Complete Auriculoventricular Blockage in Adult Patients With Systemic Lupus Erythematosus. Case Series and Review of the Literature

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Background and objective: Congenital complete atrioventricular heart block (CHB) is due to the lesion of the cardiac conduction system by specific transplacental antibodies of maternal origin. In adults with systemic lupus erythematosus (SLE), cardiac toxicity is very questionable and has been related to treatment with synthetic antimalarial drugs (AM). Here we evaluate, in our geographic area, the presence of non congenital CHB in adult patients with SLE and its possible association with AM treatment.

Patients and methods: The frequency of CHB has been studied revising the clinical records of 595 SLE patients followed at the Unit for Systemic Diseases.

Results: Five women (0.8% of the total series) suffered from CHB (2 patients developed it during a lupic crisis). All were on treatment with AM (100 vs 60% of the rest of the series) and maintained a dose of 250 mg/day (except one, with a dose of 500 mg/day) for a mean period of 90 months. The accumulated mean dose of AM was 753 g. Three patients developed cardiac insufficiency, 2 nephropathy, 2 myopathy, and 1 maculopathy. As accompanying processes we detected Sjögren’s syndrome (2) and hypothyroidism (3). The frequency of HLA DR3, positive in 80% of the cases, is higher than observed in the total series, 34% (p = .053).

Conclusions: We detected the presence of CHB in 0.8% of SLE patients. They were all treated with AM. We did not verify any relationship with anti-ENA (anti-Ro/La and anti-RNP) antibodies, as communicated by others, but rather a trend to the association with HLA DR3 (at the limit of statistical significance).

Key words: Systemic lupus erythematosus. Antimalarials. Complete atrio-ventricular heart block.

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Introduction
The development of complete atrioventricular blockage (CAVB) is the most frequent manifestation of neonatal lupus. The lesion of the conduction system, developed in utero, is considered to be the result of an inflammatory reaction related to the Ro and La antigen recognition on the surface of the myocytes undergoing a remodeling phase by specific transplacental antibodies of maternal origin. In the adult with systemic lupus erythematosus (SLE), in spite of it being mentioned by some authors, the possibility that the lesion of the conduction system is being produced by an aggression of the inflammatory-vascular type related to the abovementioned antibodies, is very doubtful (there are no described cases of CAVB in the mothers of children with neonatal lupus) and the presence of CAVB, known since 1965, is supposed to caused by other causes. The antimalarials are drugs used extensively for their immunosuppressive effects in patients with SLE and other systemic illnesses. Among the diverse toxic effects that can result from their use (gastrointestinal, retinopathy, neurotoxicity, myotoxicity), cardiotoxicity can be found. There is certain speculation about the relationship between CAVB in adults under treatment with antimalarials. Five new cases of acquired CAVB in a series of patients with SLE are presented.

Patients and Methods
The clinical history of 5 patients affected by SLE (according to the ARA) and with adult acquired CAVB, belonging to a series of 595 controlled in a systemic illnesses unit. The study is retrospective and the selection criteria was the electrocardiographic evidence of CAVB in individuals that had suggestive (syncopal episodes, detection of bradycardia) and that in those in which a pharmacologic cause of CAVB was excluded. These 5 patients underwent, at the moment of diagnosis, to treatment with antimalarials (60% of the patients of the series total had also received, in some time of their illness, the same treatment). The general and specific clinical data (related to CAVB) were evaluated, as well as the cardiac conduction studies and aspects related to the dose of antimalarial received. For the statistical analysis, and Fisher's exact test was employed.

Results
Five women, without any clinical evidence of previous cardiopathy, presented a CAVB that was irreversible in all cases, with the need for a permanent pacemaker. Five new cases of acquired CAVB in a series of patients with SLE are presented.

TABLE 1. Characteristics of the Patients*

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since onset of AVB</td>
<td>156</td>
<td>12</td>
<td>216</td>
<td>39</td>
<td>132</td>
</tr>
<tr>
<td>CQ dose/dem, mg</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>500</td>
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<tr>
<td>Duration treatment CQ, months</td>
<td>144</td>
<td>5</td>
<td>216</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Cumulative dose CQ, g</td>
<td>1080</td>
<td>375</td>
<td>1620</td>
<td>307.5</td>
<td>720</td>
</tr>
<tr>
<td>ANA titer/pattern</td>
<td>1/80 DF, SP</td>
<td>1/80 MX, SP</td>
<td>1/320 DF</td>
<td>1/640 DF</td>
<td>1/320 DF</td>
</tr>
<tr>
<td>DNA/ENA</td>
<td>−/−</td>
<td>−/−</td>
<td>a/−</td>
<td>a/−</td>
<td>−/−</td>
</tr>
<tr>
<td>Anticardiolipin abs.</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>HLA (DR)</td>
<td>DR1/DR3</td>
<td>DR1/DR3</td>
<td>DR3/DR4</td>
<td>DR3/DR3</td>
<td>DR3/DR4</td>
</tr>
<tr>
<td>Nephropathy/biopsy</td>
<td>Yes (TF)/Und</td>
<td>Yes (TF)/Und</td>
<td>Yes (TF)/Und</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Myopathy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Retinopathy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Associated Illness</td>
<td>Exp silica</td>
<td>No</td>
<td>SS/thyr</td>
<td>Hipothy</td>
<td>Hipothy</td>
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<td>Other cardiac clinical data DMC</td>
<td>DMC</td>
<td>DMC</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>C, A, P</td>
<td>C, A</td>
<td>C, A</td>
<td>C, A</td>
<td>C, A</td>
</tr>
</tbody>
</table>

*A indicates articular; BAV, atrioventricular blockage; C, cutaneous; CQ, chloroquine; DF, diffuse; ENA, extractable nuclear antigen; Exp, exposition; Hipothy, hypothyroidism; HLA, histocompatibility antigen; Und, undifferentiated; TF, terminal renal failure; DMC, dilated myocardiopathy; EMC, restrictive myocardiopathy; SP, speckled; MX, mixed; P, pulmonaty; SS, Sjögren's syndrome; thyr, thyroiditis.

20-57) and time to the diagnosis of CAVB was 110 months (limits, 12-216). The CAVB developed in the context of a crisis of SLE activity in 2 patients and in a more insidious manner in the rest of them. All patients with CAVB were being treated with chloroquine (CQ) at the moment of detection of the conduction disturbance: 100% versus 60% in the rest of the series (P<.3) and had maintained a stable dose of 250 mg/day (except in 1 case, with a dose of 500 mg/day) for a mean time of 90 months (limits, 5-2416). The mean accumulated dose of CQ was 753 g (limits, 37.5-1620). One patient had previous work exposure to silica: 3 developed heart failure (dilated cardiomyopathy in 2 and restrictive in 1); 2 with nephropathy (terminal kidney failure in 1); 2 had myopathy (muscle enzyme elevation, in patients 3 and 5 with an compatible electromyographic pattern in the first of them), subclinical in nature, with a normal muscle balance (no muscle biopsy was done); patient 5, with a larger daily dose (though not with a larger accumulated dose), developed a bilateral maculopathy due to CQ. As accompanied processes, there was evident of Sjögren’s syndrome (1 case) and hypothyroidism (3 cases). Antinuclear antibodies (ANA) were positive in all cases (limits, 1/80 and >1/640) and anti-DNA antibodies in 2. The anti-ENA were consistently negative. The frequency of HLA DR3 (in 80% of the cases with CAVB) was superior to the one observed in the series total (34%) at the limit of statistical significance (P=.053). Anticardiolipin antibodies were positive in only 2 patients.

Discussion

The first observation of cardiotoxicity due to antimalarials was published in 1971. Since then, there have been some reports of heart failure, restrictive or hypertrophic cardiomyopathy and, above all, CAVB related to these drugs. The first 3 cases of CAVB in adult patients with SLE were published in 1965. Since then, there have been a total of 23 reports. The characteristics of the first 18 can be consulted in the review by Comín-Colet et al. There has also been 6 cases of CAVB in patients with discoid lupus: 3 by Godeau et al. and another 3 by Reuss-Borst et al., Cubero et al., and Ratcliffe et al., respectively. The series we presented (5 patients; 0.8% of the authors casuistic) is the most extensive in terms of cases of CAVB in adult patients with SLE. All of them were undergoing treatment with antimalarials at the time of diagnosis. Twelve of 20 patients (60%), of the patients in the literature with enough information available, had received treatment with antimalarials. Including the 5 patients of the present series, 68% of patients had evidence of previous treatment with antimalarials in the total of communicated cases. Five of the 6 published patients with discoid lupus and CAVB had been treated with antimalarials. In the third case there was no description of the treatment but, because there was evidence of concomitant retinopathy, it is very likely that treatment with antimalarials had also been used. In general, CAVB appears after very prolonged periods of treatment with antimalarials (between 2 and 30 years) and with very elevated accumulated doses (100 to 5000 g). Nonetheless, there have been reports of cases in which the CAVB Developer alter extremely short treatments, such as the patient presented by Comín-Colet et al., in which the conduction defect developed a week alter the start of treatment with antimalarials. In our series, the accumulated dose oscillated between 37.5 (administered for 5 months) and 1620 g (216 months of treatment). Both CQ as well as hydroxychloroquine are potentially cardiotoxic. Both accumulate in lysosomes and increase pH, permitting the inhibition of phospholipases that protect the integrity of the lysosomal membrane. There is no inflammatory infiltrate or vasculitic appearance. These alterations are never seen in lupus cardiopathy without antimalarial treatment. Other possible triggering factors of CAVB, distinct from antimalarials, are manifest in SLE. In some of them, the CAVB was manifested as the context of exacerbations or activity flare), invoking the possibility of inflammatory-vasculitic lesions as conditioning the conduction abnormalities, maybe through a facilitating effect added by these drugs. The association with myopathy (skeletal or cardiac), as can be appreciated in the present series, is frequent. Nonetheless, retinopathy (the most common complication of antimalarial treatment known) is a lot less common than what be expected in patients with SLE and antimalarial therapy: only 1 case in the present series and another 2 in the literature review. We have not proven the relationship with anti-ENA (anti-Ro and anti-RNP antibodies) communicated in some cases, but a tendency bordering statistical significance in the association with HLA DR3 has been shown. The present work, which represents the most extensive series of patients with SLE and CAVB recruited, has the common limitations of the majority of studies in this field: retrospective character in the presentation of the data and variable period of treatment with antimalarials.
the selection of patients, lack of uniform simple data and, above all, the absence of anatomicopathological confirmation (difficult to obtain due to ethical motives), that insure the relationship with antimalarial treatment. In spite of this, the sum of data provided by the literature strongly supports the possibility of such a relationship.

References


