Arch Psychiatr Nervenkr (1982) 231:131–140

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

Huntington's Disease — Imbalance of Free Amino Acids in the Cerebrospinal Fluid of Patients and Offspring At-Risk

G. Oepen[1], H. Cramer[1], R. Bernasconi[2], and P. Martin[2]

[1] Abteilung für Neurologie und klinische Neurophysiologie, Hansastrasse 9, D-7800 Freiburg, Federal Republic of Germany
[2] Forschungsabteilung Ciba-Geigy AG, CH-4002 Basel, Switzerland

Summary. A total of 27 different amino acids were determined in the fasting, morning lumbar CSF of 12 patients with Huntington's Disease (HD), 8 at-risk offspring and 16 non-choreic control patients. A significant ($P<0.001$) decrease was observed for asparagine, isoleucine, leucine, phenylalanine, histidine, arginine, α-aminoadipic acid and homocarnosine in patients with HD compared to the non-choreic controls. Only *tyrosine* was increased in HD. These alterations were to an extent more pronounced in 5 neurophysiologically conspicuous offspring. The alterations suggest that amino acid imbalance is an early metabolic disturbance in HD.

Key words: Huntington's disease – Amino acid imbalance – CSF – Offspring at-risk – Tyrosine metabolism – Homocarnosine

Zusammenfassung. Bei 12 Patienten mit manifester Huntingtonscher Krankheit (HD), 8 nicht erkrankten Nachkommen und 16 nicht choreatischen Kontrollpatienten wurden 27 verschiedene Aminosäuren im Liquor cerebrospinalis (nüchterner Lumballiquor) untersucht. Asparagin, Isoleucin, Leucin, Phenylalanin, Histidin, Arginin, α-Aminoadipinsäure und Homocarnosin waren signifikant ($P<0.001$) erniedrigt bei Patienten gegenüber den Kontrollen. Diese Veränderungen waren bei 5 neurophysiologisch auffälligen Nachkommen teilweise ausgeprägter, was für eine frühzeitige metabolische Störung spricht. *Tyrosin* war als einzige Aminosäure erhöht. Die Veränderungen sprechen für eine Aminosäurenimbalanz bei Huntingtonscher Krankheit, deren Bedeutung besprochen wird.

Introduction

The genetic defect of Huntington's disease (HD) is unknown but neurochemical studies have shown metabolic deviations, among them alterations in the content of

Offprint requests to: H. Cramer

0003-9373/82/0231/0131/$02.00

a number of amino acids (a.a.) in the brain and CSF. While it was realized that many of these changes might reflect secondary events due to brain atrophy, hyperactivity or diet (for discussion see Barbeau 1979), special interest has been paid to the behaviour of a.a. such as γ-aminobutyric acid (GABA), glutamic acid and aspartic acid which are putative neurotransmitters existing in the basal ganglia. A secondary imbalance in a.a. is best differentiated from genetic defect by studying a.a. comparatively in patients with manifest chorea and in clinically unaffected members of Huntington families. Therefore we have performed a detailed study of free a.a. in the CSF of patients with HD, individuals at-risk having one affected parent or sibling and control patients with other diseases.

Materials and Methods

Subjects. Lumbar CSF was obtained after an overnight fast from 12 patients with HD, 8 clinically symptom-free first degree relatives of Huntington patients and 16 non-choreic control patients. The group of HD consisted of 6 male and 6 female patients, mean age 46 ± 8.4 years. The patients were rated according to the frequency and intensity of choreic movements, the degree of impairment of intellectual functions and the degree of general disability. On the basis of the ratings they were distributed into 3 groups, being slightly to moderately, markedly, and severely to very severely affected. Of the 8 at-risk individuals 2 were males and 6 females, mean age 32.4 ± 6 years. Five of these offspring were neurophysiologically "conspicuous" because of disturbed eye movements in electronystagmographic examinations, as reported elsewhere (Oepen et al. 1981). The non-choreic control patients consisted of 8 male and 8 female patients (mean age 31.0 ± 16.4 years) who received spinal taps because of suspicion of various neurological diseases (lumbar disc herniation, brachial plexus lesion, neural muscular atrophy, arachnitis, viral meningitis, migraine, subarachnoidal bleeding). Physical appearance, protein content (< 30 mg/dl) and cell counts (< 15 /mm^3) of CSF of these patients were normal.

During the study most of the patients were off drug treatments. Three choreic patients were on low doses of neuroleptics (perphenazine, levopromazine), 1 offspring received valproate because of infrequent seizures.

Methods. Lumbar punctures were performed at 8.30–9.00 a.m. after overnight bed rest and a fasting period of at least 12 h. CSF (2 ml) was collected directly from the spinal needle by a graduated syringe into a test tube containing 0.5 ml of sulfosalicylic acid (10%). After deproteinization the CSF was centrifuged, immediately frozen and stored at $-40°$ C until analysis. The samples were thawed at 2–4° C and 20 nM of norleucine (internal standard) dissolved in 100 µl of 0.6 *N* perchloric acid was added. The CSF samples were freeze-dried and kept at $-70°$ C until assay. On the day of assay the CSF samples were dissolved in 200 µl of a solution of 0.22 *N* lithium citrate and adjusted to pH 1.9 by adding 37% hydrochloric acid. Using the final solution 100 µl samples were injected into the amino acid analyser. The temperature at the injection block was 4° C and only 4 samples (total analysis time = 16 h) were kept in the injection block at one time. Control experiments with analytically pure glutamine revealed no sign of hydrolysis to glutamic acid using this analytical procedure. Complete amino acid analyses were carried out by automated high performance ion-exchange chromatography on a Biotronik LC 6000 E amino acid analyzer (Biotronik München, FRG) as described by Tutschek et al. (1977). A Durrum DC 4-A high efficiency cation exchange resin column (0.6×13 cm) was employed. The fluorogenic reagent was prepared from o-phthaldehyde and β-mercaptoethanol as described by Benson and Hare (1975). Peak areas were automatically integrated and the individual amino acid concentration calculated by a Sigma 10 Integrator. Standards of GABA, phosphoserine, asparagine, glutamine, tyrosine, phenylalanine, α-amino-butyric acid, α-amino adipic acid (all Fluka), phosphoethanolamine (Calbiochem) homocarnosine (Ega-Chemie), or a commercial physiological amino acid standard (Hamilton Co., type PAN and type PB combined) were prepared in 0.1 *N* HCl. With this analytical procedure the GABA peak can be detected but not quantitatively measured.

Statistic evaluation was performed using the F-test and the Scheffé-test for differences of the mean values (Sachs 1978). Correlation of pairs of amino acids were calculated. All statistic procedures were performed by use of an UNIVAC 1108[1].

Results

Table 1 shows the concentrations of the different amino acids (a.a.) in the CSF of control patients, patients with HD and in the offspring. Large individual variations in the concentration of most of the a.a. were apparent. The amino acid concentrations in non-choreic control patients were essentially in agreement with reported values in the literature (Gjessing et al. 1972; Perry et al. 1975; Monaco et al. 1979; van Sande et al. 1970). Moderately higher values than reported by Gjessing et al. and van Sande et al. were found for taurine, aspartic acid and homocarnosine. For valine, isoleucine, leucine, lysine and histidine our control values were slightly higher than those reported by these authors. Glutamic acid levels compared favourably with other results obtained by comparable methods (Gjessing et al. 1972; van Sande et al. 1970). There were no significant differences in the concentrations of amino acids between male and female subjects.

In patients with HD most amino acids showed a marked decrease. Significant decreases (Scheffé-test, $P < 0.001$) were found for asparagine, isoleucine, leucine, phenylalanine, lysine, histidine, α-aminoadipic acid and homocarnosine. Less significant differences are indicated in Table 1. The only amino acid which was increased in HD was tyrosine ($P < 0.01$).

The first degree relatives showed decreased levels of the same amino acids as the patients with manifest HD (Table 1). The decrease in offspring was often greater than in patients for taurine, alanine, valine, methionine, isoleucine, leucine, phenylalanine, lysine, histidine, arginine, citrulline and phosphoserine with similar significances of difference, compared to controls (Table 1). The lower ornithine and lysine levels in offspring appeared to correlate with those in mildly affected HD patients. For the other amino acids there was no correlation between their decrease and the degree of severity and evolution of the disease (Table 1). Only asparagine showed a tendency to be more decreased in advanced HD.

Tyrosine levels were normal in offspring but increased in HD patients with a tendency to more marked increase in severely affected patients. When the offspring were distributed into two groups according to the absence or presence of neurophysiological abnormalities, the decrease of some amino acids, especially taurine, asparagine and homocarnosine, appeared to be more pronounced in the group of conspicuous offspring than in non-conspicuous offspring (Table 2).

Since it is known that the level of one amino acid may influence the level of another, separate intercorrelations were calculated. At the $P < 0.001$ level (Scheffé-test) it is unlikely that more than a few correlations would be significantly different from zero. However, as shown in Table 3, there were marked differences between correlations observed in controls, patients and offspring at-risk. Most of the amino acids which correlated significantly had significant differences of the mean value as indicated in Table 1.

1 The help of Doz. Dr. Bammert, Institut für Med. Statistik, is gratefully acknowledged

Table 1. CSF amino acid concentrations in patients with Huntington's disease, at-risk individuals (offspring) and control patients

Amino acid	Huntington's disease (mean ± S.D. in nmoles/ml)				Offspring (8)	Control patients (16)
	mild (4)	marked (4)	severe (4)	total (12)		
Taurine	5.06 ± 2.16	4.66 ± 0.94	5.03 ± 0.75	4.91 ± 1.35**	4.53 ± 1.89*	11.32 ± 5.81
Phosphoethanolamine	1.02 ± 0.22	1.76 ± 0.88	1.73 ± 0.99	1.48 ± 0.76**	1.86 ± 0.79	3.85 ± 2.11
Aspartic acid	5.92 ± 2.61	6.42 ± 2.49	5.03 ± 0.85	5.86 ± 2.09	4.68 ± 1.09	7.37 ± 3.08
Threonine	30.61 ± 13.06	39.99 ± 10.13	32.18 ± 10.84	34.45 ± 11.19	26.40 ± 5.77	37.82 ± 12.02
Serine	29.10 ± 13.71	32.09 ± 8.40	22.03 ± 2.88	28.26 ± 9.85	20.66 ± 4.78	25.01 ± 9.03
Asparagine	6.17 ± 1.36	4.25 ± 1.48	4.08 ± 0.46	4.78 ± 1.46***	4.53 ± 3.68**	11.82 ± 4.98
Glutamic acid	28.96 ± 22.21	27.78 ± 19.69	56.82 ± 23.32	36.12 ± 23.45	20.24 ± 12.13	17.68 ± 5.48
Glutamine	352.87 ± 66.24	552.04 ± 200.79	439.57 ± 156.53	448.94 ± 162.12	419.83 ± 118.64	415.11 ± 151.75
Glycine	7.87 ± 3.59	14.19 ± 7.66	8.18 ± 4.13	10.25 ± 5.89	5.88 ± 1.46	11.12 ± 5.24
Alanine	30.49 ± 6.18	43.65 ± 15.65	43.45 ± 17.72	38.78 ± 13.86	21.95 ± 6.28***	45.68 ± 10.42
Valine	19.63 ± 5.50	23.31 ± 7.73	22.50 ± 5.55	21.75 ± 6.00*	16.67 ± 3.67**	29.88 ± 7.93
Methionine	3.03 ± 1.37	4.26 ± 1.05	4.16 ± 0.62	3.79 ± 1.15	2.20 ± 1.13*	4.77 ± 2.50
Isoleucine	5.69 ± 1.92	5.77 ± 1.57	5.48 ± 1.52	5.66 ± 1.52***	4.42 ± 1.44***	10.23 ± 3.69
Leucine	13.30 ± 3.98*	15.92 ± 4.62	15.23 ± 4.61	14.78 ± 4.10***	11.35 ± 2.69***	26.00 ± 9.20
Tyrosine	6.27 ± 3.31	8.18 ± 3.09	10.4 ± 7.90*	8.09 ± 4.70**	3.15 ± 2.32	3.50 ± 1.74
Phenylalanine	9.48 ± 2.90*	11.48 ± 3.03	9.77 ± 2.40	10.29 ± 2.80***	7.26 ± 1.06***	20.54 ± 6.42
Ammonia	20.74 ± 6.34	67.29 ± 48.90	106.16 ± 84.40	60.97 ± 58.60	53.56 ± 37.66	55.09 ± 7.55
Ornithine	3.05 ± 0.91*	7.87 ± 3.61	8.30 ± 4.10	6.23 ± 3.73	4.41 ± 1.66	8.13 ± 1.45
Lysine	20.66 ± 5.25	34.15 ± 13.50	30.55 ± 12.60	28.26 ± 11.50***	21.43 ± 4.29***	46.35 ± 7.77
Histidine	14.61 ± 5.60	14.75 ± 3.40	14.90 ± 1.40	14.74 ± 3.64***	11.82 ± 3.23***	28.82 ± 5.93
Arginine	21.79 ± 9.40	25.20 ± 3.66	20.20 ± 3.97	22.60 ± 6.21*	15.75 ± 2.76***	31.53 ± 10.95
Citrulline	0.71[a]	1.65 ± 0.51	1.65 ± 1.16[b]	1.49 ± 0.72**	0.98 ± 0.20**	5.33 ± 3.53
α-Aminobutyric acid	1.76[a]	4.06 ± 1.12	3.04 ± 0.46[c]	3.38 ± 1.17**	2.92 ± 1.24**	7.57 ± 2.47
α-Aminoadipic acid	0.11[a]	1.50 ± 0.60	0.58 ± 0.31[b]	0.96 ± 0.74***	1.92 ± 1.07*	5.49 ± 2.63
3-Methylhistidine	0.30[a]	0.53 ± 0.35	0.83 ± 0.42[b]	0.59 ± 0.36**	0.44 ± 0.08***	1.37 ± 1.09
Phosphoserine	98.00[a]	122.60 ± 31.12	151.42 ± 16.29[c]	127.86 ± 29.96*	100.75 ± 14.45**	201.42 ± 60.64
Homocarnosine	0.20 ± 0.19[c]	0.66[a]	1.75[a]	0.27 ± 0.26***	0.64 ± 0.76**	4.08 ± 2.08

[a] Single value. [b] Two values. [c] Three values

Significant difference from controls * ($P<0.05$, Scheffé-test). ** ($P<0.01$, Scheffé-test). *** ($P<0.001$, Scheffé-test)

Table 2. CSF amino acids in at-risk individuals (offspring) and control patients

Amino acid	Offspring (mean ± S.D. in nmoles/ml)			Control patients (16)
	Inconspicuous (3)	Conspicuous (5)	Total (8)	
Taurine	6.50 ± 0.99	3.22 ± 0.45	4.53 ± 1.89*	11.32 ± 5.81
Asparagine	8.38 ± 2.11	1.97 ± 0.48*	4.53 ± 3.68**	11.82 ± 4.98
Valine	18.41 ± 4.85	14.93 ± 1.07	16.67 ± 3.67**	33.74 ± 16.78
Isoleucine	5.13 ± 1.74	3.71 ± 0.83*	4.42 ± 1.44***	10.23 ± 3.69
Leucine	12.56 ± 3.71*	10.15 ± 0.19**	11.35 ± 2.69***	26.00 ± 9.20
Tyrosine	3.45 ± 3.33	2.86 ± 1.44	3.15 ± 2.32	3.50 ± 1.74
Phenylalanine	7.25 ± 0.93*	7.26 ± 1.39*	7.26 ± 1.06***	20.54 ± 6.42
Ornithine	4.74 ± 2.34	4.09 ± 1.07	4.41 ± 1.66*	8.19 ± 1.45
Lysine	22.42 ± 6.13**	20.45 ± 2.37**	21.43 ± 4.29***	46.35 ± 7.70
Histidine	13.94 ± 2.50	9.70 ± 2.54*	11.82 ± 3.23***	27.73 ± 8.43
Arginine	17.33 ± 2.08	14.18 ± 2.69*	15.75 ± 2.70***	31.53 ± 10.90
Citrulline	0.93 ± 0.18	1.01 ± 0.24	0.98 ± 0.19**	5.33 ± 3.53
α-Aminobutyric acid	3.38 ± 0.18	2.61 ± 1.65	2.92 ± 1.24**	7.57 ± 2.47
α-Aminoadipic acid	2.17 ± 1.58	1.76 ± 0.97	1.92 ± 1.07*	5.49 ± 2.63
Phosphoserine	96.51 ± 1.24	100.75 ± 14.50	100.75 ± 14.45**	201.42 ± 60.64
Homocarnosine	1.18 ± 0.98	0.24 ± 0.16	0.64 ± 0.76**	4.08 ± 2.08

* Significant from controls ($P < 0.05$, Scheffé-test)
** Significant from controls ($P < 0.01$, Scheffé-test)
*** Significant from controls ($P < 0.001$, Scheffé-test)

Table 3. Correlations of normalized amino acid levels in cerebrospinal fluid (significant $P < 0.001$)

Controls		Patients		Offspring	
($n = 16$)	r	(marked* $n = 4$, severe** $n = 4$)	r	(conspicuous $n = 5$)	r
Taurine-aspartate	+0.76	Threonine-glutamine**	−0.56	Threonine-phenylalanine	−0.99
Taurine-asparagine	+0.91	Threonine-tyrosine**	−0.99	Glutamate-ammonia	+0.99
Taurine-histidine	+0.89	Threonine-α-aminoadipic acid*	−0.99	Phenylalanine-histidine	+0.99
Aspartate-asparagine	+0.82	Serine-isoleucine**	+0.99	Phenylalanine-α-methylhistidine	+0.99
Aspartate-glycine	+0.78	Glutamine-3-methylhistidine*	+0.99	Histidine-α-methylhistidine	+0.99
Threonine-glycine	+0.82	Leucine-citrulline*	+0.99		
Asparagine-isoleucine	+0.76	Ammonia-phosphoserine*	+0.99		
Asparagine-histidine	+0.94	3-methylhistidine-phosphoserine*	+0.99		
Valine-isoleucine	+0.83				
Isoleucine-histidine	+0.78				
Leucine-isoleucine	+0.89				
Leucine-histidine	+0.78				
Arginine-phosphoserine	−0.98				

Discussion

Despite much recent work on the pathophysiology of HD, its primary disturbance remains unknown. Anatomically the disease is mainly characterized by a decrease of small neurons in the neostriatum beginning long before the clinical onset (Tellez-Nagel 1971). An important question, therefore, is whether metabolic changes can be detected before the onset of chorea. For clinical purposes, studies of CSF metabolites deserve prominent interest, and several have been previously performed. Oepen (1967) found increased levels of lysine, while Perry et al. (1973) reported significant decreases of alanine, α-aminobutyric acid, valine, isoleucine, leucine, tyrosine and phenylalanine. Simanyi et al. (1973) described an imbalance of amino acids in the CSF, with decreased levels of glutamic acid, isoleucine and tyrosine, while aspartic acid and threonine were increased. Other groups have reported marked decreases of the transmitters GABA (Glaeser et al. 1975; Manyam et al. 1978) and glutamic acid (Kim et al. 1981) as well as the dipeptide of GABA and histidine, homocarnosine (Boehlen et al. 1980). Interestingly, CSF GABA levels were also decreased in individuals at-risk for HD (Manyam et al. 1978).

Our findings in 12 HD patients and in 8 first degree relatives at-risk for HD disclose a marked *hypoaminoacidorachia* and *imbalance* of the free amino acid pool in both groups of individuals. The differential changes in amino acid concentrations argue against a pathological dilution effect of enhanced CSF production and increased elimination. Compared to non-choreic control patients significant decreases were found for the *branched chain amino acids* isoleucine, leucine and valine, for phenylalanine and homocarnosine which confirmed previous findings (Perry et al. 1973; Glaeser et al. 1975; Boehlen et al. 1980). Moreover, significant decreases were observed for taurine, phosphoethanolamine, asparagine, lysine, arginine, citrulline, α-aminobutyric acid, α-aminoadipic acid, histidine, α-methylhistidine and phosphoserine.

No significant changes of the amino acids of the *G-system* (glutamate, aspartate and glycine) were found. Of the *A- (alanine-loving) system,* neither alanine nor threonine, serine and glutamine were significantly decreased in HD. The amino acids of the G- and A-system are considered to be transported by highly sodium-dependent transport mechanisms. The absence of consistent alterations of these amino acids suggests that a primary disturbance of membrane functions is not present in HD.

Marked decrease in *offspring* and in mild chorea were observed for taurine, asparagine, alanine, the branched chain amino acids, methionine, phenylalanine, ornithine, lysine, histidine, arginine, citrulline, α-aminobutyric acid, α-aminoadipic acid, 3-methylhistidine, phosphoserine and homocarnosine. For a large number of amino acids including valine, isoleucine, phenylalanine, histidine and arginine, the lowest levels were observed in conspicuous offspring which were characterized by absence of chorea but presence of neurophysiological abnormalities especially in the optomoter system. Phosphoethanolamine, ornithine and lysine levels were lowest in mild and moderate HD. This suggests that the changes found in CSF may reflect a fundamental and primary disturbance of amino acid metabolism in cells, present in HD families.

Of the group of aromatic amino acids, phenylalanine and histidine were decreased in severe HD, while *tyrosine* was the only amino acid which was significantly increased. The concentration of tyrosine was normal in offspring but increased in HD patients parallel to the degree of severity of the disease. Increases of tyrosine in HD patients have not been reported before, and in the earlier studies of amino acids, at-risk individuals and patients with different degrees of severity have not been compared. In this respect it is of interest that Baskin and Rosenberg (1973) postulated a specific disturbance of protein synthesis in HD caused by an alteration of tyrosine ligase. According to these authors, tyrosine ligase would not discriminate between tyrosine and L-DOPA as substrates due to a point mutation. RNA acetylation and hence protein synthesis would be consequently disturbed. A general defect of RNA and protein metabolism could also explain observations such as an abnormal sensitivity to X-rays of cultured HD lymphocytes (Moshell et al. 1980). To date insufficient attention has been paid to a possible heterogeneity of metabolic aberration in HD in different kinships and countries. The possibility of a disturbance of tyrosine utilization and the role of tyrosine metabolism in the genesis of choreatic symptoms is further suggested by the observation of three-fold increases of CSF tyrosine in a patient with nonprogressive chorea (Oepen et al. unpublished observation).

Recently special interest has been paid to amino acid neurotransmitter candidates. Borri et al. (1967) found an increase of *glutamic acid* in both putamen and caudate nucleus in HD, with nonsignificant changes in other amino acids and a trend towards a decrease of aspartate, isoleucine and leucine. Significant decreases of CSF glutamic acid in HD patients were reported by Simianyi et al. (1973) and Kim et al. (1981). This amino acid is a putative neurotransmitter in corticostriatal projections and a primary disturbance of glutaminergic neurotransmission in HD was hypothesized (Kim et al. 1981). In our study, glutamic acid levels were rather increased but showed large variations and no significant differences of mean values. Complete resolution of glutamic acid may not have been achieved with our method. In fact, great variability of glutamate levels in control patients exists in the literature, with means between 1.8 nmol/ml (Perry et al. 1975) and 56.8 nmol/ml (Monaco et al. 1979). Processing of CSF may be critical in the determination of glutamic acid, since glutamine is easily hydrolyzed to glutamate at acidic pH (van Sande et al. 1970). Glutamic acid levels tend to be extremely small when CSF is deproteinized immediately prior to the assay (Bernasconi et al. unpublished observation).

The other amino acid transmitter candidates are aspartic acid and GABA. *Aspartic acid* levels were normal in our patients and in offspring. GABA was not quantitatively determined with our method. Perry et al. (1973) found normal concentrations of aspartic acid in the brain and CSF of HD patients but significantly decreased GABA levels. Decreased levels of GABA and low activity of glutamic acid decarboxylase (Bird et al. 1973) point to a deficiency of GABA as a potential inhibitory synaptic transmitter in HD.

In summary, it appears that free amino acid metabolism is profoundly disturbed in HD and also in individuals at-risk for HD. There is no common metabolic pathway for the amino acids which were found to be significantly altered. The amino acid imbalance is probably a secondary reflection of an as yet unknown

basic biochemical error underlying this hereditary disease. Deficiencies of both "structural" amino acids and neurotransmitter amino acids as well as of peptides (Cramer et al. 1981) may be responsible for the characteristic symptoms and fatal course of HD. At present, it is not known which changes determine the outbreak and progression of the disease in at-risk individuals. If decreased amino acid levels were a consequence of the disease process, marked changes should not be expected in offspring. If, on the other hand, the amino acid imbalance preceded the appearance of symptoms, a bimodal distribution should be expected in at-risk individuals, having a 50% probability of the disease. A bimodal distribution of amino acid changes is indeed observed in our first degree relatives and shows that the trend towards a decrease of many amino acids is more marked in neurophysiologically conspicuous offspring.

References

Barbeau A (1979) Update upon the biochemistry of Huntington's chorea. Adv Neurology 23: 449–462

Baskin F, Rosenberg RN (1973) Dopa as an antimetabolite in Huntington's disease. Lancet I: 582–583

Benson JR, Hare PE (1975) O-phthaldehyde: Fluorogenic detection of primary amines in the picomole range. Comparison with fluorescamine and ninhydrin. Proc Natl Acad Sci USA 72:619–622

Bird ED, Iversen LL (1974) Huntington's chorea. Post-mortem measurements of glutamic acid decarboxylase, cholin acetyltransferase and dopamine in basal ganglia. Brain 97:457–472

Boehlen P, Tell G, Schechter PJ, Koch-Weser J, Agid Y, Coquillat G, Chazot G, Fischer C (1980) Cerebrospinal fluid homocarnosine in Huntington's disease. Life Sci 26:1009–1012

Borri PF, Op den Velde WM, Hoogwinkel GJN, Bruyn GW (1967) Biochemical studies in Huntington's chorea. VI: Composition of striatal neutral lipids, phospholipids, glycolipids, fatty acids, and amino acids. Neurology (Minneap) 17:172–178

Cramer H, Kohler J, Oepen G, Schomburg G, Schröter E (1981) Huntington's chorea — Measurements of somatostatin, substance P and cyclic nucleotides in the cerebrospinal fluid. J Neurol 225:183–187

Gjessing LR, Gjesdahl P, Sjaastadt O (1972) The free amino acids in human cerebrospinal fluid. J Neurochem 19:1807–1808

Glaeser BS, Hare TA (1975) Measurement of GABA in human cerebrospinal fluid. Biochem Med 12:274–282

Kim JS, Kornhuber HH, Holzmüller B, Schmidt-Burgk W, Mergner T, Krzepinski G (1981) Reduction of cerebrospinal fluid glutamic acid in Huntington's chorea and in schizophrenic patients. Arch Psychiat Nervenkr 228:7–10

Manyam NYB, Hare TA, Katz L, Glaeser BS (1978) Huntington's disease. Cerebrospinal fluid GABA levels in at risk individuals. Arch Neurol 35:728–730

Monaco F, Pirisi A, Sechi GP, Mutani R (1979) Complicated optic atrophy (Behr's disease) associated with epilepsy and amino acid imbalance. Eur Neurol 18:101–105

Moshell AN, Barrett SF, Tarone RE, Robbins JH (1980) Radiosensitivity in Huntington's disease: implications for pathogenesis and presymptomatic diagnosis. Lancet I:9–11

Oepen G, Clarenbach P, Thoden U (1981) Disturbance of eye movements in chorea Huntington. Arch Psychiat Nervenkr 229:205–213

Oepen H (1967) Progress in neuro-genetics, vol I. Barbeau A, Brunette JR (eds) Proceedings of the 2nd Int. Congr. of Neuro-Genetics and Neuroophthalmology, Montreal, Sept. 1967, pp 571–572. Int. Congr. series no. 175, Excerpta Medica Foundation, Amsterdam

Perry TL, Hansen S, Lesk D, Kloster M (1973) Amino acids in plasma, cerebrospinal fluid, and brain of patients with Huntington's chorea. Adv Neurol:609–621

Perry TL, Hansen S, Kennedy J (1975) CSF amino acids and plasma CSF amino acid ratios in adults. J Neurochem 24:587–589

Sachs L (1978) Angewandte Statistik. Springer, Berlin Heidelberg New York

Simanyi M, Gerstenbrand F, Gründig E, Schedl R, Weiß H (1973) Der Einfluß der Verabreichung von Aminosäuren, speziell von L-Dopa und Alpha-Metholdopa, auf die Zusammensetzung des Liquor cerebrospinalis bei extrapyramidalen Syndromen. Z Neurol 204:67–80

Tellez-Nagel I (1971) Biological problems of Huntington's disease. Pacific Palisades, California, 12.–13. 3. 71, cit. Simanyi M et al. (1973)

Tutschek R, Meier KD, Gruening F, Stubba W (1977) Amino acids analysis of physiological fluids by a single column program based on stepwise elution with lithium citrate. J Chromatogr 139:211–214

Van Sande M, Mardens Y, Adriaenssens K, Loventhal A (1970) The free amino acids in human cerebrospinal fluid. J Neurochem 17:125–135

Received July 9, 1981