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Some Experiences on the Treatment of Japanese Encephalitis

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It is widely accepted that there is no known specific chemotherapeutic agent against arboxvirus-encephalitis. One who is interested in Japanese encephalitis will easily appreciate the fact that, as there are great variations in its pathological changes as to its location, extent of invasion, and accordingly in its pathophysiological aspects, real pathogenesis of encephalitis cannot easily be grasped.

We must confess that there has been no systematic research into the biochemical explanation on the pathogenesis of encephalitis to the present day, though it is a very difficult task.

At present we cannot but treat the encephalitis cases symptomatically, but the importance of basic knowledge which will be used as a therapeutic guide can not be denied. Our concept and basic knowledge of this disease, however, was lacking in objectivity and was at most conventional up to this day.

As the authors try to establish a therapeutic principle, though a symptomatic one, we first put an emphasis on the "objective" evaluation of its symptoms and causes of death, and we are eager to get the methods which will enable us to get rid the patient of the causes of death and lower the fatality rates. So we made a comprehensive filing of the result of observations for these three years (1958, 59, 62) that our data might serve as a guide in our future treatment. We dare to publish some of our practical experiences (furthermore definite results of them are lacking at this stage) in the hope that better therapeutic methods will come up through the criticisms and instructions of other coresearchers. (Table I).

The factors which are concerned with the causation and mechanism of fatal outcome in encephalitis can be mentioned circulatory failure, complications, respiratory disturbances and prostration as shown in the Table I.

The circulatory failure, one of the causes of death in encephalitis, is primarily a peripheral vascular failure with minimal or no change in the heart, resulting in rapid feeble pulse, cold extremities and cyanosis (so-called "shock").

These cases present vague but invariably toxic pictures from the initial stage of the disease and respond to adequate anti-shock therapy and vasculotonics with rather prompt relief from their signs.

It is also probable that a more frequent cause of peripheral circulatory failure in encephalitis is dehydration which results in secondary shock(peripheral vasomotor collapse). This occurs because of the lack of desire to drink water and inability to swallow food, increased perspiration, increased secretion in the upper airway, hyperventilation and vomiting with resultant hemoconcentration.

According to a study done in the epidemic of 1949, the amount of blood-volume in encephalitis patients is diminished to such a marked degree that its decrease is directly related to final prognosis and it increases gradually to normal level with the recovery of the patient. (A phenomenon seen also in cholera patient) So the replacement of lost fluid and electrolytes is essential and mandatory in the treatment of encephalitis. But to what degree the replacement should be done is not so simple a problem. In autopsies of encephalitis cases the most prominent pictures of the gross pathology are brain edema and congestion of cerebral vessels. In connection with this finding it is thought that the excessive administration of fluid will most probably be harmful and that a method which enables us to relieve this congetion and edema will be highly effective. in

Table 1. Causes of death in Encephalitis Cases (acute stage)

	Cause	Mechanisms	Signs and Symptoms	Treatment
1	Circulatory failure a) Peripheral c.f. ← 1) Essential→	(toxic)	Weak pulse, Cyanosis, shock	Antishock therapy, Vasculotonica
	2) Secondary→	dehydration	Haemoconcentration. Shock decreased blood volume. increased hematocrit.	Replacement of water and electrolyte-loss. antishock therapy, Vasculotonica.
	b) Cardiac insufficiency ←	damage on circulatory-center in medulla oblongata. Vago-Vagal reflex. Vago-Sympathetic reflex	Cardiac arrest(no changes or occ. Hyperpotassemic changes on ECG.)	Fatal †
2	Complication	atelectasis due to bronchial secretion ↓ (Bacterial infection) ↓ pneumonia	Dyspnoea, Rales on Chest Dullness. occ. dense shadow on chest X-ray. (Atelectasis, Pneumonia)	Suction, Antibiotics.
3	Respiratory failure a) Damage of resp. center →	No regulation of resp.	Irregular breathing(Cheyne-stockes, Biot type)	Fatal †
	b) Resp. M. paralysis →	Can not breathe	Usually complicated with 3 a)	Iron-lung. Respirator(almost fatal †)
	c) Mechanical resp. failure →	Air way disturbance. Hypoxia(Cranial N. paralysis in bulbar type)	Cyanosis, Dyspnoea. Rales, Stridor, Dullness	Suction, posturaldrainage (Trendelenburg position) Tracheotomy, O_2 supply)
4	Exhausion	prostration		Nasal feeding, plasma and blood transfusion.

treating patients.

These observations led us to use hypertonic solutions intravenously. 10% or 50% glucose solutions instead of 5% were administered in amount calculated to square meter of body surface. However, the final clinical results of such fluid therapy was not very promising presumably due to the variety of factors influencing the final outcome.

The decrease in serum electrolytes(esp. Na) were nearly uniform in encephalitis patients and corrections were done as far as possible, especially in children on the basis of daily blood electrolyte level with glucose solution, 3M NaCl solution, and 3M K. acetate solution.(The corrections were done in ordinary way in most cases and full correction was done in 24 hrs. in some patients.) But the results were unable to be assessed for the above-mentioned cause.

As an adjunct to the above mentioned measures polyvinylpyrrolidone derivative was used to relieve cerebral edema, to accelerate detoxifying mechanism and to replace lost fluid. But the results were not so good as reported by other authors.

We experienced four cases of sudden death due to cardiac arrest. The diagnosis of acute cardiac insufficiency was made as those cases presented little evidence of cardiac disturbance on ward round several hours before death. Those sudden cardiac arrests came probably as a result of so-called vagovagal, vagosympathetic reflex or the invasion of the medullary cardiovascular center. It is generally claimed that marked change in myocardium was an infrequent finding in encephalitis autopsies. We also found no significant change in ECG in 20 odd cases of encephalitis in 1958.

As the next cause of death should be considered complications, especially complicating pneumonias. Some clinicians laid stress on bacterial complications especially pneumonias leading to death. But according to our observations the chance of primary pneumonias was almost nil and most of the so-called primary pneumonia cases were misdiagnoses of infected atelectasis from obstructions of bronchi or bronchioles due to accumulations of secretion.

In the bulbar type of this disease the increase in amount and change in character of oral and upper-respiratory tract secretions, narrowed bronchial lumina and ineffective coughing mechanism due to vagus and allied cranial nerve disturbances are frequently found and easily lead to obstructive atelectases. Surely superimposed bacterial infections may lead to pneumonias, but this occurrence isn't so frequent as reported previously. Rather mechanical respiratory failure(q.v. (c) of (3) in the table) was found to be the principal factor.

By adequate suctioning of the upper airway, we could promptly relieve the patient of the obstructing tracheal and bronchial secretions which caused dyspnea and various physical signs of the chest, such as rales, dullness, and weak breathing sounds.

The importance of antibiotic administration(penicillin and streptomycin) together with suctioning of the airway cannot be overemphasized in an unconscious patient with disturbances in swallowing or coughing mechanism.

In the author's experience the greatest number of deaths were due to the respiratory failures. So-called bulbar and pons type which is the gravest of all types of encephalitis causes death mainly by respiratory disturbance.

As shown in the table (ⓐ of ③) cranial nerves (especially 7th, 9th, 10th, 11th) which pass through the pons and medulla are involved along with the involvement of the medullary respiratory center resulting in the so-called bulbar paralysis. Cases with these involvements lack control of respiration from a relatively early stage of disease and show cheyne-stokes, Biot or other not well defined types (mainly irregular and stridulous) of abnormal breathing with resultant death in a few days.

In cases with respiratory muscle paralysis(ⓑ of ③ in the table) there is an inability of active breathing due to the disturbance of the action of respiratory accessory muscles and diaphragm which finally lead to the arrest of respiration. Such patient can be maintained alive with the aid of iron-lung or respirator. But unlike the case with poliomyelitis the damage of the medullary respiratory center is complicated in most cases and passive breathing is made no longer available as a life-saving measure in a few days.

The authors experienced only one such case kept alive with iron-lung and respirator.

The clinical form with the mechanical respiratory failure is the only type of bulbar encephalitis in which adequate treatmet can be said life-saving.

These cases present the most important therapeutic problem to us at present. They have no diffuse involvement in the respiratory muscles but the disturbances of cranial nerves passing through the pons and medulla(cranial nerves 6th, 7th, 9th, 10 12th) lead to the accumulation of secretions, airway obstruction, atelectasis, dyspnea and cyanosis, and may result in fatal end. In those cases, tracheotomy, tracheal intubation, endotracheal suctioning, postural drainage with Trendelenburg position and oxygen inhalation should be done to keep airway free and clear as the patency of the airway determines the final outcome in them.

The above mentioned emergency measures are nothing but the clinical applications of recent advances in respiratory physiology and anesthesiology.

In practice the cooling of body surfaces in hyperpyrectic patients(surely most cases of encephalitis are hyperpyrectic) influences the clinical course in a good way by relieving dyspnea and reducing unnecessary, harmful energy expenditure. This is especially true in the case of infant and small children where the surface area is proportionately larger, pulmonary ventilatory capacity smaller and basal metabolic rate higher than adult. These physiological handicaps of the infant and small children predispose to hypoxia, asphyxia and the excessive accumulation of CO_2 in the body when the patient is hyperpyrectic and unconscious as in the case with encephalitis. Moreover hypothermia decreases cerebral edema, intracranial pressure and, above all, the oxygen demand of the central nervous

system.

These considerations led us to lay heavy weight on body surface cooling in encephalitis patient.

The last factor to be considered in the fatal outcome of encephalitis is exhausion. In serious cases as oral food intake is practically impossible, nasal feeding is required.

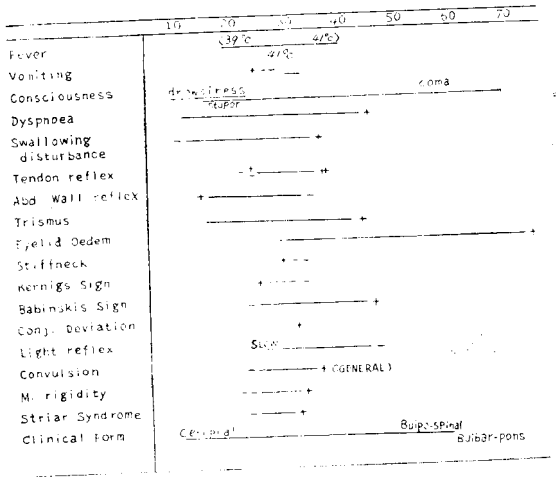
As a mean of supplying nutrient, fluid and antibodies, plasma(rather than whole blood because of preexisting hemoconcentration) in small children and whole blood in adult were given. This therapy impressed us as a good one.

As the urinary excretion of vitamin B_1 is increased in the acute stage of this disease, vitamine B and C were given in sufficient amount to our patients.

Though the evaluation of the effects of other drug therapy in the treatment of encephalitis is very difficult and confusing, we will briefly review the experiences of drug therapy in our cases and results obtained therefrom.

As a standard in evaluating the severity of individual case author calculated the fatality rate of patients with any one clinical sign or symptom. (Table 2)

Table 2. Clinical Manifestations and Prognosis (Case Mortality %)



For example the number of patient with palpebral edema was 34 of which 24 ended fatally, so the case mortality with palpebral edema is 71%. In this wise it was found that 7 symptoms and signs, namely, coma, dyspnea, excessive orotracheal secretions, trismus, palpebral edema with slight exophthalmos, positive Babinski sign and absent light reflex have fatality rates over 40%.

We arbitrarily defined as severest those cases with any 5 out of the above mentioned 7 symptoms and signs.

We administered some drugs to these severest cases and assessed the effectiveness of drugs by comparing their prognosis with those of the cases to whom drugs were not given.

Cortisone and other Steroids

Opinions differ greatly as to whether cortisone is effective in viral encephalitis. We used cortisone in 6 cases in which 4 ended fatally and one recovered with severe neurological sequelae. After all our impressions are against cortisone therapy in encephalitis. Another steroid prednisolone was used in 12 cases but the results were little better than those cases not given. The claim that it ameliorates sequelae is not very acceptable yet.

Polyvinylpyrrolidone derivatives

The effect of these preparations(periston, polybon etc.) was noted in some reports but in our experience with 6 cases 4 died and no direct improvement in clinical picture was seen. Although these preparations are not very hopeful theoretically they can be effectively used as sources of electrolytes and anti-shock agent. But its relatively high cost greatly restricts its general use.

Tranquilizers

No appreciable difference in case mortality was noted between cases given and those not given. Of the preparations chlorpromazine was used intramusculary in the years 1958, 59, and librium(Roche) and librax(in cases with increased oro-tracheal secretions in doses of 5–10 mg in children and 10–20 mg in adult). in 1962. The case mortality of chlorpromazine-administered patients was 39.1%(6 deaths out of 23 cases) and that of non-users was 34.2%(13 out of 38).

The case mortality with librium and librax (administered for a period of over 3 days) was 20% (6 out of 30) whereas those of non-users was 22% These drugs cannot be said to be an effective agent

in encephalitis but in our experience they're somewhat effective in suppressing those symptoms such as anxiety, insomnia, irritability, convulsion, and involuntary movement.

At least we haven't received any unfavorable impression on their use in encephalitis. Rather we were impressed that these drugs(especially librax) were effective in reducing salivation and airway secretion.

Adult Blood Products

Adult blood products seemed to be more effective than any above mentioned drug in our encephalitis cases as means of supplying nutrients, fluid and electrolytes, immune bodies, and reducing cerebral edema. Whole blood was given to adult and plasma to children.

Whole blood 500 cc daily or blood plasma 200-250 cc daily were used to 32 patients of which 6 died (case mortality 18.7%). This rate is far lower than that of 45 nonusers in serious state of which 16 died with a case mortality of 35.5% We think these product should better be recommended to those patients who can afford economically.

國 文 抄 錄

日本腦炎治療에 대한 몇가지 經驗

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Virus 疾患인 日本腦炎에 있어 아직 特殊化學療法이 없다는 것은 周知의 事實이다. 本病에 대한 病理學的變化가 症例에 따라 그 侵犯部位, 程度, 範圍가 다르며 따라서 그 나타나는 病態生理가 一律的이 아니고 複雜多端하므로 病機의 主體를 把握하기 힘든 狀態에 있다는 것도 本病에 대하여 關心을 가지는 人士이면 누구나 쉽게 理解될 수 있는 일이다.

이제 對症的이나마 治療方針을 樹立함에 있어 筆者들은 먼저 그 나타나는 症候와 腦炎死의 原因을 客觀的으로 檢討分析함에 努力하였고 그 死因을 究明하여 除去할 수 있는 것은 그를 改善하므로써 致死率을 低減시킬 수 있으리라는 考慮下에 數年來 얻은 바 觀察結果를 綜合整理하여 第1表를 作成하였으며 이에 依하여 患者의 治療에 臨하였던 것이다.

第1表에서 보는 바와 같이 腦炎死因으로서 循環障碍(末梢血管循環障碍 및 急性心機不全), 合併症, 呼吸障碍 및 衰弱困憊등을 들 수 있는데 이 中에서 呼吸障碍에 起因한 것이 제일 重要한 意義를 가짐이 認知되었다. 筆者들은 腦炎死의 大多數는 이 呼吸 乃至 氣道障碍 및 이에 따르는 合併症에 該當하는 것들 임을 경험하였던 것이다.

腦炎治療에 있어서는 아직까지 特異療法은 없으며 오직 一般療法으로는 對症的 補强的인 方向으로 處理할 것이며 急性期에는 隔離 安靜 臥床 등 其他 熟練된 看護處置를 必要로 하며 특히 分泌物에 의한 氣道閉塞등의 障碍에 대하여서는 細心한 注意가 必要하다. 延髓型에 있어서는 氣道內에 쉴 새 없이 滯溜되는 分泌物의 除去를 위하여 또는 意識障碍와 機能麻痺등에 대한 注意가 必要하며 其他 氣道(特히 肺炎) 尿路感染 등의 二次感染에 대한 豫防 및 褥瘡등의 豫防도 要請된다. 脫水狀態에 빠지기 쉬우므로 等張 또는 高張葡萄糖溶液 pdyvingl pyrrolidone 製劑 때로는 血漿의 靜脈內注入에 의한 水分 및 榮養供給, 其他 昏睡狀態에 들어 自意로 삼키지 못할 때에는 鼻管注入에 의한 榮養供給도 必要하다.

臨床症候의 出現與否와 그 致命率로서(第2表) 標準重症症例를 設定하여 보았는데, 昏睡, 呼吸困難, 口腔 및 氣道內分泌過多, 牙關緊急 眼浮浮腫과 輕한 眼球突出, 陽性 Babinski 症候 및 光反應(瞳孔) 消失등의 7個徵候는 豫後가 不良한 症例에서 많이 경험되었다, 따라서 今後 어떤 治療法의 適宜良否를 決定할 때에는, 上記 7個所見中 5個 以上을 兼備한 症例를 重症으로 設定하고 이런 重症例를 對象으로 하여 試圖하여 그 成績으로서 判定지을 것을 提案하였다.

이와같이 設定된 重症患者에 各種 特殊藥劑들이 試用되었으나 뚜렷하게 效果있었다고 認定된 것은 아직 없었고 오로지 水分, 榮養, 核酸 및 抗體의 供給과 腦水腫을 輕減시킬 수 있지나 않을가 하는 點등에서 血漿, 全血 또는 人血淸 Albumin 등의 投與는 若干 有效하였으며 有意義하다고 생각되었다.

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