Sporadic postinfectious neuromyasthenia

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Outbreaks of epidemic neuromyasthenia have occurred throughout the world for many years, but sporadic cases have only recently been recognized. Fifty consecutive previously well patients with prolonged and excessive fatigue after an apparent acute infection were investigated. Most were well educated, active, unmarried women aged 30 to 40 years. The precipitating infection had many clinical presentations. The chronic phase of the illness was characterized by a fairly common set of symptoms. Physical examination and laboratory testing generally gave normal results. Of the 50 patients 16 were found to be infected with Epstein-Barr virus, 7 with other viruses, 4 with parasites and 2 with *Mycoplasma pneumoniae*. The causative agent was not known in 22 cases. The mean duration of the illness was 27.6 months, and the mean proportion of time lost from work or school was 39%. Drug therapy was not beneficial; supportive therapy was useful. Further investigation is required to determine optimal management of sporadic neuromyasthenia.

La neuromyasthénie, décrite depuis longtemps dans le monde entier sous sa forme épidémique, a été reconnue récemment comme une maladie sporadique. On étudie ici 50 malades consécutifs auparavant en bonne santé chez qui une infection aiguë apparente, dont les manifestations sont variables, a été suivie d'une fatigue excessive et prolongée. Il s'agit surtout de femmes instruites, actives et célibataires, dans la trentaine. La phase chronique de la maladie se caractérise par un ensemble de symptômes assez communs. Les résultats de l'examen médical et des épreuves de laboratoire sont le plus souvent normaux. On met en cause le virus d'Epstein-Barr 16 fois, d'autres virus 7 fois, une parasitose 4 fois et le *Mycoplasma pneumoniae* 2 fois. Dans 22 cas on ne retrouve pas d'agent infectieux. La maladie dure en moyenne 27,6 mois, durant lesquels le taux d'absence du travail ou des études se chiffre en moyenne à 39%. Futilité de la pharmacothérapie, intérêt d'un traitement de soutien. Il y a lieu d'étudier plus avant la neuromyasthénie sporadique afin de connaître la meilleure conduite à tenir.

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Clinical and Community Studies

Neuromyasthenia signifies a collection of symptoms including fatigue, depression, myalgia, muscular weakness, headaches and paresthesia; few abnormal physical findings or laboratory results have been reported.[1] The disorder was originally described as occurring in outbreaks (epidemic neuromyasthenia), and approximately 30 epidemics were reported between 1934 and 1977.[2] Epidemic neuromyasthenia is widely distributed and has acquired a number of synonyms, such as Iceland disease,[3] Akureyri disease,[4] benign myalgic encephalomyelitis[5] and Royal Free disease.[6] Epidemics have occurred in closed populations such as hospitals, with high attack rates in nursing personnel. Most cases occur in young and middle-aged women; preadolescents are rarely affected. Although the illness may persist for years, with frequent relapses, gradual improvement is the rule.

Sporadic cases of neuromyasthenia are commonly seen by general practitioners and infectious disease physicians, but the subject is not dealt with in current medical or infectious disease texts.[7,8] Recent investigations have confirmed that a persistent and relapsing illness is associated with active Epstein-Barr virus (EBV) infection,[9,10] and immunologic abnormalities have been found to be associated with chronic disease after infectious mononucleosis.[11]

To better understand sporadic postinfectious neuromyasthenia, I studied the clinical and laboratory findings in patients with prolonged and excessive fatigue after an acute infection.

Methods

The criterion for inclusion in the study was the new occurrence of complaints of weakness or exhaustion persisting more than 30 days after an apparent acute infection. Patients were excluded if similar symptoms were present before the infection, if there was no acute infection or if there was serious underlying disease.

Most patients were referred to me because of my known interest in postinfectious neuromyas-

thenia. Of 62 patients considered for inclusion 12 were excluded because of serious psychiatric disease, a long history of psychosomatic complaints or prolonged asthenia without a clearly triggering acute infection. In 28 of the remaining 50 patients the cause of the acute infection was known (definite cases), and in 22 it was not (probable cases). Of the 50, 6 had initially been seen at the Tropical Diseases Unit of Toronto General Hospital, and 44 had been referred by community physicians; 25 of the latter patients had requested referral to the hospital because of a newspaper article on the illness.

I took the patients' histories and performed a physical examination an average of 8 months after the onset of symptoms. Laboratory tests were done to determine the following: complete blood count, erythrocyte sedimentation rate, serum levels of creatinine, urea, fasting glucose, electrolytes, albumin, creatine kinase, immunoglobulins, and C3 and C4, and titres of antinuclear antibody (ANA) and rheumatoid factor. Testing of liver and thyroid function (serum thyroxine [T_4] level and triiodothyronine [T_3] resin uptake) was also done. Complement fixation testing was done for *Coxiella burnetti*, cytomegalovirus (CMV), *Mycoplasma pneumoniae*, influenza A and B viruses, parainfluenza virus and adenovirus. Titres of antibody to *Toxoplasma gondii* and EBV viral capsid antigen (VCA) and early antigen (EA) were determined by means of immunofluorescence. Titres of antibody to coxsackievirus B2–B5 and A9 and echovirus 11 were determined with neutralization tests. Titres of hepatitis B surface antigen and antibody as well as of antibody to hepatitis A were measured in 12 of the patients.

Results

Demographic features

The demographic features of the patients are shown in Table I. Most were unmarried women, and at least four had been divorced. Of the 50, 80% were between the ages of 24 and 40; there were five adolescents and no preadolescents. The patients were generally well educated, independent and creative; they included six nurses, two university professors, two research psychologists, a lawyer, a social worker, an engineer, a research technologist and a teacher. The patients had been extremely persistent in their attempts to find a cause for their weakness and had generally become familiar with the literature on epidemic neuromyasthenia as well as with other current medical literature.

Only 2 of the patients smoked, and most had no history of abuse of alcohol (48) or illicit drugs (49). Before becoming ill they had been active in aerobics classes, jogging or swimming but not team sports; in addition, 37 had spent at least four evenings per week outside the home, working at additional jobs, participating in community organizations or committees, or socializing.

Clinical course

The infectious agents identified are listed in Table II. The precipitating infection had many clinical presentations, although the most common was an upper respiratory tract infection with sore throat and cervical lymphadenopathy. The illness was often characterized as being "flu-like" and was associated with muscle aching and excessive tiredness. One half of the infections occurred between July and September, and six occurred in association with foreign travel.

In all the cases of infectious mononucleosis a

Table I—Demographic features of 50 patients with sporadic neuromyasthenia

Feature	No. of patients or mean (and range)
Sex	
Female	35
Male	15
Age, yr	33.5 (14–68)
Median	32
Marital status	
Unmarried	32
Married	18
Employment	
Professional	15
Management	13
Sales	5
Clerical	5
Housewife	3
Student	7
Unemployed	2
Level of exercise before illness, h/wk	
≥ 6	16
3–5	22
1–2	5
0	7
Education*	
University	40
High school	5

*Five patients were still in grade school.

Table II—Infectious agents identified

Agent	No. of patients*
Epstein–Barr virus (EBV)	16
Coxsackievirus B	4
Giardia lamblia	2
Mycoplasma pneumoniae	2
Toxoplasma gondii	2
Hepatitis A virus	1
Herpes zoster virus	1
Cytomegalovirus	1
Unknown	22

*One patient had evidence of infection with both EBV and coxsackievirus.

Monospot test gave a negative result at the time of referral, and only two patients were known to have had a positive result at the onset of the illness. The diagnosis of EBV infection was ultimately made in 16 patients by detecting antibodies to EA (in a titre of 1:20 or higher) in association with antibodies to VCA (in a titre of 1:320 or higher). Other infectious agents were identified by means of microscopy (*Giardia*), a fourfold rise in antibody titres (*M. pneumoniae*, coxsackievirus [in two cases] and CMV), a consistently high titre (1:1024 or more) of antibody during convalescence (coxsackievirus [in two cases]) or the presence of specific IgM antibody (hepatitis A virus and *T. gondii*). Herpes zoster was diagnosed by means of the typical clinical presentation.

The chronic phase of the illness was characterized by a fairly common set of symptoms (Table III). The chief complaint was incapacitating exhaustion. Another common complaint was a marked increase in the exhaustion and weakness for 1 to 3 days after exertion, such as exercise or socializing. Exertion or tiredness was also noted to result in cervical lymphadenopathy and headaches. Many of the patients also complained of enhanced susceptibility to upper respiratory tract infections. About one third had "blue spells" and episodes of crying, which they attributed to their inability to perform tasks as they had previously. Decreased libido was common (20 patients). One quarter of the patients had symptoms of lower urinary tract irritability. A history of migraine headaches was noted in 12 of the patients or their families. Gastrointestinal, respiratory and cardiovascular symptoms were rare.

Four of the patients knew someone who had a similar illness, and five others were referred by patients in the study. In three cases there was a family history of neuromyasthenia. Three of the subjects were a father and two of his three sons; one of the sons had profound fatigue and was unable to concentrate or attend school.

The illness had a major impact on the patients and their families. In 45 cases the symptoms had persisted for more than a year (Table IV), and nine patients had had to take leaves of absence from their jobs or school. Sixteen patients had shown some improvement. Improvement was usually slow and could best be determined by comparing the current level of activity with that 6 or even 12 months earlier.

Table III—Common symptoms of neuromyasthenia

Symptom	No. of patients
Exhaustion	47
Malaise	40
Postexertional exacerbation of fatigue	38
Weakness	37
Headache	30
Fever	30
Subjective	26
Objective	4
Inability to concentrate	28
Frequent upper respiratory tract infections	27
Myalgia	25
Dizziness, lightheadedness	23
Allergies	21
Lymphadenopathy	21
Sleepiness	16

Table IV—Features of neuromyasthenia

Feature	No. of patients or mean (and range)
Duration, mo	27.6 (5–120)
Pattern	
Relapsing	42
Continuous	8
Recovery	
Nearly complete	4
Partial	12
None	34
Time lost from work or school, %	39

Clinical examination

The physical examination generally gave remarkably normal results. Findings included cervical lymphadenopathy in eight patients, inflamed throat in four and transient erythema of the face and the cape area (blushing), which was a new and troublesome problem, in four. There was no tenderness or detectable muscle weakness.

Several of the patients came to my office accompanied by a parent or spouse, who had made the appointment and who reported on changes in the patient's symptoms. Many also came to the office with prepared notes about their condition.

Laboratory results

The laboratory results were also generally normal. In six patients testing for ANA gave positive results, but the titre was high in only one. Testing for rheumatoid factor gave positive results in two patients. Four patients had slightly depressed levels of C3 or C4, and two had low levels of IgA. The hematologic results were normal except for lymphocytosis in three patients, atypical lymphocytes in two and an erythrocyte sedimentation rate greater than 20 mm/h in five.

Therapy

Symptomatic drug therapy was given in 28 cases, but there was no prospective therapeutic trial. The drugs included anti-inflammatory agents (beneficial in 3 of 9 patients), antibiotics (beneficial in 4 of 8), anxiolytics (beneficial in 3 of 10) and antidepressants (beneficial in 3 of 15). Most (10 of

15) had a poor response to antidepressants: they became more fatigued and had "cloudier thinking" while taking these agents. The patients had seen numerous physicians (a mean of 5.2) in the previous year, often without complete satisfaction, so alternative forms of therapy, such as macrobiotic diets, megadoses of vitamins, allergen injections and sublingual drops, had been tried. Several patients had been told that they had a global allergy to their environment.

Detailed and lengthy discussions were held with the patients concerning the probable initiating events, pathogenesis, prognosis and means of coping with the illness. Reassuring them that no serious underlying disease could be detected appeared to be beneficial: they became less anxious and, knowing the natural history of the illness, were able to more effectively plan their future. They were comforted to know that others had a similar affliction.

Discussion

Infectious mononucleosis is the infection most commonly associated with protracted fatigue and disability.[12,13] Prolonged exhaustion occurs predominantly in women over age 30.[13] These findings have recently been emphasized and have been more clearly associated with EBV.[9,10]

In this study, patients with infectious mononucleosis were not specifically selected; I investigated only patients with no pre-existing illness in whom severe exhaustion developed after an apparent acute infection. The findings in my patients were so similar to those in previously reported epidemics that I considered it appropriate to term their illness sporadic postinfectious neuromyasthenia. The demographic features of my patients were also strikingly similar to those of patients apparently infected with EBV:[9,10] most were well educated, active, unmarried women aged 30 to 40 years.

Pathogens other than EBV were associated with neuromyasthenia almost as frequently (13 cases) as was EBV (16 cases). None of the associations, however, are proof of a causal relation. I was unable to determine the cause of the acute infection in 22 of the patients, probably because appropriate serologic testing was done many months after the original infection.

The impact of neuromyasthenia was devastating. There was no apparent secondary gain to be had from dropping out of activities, and most of the patients wished to return to work. As in previous studies,[1,9,10] one third of those investigated admitted to depressive symptoms, and 67% had had at least one depressive episode during the previous year, as determined by means of the National Institutes of Mental Health Diagnostic Interview Schedule[14] (unpublished observations). The patients maintained that they were depressed only because they were unable to function as they had previously. However, 50% had had major depression before the onset of neuromyasthenia. Antidepressant therapy was of benefit in only 3 of 15 patients.

Epidemic neuromyasthenia may not truly be a disease but, rather, a collection of symptoms.[5,15] Because of its higher incidence in young women and institutions,[1,2,16] a parallel has been drawn with outbreaks of mass hysteria.[5] In some outbreaks there have been concurrent poliomyelitis epidemics in the community, which may have heightened anxiety.[3] It has been suggested that the entire phenomenon is an altered perception by medical personnel of what is actually a normal rate of illness for the community.[5] The fact that some patients were referred by patients already in the study and the wide variety of clinical presentations lend some support to these views. Another possibility is that these patients had psychoneuroses, of which the illness was one further manifestation.

However, there are data supporting the presence of chronic infection and subtle physiologic alterations. Antibodies to EBV EA have been found to persist for long periods in patients with neuromyasthenia, which suggests either an unrelated immunoregulatory problem or continuing infection with the virus.[9,10] In one group of patients with chronic illness after infectious mononucleosis a disorder of T-cell regulation was manifested by an increased number of suppressor T cells.[11] This abnormality disappeared after the patients had completely recovered. Sustained suppressor T-cell activity has also been seen in X-linked lymphoproliferative syndrome, which is associated with severe infectious mononucleosis.[17] In a patient with fatigue following a varicella infection ^{31}P magnetic resonance imaging revealed excessive intracellular acidosis of muscle fibres during exercise.[18] Other examples of disturbances in energy metabolism after viral illness can be linked to acquired enzyme deficiencies.[19,20] Elevated levels of 2,5-oligo-adenylate synthetase were found in most patients with neuromyasthenia following infectious mononucleosis.[10] These findings support the view that neuromyasthenia is an organic disorder.

Both views of the nature of neuromyasthenia may be correct. Perhaps a minor infection in a person with the characteristic personality and activity patterns may result in the collection of findings known as neuromyasthenia. Infectious agents such as EBV and retroviruses,[21] which are more likely to cause chronic infection, are possibly more likely to be associated with neuromyasthenia as well. Furthermore, similar infections in less active people may go unnoticed.

Irrespective of the mechanisms involved, patients with neuromyasthenia require continuing support. In some cases specific therapy, such as antiviral treatment, may prove to be of benefit. Occasionally, anti-inflammatory agents or antidepressants have been tried, with limited success. Providing the patients with adequate information concerning their illness and its prognosis as well

as continued emotional support has yielded the most promising results.

Conclusion

An illness resembling epidemic postinfectious neuromyasthenia does exist in a sporadic form in the community. It can be triggered by a variety of infectious agents. Specific therapy is unavailable, but symptomatic treatment can result in considerable improvement. Immunologic and psychologic investigations are required to better understand the pathogenesis of neuromyasthenia.

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