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Homovanillic Acid and 5-Hydorxyindoleacetic acid levels in Parkinson's Disease and Chorea in relation to drug treatment

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Abstract

The CSF HVA and 5-HIAA levels and their changes with drug treatment studied in 30 patients with idiopathic parkinson's disease (PD) and 30 patients with chores. Twenty cases of non neurological diseases formed the control for both groups and in them the mean CSF HVA level was 35.7 ± 12.5 ng/ml and the mean 5-HIAA level was 32.4 ± 1.4 ng/ml. The mean age of PD was 52.5 ± 10.4 years. The CSF HVA and 5-HIAA levels were estimated thrice in them: before starting treatment, 10 days after treatment with trihexiphenidyl 2 mg/three times a day and orphenadrine 50 mg/three times a day and the third estimation was made after another 10 days of treatment with amantadine 100 mg/twice a day in addition to the other two drugs. In them, before starting treatment the HVA levels were low, mean value being 13.3 ± 7.3 ng/ml ($P < 0.001$). It increased to 22.8 ± 8 ng/ml ($P < 0.001$) after 10 days and it further increased to 31.0 ± 22.8 ng/ml ($p < 0.001$) after 20 days of treatment . Patients with akinesia had lower levels of HVA compared to those with tremors but was not statistically significant. The mean 5-HIIA levels were low in all the 3 samples; 13.4 ± 6.2 ng/ml, 16.1 ± 5.2 ng/ml, 16.5 ± 5.9 ng/ml ($P < 0.001$) respectively.

The mean age of patients with chorea was 11.5 ± 3.1 years. Seventeen of them fulfilled Jone's criteria for Sydenham's chorea (SC) and 13 did not fulfil the criteria but resembled rheumatic chorea. HVA and 5-HIIA levels in them was estimated twice, before starting treatment and after cessation of choreic movements following treatment with trifluperidl 10 mg/day. The mean duration of treatment was 4 days. The mean HVA levels were high in them before treatment, 71.18 ± 23.0 ng/ml ($P < 0.001$) and decreased to 49.0 ± 29.5 ng/ml ($P < 0.001$) after treatment. The mean 5-HIAA levels were low both before and after treatment, 23.4 ± 9.4 ng/ml ($P < 0.001$) and 22.6 ± 10.2 ng/ml ($P < 0.05$) respectively.

Key words -
Homovanillic acid,
Hydroxy indoleacetic acid,
Parkinson's disease,
Chorea,
Trifluperiodol,
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Homovanillic acid,
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Parkinson's disease,
chorea,
trifluperiodol,
Trihexiphenidyl,
Orphenadrine

Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the CSF are the end products of dopamine and serotonin respectively. The main biochemical abnormality of parkinson's disease (PD) is depletion of dopamine in the nigro-striatial and it is sufficient to explain all the major symptoms in this disease [1]. The dopamine deficiency is paralled by a reduction of HVA in CSF. The decrease in brain serotonin level is limited to specific structures. Caudate nucleus and hippocampus serotinin levels reach 60% of control values, whereas in some cortical areas they are unchanged [1], [2]. Still it is reflected in the CSF with a significant reduction of 5-HIAA levels in PD [3], [4].

There is some information available on the concentration of CSF HVA and 5-HIIA IN Sydenham's chorea (SC) [5], [6], [7]. CSF HVA and 5-HIAA changes after treatment with neuroleptics in SC have not been reported. SC is frequently seen in India as in other developing countries. The aims of the study were

(i) to estimate the base line levels of HVA and 5-HIAA in the CSF of patients with parkinson's disease and to monitor their changes after treatment with anticcholinergic drugs for 10 days and amantadine in addition, for the next 10 days.
(ii) to correlate HVA levels in PD with predominant symptoms (akinesia, tremor and both) and duration of illness.
(iii) to estimate CSF, HVA and 5-HIAA levels in patients with chorea before treatment and to evaluate their changes after symptomatic improvement of choretic movements with trifluperidol.

Patients and methods

Thirty patients with parkinson's disease who entered this study were drug free and being evaluated for the first time. The first estimation of HVA and 5-HIAA levels in the lumbar CSF was done before administering drugs. The patients were treated with orphenadrine (Disipal) 50 mg/three times a day and trihexiphendidyl (Pacitane) 2 mg/three times a day for 10 days. The second estimation was done on the 10th day. Amantadine 100 mg/twice a day was added on the 11th day and the third estimation was done on 20th day.

Thirty patients with chorea were also drug free and were being evaluated for the first time.Seventeen of them fulfilled Jone's criteria for SC. The remaining 13 did not fulfil Jone's criteria but no other etiological factor was found in them and they resembled SC. After collecting lumbar CSF they were

administered trifluperidol 20 tablets of 0.5 mg each per day. The second sample was collected after the cessation of choreic movements.For the control group, CSF was collected during spinal anaesthesia from 20 individual with no neurological illness, but undergoing surgery for physical ailments.

Consent was obtained from all patients. The lumbar CSF was collected in the morning after taking all precautions which are known to alter the HVA and 5-HIAA levels were measured by high pressure liquid chromatographic method.(HPLC).

Instrument/techniques [8]

For the estimation of HVA and 5-HIAA, Tracor HPLC and dual piston high pressure pump and Rheodyne injector, coupled with BAS LC-48 electrochemical detector equipped with glassy carbon electrode (Bioanalytical System, Inc. USA) was used.

Reverse phase Bondapac C-18 column, (25cm × 4mm Dupont Inc. USA) was used for the separation, at ambient temperature. Mobile phase, pumped at a rate of 1.5 ml/min. Consisted of 0.1M sodium acetate buffer, pH 4.0 and 5% methanol. Both mobile phase and samples were filtered through 0.4 micron membrane (Sartorious Inc.). For calibration, internal standard mode was used and the peaks were integrated using Hewlett Packard integrator. The total run time for separation of HVA and 5-HIAA was 20 minutes. Hydroxyindole (HI) was used as an internal standard. A mixture of HVA and 5-HIAA and HI standards (in mobile phase) and CSF containing known amounts of HI were injected directly. The amount of HVA and 5-HIAA were directly read from the integrator as ng/ml.

Results

Parkinson's disease (Tables I and III)

The mean age of incidence in the group of 30 patients was 55.5 ± 10.4, the youngest being 30 years and oldest 70 years. They were 26(86.7%) males. The duration of illness varied from 1 month to 168 months (mean 28.7 ± 37.6 months). Fifteen (50%) of them had predominantly tremor, 5 (16.7%) akinesia and 10 (33.3%) had a combination of akinesia and tremor.

Table I - Parkinson's disease

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T * Predominantly tremor
A Predominantly akinesia
T + A Combination of tremor and akinesia

CSF HVA levels, before starting treatment were below normal range in 29 (96.7%), above normal range in none the mean value 13.3 ± 7.3 was statistically significantly less than the control (35.7 ± 12.5).

After treatment with trihexiphenidyl and orphenadrine for 10 days, the HVA levels increased significantly ($P < 0.001$). Yet it was below normal range in 18 (60%), above normal range in 2 (6.7%) and the mean was 22.8 ± 14.8 which was significantly less than that of the controls.

Following amantadine administration, in addition to trihexiphenidyl and orphanadrine the CSF levels of HVA increased further. It was below normal range in 14 (46.7%), above normal range in 5 (16.7%) and the mean was 31.0 ± 22.8.

The 5-HIAA levels were below normal range in all the 3 samples and the mean was 13.4 ± 6.2, 16.1 ± 5.1 and 16.5 ± 5.9 respectively (control 32.4 ± 1.4). The three sample mean values were significantly less than the control ($P < 0.001$). There was no significant difference in HVA and 5-HIAA before and after treatment in relation to age, sex and duration of illness. In all 3 samples the HVA was lowest in the group with predominant akinesa while the 5-HIAA levels were highest. However the difference was not significant statistically ($P < 0.05$).

Rheumatic Chorea (Tables II and III)

The mean age of the patients in this group of 30 was 11.5 ± 3.1, the youngest being 6 years and the oldest years. There were 20 (66.6%) females. The symptomatology in 17 (56.6%) of the patients fulfilled Jone's criteria for rheumatic etiology and 13 (43.4%) did not fulfill Jone's criteria. However, there were no detectable causes in them and they resembled rheumatic chorea. Twentyfour (80%) of them had generalised chorea involving face, tongue, trunk and limbs and 6 (20%) had hemichorea. The duration of illness at the time of starting treatment varied from 1 to 150 days (mean duration 28.0 ± 30.7 days). The duration of treatment with trifluperiodal required for cessation of movements varied from 3 to 5 days (mean 4.0 ± 0.66 days).

Table II - Chorea

Table II - Chorea

Table III - Mean values of HVA & 5-HIAA levels in CSF of controls and patients with Parkinson's disease and Chorea

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Student t-test

CSF HVA levels were above normal range in 23 (76.7%) and within normal range in 7 (23.3%) before starting treatment. HVA levels decreased with treatment . It was above normal range in 11 (36.7%), within normal range in 15 (50%) and below normal range in (13.3%).

5-HIAA levels, were below normal range in 24 (80%), before treatment, above normal range in 5 (16.7%) and within normal range in 1 (3.3%). There was no significant change after treatment. The levels were below normal range in 25 (83.3%), above normal range in 2 (6.7%) and within normal range in 3 (10%). There was no significant difference in HVA and 5-HIAA levels before and after treatment in relation to age, sex, rheumatic and non-rheumatic groups and hemi and generalised chorea.

Discussion

HVA, the major metabolite of dopamine is derived mainly from the caudate neleus. About one third of

thisenters lateral ventricles. HVA levels in cisternal and lumbar CSF is lower because of its removal from CSF in ventricular system and subarachnoid space. However, HVA level in lumbar CSF parallels its level in cisternal and ventricular CSF and basal ganglia. 5-HIAA, the principal metabilite sites of brain and spinal cord.

The diminished lumbar CSF concentrations of HVA observed in the PD patients are consistent with previously reported values [1], [9], [10], [11]. When CSF HVA levels were analysed according to the predominant symptomatalogy, it was found that patients with akinesia had lower values than those with tremors. Similar findings have been observed in other studies [1]. The HVA increases after treatment with anticholinergic drugs for 10 days and was statistically significant. This is probably due to suppression of inhibitary action of basal ganglia on substantia nigra, resulting in increased dopamine secretion. The further increase of HVA after administering amantadine for 10 days in addition to anticholilibergic drugs is probably due to the release of dopamine which is already stored. 5-HIAA levels in the group with PD is found reduced before starting treatment compared to controls and was normal or decreased in previously reported series [1]. There was no change in their levels after treatment with anticholinergic drugs and amantadine in addition.

The HVA levels in chorea was increased significantly compared to controls in both rheumatic and non-rheumatic groups. There was no obvious cause for chorea in the non-rheumatic group and they resembled rheumatic chorea clinically. The studies reporting HVA levels in SC are very few and they recorded normal, increased or decreased values [5], [12]. Trufluperidol is the most effective neuroleptic in the symptomatic treatment of chorea irrespective of underlying cause and is in use in our institution for more than fifteen years. The mean duration of treatment to control movements was 4 days. The HVA levels after controlling movements were reduced to statistically significant levels. The 5-HIAA levels were found reduced in both rheumatic and non-rheumatic group, before and after the treatment. No earlier studies are available in literature for a comparative evaluation.

In this study it is clear that PD is a pypodopaminergic state and HVA levels increase when treated with anthicholinergic drugs and amantadine. It is also associated with clinical improvement when they were assessed at the end of 10th and 20th days. In contrast SC is an hyperdopaminergic state and HVA values decrease when with a neuroleptic, along with ameliration in choreic movements.

It is very well known that PD and chorea are inversely related clincially. Leveodopa induced chorea disappears when dose of Levodopa is reduced or tetrabenazine is added. Similarly the choreic movements are controlled with phenothiazines and butrophenones, particulary those containing flurine radicles and overdose of them produce parkinsonian features.

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