DISSEMINATED HERPES SIMPLEX INFECTION*

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Infection with herpes simplex virus usually manifests clinically as vesicular lesions localized to the epithelial surfaces of the lips, face and mouth and, less frequently, the genitalia.

Dissemination in internal organs has been described by several authors (Table I).[1-11]

AUTOPSY FINDINGS IN HERPES SIMPLEX

Sixteen cases of disseminated herpes simplex virus infection have been seen at autopsy in Cape Town over a period of 18 months. These are summarized in Table II. Eight of these cases, together with the morbid anatomy and histology of the lesions, have been reported elsewhere.[12]

None of these cases were in newborn infants. Fifteen of them were from 9 to 34 months of age and 1 was 2½ months old. All save 1 were obviously malnourished. All these deaths occurred in non-European children. In 10 cases the liver lesion was macroscopic and in 4 microscopic, while in 2 cases no liver lesions were seen. The adrenal lesions, where present, were microscopic. In 1 case lung lesions due to herpes simplex virus were found. Other factors which possibly contributed to death are listed in the last column of Table II.

Oral Lesions

Lesions in the mouth and tongue are often masked clinically by becoming confluent and very extensive. The lesions are basically superficial ulcers with nuclear inclusions in the epithelial cells at the margins of the ulcers. Multinucleate giant cells, often with intra-nuclear inclusions, are not infrequently shed into the necrotic debris in the area of the ulcer. These giant cells are most characteristic and are found in only 3 conditions, viz. herpes simplex infection, herpes zoster and varicella.

The lesions frequently extend to involve the pharynx and oesophagus, and, while generally ulcerative in type, are occasionally hypertrophic, presenting as yellow nodules which

* Paper presented at the 42nd South African Medical Congress (M.A.S.A.), East London, C.P., September - October 1959

consist histologically of a coagulum of nuclear debris and fibrin.

Liver Lesions

The oral lesions may well be the result of spread by continuity, but the macroscopic hallmark of disseminated herpes simplex infection is the liver lesion (Fig. 1). The lesion in the liver, consisting of small white foci of necrosis with a haemorrhagic halo, is pathognomonic and is seen in no other condition of which we are aware. The foci may vary in size, presumably with age.

Histologically the necrotic foci are infarct-like in character in that both parenchyma and stroma are equally destroyed. Usually only nuclear remnants are visible in the centre together with red cells, lying free in an area of necrosis, or, in older lesions, in a lake of haemolysed red cells. These areas merge abruptly into surviving liver parenchyma where the only abnormalities are in the cell nuclei. There is no evidence of inflammatory reaction or proliferation of liver cells but there is some dilatation of sinusoids around the lesion.

Nuclear inclusions are prominent in the liver and take on different forms. It is suggested that these may only be stages of development of the virus within the cell nucleus. The inclusions are either single uniform eosinophilic bodies filling the distorted and swollen nucleus, or multiple small eosinophilic bodies. At some stages, under oil immersion magnification, these eosinophilic bodies appear to be set in a basophilic matrix. Sometimes a clear halo separates the inclusion from the disintegrated chromatin network which has become marginated on the inner aspect of the nuclear membrane; this being frequently distorted.

Lesions in Other Organs

In the adrenal glands foci of necrosis, basically similar to those in the liver, are seen in both cortex and medulla. In none of our cases have these lesions been macroscopic. Nuclear inclusions are present but not with the frequency or variation in form seen in the liver.

In one case lesions, which it is believed can be attributed to the herpes simplex virus, were seen in the epithelial cells lining the bronchi and trachea. The same basic pattern of necrosis was evident. In one case also there was an encephalitis. Lesions in other organs were not seen in our cases.

Virus Studies

Virus studies were carried out on organs removed at autopsy in 6 cases (Table III). In case 16 the virus was isolated from the blood taken before death. This represents one of the few instances where the virus of herpes simplex has been isolated from the blood stream. Virus isolations were carried out by Dr. W. Becker in the CSIR and UCT Virus Research Unit of the Department of Pathology at the University of Cape Town.

DISCUSSION

No concrete explanation can be given for the frequently occurring cases of disseminated herpes simplex virus infection in our autopsy material. Nearly all the cases seen have been in severely malnourished children and it may well be that there is either lack of some vital protective mechanism in these cases, which permits of dissemination of the virus, or the altered cellular metabolism in these cases may render the cells of internal organs more accessible to circulating virus. Much investigation remains to be done on this score, but in conclusion attention should be focused on the macroscopic liver lesion, which is the morbid anatomical hallmark of disseminated herpes simplex virus infection.

TABLE I. DISSEMINATED HERPES SIMPLEX—AUTOPSY FINDINGS IN VARIOUS SERIES

Author	*Lesions*	*No. of cases*	*Virus isolated*
Hass[1]	Lesions in adrenal and liver, herpetic origin mooted	1 neonate	No
Wildi[2]	Encephalitis	1 neonate	Keratitis in rabbits
Smith *et al.*[3]	Encephalitis	1 neonate	Yes
Florman and Mindlin[4]	Encephalitis	1 neonate	Yes
Quilligan and Wilson[5]	Hepatic necrosis	1 neonate	Yes
Zuelzer and Stulberg[6]	Hepatic necrosis	8 cases (6 neonates, 2 older)	In one case
France and Wilmers[7]	Hepatic necrosis	2 neonates	No
Pugh *et al.*[8]	Hepatic necrosis	1 neonate	Yes
Williams and Jack[9]	Hepatic necrosis	2 neonates	In one case
Brain *et al.*[10]	Hepatic necrosis	1 neonate	Yes
Zuelzer and Stulberg[6]	Adrenal necrosis	Some of 8 cases	In one case
Williams and Jack[9]	Adrenal necrosis	2 neonates	In one case
Brain *et al.*[10]	Adrenal necrosis	1 older child with infantile eczema	Yes

Subsequent to the presentation of this paper a further neonate case was described by Bird and Gardener.[11] There were liver and adrenal lesions and the virus of herpes simplex was isolated from organs at autopsy.

TABLE II. AUTOPSY FINDINGS IN 16 CASES OF DISSEMINATED HERPES SIMPLEX

Case	*Race and sex*	*Age*	*Hepatic necrosis*	*Adrenal necrosis*	*Nutritional state*	*Other findings*
1	C.M.	12 mths	Microscopic	Microscopic	Kwashiorkor	Small intra-alveolar haemorrhage
2	C.M.	11 mths	—	Microscopic	Kwashiorkor	Intra-alveolar haemorrhage in lung and small abscesses
3	C.M.	16 mths	Macroscopic	Microscopic	Kwashiorkor	—
4	C.F.	12 mths	Macroscopic	—	Marasmus	Broncho-pneumonia and fibrinous pleurisy
5	C.F.	12 mths	Macroscopic	Microscopic	Kwashiorkor	Hyperosmolaric
6	C.M.	34 mths	Macroscopic	Microscopic	Marasmus	Bronchopneumonia
7	N.M.	15 mths	Macroscopic	Microscopic	Marasmus	Bronchiolitis
8	C.M.	9 mths	Microscopic	Microscopic	Kwashiorkor	Encephalitis
9	C.M.	15 mths	Microscopic	Microscopic	Normal—slight fatty liver	—
10	C.F.	12 mths	Macroscopic	—	Kwashiorkor	—
11	C.F.	2½ mths	Microscopic	—	Marasmus	Herpetic lung lesions. Hyperosmolaric with sagittal sinus thrombosis
12	C.M.	25 mths	Macroscopic	Microscopic	Marasmus	—
13	C.M.	15 mths	—	Microscopic	Kwashiorkor	Bronchiolitis and bronchopneumonia
14	C.F.	10 mths	Macroscopic	Microscopic	Marasmus	—
15	N.M.	14 mths	Macroscopic	Microscopic	Malnourished	Pneumococcal meningitis
16	C.M.	18 mths	Macroscopic	Microscopic	Kwashiorkor	—

C=Coloured, N=Native, M=male, F=female.

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Fig. 1. Macroscopic liver lesions in disseminated herpes simplex.

SUMMARY

Autopsy findings in 16 cases of disseminated herpes simplex infection are listed. Virus studies were carried out on 6 of these cases. Attention is drawn to the striking macroscopic appearance of the liver.

TABLE III. VIRUS ISOLATION

Case No.	*Specimen examined*	*Virus isolation*
7	Liver	Positive.
10	Liver	Positive.
	Spleen	Positive.
	Lung	Positive.
	Heart, tongue, kidney, adrenal, brain and blood	Negative.
12	Liver	Positive.
	Spleen	Positive.
	Lung	Positive.
	Adrenal	Positive.
	Large bowel mucosa.	Positive.
	Tongue mucosa	Positive.
	Blood, heart, brain and kidney	Negative.
14	Liver	Positive.
15	Liver	Positive.
	Spleen	Positive.
16	Liver	Positive.
	Spleen	Positive.
	Lung	Positive.
	Adrenal	Positive.
	Tongue mucosa	Positive.
	Small bowel mucosa.	Positive.
	Oesophageal mucosa	Positive.
	Brain	Positive.
	Myocardium	Positive.
	Kidney	Positive.
	Blood	Positive.

Thanks are due to Mr. B Todt for the photograph and to Dr. J. W. Mostert, Superintendent of the Red Cross War Memorial Children's Hospital, for permission to publish these cases.

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