms

**Herxheimer reaction*
**Progression of symptoms*
**Symptoms fluctuation throughout the day*
Stress increases symptoms
Infectious disease increase symptoms
28 day cycle or longer
Perimenstrual relapse
Episodic relapse
Antibiotics reduce symptoms

Babesiosis screen

Severe headaches
Sweats
Chills
Severe fatigue
Severe muscle ache
Afternoon fever

Ehrlichiosis screen

Decreased white count
Decreased platelet count
Elevated liver enzymes
Splenomegaly

Treatment

Psychiatric

Medical

Oral antibiotics
IM & IV antibiotics

Other/Status/Comments

REFERENCES

1. Liegner Kenneth B: *Lyme Disease; The Sensible Pursuit of Answers*. Journal of Clinical Microbiology, August 1993, p. 1961-1963
2. Fallon BA, Rissenberg M, Liegner KB, Coyle PK, Nields JA, Bransfield RC: Neuropsychiatric Lyme Disease Symposium: American Psychiatric Association Annual Meeting, May 9, 1996
3. Knarr J: Lyme Disease patients to hold rally in Trenton; Burlington County Record, October 10, 1995
4. Abraham L: Ticked Off: Health, March/April 1995
5. LeBourdais E: Activists decry physician disinterest in Lyme Disease during Vancouver conference; Canadian Medical Association Journal, Sept. 15, 1995, 153 (6) : 822-824
6. Fallon BA, Nields JA, Burrassano JJ, Liegner KB, DeBene D, Liebowitz MR: *The Neuropsychiatric Manifestations of Lyme Borreliosis*: Psychiatric Quarterly, vol. 63, no. 1, Spring 1992
7. Fallon BA, Nields JA, Parsons B, Liebowitz MR, Klein DF: *Psychiatric Manifestations of Lyme Borreliosis*: J Clinical Psychiatry, 54:7 July 1993
8. Fallon BA, Nields JA: *Lyme Disease: a Neuropsychiatric Illness*: Am J Psychiatry, Nov 1994, 151 (11) : 1571-1583
9. Fallon BA, Schwartzberg M, Bransfield RC, Zimmerman B, Scotti A, Webber CA, Liebowitz MR: *Late-Stage Neuropsychiatric Lyme Borreliosis, Differential Diagnosis and Treatment*. Psychosomatics 1995 May-Jun; 36 (3) : 295-300
10. Fallon BA, Das S, Plutchok JJ, Tager F, Liegner K, Van Heertum R: *Functional brain imaging and neuropsychiatric testing in Lyme disease*. Clin Infect Dis Jul 1997; 25 Suppl 1 : S57-S63
11. Liegner KA: *B. burgdorferi-Seek and Ye Shall Find, Expanding the Envelope*: J Spirochetal and Tick-Borne Diseases, vol. 1, no. 4, 1994
12. Vanderhoof IT, Vanderhoof-Forschner KMB: *Lyme Disease: The Cost to Society*: Contingencies Jan/Feb 1993 p 422-48
13. Pachner AR: *Neurological Manifestations of Lyme Disease, The New "Great Imitator"*: Infectious Disease; 11 Suppl 6 : S1482-1486; 1989
14. Pies R: *Clinical Puzzles in Medical Psychiatry, the New "Great Imitator"*: Psychiatric Times p34, July 1994
15. Steinberg SH, Strickland GT, Pena C, Israel E: *Lyme Disease Surveillance in Md.*, 1992 Ann Epidemiol 1996 Jan; 6 (1) :24-29
16. Coyle BS, Strickland GT, Liang YY, Pena C, McCarter R, Israel E: *The Public Health Impact of Lyme disease in Md.*; J Infect Dis 1996 May; 173 (5) :1260-1262
17. Sigal LH: *Lyme Disease Overdiagnosis: Causes and Cure*: Hosp Prac, May 15, 1996, p. 12-27

18. Bransfield RC: *The Diagnosis of Lyme Disease*-Letter to the editor, Aug 1996
19. Bransfield RC: *A Physician Opinion Survey of the Lyme Disease Controversy*, in Review
20. Burrascano J Jr.: *Lyme Disease: Conn's Current Therapy* 1997
21. Steere AC, Dwyer E, Winchester R: *Association of Chronic Lyme Arthritis with HLA-DR4 and HLA-DR2 alleles*, N England Journal of Medicine 1990-323 : 219-223
22. Pappone PW: *There Is No Standard Approach to Lyme Disease: Your Management Must Be Individualized*: Modern Medicine, vol. 60, Sept 1992
23. Steere AC: *Lyme Arthritis: the joint lesions in Lyme borreliosis in the USA*: Ter Arkh 1995; 67 (11) : 43-45
24. Coyle PK, Schutzer SE, Belman UL, Krupp LB, Deng Z: *Cerebrospinal fluid immunological parameters in neurological Lyme disease: Molecular and Immunological Approaches*: Edited by Schutzer SE, Cold Spring Harbor, N.Y., Cold Spring Harbor Laboratory Press 1992
25. Wanick C, Prohovnik I, Kaufman M, Dwork A: *Rapidly Progressive Frontal-Type Dementia Associated with Lyme Disease*: The Journal of Neuropsychiatry and Clinical Neurosciences 1995; 7 : 345-347
26. Oksi J, Kalimo H, Marttila RJ, Marjaniemi M, Sonninen P, Nikoskelainen J, Viljanen MK: *Inflammatory brain changes in Lyme Borreliosis. A report on three patients and review of literature*; Dept of Internal Medicine, Turku University Central Hospital, Finland; Brain, 1996 Dec; 119 (Pt 6) : 2143-2154
27. Pachner AR, Delaney R, O'Neill T: *Neuroborreliosis in the non-human primate: Borrelia burgdorferi persists in the central nervous system*: Dept. of Neurology, Georgetown University School of Medicine; Ann Neurol 1995, Oct; 38 (4) : 667-669
28. Pachner AR, Delaney E, O'Neill T, Major E: *Inoculation of non-human primates with the N40 strain of Borrelia burgdorferi leads to a model of Lyme neuroborreliosis faithful to the human disease*: Dept of Neurology, Georgetown University Medical Center, Washington, DC; Neurology 1995 Jan; 45 (1) : 165-172
29. Bethancourt R: Wake Up Washington Rally, US Capitol, May 14, 1996
30. *Geriatric Psychiatry: Forgetfulness, Depression, Alzheimer's: Distinguishing Causes of Memory Loss*: Clin Psy News December 1995
31. Roberts ED, Bohm RP Jr., Cogswell FB, Lanners HN, Lowrie RC Jr., Povinelli L, Piesman J, Philipp MT: *Chronic Lyme disease in the rhesus monkey*: Dept of Pathology, Tulane Regional Primate Research Center, Tulane University Medical Center, Covington, Louisiana; Lab Invest 1995 Feb; 72 (2) : 146-160
32. Deltombe T, Hanson P, Boutsen Y, Laloux P, Clerin M: *Lyme borreliosis neuropathy. A case report*: Dept of Physical Medicine and Rehabilitation,

- University Hospital of Mont-Godinne UCL, Yvoir, Belgium; *AM J Phys Med Rehab* 1996 July-August; 75 (4) : 314-316
33. Elmore JG, Horwitz RI, Quagliarello VJ: *Acute meningitis with a negative Gram's stain: clinical and management outcomes in 171 episodes*: Dept of Medicine, Yale University School of Medicine, New Haven, Connecticut; *Am J Med* 1996 Jan; 100 (1) : 78-84
 34. Benke T, Gasse T, Hittmair-Delazer M, Schmutzhard E: *Lyme encephalopathy: Long-term neuropsychiatric deficits years after acute neuroborreliosis*: Neurology Dept., University of Innsbruck, Austria; *Acta Neurol Scand* 1995 May; 91 (5) : 353-357
 35. Ebermeyer E, Fayolle-Minon I, Mignot N, Pallot-Prades B, Alexandre C, Calmels P: *Meningoradiculitis related to Lyme disease. Course and prognosis (letter)*: *Presse Med* 1996 Feb 24; 25 (7) : 304
 36. Wang WZ, Fredrikson S, Sun JB, Link H: *Lyme neuroborreliosis: evidence for persistent up-regulation of Borrelia burgdorferi-reactive cells secreting interferon-gamma*: Division of Neurology, Karolinska Institute, Huddinge Hospital, Stockholm, Sweden; *Scan J Immunol* 1995 Dec; 42 (6) : 694-700
 37. Ragnaud JM, Morlat P, Buisson M, Perron X, Orgogozo JM, Julien J, Beylot J, Aubertin J: *Neurologic Manifestations of Lyme disease. Apropos of 25 cases*: *Rev Med Interne* 1995; 16 (7) : 487-494
 38. Corral I, Sanchis G, Garcia-Ribas G, Quereda C, Escudero R, de Blas G: *Demyelinating polyradiculitis in neuro borreliosis*: *Neurologia* 1995 Feb; 10 (2) : 110-113
 39. Coyle PK, Schutzer SE, Deng Z, Krupp LB, Belman AL, Benach JL, Luft BJ: *Detection of Borrelia burgdorferi-specific antigen in antibody-negative cerebrospinal fluid in neurologic Lyme disease*; Dept of Neurology, SUNY at Stony Brook; *Neurology* 1995 Nov; 45 (11) : 2010-2015
 40. Garcia-Monco JC: *Pathomechanisms of neuroborreliosis*: *Wien Med Wochenschr* 1995; 145 (7-8) : 174-177
 41. Garcia-Monco JC, Benach JL: *Lyme neuroborreliosis*: *Ann Neurol* 1995 Jun; 37 (6) : 691-702
 42. Issakainen J, Gnehm HE, Lucchini GM, Zbinden R: *Value of clinical symptoms, intrathecal specific antibody production and PCR in CSF in the diagnosis of childhood Lyme neuroborreliosis*: Children's Hospital, Kantonsspital Aarau; *Klin Padiatr* 1996 May-Jun; 208 (3) : 106-109
 43. Dekonenko EP, Umanskii KG, Virich IE, Kupriianova LV, Rudometov, IuP, Bagrov FI: *The basic syndromes of neurological disorders in Lyme borreliosis*: *Ter Arkh* 1995; 67 (11) : 52-53
 44. Millner M: *Neurologic manifestations of Lyme borreliosis in children*: *Wien Med Wochenschr* 1995; 145 (7-8) : 178-182
 45. Pachner AR: *Early disseminated Lyme disease: Lyme meningitis*: Dept of Neurology, Georgetown University School of Medicine, Washington, DC; *AM J Med* 1995 Apr 24; 98 (4A) : 30S; discussion 37S-43S

46. Scelsa SN, Lipton RB, Sander H, Herskovitz S: *Headache characteristics in hospitalized patients with Lyme disease*: Dept of Neurology, Montefiore Medical Center, Bronx, NY 10467; *Headache* 1995 Mar; 35 (3) : 125-130
47. Steere AC: *Musculoskeletal manifestations of Lyme disease*: Div of Rheumatology/Immunology, N. England Medical Center, Tuft's University School of Medicine, Boston, Ma. 02111; *Am J Med* 1995 Apr 24; 98 (4A) : 44S-48S; discussion 48S-51S
48. Berman DS, Wenglin BD: *Complaints attributed to chronic Lyme disease: depression or fibromyalgia? (letter)*: *Am J Med* 1995 Oct; 99 (4) : 440
49. Nagi KS, Joshi R, Thakur RK: *Cardiac manifestations of Lyme disease: a review*: *Can J Cardiol* 1996 May; 12 (5) : 503-506
50. Sigal LH: *Early disseminated Lyme disease: cardiac manifestations*: Div of Rheumatology, University of Medicine and Dentistry of NJ, Robert Wood Johnson Medical School, New Brunswick, NJ; *Am J Med* 1995 Apr 24; 98 (4A) :25S-28S; discussion 28S-29S
51. Nagi KS, Thakur RK: *Lyme carditis: indications for cardiac pacing*: *Can J Cardiol* 1995 Apr; 11 (4) : 335-338
52. Vasiljevic Z, Dmitrovic R, Naumovic Z, Ostojic M, Radosavljevic M, Karadzic A, Prostran M, Colic M: *Common for of Lyme borreliosis carditis- complete heart block with syncope: report on 3 cases*: *Cardiology* 1996 Jan/Feb; 87 (1) : 76-78
53. Sonnesyn SW, Diehl SC, Johnson RC, Kubo SH, Goodman JL: *A prospective study of the seroprevalence of Borrelia burgdorferi infection in patients with severe heart failure*: *Am J Cardiol* 1995 Jul 1; 76 (1) : 97-100
54. Horowitz HW, Belkin RN: *Acute myopericarditis resulting from Lyme disease*: *Am Heart J* 1995 Jul; 130 (1) : 176-178
55. Bartunek P, Zapletalova J, Nemec J, Gorican K, Veselka J, Mrazek V: *Lyme carditis*: *Vnitr Lek* 1995 Sep; 41 (9) : 644-646
56. Watzinger N, Fruhwald FM, Schafhalter I, Hermann J, Luha O, Zweiker R, Gasser R, Eber B, Klein W: *Coronary aneurysm in a 69 year old patient. Transthoracic echocardiography*: *Ultraschall Med* 1995 Aug; 16 (4) : 200-202
57. Anish S: *Case report: Possible Lyme endocarditis*: *New Jersey Medicine* vol. 90, no. 8, August 1993
58. Chrousos GP, Gold PW: *The Concept of Stress and Stress System Disorders: Overview of Physical and Behavioral Homeostasis*: *JAMA* vol. 267, no. 9, March 4, 1992
59. Pietrucha DM, Sensakovic JW: *Treating Lyme disease: different approaches*: *NJ Med* 1996 Jul; 93 (7) : 51-54
60. Burrascano JJ Jr.: *Managing Lyme disease: Diagnostic hints and treatment guidelines for Lyme borreliosis*, *Conn's Current Therapy* 1997

61. Isogai E, Kimura K, Fujii N, Nishikawa T, Ishii N, Postic D, Baranton G, Isogai H: *Platelet-activating-factor-mediated pathogenesis in Lyme disease*: Infect Immun 1996 Mar; 64 (3) : 1026-1029
62. Moldofsky H: *Fibromyalgia, sleep disorder and chronic fatigue syndrome*: Ciba Found Symp. 1993; 173 : 262-271