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Frequency of myocarditis in cases of fatal meningococcal infection in children: observations on 31 cases studied at autopsy

Freqüência de miocardite em casos de infecção meningocócica fatal em crianças: observação de 31 casos estudados à necropsia

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Abstract *The frequency of myocarditis associated with meningococcal disease in children was reported only in two autopsied series (United States and South Africa). Here we report the frequency of associated myocarditis in 31 children who died of meningoccal infection at Hospital Infantil N.S. da Glória in Vitória, Espirito Santo State, Brazil. The diagnosis was confirmed by isolation of* Neisseria meningitidis*. At least three sections of fragments of both atria and ventricles were studied using the Dallas Criteria for the morphologic diagnosis of myocarditis. The mean age was 47.6 ± 39.8 months and the mean survival time after the onset of symptoms was 46.1 ± 26.5h (12-112h). Myocarditis was present in 13 (41.9%) patients, being of minimal severity in 11 cases and of moderate severity in 2 cases. There were no cases with severe diffuse myocarditis. The frequency of myocarditis was not influenced by sex, presence of meningitis, survival time after the onset of symptoms or use of vasoactive drugs. The frequency of myocarditis reported here was intermediate between the values reported in the only two case series published in the literature (57% in the United States and 27% in South Africa). Although our data confirm the high frequency of myocaditis in meningoccal disease, further investigations are necessary to elucidate the contribution of myocarditis to myocardial dysfunction observed in cases of meningococcal infection in children.*

Key-words: *Myocarditis. Meningitis. Meningococcemia.*

Resumo *A freqüência de miocardite associada à infecção meningocócica em crianças foi descrita apenas em duas series de casos autopsiados (Estados Unidos e África do Sul). Nessa comunicação relataremos a freqüência de miocardite em 31 crianças falecidas com doença meningocócica no Hospital Infantil N.S. da Glória em Vitória, E. Santo. O diagnóstico foi confirmado pelo isolamento da* Neisseria meningitidis*. Três secções ou mais, dos átrios e ventrículos, foram estudadas utilizando os critérios de Dallas para o diagnóstico morfológico de miocardite. A média de idade foi de 47,6 ± 39,8 meses e o tempo médio de sobrevida após o início dos sintomas foi de 46,1 ± 26,5 horas (12-112h). Miocardite foi identificada em 13 (41,9%) casos sendo de intensidade mínima em 11 e de intensidade moderada em dois casos. Nenhum paciente apresentou quadro morfológico de miocardite grave, difusa. A frequência de miocardite não foi influenciada pelo sexo, presença de meningite, tempo de sobrevida após o início dos sintomas ou pelo uso de drogas vasoativas. A freqüência de miocardite aqui apresentada é intermediária entre as únicas duas séries relatadas na literatura (57% nos Estados Unidos e 27% na África do Sul). Embora confirme a alta freqüência de miocardite na doença meningocócica, investigações são necessárias para elucidar a contribuição da miocardite para a disfunção miocárdica observada em casos de infecção meningocócica em crianças.*

Palavras-chaves: *Miocardite. Meningite. Meningococcemia.*

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Cardiac involvement in meningococcal infection has been recognized since 1903, yet its significance has not been emphasized as a possible cause of cardiac failure[13]. Saphir[13] first noted the importance of myocarditis in meningococcal infection, describing two fatal cases.

During World War II, myocarditis was frequently described in military personnel with meningococcal infection. Among 1402 cases of myocarditis identified in a review of the records of the Armed Forces Institute of Pathology, Gore and Saphir[5] found 111 cases of meningococcal myocarditis. These authors did not report the ages of the patients or the severity of the lesions.

The first description of the morphology of meningococcal myocarditis was reported by Hardman and Earle[6]. These authors reported a myocarditis rate of 78% among 200 fatal cases of meningococcal infection, retrieved from the records of the Armed Forces Institute of Pathology (100 cases from the World War II period and 100 cases from the 1960-1966 period). Myocarditis was observed in 85% of adult cases and in 57% (28/49) of pediatric cases. These authors defined myocarditis as the presence of inflammatory cells in the interstitial tissue of the myocardium (interstitial myocarditis), graded as "minimal if a rare focus of inflammatory cells was found in the interstitial tissue of the myocardium. If inflammatory infiltrates occurred in two or more foci, the myocarditis was regarded as severe. If such inflammatory infiltrates were found in conjunction with necrosis of individual or small groups of myocardial cells, the myocarditis was considered severe and necrotizing". Based on these criteria, severe myocarditis with necrosis was observed only in adult cases (66%) but in none of the pediatric cases.

More recently, Neveling and Kaschula[11] reported the occurrence of 23 cases of myocarditis (27%) among 86 children who died of meningococcal infection in Capetown, South Africa. Using the criteria of Hardman and Earle[6], these authors found 4 cases with severe and necrotizing myocarditis, 8 with minimal myocarditis and 11 with severe myocarditis. In only one case had the diagnosis of myocarditis been suspected clinically.

Isolated case reports and small case series account for the remaining literature regarding myocarditis in meningococcal infection[3 4 5 10 12].

Clinical studies of patients with meningococcal infection in shock have not clearly demonstrated whether myocarditis is an important factor in the myocardial depression observed in this situation. Boucek et al[2] and Mercier et al[9] did not comment on the possibility of myocarditis as a cause of cardiac failure in 7 children with acute meningococcemia and in 18 patients with meningococcal shock, respectively, all monitored hemodynamically. However, Monsalve et al[10], studying 19 cases of meningococcal sepsis in children, reported severe myocarditis in three out of 5 deaths secondary to shock. These authors suggested that meningococcal myocarditis may depress myocardial function before the clinical manifestations of shock.

Because of the discrepancy in the reported frequencies of myocarditis among children with meningococcal infection and because of the incertainity surrounding its contribution to the cardiac failure observed in meningococcal shock, we studied the occurrence of myocarditis in fatal cases of meningococcal infection at Children's Hospital NS da Glória in Vitória during a seven year period. We employed the Dallas criteria for the morphologic diagnosis of myocarditis[1].

PATIENTS AND METHODS

From 1989 to 1997, 61 children who died of suspected meningococcal infection were autopsied in the Pathology Unit of the Children's Hospital NS da Glória. Thirty one patients had meningococcal infection listed as the cause of death in the medical record. In these cases, the clinical picture was suggestive of meningococcal infection as per the Epidemiologic Surveillance of Health Ministry criteria: sudden onset with fever, lethargy, petechiae, ecchymosis or purpura and signs of meningeal irritation. The confirmation was obtained via isolation of *Neisseria meningitidis* from blood, cerebral spinal fluid or skin lesions.

The data regarding myocardial lesions in the 31 patients were retrieved and the fragments of myocardium revised for the identification of inflammatory lesions. In each case, fragments of both atria and ventricles stained with hematoxylin and eosin and trichromic methods were examined. At least three sections per fragment were examined in each case.

Myocarditis was diagnosed according to Dallas classification criteria for endomyocardial

biopsies[1]. According to these criteria, myocarditis is diagnosed when myocyte degeneration and/or necrosis is associated with an inflammatory exudate adjacent to the degenerating or necrotic myocytes.

For statistical comparisons, the Chi-square test or Fisher's exact test was used. The differences were considered significant for $p < 0.05$.

RESULTS

Data concerning age, sex, time of death after admission and the presence or absence of meningitis are summarized in Table 1. The male to female ratio was 1.06:1 and the boys were older than girls, but not significantly so (53 ± 39.2 and 37.1 ± 38.1, respectively; $p = 0.163$).

Table 1 - Data regarding age, sex, duration of illness, presence or absence of meningitis, use of vasoactive drugs (VAD) and presence and intensity of myocarditis in 31 children dead with meningococcal disease at the Hospital Infantil N S da Glória in Vitória, ES, Brazil.

N	Age[a]	Sex	Illness [b]	Meningitis	VAD	Miocarditis
1	24	F	26.0	yes	no	minimal
2	48	M	12.5	yes	no	minimal
3	24	F	12.5	no	no	minimal
4	60	M	72.0	yes	yes	minimal
5	59	M	38.0	no	yes	absent
6	48	M	31.0	yes	yes	moderate
7	59	F	31.0	yes	yes	absent
8	36	F	44.0	yes	no	moderate
9	24	F	32.0	no	yes	absent
10	60	M	32.0	yes	yes	absent
11	117	M	21.5	no	yes	absent
12	21	M	49.0	no	yes	minimal
13	60	M	24.0	yes	yes	minimal
14	72	M	48.0	yes	yes	minimal
15	84	F	53.0	yes	yes	absent
16	144	M	12.0	no	no	minimal
17	4	M	27.0	no	yes	minimal
18	72	M	24.0	yes	yes	absent
19	18	F	16.0	no	yes	absent
20	12	F	74.0	no	no	absent
21	6	F	50.0	yes	yes	absent
22	144	F	60.0	yes	no	absent
23	33	F	32.0	yes	yes	absent
24	48	F	112.0	yes	yes	absent
25	108	F	91.0	yes	yes	minima
26	60	M	79.0	yes	yes	absent
27	8	M	25.0	no	no	minimal
28	14	M	42.0	yes	yes	absent
29	1	F	58.0	yes	yes	absent
30	1	M	60.0	yes	yes	absent
31	7	F	108.0	yes	no	absent

M/F = 1.06:1. [a] Age in months; mean = 47.6 ± 39.8 months (median = 48; range 1 to 144 months). [b] Survival time after the onset of symptoms: mean = $46{,}1 \pm 26.5$h (median = 40h; range 12 to 112h)

The macroscopic study of hearts showed no cardiomegaly, no severe dilatation or thrombosis. Some hearts were described as swollen and soft. Petechiae or small hemorrhages were observed in the epicardium, myocardium and endocardium in 11 cases.

Microscopic examination frequently showed myocardial edema and dilated interstitial vessels, with a large number of polymorphonuclear leucocytes in the vessel lumen in six cases. In these cases it was difficult to demonstrate extravasation of cells from the vessels. When present, these inflammatory cells were not in the vicinity of injured myocardial cells. These cases were not labeled as myocarditis (Figures 1A and B).

In 13 (41.9%) cases there were myocardial edema, dilatation of interstitial vessels and leucocytosis, along with inflammatory cells extravasated from vessels adjacent to degenerating and necrotic myocytes. These foci

of myocarditis were of moderate severity in two cases (several isolated or confluent foci ; Figure 1D) and of minimal severity in 11 cases (isolated foci, sparsely distributed in the myocardium; Figure 1C). Foci of myocarditis were observed both in the atria and ventricles. There were no cases with severe diffuse myocarditis according to the Dallas criteria.

The inflammatory cells observed in the exudates were polymorphonuclear leukocytes and macrophages and rarely lymphocytes and eosinophils (Figures 1E and F).

There was no statistically significant difference in the frequency of myocarditis between cases with and without meningitis (8/21 and 5/10, respectively; p = 0.403). Likewise, the use of vasoactive drugs did not significantly alter the frequency of myocarditis (7/22 and 6/9, respectively, among treated and untreated patients; p = 0.128).

There were no gender differences in the frequency of myocarditis (8/16 in boys and 5/15 in girls; p = 0.893). Stratification of patients into those surviving more or less than 24 hours from the onset of symptoms did not reveal a significant difference in the frequency of myocarditis (8/24 and 5/7 respectively; p = 0.295).

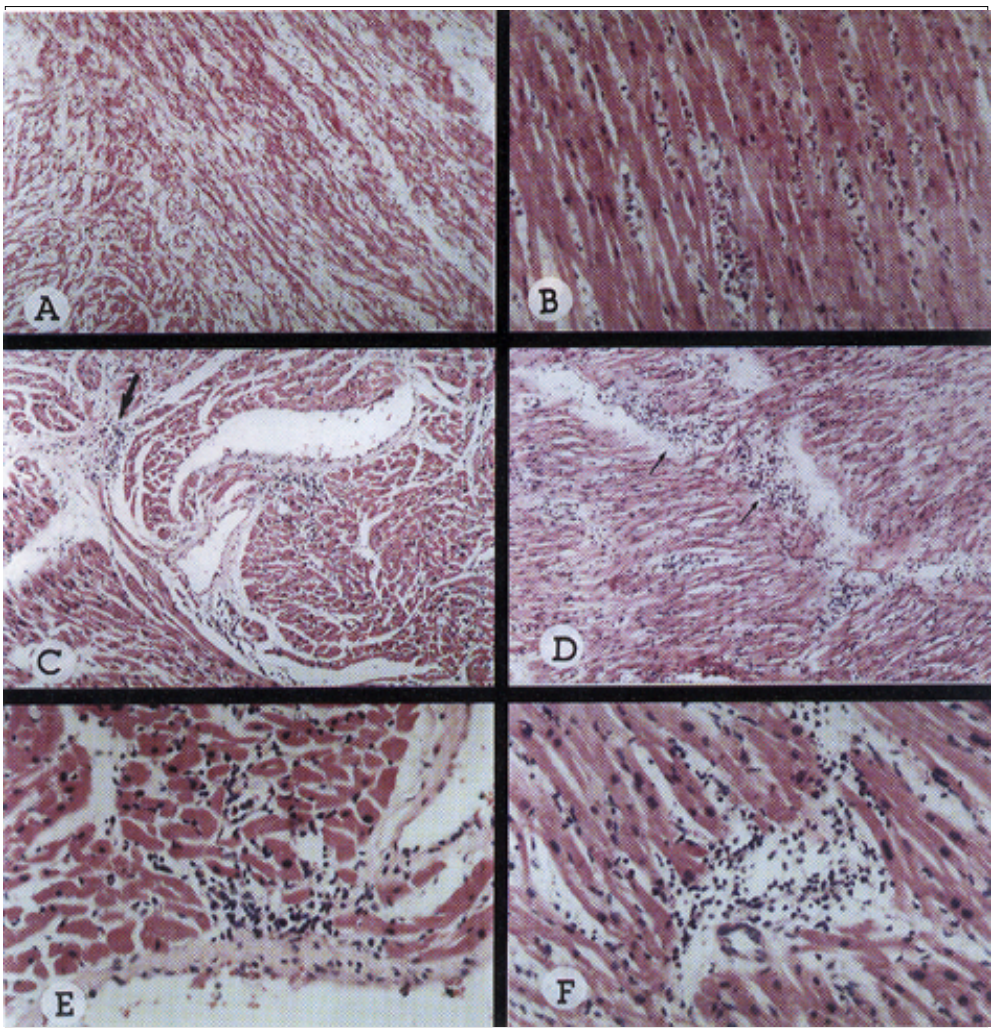

*Figure 1 - Microscopic patterns of myocarditis in children who died of meningococcal disease: **A)** Severe interstitial edema and presence of some leukocytes apparently extravasated from vessels. The scanty exudate cells do not show a relationship with severely damaged cardiocytes (Oc 10x. Ob. 10x). **B)** Hyperemia and intravascular leukocytosis. This case was not considered as myocarditis (Oc 10x Ob 40x). **C)** Minimal myocarditis. Two small foci of myocarditis. Loss of myocardyocytes is indicated in one focus (arrow) (Oc 10x Ob 10x). **D)** Myocardits of moderate intensity Two confluent foci of myocarditis (arrows) and one small focus at the top (Oc 10x Ob 10x). **E** and **F)** High power view of minimal (**E**) and moderate (**F**) myocarditis, showing predominace of polymorphonuclear neutrophils.*

DISCUSSION

Our results confirm that myocarditis is frequently present in cases of fatal meningococcal infection. The frequency observed here was lower than that observed by Hardman and Earle[6], probably because the criteria used by these authors, namely the presence of inflammatory cells in the interstitium, was the only criterion for the diagnosis of myocarditis. Among 49 cases of fatal meningococcal infection in children, these authors observed 16 cases of minimal myocarditis and 12 cases of severe myocarditis but did not observe severe or necrotizing myocarditis. Although it is difficult to compare these results with our observations, one adult case of severe and necrotizing myocarditis presented in the Hardman and Earle paper was similar to cases we defined as myocarditis of moderate intensity.

In contrast, our results showed a frequency of myocarditis higher than that reported by Neveling and Kaschula[11] in autopsies of children who died of meningococcal infection. The difference may be attributed to sampling, given that the authors studied two fragments of ventricles (interventricular septum and posterior wall of left ventricle). These authors used the same criteria as Hardman and Earle. The illustration presented as severe and necrotizing myocarditis in the Neveling and Kaschula paper is similar to what we considered moderate myocarditis. The large number of exudate cells in that figure were probably leukocytes in the lumen of vessels disrupted by edema.

The mean patient age in this series differs from that of the Hardman and Earle[6] study (mean age of 9 months, but without reference to the sex distribution of cases) but is comparable to that reported by Nevelling and Kaschula[11] (23 ± 19 months for boys and 38 ± 31 months for girls, with a male/female ratio = 1.15:1). Despite these discrepancies, mean age was probably not a factor impacting the frequencies of myocarditis reported in the three case series discussed above. The average duration of illness prior to death, a factor that may depend on the severity of myocardial injury, was similar to that observed by Nevelling and Kaschula (49 hours, range: 8-264 hours).

Vasoactive drugs may also be associated with myocardial injury in children with meningococcal infection[14]. As demonstrated in Table 1, myocarditis was less common in children treated with vasoactive drugs, though the difference was not statistically significant (31.8% and 66.8%, respectively, in treated and untreated patients; Fisher exact test: $p = 0.084$).

In conclusion, our results confirm the high frequency of myocarditis in fatal cases of meningococal infection. Although frequent, myocarditis was of minimal severity in the majority of cases. Further investigations correlating clinical presentation and pathological findings are necessary to elucidate the contribution of myocarditis to myocardial dysfunction observed in some cases of meningococcal infection.

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