Neurological Manifestations of Systemic Lupus Erythematosus

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Abstracts

Systemic lupus erythematosus (SLE) is the prototype of autoimmune disease with multisystemic damage capacity. Its diagnosis is based on clinical and immune criteria, which have been recently updated by EULAR/ACR, making positive antinuclear antibodies (ANA) a necessary part of the diagnosis criteria. Those criteria are responsible for the decrease in the neurological manifestations, in comparison with the former criteria.

Eighty seven LES patient’s retrospective hospital sample. Sociodemographic variables, autoimmune family history, years of evolution, diagnosis, antibodies, neurological clinic, image tests, electroencephalography and cerebrospinal fluid, treatment and obtained score according to EULAR/ACR criteria are being analysed.

Seventy patients and seventeen with other diagnosis are obtained, where 84.3% are women with an average age of 44.64 years, no autoimmune family history in 54.70% of the cases, an average of 15.3 years of evolution, 100% of ANA and 75% antiDNA positive. Headache, seizures, strokes and cognitive impairment are the most common neurological manifestations. 78.6% of them lack an image test, where steroids are the most used immunosuppressor (58.24%), followed by hydroxychloroquine (48.6%).

The frequency of the discussed neurological manifestations is similar to the one present in current literature, having cognitive decline a low prevalence rate. Our sample’s neurological manifestations lack of statistical significance for SLE diagnosis, being anti-DNA antibodies crucial for it. We suggest that a prospective study with less years of evolution, widening the neurological manifestations an additive criterion, can increase statistical significance.

Keywords: "Lupus"; "neurology and lupus"; "ANA and anti.DNA"; "lupus diagnostic criteria"; "EULAR / ARC criteria".

Introduction

Systemic lupus erythematosus (SLE) [1] is the autoimmune disease by excellence, whose mechanism to produce the pathology is mediated by cells, autoantibodies or immunocomplexes. It presents a low prevalence rate in Spain, 9/10,000 inhabitants, with multisystemic damage and reaching the nervous system in 60% of the cases, according to population studies with a high variability. It is more frequent in women (90%), and there is a 95% chance of survival after 5 years, 78% after 20 years: causing a decrease in the patients’ quality of life.

It’s physiopathology is complex. Upon a genetic predisposition, the intervention of a series of environmental factors induce an alteration in the immune system, which is responsible for the neurologic clinic at the end (Figure 1) [2-6].

In the nervous system’s pathogeny, [7] hematoencephalic barrier’s alteration, choroid plexus and antiphospholipid antibodies mediated vascular damage intervene. They determinate an increase in the permeability of immunoglobulins, lymphocytes, complement system and vascular and neurological damage mediator molecules.

The neurological manifestations have been divided into focal and systemic and vascular and neurological damage mediator molecules. The most frequent ones are cognitive alterations, cephalae, seizures, stroke and psychosis [11].

It is important to point out the clinical variability: from asymptomatic patients with positive antibodies- the most minor manifestation- to the most fatal clinic. They represent both opposite ends of the disease’s clinical variability.

Regarding the treatment, a differentiation must be made between the one used for treating the outbreaks and the immunosuppressor treatment, which seeks mid to large term clinical stability. The former consists mostly of steroids and sometimes intravenous cyclophosphamide. The latter uses immunosuppressors as a base, as well as several biological
treatments, such as belimumab and rituximab. Antiphospholipid syndrome’s treatment, often associated with SLE, needs antithrombotic treatment.

Until September 2019, 2012 diagnosis criteria were still valid. The new EULAR/ACR criteria (Figure 3) determine that in order to affirm that a patient has lupus, they must have ANA positive>1/80, as well as an above 10 punctuation with at least one clinical criterion. The neurological criteria have suffered a great change. Seizures, psychosis and delirium are 5, 3 and 2 points respectively, eliminating the current ones in 2012. These criteria maintain a 93.4% specificity and increase sensitivity up to 96.1%. However, they omit clinic that can be part of the disease’s manifestation and they should include a higher level of antibodies.

Figure 01

- GENETIC PREDISPOSITION (HLA DR2, DR3 AND B8)
  - LOCI (>80), STAT4 (CD4 + PROLIFERATION STIMULANT THROUGH IL-12R→GAMMA→ACTIVATION CD4+)
  - CONGENITAL COMPLEMENT DEFICITS (C1Q, C2, C4) →INHIBIT CD8 MITOCHONDRIAL METABOLISM.
  - GALECTIN 3 DEFICIT IN GERM CENTERS →INCREASE GAMMA-INF →PROLIFERATION OF LYMPHO CYTES AND AUTOANTIBODIES.
  - IL21'S ROLE AS PLASMOCYTE DIFFERENTIATION REGULATOR AND AUTOANTIBODY FORMATION.
  - BAFF IS ACTIVATOR OF LYMPHO CYTES B, REGulates THE RECOGNITION OF ANTIGENS

EFFECTS

1. ADAPTIVE AND SPECIFIC IMMUNE HYPERACTIVATION.
2. FAILURE IN THE REMOVAL OF ANTIGENS FROM THE CIRCULATORY TORRENT.
3. LOWER TOLERANCE TO THE RECOGNITION OF APOPTOTIC CELLS.
4. FAILURE IN NEGATIVE REGULATION OF CD4 AND CD8.

MANIFESTATIONS

- GENERAL (95%)
- MUSCULAR-SKELETAL (95%)
- HEMATOLOGICAL (85%)
- SKIN (80%)
- NEUROLOGICAL (60%)
- CARDIOPULMONARY (60%)
- RENAL (50%)
- GASTROINTESTINAL (45%)
- THROMBOEMBOLIC (15%)

Figure 02

| CENTRAL | PERIPHERAL |
|---------|------------|
| ASEPTIC MENINGITIS | GUILLAIN BARRE SYNDROME |
| STROKE | AUTONOMIC NEUROPATHY |
| DEMYELINATING SYNDROMES | MONONEUROPATHY |
| HEADACHE | MASTENIFORM SYNDROME |
| MOVEMENT DISORDERS | CRANIAL NEUROPATHY |
| SEIZURES | PLEXOPATHY |
| ACUTE CONFUSIONAL SYNDROME | POLYNEUROPATHY |
| ANXIETY DISORDER | |
| COGNITIVE IMPAIRMENT | |
| MOOD DISORDERS | |
| PSYCHOSIS | |
Material and Methods

Our work’s design has been done in the following way:

- Data bases bibliographic search (PubMed and Academic Google) of last 10 year’s SLE’s diagnosis criteria, etiopathogenesis, clinic and antibodies related articles.
- SLE neurological manifestations’ search in Neurology and Internal Medicine manuals.
- Retrospective and hospital-based experimental study. A data base has been created, gathering information from three different sources: a 50 lupus and anti-DNA positive patient’s hospital sample; a 27 patients with lupus and its neurological manifestations’ hospital sample- followed in the Neurosystems Unit; and a 113 anti-DNA positive patients’ hospital sample from the Immunology department, where only 10 of them have been selected, due to temporary reasons and to the fact that they had similar characteristics to the previous sources.

As a result, we gather an 87 patients’ sample. A clinical DIRAYA history analysis was carried out, mainly in neurology, internal...
medicine and nephrology. The data were gathered between 1/1/2018 and 1/9/2019. The capture-recapture method was used in order to avoid duplicities. The data were divided into the following 11 categories:

- Sociodemographic: age and sex.
- Autoimmune family history.
- Disease’s years of evolution.
- Diagnosis.
- Antibodies (ANA, anti-DNA, ENA and antiphospholipid antibodies).
- Neurological manifestations.
- Image tests and type of present injuries.
- Electroencephalography and cerebrospinal fluid.
- Anti-lupus treatment.
- Non-neurological SLE related clinic.
- Punctuation according to 2019 EULAR/ACR criteria.

The data are transformed into binary code for its SPSS analysis. An analysis by Chi-square statistics, for relating the qualitative variables among them.

Analysing our sample, we consider the following objectives:

1. Primary:
   - Determine the neurological manifestations’ prevalence of SLE diagnosed patients.
   - Determine the patient’s frequency, according to sex, age, autoimmune family history, evolution time, diagnosis’ tests and anti-lupus treatment.
   - Determine the different measured antibodies’ effectivity in diagnosis.

2. Secondary
   - Critical analysis on EULAR/ACR criteria, regarding neurological manifestations.

Our study has received the Andalusian Ethical Committee for investigation’s approval (Code 29996).

Results

The following results from our sample are obtained:

- From the 87 cases, there are 70 patients with SLE diagnosis, while the other 17 have an alternative one: 3 mixed connective tissue disease patients, 2 myotonic dystrophy patients, 1 with primary antiphospholipid syndrome, 6 non-defined collagenosis, 1 with Sjögren’s syndrome, 1 scleroderma, 1 patient with cholestasis, 1 with isolated CNS vasculitis and 1 with cutaneous lupus.
- There are 11 males and 59 females (15.7% and 84.3%).
- Age range follows a normal distribution, with an average age of 44.46 and a 14.053 DE (IC at 95% (41.29-47.99)).
- The average years of evolution follow a normal distribution, 15.31 years and 7.795 DE (IC at 95 % (13.37-17.22)).
- There is no autoimmune family history in 54.30% of the patients, being SLE the most frequent one (15.7%) (Table 1).
- Antibodies are positive in 67 patients (95.7%). Both patients with negative results have close to no data in their clinical history. There is one from MUFACE, who has almost no tracking. Therefore, it could be assumed that they all have SLE diagnosis, meaning that the entire patients are ANA positive. Regarding the different antibodies’ effectivity in diagnosis, the Chi-square method is used, in order to see the relation between both qualitative variables and to obtain statistical significance, as well as authenticity (Table 2). ANA, anti-DNA, anti-histone and antiphospholipid antibodies show statistical significance for diagnosis.
- Regarding the neurology clinic (Table 1), headache, seizures, stroke and cognitive decline are the manifestations that prevail. General manifestations are more common than the localised ones, being less frequent in the CNS. None of the analysed clinical manifestations have statistical significance for the SLE diagnosis study.
- In the complementary tests, the 78% of the patients lack brain CT/IMR. Only 15 patients have had a CT done, showing 4 lacunar strokes and 1 with white matter injury. Other 23 patients have had a IMR done, showing 5 lacunar strokes and 7 with white matter injury. 10 patients have had an electroencephalography done, where all of them showed a normal result. 4 patients have had a lumbar puncture done, where only one of them showed an anormal result: lymphocytic pleocytosis.
- About the anti-lupus treatment used, 18 patients did not take it (26.08%). The steroid-based immunosuppressor treatment is used in the 58.24%, and the most used non-steroid-based one is hydroxychloroquine (48.6%) (Table 1).

| Table 01 | Frequency | %  | +  | Rpl Reason For Positive Likelihood |
|----------|-----------|----|----|-----------------------------------|
| No       | 38        | 54.30 |    |                                   |
| 1. Family History | Yes | 20 | 28.60 |                                   |
|           | Not Included | 12 | 17.20 |                                   |
| 2. Clinic |           |    |    |                                   |
|           | Diffuse    | 20 | 48.52 |                                   |
| A)        | Focal      | 8  | 20  |                                   |
|           | Peripheral | 4  | 8.57 |                                   |
|           | Multiple   | 9  | 22.51 |                                   |
|           | Headache   | 25.70 |    |                                   |
|           | Seizures   | 11.43 |    |                                   |
### Discussion

In our sample, the age and sex distribution are correlated with the population data. It is more frequent in women. In 54% of the patients, there is no family history of autoimmune disease and when there is, most of the time it is lupus. The general neurological manifestations are more frequent than the ones in the peripheral nervous system and the localised ones. The low frequency in which cognitive decline takes place surprises us. That could be related to the population’s average age (44.64 years). Since it is relatively low, there is no real need for neuropsychological tests, therefore there are no diagnosis done.

Regarding the different antibodies’ positiveness and their relationship with SLE’s diagnosis, we obtain that the ANA have statistical significance. However, due to the fact that it can also happen in other pathologies and that 5-10% of the population can have them too, its positiveness cannot be used as part of the SLE diagnosis’ criteria since they are high sensitive, but low specificity antibodies. ENA, antihistones and antiphospholipid antibodies also have statistical significance. Anti-DNA are the most significant ones for SLE diagnosis.

The current neurological clinic criteria for diagnosis-seizures, psychosis and delirium (5,3 and 2 points, respectively) have a great importance in those ANA positive and scarce symptomatology patients. Nevertheless, in our sample they lack statistical significance for our diagnosis. Probably because of their average years’ evolution (15.33 years) and the rare frequency of those symptoms in our sample.

The conclusion that we can reach after finishing our sample’s analysis are:

- The current EULAR/ACR criteria could widen the neurological manifestations demanded for lupus’ diagnosis.
- It would be recommended to carry out a prospective study in order to value the lupus related neurological manifestations.

### Limitations

Retrospective study. Hospital study. Possible selection bias in the Neurosystemics consult’s sample (27 patients). Low percentage of patients which have had a brain CT/IMR/LP/electroencephalography.

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### Ethics approval and consent to participate

Our study has received the Andalusian Ethical Committee for investigation’s approval (Code 29996).

### List of abbreviations

- SLE: systemic lupus erythematosus.
- EULAR: European League Against Rheumatism.
- ANA: Antinuclear antibody.
- Anti-DNA: Anti deoxyribonucleic acid antibody.
- ENA: Nucleus extractable antibody.
- CNS: Central nervous system.
- SD: Standard deviation.
- MUFACE: General Mutual Funding of Civil Servants of State.
- CT: Computed tomography.
- IRM: Nuclear magnetic resonance.

### Conflict of interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.
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Author’s contributions

Hernández Chamorro FJ, Medina Rodríguez M, Palomino García A and Jiménez Hernández MD, have helped in the final preparation of this paper and was a mayor contribution in writing the manuscript. All authors read and approved the final manuscript.

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