

Homovanillic Acid in the Cerebrospinal Fluid of Parkinsonian Patients

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SUMMARY: Determinations of CSF HVA before and after Probenecid administration were made in 41 patients with Parkinson's disease. The means of HVA concentration were lower than those of controls but no correlation with clinical data was found. A negative correlation was demonstrated between post-probenecid HVA levels and subsequent score improvement with L-DOPA at 3,6 and 12 months. Post-probenecid HVA levels suggest that there are distinct forms of parkinsonism and could predict the response to L-DOPA therapy.

RÉSUMÉ: Les concentrations de AHV dans le LCR avant et après Probenecid ont été mesurées chez 41 parkinsoniens. Les concentrations moyennes de AHV étaient au-dessous de celles des contrôles mais aucune corrélation avec les faits cliniques n'a pu être démontrée. On a trouvé une corrélation négative entre les niveaux de AHV post-probenecid et l'amélioration du "score" avec L-DOPA à 3,6 et 12 mois. Les niveaux de AHV post-probenecid, suggèrent des formes différentes de parkinsonisme et pourraient prédire la réponse au traitement par L-DOPA.

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Since the demonstration of a decrease in dopamine (DA) and homovanillic acid (HVA) in the striatum of patients with Parkinson's disease (Ehringer and Hornykiewicz, 1960; Bernheimer and Hornykiewicz, 1964, 1965) various approaches have been made to study DA metabolism through the concentration of its acid metabolites in cerebrospinal fluid (CSF). About one third of the HVA released in the striatum enters the CSF in the lateral ventricle intermittently (Sourkes, 1973; Wightman et al, 1978). Although the concentration of HVA in the ventricular CSF seems related to that in the striatum (Moir et al, 1970; Wightman et al, 1978) the initial "jet" of HVA diffuses in a circulating CSF and is partially cleared by an active transport mechanism (Ashcroft et al, 1968; Wolfson et al, 1978) so that the concentration in cisternal and lumbar CSF is lower and the correlation with striatal levels disappears (Roos, 1971; Sourkes, 1973; Garelis and Sourkes, 1973). This can be compensated for to some extent by the administration of probenecid which blocks the active transport mechanism, preventing the efflux of HVA from CSF (Guldeberg et al, 1966; Forn, 1972; Wolfson et al, 1978; Aizenstein and Korf, 1978).

Several papers have reported a decreased basal HVA at ventricular (Guldeberg et al, 1967; Papeschi et al, 1970) cisternal (Jéquier and Dufresne, 1972) and lumbar (Johansson and Roos, 1967; Godwin et al, 1971; Miachon et al, 1974; Davidson, 1977) levels in parkinsonian patients, as well as a decreased accumulation after probenecid administration (Olsson and Roos, 1968; Chase and Ng, 1971; Bowers and Van Woert, 1972; Rinne et al, 1973). Some discrepancies, possibly related to the methodology, were

reported between the correlation of HVA concentrations and improvement scores after L-DOPA therapy. A negative correlation was found by some authors with basal (Jéquier and Dufresne, 1972; Gumpert et al, 1973; Miachon et al, 1974) as well as with post-probenecid levels (Lakke et al, 1971, 1973, 1974; Korf et al, 1974) but denied by others (Bowers and Van Woert, 1972; Chase and Ng, 1972; Rinne and Sonninen, 1972; Rinne et al, 1973; Weiner and Klawans, 1973).

To help clarify these problems, we studied 41 parkinsonian patients and determined CSF HVA *before and after probenecid administration*. The oral probenecid test as recommended by Chase and Ng (1972) was used, as the results are comparable to those obtained with intravenous infusion in spite of greater plasma and CSF probenecid concentrations and consequent gastrointestinal side effects (Kartzin et al, 1976). Correlations with clinical data and with response to L-DOPA treatment at 3,6 and 12 months were attempted.

MATERIAL AND METHODS

Forty-one parkinsonian patients (28 males and 13 females, mean age 59.5 ± 8.6) were assessed with a rating scale for parkinsonian symptoms (Duvoisin, 1971) and were informed about the nature of the investigation. For three days before the lumbar puncture, the patients were kept on a diet that excluded all foods known to influence monoaminergic metabolism. None of them were taking any drug for at least three weeks before determination of CSF HVA.

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In 33 patients a lumbar puncture was done to determine basal HVA values. In 36 patients the post-probenecid HVA value was determined after 6 grams of oral probenecid given in divided doses over three hours. The lumbar puncture was done three hours after the last dose.

Patients remained recumbent in bed throughout the study as well as during the preceding 12 hours. The samples of CSF were stored at -20°C until the HVA determination was carried out using the method of Gerbod and Bowers (1968). Sixteen patients without known disturbance of monoaminergic metabolism or CSF dynamics were used as controls.

L-DOPA in combination with a decarboxylase inhibitor was started after the test and improvement scores were calculated from the difference between the initial score and the results after 3,6 and 12 months of therapy. The t test for independent samples was used for statistical comparison of the means.

RESULTS

The data concerning HVA concentrations are summarized in table 1. Basal (40.5 ± 20.9 ng/ml) and post-

probenecid (69.7 ± 39.4 ng/ml) values are lower than those of controls (53.6 ± 38.9 ng/ml and 136.2 ± 35.0 ng/ml respectively) but only the last value attains statistical significance (p<0.001). There was no consistent correlation between HVA levels and age of patients, severity of illness or individual symptoms such as rigidity, tremor, bradykinesia and impairment of postural reflexes (table 2). The duration of illness was difficult to access in the majority of patients and its correlation with HVA was variable.

Fig. 1 shows the relationship between CSF post-probenecid HVA levels and the improvement scores after 3 months of L-DOPA therapy in 32 patients. A negative correlation between these values, reaches a high statistical significance (r=-0.57; p<0.001). This correlation persists after 6 and 12 months of L-DOPA therapy, but the level of significance is lower because of the smaller number of patients studied (27 and 20 respectively). In general, the patients who improved with L-DOPA therapy were slightly younger and had a significantly lower post-probenecid HVA. No other significant differences could be found in the total or partial disability scores (table 2).

TABLE 1
Concentration of HVA in Lumbar CSF

	BASAL/HVA		POST-PROBENECID/HVA	
	Controls	Parkinson's Disease	Controls	Parkinson's Disease
NUMBER	16	33	16	36
MEAN VALUE (ng/ml)	53.6±38.9	40.5±20.9	136.2±35.0	69.7±39.4
p	n.s.		<0.001	

TABLE 2
Correlation of Improvement Scores with Clinical Data and Post-Probenecid HVA

	Improvement Scores > 20%	Improvement Scores < 20%	Total
Number of Patients	22	10	32
Age	57.8 ±8.5	61.8 ±7.3	59.0 ±8.1
Rigidity Score	11.9 ±3.8	10.2 ±3.6	11.4 ±3.8
Tremor Score	6.7 ±4.9	5.9 ±4.1	6.4 ±4.7
Bradykinesia Score	25.0 ±9.3	18.7 ±6.1	23.0 ±8.9
Total Initial Score	49.9 ±15.5	44.7 ±12.0	48.3 ±14.7
Total Score at 3 Months Therapy	29.5 ±10.7	45.2 ±11.6	34.4 ±13.0
HVA Post-Probenecid	53.3 ±29.0	113.8 ±31.8	72.2 ±40.3
	p<0.001		

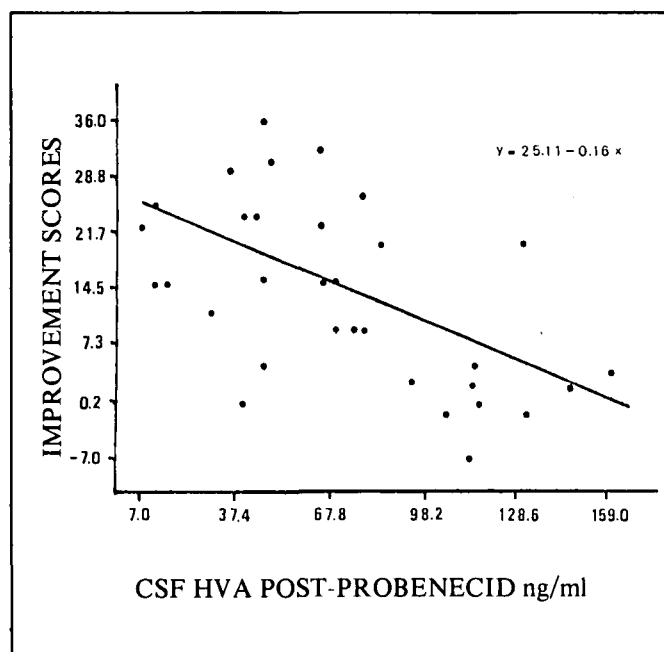


Figure 1 — Relationship between CSF post-probenecid HVA levels and improvement scores with L-DOPA.

DISCUSSION

We have previously identified two groups of parkinsonian patients based on a retrospective analysis of rate of deterioration and response to L-DOPA therapy (Gonçalves et al, 1981; Cunha et al, 1982). The first group showed rapid deterioration after a beneficial response to L-DOPA and frequent "on-off" phenomena. The second group with higher mean age, responded less well to L-DOPA and presented only occasional "on-off" phenomena. In the present study we attempted to trace biochemical differences between these groups, but failed to find any correlation between CSF HVA levels and duration, severity or clinical manifestations of disease.

However, a negative correlation was demonstrated between post-probenecid CSF HVA levels and response to L-DOPA therapy, confirming the report of Lakke et al (1971). Post-probenecid HVA levels could have predictive value in the assessment of responsiveness to L-DOPA. Higher values would predict a poor response to L-DOPA and would probably imply damage to nondopaminergic neurons (Lakke, 1974) or a more diffuse disease. In favour of this hypothesis, post-mortem studies of the brain of some parkinsonian patients do not reveal significant cell loss in the nigrostriatal system (Forno and Alvord, 1971; Bøttcher, 1975). A "multineuronal type" of parkinsonism with involvement of NA, DA, and serotonergic neurons has been suggested (Barbeau, 1976; Granerus et al, 1979).

On the other hand, lower levels of HVA reflecting a real striatal DA deficiency, could predict a good response to L-DOPA. This would imply that the DA synthesizing enzyme DOPA decarboxylase (mainly produced by DA cells) is present and that DA receptors are intact. This is not the case in more advanced forms of the disease where the enzyme deficiency and the receptor degradation could be factors which limit the response to L-DOPA.

We would like to stress the importance of standardizing the methods for determining HVA concentrations if CSF HVA levels are to be used to predict the response to L-DOPA. We recommend the probenecid method used in this paper. Even with this approach there are some uncertainties, but our results provide further evidence to support the hypothesis that there are two clinical and possibly etiological distinct sub-groups of parkinsonian patients.

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