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Cerebral Atrophy in Systemic Lupus Erythematosus: Steroid- or Disease-Induced Phenomenon?

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Thirty-two patients with systemic lupus erythematosus were evaluated clinically and with computed tomography in order to determine whether the occurrence of cerebral atrophy in systemic lupus erythematosus was due to the steroid therapy or the cerebral manifestations of the disease itself. Of these patients, 14 had central nervous system manifestations of the disease (lupus cerebritis) and 12 of the 14 were on long-term steroid therapy. Eighteen patients had no clinical evidence of lupus cerebritis and all were on long-term steroids. Of the 14 lupus cerebritis patients, 10 showed moderate cerebral atrophy, four minimal atrophy, and none were normal. Of the 18 patients without lupus cerebritis, none had moderate atrophy, six (33%) showed minimal atrophy, and 12 (67%) had normal CT scans. This data suggest that it is the lupus cerebritis rather than the steroid therapy that is responsible for the moderate cerebral atrophy. In patients suspected of lupus cerebritis, steroids should not be withheld because of concern for steroid-induced atrophy. Rather, the dose may need to be increased.

A significant number of patients with systemic lupus erythematosus (SLE) have central nervous system (CNS) involvement, which is expressed in many ways, including infarction, intracerebral hemorrhage, aneurysms, cerebral atrophy, aseptic meningitis, pseudotumor cerebri, convulsions, cranial nerve palsies, visual loss, intractable headaches, peripheral neuropathy, tremor, chorea, transverse myelopathy, organic brain syndrome, depression, and psychosis [1-9].

We noticed a high incidence of cerebral atrophy on computed tomographic (CT) scans obtained in patients with SLE. Since these patients are frequently treated with corticosteroids, it was unclear in many cases whether the cerebral atrophy was secondary to the systemic disease process or to the long-term steroid treatment. Therefore, we reviewed a large group of SLE patients to determine whether the cerebral atrophy was related to their primary disease or to its treatment.

Subjects and Methods

Clinical and CT evaluations were undertaken of 32 patients who met at least four of the criteria for SLE established by the American Rheumatism Association [10]. The 28 females and three males were 14-51 years old (average age, 28 years).

Axial CT scans were obtained on the GE 8800 and EMI 1010 units. The scans were classified as normal, minimal, or moderate atrophy. Minimal cerebral atrophy was defined as focal or diffuse sulcal widening without ventricular enlargement. Moderate cerebral atrophy was defined as sulcal widening with lateral ventricular enlargement. Ventricular enlargement was determined by the criterion of Evans [11], using the ratio of the maximum transverse diameter of the frontal horns to the greatest internal transverse diameter of the skull. Although this criterion was originally developed with pneumoencephalography, later authors [12, 13] have shown a direct correlation between ventricular size on pneumoencephalography and CT.

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TABLE 1: Steroid- vs. Disease-Induced Cerebral Atrophy with SLE

| CT Results | No. Patients | | |
|------------------|--------------|-------------|------------------------------|
| | Cerebritis | | Noncerebritis (All Steroids) |
| | Steroids | No Steroids | |
| Normal | 0 | 0 | 12 |
| Minimal atrophy | 4 | 0 | 6 |
| Moderate atrophy | 8 | 2 | 0 |
| Totals | 12 | 2 | 18 |

The clinical cerebral manifestations of SLE were termed "cerebritis" and included any abnormality of central neurologic function with a change from the prior state in the absence of other possible etiologies. Patients with clinically active renal disease or hypertension were not included. Long-term steroid therapy was defined as continuous prednisone treatment for 6 months or longer or greater than 40 mg/day for at least 3 months.

Results

Of the 32 SLE patients, 14 had clinical lupus cerebritis, and, of these, 12 were on long-term steroids. The two not on steroids were seen with lupus cerebritis and were placed on steroid therapy following CT. The 18 patients who had no clinical evidence of lupus cerebritis were all on long-term steroid therapy.

Of the 14 patients with lupus cerebritis, three had normal CT scans at the time of their initial neurologic signs, but each eventually showed moderate atrophy. Seven other patients in the cerebritis group had moderate atrophy at the time of the initial CT scan, yielding a total of 10 patients with moderate cerebral atrophy. Four cerebritis patients had minimal atrophy. None of the patients with lupus cerebritis had normal CT scans (table 1).

In the group of 18 patients without lupus cerebritis, 12 had normal CT scans, six showed minimal atrophy, and none had moderate atrophy. Statistical analysis of the significance of the difference between the two groups revealed a *p* value of less than 0.001. None of our 32 patients had CT evidence of hemorrhage or areas of diminished attenuation suggestive of a cerebral infarction.

The number of years of steroid therapy was essentially the same in the cerebritis and noncerebritis groups (average, 2.9 and 3.1 years respectively). The cerebritis group received an average of about 19% more corticosteroids than the noncerebritis group and had SLE an average of 2 years longer (6.8 and 4.8 years, respectively).

Discussion

In recent years there has been debate over the significance of corticosteroid therapy versus cerebritis as a cause of cerebral atrophy in patients with SLE [6, 7, 9, 14]. Momose et al. [14] showed a high degree of cerebral and cerebellar cortical atrophy in patients with endogenous

Cushing syndrome. Bentson et al. [9] noted that cerebral atrophy in a patient with SLE did not imply diffuse microinfarcts, "since the appearance may be related to the prolonged use of steroids." Gonzalez-Scarano et al. [7] suggested that the association of sulcal enlargement and lupus cerebritis may be of importance in confirming the clinical diagnosis of lupus cerebritis and in following the course of the disease. No authors have related the degree of cerebral atrophy with the presence of lupus cerebritis. Neither has there been an attempt to use the CT demonstration of cerebral atrophy in the management of patients with SLE.

In our study, which sought specifically to address these two important issues, we found that moderate cerebral atrophy was seen only in patients with lupus cerebritis (71%). In the noncerebritis patients, the CT scans were either normal (67%) or showed minimal atrophy (33%). Since nearly all the patients in both the cerebritis and noncerebritis groups had been on long-term steroid treatment, we concede that minimal atrophy may be related to the corticosteroid therapy, but believe that moderate atrophy is related to the disease process itself. The relatively small excess of corticosteroids (19%) received by the cerebritis patients could not account for the moderate atrophy demonstrated in 71%. Although the length of disease may influence to some degree the development of cerebral atrophy, the facts that there were some cerebritis patients with moderate atrophy who had had SLE for a short time (less than 4 years) and that there were noncerebritis patients with minimal atrophy who had had SLE for a long time (up to 15 years) indicate that the important factor in the eventual development of moderate atrophy is cerebritis per se rather than the duration of systemic disease.

Previous authors have proposed mechanisms to explain the minimal atrophy observed in patients on steroid therapy. Heinz et al. [15] stated that protein catabolism with resultant decrease in intravascular colloid osmotic pressure can cause the movement of fluid from the intravascular to the extravascular spaces, thus expanding the subarachnoid spaces, while Bentson et al. [9] mentioned that chronic steroid use may result in relative cerebral dehydration, possibly secondary to alterations in vascular permeability. While we agree that these theories can explain the presence of the minimal atrophy that we observed, the moderate atrophy in our cerebritis cases requires an alternate explanation. We believe that moderate atrophy in lupus cerebritis may be accounted for by small vessel vasculitis or perivasculitis that results in a decrease of the neuronal population. Although we do not have histologic proof of this assumption, moderate cerebral atrophy was seen only in patients with clinical central nervous system abnormalities.

Acceptance of this interpretation of the data could alter the therapeutic approach to patients with lupus cerebritis. Cerebritis should be given diagnostic preference in a lupus patient with CNS symptoms and moderate cerebral atrophy. It may warrant increasing the patient's steroid dose. On the other hand, in a lupus patient exhibiting similar symptoms but without moderate atrophy, the CNS features cannot definitely be ascribed to SLE. Change in steroid treatment may be less imperative.

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