ASSESSING DIAGNOSIS OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILE

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The whole teacher's team

and all the nice people who helped me during these three months in Toronto, Canada.
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1. INTRODUCTION

The central nervous system involvement (C.N.S.) in Systemic Lupus Erythematosus (S.L.E.) is common, (1,2,3,4) with a frequency ranging from 50 - 75%, and a high mortality rate (15 - 30%). (2) It might develop at any time during the S.L.E. disease, compromising mostly women at child-bearing age (80%). (1)

Until now the pathogenic mechanisms have not been completely understood. (5) Some of them might be summarized as:

a) Immune-Complex (I.Cx.) Action

- I.Cx. alter the permeability of blood-brain barrier at choroid plexus levels, allowing different auto-antibodies across to the cerebrospinal fluid and reach the neuronal cells.

- By depositing they might damage the vessel’s walls destroying the tissue with an inflammatory process, followed by thrombosis and lumen occlusion (Necrotizing Immune-Complex Vasculitis). (6,7)

b) Antiphospholipid auto-antibodies:

- They act against endothelial cellular membranes giving micro and diffuse compromise without any inflammatory process, associated with an hypercoagulability state, known clinically as "Antiphospholipid Syndrome". (8) Anatomically we can find endothelial hyperplasia and cell proliferation, surrounded peripherally by haemorrhagic and micro thrombosis widespread lesions. (9,10,11,12)

c) Antineuronal antibodies:

- In addition to the number of possible autoantibodies against brain tissue (13, 14, 15), during the last two years some new antineuronal antibodies have been found (97 K, Ki) (16,17). They may be binding to the surface or to the cytoplasm giving, by the auto-immune phenomenon, neurotransmission dysfunction without any anatomical change. (18)

They are undoubtedly some of the major contributing factors to the diffuse C.N.S. involvement, probably expressed by the "organic brain syndrome" or major psychotic features. Some authors had found a temporal relationship between them and C.N.S. events (18),
having been detected in both serum and cerebrospinal fluid (14), and also being present in neuronal tissues in the brain of those S.L.E. patients who succumbed to C.N.S. disease. (19,20)

A special P-spectroscopy added to Nuclear Magnetic Resonance Image (M.R.I.) (21) last year, might reflect generalized metabolic disturbance, being able to differentiate mild tissue insult from cell death. These metabolic changes might occur independent of anatomic identified lesions by Proton-M.R.I., and may be reversed with corticosteroid therapy. (21)

The combination of neuronal antibodies and M.R.I. studies appear to be particularly useful for the diagnosis of C.N.S./S.L.E. patients. (22)

The clinical neurological spectrum of this organ involvement is quite broad. In a recently published workshop (23), consensus had been achieved about the Clinical Diagnosis Criteria for Neuro-psychiatric lupus, but no agreement is established for the laboratory antibodies test neither for the image techniques. Although it is more evident that M.R.I. is consistently better than C.T. scan. (24)

Nevertheless these patients need an earlier and more aggressive treatment. Due to the with the current therapies employed (25,26), more patients can be recovered without any residual damage.

In Chile neither the antineuronal antibodies test nor spectroscopy-M.R.I. are available. Our experience of more than ten years following C.N.S./S.L.E. patients in a prospective way shows that the case fatality rate has fallen from 30 to 17% due to earlier clinical diagnosis and treatment. (27)

In Chile epidemiological studies in S.L.E. are not done, but intrahospital estimations show high prevalence of this organ’s involvement in Lupus patients.

In April 1991 a multicenter study was started between the University Clinical Hospital Rheumatology Unit and the West University Division at San Juan de Dios’s General Hospital in C.N.S./S.L.E. patients, looking for the coagulability disturbances and to be performed during 1991 - 1992.

At present we are ready to initiate another broader multicentre study adding the Rheumatology team of the East University Division at Salvador’s General Hospital trying to assess the diagnosis procedures of C.N.S./S.L.E. patients.
2. Research Question

WHAT WOULD BE THE LIKELIHOOD OF HAVING C.N.S./S.I.E. DISEASE MEASURED ONLY BY CLINICAL CRITERIA, OR BY ADDING THE ANTIPHOSPHOLIPID ANTIBODIES TEST AND IMAGE TECHNIQUES AVAILABLE?: A MULTICENTRE STUDY AT THE UNIVERSITY OF CHILE, SCHOOL OF MEDICINE.
3. OBJECTIVES

3.1 GENERAL OBJECTIVE

Establish the likelihood to have C.N.S. involvement in S.L.E. patients with regard to clinical diagnosis criteria alone, or adding to them the antiphospholipid antibodies test and image techniques available, in a Multicentre study at the University of Chile, School of Medicine.

3.2 SPECIFIC OBJECTIVES

3.2.1. Systematize the diagnostic process in C.N.S./S.L.E. through adopted clinical criteria diagnosis recently established.

3.2.2. Compare initial clinical diagnostic accuracy with diagnosis after addition of antiphospholipid antibodies test and two image techniques: C.T. scan and M.R.I.

3.2.3. Analyze the validity of the diagnostic process with respect to therapeutic decision making.
4. STUDY DESIGN

The present study is a one year descriptive before-after survey (September 1991 to December 1992). It will be done in a multicentre format between the following rheumatology units: University of Chile School of Medicine: Clinical Hospital, West Division - San Juan de Dios Hospital; East Division - Salvador Hospital.

4.1 Patients

To be included:

Each new S.L.E. patient (A.R.A./S.L.E. criteria) with the probability of C.N.S. involvement could be enrolled.

To be excluded:

Those uraemic, hypertensive, diabetic, atherosclerotic, hyperlipidemic, syphilitic, alcoholic, drug abuse, AIDS and other infectious diseases must be ruled out.

4.2 Methods

1) Preparing the Consensus:

The principal investigator and the responsible rheumatologists for each unit will work together in:

a) Writing a specially designed form with all the different issues and steps of the research procedures.

b) Creating an ordinary scale to register the different types of C.N.S./S.L.E. diagnosis applying the new neuropsychiatric criteria to have the definite C.N.S./S.L.E. diagnosis criteria.

c) Codifying each treatment proposition to be recorded.

d) Obtaining the consensus of these methods from each rheumatology unit to work together in this survey program.
2) Starting the Survey

I Pre-test diagnosis

a) Each attendant rheumatologist who first sees a new S.L.E. patient suitable for enrolment must propose his/her initial diagnosis and possible treatment of C.N.S. involvement. (Group 1. Regular Diagnosis of C.N.S./S.L.E.).

b) The principal investigator and rheumatologist responsible for each unit will see the same patient blindly with respect to the first attendant rheumatologist and propose her/his diagnosis and treatment possibility. (Group 2. Pre-test specialized diagnosis C.N.S./S.L.E.).

II Laboratory Test and Image Techniques to be done:

a) All the patients must be tested for general and specific laboratory tests for:
   - Assessment of S.L.E. activity *
   - C.N.S. involvement (A.C.L., L.A.C., V.D.R.L.)
   - Other organ involvement or disease that must be ruled out (exclusion criteria)

   Serum samples must be sent to laboratory without diagnosis.

b) Image techniques: C.T. scan and M.R.I. of the brain. The radiologist must be blinded with respect to the diagnosis probability type of clinical brain damage.

III Post-test diagnostic procedures

a) The principal investigator and the responsible rheumatologist must achieve an agreement about the "definite", diagnosis of C.N.S./S.L.E. patients and the subsequent treatment, applying the new neuropsychiatric diagnostic criteria.
After, they would explain this diagnosis to the attendant rheumatologist in their units and all together they review patients’ treatments.

b) We have to build a continuous scale with the dilutions and units of the laboratory autoantibodies tests results in agreement with the immunologist.

c) Along with the radiologist we have to create a nominal scale for the interpretation of results of Image Techniques (CT Scan and M.R.I.).
4.3 Data Analysis

a) Specificity and sensibility will be determined by the application of analytic cross tabulation (2 by 2 table) comparing the clinical diagnosis criteria between group 1 (Regular Diagnosis of C.N.S./S.L.E.) and group 2 (Pre-test diagnosis of C.N.S./S.L.E.), before and after the addition of laboratory test and image techniques.

b) Likelihood for having C.N.S. in S.L.E. patients must be analyzed plotting score clinical diagnosis Pre-test criteria against Post-test definite C.N.S./S.L.E. diagnosis, in regard to the laboratory and Image Techniques results.

c) Compare the different treatments proposed before and after the establishment of definite diagnosis in each C.N.S./S.L.E. case and show them utilizing simple tables.
ALL S.L.E. NEW PATIENTS

Group 1
Diagnosis
Treatment

Group 2
Diagnosis
Treatment

MEETING - APPLIED NEW NEUROPSYCHIATRIC
DIAGNOSTIC PRE-TEST

LAB TEST PLUS IMAGE

Post-test Diagnosis

Post-test Treatment
5. **Work Schedule.**

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<thead>
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<th>TASK TO BE PERFORMED</th>
<th>DATE</th>
<th>PERSONNEL ASSIGNED TO TASK</th>
<th>PERSONNEL REQUIRED</th>
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<td>Training assignment responsibilities to the team</td>
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<td>Responsible Researchers and clerks</td>
<td>10</td>
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<tr>
<td>Design special form protocol for consensus</td>
<td>Sept. 1991</td>
<td>Principle and Responsible Researchers</td>
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<td>Processing and analyzing of data</td>
<td>Oct. 1992</td>
<td>Principal and responsible researcher, Epidemiologist, statistician</td>
<td>06</td>
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<td>Presentation of final report</td>
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<td>Publishing of report</td>
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6. Budget

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<td>- IMMUNOLOGIST AND RADIOLOGIST</td>
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<td>- ATTENDANT RHEUMATOLOGIST</td>
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<td>TOTAL</td>
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TOTAL:  DLS. U.S. $53,475.00
EXTERNAL SUPPORT: DLS. U.S. $32,085.00
INTERNAL BUDGET: DLS. U.S. $21,390.00
BIBLIOGRAPHY


SUMMARY

Neuropsychiatric lupus, a frequent [50-70%] and serious organ involvement [mortality 15-30%], affect mostly women at childbearing age [80%].

Its diagnosis remains difficult due to lack of specific clinical features, laboratory test and image techniques. Recently a Workshop has been done and initial agreement about clinical criteria has been achieved and published. New immunology tests have been able to detected antineuronal and antiphospholipid antibodies in association with C.N.S./S.L.E. Also new image techniques, C.T. scan and M.R.I. are actually available for brain diagnosis, been M.R.I. better for characterize minimal anatomical abnormalities that may change after corticosteroid therapy if you establish them earlier in the course of these type of organ involvement.

In Chile we have a high number of C.N.S./S.L.E. in-patients hospital cases. Because I have been following them prospectively for almost ten years, we are starting together with other Rheumatology Unit, at the University of Chile School of Medicine a Multicentre study in relation with the A.C.L. antibodies and neurological damage. Therefore we are at the right moment to assess the diagnosis of C.N.S./S.L.E. involvement in a more objective way. Our proposition is at present, compare the accuracy of diagnosis using the clinical criteria alone and after the addition of those antibodies and image techniques available at our reality [A.C.L. antibodies and C.T.scan and M.R.I. image techniques].