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LIVER INVOLVEMENT IN MUMPS

A clinical, laboratorial and histopathological study of four cases

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SUMMARY

Reviewing the literature the authors were convinced that the liver involvement in mumps is very rare or has not been carefully looked for. In the Hospital de Isolamento "Emílio Ribas" they were able to select 4 cases with typical clinical and laboratorial evidences of mumps associated with clinical and laboratorial data suggesting liver involvement. Liver biopsies were taken in these patients and structural lesions were found. These changes were characterized by mild hepatitis in which, besides Kupffer cell hyperplasia, there was intralobular infiltration by mononuclear cells. Slight degenerative alterations of the hepatic cells were observed. The lesions were not characteristic but sufficiently evident to speak for an involvement of the organ related to the disease.

In conclusion it is mentioned that further studies must be done to better elucidate the role played by the liver in mumps and, furthermore, the importance that endemic parotitis may have among the agents capable of producing more serious chronic liver disease.

INTRODUCTION

The viral or epidemic parotitis, or mumps, in the great majority of cases is characterized by involvement of the salivary glands, specially the parotids. It is capable, however, of producing alterations in other organs leading to the well known complications of the disease, orchitis, oophoritis, pancreatitis and meningoencephalitis. The liver, if one relies on the literature, is seldom if ever involved.

SALLER [14] in a review of the disease comments on four cases in which jaundice apreared.

MCNICHOLL [10] describes two cases of mumps associated with a picture of hepatitis with jaundice; one during the first week of the disease, the other five weeks afterwards.

BROWNE [4] also refers to two other cases of severe mumps with jaundice.

HUMPHRIES, in PULLEN's book [13], states that hepatitis can complicate mumps but does not go further into the problem.

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WESSELHOEFT, in BANK's book [1], mentions a case of mumps with orchitis and hepatitis.

In papers dealing with complications of parotitis, as the ones by HUMPHRIES [7] and LAWRENCE & MCGAVIN [8], no references to liver involvement are issued. The same holds for the papers dealing with large numbers of cases of the disease in military personnel, as the ones by MESIANO & PEREIRA [11] and by OLIVEIRA [12].

Furthermore, in the references mentioned above, the subject of hepatitis is simply referred to without further discussion.

Recently, however, WARREN [16] described a well studied case of mumps in which hepatitis was observed characterized by jaundice, hepatomegaly and biochemical evidence of hepatic involvement; he considered the hepatic injury to be related to mumps since other causes could be excluded. He studied 44 other cases of the disease; in none hepatomegaly or jaundice was found and in more than one half of the 26, in which liver function tests were performed, he found elevated thymol turbidity values. In face of the negativity of the other tests, he interpreted the elevation as related to the serum gammaglobulin alterations proper of the disease.

During the last war, in England, 44.7% of 266 patients receiving convalescent plasma for prevention of mumps developed hepatitis about 2 to 3 months after the inoculation [2, 5, 9]. It seems more probable to us that these were cases of viral hepatitis, not related to parotitis.

MATERIAL AND METHODS

This paper is based on the study of 4 cases of epidemic parotitis with jaundice observed among the patients of the Hospital de Isolamento "Emílio Ribas", a hospital where only infectious and contagious diseases are treated.

Mumps usually is treated at home in our city. This fact makes it impossible for us to speak in terms of incidence of the complication since our 4 cases were selected among the more serious cases of the disease requiring hospital care.

The cases were clinically observed and laboratorial tests were performed as follows:

— Serum proteins, by the method of Gornall-Bardawill-David.

— Cephalin-cholesterol test by the method of Hanger.

— Thymol turbidity by the method of Maclagan, modified.

— Colloidal red test by the Ducci technic.

— Serum cholesterol by the method of Sheftel.

— Serum bilirubin levels by the Mallory and Evelyn technic.

— Urine urubilinogen by the dilution technic.

— Formol-gel-test, according to Gates-Papacostas.

— Paper electrophoretic analysis of serum proteins according to HOXTER, WAJCHEMBERG & MUNGIOLI [6].

— Liver biopsies using Vim-Silverman needles. The slices were formalin fixed, hematoxylin and eosin and silver impregnation being made.

CASE I — A.F.S., Hospital number 95,843, 22 years old, white, male. Industry worker, admitted on August, 1, 1956.

He entered the hospital after a ten-day illness, characterized by typical symptoms and signs of mumps. Three days before admission he began to complain of nausea and noticed dark urines, plus slight jaundice. At admission the patient was in good nutritional status; the parotids were slightly enlarged; he had slight jaundice, the liver being palpated as a soft mass one finger breadth below the costal margin. The spleen dullness was increased but the organ was not palpable. No signs of orchitis, pancreatitis or meningitis were detected.

TABLE I

Laboratorial data of a case of mumps with liver involvement. — Case 1.

Date	8-2-56	8-14-56	8-22-56	8-29-56	10-2-56	10-27-56	12-7-56	3-7-56
Total serum proteins (mg%)	7.8	7.5	7.8	7.7	...	7.6	8.0	8.4
Serum albumin (mg%)	4.5	4.5	4.3	5.1	...	5.3	6.0	4.9
Serum globulin (mg%)	3.3	3.0	3.5	2.6	...	2.3	2.0	3.5
Thymol turbidity test units Maclagan	1.6	3.0	2.6	1.6	2.3	2.0	2.5	1.3
Chephalin-cholesterol test	++	+++	++	+	—	++	—	++
Colloidal red test	++	++++	+++	+	++	+++	+	++
Total serum bilirubin (mg%)	1.3	0.4	0.7	0.9	1.5	1.3	0.5	0.3
One minute serum bilirubin	0.1	0.1	0.0	0.0	0.1	0.1	0.1	0.3
Urine bilirubin	—	—	—	—	—	...	—	—
Urine urubilinogen	1/50	1/40	1/30	—	—	...	—	—

TABLE II

Evolutive view of the electrophoretic pattern of serum proteins in a case of mumps with liver involvement. — Case 1.

Date	8-2-56	8-14-56	8-22-56	8-29-56
Albumin (g%)	4.20	3.30	4.20	4.20
α_1 globulin (g%)	0.36	0.39	0.40	0.30
α_2 globulin (g%)	0.75	0.82	0.75	0.72
β-globulin (g%)	0.95	1.04	1.17	0.75
γ-globulin (g%)	1.77	1.96	1.80	1.32

Table I gives the results of the laboratorial tests.

Serum cholesterol levels were between 76 and 166 mg%. Blood cell counts revealed: w.b.c. 8,900 per mm^3; slight anisocytosis; slight shift to the left; rare neutrophils with toxic granulations; slight eosinophils; moderate lymphocytosis.

Two liver biopsies were done, the first at the time of admission, the second 2 days before the patient was discharged.

In the first the lobular architecture was maintained; there was discrete infiltration of the portal fields with lymphocytes. The Kupffer cells were prominent disposing themselves rarely in small, intrasinusoidal nodular groups. The hepatic cells were orderly arranged, its cytoplasm being clear, and its nuclei being strongly stained. In the cytoplasm, specially near the centrolobular vein, there was accumulation of a brown granular pigment (Fig. 1).

In the second, the picture was similar but the hepatic cells were larger and not so orderly arranged; some had definitely piknotic nuclei. The pigment had increased in amount and distribution, and it was also found in the Kupffer cells (Fig. 2).

The patient' conditions improved rapidly; the jaundice cleared and he was discharged completely recovered 34 days after admission. In the follow-up, slight variations in the serum albumin and serum bilirubin levels were observed and the cephalin-cholesterol and colloidal red test remained positive. As to electrophoretic serum protein alteration (Table II) we observed that on the 8-14-56 there was a marked fall of albumin values, soon returning to normal; on the same day an increase of α_2 globulin (probably related to greater liver cell injury) and an increase in γ-globulin (signifying a stimulus to the R.E.S., but also incapacity of liver to metabolize protein of extra-hepatic origin) were noticed. α_1 globulin showed no deviations from normal values. β-globulin-behaviour, increasing until the 22nd to fall again after that date, reflects, in a certain way, a definite reaction against the aggressor, followed by a collapse of the defensive system after the aggressor was made absent. The constant normality of the albumin (excepting on 8-14-56) calls attention, as it shows, that the hepatic injury was not very intense.

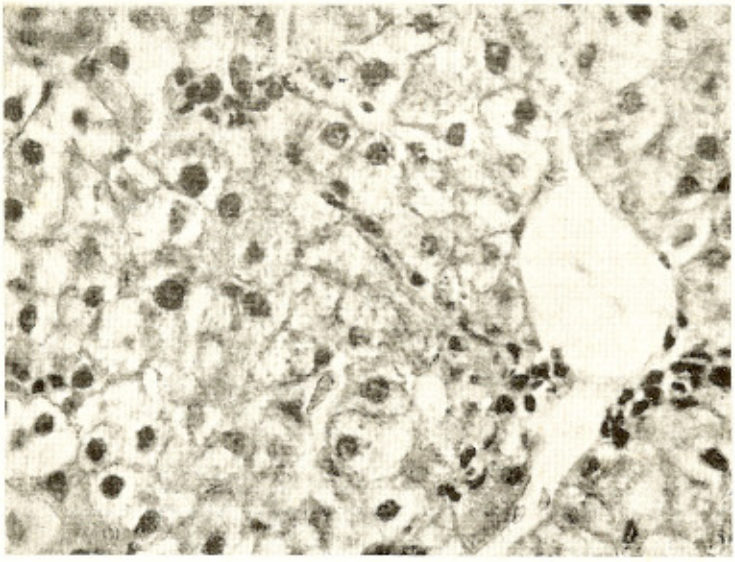

Fig. 1 — Showing small accumulation of mononuclear cells between the hepatic cells and around central vein. Some of the hepatic cells show hydropic degeneration.

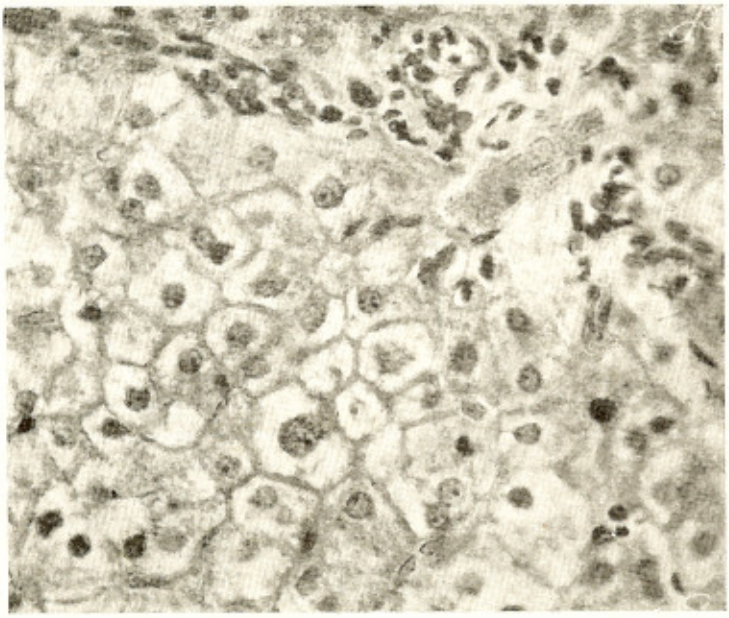

Fig. 2 — Hydropic degeneration of the hepatic cells; proliferation of the Kupffer cells and mononuclear infiltrate in the portal tract.

CASE II — I.O.B., Hospital number 96,043, 18 years old, white, male; barber; admitted on 8-30-1956.

He entered the hospital after fifteen days of disease characterized by swelling of the parotid glands and headache; seven days afterwards there was pain and swelling of the right testis accompanied by fever and dark urine. At admission he was well nourished, jaundiced, with fever and enlarged parotid glands; right orchitis was evident. His liver was enlarged, being palpable two fingers breadth below the costal margin; it was soft and not painful. The spleen was one finger breadth below the costal margin. No signs of meningitis or pancreatitis were present.

He left the hospital, for personal reasons, one day after admission and no liver function tests were performed. A liver biopsy, however, was obtained. The lobular architecture was maintained. There was infiltration of the portal fields by lymphocytes, the Kupffer cells being more prominent than in the previous case; they were arranged in lines and several nodular intrasinusoidal groups were observed. The hepatic cells were arranged in regular plates but a definite variation of its shape and volume was noted; the cytoplasm was scanty, granular, sometimes vacuolized; the nuclei varied in shape and volume, and were frequently piknotic; the brown granular pigment was again observed in their cytoplasms (Fig. 3).

CASE III — J.S.S., Hospital number 97,211, 16 years old, mulatto, male; industrial worker. Admitted on 1-17-1957.

For the last five days he had been complaining of fever, headache followed by painful enlargement of the right parotid gland and, after 24 hours, similar enlargement of the left parotid gland. Twelve hours before admission he felt a bitter taste in the mouth, digestion became difficult and he noticed darkened urines. At admission, on physical examination he was well nourished, and slightly jaundiced; both parotid glands were enlarged; the abdomen was not tense; the liver was palpable two fingers breadth below the costal margin and the spleen also palpable one finger breadth below it. No signs of testicular, pancreatic or meningeal involvement were present.

The laboratory tests performed revealed: serum proteins (total): 7.1 mg%; serum albumin 4.4 mg%. Thymol turbidity 10 units. Cephalin-cholesterol test: positive (+). Colloidal red test: positive (+). Serum bilirubins: total 0.3 mg%; one minute direct bilirubin 0.1 mg%. Bilirubin and urobilinogen in urine were negative. White blood cells: 12,600 per mm^3, relative neutropenia, lymphocytosis with atypical lymphocytes, anisocytosis. Complement-fixation test for mumps was positive 1/128.

A liver biopsy was done at admission revealing that the lobular architecture was maintained and the portal areas contained small round cell infiltration. There was marked hyperplasia of the Kupffer cells forming lines and small round accumulations. The hepatic cells were arranged in regular plates, their cytoplasm being dense and the small nuclei darkly stained, some of the nuclei were definitely piknotic, others vacuolized; a brown pigment was found in the cytoplasm in small amounts. Binucleated cells were also found (Fig. 4).

The jaundice cleared rapidly; the liver, the spleen and the parotids came to normal limits and he felt perfectly well when discharged from the hospital, nine days after admission.

CASE IV — I.C.P., Hospital number 98,352, 39 years old, mulatto, male, farmer; admitted on 6-14-1957.

He came from another hospital where he had been submitted to dilatation of the cardia for megaesophagus. The day before admission he woke up with painful enlargement of both parotid glands without fever. On physical examination he was a well nourished man without jaundice. The parotids were enlarged. The liver was palpable one finger breadth below the costal margin; the spleen was not palpable. No signs of testicular pancreatic or meningeal involvement were detected. On the third day after admission he became febrile, the enlargement

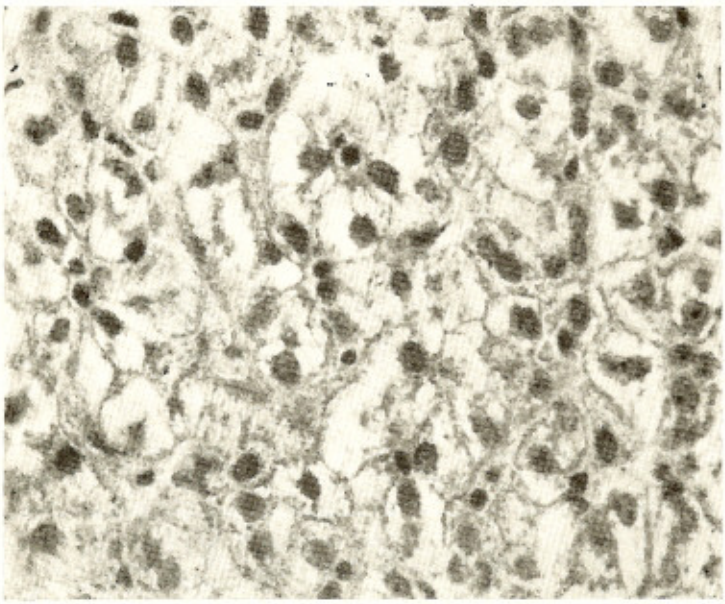

Fig. 3 — Note the extension of the hydropic degeneration and the proliferation of Kupffer cells.

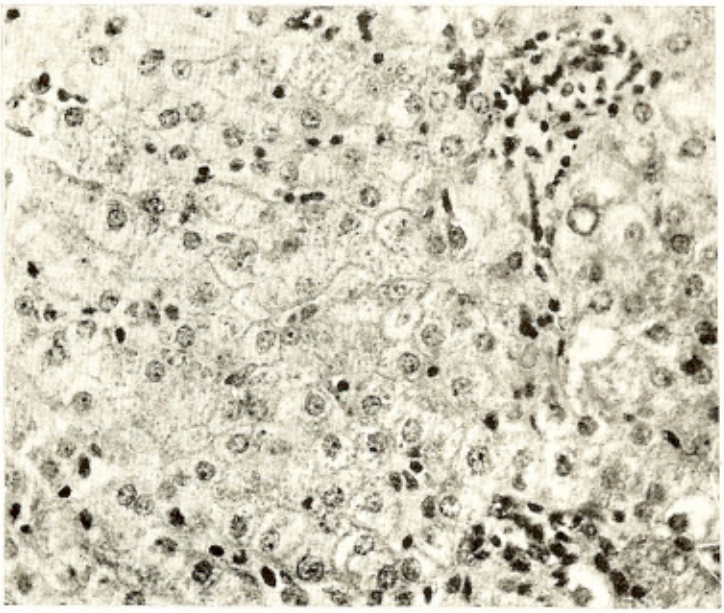

Fig. 4 — Proliferation of the Kupffer cells with focal accumulation of mononuclears in the inferior right corner.

of the parotids increased and at the same time there was painful enlargement on the left testis. After the symptoms and signs decreased he was discharged from the hospital, eleven days after admission.

Laboratory tests were done revealing: serum proteins 6.6 mg%; serum albumin 4.2 mg%; serum globulin 2.40 mg%. Thymol turbidity 4 units; cephalin-cholesterol test: positive (++); colloidal red test: negative; formol-gel test: negative; serum bilirubin: total 0.2 mg%; one minute direct bilirubin: negative; white blood cells: 6,200 per mm^3; anaeosinophilia; neutropenia; shift to the left; lymphocytosis with atypical lymphocytes. Complement fixation test for mumps: positive 1/128.

This patient never became jaundiced and there were no signs of hepatic involvement. Despite this, a liver biopsy was done on 6-12-1957, showing that the lobular architecture was maintained; the portal areas, central veins and hepatic cells appeared within the normal limits. The only change worth mentioning was a discrete hyperplasia of the Kupffer cells, rarely forming small intrasinusoidal nodules.

DISCUSSION

The four cases presented had typical clinical picture and evolution of mumps; besides, in two of them high titles of complement fixation for mumps were present. All the possible causes of enlargement of the parotid glands were carefully examined and excluded, specially in case IV, a patient with megaesophagus disease, condition in which non-inflammatory enlarged glands could be observed.

There was clinical and laboratory evidence of hepatic involvement in cases I, II and III, characterized by indigestion, jaundice, hepato and splenomegaly, accompanied by alterations of the liver function tests.

It was possible to exclude other causes of hepatic lesions as hepatotoxic agents, viral hepatitis, leptospirosis, obstructive and hemolytic jaundice an so on.

The clinical and laboratorial alterations suggesting liver involvement were accompanied by morphological alterations of the organ. They were basically characterized by hyperplasia of the Kupffer cells which appeared swollen, with large, darkly stained nuclei, slightly prominent in the lumen of the sinusoids; usually they arranged themselves in rows but rarely they accumulated themselves in small nodules within the sinusoidal lumen. In the nodules, similarly to what happens in the "residual nodules" of the viral hepatitis, lymphocytes were also present [3]. In sharp contrast with the findings in viral hepatitis [3] and in mononucleosis [15] the portal areas showed only small numbers of scattered mononuclear cells. The central veins were normal in size and aspect and the sinusoids narrowed. The hepatic cells were orderly arranged in plates but some variation in size and shape was observed; in some the cytoplasm was vacuolized, in others it was granular; their nuclei were round, with slight variations in volume, definitely piknotic nuclei being observed. In cases I, II and III, a brown granular pigment was observed in the cytoplasm of the hepatic cells usually near its biliar pole; it was definitely brown and glossy in appearance. In case I, where two biopsies were performed, the second one showed greater pigmentation, and a similar pigment was found in the enlarged Kupffer cells.

Due to the variation in size and shape of the hepatic cells nuclei and the hyperplasia of the Kupffer cells, in low power, one has the impression of hypercellularity and slight desorganization of the liver tissue similar to the picture seen in viral hepatitis; the cellular infiltration of the portal areas, however, is not present.

The changes mentioned above can be interpreted only as non specific signs of hepatic involvement. But despite their lack of specificity, they are clearly and definitely present pointing to involvement of the liver mainly characterized by intralobular reticuloendothelial hyperplasia not accompanied by equivalent alterations in the portal fields.

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These definite but non specific morphological changes were accompanied by clinical and laboratorial evidences of liver involvement of the type seen in mild hepatitis. The alterations were, however, rapidly reversible.

Considering the paucity of information from literature and the small number of our cases, we are not in a position to arrive to conclusions. The field is open to further investigations and our aim, in this paper, is to call attention to the possible role that the virus of epidemic paratitis may have in producing acute and perhaps chronic liver disease.

SUMÁRIO

Comprometimento hepático no decurso da parotidite epidêmica (caxumba). Estudo clínico, laboratorial e histopatológico de 4 casos.

Depois de cuidadosa revisão da literatura, limitada apenas a poucos e inconcludentes trabalhos, chegam os autores à convicção de que o acometimento do fígado, no decurso da parotidite epidêmica virósica, ou é realmente bastante raro ou não tem merecido a devida observação por parte dos estudiosos.

Relatam, a seguir, 4 casos observados no Hospital de Isolamento "Emílio Ribas" (Secretaria da Saúde Pública e da Assistência Social, São Paulo, Brasil), os quais, além dos elementos clínicos e laboratoriais comprobatórios do diagnóstico de caxumba, exibiam também concomitantes aspectos clínicos e laboratoriais de comprometimento parenquimatoso do fígado, atribuíveis à própria virose. Os estudos histopatológicos de amostras de fígado, obtidas por punções-biopsias, permitiram confirmar a existência de alterações estruturais do órgão, caracterizadas bàsicamente pela hiperplasia dos elementos retículo-endoteliais, com discreta infiltração linfocitária dos espaços porta; as células hepáticas, se bem que mantidas em lâminas ordenadas, mostraram variações de forma e volume, com alterações nucleares, citoplasmáticas e deposição de pigmento. As lesões encontradas evidentemente não configuram um quadro característico, mas traduzem, sem dúvida, um comprometimento hepático, imputável ao vírus da caxumba, e representado pela hiperplasia do SRE e por discretos processos degenerativos celulares.

Concluem os autores que o assunto demanda ulteriores pesquisas, que poderão pôr à prova a capacidade de agressão hepática do vírus da caxumba, e realçam a possibilidade de que esta virose possa ser o eventual agente de hepatopatias agudas, leves e muitas vêzes despercebidas, talvez responsáveis por quadros crônicos futuros.

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