Levodopa and Huntington’s chorea

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SYNOPSIS Two patients with Huntington’s chorea are reported whose psychiatric and neurological symptoms greatly improved after treatment with L-dopa. In both cases the basal values of CSF HVA were markedly decreased, being increased by the treatment with L-dopa.

The so-called clinical opposition between Parkinson’s disease and Huntington’s chorea has its pharmacological and biochemical counterparts. Choreic movements are improved by a variety of agents that deplete the brain of monoamines or interfere with dopamine at the receptor sites (for references see Barbeau, 1973).

On the contrary, treatment with L-dopa, regarded, as is well known, as a dopamine (DA) replacement therapy (‘specific though probably predominantly symptomatic’, Bernheimer et al., 1973), markedly increases the choreic movements of Huntington’s disease and, when used in patients with Parkinsonism at high doses or for a prolonged period of time, may cause the appearance of a variety of abnormal movements (Barbeau, 1969; Cotzias et al., 1969; Klawans and Garvin, 1969; Barbeau et al., 1971).

Recent determinations of dopamine catabolites in CSF showed normal or low-normal values of homovanillic acid (HVA) in Huntington’s chorea and diminished levels of HVA in Parkinson’s disease (Bernheimer et al., 1966; Hornykiewicz, 1966; Birkmayer, 1969; Klawans, 1971; Guilleminault et al., 1973; Loeb et al., in press). After a probenecid test HVA levels were similar to controls (Aquilonius and Sjöström, 1971; Lal et al., 1973) or about half that of control subjects (Chase, 1973).

Levels of 5-hydroxyindoleacetic acid (5-HIAA) (serotonin metabolite) and 3-methoxy-4-hydroxyphenylglycol (MHPG) (noradrenaline metabolite) were not found to be significantly varied in Huntington’s chorea. Moreover, studies on cerebral dopamine metabolism showed a decrease of DA and HVA in the striatum and the pallidum in Parkinson’s disease, while no significant reduction of these metabolites was found in Huntington’s disease, except in the caudate nucleus, so that a possible putaminal-dopaminergic predominance has been suggested (Bernheimer et al., 1973).

These findings in Huntington’s disease seem to have the following exceptions:

1. A substantial diminution of HVA concentration in the cerebrospinal fluid, suggesting a reduction in dopamine metabolism, has been reported (Curzon et al., 1972; Chase, 1973), even if no apparent correlation between HVA decrease and the severity of motor abnormalities could be established.

2. A few cases, some with lower levels of CSF HVA, associated with a good responsiveness to treatment with L-dopa, have been described by some authors (Tan et al., 1972; Schenk and Leijnse-Ybema, 1974).

We present two additional cases of Huntington’s chorea with reduction of the CSF content in HVA, both of which were improved by treatment with L-dopa.

METHODS

Two unrelated female patients (case 1 and 2) with Huntington’s chorea and a positive family history
Levodopa and Huntington's chorea involving two successive generations were studied (Figure). The disease, which had begun six and five years previously, showed at the onset only psychiatric disturbances, consisting of a paranoid reaction (case 1; C.A.) and a catatonic-like picture (case 2; V.I.); when referred for neurological examination they showed severe mental deterioration (Table 1) and such marked and diffuse choreic movements that speaking, walking, and feeding were rendered almost impossible.

The patients were kept untreated and on a constant diet for 15 days; lumbar punctures were performed at 9 a.m. with the patient on her side, after having been fasted and confined to bed during the preceding 12 hours; levels of HVA, 5-HIAA, and MHPG were determined fluorometrically, according to the methods of Korf et al. (1969, 1971a,b) on the first 8 ml of CSF.

During the next 10 days, phenothiazine derivatives were administered according to the following schedule: fluphenazine, 100 mg daily in case 1; perphenazine 40 mg daily in case 2. At the end of this period, while the patients showed no clinical changes, a second lumbar puncture was performed in the same way as before. After a 15 day period of rest without treatment, l-dopa (2 g/day) was administered; at the end of 15 days' treatment with levodopa a third lumbar puncture was carried out.

RESULTS

The CSF HVA values of our two patients with Huntington's chorea were at the lower end of the range as compared with controls and the values reported in the literature for chorea major (Table 2; see, however, Chase, 1973).

Phenothiazine therapy proved unsuccessful for both psychiatric and choreic symptoms which, sometimes, appeared to become worse. Moreover, it did not produce significant variations in CSF HVA (Table 2). On the contrary, l-dopa, at dose levels which substantially increase central dopamine metabolism, markedly improved both psychiatric and choreic movements: both patients

![Figure](The pedigrees of the two families.)

**TABLE 1**

**SUMMARY OF RELEVANT CLINICAL FINDINGS**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Psychiatric onset</th>
<th>Illness duration (yr)</th>
<th>Clinical picture</th>
<th>Wechsler-Bellevue intellectual impairment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Psychiatric disturbances</td>
<td>Choreic movements</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>52</td>
<td>Yes</td>
<td>6</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>42</td>
<td>Yes</td>
<td>5</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
</tbody>
</table>
TABLE 2
CSF LEVELS OF MONOAMINE METABOLITES

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>After L-dopa</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>MHPG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>After L-dopa</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>5-HIAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>After L-dopa</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>

were able to walk and feed without any help, the abnormal movements, especially those of the face, were markedly reduced, speech became almost fluent, and the two patients showed a marked improvement in behaviour, becoming less excitable and more controlled.

The L-dopa treatment brought about a marked increase in the level of CSF HVA in both patients, to three and five times respectively their previous values (Table 2).

COMMENT

Our two cases add to four other similar ones from the literature on Huntington’s chorea (two cases of Tan et al. (1972) and two cases of Schenk and Leijinse-Ybema (1974).

We are fully aware that our method of measuring HVA and other metabolites, as Barbeau (1973) pointed out, only scratches the surface of Dopa metabolism. Nevertheless, we think that the existence of cases of the type described above—that is, which show, on the one hand, a great improvement of psychiatric symptoms and choreic movements after treatment with L-dopa and, on the other, a clear-cut decrease in CSF HVA basal values, followed by a marked increase after L-dopa therapy—deserves careful attention, in spite of the great individual variations in the values of MHPG and 5-HIAA, both in basal conditions and after therapy. In our cases, the HVA values did not show significant variations after phenothiazine treatment.

Disturbances of dopamine metabolism in Huntington’s chorea may be related to decrease (Klawans, 1970) or increase in DA turnover (Curzon et al., 1972; Bernheimer and Hornykiewicz, 1973; Chase, 1973), which, in turn, is dependent on the state of striatal DA receptors (Hornykiewicz, 1971).

There are good reasons to support the theory that the unbalanced dopaminergic relationship between the caudate nucleus and the putamen (Hornykiewicz, 1973) and/or the excessive stimulation of a damaged striatum by a relatively normal nigrostriatal DA pathway (Mardsen, 1975) could be the cause of choreic movements. Nevertheless, the fact that in our cases L-dopa proved to be effective in checking choreic movements cannot be accounted for by this theory and must simply be taken as evidence for the existence of a peculiar variety of the disease for which there is still no convincing pathophysiological explanation.

REFERENCES


Hornykiewicz, O. (1966). Dopamine (3-hydroxytryptamine) and brain function. Pharmacological Reviews, 18, 925–964.


