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Non-Ketotic Hyperglycemia and Recurrent Seizures

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Abstract

Non-ketotic hyperglycemia (NKHC) is an important cause of recurrent convulsions in the middle aged and elderly persons. Thirty-two patients (17 men, 15 women) with an average age of 58.6 yrs with recurrent convulsions and NKHC admitted to NIMHANS over a period of 8 years are discussed here. Fifteen patients were known hypertensives and fourteen patients were known diabetics, on irregular medication. Four persons had a history of TIA / RIND and 5 persons had seizures some time in their past. Twenty-nine persons presented with recurrent focal motor seizures with or without generalization while only 3 patients presented with generalized seizures. Hyperglycemia (average blood sugar 542 mg%) and hyperosmolarity (average 322) were observed in all. Seizures were controlled only after control of metabolic parameters. Radiological investigations - CT (7), angiogram (5) and partial autopsy of the brain (3) did not reveal any evidence of infarction either recent or old. Even the motor paralysis noticed in 21 persons at the onset of illness was transient in all except one.

Key words -
Diabetes mellitus,
Non-ketotic hyperglycemia,
Status epilepticus,
Epilepsia Partialis Continua

Diabetes Mellitus is known for its protean neurological manifestations. Non-ketotic hyperglycemic coma (NKHC) is well recognised and at times the first manifestation of diabetes mellitus especially in elderly individuals. Besides this, epilepsia partialis continua (EPC), focal motor seizures, tonic seizures and movement induced seizures have also been reported in the NKHC [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11]. Hyperglycemia, hyper-osmolarity, intra-cellular dehydration and intra vascular thrombosis have been incriminated in the genesis of these seizures. Although in majority of patients pre-existing brain lesions like tumor, infarct and trauma have been considered to be essential for precipitation of seizures, pathological reports supporting these mechanisms are only few [1], [3], [6]. The present communication describes clinical features of 32 cases of uncontrolled seizures who had non-ketonic hyperglycemia along with pathological report of the

brain from 3 autopsied cases from this group.

Material and Methods

Thirty-two patients with highly recurrent seizures with hyperglycemia and with or without mild ketoacidosis, seen over a period of eight years form the basis of this report. Past history of epilepsy, head injury, hypertension, diabetes mellitus and ischemic heart disease was enquired in all. Detailed systemic and neurological examination was carried out at the time of admission and at discharge from hospital. Blood glucose, urea, creatinine and serum electrolytes and osmolarity were estimated within 24 hours of admission. Blood glucose was monitored regularly till it was controlled, with Insulin and fluid therapy. Out of the nine deaths in the hospital, autopsy of the brain was conducted in three patients. Special attention was paid to the presence of either recent or old infarction and vascular changes.

Results

There were 17 men and 15 women in the age range of 35 to 85 years (mean 58.6 years). Five patients had past history of seizures and 14 patients (44%) had diabetes and were on irregular medication. Fifteen (47%) patients had established hypertension and four patients had past history of TIA / minor stroke (Table I). The chief presenting symptom was recurrent focal motor seizures with or without generalization (Table II). At admission 17 patients were fully conscious while one was deeply comatose. The remaining patients were in altered sensorium. Twenty-one patients had some degree of focal motor weakness at admission. It was mild in all and persisted in only one patient after the control of seizures. The blood sugar at admission ranged from 375 mg% to 1088 mg% with an average of 542 mg%. Serum osmolarity ranged from 224 to 360 (mean 322). Serum sodium ranged from 123, Eq/L to 145 mEq/L (mean 136 mEq/L). Control of seizure was achieved in 2-96 hrs (mean 29.76 hr) and corresponded with the improvement in metabolic parameters. Diazepam infusion was required in five patients who had status epilepticus. Ketone bodies were absent in 24 patients (75%) and were only in traces in 8 patients. Computed tomographic scan of the brain done in 7 patients revealed cortical atrophy and ventricular dilatation in one while it was essentially normal in others. Carotida angiography carried out in 5 patients was also normal in all. Twenty-three patients recovered and follow up data at 12 months in them revealed that 9 patients were seizure free (seven of them were on anticonvulsants) and one patient had recurrent seizures despite medication. Only one patient has residual minimal hemiparesis even after 2 years. Nine patients expired due to progressive coma, complicated by peripheral circulatory failure in 3 patients and myocardial infarction in one patient. Partial autopsy of brain was conducted in three of them (Fig 1-4). In case 1, sections of brain revealed vascular changes characteristic of chronic hypertension, namely medial hyperplasia and hyalinization. Around a few deep parenchymal vessels were seen hemosiderin laden macrophages suggesting old leak of RBCs. The brain showed diffuse edema with geographic region in the deep parietal lobe resembling demyelination but without any inflammatory changes. There were no features of infarction. In case 2 microscopic evidences favoured the diagnosis of pyogenic meningitis. The parencyhmal vessels showed mild thickening but not significant enough to be labelled as a hypertensive change.

There was neither any vascular occlusion nor recent or healed infarction. In case 3, gross examination of the brain revealed moderate cortical atrophy particularly marked on the frontal and temporal lobes. Vessels within the parenchyma showed chronic hypertensive changes. Similar to cases 1 and 2 there were no features to suggest vessel occlusion or infarction.

Table I - Past history (n=32)

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Table II - Symptoms and signs (n=32)

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- ***A parenchymal vessel showing hyalinization and calcification of the wall (HE × 125)***
- ***A large vascular channel with mild thickening of wall and hyalinization (HE × 125)***
- ***A medium sized parenchymal vessel with hyalinization of wall. There is fibrosis with numerous haemosiderin laden macrophages in the perivascular shape (HE × 80)***
- ***An area of white matter tissue pallor around a thin walled capillary (HE × 25)***

Discussion

Non ketotic hyperglycemia (NKHC) is characterized by hyperglycemia, dehydration, alteration in consciousness with minimal or absent ketoacidosis and mortality ranging from 40%-70% [11]. The prognosis is better when consciousness is preserved. Nearly 25% of patients present with seizures (75% being focal motor) with or without focal neurological deficit. Of the 395 patients with status epilepticus and 52 cases with epilepsia partialis continua, seen at NIMHANS, 32 patients had hyperglycemia without significant keto acidosis. Twenty-nine of the 32 patients in the present report had focal seizures which is similar to earlier reports. The initial communication regarding the focal motor seizure in NKHC was by Maccario et al [6] and this was followed by report of tonic focal seizures, movement induced seizure, epilepsia partialis continua, choreoathetosis and ballismus or position induced focal seizures [1], [2], [3], [4], [5], [6], [7], [8]. Seizures in ketotic coma are rare, since ketoacidosis is considered to protect the brain from convulsions [7]. Singh et al [4] in a study of 21 patients observed that seizures occur initially when the hperglycemia is less severe and osmolarity and serum sodium are normal or slightly raised. We also did not observe severe changes in the serum osmolarity or serum sodium concentrations. Consciousness in NKHC may be relatively spared as was evident in the present series.

Seizures are relatively resistant to anticonvulsants and often respond only after metabolic factors are controlled. Generalized seizures are probably precipitated by metabolic changes. However, focal seizures are usually attributed to underlying structural lesion [7]. It is postulated that small silent ischemic or other lesions are provoked by metabolic events like hyperglycemia, hypernatremia and hyperosmolarity which result in cellular dehydration [1], [2], [3]. Experimental studies have shown activation of existing foci with hypertonic solutions [10]. However, large number of patients in the present series as well as previous reports did not have severe hyperglycemia or hyperosmolarity [11]. Relatively older age of the patient (a mean age of -58.6 years in the present report series) also may suggest that silent ischemic or acute microvascular lesions are responsible for focal seizures. The fact

that 47% of the patients in the present series were hypertensive suggests that contribution of long standing hypertension needs to be examined. One of the brain autopsied showed changes of chronic hypertension, while another revealed features of pyogenic meningitis. But all the 3 brains examined at autopsies did not reveal any infarction recent or old. CT Scan done in 7 patients also did not reveal any evidence of recent or old infarction. Though the brain showed evidence of sclerosis of vessel wall, there were no recent infarcts or gliotic scars.

Therefore the hypothesis of silent infarction and epileptic focus causing convulsions and other neurological deficits cannot be generalized. In fact, in all our cases the changes were more acute and diffuse with no convincing focal pathology. (The cerebral oedema and dark eosinophilic neurons can be attributed to a terminal non-specific hypoxic change). Therefore in addition to infarction there may be many factors like pre-existing epilepsy, ischaemia, infection and metabolic abnormalities which can result in uncontrolled focal/generalized seizures in non-ketotic hyperglycemic state. The presence of changes of chronic hypertension in the cerebral vessels was only in age related and coincidental finding or has any relationship to precipitation of convulsions in these patients is not clear.

Conclusions

The limited radiological and pathological evidences do not support the theory of pre-existing infarction as the cause of recurrent seizures in the non-ketotic hyperglycemia. In addition to the metabolic parameters the role of infection and effect of long standing hypertension needs to be considered.

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