RHEUMATIC BRAIN DISEASE AS A CAUSE OF CONVULSIONS

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THE classical symptoms of acute rheumatic fever have been recognized for many years, but the other manifestations of this protean process were long interpreted as simply sequelae of the acute infection. It is now universally agreed that the endocardium harbors primary lesions,[22] but it is not so commonly realized that the brain may be similarly affected. Certainly the details of the etiology of rheumatic fever are not yet understood. It does appear, however, that the disease is basically an inflammatory condition of fibrous connective tissue. As such the brain cannot be excluded as a potential site. Indeed, rheumatic lesions have been found in lungs,[2,28] kidneys,[10,24] spleen, ovaries,[24] testes,[24] pancreas,[24] coronary arteries,[12,15] in peripheral arteries[24] and in the brain.

Many theories of the pathogenesis of brain complications have been proposed; most have assumed that the lesions were secondary to rheumatic heart disease. Some investigators have said that cardiac valvular lesions brought on circulatory changes in the brain causing stasis and ischemia. Evidence against this theory is the fact that the majority of patients with rheumatic brain disease, including those presented here have no history of congestive heart failure. It has also been conjectured that minute emboli may detach from rheumatic vegetations and lodge in vessels of the brain, but the cohesive properties of these vegetations speak against this mechanism. It is true, in patients with mitral stenosis and auricular fibrillation, mural thrombi may beget emboli, but pathologists deny that such emboli form foci for the endarteritic changes which characterize rheumatic brain disease. Of the cases to be presented in only one was there suspicion of an irregularity of cardiac rhythm.

From statistics, even after allowing for the distortions which commonly arise in this approach, several striking inferences can be drawn. Bruetsch[20] reported a 5 per cent incidence of rheumatic heart disease in 500 consecutive and unselected necropsies from a mental hospital, and a somewhat higher figure clinically in all admissions to that hospital over a recent two year period. This is compared to a general incidence in the United States of less than 1 per cent.[14] More dramatic than this, however, the same observer, reported that in his last 30 consecutive necropsies on patients with rheumatic heart disease, he found only one brain in which rheumatic lesions could not be found.

In chronic cases, the brain pathology has been described as basically an obliterating proliferative endarteritis[4] which is most common in small meningeal and cortical vessels and is accompanied subsequently by softening of the cortex. There is no typical distribution of the lesions; usually only short segments of small vessels are involved, the larger vessels of the basal ganglia are

not commonly affected. Neuberger's[19] necropsy studies of acute cases revealed the presence of small fibrocytic nodules in meningeal vessel walls together with patchy fibrosis and lymphocytic infiltration into the meninges. Others have drawn attention to the similarity between the endarteritis in the cortex and in rheumatic myocardium.

The histopathology is by no means specific and a differentiation from syphilitic endarteritis cannot be made with a microscope. A diagnosis can be reached only after finding other rheumatic lesions in the body and after excluding syphilis so far as is clinically possible. Even then, other possibilities for consideration must include thromboangiitis obliterans, lupus erythematosus and periarteritis nodosa, the latter being so similar microscopically that Fahr[10] has suggested that rheumatic vascular lesions may contribute to its pathogenesis. In acute rheumatic fever, the microscopic changes in the brain are much the same as those found in other severe infections or toxemias.[27] Aschoff nodules are not found in the brain, possibly, because there is relatively so little connective tissue as Boyd[1] suggests or because Aschoff nodules represent a specific response in the myocardium.

Rheumatic brain lesions have been incriminated as precursors of a large number of neurologic and psychiatric aberrations.[3,5,6,8,9,11,13,23,26] The degree to which clinical manifestations develop appears to depend on the size, number and locale of the foci. The nature of the symptoms is further determined by the age and personality of the patient at the time of involvement. In childhood, deviations range from mild behavior disorders to pronounced mental deficiency. Young adults tend to develop schizophrenic reactions,[6] while involutional melancholia and manic depressive psychoses are common in older age groups. The literature reveals that nearly any psychiatric syndrome may be produced; there is no particular psychopathologic content, and one is frequently unable to distinguish psychogenic from organic etiologies.

Although suggested in 1843,[18] it has only recently been recognized that chronic rheumatic infection may cause epilepsy. Walker[25] in 1936, did not include rheumatic brain disease among more than 70 causes of convulsions. Seizures resembling cryptogenic epilepsy in patients with rheumatic heart disease were reported profusely in the French literature of the 1930's. Foster[11] has shown that the incidence of seizures is two and one half to seven times higher in patients with rheumatic heart disease than in large control groups. It is probable that many cases are diagnosed as idiopathic epilepsy which are actually due to organic brain disease of rheumatic etiology. Bruetsch[5] has reported 3 such cases which presented rather extensive heart and brain disease at necropsy.

Though we lack pathologic confirmation of diagnoses coded as rheumatic brain disease in our files, we feel that the data yield several clinically significant points. These cases include 5 patients with histories of recurrent generalized convulsive seizures, several of whom had previously been diagnosed as idiopathic epilepsy. In none of these patients was there any suspicion that syphilis, trauma, expanding intracranial lesion, arteriosclerosis, alcohol, kidney failure or other epileptogenic factors were of significance in causing the dis-

order. There was a remote family history of epilepsy in only 1 case. Each patient had clinically demonstrable rheumatic heart disease; and all had electro-encephalograms which were abnormal, but which revealed no single unique characteristic feature.

The average age of these patients was 45.6 years and the onset of their seizures had occurred at an average age of 38.6 years. None had had convulsions before they were 34 years old. Studies with large groups of cases[11,16,17,21] indicate that the incidence of idiopathic epilepsy, with seizures first appearing after the age of 20, is low, and is practically negligible when the onset occurs past 30. Thus the diagnosis of idiopathic epilepsy in patients over 20 years old should be made only after all other factors have been exhaustively eliminated. We feel that we have, in these cases, ruled out all known organic factors exclusive of rheumatic brain disease to which we believe these seizures have been due.

Three of these 5 patients had a past history of a definite migratory polyarthritis or chorea; their convulsive seizures, however, did not begin until ten, twelve and thirty-two years later. This latent period has also been noted by other observers and it may be explained by the fact that the arteritis in the brain develops during an asymptomatic period while the patient is enjoying good general health (table).

TABLE

Case Number	Age of Patient	Age of Onset of Seizures	Age at Time of Arthritis Symptoms	Latent Period
1	52	42	30	12
2	45	34	....	....
3	41	40	30	10
4	36	35	....	....
5	54	42	10*	32
Average	45.6	38.6		

*Approximate

Demonstrating the Chronology of Events in the Development of Rheumatic Epilepsy

Case Reports

Case 1. A 52-year-old white woman first came to Cleveland Clinic on June 11, 1947. She stated that she had begun to experience recurrent convulsive seizures in 1937. An objective history revealed that during these attacks, which usually were without premonitory symptoms, chronic movements began in the head and then rapidly became generalized and frequently tonic. Excess salivation was noted and she occasionally bit her tongue. Convulsions were of three to four minutes' duration, and postconvulsive confusion lasted about twenty minutes; they were occasionally diurnal but much more commonly nocturnal. The frequency had been quite variable, and intervals between convulsions had varied from three weeks to six months since their onset.

There was no familial history of epilepsy or migraine, and the past history was not essentially contributory except that she had had a migratory polyarthritis twenty-two years

before, with an immediately subsequent diagnosis of "heart involvement." There had been no trauma prior to 1937 and no history of venereal disease.

Physical examination revealed an oral temperature of 99.2 F., a blood pressure of 116/64, and a pulse rate of 80. The heart was normal in size and the rhythm was regular. There was a grade 3 blowing diastolic murmur along the left border of the sternum and grade 1 apical systolic murmur. There were no thrills and no gallop rhythm. The Cardiology Department reported these findings as indicating the presence of rheumatic heart disease with aortic insufficiency. The rest of the physical examination, including a neurologic survey was negative.

In the laboratory, Wassermann and Kahn reactions were negative, a three hour postprandial blood sugar determination was 100 mg. per 100 cc., the hemoglobin estimation was 12.5 Gm. per 100 cc., and the leukocyte count was 7,700 per cu. mm. Skull and chest x-rays were essentially negative. An electro-encephalogram showed little normal alpha activity, generalized low voltage and indistinct waves, and some irregular slow waves from the right parietal region which were not found on the left. It was interpreted as "An abnormal electro-encephalogram which is more suggestive of an organic brain disease than idiopathic epilepsy."

Case 2. A 45-year-old white woman, was examined at the Cleveland Clinic on April 4, 1947 at which time her chief complaint was "convulsions," the first of which had occurred eleven years before. Loss of consciousness always occurred without premonition, and was followed by a generalized clonic convulsion lasting for approximately one minute and unconsciousness lasting for fifteen minutes. There was no characteristic time of day for the occurrence, and the frequency though variable was generally increasing and the tendency to appear during the week preceding menstruation was striking.

One paternal uncle had been epileptic, otherwise her past history was not significant.

On physical examination, temperature was 98.6 F., pulse 80, and blood pressure 130/74. Her heart was slightly enlarged to percussion, there was a grade 3 blowing systolic murmur at the apex and a grade 2 systolic murmur at the aortic area. The diagnosis in the Cardiology Department was rheumatic heart disease with mitral insufficiency and probably aortic stenosis. The physical examination was otherwise negative.

Cerebrospinal fluid and serologic examinations were negative in 1946. An x-ray of the skull was normal. The electro-encephalogram showed a generalized slow dysrhythmia with frequencies of 5 to 7 per second and voltages to 125 microvolts. The interpretation was "An abnormal encephalogram with no evidence of a focal cortical lesion."

Case 3. A 41-year-old white man, was first seen at Cleveland Clinic on February 5, 1948, at which time he reported that during the past year he had experienced two nocturnal convulsive seizures. He had been subjectively unaware of these attacks except that he experienced a generalized muscular soreness the next day.

No family history of epilepsy or migraine was elicitable, but the past history revealed that the patient had experienced a rather severe and extensive polyarthritis in 1937, since which time he has been told of the presence of a "heart murmur." The detailed history was not additionally significant.

Physical examination of the heart disclosed a grade 4 apical systolic murmur at the apex which was interpreted by the Cardiology Department as indicating rheumatic heart disease with mitral insufficiency.

Laboratory studies included negative Wassermann and Kahn tests, a fasting blood sugar level of 84 mg. per 100 cc., a sedimentation rate of 0.65 mm. (0.45 mm.-normal), a hemoglobin estimation of 14.5 Gm. per 100 cc., and a leukocyte count of 6200 per cu. mm. X-rays of the chest and skull were negative. The electro-encephalogram showed a poor alpha pattern, low voltage, and some focal slow waves from the right frontal region. It was interpreted as "An abnormal electro-encephalogram with some suggestion of localization in the right frontal region."

Case 4. A 36-year-old white man was first seen at Cleveland Clinic on February 4, 1947. He had suffered recurrent grand mal convulsive seizures for the past year. There had been 5 episodes all of which, except one, had been nocturnal, each of which had lasted

about five minutes and had been followed by mental confusion and apathy. There was no family history of epilepsy or migraine, no past history of rheumatic fever.

Physical examination showed a temperature of 99.4 F., a pulse of 100, and a blood pressure of 104/64. The heart was enlarged to percussion; there was a grade 4 diastolic cresendo murmur and thrill at the apex. These findings were interpreted as those of rheumatic heart disease with mitral stenosis. There was nothing additionally significant in the physical examination.

The Wassermann and Kahn tests were negative, the blood sugar was normal. There was 14.5 Gm. of hemoglobin per 100 cc., and the leukocyte count was 14,600 per cu. mm. A skull x-ray was negative. The electro-encephalographic record showed no definite alpha pattern and low voltage waves. It was interpreted as "A borderline record with no definite evidence of epilepsy nor of a focal cortical lesion."

Case 5. A man, aged 54, was first seen on September 16, 1941. He gave a history of recurrent grand mal seizures for twelve years. There was a past history of rheumatic fever and a "heart leak" first noted in childhood. His physical examination included the findings of an apical diastolic murmur and an irregular irregularity which were interpreted as indicating rheumatic heart disease with mitral stenosis and auricular fibrillation. The remainder of the physical examination was not contributory.

The electro-encephalogram revealed a dysrhythmia most evident in the left frontal area where a convulsive focus was indicated.

Summary

Of the criteria for the diagnosis of rheumatic brain disease prior to necropsy, the clinical demonstration of rheumatic heart disease is most imperative and a history of acute rheumatic fever is desirable. It is even more difficult to evaluate inflammatory activity in the central nervous system than in the heart. Febrile responses are infrequent, but correlation of the activity with rise in the sedimentation rate and leukocyte count has been reported. Electroencephalography appears to be of no specific diagnostic value; the records in the cases reported were abnormal but showed no deviation which might be considered in any way pathognomonic of the lesion.

An accurate history stressing time relationships is of decided importance. Knowledge of the age of the patient at the time of the onset of his symptoms is a valuable aid in distinguishing between seizures due to rheumatic brain disease and those included in the catch-all classification of idiopathic epilepsy. The latent period between the active polyarthritis and the appearance of symptoms indicating central nervous system involvement is observed so commonly that its significance cannot be doubted, though its explanation is far from clear.

Since chronic rheumatic processes are frequently insidious and, at times, even asymptomatic, they may cause much more psychiatric and neurologic illness than suspected. On the other hand, we should guard against taking advantage of the admittedly vague aspect of the diagnosis in the attempt to classify disease beyond our science and art. A conservative consideration of rheumatic brain disease along with other causes of convulsions is desirable.

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