

Generalized Histoplasmosis in El Salvador, C. A. A report of 13 cases in children under two years of age

by

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Acute, disseminated, progressive histoplasmosis in very small children has well defined characteristics and is entirely different from histoplasmosis in the adult. In general it has a rapid evolution and is fatal within one to six weeks. If it lasts more than six weeks the case is arbitrarily classified as chronic, according to FURCOLOW (7).

With the exception of the publications from Panama, we found no other reports of histoplasmosis in Central America. However one of us (A. T.) studied a fatal case in 1958 involving a three and a half year old Costa Rican girl. *H. capsulatum* was isolated from the blood and lymph nodes. This observation remains unpublished.

The purpose of this paper is to present the first thirteen cases of disseminated histoplasmosis studied in El Salvador.

MATERIAL AND METHODS

The material includes three cases of histoplasmosis which had been diagnosed as kala-azar in their autopsies in 1951, 1952 and 1955 respectively. Since then we have confirmed the diagnosis in five more cases that came to the autopsy table in 1959, 1961, 1962, 1963 and 1964 respectively. These cases were diagnosed exclusively on the presence of large quantities of *H. capsulatum* in the tis-

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sues of various organs. In 1964 we isolated the fungus from three cases at autopsy, and from one living patient. In the first six months of 1965 we found two new cases at autopsy, which raised the total number of known cases in El Salvador to thirteen. All the patients were seen either at Hospital Rosales (General Hospital) or Hospital Bloom (Children's Hospital).

The diagnosis was confirmed in all cases except one at autopsy and in some of these cases by studying biopsy material. The methods used were microscopic observation of stained tissues or smears and cultures. Also, the fluorescent antibody technique was used.

In eight cases (Nos. 1, 2, 3, 4, 5, 6, 7, 12, Table 1) the diagnostic method was exclusively microscopic observation of abundant forms of histoplasma in tissues from various organs that were stained with hematoxylin-eosin, Hotchkiss-McManus and/or Gomori-Grocott. In four cases (8, 10, 11, 13), besides the histopathological study, cultures of *Histoplasma capsulatum* were also obtained from material taken during autopsy (Nos. 8, 13) or by splenic puncture during life (Nos. 10, 11). In the patient in which autopsy was not possible (Nº 9), the fungus was observed in great quantities in slides of materials obtained by splenic and sternal punctures and stained with Giemsa. *H. capsulatum* was grown in culture from the same material. *H. capsulatum* was demonstrated in three cases (Nos. 10, 11, 13) by the fluorescent antibody technique. In two of them (Nos. 10, 11) the patients were still living.

The culture media used were "Mycosel" and Sabouraud's with penicillin and streptomycin, incubated at room temperature ($26 \pm 3^\circ \text{C}$). For the yeast phase, brain-heart infusion agar with 10 % rabbit blood and 2 % glucose was used. In cases of autopsy material with abundant bacterial contamination, the tissue was ground and intraperitoneally inoculated into mice which were treated during the following five days with penicillin and streptomycin. The mice were sacrificed at two and four weeks. The spleen of the sacrificed animals was minced with sterile scissors and cultured on "Mycosel" that was incubated at room temperature.

The diagnosis was made during life in only three patients, all of whom died a short time afterwards. In these three patients serological tests, which generally have little value in cases as serious as these, were not performed.

ANALYSIS OF THE CASES

SEX AND AGE: Of the thirteen cases studied, eight were females and five were males; the age varied between six weeks and eighteen months.

GEOGRAPHICAL DISTRIBUTION. With the exception of one case coming from a rural area, all others were from the metropolitan area of San Salvador.

ECOLOGICAL DATA. The metropolitan area has approximately 60 km² and 404,838 inhabitants. It is located between 650 and 800 m above sea level. The mean annual temperature varies between 22 and 24°C according to the alti-

tude. The area from which the patients came can be considered semi rural.

REASON FOR SEEKING CONSULTATION. The chief complaint was fever in twelve cases, two of which also had diarrhea; one consulted for abdominal "inflammation".

EVOLUTION. The time between the onset of the first symptom and the first medical consultation was variable (three days to two months and ten days); it must be considered that the information given by the majority of these people, with low cultural level, was not reliable. The period of hospitalization fluctuated between five days and four and one half months.

SYMPTOMATOLOGY. In Table 1 clinical signs observed in the thirteen cases are shown. Fever, hepato-splenomegaly and anemia were the most constant findings and were present in twelve of the cases. The large splenomegaly observed in these children was much more marked than that shown in cases of other splenomegaly-producing diseases in El Salvador.

Six showed icterus, seven presented leukopenia, three had hemorrhages and two showed signs of meningeal irritation.

Six of the last seven patients had thrombocytopenia. There were no data regarding platelet counts in the six cases observed before 1962. Reticulocytosis was observed in four of the last five cases. This information was not available in the eight previous cases. Radiological pulmonary lesions were present in only four of the cases.

HISTOPATHOLOGICAL FINDINGS. All the cases studied, except one, were brought to autopsy. In all cases, *H. capsulatum* was found in the lungs, liver, spleen, and lymph nodes although the number of parasites in the latter and spleen was much greater than in the lungs and liver (Table 2).

Six of the eight cases in which red bone marrow sections were made showed histoplasma.

In only one of seven cases in which the central nervous system was studied, macrophages with parasites were found infiltrating the pia mater.

The myocardium was studied in eleven autopsies but no histoplasma cells were found in any of the sections.

Three of nine studies showed parasites in the kidneys.

In the intestines, macrophages with parasites were observed in five of six cases.

The adrenals were studied in eight autopsies, three of which showed the presence of the fungus.

Finally, two out of five thyroids were positive for *H. capsulatum*.

TABLE 1

Symptomatology of thirteen cases of generalized histoplasmosis in children of El Salvador

Case number	Age in months	Sex	Fever	Hepato-splenomegaly	Icterus	Meningeal signs	Hemorrhages	Anemia	Leukopenia	Thrombocytopenia	Reticulocytosis	Pulmonary lesions (X - Ray)
1	3	F	+	++	0	0	0	+++	+			0
2	4	M	+	++	+	0	0	+	0			+
3	5	M	+	++	+	0	0	+	+			0
4	18	F	+	+	+**	0	0	++	+			0
5	12	F	+	++	0	0	0	+	0			+
6	9½	F	+	+	+	0	+	++	+			0
7	4	M	+	0	0	+	0	0	+	+		0
8	1½	M	+	+	+	+	0	+	0	+		0
9	5	M	+	++	0	0	0	+	0	0	+	0
10	10	F	+	+	0	0	0	+	0	+	+	0
11	3	F	+	++	+	0	0	+++	+	+	0	+
12	3	F	+	++ ^c	+	0	+	+	0	+	+	0
13	3	F	0	+	0	0	+	+++	+	+	+	+

+, ++ = Grades of Intensity.

0 = Negative.

* Clinically found to be within the upper limits of normal. At autopsy a frank increase in weight and size was found in both organs.

** There was a suggestion of a slight icteric tinge, but the total bilirubin determination was 1.32 mg %.

TABLE 2

Presence of parasites in diverse tissues and time of evolution of the disease

Nº	Lung	Liver	Spleen	Ganglia	Bone marrow	C.N.S.	Heart	Kidneys	Intestine	Adrenals	Thyroid	Time of evolution
1	+	+	+	+		+	0	0				2 m.
2	+	+	+	+			0	0	0			40 d.
3	+	+	+	+	+					0		1½ m.
4	+	+	+	+	+	0	0	+	+	0		40 d.
5	+	+	+	+	+		0	+	+	+	+	4 m. 3 w.
6	+	+	+	+	+	0	0	+	+	+	+	
7	+	+	+	+	0	0	0	0		0		49 d.
8	+	+	+	+	0		0		0	+		1 m.
10 ^c	+	+	+	+	+	0	0		+		0	1 m.
11	+	+	+	+		0	0	0		0	0	3 m.
12	+	+	+	+			0	0	+	0	0	1 m.
13	+	+	+	+	+	0	0	0				18 d.

+ = Presence of *Histoplasma*.^c Autopsy not performed in patient 9.

0 = Fungus not found.

DISCUSSION

Despite the fact that the first three cases of histoplasmosis described in Panama by DARLING (3, 4) were adults, the majority of patients that present the acute disseminated form are children under two years. Almost twenty years ago IAMS, *et al.* (8) pointed out that of the eighty-eight cases described in the literature up to that time, twenty-eight were children, and of these, twenty were less than fifteen months old. A few years later CANCELA FREIJO (2) reviewed the literature up to that period. He counted 136 cases, twenty-five of which were children younger than two years. More recently FURCOLOW (6) points out that the highest mortality occurs under one year and between the age of forty-six and sixty-five. The graphical data presented by him indicate that of the 490 cases, approximately fifty were in children under two years. Also it is evident that the frequency of histoplasmosis decreases during the first five years of life and that in the first two years the majority of the cases are fatal.

As we said previously, Darling's three cases were adults. In Panama, a case was afterwards described involving a child four months old (5); this is the first case in a child and the first in a native of Panama. Later other reports were published from the same country: an adult (11), four more adults (13), a seven month old child (1), and finally one concerning six children (12). Therefore, sixteen cases of generalized histoplasmosis have been described in Panama, four in children under two years. It is interesting to note that the last two cases, being treated with sulfonamides, were cured (12).

The picture of the thirteen cases of generalized histoplasmosis presented here did not differ from the general one known to occur in very young children. In all tissues studied, the fungus was present frequently or occasionally, being more abundant in lymph nodes, spleen, liver and lungs. The myocardium was the only tissue not found parasitized in any case. It is interesting to note that in one of the other reticuloendothelioses, visceral leishmaniasis, whose pathology is quite similar to that of histoplasmosis, the myocardium is also spared (9).

Our experience is totally different from that found in Argentina; NEGRONI (10) reviewed fifty-one cases which appeared since 1940 in that country. There were many cases of generalized histoplasmosis among these but all were adults older than twenty three years.

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SUMMARY

The general characteristics of thirteen cases of disseminated histoplasmosis in children under eighteen months of age, all native of El Salvador, Central America, are presented. These cases indicate a high prevalence of the disease in this country; all appeared between 1951 and 1965.

RESUMEN

Se relatan las características de 13 casos de histoplasmosis generalizada en niños de menos de 18 meses, oriundos todos de El Salvador. De estos casos, en 8 el diagnóstico fue microscópico por hallazgo del hongo en tejidos; de 4 se obtuvieron cultivos (2 durante la vida y 2 durante la autopsia) y en el último, que no se pudo autopsiar, el diagnóstico se hizo por hallazgo del hongo en material de punción y por cultivo. Estos casos, que aparecieron entre 1951 y 1965 indican una alta prevalencia de la enfermedad en El Salvador.

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