SERUM AND CEREBROSPINAL FLUID ENZYMES IN TOXAEMIAS OF PREGNANCY

by

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Toxemia is one of the most variable and elusive diseases confronting the obstetrician today. Several reports have appeared concerning the level of various enzyme in sera of patients with different types of toxemias Borglin (1959), Bagga *et al* (1969), Curzen and Moris (1966), Lee and Lewis (1963), Young and Beller (1968) but little is known concerning the effect of eclampsia and pre-eclampsia on enzyme levels in the cerebrospinal fluid (CSF) of patients in labour with these diseases. One becomes interested in whether serum levels of these enzymes contributed to the CSF enzymes levels because Morrison *et al* (1971) reported that CSF protein was greatly increased in these patients. The enzymes also through the elevated CSF protein may indicate that the integrity of the blood brain barrier of these patients is altered, permitting the passage of colloid from the serum to the CSF.

Our studies were concerned with patients coming with eclampsia and pre-eclampsia. These patients were compared with normal labour patients and patients with seizure disorders and chronic hypertensive vascular diseases. A comparison was made in regards to the levels of certain enzyme of the CSF and serum. The enzymes studied were creatine Phosphokinase (CPK), glutamic oxaloacetic transminase (GPT), lactic dehydrogenase, and alphahydroxy butyric dehydrogenase (HBD).

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Material and Method

The present study was carried out on 92 patients admitted in the third trimester of pregnancy to the S.V.B.P. Hospital, Meerut. On the basis of condition of the patients, they were divided into five groups as shown in Table I. The first group was composed of 25 normal pregnant women in which the prenatal history was known. The second group consisted of 5 patients with idiopathic seizure disorders but no other detectable complications. The last three groups consisted of 62 patients who were diagnosed as having various forms of toxemia according to the strict adherence to the criteria of the American Committee on Maternal Welfare (definition and classification of toxemias. Brought up to date sub-committee of the American Committee on maternal welfare, 1964). Group three consisted of

33 patients with severe pre-eclampsia. The fourh group contained 20 patients with eclampsia and the fifth group was composed of 8 chronic hypertensive vascular disease patients without superimposed toxemia. All patients used in this study were considered to be normal in other respects and were equally distributed as to age, gravidity and parity.

Blood and CSF were collected from each patient prior to delivery and were centrifuged immediately at 5000 r.p.m. to remove erythrocytes. Samples with detectable hemolysis were discarded. Estimation of creatine phosphokinase (CPK). Duma and Siegel (1965), Glutamic oxaloacetic transaminase (GOT) Reitman and Frankel (1957), Glutamic Pyruvic transaminase (GPT) Reitman and Frankel (1957), alphahydroxy butyric dehydrogenase Rosalki and Wilkinson (1960) and Lactic dehydrogenase (LDH) Wootten (1964) were made on the same day or within three days after stored at-20°C.

Results

All the serum enzymes studied for each of the 5 groups are shown in Table I. In normal pregnancy, patients with hypertensive vascular disease and seizure disorders, all the enzymes were well within the normal limit except CPK which was considerably raised in normal pregnancy as well as in seizure disorders. In eclamptic and to lesser extent, the pre-eclamptic patients had increased levels of all the serum enzymes.

Eclamptic patients were divided in 3 groups, and their serum enzymes are shown in Table II. In most severe group concentration of all the enzymes was greatly raised while in moderately severe and mildly severe groups the enzymes concentrations were raised according to the severity of the disease.

TABLE I

Serum Enzymes in Normal Pregnancy, Pre-eclampsia, Eclampsia, Seizure disorders and Hypertensive Vascular Disease

Group	No.	CPK IU/L	GPT IU/L	GOT IU/L	SHBD IU/L	LDH IU/L
Control		8.0 — 66.0	4.0 — 16.0	2-21	67 — 135	75 — 187
		44.2 ± 12.2	11.3 ± 3.6	11.5 ± 6.3	95.5 ± 10.2	143.6 ± 23.2
Normal pregnancy	25	15.6 — 82.4	7.3 — 14.5	3.3 — 18.9	83 — 130	91 — 183
		68.3 ± 18.8	12.6 ± 3.1	13.2 ± 3.6	97.8 ± 11.3	154.4 ± 26.1
Seizure disorder	5	86.3 — 215.7	8.8 — 16.0	4.8 — 20.6	87 — 131	105 — 187
		153.6 ± 33.6	13.2 ± 3.8	16.3 ± 4.1	103.6 ± 12.5	155.6 ± 22.3
Pre-eclampsia	33	27.4 — 122.6	9.2 — 25.6	15.3 — 48.5	93 — 167	145 — 293
		84.4 ± 21.3	18.8 ± 5.4	28.7 ± 6.3	127.2 ± 16.8	203 ± 26.4
Eclampsia	20	74.8 — 257.3	32.6 — 107.3	44.2 — 136.5	155 — 247	215 — 465
		197.5 ± 42.6	76.7 ± 14.5	89.4 ± 12.8	187.3 ± 22.2	312 ± 33.5
Hypertensive Vascular disease	9	9.6 — 58.9	6.8 — 14.8	2.7 — 18.6	77 — 125	83 — 158
		46.8 ± 13.3	9.8 ± 2.6	11.6 ± 3.3	93.5 ± 11.3	124.5 ± 21.3

TABLE II

Serum Enzymes in Eclamptic Patients at different stages

Class	No.	Serum Enzymes in Eclampsia				
		CPK	GPT	GOT	HBD	LDH
Severe	2	216.2—257.3 236.7	97.6 — 107.3 102.5	122.2 — 136.5 129.5	193 — 247 220.2	443 — 465 454.0
Moderately Severe	5	144.4 — 197.5 166.7 ± 17.6	54.8 — 88.7 63.4 ± 7.6	63.3 — 115.5 93.9 ± 6.9	167 — 188 163.2 ± 16.1	387 — 422 401.4 ± 28.6
Mild	13	74.8 — 112.6 93.3 ± 11.2	32.6 — 48.3 41.6 ± 6.1	44.2 — 54.1 49.4 ± 6.3	144 — 177 152.2 ± 11.6	215 — 352 283.1 ± 34.2

TABLE III

C.S.F. Enzymes in Pre-eclampsia, Eclampsia, Normal pregnancy, Seizure disorder and Hypertensive vascular disease

Group	No.	CPK IU/L	GPT IU/L	GOT IU/L	HBD IU/L	LDH IU/L	Protein
Control	25	5.0 — 12.6 6.3 ± 1.8	3.3 — 8.8 5.2 ± 1.3	2.2 — 10.4 6.1 ± 1.5	3.8 — 15.6 11.3 ± 2.6	7.3 — 21.2 13.3 ± 3.2	25.5 ± 3.8
Normal pregnancy	25	3.8 — 7.6 5.3 ± 1.7	4.1 — 8.0 6.4 ± 1.2	1.0 — 5.6 3.1 ± 1.03	3.5 — 12.8 8.6 ± 2.2	3.3 — 18.3 9.4 ± 2.8	27.6 ± 4.2
Seizure disorder	5	2.6 — 7.9 5.1 ± 1.6	3.6 — 7.5 5.3 ± 1.8	2.6 — 7.8 5.8 ± 1.17	3.6 — 14.5 9.2 ± 2.7	5.8 — 19.6 12.6 ± 3.5	26.3 ± 3.6
Pre-eclampsia	33	2.1 — 9.2 4.3 ± 1.1	4.5 — 8.0 6.1 ± 1.7	3.3 — 8.2 6.3 ± 1.8	5.7 — 22.6 16.6 ± 4.4	6.2 — 21.0 13.3 ± 3.8	33.3 ± 9.6
Eclampsia	20	2.8 — 9.9 4.5 ± 1.3	5.0 — 8.0 6.5 ± 1.6	5.4 — 10.0 7.2 ± 1.8	16.3 — 63.6 41.6 ± 11.5	5.8 — 21.0 12.8 ± 3.3	83.4 ± 12.1
Hypertensive vascular disease	9	3.1 — 10.0 5.6 ± 1.2	3.8 — 8.0 5.2 ± 1.6	2.8 — 7.6 4.3 ± 1.4	3.8 — 14.0 10.5 ± 3.8	4.4 — 15.6 9.3 ± 2.6	25.8 ± 4.6

CSF enzymes studied for each of the 5 groups are shown in Table III. All the enzymes were well within the normal range in each of the 5 group except HBD which was slightly raised in pre-eclamptic and significantly raised in eclamptic patients ($p < 0.01$).

Discussion

As shown in Table I, in normal pregnancy serum CPK was considerably raised while other four enzymes were well within the normal range. These observations have been supported by various workers who reported that this rise was due to the release of CPK from the uterine musculature during labour (Kenttinen and Pyorala, 1963), because uterus contains about 0.15 unit of CPK considering 1 unit for muscles (Dawson and Fine, (1967). Few authors reported a little increase of LDH and HBD (Kenttinen and Pyorala, 1963; Morrison *et al*, 1971). Theisen *et al* (1961) in normal pregnancy, while in our study there were no increase in these enzymes.

All the patients with seizure disorders had elevated CPK values. This elevation was apparently due in part to skeletal muscle changes resulting from seizures. The number of seizures endured by a patient was directly related to the level of CPK detected in the serum. The other enzymes tested were well within the normal range because their content in sketetal muscle is low and the seizure's primary effect is on skeletal muscle.

In pre-eclamptic patients serum CPK was considerably raised while other enzymes, GOT, GPT, LDH and HBD were slightly increased because of the segmental vasospasm which are characteristic of these disease (Theisen *et al*, 1961). The elevation serum CPK is presumably due in part to labour and partially to anoxia resulting from a decreased uterine blood flow due to segmental vasospasm.

All the eclamptic patients had significantly raised levels of all the enzymes. In these patients the higher level of serum CPK is due primarily to seizures that damage skeletal muscles and as well as labour, while anoxia contributes the elevation of all the enzymes due to segmental vasospasm. The levels of CPK, SGOT, SGPT, LDH and HBD are closely related to the severity of disease in patients with eclampsia (Table II). The patients with severe eclampsia have highest level of serum enzymes. For instance, the 2 deaths, both of which showed extensive destruction of all the parenchymal organs clinically had the highest level of serum enzymes. The 5 patients who were classified as moderately severe displayed extensive tissue damage clinically with high levels of enzyme activity, had late recovery and this extended length of time in these patients reflects the severity of damage. Fourteen patients who were classified as mild had fever neurological manifestations than the severe eclamptic patients and did not have evidence of renal (hematuria or oliguria) or hepatic (epigastric pain or tenderness on examination) involvement had significantly raised level of serum enzymes. Although the serum enzyme levels were elevated in all the eclamptic patients according to the severity of disease the measurement of serum enzymes alone would not suffice as a criteria for prognosis of these patients. One reason is that an individual may have extensive liver damage, producing a dramatic rise in the predominant liver enzymes, but the patient may have very little carebral or renal complications. In these patients the CPK level can be compared because it is not raised in liver

disease and their condition would not necessarily be critical .On the other hand, a patient could have extensive cerebral damage with little or no lung or liver damage. In this case, only CPK will be significantly raised, while modest elevation of serum enzymes would be detected. Thus serial estimation of CPK would provide the prognosis of the disease.

The CSF values of CPK, GPT, GOT and LDH were well within the normal range in all the groups of patients. Whereas HBD was slightly raised in 18 of the 33 patients of pre-eclampsia while it was significantly raised in all the patients of eclampsia and furthermore the degree of increase was proportional to the severity of disease. All the 2 patients who were severily ill had highest HBD level in CSF, died.

When the data in Table I are compared with that in Table III, no correlation has been observed between the level of enzymes of the serum with those of the CSF. Thus, elevation of CSF enzymes in patients with eclampsia is independent of serum levels and appears to be derived from damage, but not necessarily death of brain cells themselves. For example, the level of CPK in the serum was elevated in patients with seizure disorders due to skeletal muscle changes while in CSF it did not reflect this increase (Table III). Furthermore the patients with eclampsia also had elevated CPK levels because of seizure, labor, and segmental vasospasm, which are characteristics of the disease, but CPK of the CSF did not show any increase in the severe eclamptic patients. This provided an additional evidence that the serum enzymes do not contribute to the level of enzymes of the CSF. The other enzymes that are elevated in severe eclamptic patients are not elevated in the same proportion as seen in the serum of these patients. The integrity of the blood brain barrier, however, appear to be disturbed, permitting the passage of HBD and other proteins in to CSF. The proteins of the eclamptic patients presumably result from damage to cerebral cell themselves. But the failure of an observed elevation of CPK in the CSF of eclamptic patients is not clearly understood because high concentration of CPK has been observed in brain tissues Colombo *et al* (1962), but not as high as skeletal, smooth, and cardiac muscle. On the other hand, it is difficult to explain the pronounced increase in HBD without increase in CPK. Miyasak (1958) suggested that the enzymes and protains come directly from the cerebral cells while Lending *et al* (1959) suggested from the serum. This appears likely in view that an elevation of protein and certain enzymes in the CSF is characteristic of other types of neurologic disease (Chutorian *et al*, 1966; Cunningham *et al*, 1965; Green *et al*, 1957; Jakoby and Jakoby, 1958; Lending *et al*, 1959). The extent of elevation of serum enzymes levels of the eclamptic patients is directly proportional to the severity of disease (Table II). However, the level of protein in the CSF of eclamptic patients is independent of the patients' condition but characteristic of the disease, since the elevation of serum CPK is directly related to number of seizures that patient has had, while in pre-eclamptic patients, this elevation is due to labour and vasospasm. The elevation of serum CPK and other enzymes in pre-eclamptic patient are lower than those observed in eclamptic patients, which shows that there was more tissue distribution in eclamptic patients (Table I). Furthermore, the pre-eclamptic patient does not have an elevated protein or enzyme levels in the CSF. The patients

with hypertensive vascular disease characterized by vasoconstrictions did not cause a detectable alteration of CSF and serum enzymes. Although the eclamptic patients exhibit some of the symptoms of each of the other disease studied, they displayed characteristics which are unique to the disease.

Summary

A comparison was made of enzymes levels for creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), lactic dehydrogenase (LDH), and alphahydroxy butyric dehydrogenase (HBD) in the serum and cerebrospinal fluid (CSF) of patients with eclampsia, pre-eclampsia, seizure disorder, and chronic hypertensive vascular disease. In eclamptic and to a lesser extent, the pre-eclamptic patients had increased levels of all the serum enzymes and that was attributed to segmental vasospasm which is characteristic of both types of toxemias. Serum C.P.K. was also elevated in normal pregnancy and as well as in seizure disorder due to release of this enzyme from uterine musculature during labour and skelatal muscle changes resulting from seizures. Examination of CSF revealed that eclamptic patients had elevated proteins and enzyme HBD level, which could be correlated to the diagnosis of the severity of the disease. None of the other diseases studied caused an increase of these parameters of the C.S.F.

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