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Isolated Persistent Hypermethioninemia

S. Harvey Mudd,[1] Harvey L. Levy,[2] Albert Tangerman,[3] Christian Boujet,[4] Neil Buist,[5] Anne Davidson-Mundt,[6,*] Louanne Hudgins,[7,†] Kazuhiko Oyanagi,[8] Masayoshi Nagao,[9] and William G. Wilson[10]

[1] Laboratory of General and Comparative Biochemistry, National Institute of Mental Health, Bethesda; [2]Massachusetts General Hospital and Children's Hospital, Harvard Medical School, Boston; [3]Division of Gastrointestinal and Liver Diseases, University Hospital Nijmegen, Nijmegen; [4]Laboratoire de Biochimie Métabolique et Exploration Nutritionnelle, Centre Hospitalier Universitaire de Grenoble, Grenoble; [5]Child Development and Rehabilitation Center, Oregon Health Sciences University, Portland; [6]The Children's Hospital, University of Colorado Health Sciences Center, Denver; [7]Maricopa Medical Center, University of Arizona Health Sciences Center, Phoenix; [8]O-dori Children's Clinic, Sapporo; [9]National Otaru Hospital, Otaru, Japan; and [10]University of Virginia Children's Medical Center, Charlottesville

Summary

New information has been obtained on 30 patients with isolated persistent hypermethioninemia, most of them previously unreported. Biopsies to confirm the presumptive diagnosis of partially deficient activity of ATP: L-methionine *S*-adenosyltransferase (MAT; E.C.2.5.1.6) in liver were not performed on most of these patients. However, none showed the clinical findings or the extreme elevations of serum folate previously described in other patients with isolated hypermethioninemia considered not to have hepatic MAT deficiency. Patients ascertained on biochemical grounds had no neurological abnormalities, and 27/30 had IQs or Bayley development-index scores within normal limits or were judged to have normal mental development. Methionine transamination metabolites accumulated abnormally only when plasma methionine concentrations exceeded 300–350 μM and did so more markedly after 0.9 years of age. Data were obtained on urinary organic acids as well as plasma creatinine concentrations. Patterns of inheritance of isolated hypermethioninemia were variable. Considerations as to the optimal management of this group of patients are discussed.

Introduction

Persistent isolated hypermethioninemia (i.e., not associated with either hyperhomocyst(e)inemia and homocystinuria due to cystathionine β-synthase deficiency, tyrosinemia type I, or liver disease) has been demonstrated, in six patients, to be due to deficient activity of ATP:L-methionine adenosyltransferase (MAT; E.C.2.5.1.6) in liver (Gaull and Tallan 1974; Finkelstein et al. 1975; Gout et al. 1977; Gaull et al. 1981*b*; Gahl et al. 1987, 1988) (fig. 1). However, other patients with isolated hypermethioninemia have had normal hepatic MAT activity (Gaull et al. 1981*a*; Jhaveri et al. 1982; Tsuchiyama et al. 1982; Uetsuji 1986; Labrune et al. 1990), while still others never have had their hepatic MAT assayed (Guizar-Vazquez et al. 1980; Congdon et al. 1981; Al Mardini et al. 1988; Boujet et al. 1990; Surtees et al. 1991; Blom et al. 1992). This procedure is critical for diagnosis, because (*a*) there are at least two genes for mammalian MAT (Kotb and Geller 1993) and (*b*) patients with proved hepatic MAT deficiency have had normal MAT activities in cultured skin fibroblasts, red blood cells, and/or cultured lymphoid cells (Tallan and Cohen 1976; Gaull et al. 1981*b*; Gahl et al. 1988).

The minimal information regarding clinical outcome in patients either with proved MAT deficiency in liver (Mudd et al. 1995) or ascertained, without bias, to have isolated hypermethioninemia but without an enzyme diagnosis (Surtees et al. 1991; Blom et al. 1992) suggests the absence of major clinical problems, at least at young ages. However, one girl with isolated hypermethioninemia manifested abnormal neurological signs and symptoms at age 11 years, with magnetic resonance imaging (MRI) evidence of brain demyelination. After treatment with *S*-adenosyl-L-methionine (AdoMet), the metabolic product of MAT, for 12 mo the patient's clinical abnormalities "completely resolved" and brain MRI showed restoration of normal myelination (Surtees et al. 1991). Because of the many uncertainties about patients with isolated persistent hypermethioninemia, we investigated the clinical outcomes and metabolic characteristics of 30 such patients.

Patients and Methods

Patients

Patients either were known to the authors or were recruited by contacting physicians in genetic clinics or

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Address for correspondence and reprints: Dr. S. Harvey Mudd, NIMH/DIRP/LGCB, Building 36, Room 3D-06, 36 Convent Drive MSC 4094, Bethesda, MD 20892-4094.

* Present address: City and County of Denver, Department of Health and Hospitals, Denver.

† Present address: Children's Hospital and Medical Center and University of Washington School of Medicine, Seattle.

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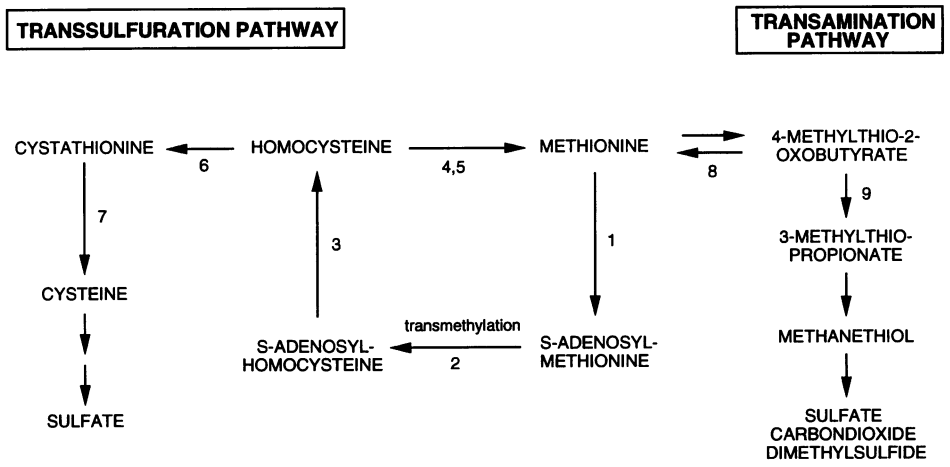

Figure 1 Pathways of methionine metabolism in man, relevant to patients with isolated persistent hypermethioninemia (adopted, with permission, from Blom et al. [1992]). 1, MAT; 2, various methyltransferase reactions; 3, *S*-adenosyl-L-homocysteine hydrolase (E.C.3.3.1.1); 4, betaine-homocysteine *S*-methyltransferase (E.C.2.1.1.5); 5, N^5-methyltetrahydrofolatehomocysteine *S*-methyltransferase (E.C.2.1.1.13); 6, cystathionine β-synthase (E.C.4.2.1.22); 7, cystathionine-γ-lyase (E.C.4.4.1.1); 8, methionine transaminase (thought to be catalyzed at least in part by glutamine transaminase [E.C.2.6.1.15], perhaps with the participation of other transaminases [Mudd et al. 1989]; and 9, 2-keto-4-methylthiobutyrate oxidative decarboxylase (thought to be catalyzed by branched-chain 2-ketoacid dehydrogenase [E.C.1.2.4.4] [Livesey 1980; Jones and Yeaman 1986]).

newborn screening programs, as well as authors of published papers about patients with isolated hypermethioninemia. Patients were admitted to the study if five criteria were met: (1) Hypermethioninemia was present from the youngest age tested and persisted through the last sample obtained (tables 1 and 2). So as not to prejudge what degree of hypermethioninemia might be associated with any particular clinical or metabolic outcome, any patient who met this criterion (and the others specified here) was included, even if the elevation was relatively mild. (2) Homocystine was not abnormally elevated in plasma or, when measured, in urine (data not shown). (3) Severe and persistent abnormal elevations of plasma tyrosine were not present (table 2). (4) Evidence of liver disease was absent (data not shown). (5) New information about that patient had been obtained.

Methods

Many of the amino acid and folate concentrations reported in this paper for the early years in patients had been measured in different laboratories using standard procedures. Those from the later ages in each patient have been analyzed in central laboratories. Analyses of amino acids were performed in the Amino Acid Laboratory of the Massachusetts General Hospital, on a Beckman 6300 Amino Acid Analyzer (Beckman Instruments, Spinco Division), after deproteinization with sulfosalicylic acid and with use of *S*-2-aminoethyl-L-cysteine as an internal standard. Assays of compounds resulting from the action of the methionine transamination pathway were performed at University Hospital of Nijmegen, by the group of one of the authors of this paper (A.T.). Methionine transamination metabolites were determined as described elsewhere (Blom et al. 1989*b*,) as the sum of the methanethiol released sequentially into the gas phase at pH 7 (protein-S-S-CH_3), pH 10 (X-S-S-CH_3), and pH 12.5–13 (chiefly, 2-keto-4-methylthiobutyrate) (Blom et al. 1989*b*). Dimethylsulfide in urine was measured in essentially the same way as described for blood (Tangerman et al. 1985). Organic acids were analyzed in the Amino Acid Laboratory of the Massachusetts General Hospital, in ethyl acetate extracts of urine. After conversion to trimethylsilyl derivatives, compounds were separated on an HP-1 column (Hewlett-Packard) and were detected with a Hewlett-Packard 5970 mass selective detector. Folate concentrations in serum or plasma and red blood cells were measured commercially at MetPath, by a competitive protein binding assay.

Results

The 30 patients with persistent isolated hypermethioninemia for whom new information was obtained during the present study are described in table 1. Previously reported patients not included in table 1 because no new information was obtained about them are 4 with proved deficient MAT activity in liver (Gaull et al. 1981*b;* Gahl et al. 1987, 1988; Mudd et al. 1989, 1995) and 12 with isolated hypermethioninemia but without assay of MAT in liver (Guizar-Vazquez et al. 1980; Congdon et al. 1981; Al Mardini et al. 1988; Boujet et al. 1990; Surtees

Table 1

Patients with Isolated Hypermethioninemia

Group[a] and Patient (Sex)	Affected Sibling	Age[b] (years)	Ascertainment[c]	Plasma Methionine[d] (μM)	Mental Status[e] (age in years)	Neurological and/or Muscular Status
Methionine adenosyltransferase activity, in liver, reported as deficient:						
1 (M)[f]	...	24.5	NBS	770–1,240	Normal	Normal
2 (F)[g]	...	20.4	NBS	100–1,270	IQ 101 (20.4)	Normal
Methionine adenosyltransferase activity, in liver, unknown or equivocal:						
3 (F)	...	4.1	NBS	686–2,541	DQ 124 (2.8)	Normal
4 (M)	6	9.2	FS	1,800	Normal	Febrile convulsion[h]
5 (F)	...	9.9	NBS	1,721–1,870	IQ 85 (7.5)	Transient hypertonia
6 (F)	4	1.0	NBS	1,262–1,660	Normal	Normal
7 (M)	...	2.4	NBS	1,226–1,664	DQ 96 (.8)	Growth delay
8 (F)		14.1	Dystonia	1,114–1,629	Retarded	Dystonia/demyelination[i]
9 (M)	...	1.8	NBS	759–1,467	Normal	Normal
10 (M)	11	5.9	NBS	484–742	IQ 111 (4.3)	Normal
11 (F)	10	9.6	NBS	374–902	IQ 123 (7.8)	Normal
12 (M)	16	.8	NBS	515	Normal	Normal
13 (F)	...	2.6	NBS	451–758	DQ 105 (.8)	Normal
14 (F)	...	2.8	NBS	185–467	DQ 115 (1.0)	Normal
15 (M)[j]	...	10.0	NBS	236–284	Normal	Normal
16 (F)	12	2.0	NBS	225–286	Normal	Normal
17 (M)	25	12.0	NBS	175–337	IQ 83 (10.1)	Normal
18 (F)	...	.4	NBS	186–251	Normal	Normal
19 (M)	28	.3	NBS	197–242	Normal	Normal
20 (F)	...	2.4	NBS	113–299	DQ 101 (1.7)	Normal
21 (F)[k]	...	8.0	NBS	125–233	Normal	Normal
22 (F)	27	38	FS	148	Normal	Normal
23 (F)	...	36	FS	143	Normal	Normal
24 (M)	...	1.1	NBS	80–302	DQ 111 (.7)	Normal
25 (M)	17	3.7	NBS	71–236	DQ 102 (1.8)	Normal
26 (M)[l]	...	9.0	NBS	78–166	Normal	Normal
27 (F)	22	35	FS	111	Normal	Normal
28 (M)	19	1.6	FS	106	Normal	Normal
29 (M)	...	2.0	NBS	66–117	Normal	Normal
30 (F)	...	6.2	NBS	38–107	IQ 100 (6.2)	Normal

[a] Within each group, patients are listed roughly in descending order according to their plasma methionine concentrations.

[b] At last report.

[c] NBS = routine screening of newborns for hypermethioninemia; and FS = family screening because of affected propositus.

[d] On normal diet. Reference range: 5–34 (3 mo–6 years); 23–45 (adult). Note that the reference ranges listed for amino acids and folates in this table and tables 2 and 3 apply strictly only to measurements performed in the central laboratories (see Methods).

[e] If available, IQ or DQ is listed; otherwise, the best estimate of mental status is given.

[f] Patient of Gout et al. (1977)

[g] Patient 1 of Gaull et al. (1991*b*).

[h] Single episode at age 3 mo.

[i] MRI findings suggestive of "myelination arrest."

[j] Patient 5 of Uetsuji (1986).

[k] Patient 7 of Uetsuji (1986).

[l] Patient 6 of Uetsuji (1986).

et al. 1991; Blom et al. 1992). The 30 patients (14 males and 16 females) are separated into two categories:

1. Hepatic MAT activity proved to be deficient. Patients 1 and 2 had previously been shown to have partial deficiencies of MAT activity in liver (Gout et al. 1977; Gaull et al. 1981*b*). Patient 1 is now 24 years of age. He is a university student, engages in normal activities, and participates in active sports. Patient 2, now 20 years old, is in good general health and free of neurological problems. Her full-scale IQ score (Wechsler Adult Intelligence Scale—Revised) was 101, with a verbal score of 91 and a performance score of 115. The current plasma methionine concentrations in patients 1 and 2 were 1,030 and 395 μM, respectively (table 2), both values within the ranges reported during early ages (Gout et al. 1977; Gaull et al. 1981*b*).
2. Liver MAT activity not measured or equivocal. The remaining patients have not had direct assays of MAT in liver. (Patient 21 is an exception to this statement. Uetsuji [1986] reported that the MAT activity in liver of this girl, assayed at 131 μM methionine, was 1.30, within the control range of 0.82–1.89 nmol/mg protein/h, and concluded that MAT activity was normal in her liver. However, the maximal velocity of her MAT was 3.44, below the rates of the two control liver specimens assayed [values 7.69 and 9.10 nmol/mg protein/h]. Thus it seems possible that, when assayed at high methionine concentrations, the MAT activity in liver of this patient is indeed deficient, a situation similar to that for the patients with proved partial MAT deficiency in liver [Finkelstein et al. 1975; Gahl et al. 1987]; and therefore, in table 1, patient 21 has been included among those for whom the status of MAT activity in liver is "equivocal.") All patients except patient 8 were identified without ascertainment bias, i.e., by routine newborn or family screening. Most are still relatively young: 15/30 are in or below their 5th year; 7/30 are between their 6th and 10th years; and 8/30 are beyond their 10th year. Eighteen have been on normal diets throughout their lives. Twelve (patients 1, 3, 5, 7, 9, 13–16, 20, 21, and 26) were placed on methionine-restricted diets at age 0.04–0.5 years and were kept on these diets until age 0.6–8 years. For those who were thought to comply well, plasma methionines decreased to more moderately elevated levels, as shown by the data for patients 3, 7, and 9 (table 3) and those reported for patient 21 (Uetsuji 1986).

IQs or Bayley development-index scores (DQs) were >90, or the patient was judged to be normal in mental development, in 27/30 cases. The patient was judged to be retarded, or the IQs were <90, in three cases. Of the seven cases ascertained without bias who were beyond their 10th year, six (patients 1, 2, 15, 22, 23, and 27) either were judged to be mentally normal or had normal IQs; one (patient 17) had a subnormal IQ.

Persistent neurological abnormalities were absent except in patient 8, who developed a right-sided movement disorder at age 7 years. At age 9 years she had right-sided dystonia and dysmetria, and computed-tomography and MRI scans showed abnormalities of the left posterior putamen that were consistent with either an old infarct or a degenerative process. A repeat MRI at age 11.4 years showed "myelination arrest."

None of the patients showed the clinical abnormalities often seen in those with homocystinuria due to cystathionine β-synthase deficiency with its accompanying hypermethioninemia: dislocation of optic lenses, manifestations of osteoporosis, or vascular accidents. There have been no deaths in this patient group.

Folate Concentrations

Among the patients with isolated hypermethioninemia who were reported to have normal MAT activities in their liver, five had marked increases in serum folate concentrations (Gaull et al. 1981*a*; Tsuchiyama et al. 1982; Uetsuji 1986). Possibly they have altered folate metabolism. Accordingly, folate concentrations were measured in as many as possible (27) of the present patients. No extreme elevations of serum or plasma folate, such as those reported by Tsuchiyama et al. (1982), were observed (table 2). There was a tendency toward mild elevations of plasma folate persisting beyond 1 year of age in the patients with higher methionine concentrations, but normal red blood cell folate concentrations of 336, 421, and 314 ng/ml (reference range 200–700 ng/ml) were found in, respectively, patients 10 and 11 at times when their plasma folates were raised (5.9 and 9.6 years, respectively) and in patient 3 at 4.4 years.

Transamination Metabolites

The concentrations of compounds formed by the action of the methionine transamination pathway were abnormally elevated in 11 patients (table 3). When transamination metabolite concentrations are plotted as a function of plasma methionine (fig. 2), it becomes clear that transamination metabolites did not accumulate abnormally in either plasma or urine at plasma methionine concentrations <~300–350 μM but did so progressively at methionine concentrations above this region.

Furthermore, there appears to be an age-dependent maturation process affecting methionine transamination (table 3 and fig. 2). At ≤0.9 years of age, elevations of transamination metabolites were either nonexistent, even at a methionine concentration significantly >300–350 μM (patient 7; 0.2 years), or (patients 7, 9, and 13) were far less than were found in the same patient with

Table 2

Age-Related Methionine, Tyrosine, and Folate Concentrations

Patient	Plasma Methionine[a] (age) (μM)	Plasma Tyrosine[b] (age) (μM)	Serum Folate[c] (age) (ng/ml)
1	1,240 (.05)[d]		16.5[d]
	770–1,140 (.1–.2)[d]		
	1,030 (24.1)		16 (24.1)
2	1,270 (.4)[e]	55 (20.4)	>16 (1.5)[e]
	100–800 (1.5–6.0)[e]		20 (6)[e]
	395 (20.4)		4 (20.4)
3	2,373 (.3)	88 (.3)	29 (2.5)
	686–2,541 (.4–4.0)	79 (4.0)	43 (4.0)
	1,152 (4.4)	39 (4.4)	12 (4.4)
4	1,800 (9)	64 (9)	
5	1,870 (.15)	70 (.15)	>20 (.16)
	1,028–1,721 (.16–3)		32 (3.8)
	1,160 (4)		40 (4.6)
6	1,550 (.04)	45–74 (.04–1.0)	
	1,262–1,660 (≤1.0)		
7	1,226 (.02)	188 (.04)	18 (.18)
	1,769 (.9)	62 (.9)	13 (2.4)
	1,471 (2.4)	21 (2.4)	
8	1,629 (8.6)	50 (13.6)	39 (13.6)
	1,443 (10.2)		>20 (13.8)
	1,114 (13.6)		
9	966 (.08)	80 (.10)	17 (.2)
	759–1,467 (.10–1.4)	57 (1.4)	
	780 (1.8)	58 (1.8)	
10	670 (.04)	125 (1.4)	20 (4.3)
	484–742 (.2–5.8)	111 (4.3)	18 (5.8)
	528 (5.9)	82 (5.9)	47 (5.9)
11	591 (.02)	44 (3.8)	27 (7.9)
	374–902 (.2–9.4)	98 (7.9)	16 (9.4)
	455 (9.6)	81 (9.6)	45 (9.6)
12	515 (.2)	49 (.2)	
13	451 (.04)	73 (.7)	>20 (.6)
	422–758 (.05–.8)	29 (2.6)	20 (.8)
	469 (2.6)		7 (2.6)
14	440 (.06)	62 (.7)	>20 (.4)
	323–467 (.07–1.1)	61 (2.8)	20 (.7)
	185 (2.8)		17 (2.8)
15	295[f]		30[f]
	236–335 (10)	77 (10)	10–12 (10)
16	239 (.11)	81 (.12)	8 (.15)
	225 (.13)	357 (.13)	
	286 (.15)	68 (.24)	
17	337 (.2)	99 (.2)	98 (.2)
	175 (10.1)	67 (10.1)	12 (10.1)
18	251 (.21)	146 (.21)	>20 (.36)
	186 (.36)	116 (.36)	
19	197 (.16)	130 (.3)	20 (.3)
	242 (.3)		
20	299 (.06)	132 (.07)	33 (.7)
	113 (1.7)	56 (1.7)	27 (1.5)
	196 (2.4)	49 (2.4)	16 (2.4)
21	160–391[f]		10[f]
	125–233 (8)	78 (8)	6–9 (8)
22	148 (adult)	50 (adult)	7 (adult)

(*continued*)

Table 2 (continued)

Patient	Plasma Methionine[a] (age) (μM)	Plasma Tyrosine[b] (age) (μM)	Serum Folate[c] (age) (ng/ml)
23	143 (adult)	73 (adult)	5 (adult)
24	206 (.04)	108 (.04)	28 (.3)
	80–302 (.06–.3)	88 (.3)	
	108 (.7)		
25	236 (.2)	48 (.2)	37 (.4)
	71 (1.8)	41 (1.8)	11 (1.8)
26	375[f]		13[f]
	85–166 (9)	101 (9)	3–6 (9)
27	111 (adult)	62 (adult)	5 (adult)
28	106 (1.6)	114 (1.6)	14 (1.6)
29	117 (.1)	69 (.2)	17 (.2)
	81 (.2)		
	66 (.7)		
30	106 (.07)	85 (.07)	7 (6.0)
	34–86 (.13–2.7)	70 (6.0)	
	84 (6.0)		

[a] Reference range is as in table 1. Values are for periods of unrestricted diet. For each patient, the earliest and latest values available are listed. If interim values are available, the range of such values is given (with the age range in parentheses).

[b] Upper limit of normal: 180 μM (Goldsmith and Laberge 1989).

[c] Adult reference range: 3–16 ng/ml.

[d] Values reported by Gout et al. (1977).

[e] Values reported by Gaull et al. (1981*b*).

[f] Values reported by Uetsuji (1986). Although the ages at which samples for these measurements were obtained were not specified, in all instances the patient appears to have been <.25 years of age.

similar or lower plasma methionine concentrations at later ages.

Measurements of the distributions of transamination metabolites among protein-S-S-CH_3, X-S-S-CH_3, and a fraction consisting chiefly of 2-keto-4-methylthiobutyrate (Blom et al. 1989*b*) revealed that in plasma the latter material contributed 31.3% ± 5.8% (standard error of the mean; n = 14). In fresh samples the remaining 69% consisted chiefly of X-S-S-CH_3, but in samples stored at room temperature for several hours it consisted mainly of protein-S-SCH_3. Protein-S-S-CH_3 is known to arise by in vitro degradation of X-S-S-CH_3 to methanethiol that then binds to plasma proteins (Tangerman et al. 1985). In urine, the 2-keto-4-methylthiobutyrate fraction contributed only 8.9% ± 2.0% (n = 16). The remainder consisted of X-S-S-CH_3. Thus, both in *fresh* plasma and in urine this mixed disulfide contributes the major portion of the methionine transamination products. No patient excreted almost solely 2-keto-4-methylthiobutyrate.

Dimethylsulfide, a volatile compound formed by methylation of methanethiol (Weisiger et al. 1980), caused the bad odor in the breath of a patient with proved MAT deficiency in liver (Gahl et al. 1988) and was also highly elevated (400 nM) in the urine of this patient. Among the patients in the present study, urinary dimethylsulfide was elevated only in most of those with more extreme elevations of total urinary transamination metabolites (table 3).

Creatine and Creatinine

Synthesis of creatine/creatinine normally consumes some 75%–80% of the total AdoMet synthesized by a young adult (Mudd and Poole 1975; Mudd et al. 1980). Plasma creatinine concentrations were normal in seven patients (patients 3, 8–11, 13, and 14; ages 1.8–9.6 years) and were marginally low, at 18 μM, in one (patient 20; age 2.4 years; reference range 27–62 μM), but they were not as low as the values, 7–10 μM, found in a recently described boy with severe neurological disease due to a block in the synthesis of creatine (Stöckler et al. 1994). A more satisfactory index of creatine/creatinine formation might be provided by the 24-h excretion of creatinine, but suitable specimens were available only from patient 8. Her 24-h urine contained 15.3 mg creatinine/kg body weight. The published norm for 24-h excretion most relevant to this patient, described as "lean, but not emaciated," is that of 30.7 mg/kg in "very thin" girls (Talbot 1938). For patient 8, plasma creatinine values were normal, 27–44 μM, with most values being 35 μM.

Table 3

Transamination Metabolites

Patient	Plasma Methionine[a] (μM)	Transamination Products		Urine Dimethylsulfide[d] (nM)	Age (years)
		Plasma Total[b] (μM)	Urine Total[c] (mmol/mol creatinine)		
1	1,030	15.0	ND[e]	ND	24.1
	ND	ND	119	80	24.5
2	395	2.15	7.2	<10	20.4
3	[381]	[.52]	[2.0]	ND	2.5
	[535]	[12.9]	[19.9]	[<10]	3.4
	687	20.9	506	500	3.5
	712	25.1	304	1,645	3.7
	686	12.5	151	80	4.0
	1,153	7.7	43.1	330	4.4
5	777–1,028	ND	37–59	ND	1.5–1.6
7	[755]	[.26]	[1.9]	ND	.2
	1,770	9.51	11.4	<10	.9
	1,471	33.3	223	130	2.4
8	1,114	41.2	992	535	13.6
9	1,467	1.86	4.9	<10	.1
	[291]	[.23]	[1.5]	ND	1.0
	[108]	[.19]	[1.8]	ND	1.2
	759	37.5	884	<10	1.4
	780	18.3	299	<10	1.8
10	528	5.01	45.2	<10	4.3
	629	ND	75.6	10	5.8
	528	6.21	ND	ND	5.9
11	510	3.65	26.4	<10	7.9
	388	ND	8.7	<10	9.4
	455	3.27	ND	ND	9.6
13	422	.45	1.5	<10	.8
	469	6.26	23.9	<10	2.6
14	323	.30	1.8	ND	1.1
	185	.26	3.3	<10	2.8
15	335	1.68	7.3	ND	10
17	175	.23	2.1	<10	10.1
18	186	.25	ND	ND	.4
	181	ND	2.2	<10	.7
20	196	.23	1.0	ND	2.4
21	128	.23	ND	ND	8
22	148	.12	ND	ND	38
23	143	.17	ND	ND	36
24	88	.26	1.1	ND	.3
25	71	.23	3.4	<10	1.8
26	166	.19	.4	ND	9
27	111	.22	ND	ND	35
28	106	.35	ND	ND	1.6
29	66	.17	1.0	ND	.7
30	84	<.20	1.9	<10	6.0

NOTE.—Values in brackets were determined in samples obtained during a period of dietary methionine restriction.

[a] Reference range is as in table 1. Methionine concentrations were determined on plasma samples obtained the same day as were the samples for measurement of transamination metabolites. Patient 5 is an exception. For this patient, two urine samples were obtained 1 mo apart for measurement of transamination metabolites. Because no plasma samples were drawn at those times, the methionine concentrations listed are for the available plasma samples drawn closest in time (one before and one after) to the procurement of the urine samples.

[b] Reference range: .20–.54 μM.

[c] Reference range: 1.2–4.6 mmol/mol creatinine (mean ± SD: 2.2 ± 1.0).

[d] Reference range: trace to 2 nM.

[e] Not determined.

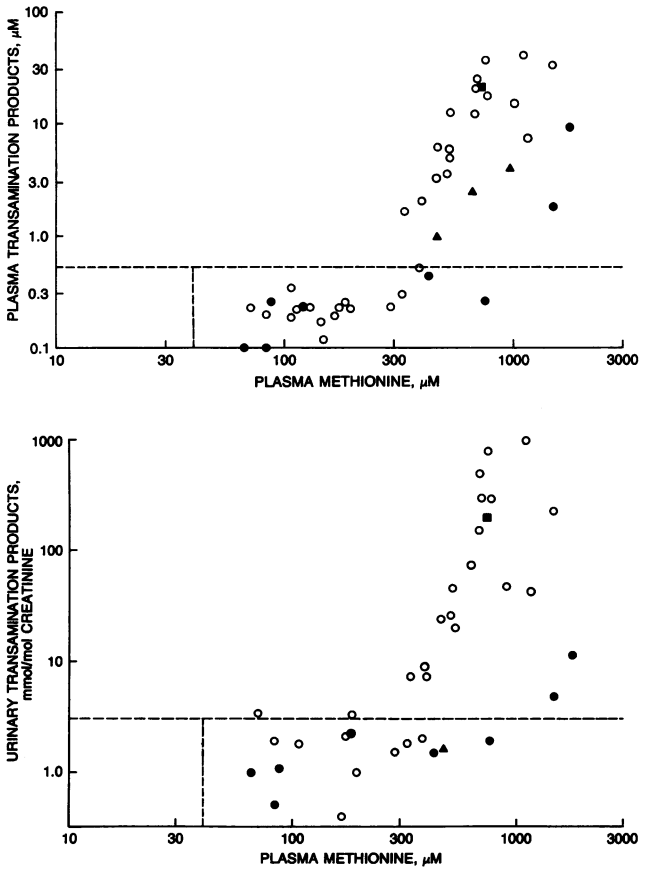

Figure 2 All available data are plotted. The horizontal dashed line represents the upper limit of the reference range for methionine transamination metabolites, and the vertical dashed line represents the upper limit of the reference range for plasma methionine. ○ = Sample taken at patient age >0.9 years; ● = sample taken at patient age ≤0.9 years; ■ = value reported by Blom et al. (1989*a*) for a 31-year-old man with proved partially deficient activity of hepatic MAT; and ▲ = value reported by Blom et al. (1989*a*) for an 18-year-old patient with hypermethioninemia due to pyridoxine nonresponsive cystathionine β-synthase deficiency (Blom et al. 1989*a*). For patient 30, too little plasma was available for an exact determination of transamination products, and an upper limit of <0.20 is listed in table 3. For simplicity, this value has been plotted as 0.10. *Upper panel,* Concentration of plasma methionine transamination metabolites, as a function of plasma methionine concentration. *Lower panel,* Concentration of urinary methionine transamination metabolites, as a function of plasma methionine concentration.

Urinary Organic Acids

A single child has been reported with isolated hypermethioninemia accompanied by abnormalities of urinary organic acids and elevations of plasma β-alanine and 3-aminoisobutyrate postulated to be due to a defect in oxidation of (substituted) malonic semialdehydes (Congdon et al. 1981; Pollitt et al. 1985). Urinary organic acids, measured in nine of the present patients (2, 3, 5, 7–10, 13, and 30; ages 1.0–20.4 years) were normal in each; nor was plasma β-alanine or 3-aminoisobutyrate increased.

Patterns of Inheritance

Plasma methionine concentrations were obtained for 27 parents (from 14 families). For nine pairs of parents (of patients 2, 10/11, 13, 14, 19/28, 20, 24, 29, and 30), both had concentrations within the reference range, consistent with a Mendelian recessive pattern of inheritance. One family showed another pattern: patients 22, 27, and 23 are, respectively, two sisters and a first cousin and are the mothers, respectively, of patients 26, 15, and 21 (Uetsuji 1986). Each of these individuals had a similar degree of mild hypermethioninemia. Together with the fact that the (unrelated) fathers of patients 15 and 21 had normal plasma methionine levels, these results indicate a Mendelian dominant pattern of inheritance. Two pairs of parents conformed to neither of the above patterns: the father of patient 3 and the mother of patient 9 had mildly elevated plasma methionines, 48 and 57 μM, respectively (much less abnormal than those of the affected children); the other parents of these patients had normal plasma methionine concentrations.

Discussion

In this paper we have presented new data that (*a*) extend by many years the clinical and metabolic histories of two of the six patients proved to have deficient MAT activity in liver and (*b*) provide information about 27 previously unreported patients ascertained, without bias, to have isolated hypermethioninemia. The latter group constitutes a significant addition to the seven such patients previously reported (Surtees et al. 1991; Blom et al. 1992).

The Etiology of the Hypermethioninemia

The 28 patients without enzyme evidence of hepatic MAT deficiency gave no indication of any other reason for their hypermethioninemia. No patient (with the possible exception of patient 8, who was dystonic) had either the specific clinical abnormalities or the marked elevations of serum folate previously reported in various individuals with isolated hypermethioninemia and normal MAT activities in liver (Gaull et al. 1981*a;* Jhaveri et al. 1982; Tsuchiyama et al. 1982; Uetsuji 1986; Labrune et al. 1990). No patient manifested the amino acid or organic acid abnormalities associated in one case with isolated hypermethioninmeia (Congdon et al. 1981; Pollitt et al. 1985).

Theoretically, a defect in either methionine transamination or the decarboxylation of 2-keto-4-methylthiobutyrate might also produce hypermethioninemia. Both possibilities seem unlikely. The methionine transamination reaction serves chiefly to convert 2-keto-4-methylthiobutyrate arising as a result of polyamine synthesis back to methionine (Backlund et al. 1982). A defect in this step would more probably produce a reduction,

rather than an elevation, of methionine. A defect in 2-keto-4-methylthiobutyrate decarboxylation would lead to accumulation of this metabolite, without elevation of the other metabolites of the methionine transamination pathway. The opposite was seen. All patients with highly elevated methionine values showed increased values of a variety of transamination metabolites, indicative of an increased flux through the whole transamination pathway (Gahl et al. 1988; Blom et al. 1989*b*). A threshold for accumulation of transamination metabolites near a plasma methionine of 300–350 μM might explain the absence of such an accumulation in the present patients who had plasma methionine values below this threshold value.

Clinical Aspects

Neurological problems are absent in the 29 patients ascertained without bias, as was the case for 6/7 patients previously reported patients so ascertained (Surtees et al. 1991; Blom et al. 1992). Nevertheless, there are several reasons to reserve judgment as to the long-term incidence of clinical problems in patients with persistent isolated hypermethioninemia: (*a*) Many of the patients in the present study, as well as several of those known to have deficiency of hepatic MAT (Mudd et al. 1995), were still young at last report. (*b*) The presence of subnormal IQs in 3/30 of the present patients may be a cause for concern. (*c*) Several of those with normal IQs had scores <110, a score that is now considered the approximate average among individuals assessed and scored by the IQ tests currently in use (Smith et al. 1990). (*d*) Patient 8, ascertained because of tremor, dystonia and dysmetria, had MRI evidence of a myelination problem, as did the patient of Surtees et al. (1991). Patient 8 also had findings suggestive of a partial creatine deficiency. However, the relationship of her neurological problems to hypermethioninemia is thrown into question by the facts that her younger brother, age 7 years, also has both dystonia of one arm and verbal articulation problems but has normal plasma amino acid concentrations; MRI study of his brain revealed no evidence of a myelination problem. A determination of the cerebrospinal fluid (CSF) AdoMet concentration in patient 8 would be of interest.

Methionine Transamination

The methionine transamination pathway appears to manifest not only a threshold plasma methionine concentration near 300–350 μM for abnormal accumulation of transamination metabolites but also an age-dependent maturation during the 1st year or so of life. This delayed appearance of the accumulation of methionine transamination metabolites appears analogous to similar delays in the capacities to transaminate either phenylalanine (Armstrong and Binkley 1956; Rey et al. 1974) or histidine (Levy et al. 1971).

The putative threshold could account for two sets of earlier observations:

1. Absence of elevations of methionine transamination metabolites in most of the patients with hypermethioninemia due to cystathionine β-synthase deficiency who were studied by Blom et al. (1989*a*). With one exception, these patients had plasma methionine concentrations <300 μM. However, as postulated by Blom et al. (1989*a*) and consistent with the points for the cystathionine β-synthase–deficient man in figure 2, in this situation there may also be a specific functional impairment in the methionine transamination pathway.
2. Failure of the hypermethioninemic patients with virtually normal MAT activities in liver, described by Labrune et al. (1990), to excrete elevated amounts of 2-keto-4-methylthiobutyrate. The authors commented that these observations are consistent with a deficiency in methionine transamination. However, the latter suggestion may perhaps now be discounted, since the measurements of 2-keto-4-methylthiobutyrate appear to have been performed when hypermethioninemia was moderated, by methionine-restricted diets, to concentrations significantly <300 μM.

Mode of Inheritance

The mode(s) of inheritance of isolated hypermethioninemia revealed by the present work are variable: in some families the pattern is clearly Mendelian recessive; in another, Mendelian dominant; and in others, intermediate, with one parent having a normal level of plasma methionine and the other showing a hypermethioninemia milder than that in the affected child. Previous reports have also indicated variability (Gout et al. 1977; Gaull et al. 1981*b*), and another family with mild hypermethioninemia of unknown origin had a clearly Mendelian dominant pattern of inheritance (Blom et al. 1992). Some of this variability could be due to differences in the etiology of the hypermethioninemias. Alternatively, since adult hepatic MAT exists normally as either dimers or tetramers of identical subunits, a mutant subunit might negatively affect the activity of a normal subunit with which it is associated (Blom et al. 1992). Depending on the strength of this interaction, MAT activity in liver of a heterozygote could vary sufficiently that the pattern of inheritance would be recessive, dominant, or intermediate.

Management

In the absence of definitive diagnosis, there is uncertainty as to the cause of isolated hypermethioninemia in many

individuals. For those assumed to have a deficiency of MAT activity in liver, should dietary methionine intake be limited? As documented in the Results section (above), such diets can moderate the abnormal elevations of both methionine and its transamination metabolites. There are reasons that argue both for and against the therapeutic usefulness of such a result: (*a*) On the one hand, an elevated methionine may usefully increase AdoMet, by promoting flux through any residual activity of MAT with a low affinity for methionine. The patient of Surtees et al. (1991) appeared to benefit neurologically from administration of AdoMet sufficient to raise the CSF concentration of this compound, emphasizing that any regimen that might decrease the rate of synthesis of AdoMet should be undertaken with great caution. (*b*) On the other hand, elevated plasma concentrations of methionine might inhibit the transport, into brain, of the neutral amino acids with which methionine shares a common transport mechanism (Lane and Neuhoff 1980). The deleterious effects of the elevated phenylalanine that occur in phenylketonuria may be due, at least in part, to such competition for transport into brain, particularly with tyrosine (Diamond et al. 1994). However, the kinetic constants for transport of amino acids across the blood-brain barrier of the rat indicate that methionine has a far higher K_m for this system than does phenylalanine (40 μM, compared with 11 μM) (Smith et al. 1987). With these reported values, it can be calculated that, to inhibit tyrosine uptake to the same extent as do 360 or 605 μM phenylalanine, concentrations of some 1,100 or 1,900 μM methionine, respectively, would be required. A phenylalanine concentration of 360 μM is considered harmless; a concentration of 605 μM might lead, at most, to subtle cognitive deficits (Diamond et al. 1992). Thus, the methionine concentrations in most patients with isolated hypermethioninemia are not likely to produce serious harmful effects by inhibition of amino acid transport into brain. It might be supposed that elevated methionine transamination products would exert toxic effects. However, no such effects have been documented (Blom et al.1898*b*), and the oldest known patient with proved deficient activity of MAT in liver was free of major clinical problems at last report at age 38 years (Mudd et al. 1995), in spite of markedly elevated transamination metabolites and a bad breath odor due to dimethylsulfide (Gahl et al. 1988). In view of these considerations, as well as the empirical fact that the majority of patients with isolated persistent hypermethioninemia have remained clinically normal without dietary methionine restriction, our present approach is not to use such restriction in managing these patients. If needed, treatment with AdoMet offers a hopeful alternative.

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