Acute hepatitis due to Herpes simplex virus in an adult

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SYNOPSIS A case is described of herpetic hepatitis in a pregnant woman with primary herpetic stomatitis. Intranuclear inclusion bodies and virus particles were found in hepatocytes, and herpes virus was isolated from a liver biopsy and from oral swabs but not from blood. From rising titres of neutralizing and complement-fixing antibody it is concluded that the oral infection was a primary one. Factors predisposing to the hepatitis are discussed.

Acute hepatitis due to the virus of Herpes simplex does not appear to have been hitherto reported in adults, though the condition has been well described in infants, in whom it presents as an acute fatal infection occurring soon after birth. It has been reported in older children (up to the age of 5) who were suffering from kwashiorkor (malnourishment) by Becker, Naude, Kipps, and McKenzie (1963) and by Kipps, Becker, Wainwright, and McKenzie (1967). We describe below a case in a pregnant woman in whom the diagnosis was established by liver biopsy and virus isolation. She survived the infection.

CASE REPORT

A 24-year-old housewife was admitted on 10 May 1965 to the East Birmingham Hospital in the 28th week of her second pregnancy. She had been in good health until seven days before her admission when she began to vomit and at the same time complained of sore throat and mouth, constipation, backache, and anorexia. For this she was given oral tetracycline and trifluoperazine (Stelazine). Her condition deteriorated rapidly on the day of admission when her doctor found her dehydrated, jaundiced, and collapsed.

On admission she was collapsed and stuporous with a temperature of 100.4°F, pulse rate 144, blood pressure 135/70 mm Hg. Positive physical findings were severe herpetic ulceration of the mouth and fauces, slight icterus, and a uterus enlarged to the size of a seven months' pregnancy. The faeces were pale. On the negative side there were no localizing signs in the central nervous system, the liver and spleen could not be felt, and rectal examination was negative.

Preliminary investigation showed a white blood count of 7,500 with 5% myelocytes and 3% metamyelocytes.

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There were occasional nucleated red cells, and platelets were reduced to 80,000. Marrow puncture excluded the possibility of leukaemia, the picture being quite normal.

The possibility of hepatitis was suggested by our colleague Dr Felix-Davies, and as it seemed important to know the liver histology he was asked to do a liver biopsy: steroids might well have been beneficial if this were an acute yellow atrophy but would be contraindicated for herpetic hepatitis. Histological examination of frozen sections of this biopsy showed small intranuclear inclusions in hepatocytes surrounding small areas of necrosis. The appearances were strongly suggestive of herpetic hepatitis.

The correct diagnosis was therefore made within 24 hours of the patient's admission and it was decided to treat her primarily by adjusting the electrolyte and fluid balance using intravenous fluids, including an adequate calorie intake in the form of fructose. She also received ampicillin six hourly, nystatin and gentian violet for her mouth, and 500 mg of gamma globulin on 12 May.

The blood urea level fell from 105 to 12 mg/100 ml in five days, gradually rising to 25 on the last estimation. Alanine aminotransferase (SGPT) (E.C. code no. 2.6.1.2.) fell from 220 to 40 R.F. u/ml serum in four days, rising to 95 on the 14th day, perhaps due to absorption from the dead foetus. Bilirubin similarly fell from 6-8 mg/100 ml serum, the level on admission. The primitive white cell count reached a maximum of 15% of circulating leucocytes on the second day and 6% of all circulating nucleated cells were normoblasts. A further liver biopsy on 20 August showed normal histology.

The patient's clinical course was equally dramatic and after being desperately ill for three or four days she steadily improved and was delivered of a macerated foetus on 2 June. When seen in the Out-patient Department six weeks after admission she was in normal health, the lesions in the mouth having recovered completely.

Since then she has given birth after a normal pregnancy to a normal child.
HISTOLOGICAL EXAMINATION OF THE LIVER BIOPSY

METHOD The liver biopsy was fixed in 6% glutaraldehyde in M/30 cacodylate buffer, pH 7-2, for two hours. After fixation, some pieces which appeared abnormal to the naked eye were cut into pieces not more than 1 mm cube, further fixed in Caulfield’s osmic tetroxide solution, and embedded in methacrylate-styrene (Kushida, 1963). Sections were stained with uranyl acetate and lead citrate and examined in the electron microscope. Sections were also cut for conventional histology after freezing for fat stains, or, after embedding in paraffin wax, were stained with haematoxylin and eosin for reticulin.

RESULTS The biopsy specimens were found to contain several areas of necrosis approximately 1 mm diameter (Fig. 1). The surviving liver cells showed cloudy swelling and, in the frozen sections, many globules staining with Scharlach R. Nuclei of some liver cells among those surviving immediately around the areas of necrosis, but not elsewhere, were shrunken and full of eosinophilic material, the chromatin being concentrated around the nuclear membrane (Fig. 2). Classical intranuclear inclusions of Cowdry’s type A, with a clear space between the inclusions and the nuclear membrane, were not seen. The reticulin framework of the liver was intact both in the areas of necrosis and in areas of surviving liver cells, suggesting that the necrosis was recent. The areas of necrosis were densely infiltrated with polymorphonuclear cells, and mononuclear cells were also fairly numerous.

Sections examined by electron microscopy were found to contain numerous cells whose cytoplasm contained many empty spaces, presumably where fat globules had been dissolved during preparation but which were otherwise comparatively normal. Cells whose cytoplasm was similarly vacuolated but in which the mitochondria appeared swollen were also seen (Fig. 3). Many mitochondria appeared also to have lost their cristae, or contained small and irregular cristae (Fig. 4). Dense osmiophilic 'myelin type' figures were also found in the cytoplasm of many cells. In some cells the mitochondria were seen to contain a peculiar dense longitudinal bar of osmiophilic material (Fig. 5); no obvious sub-

**FIG. 1.** Sections of liver biopsy. An area of necrosis in the lower right hand corner is bounded by a zone of infiltration with polymorphonuclear cells and macrophages. × 100; haematoxylin and eosin.

**FIG. 2.** Intranuclear inclusions in cells at the margin of the liver lesion. The chromatin lines the nuclear membrane, and the nuclei are full of eosinophilic material. × 1,500 haematoxylin and eosin.
structure could be detected in these. It did not seem probable that this was a fixation or cutting artefact because mitochondria not so affected were found in the same cells. The laminar or linear crystalline structures sometimes found in mitochondria of normal human liver cells (Mugnaini, 1964) were not seen; the sections were thin enough to have enabled such structures to be detected.

In all the liver cells not obviously very severely damaged large numbers of granules presumed to be glycogen were found in the cytoplasm (Fig. 5).

Prolonged searching was required to find cells containing particles identifiable as herpes-type viruses. These cells were found to be shrunken, with dense cytoplasm (Fig. 6). The nuclei contained uniformly finely fibrous or granular material, in which were embedded virus elementary bodies—the 'single-membrane' type of particle usually found in herpes-infected nuclei (Fig. 7). The oval shape seen in the micrograph is an artefact caused by compression during cutting of the sections.

No virus particles of the 'double-membrane' type could be found in the cytoplasm of the infected cells.

VIROLOGICAL INVESTIGATIONS

METHOD Smears of scrapings taken from the base of ulcers, left where vesicles in the mouth had ruptured, were stained by haematoxylin and eosin. Numerous Tsanck cells characteristic of infection by viruses of the herpes group were found.

Scrapings from mouth lesions, homogenized fragments of liver biopsy, and blood (both as homogenized clot and serum) were inoculated into tissue cultures of human amnion, human fibroblasts, HeLa cells, and monkey
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RESULTS

Herpes simplex virus was isolated with ease from the scrapings from the mouth lesions, causing confluent pocks to appear on the chorioallantoic membranes. Herpes virus was also isolated from homogenized liver biopsy in human amnion cultures but not in monkey kidney, HeLa or human fibroblast cultures; no virus could be isolated from whole blood, buffy coat, serum, or cerebrospinal fluid.

One sample of serum taken the day after admission contained no detectable complement-fixing or neutralizing antibodies for Herpes simplex virus. Serum taken 14 days after admission had a complement-fixation titre of 1:64 and a neutralizing titre of 1:8 against 100 pock-forming units of Herpes simplex virus; serum taken five months after admission had a complement-fixation titre of 1:256 and a neutralizing titre of 1:256 against 100 TCD₅₀ of Herpes simplex virus, and produced four lines of precipitation against herpes virus antigens on a gel diffusion plate; these lines gave a reaction of identity with similar lines produced by the same antigen with a rabbit hyperimmune serum. (We are indebted to Dr D. H. Watson for performing the gel diffusion test.)

DISCUSSION

Generalized visceral Herpes simplex infection of neonates is familiar to most pathologists. The multiple focal necroses of the liver found in infection at this age have however rarely been found in older children, and then have been reported only

FIG. 4. Cytoplasm of a liver cell showing loss of cristae in mitochondria. An inflammatory cell is seen in contact with it. × 15,600; lead citrate.
in cases of eczema herpeticum (at the age of 1 year) or in cases of malignant malnutrition (kwashiorkor) up to the age of 3, or perhaps 6, years. We have been unable to find any published reference to disseminated multifocal *Herpes simplex* hepatitis in an adult. The appearance of the condition in children suffering from kwashiorkor suggests that some preexisting biochemical disorder or deficiency makes the liver more susceptible to herpes virus infection.

In our patient three factors all tending to liver damage were present: (1) hyperemesis gravidarum, (2) tetracycline therapy, and (3) Stelazine therapy.

The first is a well known cause of liver failure and needs no discussion. Tetracycline is well known as a cause of liver damage and jaundice when given parenterally, especially in pregnancy, though it is usually regarded as safe in this respect when given by mouth (Dowling and Lepper, 1964; Kunelis, Peters, and Edmondson, 1965; Schultz, Adamson, Workman, and Norman, 1963). In combination with the other stresses it may nevertheless have made its contribution to liver susceptibility even though given orally to this patient. Cases of jaundice associated with the administration of Stelazine have been rarely reported (Kohn and Myerson, 1961) but the remarks about tetracycline are perhaps applicable here also.

The evidence for the herpetic aetiology of the liver lesions is: 1 The histological nature of the lesions, which resembled those of neonatal herpetic hepatitis both in their size and distribution, and also in the presence of inclusions in the cells around areas of necrosis. 2 The findings by electron microscopy of particles morphologically indistinguishable
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from *Herpes simplex* virus in the nuclei of liver cells, and the presence within the nuclei of the changes associated with herpes virus infection. 3 The isolation of *Herpes simplex* virus from the liver biopsy. In primary *Herpes simplex* virus infection viraemia occurs, and it might be argued that the liver contained some blood and thus might contain virus; but attempts at isolation of herpes virus from blood taken at the same time as the liver biopsy were unsuccessful, although the volume inoculated was much greater than could have been present in the biopsy. The tissue, therefore, presumably did contain viable virus.

In infants dying of generalized visceral herpes infection, necrotic foci are usually found in the brain as well as in the abdominal viscera. Although we have no direct evidence of herpetic encephalitis in this patient (attempts to isolate virus from cerebrospinal fluid were unsuccessful) her degree of stupor on and shortly after admission seemed out of proportion to the extent of the biochemical derangement. Electroencephalographic examination in convalescence showed some abnormality but did not afford conclusive evidence of encephalitis. The evidence of viral encephalitic infection is therefore insufficient to establish that this probably occurred.
FIG. 7. Herpes-type particles within the nucleus of an infected liver cell. × 90,700; lead citrate.

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