Quebec Cooperative Study
of Friedreich's Ataxia

Amino Acid Metabolism in Friedreich's Ataxia

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SUMMARY: *A study of amino acids determined by sequential Multi-sample Amino Acid Automatic Analyzer in plasma, urine and cerebrospinal fluid (CSF) in patients with Friedreich's ataxia and control subjects has revealed a number of mathematically significant variations from normal. Of practical physiological importance are the following: a high urinary excretion of alanine with slightly elevated plasma levels; a low plasma and CSF concentration of aspartic acid in the presence of normal urinary values and finally a low CSF concentration of taurine accompanied by normal plasma levels, but elevated urinary output and renal clearance rates. We postulate that the modifications in alanine and aspartic acid are less specific and probably secondary, but there could be a genetic defect in the membrane transport of taurine and the other β-amino acids in Friedreich's ataxia.*

RÉSUMÉ: *Une étude des acides aminés par détermination automatique dans le plasma, les urines et le liquide céphalo-rachidien (LCR) chez des patients avec ataxie de Friedreich et chez des sujets normaux contrôles, a révélé un certain nombre de variations de la norme mathématiquement significatives. D'importance physiologique cependant on note: une excrétion urinaire élevée d'alanine avec des niveaux plasmatiques à tendance vers la hausse; un taux plasmatique et dans le LCR bas d'acide aspartique en présence de concentrations urinaires essentiellement normales; et finalement, une concentration de taurine basse dans le LCR accompagnée de taux plasmatiques normaux, mais d'excrétion urinaire et de clearance rénale élevées. Nous postulons que les modifications en alanine et acide aspartique sont moins spécifiques et probablement secondaires, mais qu'il pourrait exister un défaut génétique dans le transport membranaire de la taurine et des autres acides β-aminés dans l'ataxie de Friedreich.*

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INTRODUCTION

In the last few years, a number of genetic diseases with ataxia have been identified and characterized as enzymatic defects in lipid, purine, carbohydrate or aminoacid metabolism. The latter can involve a transport defect as in Hartnup Syndrome, or an inborn error of metabolism as in congenital hyperammonemia such as OTC type 2. However, the majority of these metabolic diseases present clinically as a reversible episodic ataxia of acute onset and do not follow a progressive course (Scriver and Rosenberg, 1973; Bacchus, 1976; Stanbury et al., 1976). Moreover, many of them are accompanied by manifestations of nervous system dysfunction such as mental retardation and seizures which are not cardinal features of Friedreich's ataxia.

In the course of our survey of Friedreich's ataxia, it was important to include investigations of serum, urine and CSF amino acids as a variety of apparently inconstant modifications had been reported both in animal and human models of ataxia (see discussion).

SUBJECTS AND METHODS

The patients investigated in this protocol are taken from the 50 subjects originally accepted and 2 further ataxic siblings of a patient in Group IIa. As detailed in a previous paper, these patients are subdivided into 4 groups: Group Ia: typical Friedreich's ataxia, complete picture (33 patients); Group Ib: typical Friedreich's ataxia without pes cavus (3 patients); Group IIa: recessive ataxia of the Roussy-Levy type (6 patients); Group IIb: heterogeneous grouping of recessive ataxias (8 patients). The subjects who were

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studied all belonged to groups Ia and Ib.

Blood

The venous blood samples from 38 Friedreich's patients (Groups Ia, Ib and 2 ataxic siblings not otherwise included in study) were taken after overnight fasting and were immediately centrifuged at 2,000 g. for 2 minutes. The serum was immediately analyzed and/or stored at —20°C. Serum was deproteinized by adding 100 μ l of a 9% sulfosalicilic acid (SSA) solution to 100μ l of serum and μ Mole of norleucine as an internal standard. The mixture was centrifuged at 5,000 g. for 2 minutes. The supernatant was immediately analyzed or stored at —20°C. The concentration of amino acids was expressed in μ Mole/100 ml.

Urine

Twenty-four urine samples (21 from Group Ia, 3 from Group Ib) were collected in bottles containing a few drops of toluene. The total volume was recorded and urinary creatinine was measured by the Jaffe reaction to determine the completeness of the 24 hours collection. The volume of urine analyzed was calculated according to the concentration of alpha-amino nitrogen (O'Brien, 1968). A volume equivalent to 10μg of alpha-amino nitrogen was mixed with an equal volume of 9% SSA 10 μ Mole of norleucine and centrifuged. Then the supernatant was absorbed on a cartridge. The variation in sample volume was from 25 μ l to 250μ l. The results were expressed as μ M/min/1.73 m².

CSF

Cerebrospinal fluid samples (15 patients from Group Ia) were collected by lumbar puncture usually performed in the morning when the subjects were fasting. 500μ l of CSF were deproteinized with dry SSA with 0.1 μ Mole of norleucine added as an internal standard. Centrifugation was carried out for 10 minutes at 6,000 r.p.m. The concentration of each of the ninhydrin-positive substances is expressed in μ M/100 ml of CSF.

TABLE 1

FREE AMINO ACID CONCENTRATION DETERMINED IN PLASMA OF TWO GROUPS OF PATIENTS

AMINO ACIDS	CONTROL GROUP*		FRIEDREICH'S ATAXIA**		p
	MEAN	S.D.	MEAN	S.D.	
Taurine	4.393	2.928	4.378	3.356	
Phosphoethanolamine	< 0.1	0.0	0.057	0.197	
Aspartic acid	1.798	0.0	0.956	0.550	< 0.001
Hydroxyproline	0.375	1.018	0.969	2.106	
Threonine	11.439	3.753	11.401	3.577	
Serine	12.065	3.827	11.723	2.829	
Asparagine	4.384	1.665	3.205	1.799	< 0.005
Glutamic acid	16.270	8.076	14.015	8.043	
Glutamine	47.986	33.366	54.067	33.044	
Proline	16.765	6.376	16.856	6.713	
Glycine	23.496	5.130	18.948	4.885	< 0.001
Alanine	30.132	12.352	32.263	11.720	
Citrulline	2.091	1.548	1.893	1.212	
α-amino-N-butyric acid	1.232	0.926	1.876	0.972	< 0.005
Cystine	2.423	2.096	1.792	2.154	
Valine	19.266	4.672	20.865	4.409	
Methionine	1.783	0.818	1.718	0.861	
Isoleucine	6.034	1.711	5.966	1.644	
Leucine	11.606	3.251	11.004	2.742	
Tyrosine	4.993	1.467	4.810	1.734	
Phenylalanine	5.418	1.339	4.395	1.285	< 0.002
β-alanine	0.0	0.0	0.021	0.131	
BAIB	0.0	0.0	0.0	0.0	
Ornithine	8.504	4.065	4.651	2.005	< 0.001
Lysine	15.696	5.462	14.846	4.496	
Histidine	8.375	2.609	5.811	1.736	< 0.001
Arginine	6.424	3.486	5.480	2.953	

All values in μM/100 ml

* Based on 37 normal adults

** Based on 38 cases

Control patients

The diet and the physical activity were not controlled in this study. The 24 hours urine collection was as described previously. Blood samples were taken from normal subjects (without neurological and psychiatric disorders) after overnight fasting. The blood samples were processed as for the patients in the study. The controls (6 males aged 12 to 17) had undergone lumbar puncture as part of a diagnostic study of their illness or as part of a study with pneumoencephalogram. We are currently processing CSF from non-neurological patients without metabolic disorders in the 0-20 age group to establish our normal free amino acid levels and the plasma/CSF ratio.

All samples for amino acid analysis were frozen to —20°C as soon as possible, usually after deproteinisation with SSA. The supernatant of all samples were chromatographed on a Technicon Sequential Multi-samples amino acid Automatic Analyzer (TSM) with the chromobeads type "C" resin. The gradient buffer solution were the same lithium buffers as have been described by Perry, et al, (1971) allowing the accurate determination of aspartic acid and glutamic acid and their corresponding amides. The peak area of each amino acid recorded on the chromatogram was determined with a Gellman planimeter. A calibration mixture with known amounts of amino acids was analyzed with every five samples as a control on the analyzer. Renal clearance rates, expressed in ml/min/1.73 M², were calculated from the results of plasma

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TABLE 2

FREE AMINO ACID CONCENTRATION DETERMINED IN URINE OF TWO GROUPS OF PATIENTS

AMINO ACIDS	CONTROL GROUP*		FRIEDREICH'S ATAXIA**		p
	MEAN	S.D.	MEAN	S.D.	
Taurine	47.217	46.086	91.510	67.038	< 0.05
Phosphoethanolamine	2.022	3.742	5.164	5.620	< 0.05
Aspartic Acid	7.780	3.708	9.130	6.155	
Hydroxyproline	< 0.1	0.0	5.377	22.197	
Threonine	8.772	6.582	15.566	19.168	
Serine	13.157	11.071	26.483	20.867	< 0.02
Asparagine	4.416	3.922	8.443	12.533	
Glutamic acid	8.400	5.645	11.361	15.566	
Glutamine	20.065	17.609	23.477	19.496	
Sarcosine	1.499	1.022	4.731	4.657	< 0.05
Proline	0.520	2.550	0.108	0.470	
Glycine	120.896	197.768	119.942	186.259	
Alanine	17.914	9.502	30.525	24.074	< 0.05
Citrulline	< 0.1	0.0	0.286	1.118	
α-amino-N-butyric acid	0.705	0.774	2.709	4.073	< 0.05
Valine	1.715	1.147	3.129	2.362	< 0.05
Cystine	1.867	1.452	2.342	1.679	
Cystathionine	2.319	2.492	2.537	1.807	
Methionine	0.464	0.799	1.391	2.307	
Isoleucine	0.984	0.846	2.048	1.797	< 0.05
Leucine	2.541	1.188	3.485	2.974	
Tyrosine	5.319	2.710	10.093	7.587	< 0.02
Phenylalanine	3.049	1.553	4.374	3.238	
β-alanine	0.829	1.355	6.449	11.534	< 0.05
β-amino-isobutyric acid	4.595	4.549	10.084	13.837	
Ornithine	8.537	5.604	14.066	14.333	
Lysine	5.455	4.438	7.191	6.694	
Histidine	46.866	22.162	52.705	27.598	
3-Methylhistidine	16.611	7.815	21.002	20.168	
Carnosine	3.189	3.678	8.069	16.136	
Arginine	< 0.1	0.0	0.507	0.927	

All values in μM/min/1.73 m^2

* based on 24 normal adults
** based on 19 cases

and urine concentrations, with knowledge of 24 hours urinary volume, and patient's weight and height.

RESULTS

a) Plasma

Concentrations of 25 free amino acids were determined in 37 normal adult subjects and 38 patients with Friedreich's ataxia. As seen in Table 1, a number of variations from normal were observed. Significant decreases were found in seven: aspartic acid, asparagine, glycine, α-amino-N-butyric acid, phenylalanine, ornithine and histidine. All other amino acids had normal plasma concentrations except alanine which was slightly elevated.

b) Urine

Similarly, the concentration of 31 free amino acids or dipeptides was measured in 19 Friedreich's ataxia cases and 24 normal adults as controls (Table 2). Significant increases were found for ten: taurine, phosphoethanolamine, serine, sarcosine, alanine, α-amino-N-butyric acid, valine, isoleucine, tyrosine and β-alanine. Again all other determinations were within normal limits.

c) CSF

Despite the technical difficulties inherent in CSF amino acid determination, we were able to measure with confidence 21 amino acids in 15 cases of Friedreich's ataxia. It was difficult to obtain sufficient numbers of non-neurological patients to permit statistical evaluation and comparisons. Table 3 shows, with reservations, our temporary results and those from the literature on pooled control CSF. From these figures, only two apparently significant variations were found: decreases in taurine and aspartic acid concentrations.

d) Renal clearance rates were calculated for 12 patients with Friedreich's ataxia from Group Ia and the control subjects (see above) analyzed in the same laboratory. As seen in Table 4, two amino acids, taurine and aspartic acid, were found to have abnormal values. The clearance rates of both substances were considerably increased. All other rates were within normal limits.

DISCUSSION

It is notoriously difficult to draw conclusions on the state of a specific amino acid's metabolism from single values of concentrations in blood, urine and particularly CSF. Too many factors play modifying roles: diet, exercise, stress, and hormonal imbalances (Scriver and Rosenberg, 1973). Correct interpretations can usually be given only after thoroughly balanced metabolic studies of both static and dynamic character (Christensen, 1959; Scriver and Hechtman, 1970; Segal, 1976). However, in the absence of tissue determinations, the types of results obtained in the present study are sufficient to indicate pathways for research. This is particularly so in entities that have not yet been well studied such as Friedreich's ataxia.

Only a few investigations of the amino acid pattern in the ataxias are available from the literature. In animals, the best studied model is that of the ataxic rabbit (Robinson, 1970). Weinstein and colla-

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borators (1964) examined the amino acid content in blood and brain and reported essentially negative findings. The pertinent features (as determined from our own study) are given in Table 5.

Some investigations have been carried out in ataxic men. Berio et al. (1973), from bidimensional chromatography isolated unidentified amines in 3 cases of Friedreich's ataxia, also found in diffuse cortical atrophy and serious hepatic insufficiency due to neoplasia. In Nigerian nutritional ataxic neuropathy, Osuntokun et al. (1968) studied the free plasma amino acid levels from 9 patients. While taurine and alanine were low, glutamic acid and aspartic acid were elevated. More to the point, were findings in the spinal cord of 3 cases of Friedreich's ataxia compared to 4 of motor neuron disease, in the studies of Robinson (1968). Both Friedreich's ataxia and motor neuron disease showed significant decreases in aspartic and glutamic acid, and marginally lower ones in taurine. (Table 5).

Our results from Tables 1, 2, 3, 4 are summarized in Table 6. Although a number of variations from normal can be noted in plasma and urine (these are single, random determinations), only two abnormalities stand-out clearly: Taurine, which is found in normal levels in the plasma is significantly increased in the urine and in low concentration in the CSF. The renal clearance rate of taurine is significantly increased. Aspartic acid is in low concentration in the blood and CSF, but normal in the urine. Calculation of the clearance rate is therefore significantly increased.

It should be remembered that these findings are averages from large numbers of patients. This method, while useful for screening purposes, has a high risk of masking individual pathognomonic clusters. Since we feel that even our subgroups, i.e., groups Ia and Ib, are not homogeneous, averaging may be dangerous. On the other hand, the constancy of this double finding may be important in relation to the ataxias. By the nature of our investigation, we are unable to state whether this decrease is specific for the ataxias and not present in other chronic disorders. The findings of Robinson (1968), in motor neuron disease, of low aspartic and glutamic acid concentrations, may indicate that a defect in these two amino acids may not be specific to Friedreich's ataxia. Recently, Perry and collaborators (1976) have reported low brain aspartic acid contents in a dominant form of hereditary ataxia in man.

L-aspartate is possibly an excitatory synaptic transmitter in the mammalian central nervous system. It is widely distributed throughout the brain, as indicated by the localization of its oxidase (Davies and Johnston, 1975). In kidneys and probably in some membranes, aspartic acid is transferred using the same system as the other decarboxylic amino acid, glutamic acid. In our studies, aspartic acid is low in the CSF, possibly indicating a tissue deficiency as found by Robinson (1968). Although the calculated clearance rate is high, this is due mainly to the low plasma levels, since urinary excretion is essentially

TABLE 3

CSF AMINO ACIDS IN FRIEDREICH'S ATAXIA AND CONTROLS

(mean ± S.D.) μmoles/100 ml.

AMINO ACID	FRIEDREICH'S ATAXIA	SCRIVER & ROSENBERG 1973
Number of subjects	15	Pool
Taurine	0.05 ± 0.07*	0.19 - 1.4
Aspartic acid	0.08 ± 0.10*	0.16 - 0.7
Threonine	1.65 ± 0.58	0.99 - 5.1
Serine	1.80 ± 0.48	1.3 - 7.0
Asparagine	0.27 ± 0.14	—
Glutamic acid	1.83 ± 2.12	0
Glutamine	29.05 ±11.62	—
Glycine	0.44 ± 0.17	0.16 - 1.9
Alanine	2.39 ± 0.85	1.26 - 3.6
Citruline	0.04 ± 0.07	—
Valine	1.47 ± 0.28	0.3 - 2.6
Methionine	0.21 ± 0.10	0.1 - 0.4
Isoleucine	0.51 ± 0.16	0.2 - 1.4
Leucine	1.79 ± 1.48	0.6 - 1.8
Tyrosine	1.03 ± 0.54	0.1 - 1.1
Phenylalanine	1.00 ± 0.46	0.2 - 1.0
Ornithine	0.38 ± 0.14	0.3 - 0.8
Lysine	2.04 ± 0.65	1.3 - 4.2
Histidine	1.08 ± 0.38	0.2 - 3.1
Carnosine	0.24 ± 0.29	—
Arginine	1.88 ± 0.58	0.6 - 2.9

* Significantly different ($p < 0.05$) from literature findings.

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TABLE 4

RENAL CLEARANCE RATES OF AMINO ACIDS

IN FRIEDREICH'S ATAXIA

(ml/min/1.73 m^2)

	OUR RESULTS (mean ± S.D.)	CALCULATED (Control range)	PLUM (1975) min. max.	CUSWORTH & DENT (1960)
Number of patients	12	—	—	4
Taurine	58.87 ± 65.50	1.7 -16.2	0.2 -20.0	1.7 -14.0
Aspartic acid	7.14 ± 4.47	0 - 2.4	0.5 - 1.5	0 - 2.4
Serine	1.81 ± 0.93	0.3 - 3.0	0.4 - 5.6	1.9 - 3.0
Glutamic acid	0.41 ± 0.34	0.3 - 0.8	0 - 4.0	0.3 - 0.7
Glycine	4.23 ± 2.02	1.6 - 6.0	0.8 -19.0	2.7 - 5.8
Alanine	0.73 ± 0.30	0.3 - 0.9	0.2 - 1.9	0.3 - 0.9
Valine	0.16 ± 0.10	0 - 0.3	0.04- 0.64	0.1 - 0.3
Methionine	0.42 ± 0.30	0.3 - 1.1	0 - 3.9	1.1
Isoleucine	0.50 ± 0.66	0.2 - 1.0	0 - 2.5	0.2 - 1.0
Leucine	0.24 ± 0.17	0.1 - 0.9	0.2 - 2.2	0.2 - 0.9
Tyrosine	1.33 ± 0.92	0.8 - 2.5	0.4 - 4.0	1.0 - 1.7
Phenylalanine	0.79 ± 0.41	0.6 - 1.8	0.2 - 1.9	0.7 - 1.4
Ornithine	2.78 ± 2.04	0 - 1.0	—	Tr.
Lysine	0.42 ± 0.28	0.1 - 1.9	0.15- 4.2	0.2 - 1.9
Histidine	6.62 ± 3.83	2.1 - 9.1	1.0 -15.0	4.7 - 9.1

normal. This suggests a tubular reabsorption defect but cannot rule out a defect in synthesis, an abnormally high utilization for metabolic functions (such as the citric acid cycle) or β-decarboxylation into β-alanine. Our studies to date do not settle this problem.

In contrast, the abnormalities in taurine which we have found appear to be closer to the primary events. Taurine (2-aminoethanesulfonic acid) is an ubiquitous amino acid (Jacobsen and Smith, 1968; Huxtable and Barbeau, 1976). It has been found in large amounts in muscle, brain, heart and posterior spinal cord (Barbeau et al., 1975). It is also found in high concentration in the urine (Pentz 1968), where it is influenced by a number of drugs (Rylance and Nyhall, 1971) hormones (Hellstrom and Shuberth, 1970) or even dietary input (Evered et al., 1969). Not only is there an uptake for taurine into the brain (Kaczmarek and Davison, 1972), but recently Scriver and associates (Chesney et al., 1975; Goldman and Scriver, 1967; Chesney et al., 1976-unpublished), studying the mouse model of hereditary hyperprolinemia with increased taurine excretion described by Blake et al. (1974), have confirmed the existence of a β-amino preferring system for tubular reabsorption in mammalian kidney and have defined its characteristics. This transport system handles β-alanine, taurine and β-aminoisobutyric acid (BAIB). While β-alanine in the kidney has a very active metabolism, taurine appears to be metabolically inert.

Abnormally high urinary excretion of taurine has been reported in camptodactyly with mental deficiency (Nevin et al., 1964) and in familial cerebellar dyssynergia (Hall, 1974). In our studies, normal plasma values are accompanied by low CSF concentrations, but high urinary values and a high renal clearance rate. Although not diagnostic, these findings are compatible with a tubular reabsorption defect specific for taurine and the β-amino acids. The urinary excretion of β-alanine is increased 6 fold, while that of BAIB is doubled (as was that of taurine). Unfortunately, the values for plasma β-alanine and BAIB with our method are so low that it is difficult to measure it properly. Only one patient had detectable amounts of plasma β-alanine. It seems as if the tubular defect could be mostly due to the metabolism of any of the β-amino acids, principally β-alanine, with competition for the same site and resultant renal loss of taurine and BIAB. Scriver et al. (1966) have already reported the case of an infant with elevated plasma β-alanine, β-aminoaciduria, somnolence and seizures, indicating that such a specific tubular defect is possible.

The significantly elevated urinary excretion of alanine in the presence of slightly elevated plasma levels is of interest since it resembles the findings in a single case with acidosis and the clinical features of Friedreich's ataxia reported by Dunn and co-workers (1969). This suggests some form of chronic "overflow" phenomenon rather than a tubular defect for this amino acid.

TABLE 5

AMINO ACID CONCENTRATIONS IN SOME ATAXIAS

AUTHOR	ASPARTIC ACID	GLUTAMIC ACID	TAURINE	ALANINE
1) WEINSTEIN (1964)				
A) Blood (μM/ml)				
a) Ataxic rabbits	0.02	0.11	0.14	0.53
b) Control rabbits	0.02	0.08	0.15	0.35
B) Brain (μM/g wet wt)				
a) Ataxic rabbits	1.78	8.93	1.90	0.79
b) Control rabbits	2.05	9.60	1.46	0.56
2) OSUNTOKUM (1968)				
A) Plasma (mg/100 ml)				
a) Nigerian ataxic neuropathy (9 pts, mean)	0.57	1.58	0.41	2.03
b) Controls	0.03 ± 0.03	0.70 ± 0.3	0.55 ± 0.18	3.4 ± 0.3
3) ROBINSON (1968)				
A) Spinal cord (μM/g dry wt)				
a) Controls	6.03 (4.6-7.46)	18.9 (17.1-20.7)	3.40 (2.40-4.40)	14.4 (8.9-19.9)
b) Friedreich's (3)	2.53	10.20	2.89	15.03
c) M.N.D. (4)	3.37	13.00	2.40	12.60

M.N.D.: Motor neuron disease

Values expressed as means (ranges)

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TABLE 6

SUMMARY OF AMINO ACID DATA IN FRIEDREICH'S ATAXIA

(N = Normal; H: high; L: Low)

AMINO ACID	PLASMA	URINE	CSF	RENAL CLEARANCE
Taurine	N	H	L	H
Aspartic acid	L	N	L	H
Threonine	N	N	N	—
Serine	N	H	N	N
Asparagine	L	N	—	—
Glutamic acid	N	N	N	N
Glutamine	N	N	N	—
Glycine	L	N	N	N
Alanine	N	H	N	N
Citruline	N	N	L	—
Valine	N	H	N	N
Methionine	N	N	N	N
Isoleucine	N	H	N	N
Leucine	N	N	N	N
Tyrosine	N	H	N	N
Phenylalanine	L	N	N	N
Ornithine	L	N	N	N
Lysine	N	N	N	N
Histidine	L	N	N	N
β-alanine	—	H	—	—

CONCLUSION

Our preliminary studies of amino acids in Friedreich's have revealed a fairly constant defect in aspartic acid and taurine levels and excretion. While the deficiency in the former amino acid is probably secondary to some metabolic event in another pathway, the decrease in taurine could result from a specific impairment in membrane transport for β -amino acids in some of these ataxic patients. More detailed metabolic studies are in progress to elucidate the defect and to decide whether it is primary or secondary to the disease.

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