

*Short report*

## Homovanilic acid in Huntington's disease and Sydenham's chorea

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**SUMMARY** Homovanilic acid (HVA) was determined in the lumbar CSF of 12 patients with Huntington's disease and 12 with Sydenham's chorea before and after probenecid administration. The means of HVA concentration (basal and after probenecid) were lower in those with Huntington's disease than in controls, and were even lower in a sub-group characterised by increased tone and slowness of voluntary movement. There was no correlation between CSF HVA values and the severity of abnormal movements, nor with length of the illness and age of the patients with Huntington's disease. The mean basal HVA concentration did not differ from controls in those with Sydenham's chorea but the accumulation with probenecid was significantly lower. These results suggest a decrease in cerebral dopamine release in both forms of chorea.

About one third of the homovanilic acid (HVA) derived from the catabolism of dopamine (DA) and released in the striatum enters the CSF in the lateral ventricle.<sup>1 2</sup> There is some evidence to suggest that the concentration of this acid metabolite in ventricular CSF, is related to the concentration in the striatum.<sup>2-4</sup> But the concentration of HVA in the cisternal and lumbar CSF is lower, and the correlation with striatal levels disappears.<sup>1 5 6</sup> At least three mechanisms are responsible for the lower HVA levels-lumbar CSF (1) the diffusion of the HVA "jet," (2) the CSF circulation, (3) an active transport mechanism localised in the fourth ventricle and sub-arachnoid space.<sup>7-8</sup> This active transport mechanism can be blocked with probenecid, which prevents the efflux of HVA and 5-HIAA from CSF.<sup>8-11</sup> There has been considerable variation in the dose and timing of probenecid administration to man.<sup>12-15</sup>

Various groups of patients with Huntington's disease have been reported to have decreased or low normal concentrations of HVA in the CSF,<sup>16-21</sup> although other authors have found values similar to controls.<sup>22-23</sup> Some papers have reported on small number of cases, with a great variability of values.<sup>24-25</sup> A very low basal HVA

level was described by Curzon<sup>16</sup> in two patients with severe akinetic-rigid Huntington's disease. The increment of CSF HVA after probenecid was reported as normal in two patients,<sup>26</sup> but decreased in two other papers reporting groups of eight and two patients respectively with Huntington's disease.<sup>18 27</sup>

There is little information available on the concentrations of CSF HVA in Sydenham's chorea, but again values within the range of normal have been reported.<sup>16 29</sup>

We have studied two groups of patients, 12 with Sydenham's chorea and 12 with Huntington's disease. CSF HVA was determined before and after probenecid administration. Correlations with clinical data were made.

### Material and methods

The main features of the Huntington's disease and Sydenham's chorea patients are summarised in tables 1 and 2. Severity of abnormal movements was assessed by the AIM scale (maximum 42) and the criteria for gradation of rigidity and bradykinesia were those defined by Duvoisin.<sup>30</sup> None of the patients was taking any drug for at least three weeks before determination of CSF HVA. The nature of the investigation was explained to the patient or to a responsible relative and consent was obtained. Three days before the lumbar puncture the patient was kept on a diet that excluded all the foods known to influence monoaminergic metabolism.

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Table 1 Huntington's disease

Sex	Age	Family history	Severity of abnormal movements	Rigidity	Bradykinesia	Dementia	Basal HVA (ng/ml)	Post-probenecid HVA (ng/ml)
M	43	+	10	2	2	+	26	52
M	46	+	28	0	0	+++	—	62
F	57	+	36	0	0	+++	—	115
F	43	+	22	2	2	++	16	32
M	33	+	15	0	0	+	28	158
M	44	+	20	0	0	++	63	66
M	48	+	32	0	0	++	47	91
F	61	+	18	2	1	+	11	13
F	38	+	12	2	2	+	19	—
F	41	+	31	0	0	+	38	113
F	47	+	38	0	0	++++	8	36
M	43	+	24	2	2	+++	11	21
$\bar{x} \pm 1$ SD							26.7 ± 17.0	69.0 ± 43.4
Control							53.6 ± 38.9	136.2 ± 35.0

In ten Huntington's and nine Sydenham's chorea patients a lumbar puncture was done to determine basal HVA values. In eleven patients with Huntington's disease 6 g of probenecid were given in three doses at three hours intervals and a lumbar puncture was done three hours after the last dose. A similar procedure was done on ten Sydenham's chorea patients, with the total dosage of probenecid of 90 mg/kg. Nine patients with Huntington's disease and seven with Sydenham's chorea had CSF HVA determinations before and after probenecid. The samples of the first 5 ml of CSF were stored at -20°C until determination of HVA by the method of Gerbode and Bowers.<sup>31</sup> Sixteen patients with neurological or psychiatric disorders not known to disturb monoaminergic metabolism or CSF dynamics were used as controls (basal HVA value 53.6 ± 38.9 ng/ml; post-probenecid HVA value 136.2 ± 35 ng/ml (mean ± 1 SD).

**Results**

The data are summarised in tables 1 and 2. The mean CSF HVA in the patients with Huntington's

Table 2 Sydenham's chorea

Age	Sex	Basal value (ng/ml)	Post-probenecid value (ng/ml)
12	F	36	48
12	F	48	71
22	F	—	66
13	F	52	—
11	M	—	131
12	M	85	91
9	F	24	37
10	F	48	92
8	M	21	124
11	M	33	100
13	M	32	—
14	F	—	40
$\bar{x} \pm 1$ SD		42.1 ± 18.3	80.0 ± 31.5
Control		53.6 ± 38.9	136.2 ± 35.0

disease after probenecid was less than in controls (p < 0.001). There also was a reduction of the mean increment, but it did not reach statistical significance. In general, those patients with Huntington's disease in whom rigidity and slowness of movement were detected had mean post-probenecid concentration less than those in the group on which those symptoms were not present. No correlation was found between HVA values and severity of abnormal movements, nor with length of history or age of the patients with Huntington's disease. The mean basal value in Sydenham's chorea did not differ from controls, but there was a smaller increment with probenecid administration, so that the post-probenecid level was less than that in controls (p < 0.005).

**Discussion**

There is some difference of opinion over the findings of different authors regarding concentrations of striatal DA in Huntington's disease. Ehringer and Hornykiewicz<sup>32 33</sup> originally found values similar to controls, but subsequently a decrease in striatal DA has been reported.<sup>34-36</sup> Spokes,<sup>37</sup> in a recent paper, found an increase of DA concentration per mg of tissue, but the concentration tended to be less in rigid chorea.

The variability of values found for DA concentration in the striatum may be one of the factors to explain the variability of findings on CSF HVA in Huntington's disease, but the reduction in CSF HVA, especially after probenecid, seems to imply a reduction of cerebral DA release, particularly in those with increased tone and slowness of movement. This latter group of patients with Huntington's disease with a decreased accumulation of HVA, also has been

reported to exhibit an increased incidence of paranoid psychosis.<sup>38</sup> However, there was no correlation of CSF HVA with the severity of abnormal movements suggesting that factors other than DA metabolism, including alteration of other neurotransmitters, such as acetylcholine and  $\gamma$ -aminobutyric acid and substance P, may be responsible for the severity of chorea.<sup>39-42</sup>

In Sydenham's chorea, a fast disappearing disease, the reduction of accumulation of HVA after probenecid again suggests a decrease in DA turnover.

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