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<0.053).

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 atrioventricular heart block.

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Original Articles

Bloqueo auriculoventricular completo en pacientes adultos con lupus eritematoso sistémico. Casuística propia y revisión de la bibliografía

Fundamento y objetivo: El bloqueo auriculoventricular completo (BAVC) congénito se debe, en la mayoría de los pacientes, a lesión del sistema de conducción por anticuerpos trasplacentarios de origen materno (lupus neonatal). En el adulto con lupus eritematoso sistémico (LES) es muy dudosa la cardiotoxicidad por dichos anticuerpos y se ha relacionado con el tratamiento con antipalúdicos de síntesis (APS). Se valora, en nuestro medio, la presencia de BAVC (no congénito) en pacientes adultos con LES y su posible asociación con el tratamiento con APS.

Pacientes y métodos: Se ha estudiado la frecuencia de BAVC en una serie de 595 pacientes afectados de LES controlados en una unidad de enfermedades sistémicas.

Resultados: Cinco mujeres (0,8% del total) presentaron un BAVC (desarrollado en una crisis lúpica en 2 pacientes). Todas estaban en tratamiento con APS (el 100 frente al 60% en el resto de la serie) y mantuvieron una dosis de 250 mg/día (excepto una, con dosis de 500 mg/día) por un tiempo medio de 90 meses. La dosis media acumulada de APS fue de 753 g. Tres pacientes desarrollaron insuficiencia cardíaca; 2, nefropatía; 2, miopatía; y una, maculopatía. Como procesos acompañantes se constató síndrome de Sjögren (2) e hipotiroidismo (3). La frecuencia de HLA DR3, positiva en 80% de los casos, es superior a la observada en la serie total, 34% (p = 0,053).

Conclusiones: Constatamos la presencia de BAVC en el 0,8% de pacientes con LES. Todos ellos en tratamiento con APS. No hemos comprobado relación con anticuerpos anti-ENA (anti-Ro y anti-RNP) comunicada en algunos casos, pero sí una tendencia a la asociación con HLA DR3 (en el límite de significación estadística).

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-vasculitic 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 were 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* |
|-----------------------------------------|--------------------------------|--|---|---|
| Months since onset of AVB | 156 | 12 | 216 | 39 | 132 |
| CQ dose/day, mg | 250 | 250 | 250 | 250 | 500 |
| Duration treatment CQ, months | 44 | 6 | 216 | 41 | 48 |
| Cumulative dose CQ, g | 1080 | 175 | 1620 | 3075 | 720 |
| ANA titer/pattern | 1/80 DF, SP | 1/80 MX, SP | 1/320 DF | 1/640 DF | 1/320 DF |
| DNA/ENA |/–/– |/–/– |/–/– |/–/– |/–/– |
| Anticardiolipin abs. | – | – | + | – | – |
| HLA (DR) | DR2/DR13 | DR3/DR7 | DR3/DR14 | DR3/DR13 | DR3/DR4 |
| Nephropathy/biopsy | Yes (TRF)/Und | No | Yes/II | No | No |
| Myopathy | No | No | Yes | No | Yes |
| Retinopathy | No | No | No | No | Yes |
| Associated Illness | Exp silica | No | SS/thyr | Hipothyr | Hipothyr |
| Other cardiac clinical data | DMC | DMC | RMC | No | No |
| Clinical manifestations | C, A, P | C, A | C, A | C, A | C, A |

* A indicates articular; BAV, atrioventricular blockage; C, cutaneous; CQ, chloroquine; DF, diffuse; ENA, extractable nuclear antigen; Exp, exposition; hipothyr, hypothyroidism; HLA, histocompatibility antigen; Und, undifferentiated; TRF, terminal renal failure; DMC, dilated myocardopathy; RMC, restrictive myocardopathy; SP, speckled; MX, mixed; P, pulmonar; SS, Sjögren’s syndrome; thyr, thyroiditis.
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 1965.3,5 Since then, there have been a total of 23 reports.14 The characteristics of the first 18 can be consulted in the review by Comín-Colet et al.9 There has also been 6 cases of CAVB in patients with discoid lupus: 3 by Godeau et al.10 and another 3 by Reuss-Borst et al.11,12 Cubero et al.13 and Rutcliff et al.14 respectively. The series we presented (5 patients; 0.8% of the authors caustic) 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.9,14 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.9,15,16 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.15 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).14,15 Nonetheless, there have been reports of cases in which the CAVB Developer after extremely short treatments, such as the case presented by Comín-Colet et al.9,12 in which the conduction defect developed a week after 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.3,15,16 Ladipo et al.17 and Nord et al.18 observed, in patients with SLE with cardiac complications secondary to the use of antimalarials, specific histological modifications that preferentially affect the septum (that justify the frequency of conduction abnormalities). These modifications consist of vacuolization, hypertrophy, disorganization of myocardial muscle fibers, and fibrosis. The ultrastructural examination shows phagocytic necrosis that in turn generates dense heterogeneous corporules, pseudomyeloid formations, and curved bodies, alterations similar to the ones observed in cases of antimalarial toxicity on skeletal muscle, whose elevated frequency has recently been described.3,15 There is no inflammatory infiltrate or vasculitic appearance. These alterations are never seen in lupus cardiomyopathy without antimalarial treatment.19 Other possible triggering factors of CAVB, distinct from antimalarials, are manifest in SLE. In some of them, the CAVB was manifest in the context of an acute flare of the underlying disease,2,23 occasionally coinciding with a short treatment with antimalarials (as the case cited by Comín-Colet et al.9 and cases 2 and 4 of the present series in which the development of CAVB coincide with a lupus activity flare), invoking the possibility of inflammatory-vasculitic lesions as conditioning the conduction abnormality, maybe through a facilitating effect added by these drugs.3 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.3,12 We have not proven the relationship with anti-ENA (anti-Ro and anti-RNP antibodies)2,24,25 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 selection of patients, lack of uniform simple data and, above all, the absence of anatomopathological 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


