Rheumatic Carditis Treated with High Doses of Pulsetherapy Methylprednisolone. Results in 70 Children Over 12 Years

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Purpose - *To report the result of patients treated with IV methylprednisolone divided into three groups and compare their follow-up during the last 12 years.*

Methods - *Seventy children with active rheumatic carditis (76 episodes) in heart failure Class III and IV (NYHA) were studied. The diagnosis was based on modified Jones' criteria. After ruling out infections and strongyloidiasis, treatment with IV methylprednisolone bolus was started three times a week until the laboratory tests became negative. Patients were divided into 3 groups, according to the time of hospital admittance: Groups 1, 2 and 3, comprising of 40, 18 and 12 children, respectively.*

Results - *Eighteen children in Group 1 (45%) were in their 1st attack: 2 series of pulsetherapy were used in 10 (25%), 3 in 9 (23%) and 4 in 21 (52%). In Group 2, 14 cases (77%) were in their 1st attack: 2 series were used in 7 (39%), 4 in 9 (50%) and 5 in 2 (11%). The echocardiogram showed a flail mitral valve in 12 (66%) of these patients (1 death occurred after mitral valvoplasty). In Group 3, 6 patients needed 5 or more series of pulsetherapy and a flail mitral valve was present in 5 (41%). One child underwent mitral valve replacement while still in the active phase, after 8 series of pulsetherapy, and another died. The number of patients who needed 5 or more series was significantly higher in Group 3.*

Conclusion - *There were variations in the presentation and evolution of the cases during these 12 year. The established pulsetherapy protocol continues to be useful to treat severe cases.*

Keywords: rheumatic carditis, methylprednisolone, children

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Data from the World Health Organization reveal that 3% of the children experiencing infection of the upper respiratory tract by group A β-hemolytic streptococci develop rheumatic fever, of whom, 30% have carditis [1]. 30% to 70% of the patients with rheumatic sequelae do not report previous oropharynx infection [2,3]. Some of these children of preschool age might have severe congestive heart failure (CHF) due to severe carditis and rupture of mitral chordae tendineae, as already previously reported [4]. In such cases, treatment with intravenous methylprednisolone proved efficient [5,6]. This study aims to report the results of the treatment of 3 groups of children with intravenous methylprednisolone.

Methods

Of 120 children with rheumatic fever admitted to the Hospital Universitário Antônio Pedro (HUAP), from January 86 to June 98, 70 cases (a total of 76 episodes) with active carditis treated with recurrent therapy with methylprednisolone were prospectively studied. These 70 children presented with NYHA class III and IV CHF. The diagnosis of rheumatic fever was based on the modified Jones critera [7,8]. Ages varied from 3 to 17 years. Intravenous, instead of oral, corticoid therapy was chosen due to the severity of the cases. The remaining 50 children were either medicated with oral prednisolone and were discharged during the phase of dose reduction or needed only nonsteroidal anti-inflammatory drugs.

The protocol used for immunosuppression with intravenous methylprednisolone has been previously described [5,6]. Prior to corticoid therapy, eradication of the streptococcal infection was initiated with penicillin for 10 days. Treatment for worms, eradication of dental infections and a tuberculin test were also performed. In each series, 40mg/kg/day of methylprednisolone (maximum of 1g) were used diluted in 200mg of intravenous 5% glucose solution,

during a fasting period, for three consecutive days per week. The series were repeated until normalization of the tests for rheumatic activity occurred. On the third day of each series, an electrolytic profile was performed. In case of clinical intercurrent events, such as high fever, skin lesions, etc, pulsetherapy was interrupted until the absence of bacterial complications was proved. Secondary prophylaxis was initiated right after eradication and benzyl penicillin was used every two weeks in the first two years and then every 21 days. After discharge, patients were required to return for follow-up on an outpatient care basis.

The 70 children were divided into 3 groups: group 1 consisting of 40 patients (total of 44 episodes) admitted from January 86 to December 92; group 2 consisting of 18 patients (total of 18 episodes) admitted from January 93 to April 95; and group 3 consisting of 12 patients (total of 14 episodes) admitted from May 95 to June 98.

A statistical study was performed using the variables in the three groups, comparing two at a time and using Fisher's exact test.

Results

In group 1 (40 cases), 18 (45%) patients were having their first attack. All were in NYHA class III and IV of CHF. Two series of pulsetherapy were used in 10 cases (25%), 3 series in 9 (23%) and 4 series in 21 (52%) patients. There were no severe complications, and the only intercurrent events originated from hypervolemia with a mild increase of the signs of venous congestion, which were controlled with an increase in the dose of furosemide. This was observed only in the days where intravenous corticoid therapy was performed. An epileptic child had a convulson during medication. Another patient died after 3 episodes of activity. The autopsy revealed a lymphomonocytic inflammatory infiltrate with some Aschoff bodies in the myocardium and extensive areas of destruction of fibers with an eosinophilic aspect. No signs of ruptured chordae tendineae were observed. Years later, another patient, already an adult, died in another hospital after the surgical replacement of the mitral valve (MV).

In group 2, there were 18 children ranging in age from 4 to 15 years, 14 of whom were having their first attack. Two series were used in 7 (39%) patients, 4 in 9 (50%), and 5 in 2 (11%). Twelve (66%) patients in this group experienced rupture of the MV chordae tendineae; 10 ruptures were in the anterior area and 2 were in the posterior. The affected chordae tendineae were significantly longer than the normal ones (29.85±4.7mm and 18.19±4.26mm, respectively) similar to that which has been described in previous studies [4].

No severe complications were observed in group 2. The only intercurrent events resulted from a slight increase in the venous congestion, already mentioned. One child in this group died in another hospital as a result of bacterial endocarditis, four months after mitral valvoplasty. Three other children underwent surgery.

In group 3, there were 12 children between the ages of 3 and 12 years, 7 of which were having their first attack. Two children stopped prophylaxis and their disease reactivated; intravenous immunosuppression was restarted, then. Two (17%) episodes required only 2 series of pulsetherapy, 4 (33%) episodes required 3 series and 6 (50%) episodes needed 5 or more series.

In group 3, there were 5 (41%) cases of rupture of the MV chordae tendineae (4 of which were in the anterior chorda tendinea and 1 in the posterior). So far, one child, who had had several admissions due to reactivation of the carditis and evolued to refractory CHF, has died. The autopsy revealed active myocarditis with Aschoff bodies, destruction of fibers and extensive areas of fibrosis. Two children underwent surgical valve replacement, one of the mitral valve and the other of the aortic valve. In one patient of this group, the disease reactivated without interruption of the secondary prophylaxis with benzyl penicillin, and 8 series of pulsetherapy were required. There was severe mitral regurgitation and the laboratory tests did not normalize. The patient then underwent MV replacement during the active phase of the disease and, currently, is clinically and laboratorially well.

In the long-term follow-up, several cases that had echocardiographic images of MV chordal rupture do not show this aspect any more and the measures of the chordae tendineae have decreased.

Through statistical analysis, it was observed that the number of patients in group 3, who needed 5 or more series of recurrent therapy, was significantly larger than in other groups ($p<0.0001$). When comparing the cases of MV chordal rupture and death, there was a significant difference between groups 1 and 2 ($p=0.028$).

Discussion

In the first 40 cases, we observed the best results with intravenous methylprednisolone. Recurrences resulted from interruption of the secondary prophylaxis in 4 patients. Two of them evolved to death after several recurrences and refractory CHF, and an autopsy was performed on one of them. The results were similar to those of Couto et al [5,9], as already mentioned. Some patients of this group, although adults, continue to attend the outpatient clinic of the HUAP, on a regular basis. Most of the patients, however, have lost contact with us over the years.

The patients who died in group 1 are examples of cases with a poor evolution when secondary prophylaxis is inadequate or interrupted or when carditis turns into a chronic condition. Decourt et al [10], analyzing tissues from the papillary muscle and appendages of the atria surgically removed, found Aschoff bodies in 33.7%. Edwards et al [11] did not observe these bodies in cases of active valvulitis but vegetations with nonspecific inflammatory tissue and edema. They discuss the pathognomonic lesion of the disease, which is the Aschoff body, and if it represents activity of the disease. Kemeni et al [12] demonstrated that the Aschoff

and Anitschkow cells do not exhibit immunoreaction with several markers of macrophages, Langerhans cells and endothelial cells.

In group 2, 66% of the patients showed an echocardiographic aspect of MV chordal rupture, which was not observed in the previous cases. Most of the children were having their first attack of the disease. This clinical finding of chordal rupture, unknown to us until then, began to be observed in our service in 1993. In the medical literature, there are similar descriptions by several authors [13-15].

In this group, the clinical manifestations of the first attack were more severe, and in 11% of the cases, the therapeutical response to the intravenous corticoid therapy was only obtained after 5 series, which was not previously observed.

In group 3, we describe the most recent cases. There was a case of MV replacement during the active phase of the disease. Some authors [16,17] observed an association between calcification and amyloidosis in the chronic rheumatic valvulitis with an intense inflammatory process. Rheumatic valvar amyloidosis seems to relate to a higher aggression of the extracellular matrix and appearance of new antigenic products. Therefore, one can infer that the cells of the Aschoff body are not completely differentiated or are degenerated cells that lost their antigenic characteristics. Fragments of the antigens of the streptococcal wall may be gradually freed, explaining the chronic phase of the disease [16].

In the chronic and active valvulitis, there is a predominance of inflammatory cells, of helper lymphocytes (CD4) and of macrophages [17,18]. It is believed that the inflammatory process in the chronic valvulitis stimulates the formation of collagen, i. e., the chronic lesion is an active and continuous process determined by antigenic streptococcal fractions present in the site.

Among the most recent cases (group 3), there was our youngest child (3 years of age). We also observed that in 50% of these cases, it was more difficult, both from a clinical and laboratory point of view, to control the activity of the disease with intravenous methylprednisolone. A greater number of series of pulsetherapy was necessary.

We do not have a complete explanation for the differences of presentation and evolution of the cases in the 3 groups. We might perhaps justify the chordal rupture aspect at the first attack in so many cases of group 2 as a consequence of infection by more aggressive strains. We also had some patients with rheumatic activity without interrupting prophylaxis. There is no reference in the literature to resistance to penicillin by group A β-hemolytic streptococcus. In 5 to 30% of the adequately medicated patients, the streptococci continue on the oropharynx despite the treatment, causing recurrence of the pharyngitis. Bacteria producing β-lactamase, such as *M. catarrhalis*, *S. aureus* and some anaerobic ones, may be concomitant on the oropharynx and can inactivate penicillin [19,20].

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