Distinct pattern of cognitive impairment noted in study of Lyme patients

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The Lyme Times, Vol. 20, January-March 1998, pp. 29 -32

I. Cognitive Characteristics of Chronic Lyme Encephalopathy

On the basis of both a formal neuropsychological study of 49 patients (APA 5/96) and on clinical observation and comprehensive neuropsychological examination of well over 100 patients, a distinct pattern of cognitive impairment occurring chronic Lyme disease can be described. These patients consistently demonstrate deficits in directed, sustained and divided attention, planning and organization of responses, temporal ordering, verbal fluency, abstract reasoning, speed of processing, and motor programming. The overall pattern of intellectual impairment is not unlike that seen with diffuse brain injury, and it most often results in some degree of work-related disability.

Although performance is impaired on measures of cognitive functions associated with specific brain regions -- receptive and expressive language, visuospatial problem solving and memory -- the quality of performance is not suggestive of focal lesions in these areas. Rather, deficits are secondary to impairment of higher level integrative functions, likely mediated by complex neuronal systems. Specifically, the receptive language deficit is secondary to impaired auditory tracking and slowing of mental processing. The expressive language deficit is secondary to impaired word retrieval and response planning, The visuospatial problem solving deficit is secondary to impairment of mental flexibility, conceptualization and the ability to compare and contrast necessary in decision making. Finally, deficits on test of memory function are most often secondary to impairment of the encoding or initial processing of information, which depends on attention, and the retrieval of stored information. The storage of new information, or memory per se, is rarely impaired.

This pattern suggests that cognitive dysfunction in chronic Lyme, while expressed variably across individual patients, results from a common factor -- the breakdown of diffusely represented processes involving both integration and activation, and impacting primarily on attention and reasoning. The fluctuation of impairment over short periods of time suggest that a physiologic rather than a structural mechanism is responsible.

II. Neuropsychological deficits in chronic Lyme disease (A study presented at the annual meeting of The American Psychiatric Association , May 1996)

The neuro-psychological characteristics of 49 patients with Lyme disease were examined. The study set out to answer three questions:

1) Do all patients with subjectively perceived cognitive dysfunction have measurable intellectual impairment on objective testing?

2) In those without measurable impairment, does depression account for the perception of cognitive dysfunction?

3) What is the nature of the cognitive impairment in Lyme disease when it does occur?

Subjects were patients seen consecutively between 1990 and 1994 in a private neuropsycological practice with complaints of cognitive dysfunction and a symptom complex consistent with Lyme disease. Diagnosis was based on former CDC criteria. Mean duration of illness, defined as the time from the onset of general symptoms to the neuro-psychological exam, was 4.7 years (range: 3.3 to 14 years). Mean age was 39.9 years (range: 21 to 58 years) from 18 to 60 years. Mean level of education was 15.3 years (range 12 to 20 years).

Subjects were interviewed and administered a comprehensive battery of tests, including the complete WAIS-R and WMS-R, and additional test of language, attention, reasoning, visuospatial processing and complex motor function. They also completed the Beck Depression Inventory and a symptom checklist. Tests were divided into seven groups based on the cognitive functions they are presumed to measure: Attention, Memory, Language, Visuospatial Processing, Reasoning, Verbal Fluency and Motor programming.

Subjects were grouped into three levels of impairment based on their neuropsychological performance: Intact (N=11; 22%), with no functions impaired, Moderate (N=31; 63%) with two functions impaired, and Severe (N=7; 14%) with three or more functions impaired. Subjects in the Severe group met diagnostic criteria for dementia. The correlation between depression and cognitive impairment was nonsignificant, but the trend was positive, rather that negative. Anxiety by self report was significantly greater in the impaired groups that the Intact group. Duration of illness was greater in the Severe group (nonsignificant).

Of the 38 subjects with cognitive impairment, deficits of attention were most common, occurring in 26 subjects (68%) Deficits of memory storage were least common, occurring in 8 subjects (21%), Motor, Verbal Fluency, Visuospatial, Language and Reasoning deficits occurred in 24, 26, 29, 36 and 36% of the subjects respectively.

III. Possible Pathophysiologic Mechanisms of Cognitive Impairment in Lyme Disease

Based on these findings and on patients' reports, two characteristics of Lyme Encephalopathy arise which provide insight as to possible neurophysiologic mechanisms:

One, the nonfocal nature of the cognitive functions affected, and

Two, the subtle fluctuations and reportedly abrupt and global shifts in cognitive function from one day to another in a given patient.

Four broad categories of possible neurophysiologic mechanisms might be compatible with this pattern:

1) Diffuse cerebral diffusion abnormalities -- Single photon emission computerized tomography (SPECT) scans of the brain in Lyme disease often display a diffuse pattern consistent with heterogeneous areas of hyperfusion and/or diminished neuronal metabolism. While vasodilators are often capable of reversing these abnormal patterns

on SPECT scan, this reversal does not consistently correlate with a symptomatic improvement in cognitive function.

2) Alterations in cellular metabolism at the cortical level -- Evidence of alterations in neurotransmitter function is suggested by clinical evidence of cognitive improvement following treatment with selective serotonin reuptake inhibitors (SSRI's) which appears to be independent of their antidepressant effect. Systematic studies of the impact of SSRI's on cognitive function, as well as the role of other transmitters, are required.

3) Neuro transmitter abnormalities (imbalances of synthesis and/or receptor activity) -- Neurotoxic substances may well play a role in Lyme Encephalopathy, given the neurotropic nature to *Treponema pallidim*, and the close parallel between syphilis and Lyme disease, it is possible that *Borrelia burgdorferi* could produce intracellular or extracellular neurotoxins which we have yet to identify.

4) Neurotoxic substances produced endogenously or possibly exogenously -- Endogenous neurotoxins have been identified as by-products of the humoral immune response. Among these is quinolinic acid, a product of the interleukin cascade system, which accumulates as a result of the humoral response to acute infectious agents and functions as a neuronal excitotoxin. As there are many similarities between Lyme Encephalopathy and the nonspecific mental dysfunction of acute systemic infections, such as influenza, it is quite possible that continued stimulation of production of quinolinic acid and other cytokines plays a role in the pathophysiology of Lyme encephalopathy.

IV. Clinical Impressions and Implications for Diagnosis and Treatment in Chronic Lyme Disease

This study demonstrates that for the majority of chronic Lyme patients with cognitive complaints, there is in fact a measurable and significant decline in intellectual acuity. The nature and severity of the cognitive impairment is such that it interferes with all aspects of normal functioning: employment, home, marriage, social interactions, and general emotional well-being. Rather than the cognitive complaints being secondary to anxiety or depression, as is sometimes suspected, depression and anxiety increase with, and are apparently secondary to, cognitive impairment and the emotional and practical impact of a loss of competence. Thus, while patients with chronic Lyme disease can present a confusing and "psychiatric" picture to the clinician, it is important that their concerns be properly investigated and addressed.

Patients with Lyme encephalopathy complain of problems with memory and concentration, word retrieval, confusion, problems with thinking, "mental fogginess", a decline in job performance, difficulty with calculations, directions, and judgment. Decreased initiative, manifest as difficulty getting started with or following through with projects is often noted. Mood disturbance is common with complaints of irritability, explosiveness or "a short fuse," sadness, hopelessness or guilt, increased anxiety or mood swings. Sleep disturbance is also common, and can present as initial, middle or terminal insomnia or some combination of these. Fatigue is universal. Headache is common, and of course joint and muscle pain. Increased sensitivity to light and noise, visual disturbance, and tingling in the extremities are also common.

On interview, patients with Lyme encephalopathy tend to be vague and disorganized in the presentation of the history of their illness. This is despite their close attention to their symptoms and having recounted them many times before. Although in most cases memory of discreet events - tests, dates, diagnoses, responses to medications - is intact, the patient is unable to recall them spontaneously or organize them in temporal order. They may be unclear as to their chief complaint. They may completely lose track of what they were saying, sometimes repeatedly, or of what the question was. They may get off on a tangent and have trouble re-orienting themselves. Frequent prompting and refocusing will be necessary; beginning the interview with an open-ended question like "Tell me what the problem is" will allow these qualities to become clear.

Often patients with chronic Lyme disease will seem overly focused on their illness, or overly concerned with convincing the clinician that they are ill. The clinician may be tempted to interpret this as evidence of a primary psychiatric disorder. It is important to understand that the frustration many of these patients experience is real, and results from the general attitude of doubt toward Lyme disease as a serious and chronic illness, the invisibility of their symptoms, the difficulty in getting a definitive diagnosis and getting approval for extended treatment from insurance carriers. Many have been accused of hypochondriasis or malingering. As with head injury, the patient may "look fine" though they are having difficulty with very basic work, social and day to day functioning.

The cognitive deficits in chronic Lyme disease involve primarily attention and arousal mechanisms. Patients have difficulty keeping track of external and internal events, retrieval of information from memory and with planning and sequencing, as occurs in attention deficit disorder. However their experience is different from that of ADD, in that rather than having the experience that there are many thoughts competing for attention, the Lyme patient has difficulty bringing any thought into clear focus. They experience difficulty thinking. One patient described it as the universe ending six inches from his face. He can't process information that is not immediately apparent, immediately experienced. Another said that when he tries to think about something, or figure something out, all he can do is repeat the question -- he can't get to the meaning. This is like the idea of "surface" versus "deep" processing in cognitive psychology. Reading a passage for typing errors would be surface processing, while reading for meaning is deep processing. One patient, a physician, described it as a "mental intention tremor" -- the more she tries to focus on something the more out of focus it becomes.

The clinician should proceed with empathy and reason. Specific cognitive complaints in previously high functioning individuals are unusual and indicative of serious illness, either psychiatric or neurologic. Comprehensive neuropsychological evaluation will most often differentiate the two.

Where the neuropsychological exam is normal or there is a significant psychiatric component, a psychiatric evaluation is advised. Psychiatric symptomatology is not uncommon in Lyme and the presence of depression, anxiety, obsessive compulsive symptoms, flat affect and so on may cloud the issue of significant cognitive decline. Both the cognitive and psychiatric symptoms would be expected to improve with antibiotic treatment in Lyme encephalopathy. However sometimes concurrent treatment with psychotropic medication is necessary.

Unfortunately for some patients, significant cognitive impairment persists even after years of antibiotic treatment. These patients may never be able to return to their

premorbid level of employment, or be gainfully employed at all. Cognitive remediation can help them learn strategies for improving memory and concentration and relieving stress. Support and advice in regard to living with a chronic condition is equally important. Strategies include reducing work hours when possible, taking regular rest periods during the day, limiting the number of outings in a week, and using a calendar to stay organized and structure their time.

V. Cognitive impairment in Lyme disease: specific functions and the impact of deficits

1. Attention and mental tracking. Includes directed and sustained attention: the ability to direct and maintain one's focus on a particular event or idea, whether in the environment or internally; and divided attention: the ability to simultaneously attend to two events, or do two or more things at a time, or to retain awareness of one thing while doing another.

> Impact: difficulty functioning effectively in many situations, remembering what one was doing before a distraction, keeping track of conversation, taking notes while someone is speaking, remembering that someone is on hold, or what you were about to say.

2. Memory: Retaining new information.

> Impact: secondary to impaired attention, slowing of processing and the retrieval of stored information, but not storage per se; a tendency to lose or forget things; miss appointments; repeat oneself.

3. Receptive language: understanding spoken or written language

> Impact: secondary to impaired attention and speed of processing; difficulty participating in meetings or social conversation; difficulty with reading comprehension.

4. Expressive language: Using spoken or written language to express ideas

> Impact: difficulty finding the right word; using the wrong word and not noticing; not being able to express oneself or communicate.

5. Visuospatial Processing: Efficient scanning of the visual field, making sense of how things are related in space; visuospatial conceptualization and problem solving.

> Impact: a tendency to get lost; difficulty with reading comprehension.

6. Abstract reasoning: The ability to generalize from the particular; to identify the common factor between related concepts; to compare and contrast two things or ideas; to see the "big picture"; to identify the critical factor in a situation; to anticipate consequences and make inferences regarding cause and effect.

> Impact: difficulty with decision making, planning, and problem solving.

7. Speed of mental and motor processing: The ability to think and respond quickly; critical to understanding speech which occurs at a fairly constant rate.

> Impact: difficulty understanding or keeping up a conversation; functioning in a timely manner in day to day situations; meeting deadlines.

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