

Hypermethioninaemia due to methionine adenosyltransferase I/III (MAT I/III) deficiency: Diagnosis in an expanded neonatal screening programme

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Summary The Expanded Newborn Screening Program (MS/MS) in the region of Galicia (NW Spain) was initiated in 2000 and includes the measurement of methionine levels in dried blood spots. Between June 2000 and June 2007, 140 818 newborns were analysed, and six cases of persistent hypermethioninaemia were

detected: one homocystinuria due to cystathionine β -synthase (C β S) deficiency, and five methionine adenosyltransferase I/III (MAT I/III) deficiencies. The five cases of MAT I/III deficiency represent an incidence of 1/28 163 newborns. In these five patients, methionine levels in dried blood spots ranged from 50 to 147 $\mu\text{mol/L}$. At confirmation of the persistence of the hypermethioninaemia in a subsequent plasma sample, plasma methionine concentrations were moderately elevated in 4 of the 5 patients (mean 256 $\mu\text{mol/L}$), while total homocysteine (tHcy) was normal; the remaining patient showed plasma methionine of 573 $\mu\text{mol/L}$ and tHcy of 22.8 $\mu\text{mol/L}$. All five patients were heterozygous for the same dominant mutation, R264H in the *MAT1A* gene. With a diet not exceeding recommended protein requirements for their age, all patients maintained methionine levels below 300 $\mu\text{mol/L}$. Currently, with a mean of 2.5 years since diagnosis, the patients are asymptomatic and show developmental quotients within the normal range. Our results show a rather high frequency of hypermethioninaemia due to MAT I/III deficiency in the Galician neonatal population, indicating a need for further studies to evaluate the impact of persistent isolated hypermethioninaemia in neonatal screening programmes.

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Abbreviations

C β S	cystathionine β -synthase
MAT I/III	methionine adenosyltransferase I/III
MS/MS	tandem mass spectrometry
AdoMet	S-adenosylmethionine
tHcy	total homocysteine

Introduction

Expanded neonatal screening programmes based on analysis of dried blood spots by tandem mass spectrometry (MS/MS) habitually include methionine measurement (Wilcken et al 2003). This permits diagnosis of classic homocystinuria (cystathionine β -synthase (C β S) deficiency) and hypermethioninaemia without homocystinuria. In addition to situations of transitory neonatal hypermethioninaemia, related to high methionine intake, and once type I tyrosinaemia and severe hepatic disease have been ruled out, isolated and persistent cases of hypermethioninaemia can be detected (Mudd et al 1995, 2001). With rare exceptions, this disorder is due to a methionine adenosyltransferase I/III (MAT I/III) deficiency.

MAT is the enzyme catalysing the synthesis of S-adenosylmethionine (AdoMet) from methionine and ATP. In mammals three forms of MAT have been described: MAT I, MAT II and MAT III. MAT II is encoded by the *MAT2A* gene, expressed mainly in extrahepatic tissues, fetal liver and hepatocarcinoma. MAT I and MAT III, expressed mainly in adult liver, are a tetramer and a dimer, respectively, of the same polypeptide chain, encoded by the *MAT1A* gene. MAT I/III deficiency (OMIM 250850) is caused by mutations in the *MAT1A* gene that abolish or reduce the activity of this enzyme, leading to persistent hypermethioninaemia, as noted above. It can show either recessive or dominant autosomal inheritance (Blom et al 1992; Chamberlin et al 1997; Mudd et al 1995; Nagao and Oyanagi 1997). Most affected individuals do not present clinical symptoms, but some of those with the most severe losses of activity have developed neurological problems (tremor, dystonia, dysmetria, language difficulties or myelination disorders) and/or reduced intelligence or developmental quotients (Chamberlin et al 1996, 1997; Mudd et al 2000, 2001).

Cases of isolated persistent hypermethioninaemia have been diagnosed previously in neonatal screening programmes (Chien et al 2005; Kim et al 2002), but assessment of the impact of this abnormality in the population requires further studies. In our region, Galicia, the expanded neonatal screening programme using MS/MS was introduced in June 2000, and to date 140 818 newborns have been analysed. A total of 6 cases of persistent hypermethioninaemia have been detected: one case of C β S deficiency and 5 cases of MAT I/III deficiency (plus an additional case of MAT I/III deficiency, a sister, diagnosed subsequently). The patients with MAT I/III deficiency are all heterozygous for the same dominant mutation in the *MAT1A*

gene. Here we report the diagnosis and follow-up of these cases.

Patients and methods

Patients

The five children (3 male, 2 female) who have now been diagnosed with MAT I/III deficiency were identified in their neonatal periods in Galicia over the last 7 years (between June 2000 and June 2007) in the Galician Program for Early Detection of Metabolic Alterations. The five children were all from Galician families, from different locations in the region. All have been monitored from diagnosis until the present in the Metabolic Disorders Unit of the University Clinical Hospital of Santiago de Compostela. All five showed methionine levels above the cut-off level in dried blood spots taken in the first few days of life (our newborn screening programme recommends the third day of life of the newborn). Quantitative analyses were also performed of amino acids and total homocysteine (tHcy) in plasma, and amino acids in urine. Once hypermethioninaemia without homocystinuria had been demonstrated (plasma tHcy normal or only slightly elevated), analysis of the *MAT1A* gene was performed.

Age, presence/absence of symptoms at diagnosis, and methionine levels at diagnosis and at confirmation were recorded for each case. Clinical course was subsequently monitored, recording mean and range of methionine level over time. The patients received a diet that did not exceed the recommended protein requirement for their age, permitting normal growth and development. Possible correlations between psychomotor development and methionine level were investigated at diagnosis and subsequently.

Methods

Neonatal screening by MS/MS analysis of dried blood spots in filter paper, obtained on the third day of life of the newborn

A blood paper disc was eluted with a solution of methanol containing internal standards of amino acids and acylcarnitines labelled isotopically with [$^2\text{H}_3$]-methionine (Cambridge Isotopes Laboratories, Inc., Andover, MA, USA). Derivatization to butyl esters was achieved by addition of a solution of hydrogen chloride in 1-butanol (Riedel-de Haën, ref. 35072). The residue was reconstituted with the mobile phase

(acetonitrile–water 1:1, formic acid 0.05%). An aliquot was injected into the mass spectrometer (Sciex API 2000). If the measured concentration exceeded the 99th centile for the study population, a second sample was requested. For methionine, this value ranged between 48 and 56 $\mu\text{mol/L}$ over the study period.

Quantitative analysis of amino acids in samples of plasma and urine

This was carried out by ion-exchange chromatography (Biochrom 30 autoanalyser) after deproteinization of the sample (plasma or urine) with 5-sulfosalicylic acid, with post-column reaction with ninhydrin, and making use of L-norleucine as internal standard. The concentration of urinary amino acids is referred to creatinine concentration. Amino acid levels were evaluated with respect to reference ranges for the corresponding age group.

Plasma tHcy

Plasma tHcy was determined by HPLC with fluorometric detection using a Hitachi apparatus and a specific kit (Immundiagnostik AG, Bensheim, Germany). The tHcy level was considered to be elevated at concentrations above 15 $\mu\text{mol/L}$.

Molecular study

DNA was isolated from 300 μl blood samples using the Puregene DNA isolation kit (Gentra Systems, Inc., Minneapolis, USA). The *MAT1A* gene was characterized by amplifying the coding regions of exons I to IX and the corresponding intron–exon junctions by PCR using nine pairs of oligonucleotide primers containing 5'-untranslated, 3'-untranslated and intron sequences of the *MAT1A* gene as previously described (Ubagai et al 1995). All amplified fragments were sequenced

using an ABI Prism DNA sequencing kit (Perkin Elmer, Waltham, MA, USA) and then processed on an ABI Prism 310 genetic analyser (Perkin Elmer). The sequences from all exons I to IX were examined to identify the presence of mutations.

Anthropometric evaluation

Body weight, body length and head circumference were measured and expressed as centiles with respect to the reference population.

Evaluation of cognitive and psychomotor development

The McCarthy Scales of Children's Abilities (MSCA) were used for preschool-age children, and the Brunet-Lézine scale for the child aged 13 months at evaluation. Cognitive and developmental quotients were considered normal from 85.

Results

Since the extension of the Galician Neonatal Screening Program for Metabolic Abnormalities in June 2000 by the introduction of tandem mass spectrometry, 6 cases of persistent hypermethioninaemia have been detected (up to June 2007). Over this period, a total of 140 818 newborns have been screened, indicating that persistent hypermethioninaemia has an incidence of 1 in 23 470 in our region.

The six babies reported upon here were full-term and had normal birth weights, and their methionine elevations persisted. One of them was confirmed to have C β S deficiency by enzymatic studies in fibroblasts and by genetic studies. The five remaining cases were confirmed by molecular studies of the *MAT1A* gene as MAT I/III deficiency, giving a frequency of one case in 28 163, similar to the results from Portugal reported

Table 1 Characteristics of the patients with MAT I/III deficiency

Patient	Current age	Sex	Neonatal screening (MS/MS)		Confirmation (plasma)			Mutation <i>MAT1A</i>	Nucleotide change
			Age	Met ^a	Age	Met ^a	tHcy ^a		
1	2 y 10 m	F	6 d	50	35 d	573	22.8	R264H	791 g/a
2	2 y 8 m	M	3 d	100	1 m 15 d	189	8.9	R264H	791 g/a
3	2 y 7 m	F	5 d	88	2 m 21 d	341	9.7	R264H	791 g/a
4	2 y 6 m	M	3 d	147	2 m 13 d	331	12.4	R264H	791 g/a
5	1 y 4 m	M	5 d	100	25 d	164	11.0	R264H	791 g/a

y, year; m, month; d, day.

^a $\mu\text{mol/L}$.

recently (Martins et al 2007), but a higher incidence than that reported for other areas, such as Taiwan (Chien et al 2005; Hwu 2004). However, for almost all the infants reported from Taiwan the cut-off point for methionine was 134 $\mu\text{mol/L}$, considerably higher than the cut-off range, 48–56 $\mu\text{mol/L}$, used in our present programme.

All five of our cases were heterozygous for the same mutation in MAT1A, R264H (G > A at nucleotide 791). This mutation shows a dominant phenotype, since the mutated subunit sequesters normal subunits to form inactive dimers (Chamberlin et al 1997; Perez-Mato et al 2001). Table 1 shows methionine levels in neonatal screening samples taken within 3–6 days of birth (the programme recommends sampling on day 3 of life). All patients initially presented with only moderately elevated values (mean 97 $\mu\text{mol/L}$, range 50–147). Persistence of the isolated hypermethioninaemia was confirmed in subsequent plasma samples in which the methionine levels were higher than at detection but still only moderately elevated in 4 of the 5 cases (patients 2, 3, 4 and 5) (mean 256 $\mu\text{mol/L}$, range 164–341), with tHcy values within the normal range (mean 10.5 $\mu\text{mol/L}$, range 8.9–12.4 $\mu\text{mol/L}$). Only patient 1 showed more markedly elevated plasma methionine (573 $\mu\text{mol/L}$), together with slightly elevated tHcy (22.8 $\mu\text{mol/L}$). Interestingly, this was the case with the lowest level of methionine at initial diagnosis (50 $\mu\text{mol/L}$ at 6 days of age). This was also the first patient with persistent hypermethioninaemia detected in our region's neonatal screening programme. However, mild elevations of plasma tHcy are known to occur in MAT I/III deficiency (Ito et al 2003; Linnebank et al 2005; Stabler et al 2002). Furthermore, in patient 1 the plasma values of AdoMet and S-adenosylhomocysteine were not elevated (128 and 32 $\mu\text{mol/L}$, respectively), and cystathionine was somewhat above the reference range (575

nmol/L). These findings were supportive of MAT I/III deficiency and against C β S deficiency. In the 4 patients detected subsequently, these components were not determined, but sequencing of their MAT1A genes showed R264H mutations, indicating the presence of MAT I/III deficiency and providing an explanation for their hypermethioninaemia (Andria et al 2005; Mudd et al 2003).

Plasma methionine was assayed in both parents of five of the patients. In each family one of the parents had an elevated concentration (Table 2), as expected in view of the Mendelian dominance of R264H. The father of patient 2 did not consent to an assay. In addition, a new case of MAT I/III deficiency was detected in a sister of patient 1, currently aged 7 years (plasma methionine 124 $\mu\text{mol/L}$). This girl, who likewise showed the R264H mutation, was born before the expanded screening programme commenced. Four of the parents who show hypermethioninaemia are clinically well. The father of patient 4 has a cardiopathy not related to his hypermethioninaemia, and shows moderately elevated levels of (hepatic) transaminases, attributed to the pharmacological treatment he receives.

All patients were prescribed free diets appropriate for their ages without an excess of proteins but an intake within the normal limits (FAO/WHO). Physical development was normal in all patients, and none showed clinical symptoms. Table 2 summarizes follow-up of the patients studied, from confirmation of diagnosis until the present, showing mean methionine levels, number of determinations in each patient, and minimum and maximum values recorded for each patient. As can be seen, mean methionine levels were in all cases below 300 $\mu\text{mol/L}$. Developmental quotients (DQs) were not significantly correlated with methionine levels at diagnosis and these quotients remained within the normal range in all cases, though

Table 2 Follow-up and family study of the 5 cases

Patient	Plasma methionine ^a		DQ		Family study (plasma Met ^a)	
	Mean (min–max)	n ^b			Father	Mother
1	163.8 (43–585)	11	100	2 y 8 m	74	27 (N)
2	152.1 (84–247)	10	103	2 y 6 m	n.a.	23 (N)
3	237.0 (149–364)	8	88	2 y 6 m	24 (N)	76
4	183.4 (58–330)	8	101	2 y 6 m	205	19 (N)
5	117.2 (49–173)	5	101	13 m	25 (N)	85

y, year; m, month; (N) normal range; n.a., not assayed.

^a $\mu\text{mol/L}$.

^bNumber of determinations.

patient 3 (with the highest mean methionine level at regular monitoring) showed the lowest DQ (88, at the lower limit of the normal range).

Discussion

Neonatal screening for hypermethioninaemia is not easy, for diverse reasons. On the one hand, methionine levels in blood are not always high enough for detection of CBS deficiency during the first days of life and, on the other hand, differential diagnosis may be complicated, leading to a high number of requests for repeat sampling in view of elevated methionine, with consequent high economic and social costs in a population-level screening programme. However, once transient hypermethioninaemias due to use of milk with high methionine content have been ruled out (above all in premature newborns and other newborns with low body weight (see ten Hoedt et al 2007)), it is important to note that detection of cases of MAT I/III deficiency can be achieved only by monitoring of hypermethioninaemia, however moderate this may be; patient 1 in the present study is a clear example of this situation because she showed a blood methionine level in the first sample of 50 $\mu\text{mol/L}$, very near to the cut-off (Table 1).

Advances in knowledge of mutations in the *MAT1A* gene have allowed non-aggressive diagnosis of both the presence of MAT I/III deficiency and the extent of the deficit in enzyme activity, removing any need for hepatic biopsy (Chamberlin et al 1997, 2000; Kim et al 2002). The gradual worldwide spread of expanded neonatal screening programmes (using MS/MS) will lead to the detection of an increasing number of cases of isolated persistent hypermethioninaemias due to deficient MAT I/III activity. In the population considered in the present study, for example, diagnosis of the sister of patient 1 was late, because methionine level had not been determined in the neonatal period.

The most suitable management of individuals with MAT I/III mutations has not been definitively established, in part because relatively few patients are known; in part because, having usually been detected by newborn screening, these patients are still young; and in part because the optimal treatment will probably vary with the type of causative *MAT1A* mutation(s). To date, among the very few individuals known to have complete loss of MAT I/III activity some have developed adverse clinical manifestations (mental retardation; neurological disorders, especially myelination defects; and body odour). The observed neurotoxicity may perhaps be attributable to deficient

formation of AdoMet and, in a single reported case, treatment with AdoMet was accompanied by reversal of demyelination (Surtees et al 1991). In addition, high levels of methionine ($>1000 \mu\text{mol/L}$) may inhibit transport of other neutral amino acids into the brain, with neurotoxic effects (Mudd et al 1995). However, other individuals with no MAT I/III activity have remained clinically normal (Hazelwood et al 1998; Mudd et al 2001). Synthesis of AdoMet by MAT II, encoded by a different gene, may sustain these individuals. The known individuals with point mutations in *MAT1A* and some residual, albeit far below normal, MAT I/III activity have so far been clinically normal. With respect to heterozygosity for the *MAT1A* R264H mutation, it is encouraging that the parents of our patients, including the father of patient 4 with a particularly high plasma methionine level (205 $\mu\text{mol/L}$), as well as other reported individuals with raised plasma methionine due to such heterozygosity have all been free of clinical difficulties attributable to this mutation, even those who are elderly (Mudd et al 2001). Although there was clearly overlap in the ranges, the plasma methionine values found in the parents tended to be lower than those in their affected children (Table 2). Similar tendencies are apparent in the other families for which generational values have been reported (Chamberlin et al 1997; Nagao and Oyanagi 1997). The reasons for such a trend are not established, but it may be dependent upon developmental changes with ageing: plasma methionines tended, on the whole, to decrease in the two R264 heterozygous children (Chamberlin et al 1997) for whom age-dependent values were reported by Blom and co-workers (Blom et al 1992); and Nagao and co-workers found in three heterozygous children a mean plasma methionine of 354 $\mu\text{mol/L}$ (range 295–391 $\mu\text{mol/L}$) at age 0.1 years that had decreased to a mean of 226 $\mu\text{mol/L}$ (range 128–385 $\mu\text{mol/L}$) at ages 10–12 years. For the heterozygous parents of these children the mean was 181 $\mu\text{mol/L}$ (range 155–201 $\mu\text{mol/L}$) at ages 26–28 years and 134 $\mu\text{mol/L}$ (range 111–148 $\mu\text{mol/L}$) at ages 37–40 years (Nagao and Oyanagi 1997).

None of our patients showed neurological symptoms, and thus none of them received treatment. Some authors (Chien et al 2005) have limited dietary methionine intake for patients with persistent isolated hypermethioninaemia, maintaining plasma levels below 150 $\mu\text{mol/L}$. However, there is concern that such limitation may be counterproductive if it further reduces synthesis of AdoMet in those with some residual MAT I/III activity. At methionine levels above 300 $\mu\text{mol/L}$, metabolites produced by transamination may give rise to the offensive body odour seen

in some patients, although there is no clear evidence that this is otherwise harmful (Andria et al 2005; Gahl et al 1988; Mudd et al 1995). We therefore consider that strict limitation of dietary methionine intake is unnecessary and indeed inadvisable. In our patient 1, in view of the plasma methionine above 500 $\mu\text{mol/L}$ and the slightly elevated tHcy, we initially considered use of a methionine-restricted diet. However, methionine levels dropped to a mean of 164 $\mu\text{mol/L}$ on a normal diet, the presence of the R264H mutation was established, and dietary treatment was not carried out. The correlation between DQ and methionine levels observed in patient 3 does not appear to be important, but will be monitored in future follow-ups.

With respect to management of MAT I/III deficiency, one note of caution may be mentioned: Recently, a patient with a plasma methionine of 740 $\mu\text{mol/L}$ and a tHcy of 37 $\mu\text{mol/L}$ was described who was suspected of having C β S deficiency. During treatment that included betaine administration, the methionine rose to 960–1560 $\mu\text{mol/L}$ and the patient developed brain oedema. When it was realized that the correct diagnosis was MAT I/III deficiency, the betaine was discontinued and the brain oedema largely resolved (Tada et al 2004). There is evidence that extreme elevations of methionine due to a variety of causes (perhaps especially when accompanied by betaine administration) may lead to severe brain oedema (Braverman et al 2005). This possibility should be borne in mind when dealing with MAT I/III deficiency.

Conclusions

The incidence of MAT I/III deficiency in our population is higher than has been reported in some previous studies. It is worth noting that all of our patients showed the same dominant mutation in *MAT1A*, despite the fact that, to date, 27 mutations of this gene have been published. Biochemical and clinical monitoring of these patients is important in case they need *S*-adenosylmethionine supplementation, or, far less likely, dietary restriction of methionine intake.

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