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Fatal Disseminated Herpes Simplex Virus Infection in Malnourished Infants*

Keriman Tınaztepe, M. D. / Ümit Saatçi, M. D.*****
Behçet Tınaztepe, M. D.** / Hamdi Öğüş, M. D.******

Primary herpes virus infection is fairly common and the majority of cases are asymptomatic.[1] In infants and children symptomatic primary infections usually present themselves as acute gingivostomatitis, primary herpetic dermatitis, eczema herpeticum keratoconjunctivitis and occacionally as a generalized disease and encephalitis.[2-4] As it is known, the generalized form usually occurs in neonates or in children with an underlying disease. In such instances, little is known about the factors which contribute to the fatal outcome.

In 1967, the largest series consisting of 92 cases of disseminated herpes simplex infection beyond the new-born period was reported from Africa by Kipps et al.[5] In this series 68 % of the cases showed associated severe malnutrition. These authors also pointed out that severe malnutrition and/or kwashiorkor was previously present in the patients and diseases such as measles and purulent meningitis were predisposing factors in the development of the generalized herpetic infection. In this series the diagnosis was confirmed by virological investigation in 33 cases, while in the remaining 60, the diagnosis depended on clinical signs and histopathological changes found on post-mortem examination.

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Professor of Pediatrics and Pediatric Pathologist.
*** Associate Professor of Pediatrics.
**** Professor of Pathology.
***** Resident in Pathology.

On morphological grounds, it seems pathognomonic that the virus may be the cause of the characteristic lesions in the viscera. These typical findings consist of focal necrosis with intranuclear inclusions in various internal organs such as the liver and/or adrenals. The purpose of this communication is to present two cases of fatal generalized herpes virus infection beyond the new-born period seen at Hacettepe Children's Hospital, in which the diagnosis was based on histopathological findings of post-mortem studies. The presented cases also showed central nervous system involvement as an herpetic encephalitis and kwashiorkor as an associated condition. To the best of our knowledge this is the first report of such an association in Turkey.

Case Reports

Case 1: (U. T. 68/48190) : A one year old female patient was admitted to Hacettepe Children's Hospital with complaints of diarrhea and vomiting, swelling of the body and ulcers in the mouth. The diarrhea and vomiting started a month prior to admission followed by swelling of the body. Three days before admission she suffered from a sore mouth. Her past history revealed measles and chicken-pox at six months of age. She had not been given any of the usual immunisations. She was being breastfed and given juice from food eaten at home, rice flour mixed with sugar and water were added to the diet. She could sit but not walk. The family history was not remarkable. Physical examination revealed: Weight 5,400 kg., height 70 cm., temperature 38°C, respiration 36 per minute, pulse rate 140 per minute. Her general condition was poor, subcutaneous fat tissue was decreased, the hair was dry, fontanelle was open 1x1.5 cm., the tongue, oral mucosa, and palate were covered with ulcers. Scleras were icteric. The findings in respiratory and circulatory systems were not remarkable.

The edge of the liver was 5 cm. below the costal margin, the spleen was not palpable and there was oedema in the four extremities. Laboratory findings: Hb was 7.20-10.80 gm. %, white blood cells 14,400 per mm^3 with increased neutrophils. Urinalyses showed one plus protein, in the sediment there were 5-6 erythrocytes, and 3-4 leucocytes. NPN: was 41 mg%, blood sugar 43 mg% and blood electrolytes were within normal limits. Total blood protein was 4.2 gm%, with albumin of 2.3 gm %, total biluribin was 2 mg% (direct being 1.4 mg), SGOT 150 U, SGPT 123 U, thymol 8 U, serum electrophoresis was normal. PPD was negative. The cultures of blood and cerebrospinal fluid yielded no growth. Throat and stool cultures were normal. The patient was given intravenous fluid and antibiotics in the

forms of penicillin, ampicillin, mycostatin. Her clinical diagnoses were that of kwashiorkor, moniliasis, gastroenteritis and sepsis. Convulsions, hematemesis and melena were observed during the treatment of the case. Although the convulsions in the patient were partly controlled by anticonvulsive treatment, her general condition worsened and the patient died four days after admission. At necropsy, generalized jaundice and oedema were found. Numerous ulcerations were present in the mouth including the palate, tongue and oesophagus. The most striking findings were the disseminated pin-head sized yellowish grey areas in the liver. They were less prominent in the adrenals. (Figure 1). There was hepatomegaly, the liver weight being 350 gm. (normal weight for this age is 261 gm.). Thymus was atrophic and there was a moderate degree of oedema of the brain.

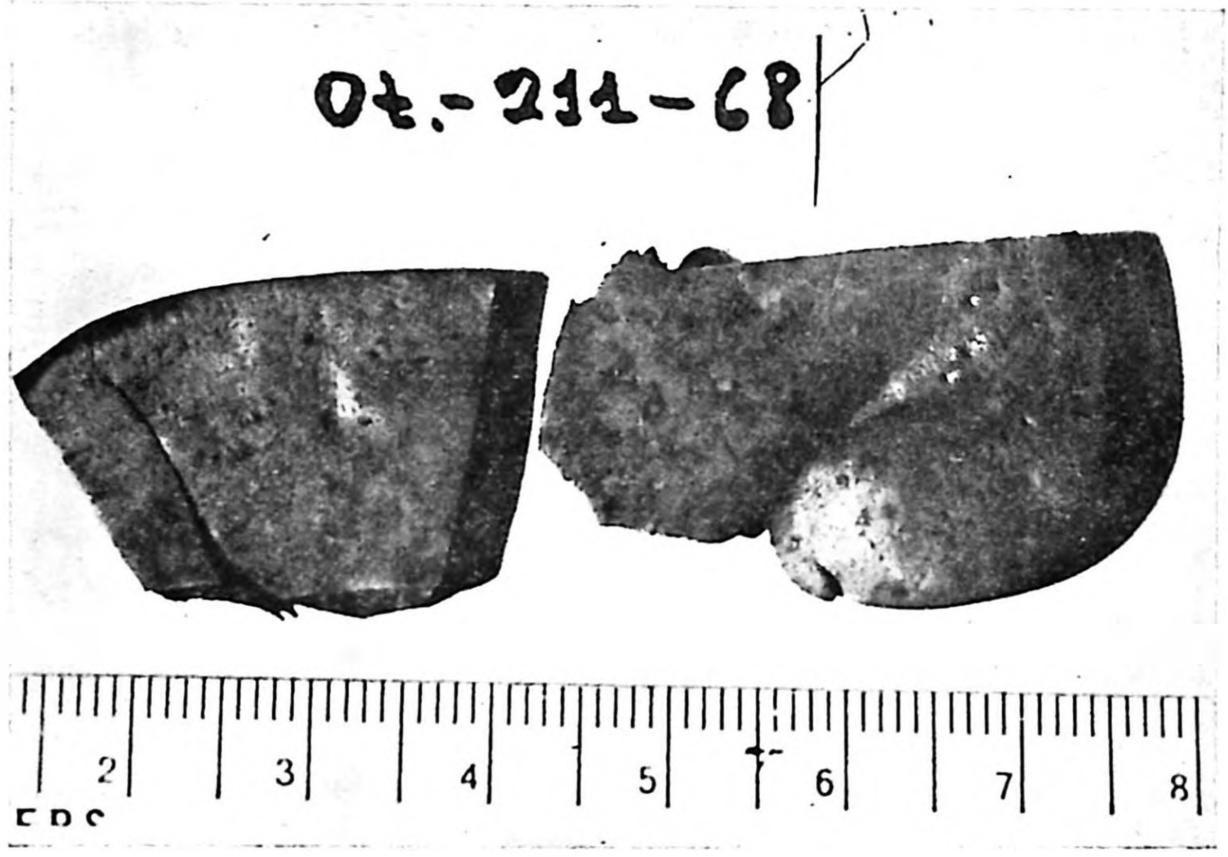

Figure 1
A piece of liver showing pin-head sized pale mottlings on both the capsuler and cut surfaces.

Microscopic examination revealed diffuse marked fatty metamorphosis of the liver. In addition to this, macroscopically observed mottlings in the liver were found to be areas of coagulation necrosis, some of which were surrounded by hemorrhage. (Figure 2). In the hepatic cells at the periphery of necrotic areas, eosinophilic stained intranuclear

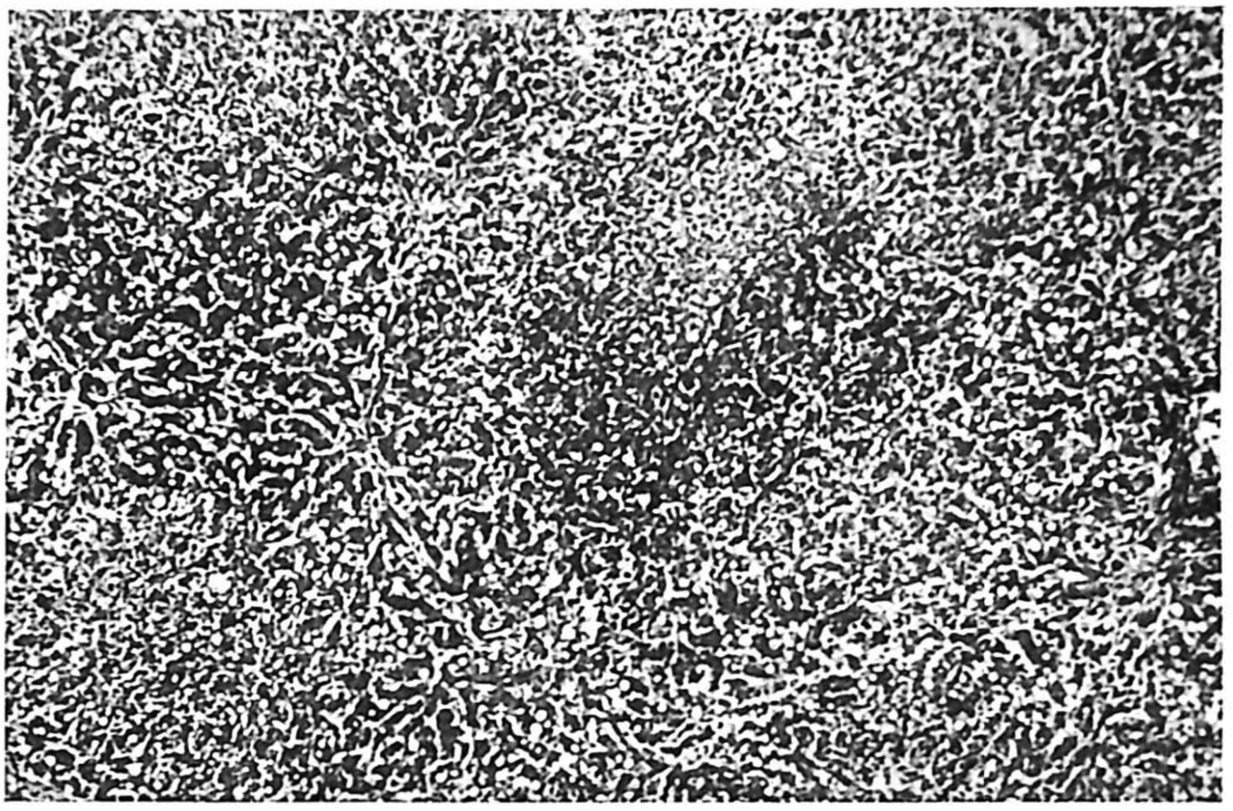

Figure 2
Under the medium power magnification in the center, liver is showing necrosis surrounded by hemorrhage. Rather diffusely distributed vacuoles in the hepatocytes are present (Fatty metamorphoses). (Hand E. 150 x).

inclusions were found. (Figure 3). Similar lesions were also present in the adrenals. At the periphery of the areas showing ulceration in the tongue, pharynx and oesophagus, balloon degeneration and vesicle formation of the surface epithelium were found. (Figure 4). In these vesicles multinucleated giant cells and desquamated epithelial cells bearing eosinophilic intranuclear inclusions were present. The central nervous system findings consisted of diffuse oedema, occasional minimal perivascular infiltration in the subcortical areas, neuronophagy, and some glial cells showing intranuclear inclusions. The pancreas revealed atrophy and cystic dilatation of some of the acini with inspissated pink material in their luminae. Atrophic thymus showed rare Hassal's corpuscles in contrast to the usual involutional changes.

Case 2 : (D. A 68/21744). A ten month old male infant was admitted to Hacettepe Children's Hospital with complaints of diarrhea, vomiting, coughing and fever. His history revealed the onset of diarrhea and fever to be one week before admission, the presence of coughing and vomiting for the three days prior to admission. He had pneumonia when he was four months old. Polio and BCG vaccinations were given before six months of age. He was being breast fed with the occasional addition of juice from home

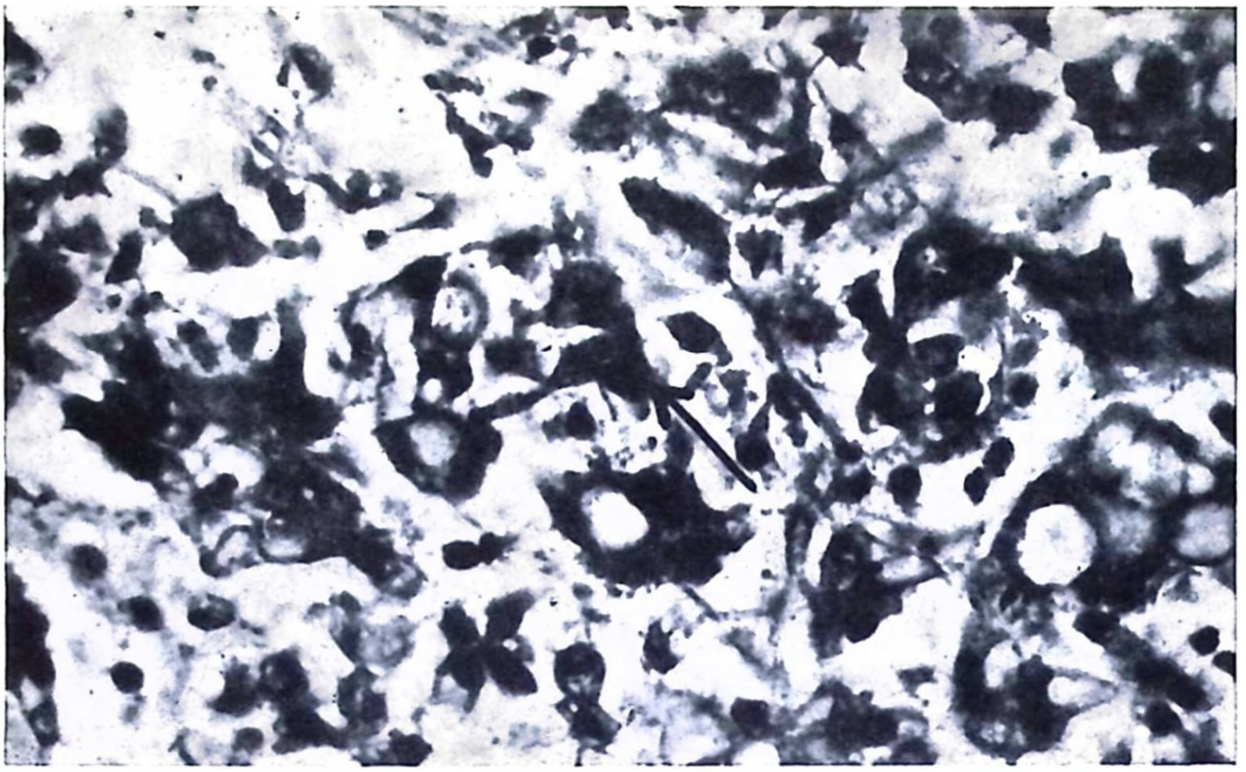

Figure 3

Under the high magnification, intranucleer inclusion are seen in the hepatocytes. Hand E. 500 x.

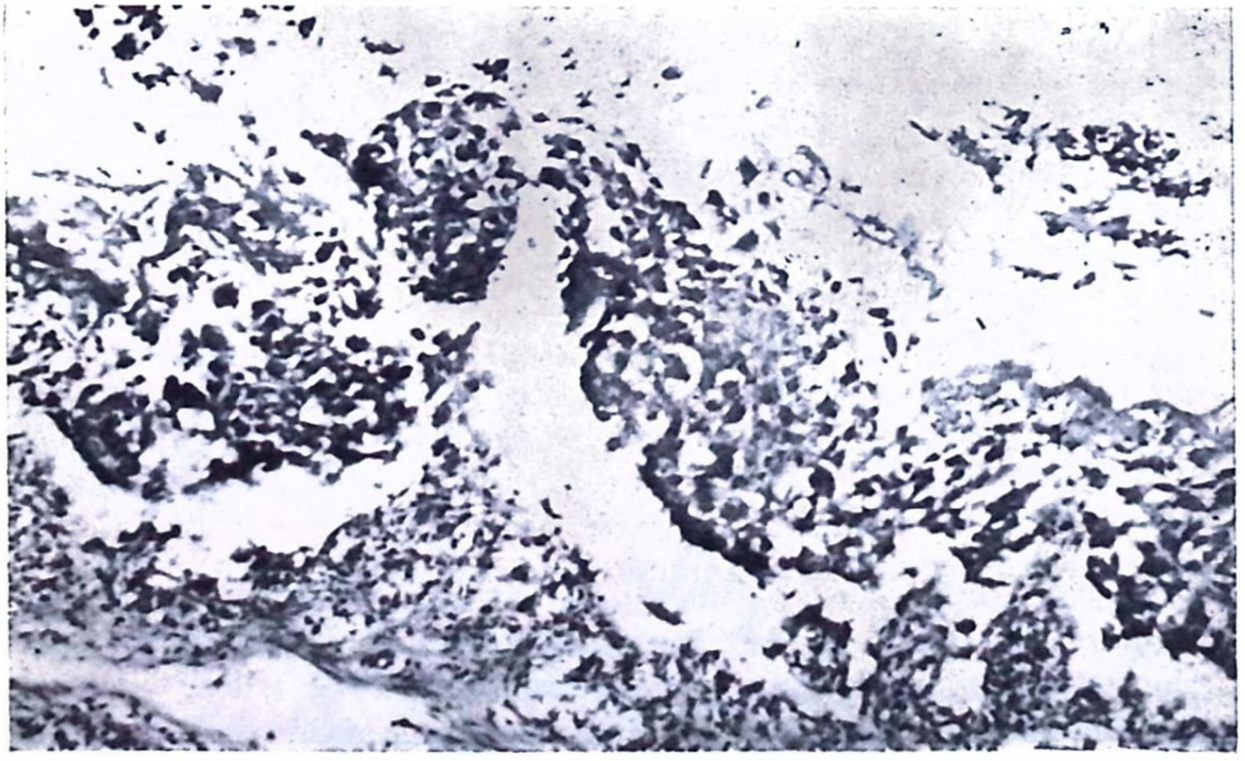

Figure 4

Vesicle formation is present in the mucosa of the esophagus. There is balloon degeneration of the surface epithelial cells, some of which are showing intranuclear inclusion. Hand E. 160 x.

food. The patient was able to sit and had two teeth. Physical examination revealed a temperature of 36.8°C, pulse rate of 116 per minute, respiration 30 per minute, height 70 cm., weight 6,300 gm. The fontanelle was open and depressed. Two upper incisors were present. The throat and both ear drums were hyperemic. The findings of the respiratory and circulatory systems were not remarkable.

The liver was 3 cm. below the costal margin. The spleen was nonpalpable, there was generalized edema. Other system findings were within normal limits.

Laboratory examination: Hb: 14.55 - 11.12 gm %, in differential count neurophils were dominant. Urinalysis revealed no abnormalities. Biochemical findings were as follows: NPN: 54 mg., blood electrolytes: CO_2: 6.9 - 18.83 mEq/Lt, Na: 118 - 134 mEq/Lt. K: 3-4.3 mEq/Lt, and Cl: 83-105 mEq/Lt, PPD negative. Stool culture and throat cultures yielded no pathogenic organisms. There was no growth in the blood culture. The patient was given intravenous fluid penicillin chloramphenicol with the clinical diagnosis of acute, gastroenteritis, otitis media and malnutrition. During the treatment, crepitan rales developed. Ulcerous white lesions which were interpreted as moniliasis were seen in the mouth on the fifth day of hospitalization. The patient's vomiting which could not be controlled increased on the 10th day of hospitalization leading to general failure and death.

Postmortem examination: Cerebral edema, hepatomegaly, (case: 300 gm,) N: 261 gm. ulceration of the oesophagus, and otitis media were observed on macroscopic examination. Microscopic examination revealed areas of necrosis in the adrenals and intranuclear inclusions in the cells of the periphery, similar to those seen in Case I. Although areas showing focal nonspecific parenchymal destruction were seen in the liver no intranuclear inclusions could be detected. The structure of the liver, generally showed diffuse fatty metamorphosis, and focal portal fibrosis. Other histopathological findings consisted of esophagitis, interstitial pneumonia and focal interstitial myocarditis. As in Case I, the findings in the brain were identified as herpetic encephalitis.

Discussion

Recently an increasing number of cases of fulminating generalized herpes simplex infection have been reported in the literature. In 1935 Hass described for the first time the unique lesions in the adrenals and the liver of a premature baby which were attributed to diffuse herpetic infection.[6] Later on, in a study of chicken embryos inoculated with the virus of herpes simplex, it was observed that these pathogens affected

the mesodermal and endodermal, as well as the ectodermal structures.[7] The morphological features of the lesions in the chick embryos were focal necrosis and intranuclear inclusion in the cells. Various authors reported the formation of similar type visceral necrotic lesions as a result of this pathogenic agent.[8 9] All the cases of disseminated herpes simplex infection published up to 1959, with the exception of two cases in the series Zuelzer and Stulberg in 1952 and of one case of Brian et al in 1957, were in the neonatal age group.[2 3] McKenzie et al in 1959 reported 8 cases, the ages of which ranged between 9-16 months who displayed rather serious stages of malnutrition.[8]

Virus studies were available on three cases. The authors pointed out that there was malnutrition in these patients and stressed once again that the histopathological findings in the liver and various organs were characteristic features.

The systemic herpes simplex virus infection showing diffuse lesions in the internal organs is not a new entity. The disease affects the newborn probably transplacentally or during passage through the infected delivery canal or in the postnatal period due to contact with persons suffering from herpetic infection in the environment.[10] The antibodies of the herpes virus pass through the placenta to the fetus. The titre of antibody in the newborn baby has been observed to be the same as that of the mother. However antibody titre acquired transplacentally may sometimes be low in value and may not be able to protect the newborn baby against infection or there may possibly be sensitivity of the newborn to this infection. In older children the most common symptom of this infection is encephalitis.[11]

The existence of malnutrition as well as edema and the involvement of the central nervous system in this systemic disease were the particular features of the two cases presented above.

The first case was classified as kwashiorkor following the clinical findings as well as the determination of serum proteins. No determination of serum proteins was available in the second case. Nevertheless the background of nutritional oedema and the histopathological findings on the liver and the pancreas were consistent with the diagnosis of kwashiorkor. The first case was admitted to hospital suffering from aphtous stomatitis. As for the second case, lesions in the patient's mouth appeared on the fifth day following hospitalisation. The first case suffered from vomiting and convulsions and the second displayed a kind of vomiting that could not be controlled as a distinct symptom of the central nervous system. As previously stated, the largest series of fatal

disseminated herpes virus infection after the neonatal period in literature was from South Africa. In this series there were 92 cases with ages ranging between 9-36 months. The ratio of these children showing malnutrition was 89%. Most of them suffered from kwashiorkor.[5] Stomatitis was present in most of these patients. Although the diagnosis of 1/3 of the cases was based on virological studies, the remaining 2/3 were diagnosed according to histopathological findings of post mortem examination.

Systemic infections such as measles and purulent meningitis besides malnutrition were identified as predisposing factors. As is known, children showing kwashiorkor or progressive malnutrition have decreased resistance to viral and bacterial infections. In these children these infections pursue a fulminating course. Antibody production, serum level of antibody and turnover rates appear to be normal in kwashiorkor.[12] It would seem likely, therefore, that delayed hypersensitivity might be deficient in the same way as BCG is frequently defective in malnourished children.[13] These reactions are mediated by thymic dependent lymphocytes and thymic atrophy is extreme in children who died as a result of kwashiorkor.

The diagnosis of generalized herpes simplex infection is generally made by the isolation of the virus in blood and tissues. However the histopathological findings in the tissues described above are pathognomonic. The brain biopsy material in cases showing encephalitis was used for direct virus isolation fluorescence antibody technique and the demonstration of characteristic intranuclear inclusions.[9 11] The prognosis of this disease is obscure and generally fatal. It has been reported that an early diagnosis and treatment with 5-iodo- 2-deoxyuridine may sometimes lead to improvement without sequel.[14 15] In cases of malnutrition with stomatitis, it would be appropriate to suspect a generalized herpes simplex infection in children displaying symptoms such as a poor general condition, hemorrhage, jaundice and rapidly progressing encephalitis. Although it is not possible to protect children against the herpes virus infection, care should be taken to ensure that no one with herpetic infection enters the newborn or premature baby units or clinics where there are children suffering from malnutrition and receiving treatment, as these babies are sensitive to infection.

Summary

Two cases of infants suffering from malnutrition and displaying a fatal generalized herpes simplex infection have been presented and the literature relating to the subject has been reviewed.

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