

Gyrate Atrophy of the Choroid and Retina

AMINO ACID METABOLISM AND CORRECTION OF HYPERORNITHINEMIA WITH AN ARGININE-DEFICIENT DIET

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ABSTRACT Four patients with gyrate atrophy of the choroid and retina were studied, all of whom exhibited the hyperornithinemia characteristic of this disorder. Elevated plasma histidine and diminished plasma lysine and branched-chain amino acids were also noted. The renal clearances of these four amino acids were not sufficiently elevated to explain their low plasma levels. In one subject, an arginine-deficient diet led to progressive reduction in plasma ornithine from 13 times normal to the upper limits of normal, along with the disappearance of ornithinuria and lysinuria. Orally administered α -aminoisobutyric acid facilitated the fall in plasma ornithine by increasing renal losses of ornithine. It also increased the clearances of most other amino acids. When plasma ornithine approached normal ($< 200 \mu\text{M}$), plasma lysine became normal, plasma arginine became subnormal, and renal clearances of basic amino acids decreased. Long-term (1.5 yr) maintenance with a diet containing 10–20 g of protein plus essential amino acids served to keep plasma ornithine at between 55–355 μM ; chorioretinal degeneration did not progress and vision apparently improved.

INTRODUCTION

Gyrate atrophy of the choroid and retina (GA)¹ is a chorioretinal degeneration characterized by the onset of night blindness and diminished peripheral vision in

the second decade progressing to blindness in the fifth decade (1). As first reported by Simell and Takki (2), all GA patients have striking hyperornithinemia and overflow ornithinuria (1–4). Some patients have also been noted to have hypolysinemia (1, 3, 5). Other plasma amino acids have generally been described as normal in GA; however, few specific data have been published (1, 5).

A deficiency of the mitochondrial matrix enzyme ornithine- δ -aminotransferase (OAT) has been demonstrated in phytohemagglutinin-stimulated lymphocytes (6) and cultured fibroblasts of GA patients (7–9). OAT is a pyridoxine-dependent omega transaminase that catalyzes the reversible interconversion of ornithine and glutamate semialdehyde (10). Glutamate semialdehyde is in spontaneous, nonenzymatic equilibrium with Δ^1 -pyrroline-5-carboxylate, which can be enzymatically converted to glutamate or proline (Fig. 1). On a normal diet, containing more protein (and hence, arginine) than the daily requirement, the flux of the OAT reaction is toward the formation of glutamate semialdehyde, thus disposing of the excess ornithine derived from dietary arginine. However, the reaction is reversible and together with the enzymes of the urea cycle, forms the only known pathway in mammals for the *de novo* synthesis of arginine (11).

The pathophysiologic mechanisms responsible for the chorioretinal degeneration in GA are not known. Hyperornithinemia or associated secondary metabolic abnormalities may play an important role. If so, reduction in plasma ornithine should be beneficial. High-dose pyridoxine therapy has resulted in partial reductions in plasma ornithine in GA patients in two families (12, 13); however, the majority of patients do not respond to pyridoxine.

We sought to better understand the metabolic ab-

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¹Abbreviations used in this paper: AIB, α -aminoisobutyric acid; GA, gyrate atrophy of the choroid and retina; OAT, ornithine- δ -aminotransferase.

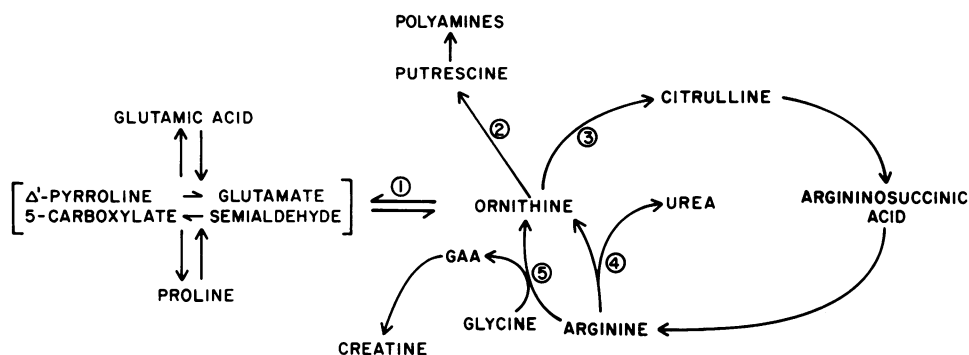


FIGURE 1 Pathways of ornithine metabolism. The numbers indicate the following enzymes: 1, OAT; 2, ornithine decarboxylase; 3, ornithine transcarbamylase; 4, arginase; 5, glycine transaminase. Glutamate semialdehyde and Δ^1 pyrroline-5-carboxylate are in spontaneous, nonenzymatic equilibrium. GAA, guanidino acetic acid.

normalities in GA, and to develop a therapeutic approach that would result in a substantial reduction in plasma ornithine in all patients. We reasoned that because of the block in the OAT pathway, arginine is an essential amino acid in GA patients and is the sole source of ornithine (Fig. 1). Limitation of dietary arginine in adults with GA should result in gradual reduction of plasma ornithine as ornithine is excreted in urine and consumed for polyamine biosynthesis. The amount of ornithine required for polyamine synthesis has not been measured directly. It has been estimated, however, to be ~ 0.5 mmol/d (14). In growing children, an additional amount of arginine (and ornithine) would be used to support the net increase in body protein. Thus, for each GA patient, there should be an optimal arginine intake above which ornithine accumulates and below which arginine becomes rate-limiting for protein synthesis.

Amino acids or other compounds that interfere with dibasic amino acid transport should allow for a higher optimal arginine intake by increasing renal losses of ornithine (and arginine). Lysine and the nonmetabolizable amino acid α -aminoisobutyric acid (AIB) have both been reported to increase renal excretion of the dibasic amino acids (15–17) and might be useful in GA. Recently, Giordano et al. (18) have reported that lysine supplementation diminished plasma ornithine significantly in a child with GA.

We now report the characteristic amino acid patterns in four patients with GA. We also report the effects of an arginine-deficient diet and of agents to augment ornithinuria on the plasma levels and renal excretion of ornithine and other amino acids in a single, pyridoxine-unresponsive GA patient.

METHODS

Subjects. 11 plasma aminograms were obtained from four GA patients (three females and one male, aged 25–56 yr) all of

whom have the characteristic fundoscopic picture of GA. All were unresponsive to pyridoxine in vivo as evidenced by a lack of a significant reduction in plasma ornithine when treated with 500 mg of pyridoxine hydrochloride daily for 2–8 wk and all lacked detectable OAT activity in their cultured fibroblasts as measured by a radioisotopic assay (6) at high (1.6 mM) and low (16 μ M) pyridoxine concentrations.² Plasma for amino acid analysis also was obtained from 13 normal fasting males and 9 normal fasting females, ranging in age from 21 to 54 yr.

One of the patients, Z.F., was studied in more detail and was placed on an arginine-deficient diet. She is a 35-yr old white female who has been described in previous reports (6, 19) and who gave informed consent after receiving an explanation of the nature and possible deleterious effects of the diet. Physical and neurologic examinations are normal except for the ophthalmologic findings. She has severely constricted visual fields with a corrected visual acuity of 20/30 in the left eye. Acuity in the right eye is much less as a result of the residuum of an intraocular hemorrhage.

Dietary management in patient Z.F. In an initial hospitalization Z.F.'s arginine intake was moderately restricted for 3 wk by means of a 20-g/d protein diet (20) supplemented with 10 g/d of essential amino acids,³ vitamins and minerals. During a second hospitalization 4 mo later, dietary arginine was more severely restricted by 3-g protein diet (21) supplemented with 20 g of essential amino acids plus required vitamins and minerals. Caloric intake was determined daily and maintained at near 2,000 cal/d with fat and carbohydrates. Arginine intake was estimated to be 5% and lysine intake 6% of the total protein intake⁴ (22). After 6 wk on this diet she was discharged on a 10-g protein, 2,000-cal diet supplemented with 20 g of essential amino acids, vitamins, and minerals. (Details of diet in Appendix.)

² Valle, D., A. Boison, and M. Kaiser-Kupfer. Manuscript in preparation.

³ These were supplied as capsules each containing valine (78 mg); leucine (109 mg); isoleucine (63 mg); methionine (60 mg); phenylalanine (122 mg); tryptophan (15 mg); lysine (98 mg); histidine (26 mg); and threonine (58 mg). All amino acids were purchased from Ajinomoto Co., New York.

⁴ The amount of arginine in the proteins of 34 representative foods is $5.3 \pm 1.4\%$. Certain foods, particularly nuts, have a high arginine content and should be avoided. The lysine content of the same food proteins was $6.2 \pm 2.1\%$.

While in the hospital, Z.F.'s response to the diets was monitored by daily weighings; tri-weekly plasma amino-acids and ammonia measurements; bi-weekly determinations of serum electrolytes and transaminases, and 24-h urinary excretion determinations of urea nitrogen, creatinine, and amino acids. Electroencephalograms were obtained whenever there was a significant change in plasma ornithine. At home, she was monitored with monthly aminograms.

Complete ophthalmologic evaluations were performed before institution of any diet and at 6-mo intervals after dietary control of plasma ornithine. The evaluations included funduscopic examination, fundal photography, visual fields, dark adaptometry, fluorescein angiograms, electroretinograms, and electrooculograms.

Amino acid and ammonia determinations. The fasting patient's heparinized blood samples were obtained by venipuncture at 8 a. m. and processed immediately. For measurement of all amino acids other than glutamate and glutamine, the plasma was deproteinized with sulfosalicylic acid and the resulting filtrate analyzed with a Beckman 119C amino acid analyzer (Beckman Instruments, Inc., Fullerton, Calif.) using lithium citrate buffers. Urine and cerebrospinal fluid samples were similarly deproteinized and analyzed, except that samples containing AIB were analyzed on a Technicon amino acid analyzer (Technicon Instruments Corp., Tarrytown, N. Y.) using sodium citrate buffers at 60°C. Under these conditions AIB elutes between alanine and valine, while it co-elutes with citrulline in the Beckman system. Urinary concentrations of the δ -lactam of ornithine (23, 24) were also determined in these runs, using a standard prepared from ornithine as described by Oberholzer and Bridden (23). The lactam elutes just before arginine in the Technicon system. Plasma concentrations of glutamate and glutamine were measured by enzymatic fluorometric techniques (25) and plasma ammonium by a micro-ion exchange method as previously described (25). Recovery of exogenous ammonium, glutamate, or glutamine added to GA plasma was within 95% of the expected value using these methods.

RESULTS

The fasting patient's plasma amino acid and ammonia concentrations of the four GA patients were all similar and demonstrated several abnormalities in addition to hyperornithinemia (Table I). The mean GA lysine concentration was $121 \pm 9 \mu\text{M}$ (mean ± 1 SEM) a value that is 58% that of the normal mean and below the normal range. Plasma ammonia and its precursors, glutamate and glutamine, were also strikingly reduced in the GA patients. Despite the massive increase in ornithine, there was only a modest increase in arginine and there was no detectable δ -lactam of ornithine. There were also modest but statistically significant changes in leucine, isoleucine, histidine, and tyrosine.

In preparation for institution of restriction of dietary arginine, one of the patients, Z.F., was studied in greater detail. Her serum electrolytes, fasting blood sugar, transaminases and complete blood count were normal. Creatinine clearance was 99 ml/min. Psychometric evaluations adjusted for her visual impairment showed her to be of superior intelligence. Electroencephalograms are described below. Sensory and motor nerve conduction velocities and electromyog-

TABLE I
Plasma Amino Acid and Ammonium Concentrations in Patients with GA of the Choroid and Retina, Mean \pm SEM

	Normal subjects (22)	GA patients (4)	Patient Z.F.	
			Regular diet (6)	Arginine-restricted diet (13)
	μM		μM	
Taurine	51 \pm 4	48 \pm 1	49 \pm 3	39 \pm 2*
Aspartate	6 \pm 1	8 \pm 1	6 \pm 1	8 \pm 1
Threonine	158 \pm 8	164 \pm 18	154 \pm 21	213 \pm 14§
Serine	140 \pm 8	168 \pm 8†	180 \pm 20	192 \pm 19
Proline	189 \pm 12	169 \pm 6	167 \pm 9	283 \pm 13*
Glycine	297 \pm 18	275 \pm 19	271 \pm 30	450 \pm 40*
Alanine	469 \pm 34	365 \pm 85	259 \pm 12	599 \pm 40*
Citrulline	38 \pm 3	32 \pm 4	37 \pm 2	23 \pm 2*
Valine	237 \pm 9	204 \pm 10†	195 \pm 8	175 \pm 7
Cystine	134 \pm 6	144 \pm 7	125 \pm 4	110 \pm 3*
Methionine	31 \pm 2	29 \pm 3	26 \pm 2	34 \pm 2*
Isoleucine	69 \pm 4	55 \pm 2	56 \pm 1	59 \pm 2
Leucine	136 \pm 6	106 \pm 3	112 \pm 2	102 \pm 3*
Tyrosine	74 \pm 4	55 \pm 3	59 \pm 3	61 \pm 2
Phenylalanine	68 \pm 4	58 \pm 4	63 \pm 1	52 \pm 3*
Ornithine	75 \pm 5	1001 \pm 22	964 \pm 35	142 \pm 10*
Lysine	207 \pm 9	121 \pm 9	118 \pm 11	195 \pm 5*
Histidine	84 \pm 4	99 \pm 5†	98 \pm 13	94 \pm 5
Arginine	101 \pm 6	128 \pm 8†	121 \pm 11	67 \pm 2*
Glutamate	35 \pm 7	16 \pm 3	9 \pm 1	25 \pm 2*
Glutamine	669 \pm 21	505 \pm 14	452 \pm 25	720 \pm 29*
Ammonia	20 \pm 2	9 \pm 1	10 \pm 1	18 \pm 1*

Observations in 22 normal subjects and in four patients with gyrate atrophy are compared in the first two columns. Repeated observations on one patient while on regular diet ($n = 6$), and later after plasma ornithine fell to $<200 \mu\text{M}$ ($n = 13$) while ingesting 3-g protein diet supplemented with 20 g of essential amino acids are compared in the second two columns.

* Significantly different from patient Z.F. on a regular diet ($P < 0.01$).

† Significantly different from normal subjects ($P < 0.025$).

§ Significantly different from patient Z.F. on a regular diet ($P < 0.05$).

^{||} Significantly different from normal subjects ($P < 0.01$).

raphy were normal. Plasma and cerebrospinal fluid γ -amino butyric acid concentrations were normal at 115 and 87 pmol/ml, respectively.⁵ Amino acid analysis of her cerebrospinal fluid showed ornithine and lysine to be 217 and 17 μM , respectively. The ornithine value is ~ 40 times normal whereas the lysine value is normal (26).

Because of the report by McCullough et al. (4) that plasma ornithine in a GA patient decreased by 50% during glucose loading, we subjected Z.F. to an oral

⁵ Measured by radioimmunoassay by Dr. Joseph Coyle.

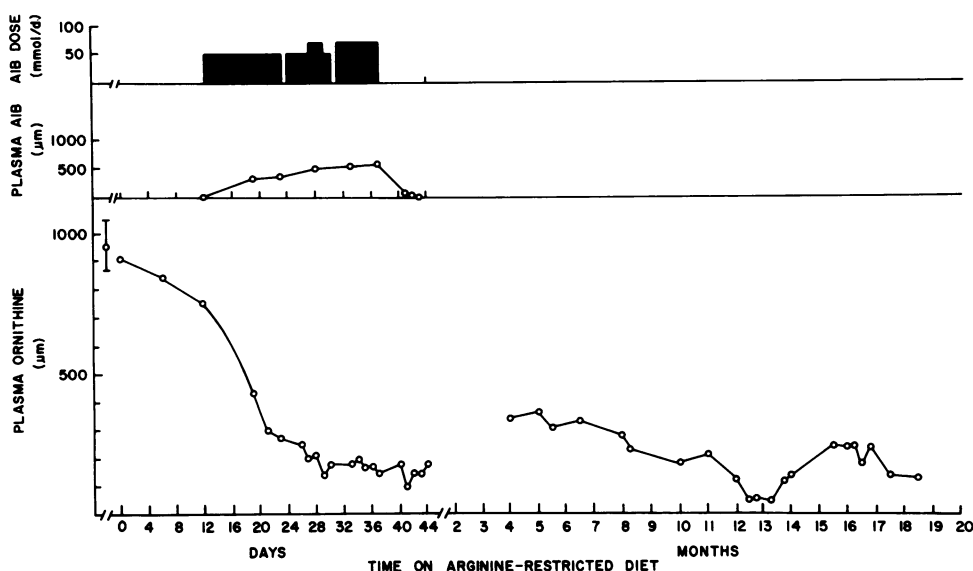


FIGURE 2 Effects of an arginine-restricted diet and oral AIB on plasma ornithine and AIB concentrations. The initial plasma ornithine value represents the mean (± 2 SD) of eight determinations over 4 mo on an unrestricted diet. Arginine intake (estimated as 5% of prescribed protein intake) ranged from 20 to 34 mmol/d on the unrestricted diet, was 0.9 mmol/d during days 1 through 44 and ranged from 2 to 6 mmol/d during the ensuing months. Documentation of actual protein intake was only possible while the patient was in the hospital (i.e., the period of lowest arginine intake).

glucose tolerance test. Blood sugar rose from a fasting value of 89 mg/dl to a peak of 185 mg/dl at 60 min and returned to 115 mg/dl at 180 min. Plasma insulin rose from 17.3 to 100.4 U/ml at 60 min. Plasma ornithine decreased 27% from a fasting value of 956 to a value of 699 μ M at 180 min. Most other amino acid concentrations also decreased over this time period, many to a greater extent than ornithine, suggesting that the reduction of plasma ornithine was part of a general effect of insulin on amino acid transport into cells (27).

In an initial trial of dietary therapy in Z.F., dietary protein was reduced to 20 g/d (~ 6 mmol/d of arginine) for 22 d. During the first week there was a slow reduction of plasma ornithine from her mean value on an unrestricted diet of 956 ± 21 μ M to values between 750 and 800 μ M. Over the next 2 wk, there was no further decline in plasma ornithine.

Ornithine excretion decreased from a mean of 6 mmol/d on an unrestricted diet (of which 10–15% was as the δ -lactam) to 0.5 mmol/d after 8 d on the restricted diet. We attempted to increase ornithine excretion by increasing dietary lysine from 16 mmol/d (derived from dietary protein plus the amino acid supplement) to 40 mmol/d. This resulted in a doubling of plasma lysine over the next 5 d from 137 to 271 μ M. Instead of falling, plasma ornithine rose during this same period from 716 to 777 μ M. Despite the increased lysine intake, excretion scarcely changed, suggesting that most of the administered lysine was being degraded and was not having the desired effect on ornithine excretion.

We studied Z.F. again 4 mo later. She was on an unrestricted diet during the interval between studies. During the second hospitalization her protein intake was decreased to 3 g/day (~ 1 mmol of arginine/d) and supplemented with 20 g/d of essential amino acids. Her plasma ornithine fell from 905 to 740 μ M over 12 d. We then added the nonmetabolizable amino acid AIB (5 g/d) to the diet in hopes of augmenting ornithine excretion. Coincident with adding AIB, there was a more rapid decline in plasma ornithine to values < 200 μ M (Fig. 2). Despite an additional increase of AIB to 7.5 g/d, there was no further reduction in plasma ornithine over the next week and AIB was discontinued. Off AIB, plasma ornithine remained unchanged and plasma AIB, which had been as high as 620 μ M, decreased to 0 within 6 d.

In association with the reduction of ornithine to < 200 μ M, the abnormally low plasma concentrations of lysine, glutamate, glutamine, and ammonia characteristic of untreated GA all returned to normal (Table I). The concentrations of several other amino acids were also altered, presumably resulting from the differences in amino acid composition of her low arginine diet vs. her regular diet.

The effect of AIB on the renal excretion of ornithine at various plasma ornithine concentrations is shown in Fig. 3. In response to the decreased arginine intake, plasma ornithine and ornithine excretion fell. At plasma ornithine concentrations close to 700 μ M, ornithine excretion was < 0.2 mmol/d. Addition of AIB

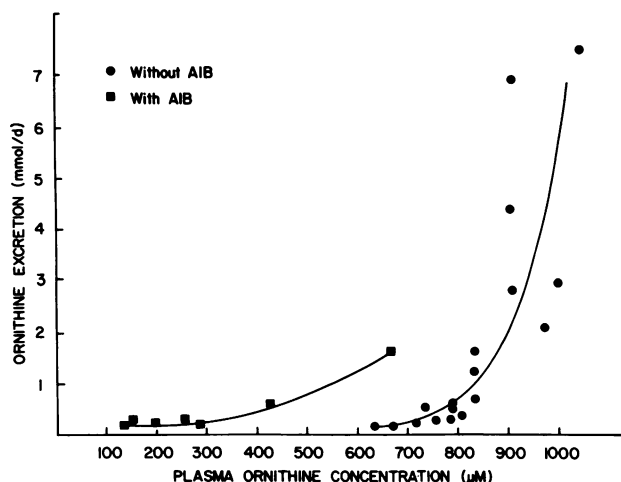


FIGURE 3 The effect of the ingestion AIB (5 g/d) on the relationship of ornithine excretion to plasma ornithine concentration.

resulted in increased ornithine excretion despite a further reduction in the plasma ornithine concentration. At plasma concentrations of 400–650 μM , ornithine excretion on AIB exceeded that measured off AIB by at least 10-fold. Even at plasma ornithine concentrations of 200–300 μM , ornithine excretion on AIB (0.22 mmol/d) was much greater than off AIB (0.04 mmol/d). This effect of AIB on the renal transport of ornithine is also reflected in the clearance data presented in Table II. At ornithine concentrations $<300 \mu\text{M}$, AIB increased the clearance of ornithine, cystine, and lysine to values 5–10-fold greater than when Z.F. was off AIB. The clearances of several other amino acids (particularly glycine, serine and alanine) were also increased by AIB. The effects of AIB are in general agreement with those observed by Christiansen and co-workers (17) in studies on rats.

The effect of hyperornithinemia on the renal clearance of amino acids is also apparent from the data in Table II. Comparison of the clearances in the untreated state (plasma ornithine $\sim 1,000 \mu\text{M}$) with those when ornithine is low (200–300 μM) shows that the clearances of ornithine, lysine, arginine, and cystine are increased by the high-filtered load of ornithine. These results are qualitatively consistent with the ornithine loading studies of Simell and Perheentupa (28) in normal subjects.

The reduction of plasma ornithine was associated with a significant change in the patient's electroencephalograms. Two recordings made when plasma ornithine was $>900 \mu\text{M}$ were read as definitely abnormal with mild diffuse slow and sharp wave activity. A repetition when the plasma ornithine was 700 μM , was improved but still abnormal and five recordings made over an 18-mo interval when her ornithine concentrations have been $<426 \mu\text{M}$, have all been normal.

TABLE II

Renal Clearance of Selected Amino Acids in a Patient with GA of the Choroid and Retina

	Renal clearance		
	Regular diet* (5)	Arginine restricted diet* (3)	Arginine-restricted diet plus AIB† (7)
	ml/min \pm SE		
Serine	1.6 \pm 0.2	0.72 \pm 0.07§	2.7 \pm 0.20¶
Glycine	3.0 \pm 0.4	2.20 \pm 0.20	6.6 \pm 0.50¶
Alanine	0.5 \pm 0.1	0.18 \pm 0.01§	0.55 \pm 0.04¶
Cystine	3.8 \pm 0.8	0.48 \pm 0.05§	3.8 \pm 0.7¶
Ornithine	3.7 \pm 0.9	0.12 \pm 0.01§	0.62 \pm 0.08¶
Lysine	8.5 \pm 1.8	0.16 \pm 0.03§	2.3 \pm 0.4¶
Histidine	5.9 \pm 1.4	2.80 \pm 0.20¶	4.9 \pm 0.3¶
Arginine	1.8 \pm 0.4	0.16 \pm 0.02§	0.20 \pm 0.03

* The mean (and ranges) of plasma ornithine concentrations during these diet periods were as follows: regular diet, 956 μM (815–1,061 μM); arginine-restricted diet, 248 μM (275–222 μM); arginine-restricted plus AIB, 181 μM (296–147 μM).

† AIB, α -aminosobutyric acid.

§ Different from the clearance on a regular diet ($P < 0.01$).

¶ Different from the clearance on a regular diet ($P < 0.05$).

¶ Different from the clearance on an arginine-restricted diet ($P < 0.01$).

After 42 d of arginine restriction, Z.F. was discharged from the hospital on a 10–20 g/d protein diet supplemented with 20 g/d of essential amino acids. She has been maintained on this for 18 mo. Her activity and general health have been good. Plasma albumin, liver function tests, and hematologic parameters have all remained in the normal range. Plasma amino acids have been measured at approximately monthly intervals over the ensuing 18 mo. Ornithine values increased twofold soon after discharge, but then gradually declined probably as a result of closer adherence to the diet (Fig. 2). The concentrations of lysine, glutamate, and glutamine have remained significantly increased over initial values, whereas other amino acids have shown the same general pattern as in Table I. Hyperammonemia has not been observed.

Complete ophthalmologic evaluations after 6, 12, and 18 mo of reduced ornithine levels have shown no apparent progression of the chorioretinal degeneration. After 15 mo on the diet, the patient spontaneously reported an improvement in her ability to adapt to, and see at low levels of illumination. This subjective improvement in dark adaptation has persisted and has been confirmed by measurements of dark adaptometry.⁶

⁶ Kaiser-Kupfer, M., D. Valle, M. Walser, and S. Brusilow. Manuscript in preparation.

DISCUSSION

These results demonstrate that in addition to marked hyperornithinemia, GA patients have abnormalities in the concentrations of other amino acids, most notably reductions in lysine, glutamate, and glutamine. Plasma ammonia values are also reduced. Limitation of dietary arginine intake to ~ 1 mmol/d in a single GA patient resulted in a gradual sixfold decrease in plasma ornithine as well as significant increases in lysine, glutamate, and ammonia (29).

This reduction of ornithine in response to restriction of dietary arginine strongly supports the idea that arginine is the only significant source of ornithine in individuals lacking OAT. The possibility of an alternate pathway of *de novo* ornithine synthesis in man (e.g., via *N*-acetyl glutamate as in microorganisms, [30]) is unlikely in view of these results. The corollary of this argument in normals is that the OAT reaction is the only means of *de novo* ornithine synthesis. Thus, despite the facts that the OAT reaction normally functions to degrade ornithine (and arginine) and that the equilibrium constant of the OAT reaction is 70 in favor of PC synthesis (10), the OAT reaction may, under certain conditions, fulfill an anapleurotic function and serve to form ornithine. Conversion of glutamate to ornithine has recently been reported to occur in rat intestinal homogenates (31), presumably through the OAT reaction. This pathway must explain the apparent nonessentiality of arginine in man (32–34). Those animals in which arginine is essential or semiessential must not be able to achieve the conditions required for adequate reverse flux through the OAT reaction.

Because GA patients are unable to synthesize ornithine (and arginine) *de novo*, it is theoretically possible that ornithine and arginine could be so severely reduced by this diet that clinically significant hyperammonemia could occur (35). Hypoornithinemia, therefore, should be avoided.

The reason for the reduced levels of ammonia and its precursors, glutamate and glutamine in untreated patients with GA is not known. McCulloch et al. (5) have reported similar reductions in whole blood glutamate concentrations. A possible explanation for this reduction in urea precursors is that the high concentrations of ornithine serve to reset the balance between urea precursors and urea production. In the presence of excessive amounts of ornithine, the concentration of urea precursors falls to lower levels. The final result of the increased ornithine and decreased ammonia is a normal (i.e., appropriate for protein intake) rate of urea production.

Plasma lysine values increased significantly to normal in association with correction of hyperornithinemia. This occurred despite that fact that the lysine intake (assuming similar absorption) on the 3-g protein, 20-g essential amino acid diet (16 mmol/d) is less than that

on a typical 70-g protein diet even when allowance is made for the increased urinary excretion of lysine in GA patients (29 intake minus 2 mmol/d excreted). This suggests that the hypolysinemia in untreated GA is not a result of renal losses but an effect of the high ornithine levels on lysine catabolism or distribution.

Ingestion of 5 g of AIB/d resulted in plasma AIB concentrations of between 300 and 600 μ M with no adverse affects. At these plasma levels, AIB increased the clearance of ornithine and several other basic amino acids. The possible role for long-term usage of AIB or other nonmetabolized amino acids as an adjunct to dietary therapy of GA, remains to be investigated.

When the pathophysiology of GA involves either a direct toxic effect of ornithine or a toxic effect of some of the secondary metabolic abnormalities (e.g., hypolysinemia) then GA patients should benefit from dietary restriction of arginine. Continued long-term ophthalmologic follow-up will be required to determine if the progression of the chorioretinal degeneration is halted by this therapeutic approach. If the pathophysiology involves a tissue-specific deficit of the reaction product, this diet would be of no help. In fact, it could be deleterious if there were residual enzyme activity capable of catalyzing limited formation of product at the high substrate concentrations. The observation that, for the last 19 mo on diet, our patient's ophthalmologic parameters have not deteriorated and in fact, have modestly improved suggests that this diet may be of benefit to GA patients.

APPENDIX

Arginine Deficient Diet for Patients with Gyrate Atrophy of the Choroid and Retina

Principal of the diet:

Patients with gyrate atrophy have high plasma levels of ornithine as a result of a deficiency of ornithine aminotransferase. The only known source of ornithine in these patients is arginine which in turn derives either from dietary protein or breakdown of endogenous protein. Thus, by limiting protein intake and by providing essential amino acids and calories to prevent excessive breakdown of endogenous protein, it is possible to lower plasma ornithine levels in these patients. Our approach has been to reduce plasma ornithine as rapidly as possible with a very low protein diet (3 g protein) and then increase protein intake to more tolerable levels with a 10–20-g protein diet. Adequate vitamins and minerals must also be supplied.

Components of the diet

Essential amino acids. We obtain nutritional grade amino acids from Ajinomoto Co. (Ajinomoto USA Inc., New York). We mix the amino acids and prepare capsules as follows:

Amino acid	Milligrams per capsule
Valine	78.1
Leucine	109.4

Amino acid	Milligrams per capsule
Isoleucine	63.1
Methionine	68.8
Phenylalanine	122.8
Tryptophan	15.2
Lysine acetate	98.2
Histidine	26.4
Threonine	58.0
	640 mg

The essential amino acids can be given either as capsules or as powder. When the patients are on the 3-g protein diet, we prefer to give them as powder to eliminate the gelatin in the capsules. Most patients mix the powdered essential amino acids with lemonade or coffee to make them more palatable.

Vitamins and minerals. We give 1 VITAKAP-M (Abbott Laboratories, North Chicago, Ill.) per d.

Glucose polymers. Glucose polymer formula is best tolerated when taken with an equal volume of carbonated beverage. Glucose polymer powder is well tolerated as 250 g powder mixed with 750 ml of liquid. The use of cranberry juice, reconstituted frozen lemonade, limeade, unsweetened soft drink or iced tea is recommended. Those used in our study are listed below.

Calpower	Henkel Corporation, Minneapolis, Minn.;
Hycal	Beecham Massengill Pharmaceuticals Div. Beecham, Inc., Bristol, Tenn.;
Mor-rex	CPC International, Inc., Englewood, N. J.;
Polycose	Ross Laboratories, Div. Abbott Laboratories, Columbus, Ohio.

Low protein bread, rusks, pasta, gelatin, and cookies. Available from Henkel Corporation, Minneapolis, Minn.

Menu samples for 3-g protein, 2,000-cal diet

Breakfast:

Glucose polymer formula*
 ½ cup canned fruit
 2 slices toasted Paygel-P bread or
 2 Aprotin rusks
 Butter, jelly or honey
 Coffee or tea

Lunch and dinner:

Glucose polymer formula*
 Small tossed salad with oil and vinegar
 or Aprotin spaghetti with tomato sauce
 2 slices Aprotin bread or 2 Aprotin rusks
 Butter, jelly or honey
 Fresh or canned fruit or lemon pudding or
 Prono gelatin or Italian ice
 Rich's whipped topping
 Tea, coffee, or carbonated beverage

Between meals:

Glucose polymer formula*
 Low protein cookies
 Hard candy
 Paygel-P bread or Aprotin rusks

Butter, jelly, or honey
 Prono gelatin, popsicles

* Glucose polymers supply ~50% of the calories.

Menus for 10–20-g protein, 2,000-cal diet

These can be prepared from the references listed below: Glucose polymers can be used to maintain caloric intake and the low protein pastas (see above) are also useful. In practice, we find it best to determine the individual likes and dislikes and then provide appropriate lists of foods and their protein content (these may have to be printed in large type depending on the residual vision of the patient). With good instructions, the patients (or their parents) are able to plan their own menus and keep diet records.

We continue to supplement the protein intake with 15 g of essential amino acids/d.

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ADDENDUM

During the preparation of this manuscript, we learned of another GA patient who is on a low-arginine diet. This patient, an 8-yr-old boy, was independently placed on such a diet by Dr. M. S. McBean at the Royal Hospital for Sick Children, Glasgow, Scotland, and has had a reduction in plasma ornithine to normal levels.

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