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Herpes Encephalitis

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Four cases of encephalitis due to Herpesvirus hominis are described. The diagnosis was based on the isolation of the virus from the CSF fluid and on changes in the antibody titre. In three cases labial herpes was observed in the acute phase of the disease; besides, characteristic changes in the EEG facilitated the early diagnosis. Encephalitis recurred repeatedly in 2 cases of steroid treatment, whereas permanent recovery was obtained in 2 other cases in which only symptomatic treatment had been employed. With a view to preventing relapses, persistent herpetic vesicles of the lip were opened and locally treated with idoxuridine.

In general, primary herpesvirus infection induces mild and benign, mostly labial inflammatory lesions and certain individuals are prone to relapses [5, 12, 21]. However, the infection causes in some cases fatal necrotizing inflammation of the nervous system. It is still obscure whether it is by haematogenic dissemination or through the fibres of the olfactory nerve that the virus gains access to the brain [3]. While the presence of extensive cerebral lesions points to the first, virological studies point to the second alternative [10].

Four cases of herpes encephalitis, diagnosed *in vivo,* are described in the following. Every child survived the illness.

Methods

Isolation of virus

a) False air sacs were created in 10 to 11 day-old embryonated chicken eggs, according to the method of Nadeje et al. [20]. The inoculated eggs were incubated for 72 hours at 36° C, and the pocks examined in Petri dishes in front of a dark background. By this method, herpes simplex type I can be distinguished from type II [22].

b) A monolayer prepared from monkey kidney cell line III/1 was seeded with the virus. The culture medium used for reproduction contained 45% Parker's 199 or 40% Hanks solution, 10% bovine serum and 5% lactalbumin hydrolysate. Parker's 199 served as maintenance medium. We observed the effect for 7 days under the light microscope.

Each substance was passaged at least three times. The strain neutralized by our

immune serum of adequate titre was accepted as herpes simplex.

Production of immune serum

Serum HV/24 was adapted to rabbit skin. Incomplete Freund's adjuvant was added to the virus suspension obtained from the rabbit skin, and the rabbits were immunized by four intramuscular doses.

Neutralization test

We added 0.5 ml of serially diluted sera (1:25 to 1:800) to 0.5 ml chorio-allantoic membrane triturate containing the virus suspensions. After one hour incubation at 37° C we seeded the false air sacs with 0.1 ml of the mixture and assumed that the control contained 20 to 80 pox-forming units of virus. The number of pocks was determined after an incubation of 72 hours. The dilution which produced 60% inhibition as compared to the control was regarded as the neutralization titre. A fourfold rise of titre was accepted as positive.

Case Reports

Case 1. L. K., male, 11 years of age. A week before admission in October, 1970, the boy had developed labial herpes and a few days later consumed much alcohol at a vintage. When admitted, the patient had headache, experienced restlessness, mild dizziness and showed signs of disorientation; they were followed by unconsciousness with high fever and convulsions which latter were controlled by cyclobarbital and diazepam without the restoration of consciousness. Neurological examination revealed an epileptic state with brain-stem disorientation and possible intoxication. The EEG pattern pointed to encephalitis, and the course of the illness as well as the presence of marked cheilitis referred to the possibility of herpes encephalitis. We did not administer steroids only symptomatic treatment and vigorous dehydration. Consciousness cleared up in a few hours; Herpesvirus hominis was recovered from the throat swab and the CSF. The neutralization titre of the serum rose from 1:20 to more than 1:200 in the course of a year. The patient, discharged a month after admission, has since been symptomfree.

Case 2. S. H., male, 4 years of age. Pneumonia and otitis had been followed by dysphagia for 3 days. Two weeks thereafter the child had become weak, complained of nausea, walked in an unsteady manner, but had had no fever. He was then referred to us on account of repeated convulsions, circulatory and respiratory disturbances in a state of unconsciousness. Ophthalmological examination revealed a 2—3 dioptre prominence of the papilla. The EEG at admission showed diffuse oedema and continuous convulsive activity. The CSF showed increased pressure, protein 70 mg and sugar 72 mg per 100 ml. Type I herpes simplex was isolated from the CSF, throat swab and blood. Gradually improving, the child was discharged after a month.

Case 3. M. C., male, 2 years of age, had been treated in a hospital for tonsillitis followed by a week of unconsciousness and repeated convulsions. The loss of consciousness lasted for another 4 days after the child's transfer to our department, despite energetic symptomatic treatment, dehydration and the administration of steroids. A crust, suggestive of herpes, was observed on the lip. Cultivation yielded type I herpes simplex from the blood and from the otherwise negative CSF. Consciousness gradually returned after 4 days, and the patient was discharged in a satisfactory condition after 6 weeks.

The child had to be readmitted 5 months later on account of repeated vomiting, facial twitching, irritability and headache. The EEG showed dissolution of background activity and a slow focus in the left temporo-occipital region. Herpes-

virus was again recovered from the CSF. The remission in this instance was spontaneous and required no steroid treatment. The child had become completely symptom-free after 2 months, but the persisting herpes vesicle of the lip had to be cleared and necessitated a 6-day local treatment with idoxuridine. Although the child developed no symptoms during the last 6 months, he had a relapse of cheilitis and the throat swab continued yielding herpes virus. The neutralization titre has not risen above 1:20.

Case 4. E. S., female, 4 years of age, had had tonsillitis on December 31, 1970. She had become somnolent 3 days later and discharged watery stools. She had become unconscious and had generalized convulsions on the next day. Referred to us, we found somnolence and hypotension; the patient reacted vigorously to stimuli; Babinski's sign was bilaterally positive. The CSF was normal, but herpesvirus was isolated from it even on January 16th as also from the throat swab, although this was the only patient who had no labial herpes when admitted. The development of labial herpes was accompanied by an EEG picture which showed diffuse oedema with slow waves on the right side. We determined the neutralizing antibodies five times in the course of the illness: in the first three instances there was no change in the titre despite prednisolone treatment, and only after August 6th did we observe a significant rise (Table I). Improvement of the clinical condition was slow in spite of dehydration and steroid therapy; the patient had repeated convulsions and contact with her was hardly possible. At her discharge after 3 months, the child was still suffering from visual disturbances and aphasia.

Visual acuity was restored during the next 2 months of home care, and the patient showed a good mental development. She was then readmitted on June 20th on account of twitchings of the right-side extremities, and we isolated herpesvirus from the CSF fluid once more. At the beginning of July, the child developed central facial paresis and flaccid paralysis of the extremities on the right side, further hyporeflexia over the entire body with bilaterally positive spontaneous Babinski phenomenon. The EEG curve pointed to grave oedema with slow left-side focus and bilateral diffuse spike potentials. The difference between the two hemispheres became more and more pronounced in the subsequent EEG curves. The grave neural phenomena were accompanied by the development of acute uraemia. Peritoneal dialysis over 9 days stopped the retention of nitrogen and gradually restored normal renal activity. A sudden convulsion of 6 hours supervened in August and one of 2 hours in September. Herpesvirus persisted in the CSF collected at these dates. We instituted anticonvulsive therapy, opened the herpetic vesicle persisting on the lip and treated it with idoxuridine. Although no more relapses have since been observed, the partial right-side paralysis is still present and the child has remained aggressive, while her vision, memory, speech and gait are appropiate to her age.

TABLE I

Neutralizing antibody in patient No. 4

Antibody titre	Day				
	Jan. 16	March 2	July 16	Aug. 6	Oct. 8
titre	1:10	1:25	1:25	1:50	1:100

DISCUSSION

According to TOMLINSON and MCCALLUM [27], the cases of herpes encephalitis reported until 1970 totalled 108; 55% were fatal, and only 23% had healed without residual symptoms [8, 9, 18]. Since the cases described in the foregoing showed a

favourable course, they justify a few diagnostic and therapeutic conclusions.

Clinical aspects

The illness invariably started with hyperacute encephalitis accompanied by convulsions and loss of consciousness. In themselves, these phenomena carry no diagnostic implications since they may be induced by various other viruses, allergy or intoxication [14]. The CSF changes afford no clue either, for normal cell counts and chemical results have been observed despite viral affection [23, 25]. Chapped lip with already crusting herpetic vesicle seems to be a more suggestive symptom: it allowed in two cases to establish an early correct diagnosis. This is in contradiction with certain literary data, for some authors do not regard labial eruptions as characteristic of herpes encephalitis [7, 30], although other authors accept them as such [1, 15]. When describing the case of a dangerously ill patient, the existence of labial herpes, an apparently insignificant condition, may easily be overlooked. Early diagnosis is further facilitated by the EEG curve [4, 6, 26] which in our cases showed cerebral oedema and convulsive activity of different degree on the two sides.

Course of the illness

In two cases a relapse occurred after a symptom-free period. It is known that the herpesvirus is readily incorporated by human ectoderma. DNA, and that under certain conditions the symptoms become manifest anew, a phenomenon apparently occurring also in cases of herpes encephalitis. This fluctuation distinguishes the disease from the other forms of encephalitis which usually terminate with complete recovery, healing with residual symptoms, gradual progress or lethality. We failed to find out whether the viruses inducing relapses were stored in the brain cells or the reinfection originated from the lip. The fact that in two cases we observed herpes viraemia and that vesicles appeared on the lip in the period of remission shows that the source of herpetic reinfection may be extraneural.

In Case No. 4 the neural relapse was accompanied by uraemia due to renal failure which disappeared after dialysis. Therefore, lesion of certain organs caused by circulating immune complexes has to be reckoned with also in cases of generalized herpetic infection [19].

Therapy

(1) Steroid treatment. Opinions regarding its usefulness are divided. Steroids inhibit the synthesis of interferon and counteract cellular immunity, phenomena that are theoretically disadvantageous in viral infections [13]. Corticoid therapy is, on the other hand, necessary in cases of allergic encephalitis [28], and is usually prescribed for security's sake. Two of our patients who had received

no steroid recovered within a month and have remained symptom-free for the last year. The other two patients were given prednisolone during 2 and 4 weeks, respectively; one of them developed one, the other four virologically proved relapses with grave loss of consciousness. This seems to support LONGSON and BESWICK [16] who are against steroid treatment.

(2) Intensive dehydration [23]. Oral administration of glycerol and intravenous mannitol were found highly useful in dangerous cases.

(3) Idoxuridine inhibits the synthesis of herpesvirus; being analogous to the nucleotide, it is incorporated into the DNA. BREEDEN et al. [2] recommended it in adult encephalitis, while MARSHALL [17] used it for the treatment of children. Administered intravenously after several days of unconsciousness, idoxuridine ensured recovery in several cases [7]. Others [27, 29] regard the drug as unsatisfactory and, holding that it damages the bone marrow and the liver, employ it in vitally dangerous cases only. We administered it locally in 2 cases of labial herpes in order to prevent relapses [11]. These patients have had no relapse since, but definite conclusions in this respect require further observation.

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