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HUMAN RABIES. I — INTENSIVE TREATMENT

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SUMMARY

The Authors present the evolution of 7 patients with rabic encephalitis treated in the ICU of the Federal School of Medicine (F.U.M.G.). They justify the admission of these patients and report the treatment performed. The treatment aimed at the control of symptoms and the maintenance of vital functions. Although all the patients died, the Authors consider that the attempts at this treatment should be continued: a) because this small experience accumulated in the treatment of 7 patients is not sufficient to remove the interference of other agents which although potencially lethal should be removed; b) clinical and anatomopathologic experience showed that in spite of extreme gravity, the cases presented variations in their intensities; c) with regard to future specific therapeutic trials. These facts lead the Authors to suppose that there are different degrees of the disease and that some patients in a less serious situation can be recovered with the use of supportive conducts and maintenance of vital functions, until the end of the acute phase of the encephalitis.

INTRODUCTION

Human rabies encephalitis has been considered as a fatal disease. Perhaps, due to this fatal concept, therapeutic methods aiming at the maintenance of the vital functions were put at the disposal of a small numbers of patients. Similar methods have enabled the recovery of patients with rabic encephalitis and of other etiologies, including virotics.

At the moment, one cannot remove the interference of factors which acting as complications of the disease would be in many cases, considered the direct responsible for death. These factors could be excluded with the use of adequate conducts for the maintenance of the vital functions, during the acute phase of the disease, and in this way, in a certain number of patients the disease could perhaps be self-limited [4].

This hypothesis is reinforced by clinical and experimental studies, which show the necessity of re-evaluating the fatalistic concept of rabies (HATTWICK et al. [4]; KRAUT [6]; NILSSON [9]; RIZZOTO & OSBORN [11]). These factors led us to confine patients with rabies

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encephalitis in the Intensive Care Unit (ICU) where only potentially recoverable patients are admitted [7].

MATERIAL AND METHODS

Seven patients admitted to the ICU during the year of 1972 are reported in this study and shown in Table I.

The diagnosis of rabic encephalitis was based on clinical, epidemiologic and laboratorial data. Among the *intra-vitam* virus isolation and serological procedures were used the direct immunofluorescence test (F.A.T.), the indirect method of F.A.T. (I.F.A.T.) of corneal impressions, saliva, cerebrospinal fluid and aquous humor, besides blood antibody titration (REIS et al. [10]). The confirmation of rabies diagnosis was performed by suckling mouse inoculation and histopathologic and virological studies of autopsied patients. The virus was recovered from all the patient's saliva, except in one who received antirabies horse serum for 10 days. In three out of six patients the virus was isolated while the patient was still alive. From all the seven patients virus was isolated from Ammon's horn, cerebral cortex, cerebellum, and Gasserian ganglion at postmortem examination.

When admitted, the patients were isolated and kept under constant observation, aided by continuous electrocardiographic monotorization and laboratorial tests. Among these, the most frequently used were serial pH determination, arterial gases and electrolytes dosages in the serum and urine. Clinical evaluations were made at a minimum rate of three times a day.

Treatment

The fundamental aims of the treatment were to abolish the symptoms and to maintain the vital functions.

In addition to these conducts, one patient (No. 1) received antirabic horse serum (12 ml, IM daily) during ten days; patient no. 5 received suckling mouse vaccine (1 ml, IM, every 12 hours) during seven days and two other patients (no. 5 and 6) received vitamin C (12 g daily) during the entire hospitalization.

The symptomatic treatment consisted in: a) maintaining the patient in a sedative state through the use of chlorpromazine, diazepam, promethazine, and meperidine; b) controlling the seizures by using diazepam, diphenylhydantoin and phenobarbital; c) controlling the infections by means of routine prophylactic conducts. When infections were diagnosed, the antibiotic choice was mainly based on the results of antibiogram and sensitivity tests. In order to control hidrophobia and aerophobia, stimulus was avoided.

Maintenance of the vital functions

1) *Respiratory system* — Tracheostomy was performed in all patients after the admis-

TABLE I

Characteristics of 7 cases of human rabic encephalitis

no.	Patients	Sex	Age (years)	Place of Bite	Incubation period (days)	Responsible rabid animal	Antirabies vaccine treatment	Permanence in the ICU (days)	Diagnosis (*)
1	I.S.	M	24	hand	66	cat	no	13	no
2	A.L.F.	M	14	hand	425	dog	14 doses	21	yes
3	J.D.S.	F	8	leg	81	dog	no	13	yes
4	M.G.F.	M	42	hand	90	dog	no	14	yes
5	R.P.G.	M	14	face	12	dog	4 doses	12	yes
6	G.R.	M	11	leg	90	dog	no	11	yes
7	W.L.C.	M	40	nose	62	dog	no	15	yes

(*) Diagnosis made by isolation of rabies virus from saliva swab taken *in vivo*

sion. Seizures and apnea followed by tracheal suctioning were avoided by previous sedation and administration of a sufficient dose of muscle relaxant drug. Special care of asepsis was taken when aspiration of secretions was indicated. Respiratory physiotherapy, hyperventilation and other conducts which aimed at prophylaxis and treatment of the respiratory complications were used in all cases.

A prolonged artificial ventilation was performed in all cases with Bird Mark 7. The indication and use of the respirator was based on clinical picture (signs of respiratory arrest or exhaustion) and specially in the results of the arterial gases dosage. When the patient competed with the respirator or when respiratory frequency was very elevated, controlled respiration was used. Sedation was increased for this purpose. When this method was insufficient, muscle relaxant drugs of the curare group were introduced in the therapy scheme. Serial determinations of pH and of arterial gases, frequent clinical and radiological examinations were used to evaluate the respiratory conditions of the patients.

2) *Maintenance of metabolic conditions* — The metabolic situation of the patients was maintained within the conditions closer to the physiological ones. The hydroelectrolytic and caloric replacement was based on clinical evaluations and data provided by the hydroelectrolytic balance and laboratorial tests. The means of administration preferred was nasogastric tube. Whenever it became impracticable, parenteral feeding was used. In some cases, hypercaloric parenteral feeding was administered. Attempts were made to avoid extraordinary losses such as those produced by fever and gastric hypersecretion through symptomatic treatment.

3) *Neurologic manifestations* — Only symptomatic therapy was used. It aimed at the control of manifestations such as hallucination, agitation, hydrophobia, and aerophobia. Whenever there was state of coma, habitual methods were used in order to prevent complications.

4) *Cardiovascular manifestations* — The treatment of cardiovascular arrhythmias consisted, in most cases, in the removal of the probable causes and in some, in the use of digitalis. Treatment of shock and hypotension consisted in quantitative and qualitative replacement of volume and vasopressors. The symptomatic conducts of cardiopulmonar resuscitation were used whenever there was no evidence of irreversible brain damage. The complications of this system are shown in Table II.

TABLE II

Complications in 7 patients with rabic encephalitis during the permanence in the ICU (*)

Complications	No. of patients	Probable causes	Treatment
Hypotension	7	Lesion of C.N.S. Dehydration	Vasopressor (norepinephrine) Hydration
Hypertension	7	Lesion of C.N.S.	None
Cardiac arrhythmias	7	Hydro-electrolitic and acid-basic disturbances	Digitalis when indicated Treatment of probable etiology
Shock	3	Excessive sedation Dehydration Central mechanism	Treatment of shock
Cardiac arrest	3	Hypoxia Hypotension	Cardiopulmonar resuscitation

(*) ICU = Intensive Care Unit

5) *Gastrointestinal manifestations* — The treatment was exclusively symptomatic and complications were avoided with continuous drainage through nasogastric sonda, atropine in the presence of gastric hypersecretion and vomiting, and oropharynx aspiration to siallorhea.

6) *Genital-urinary manifestations* — The methods can be summarized as follows: a) prophylaxis of the urinary infections through special asepsis care during the use of vesical catheter; b) treatment of the complications such as urinary retention (vesical permanent catheter), oliguria and anuria (hydration and use of diuretics of hypotension correction), and genito-urinary infections (antibioticotherapy).

RESULTS

The results will be analyzed regarding the aims of the treatment: to abolish the symptoms and maintain the vital functions.

1) *Treatment of the symptoms* — The sedation of the patients represented a problem of difficult solution. It was inadequate in all cases as it required association of elevated doses of sedatives and hypnotics, which sometimes caused serious side effects such as respiratory depression requiring ventilatory assistance. Hydrophobia and aerophobia were controlled.

2) *Maintenance of the vital functions*: a) *respiration* — All patients showed respiratory complications. Apnea was observed in all cases and attributed to damage of the central nervous system. It was always preceded by respiratory arrhythmias (tachypnea or irregular respiration). Bronchopneumonia was diagnosed in five patients and necropsy confirmed it. In one patient (no. 4), necropsy showed severe diffuse catarrhal bronchitis. Atelectasis occurred in all cases, being easily controlled with physiotherapy and pulmonary hyperventilations, except in one case in which the postmortem examination showed persistent pulmonary collapse (no. 4). The bacterial etiology was confirmed in all cases. All patients were kept under prolonged assisted artificial respiration in the beginning of the treatment and controlled afterwards. Assisted respiration in all cases was unsatisfactory. Tachypnea and irregularity of the respiratory

TABLE III

Metabolic disturbances in 7 patients with rabic encephalitis during the permanence in the ICU

Disturbances		No. of patients	Probable causes	Treatment
Alkalosis	Respiratory	7	Tachypnea, irregular respiration	Sedation
	Metabolic	7	Gastric hypersecretion	Reposition of losses
Acidoses	Respiratory	3	Hypoventilation	Mechanic respirator
	Metabolic	7	Shock Hypoxemia	Etiology treatment Sodium bicarbonate
Hypoglycemia		1	Excessive insuline	Parenteral glucosis
Hyperglycemia		4	Parenteral feeding	Regular insuline
Hydro-electrolitic and Acid-basic disturbances		7	Excessive losses Dilution	Adequate hydro-electrolitic infusion

rhythm produced serious respiratory alkalosis of difficult control, in spite of the administration of elevated doses of sedatives. In some cases, the use of muscular relaxant drugs of the curare group was necessary to maintain satisfactory ventilation through controlled respiration. The presence of abundant secretions in the tracheobronchial tree required, from the beginning, tracheostomy and frequent aspiration of secretions and intensive respiratory physiotherapy. Two patients (no. 4 and 6) were admitted showing signs of pulmonary infection. In the remaining ones, it appeared during the confinement period; b) *Metabolism.* The impossibility of using oral feeding or the risks resulting from it, showed that the introduction of a nasalgastric catheter was necessary at the admission of all the patients. However, oral feeding became impracticable due to the presence of stasis of abundant gastric secretion. This fact was observed in all the patients and impeded the use of the mouth, in spite of the administration of antispasmodics.

In 2 patients on whom a study of gastric secretion was made, a normal histalog response was observed. In one patient (no. 7), necropsy showed the presence of injuries of the stomach nervous plexus, with intensive gastritis, which could probably explain the abundant gastric secretion (data to be published).

The maintenance of the hydro-electrolytic and acid-basic balance became very difficult because of the necessity of administrating large volume of fluids, in order to replace the losses due to intense sudoresis, hypertermia, oropharynx and gastric hypersecretion and polyuria. The latter resulted from the elevated volume of fluids which had to be administered in a short period of time. The ventilation disturbances producing serious alkalosis made the maintenance of a hydroelectrolytic and adequate acid-balance even more difficult; c) *Circulation.* Hypotension was observed in all the patients and was probably due to dehydration and injury of the CNS. In spite of the metabolic control, in 4 patients the hypotension was controlled by adequate replacement of water and electrolytes; in 2 patients it appeared without apparent cause. In these circumstances, hypotension was attributed to neurologic lesion and corrected with the administration of noradrenaline (data to be published). In 2 patients the classical shock picture attributed to central mechanism (encephalitis or excessive sedation) was settled. Artificial support or arterial pressure with adrenaline was kept in three cases until the neurologist considered the patients in irreversible coma.

TABLE IV

Evolution of seven cases of human rabics in relation to type and day of onset of the main complications

Complications / Patients	Apnea	Pulmonary infection	Cardiac arrest (*)	Coma	Decerebration (**)	Hospitalization period	Duration of the disease
I.S.	2	4	—	2	—	13	21
A.L.F.	1	5	17	6	21	21	20
J.D.S.	1	—	—	6	—	13	15
M.G.F.	1	1	8	8	—	14	28
R.P.G.	1	—	—	—	6	11	12
G.R.	1	—	—	6	—	11	11
W.L.C.	6	1	6	9	—	15	18

(*) Patients in whom cardio-pulmonary resuscitation was effective
(**) Electroencephalogram confirmed

The cardiac arrhythmias found, were extrasystoles and sinus tachycardia treated with digitalis in two cases. The most probable cause of such arrhythmias was attributed to metabolic disturbance, although the histopathology had demonstrated the presence of miocardosis in all cases. The anatomopathologic data did not show presence of miocarditis in any of the patients (data to be published). Arterial hypertension which appeared in all patients during hospitalization was attributed to neurologic damage. During evolution in the ICU, three patients showed episodes of cardiac arrest, being recovered from them.

The support procedures of the vital function were interrupted when the neurological finding and electroencephalograms considered irreversible the neurologic function. In Table IV, the relationship between the number of days in the ICU and the uprising of the main complications are shown.

DISCUSSION

The analysis of the results obtained from the maintenance of the vital functions of clinically manifest human rabies enhances some speculations on the controversial evolution of rabies. As a matter of fact, before using the supportive treatment, diagnosis of our rabies patients was based on epidemiologic and clinical data. The virologic diagnosis was therefore performed by histopathology of brain material after death. The most usual clinical course was the one well known and described in the literature, and the duration of the illness ranged from 3 to 14 days with an average of 5 days (NEVES [7]). With the introduction of the supportive treatment in the ICU, the duration of clinical rabies ranged from 11 to 28 days (average of 18 days). In these circumstances, contrary to the previous routine procedures, diagnosis of rabies could be supported in laboratory investigations while the patient was still alive (REIS et al. [10]).

There are controversies involving the published papers on recovery from rabies. Although it is not relevant to discuss here if rabies is invariably fatal, even the interesting case reported by HATTWICK et al. [4] was based mainly on epidemiologic, clinical, and serum neutralization data. This means that no virologic diagnosis was performed, in spite of several laboratory investigations. On the other hand, the other reports of nonfatal human rabies referred to in the literature, contain detailed information on clinical and epidemiologic data, but fail in demonstrating rabies virus as an unquestionable document. With this in mind, *intra-vitam* diagnosis of rabies, as a result of the maintenance of the vital functions of patients, represents an important contribution to the evaluation of true spontaneous recovery from rabies.

The present study enables us to admit the interference of several factors acting as complications of the disease, and hence, also responsible for the mechanism of death. On the other hand, clinical and anatomopathologic studies demonstrated that in spite of the severity of the encephalitis, some cases exhibited discrete variations in their clinical development (data to be published). It is too soon to determine, however, whether opportune treatment of the potencially lethal complications would be effective in self-limiting the course of acute encephalitis.

We must re-emphasize that in this study the treatment aimed basically at the control of the symptoms and the support of the vital functions. The specific therapeutic procedures were limited to the he application of anti-rabic horse serum to one patient and of anti-rabic vaccine to another one. The administration of elevated doses of vitamin C in two other patients was based on the hypothesis that it could be followed by an increase in the production of endogenous interferon (ATANASIU et al. [1] BARROETTA & ATANASIU [2]; FENJE & POSTIC [3]; HILDRETH [5]; WAGNER [13]). However, it was abandoned because its questionable therapeutic value did not justify the difficulties which its usage introduced in the interpretation of glycosuria during the hypercaloric parenteral feeding. In one of our patients, a false-positive glycosuria was responsible for the excessive use of insuline and consequent hypoglycemy. It became impossible in this case to evaluate the role of this disturbance in the evolution of the clinical picture.

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The control of symptoms and the maintenance of vital functions were quite unsatisfactory in all cases. Sedation during the agitation period required elevated doses of an association of drugs which sometimes were accompained by serious and undesirable side-effects such as respiratory depression, urinary retention, aggravation of coma and hemodynamic disturbances.

Respiratory function required premature and constant use of artificial therapeutic procedures besides intensive nursing care. The irregularities on the respiratory rhythm impeded an adequate ventilation in all cases, and represented one of the most difficult problems of maintenance until the moment when apnea settled in. Other sort of problems included the control of excessive quantity of secretions in the tracheo-bronchial tree, the drainage of gastric hypersecretion, the obtainance of adequate metabolic balance, and the prevention and/or treatment of neurologic and cardiovascular manifestations.

Based on this experience, actually we do not know whether a more agressive supportive care alone will be sufficient to cure rabies, as pointed out by HATTWICK et al. [4]. We do believe, however, that this care would mainly emphasize the preventive procedures, in order to antecipate and treat all the intercurrent and potencially lethal complications, but not to enhance a doubtful scope to cure rabies. Although none of the patients here described recovered from rabies, attempts should be made to improve the maintenance of vital functions, with regard to future specific therapeutic trials.

RESUMO

Raiva humana. I — Tratamento intensivo

Os Autores apresentam a evolução de 7 pacientes com encefalite rábica tratados no CTI da Faculdade de Medicina da Universidade Federal de Minas Gerais. Justificam não só a admissão desses pacientes, como descrevem o tratamento realizado. Este teve por objetivo o controle dos sintomas e a manutenção das funções vitais. Embora todos os pacientes tenham falecido, admitem que as tentativas de tratamento da encefalite devam prosseguir, em virtude dos seguintes fatos: a) a pequena experiência acumulada com o tratamento de 7 pacientes não é suficiente para afastar a interferência de outros fatores que, embora potencialmente letais, possam ser removidos; b) a experiência clínica e anátomo-patológica mostraram que, apesar da sua gravidade, os casos apresentam discretas variações em sua intensidade. Estes fatos levam a supor que existem diversos graus da doença e que alguns pacientes, menos graves, possam vir a ser recuperados com o emprego de medidas de sustentação e de manutenção das funções vitais, até que termine a fase aguda da doença.

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