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Aminoaciduria
arginine
hereditary disease
kidney
lysine
membrane transport
metabolic disease
ornithine

# Hyperdibasicaminoaciduria: An Inherited Disorder of Amino Acid Transport[34]

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*Extract*

A dominantly inherited trait, expressed as 'hyperdibasicaminoaciduria', has been identified in 13 of 33 members in a French Canadian pedigree (fig. 1). The female proband was 18 months old when first identified. The medical problems which brought her to our attention were her small stature and symptoms compatible with a mild malabsorption syndrome. Neither the small stature nor the intestinal complaints could be linked confidently with the appearance of the inherited trait; it is more reasonable to assume that the incidental appearance of a medical problem in the proband brought the otherwise benign trait to attention.

The trait was characterized by abnormally high urinary excretion rates for the diaminomonocarboxylic ('dibasic') compounds, lysine, ornithine, and arginine; cystine, which is excreted in abnormal amounts along with the dibasic amino acids in classical cystinuria, was excreted normally in this instance (table I and figs. 2A and 2B). This constitutes the distinctive characteristic of the trait. It allows one to discriminate the carriers of the trait, who presumably are heterozygotes, from carriers of the various cystinuric genotypes. The trait is expressed consistently with regard to interindividual variation (table I) and intraindividual variation (table II).

The plasma concentrations of the affected amino acids were normal in carriers of the trait, while the endogenous renal clearance rates were modestly elevated (table III). A defect in net tubular absorption of the relevant amino acids thus existed. The mutant transport trait was apparently also expressed in the intestine. This is assumed because net accumulation of lysine in plasma after loading by mouth was less in carriers of the trait than in normal subjects (fig. 3 and table IV); in contrast, in the single patient tested, intestinal absorption of cystine was not impaired.

The characteristics of the trait suggest that the diaminomonocarboxylic amino acids share a transport system in kidney and intestine which excludes cystine.

*Speculation*

The discovery of a mutant trait, in which transport of diaminomonocarboxylic acids alone is impaired, illustrates the specificity of membrane transport systems for amino acids. In this instance, the belief that cystine is *not* transported on the 'dibasic' system is confirmed. Thus, an interpretation of the physical and chemical basis for classical cystinuria, where cystine and 'dibasic' amino acids are affected together, still remains a major challenge to the investigator.

*Introduction*

A consideration of the 'inborn errors of membrane transport' [17] indicates that renal tubular absorption of amino acids is a mediated process under genetic control [25]. A similar interpretation applies to intestinal uptake of amino acids [27, 33, 35]. The mechanisms of uptake are complex, and it is likely that a single amino acid has access to more than one mode of uptake; in addition, several transport systems provide for reabsorption in kidney of the different chemical groups of amino acids filtered from plasma into the tubular fluid [25].

Cellular uptake of diaminomonocarboxylic ('dibasic') acids has long occupied the interest of investigators, in particular because of the attendant defect in cystine transport in the human and canine disease now known as classical cystinuria [12, 16]. No encompassing explanation has yet been advanced to indicate why transport of the chemically 'neutral' substance, cystine, should be affected in a trait which also impairs transport of 'dibasic' amino acids. It has been shown conclusively that L-cystine uptake by kidney tissue is not accommodated on the system shared by the dibasic amino acids [19, 36], and that the mutual interaction during transport of these compounds and their derivatives probably occurs only during efflux of cysteine [24]. SEGAL and CRAWHALL [31] have even succeeded in showing that cystine uptake is independent of cysteine influx. Further support for the separateness of cystine transport is available from the interesting mutant transport trait described by BRODEHL *et al.* [3], who observed isolated hypercystinuria, *without* hyperdibasicaminoaciduria in a human pedigree. One must conclude, therefore, that regardless of how 'cystinuria' occurs in the classical cystinuric trait, the cellular uptake of cystine is mediated by a separate system, unallied to that shared by dibasic amino acids.

The foregoing reasoning leads one to anticipate the discovery at some time of a specific inborn error of amino acid transport, the phenotype of which will be 'hyperdibasicaminoaciduria'. Such a trait has been recognized and is described here; it is dominantly inherited and is, therefore, presumably the heterozygous form of a trait, the homozygous form of which may still be unknown. Whether the recently described disorder, called 'protein intolerance', which is associated with defective transport of lysine and arginine [9, 10, 11, 13], is the homozygous form of this, or another trait, is discussed.

*Case History*

An 18-month-old white French Canadian girl was admitted to the Montreal Children's Hospital in 1965 for elective investigation of small stature. Gestation was 32 weeks and birth weight was 4 pounds. Recurrent vomiting, without diarrhea, during the first 6 months of life was the only recorded illness in the past history. On admission, the child was in satisfactory health. Her weight and height were 6.5 kg and 71 cm, respectively; both were below the third percentile. Body proportions were normal, the nutritional status was not exceptional, and there were no abnormal physical findings. Routine laboratory examinations included: urinalysis, normal; urine culture $\times$ 3, negative; hemoglobin, 10.4 g %; total white blood cells count on 10 analyses, 8000–12,000/mm$^3$, with a mild polymorphonuclear leucocytosis; BUN, 14 mg %; Ca, 9.4 mg %; $PO_4$, 5.2 mg %. The concentration of chloride in sweat was 12.8 mEq/l. Radiological examination showed the bone age to be 12 months; there were no other abnormalities in the appearance of the bones. The barium study of the gastrointestinal tract showed irregular dilatation, slight flattening and thickening of mucosal folds, and segmentation, findings consistent with the malabsorption syndrome. An intestinal biopsy was not performed. The child was discharged on a gluten-free diet.

Urine was also examined for amino acid content at the time of the first admission. The cyanide-nitroprusside test was negative, but partition chromatography in a phenollutidine two-dimensional system [5] revealed an intense ninhydrin-positive spot in the area allocated to the dibasic amino acids, lysine, arginine, and ornithine. This finding was the basis for subsequent investigation and for the present report.

The child was not seen by us until she was admitted again at 42 months of age. She had gained in weight and height proportionately, but was still below the third percentile for both parameters. The remainder of the physical examination was again normal.

Roentgen investigation of the intestinal tract at that time revealed no abnormality. Several routine urine analyses were normal. The hemoglobin concentration was 8.0 g %; hypochromia and microcytosis were demonstrated; otherwise the formed elements of the blood were normal. The chemical tests previously performed were repeated and again found to be normal. The ammonia concentration in blood and after fasting was also normal (0.9 $\mu$g/ml). Examination of feces for parasites was negative.

Partition chromatograms of urine again showed specific hyperaminoaciduria involving the dibasic amino acids, whereas the cyanide-nitroprusside test for cystine was negative. The endogenous renal clearance rates of the dibasic amino acids, but not of cystine,

were increased above normal. The results of further special investigations are reported below. The patient was given iron therapy and discharged. She has been seen since then on several occasions. She remains in good health and continues to grow in weight and stature proportionately at an adequate rate, but still below the normal range.

### *Family History*

Both parents are health French-Canadians. The patient has two male and three female siblings, all of small stature, falling on, or below, the 3rd percentile for weight and height. Small stature was, in fact, characteristic for all members of the pedigree (fig. 1). None had vomiting or diarrhea in infancy, and there were no early or unexplained deaths.

### *Special Investigations*

*Clinical Methods*

*Urine:* All 'random' urine samples were collected before breakfast, after an overnight fast, and were kept frozen at –20° until analyzed.

*Plasma:* Venous blood samples were collected from the antecubital vein in heparinized syringes. The blood was centrifuged immediately at 2000 rpm for 10 minutes; the plasma was then removed and deproteinized with picric acid (0.437 N) (picric acid: plasma, 5:1 v/v). The picric acid was then removed on Dowex $2 \times 8$ resin according to the standard technique [1]. The sample was then reconstituted in pH 2.2 sodium citrate buffer before application to the ion exchange resin columns of a Beckman-Spinco amino acid analyzer.

Blood samples, drawn during an L-cystine loading test, were treated with iodoacetate in the manner described by BRIGHAM, STEIN and MOORE [2] to prevent oxidation of cysteine to cystine.

*Endogenous Renal Clearance Rates*

Short-term endogenous renal clearance tests were performed in the manner described previously [28].

*Amino Acid Loading Tests*

The tests were performed in the morning, after an overnight fast. L-lysine monohydrochloride (100 mg/kg) [37] was given in water by mouth to five normal adult subjects and three patients, including the proband (III.27), her sister (III.24), and her father (II.6). Heparinized venous blood was drawn at 0, 30, 60, 90, and 180 minutes from the antecubital vein, using a heparinized No. 21 guage scalp vein needle which was left in place until termination of the test. This precluded multiple venipunctures which might possibly affect the concentration of amino acid in plasma [23].

L-cystine [37] (120 mg/kg) was given as a slurry in water to the father (II.6) of the proband; the container was rinsed several times with water to assure delivery of the complete dose of the amino acid. Blood samples were drawn at 0, 60 and 120 minutes, using the same withdrawal technique described for the lysine load.

*Analytical Methods*

*Qualitative:* The cyanide-nitroprusside reaction [14] was performed on urine samples obtained from all family members. An immediate and persistent magenta color with this test indicates the presence of a disulfide; in the present study, cystine in excess of 45 mg/g urinary creatinine gave a positive test.

Partition chromatography in two dimensions on 10-inch square Whatman No. 4 filter paper was employed to identify amino acids in urine in the manner of DENT [5]. Water-saturated phenol [38] was used for development in the first dimension during the day in an ammonia atmosphere. After drying overnight at 40°, the chromatograms were developed in the second direction in 2,6-lutidine [39] for 8 hours and air-dried overnight. They were then stained using a ninhydrin-isatin mixture in acetone [29]. Amounts of urine equivalent to 250 $\mu$g of total nitrogen were applied for purposes of standardization.

Levels of amino acids in plasma were also examined by a one-dimensional partition chromatographic method employing a mixture of butanol:acetic acid:water (12:3:5 v/v) to develop the chromatogram on Whatman 3 MM paper [29].

*Quantitative:* The amino acid content of urine and plasma was measured by elution chromatography on ion exchange resins according to the methods of SPACKMAN, STEIN and MOORE [32] on a Beckman-Spinco model 120 amino acid analyzer modified for simultaneous analysis of 'neutral' and 'basic' amino acids [30]. The error of analysis by this method averages less than 3 percent.

*Creatinine:* Urinary creatinine was determined by Folin's method [8] on a Technicon auto-analyzer.

### *Results*

The trait which attracted our attention was the occurrence of specific hyperdibasicaminoaciduria without cystinuria. This trait was consistently expressed in the proband over a two-year observation period; the frequency of its occurrence in her family was then investigated.

*Pedigree Analysis*

There were 33 surviving kin in three generations of this French Canadian family (fig. 1). The trait is domi-

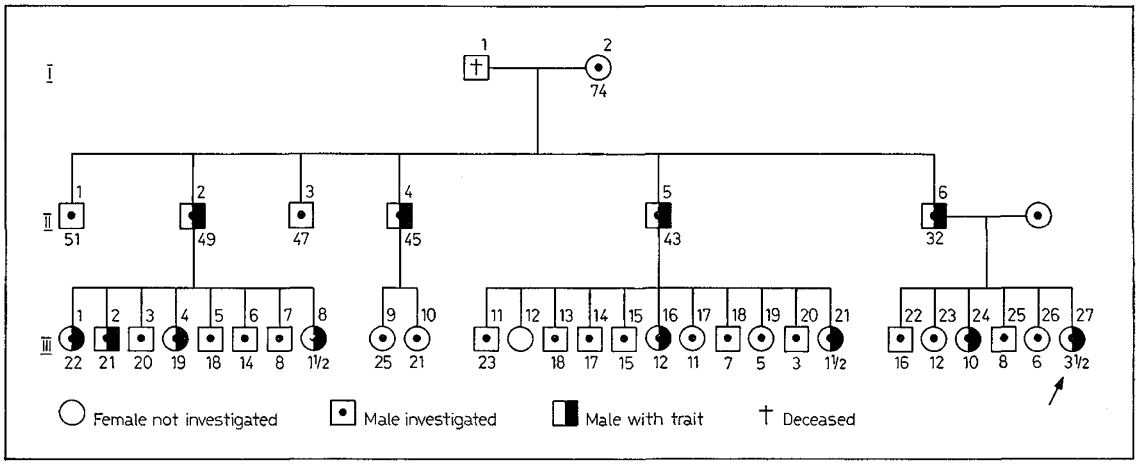


*Fig. 1.* A French Canadian pedigree, in which urinary hyperexcretion of lysine, arginine and ornithine, but not of cystine, occurs as a dominantly inherited trait. The proband presented with small stature and mild intestinal malabsorption; her immediate family all have small stature (< 3rd percentile for height and weight). None of the other 12 carriers of the trait has had intestinal symptoms.

*Table I.* Urinary excretion of cystine and 'dibasic' amino acids by 13 carriers of trait (Excretion rate expressed as mg amino acid/g creatinine)

| Subject[1] | Cystine | Lysine | Arginine | Ornithine |
|---|---|---|---|---|
| II.2 | 44.9 | 160.4 | 10.2 | 16.2 |
| II.4 | 34.4 | 177.7 | 14.2 | 16.2 |
| II.5 | 22.4 | 169.7 | 13.5 | 6.4 |
| II.6 | 14.2 | 154.6 | 12.2 | 5.6 |
| III.1 | 33.7 | 73.0 | 6.4 | 4.8 |
| III.2 | 30.7 | 39.7 | 5.6 | 10.9 |
| III.4 | 21.1 | 100.6 | 5.9 | 8.0 |
| III.8 | 51.3 | 144.4 | 16.4 | 13.9 |
| III.9 | 9.4 | 54.1 | 4.6 | 5.1 |
| III.16 | 12.7 | 177.0 | 11.0 | 62.4 |
| III.21 | 49.1 | 191.4 | 12.5 | 8.0 |
| III.24 | 17.2 | 285.6 | 10.0 | 26.5 |
| III.27 | 20.0 | 264.9 | 12.3 | 10.8 |
| Mean (Mean±SD) | 27.8 | 153.3 | 10.4 | 15.0 |
| Normal [30] (Mean±SD) | 22±9[2] | 15±5 | 2.1±0.9 | 2.2±2.3 |

[1] See figure 1 for designation in pedigree.

[2] Up to 60 mg/g creatinine considered as normal by CRAWHALL *et al.* [4].

nantly inherited and appears in thirteen otherwise healthy members. Since the paternal grandmother did not show the trait, we assume that the deceased paternal grandfather was the carrier. The presence of the trait was confirmed in every case, both by partition and by elution chromatographic analysis of urinary amino acids (table I).

*Quantitative Nature of the Trait*

The urinary excretion rates (mg amino acid/g urinary creatinine) of amino acids in the proband was abnormal only with respect to the 'dibasic' compounds, lysine, ornithine, and arginine. The same finding was demonstrated quantitatively in the other twelve carriers (table I). There is some variability in expression of the trait, and excretion of arginine or ornithine may be only slightly abnormal (e.g. subjects II.5, II.6, III.1, III.9), whereas lysine excretion is always increased.

The excretion rate of cystine was consistently different from that of the dibasic amino acids in all thirteen subjects. The mean cystine excretion rate was normal (table I), although three subjects (II.2, III.8 and III.21) excreted this compound in amour just sufficient to produce a slightly positive test with the cyanide-nitroprusside reagent.

The dichotomy between the normal rate of excretion of cystine and of the hyperexcretion of the three diaminomonocarboxylic amino acids is clearly evident in figures 2A and 2B. The shaded portions of these two graphs indicate the excretion rates expected of subjects heterozygous for the various classical cystinuric traits [15, 16, 20].

The trait was known to be expressed consistently over many months in the proband. Confirmation of this feature was also obtained in other affected members of her family (table II), indicating that intra-individual expression of the trait is constant in carriers.

*Table II.* Intraindividual variation in excretion of amino acids in urine of 5 subjects (mg amino acid/g creatinine)

| | II.2[1] | | II.4 | | II.5 | | II.6 | | III.27 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | A[2] | B[2] | A | B | A | B | A | B | A | B |
| Cystine | 44.9 | 46.7 | 34.7 | 15.7 | 22.4 | 43.6 | 14.2 | 17.2 | 25.0 | 20.0 |
| Lysine | 160.4 | 88.6 | 177.7 | 120.8 | 169.7 | 461.0 | 154.6 | 268.5 | 153.8 | 264.9 |
| Ornithine | 16.2 | 5.9 | 16.2 | 10.8 | 6.4 | 41.8 | 5.6 | 26.5 | 11.8 | 12.3 |
| Arginine | 10.2 | 6.5 | 14.2 | 8.6 | 13.5 | 15.7 | 12.2 | 10.0 | 18.1 | 10.8 |

[1] See figure 1 for designation in pedigree.
[2] A: 1st study; B: 2nd study. Studies performed on a random urine collected after an overnight fast.

*Mechanism of the Hyperdibasicaminoaciduria*

Examination by partition chromatography of amino acids in plasma did not reveal any hyperaminoacidemia in carriers of the trait. This was confirmed when the endogenous renal clearance rates of plasma amino acids were measured.

The endogenous renal clearance of the dibasic amino acids was elevated (table III), whereas that of cystine and other amino acids was normal. As noted with the urinary excretion rates, the renal handling of arginine and ornithine tended to be less abnormal than that of lysine. An impairment of net tubular absorption is implied from these findings.

*Assessment of Intestinal Absorption of Amino Acids*

L-lysine was administered by mouth to three affected subjects, and the change in the plasma concentration of this amino acid was then compared with results obtained in five normal subjects. The concentration of lysine in plasma after loading was lower in the affected subjects than in the control subjects (fig. 3). The initial plasma concentrations of lysine, however, were also slightly lower in the patients than in the control subjects, although the values were still in the normal range (table III). Therefore, the net increment of lysine above the initial plasma value was calculated for all subjects (table IV) to determine whether the net retention of lysine in plasma was significantly different between control and test subjects. The change in lysine concentrations of plasma in the first 3 hours after loading in the test subjects was significantly less than in the control subjects ($p < 0.05$); however, evaluation at any single period showed less obvious differences. We therefore concluded that uptake of L-lysine from intestine was probably slightly diminished in the carriers of the trait.

The excretion of lysine in urine after administration of the standardized load was also evaluated (table V).

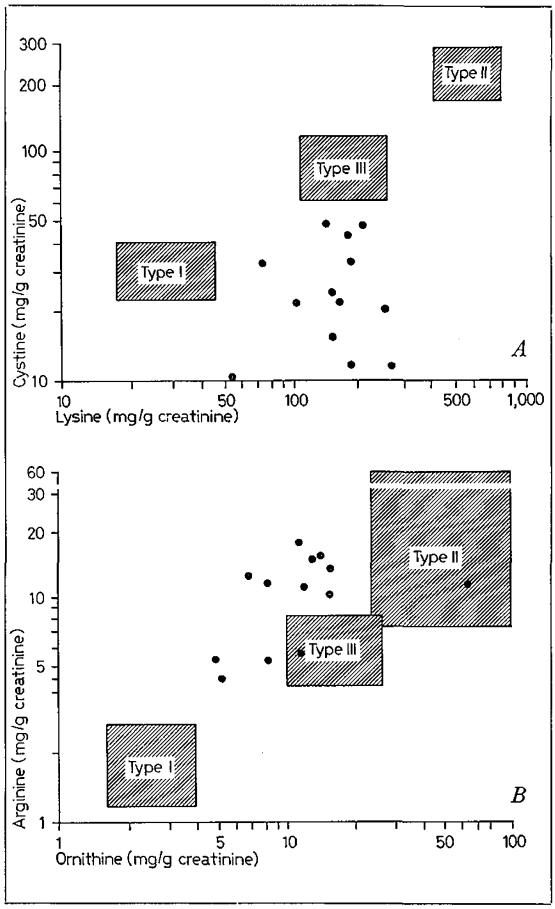


*Fig. 2. A.* Urinary excretion of lysine in relation to cystine; *B.* ornithine in relation to arginine by 13 carriers of the 'hyperdibasicaminoaciduria' trait. The hatched areas of the figures represent the excretion (mean $\pm$ SD) of amino acids by the three types of cystinuric heterozygotes [20]. The absence of hypercystinuria in relation to the excretion of 'dibasic' amino acids distinguishes the new trait from the cystinuric traits.

Subjects with the trait excreted a greater fraction of the lysine load in the urine than did control subjects in the first three hours after the load, even though the net increment in plasma after the load, and hence in the glomerular filtrate, was less than that in the normal subjects. This response illustrates further the nature of the trait, namely, an impairment of net tubular conservation of substrate. Subjects with the trait also showed a greater increment in urinary excretion of ornithine and arginine than did the normal subjects; the increment was roughly proportional to the net loss of lysine in urine. This finding is explained if one assumes that lysine competes with the other two dibasic amino acids for a shared transport site [6, 19, 36]; the inhibitory effect in this situation is proportional to the amount of inhibitor (lysine) in the tubular urine. Competitive inhibition would be expected in the heterozygote for the trait, in whom about half of the transport sites are functioning normally.

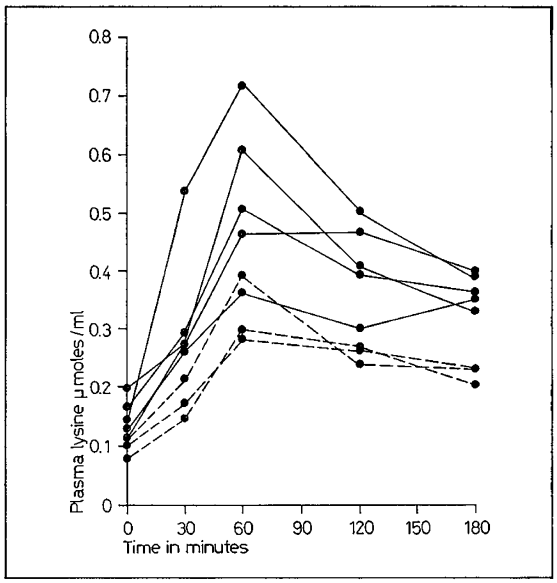


*Fig. 3.* Plasma lysine concentration in control subjects (solid circles) and 3 carriers of the hyperdibasicaminoaciduria trait after oral ingestion of L-lysine monohydrochloride (100 mg/kg).

L-cystine was administered successfully to one affected subject (II.6). The net increase of cystine in plasma was 6.7 μg/ml at 60 minutes, and 13.2 μg/ml at 120 minutes. These values, according to the criteria of ROSENBERG *et al.* [16, 18, 21], exclude a defect in cystine absorption from the intestine.

## *Discussion*

A dominantly inherited trait is described in this communication. The trait is a specific abnormality characterized by increased excretion of diaminomonocarboxylic acids in urine. Plasma concentrations of the involved compounds (lysine, ornithine, and arginine) are normal; consequently, endogenous renal clearance of these substances must be elevated. The probability that hyperlysinemia exists in these patients, causing the dibasicaminoaciduria by a 'combined' mechanism [25], is ruled out by this finding. This

*Table IV.* Net change in plasma L-lysine concentration after loading by mouth with 100 mg/kg

| Subject | Time of sample (in minutes) | | | | Sum of net change |
|---|---|---|---|---|---|
| | 30 | 60 | 120 | 180 | |
| | μ moles/l | | | | |
| Control | 166 | 495 | 293 | 229 | 1183 |
| Control | 126 | 343 | 232 | 191 | 892 |
| Control | 81 | 270 | 271 | 204 | 862 |
| Control | 397 | 585 | 365 | 253 | 1600 |
| Control | 138 | 237 | 175 | 225 | 775 |
| Mean | | | | | 1062.4[1] |
| ± SD | | | | | 336.8 |
| II.6 | 72 | 175 | 164 | 136 | 547 |
| III.24 | 108 | 285 | 135 | 125 | 653 |
| III.27 | 119 | 224 | 196 | 132 | 671 |
| Mean | | | | | 623.7[1] |
| ± SD | | | | | 66.9 |

[1] $0.05 > p > 0.02$, by Student's t test.

*Table III.* Plasma concentration and endogenous renal clearance of cystine, lysine, ornithine, and arginine in 3 family members

| Subject[1] | Plasma ($\mu$ moles/l) | | | | Clearance (ml/min/1.73 m²) | | | |
|---|---|---|---|---|---|---|---|---|
| | Cystine | Lysine | Ornithine | Arginine | Cystine | Lysine | Ornithine | Arginine |
| II.6 | 52 | 116 | 65 | 63 | 0.9 | 5.1 | 0.6 | 0.2 |
| III.24 | — | 138 | 56 | 83 | — | 10.9 | 1.7 | 1.1 |
| III.27 | 32 | 91 | 38 | 2 | 1.4 | 5.4 | 1.1 | 7.0 |
| Normal adult[2] | 48–141 | 82–236 | 29–125 | 21–137 | 0.7–2.9 | 0.2–1.9 | < 0.3 | 0.2–0.8 |
| Children[2] | 44±7 | 130±20 | 46±8 | 85±15 | 0.8±0.2 | 1.2±0.4 | 0.4±0.1 | 0.3±0.1 |

[1] See figure 1 for designation in pedigree.
[2] Compiled from literature [22].

*Table V.* Urinary excretion of dibasic amino acids after L-lysine load[1]

| Subject | | Total dose (g) | Peak plasma $\mu$M/ml | Pre-load | | Post-load | | $\Delta$ | % of load excr. in 180 min |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $\mu$M/min | $\mu$M/min /1.73 m² | $\mu$M/min | $\mu$M/min /1.73 m² | $\mu$M/min /1.73 m² | |
| Control | | | | | | | | | |
| No. 1 (1.78 m²) | lysine | 7.045 | 0.509 | 0.138 | 0.134 | 0.868 | 0.841 | +0.708 | 0.2 |
| | ornithine | | | 0.023 | 0.022 | 0.035 | 0.033 | +0.012 | |
| | arginine | | | 0.012 | 0.012 | 0.017 | 0.016 | +0.005 | |
| No. 2 (1.76 m²) | lysine | 6.954 | 0.465 | 0.044 | 0.043 | 0.200 | 0.194 | +0.151 | 0.06 |
| | ornithine | | | 0.017 | 0.016 | 0.012 | 0.012 | —0.005 | |
| | arginine | | | 0.011 | 0.011 | 0.008 | 0.008 | —0.003 | |
| Patients[2] | | | | | | | | | |
| III.24 (0.86 m²) | lysine | 2.370 | 0.390 | 0.773 | 1.550 | 3.985 | 8.000 | +6.450 | 3.3 |
| | ornithine | | | 0.036 | 0.072 | 0.112 | 0.225 | +0.153 | |
| | arginine | | | 0.030 | 0.060 | 0.157 | 0.315 | +0.255 | |
| II.6 (1.50 m²) | lysine | 5.045 | 0.276 | 0.515 | 0.592 | 2.590 | 2.978 | +2.386 | 1.1 |
| | ornithine | | | 0.033 | 0.038 | 0.080 | 0.092 | +0.054 | |
| | arginine | | | 0.010 | 0.012 | 0.060 | 0.072 | +0.060 | |
| III.27 (0.5 m²) | lysine | 1.090 | 0.300 | 0.080 | 0.277 | 0.809 | 2.790 | +2.513 | 1.6 |
| | ornithine | | | 0.008 | 0.028 | 0.016 | 0.055 | +0.027 | |
| | arginine | | | 0.040 | 0.138 | 0.030 | 0.104 | —0.034 | |

[1] Lysine load, 100 mg/kg. [2] See figure 1 for designation in pedigree.

indicates impaired net renal tubular absorption; the trait appears, therefore, to be another in the group of 'inborn errors of membrane transport' [17, 25].

Because this condition is dominantly inherited, we presume it is a heterozygous mutant transport phenotype. There are other inherited disorders of amino acid transport in which the heterozygote also exhibits an abnormal phenotype. In two types of classical cystinuria [18], heterozygotes have modestly elevated rates of urinary excretion of cystine and of the three dibasic amino acids [15, 20]. In hereditary renal iminoglycinuria [26], the carriers have a modest hyperglycinuria, but no iminoaciduria, a finding recognized initially by DE VRIES *et al.* [7] as a dominantly inherited trait. In such cases, careful study of the presumed heterozygote provided information of considerable importance about the trait in question.

We propose that the 'dibasic' trait is not another form of classical cystinuria, because cystine excretion was not elevated in our group of patients. According to ROSENBERG *et al.* [18, 20], who used refined modes of amino acid analysis, an isolated 'dibasic' trait has not been identified consistently in any classical cystinuric pedigree, although they did identify two unrelated type III cystinuric heterozygotes, in whom the cystine excretion was at the upper limit of normal, whereas lysine excretion was definitely abnormal. In comparing the results in our patients with those reported by ROSENBERG *et al.* [20], it must be recognized that these investigators apparently used a chemical method [4] to determine cystine in urine; at its lower limits of detection, this method gives slightly higher readings than the corresponding ion-exchange chromatographic method used in the present study. In this regard, some values for cystine excretion, although slightly above the usual normal range established by ion-exchange column chromatography [28], are normal by the chemical method [4, 18, 20]. Nonetheless, it seems unlikely that the present pedigree represents only another form of cystinuria; if so, it is, with the above exceptions, a hitherto unreported form of the trait. Because there is much evidence [3, 18, 19, 24, 31, 36] that cystine uptake in kidney is dissociated from the transport of dibasic amino acids, we suspect that we have observed an 'experiment of nature', which tests and supports the hypothesis that the transport systems for cystine and the dibasic amino acids are different functional and genetic entities.

The evidence in favor of selective genetic control of a specific membrane transport site, shared only by dibasic amino acids, would be firmer if the homozygous form of the trait had been identified in the present pedigree. In this context, the description of the presumed autosomal recessive trait, called 'protein intolerance with dibasicaminoaciduria' by the Finnish workers [9, 10, 11, 13], becomes relevant. They described eleven children, including one pair of siblings from consanguinous parents and other pairs of siblings, each exhibiting vomiting and diarrhea, failure to thrive, hepatomegally and diffuse cirrhosis, accompanied by low blood urea concentrations, hyperammonemia, and leucopenia [11]. Symptoms were exaggerated by a high protein diet and alleviated by a reduction of protein intake or dietary supplements of arginine. The hyperammonemia and reduced urea synthesis could not be attributed to a measurable deficiency of enzymes of the urea cycle [10]; a low concentration of arginine relative to lysine in body fluids was proposed as a possible mechanism for the disturbance.

The most interesting and relevant feature of the Finnish trait was a persistent hyperaminoaciduria in each patient involving lysine and arginine [11]; ornithine values were not given and the excretion of other amino acids was normal. The hyperaminoaciduria was attributed to altered tubular transport. The parents and siblings of the Finnish subjects were also studied for the pattern of aminoaciduria [11]; no consistent abnormality was apparently found. Intestinal transport in five probands was evaluated *in vivo* by perfusion and *in vitro* on biopsy specimens obtained from the jejunum [9]; no impairment of lysine or arginine uptake was found.

The findings in the Finnish patients contrast with the absence of any symptoms in our patients; this discrepancy might indicate a difference between the Finnish and the French Canadian traits. Our subjects, however, are presumed to be heterozygotes in whom clinical manifestations would be minimal or absent. The mild clinical symptoms documented in the proband could have been manifestations of the trait provoked by the higher protein intakes of infancy. If that were the case, then none of the other 12 carriers with the same trait happened to develop symptoms. This suggests rather that the clinical symptoms of the proband were incidental to the presence of the trait.

There are significant discrepancies between the Finnish and French Canadian pedigrees. They include the supposed absence of dibasic aminoaciduria in the parents of the Finnish patients [11] and its presence in the French Canadian carriers, and the appearance of an intestinal transport defect in the French Canadians and its apparent absence in the Finnish subjects [9]. Discrepancies such as these, however, which have been described in other inherited transport traits, usually point to the occurrence of genetic heterogeneity in the trait. For instance, Type I cystinuric homozygotes have an intestinal and renal transport defect, but heterozygotes do not exhibit an abnormal urinary phenotype, although intestinal uptake is modestly impaired [16].

Type II cystinuria is characterized by an intestinal and renal transport defect in homozygotes, and the parents have a partial renal phenotype. Type III homozygotes have no obvious intestinal defect, and their parents exhibit the partial renal transport defect [18]. The three types of cystinuria represent mutation of different alleles at the same locus [15, 16, 20]. By analogy, the Finnish and French Canadian forms of the hyperdibasicaminoaciduric trait might also be mutant forms of different alleles at the particular gene locus which controls absorptive transport of the 'dibasic' amino acids. Further studies on new pedigrees will be of interest in this respect; the discovery of a heteroallelic homozygous form of the dibasic trait would confirm the presence of more than one pair of mutant alleles at this locus.

*Summary*

Investigation of a three and one-half-year-old French Canadian female, because of mild malabsorption syndrome and small stature, revealed elevated urinary excretion of the diaminomonocarboxylic ('dibasic') amino acids, lysine, arginine, and ornithine, without cystinuria. This aminoaciduria appeared as a dominantly inherited trait in 13 of 33 kin in the pedigree; short stature was a common independent finding in the pedigree, and no other carriers of the trait had clinical symptoms.

Plasma concentrations of the relevant amino acids were normal; the endogenous renal clearance of the dibasic amino acids, but not of cystine, was increased. Intestinal absorption of L-lysine, but not of L-cystine, was impaired.

The affected members are deemed heterozygous for a trait reflecting impaired renal and intestinal transport of lysine, arginine, and ornithine; the presumed homozygous form of the trait was not found in this pedigree, but may occur as 'protein intolerance with dibasicaminoaciduria', a condition recently reported from Finland. The trait provides evidence for genetic control of a membrane transport system shared exclusively by the dibasic amino acids.

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