3-Methylglutaconic aciduria, a frequent but underrecognized finding in carbamoyl phosphate synthetase I deficiency

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A B S T R A C T

The urea cycle disorder carbamoyl phosphate synthetase I deficiency is an important differential diagnosis in the encephalopathic neonate. This intoxication type inborn error of metabolism often leads to neonatal death or severe and irreversible damage of the central nervous system, even despite appropriate treatment. Timely diagnosis is crucial, but can be difficult on routine metabolite level.

Here, we report ten neonates from eight families (finally) diagnosed with CPS1 deficiency at three tertiary metabolic centres. In seven of them the laboratory findings were dominated by significantly elevated urinary 3-methylglutaconic acid levels which complicated the diagnostic process. Our findings are both important for the differential diagnosis of patients with urea cycle disorders and also broaden the differential diagnosis of hyperammonemia associated with 3-methylglutaconic aciduria, which was earlier only reported in TMEM70 and SERAC1 defect.

1. Introduction

The urea cycle disorder carbamoyl phosphate synthetase I deficiency (Congenital hyperammonemia type I, CPS1, MIM #608307) is an important differential diagnosis in the encephalopathic neonate. Clinical features like poor feeding, lethargy, irritability, vomiting, coma and seizures, usually rapidly develop in neonates apparently healthy at birth. This intoxication type inborn error of metabolism often leads to neonatal death or severe and irreversible damage of the central nervous system, even despite appropriate (protein restriction, ammonia detox-
3.1. Case reports

suddenly deteriorated after the apparently healthy at term. His older sister was born prematurely, had been reported in distinct disorders (due to mutations in routine metabolite level. Patient [5].

3.2. Family 2 (patients 2, 3 and 4)

Patient 2 was born after an uneventful pregnancy to healthy unrelated Polish parents. Two older siblings were healthy. The boy was breast-fed on demand. On the second day of life he rapidly developed a cardiovascular shock and died by the end of the day. Blood gas analysis, the only laboratory test performed, showed severe metabolic acidosis. Urine was taken shortly before death and sent to the CMHI for metabolic screening. Autopsy showed fatty liver degeneration.

The younger brother, patient 3, was born seemingly healthy. At the 3rd day of life he was referred to the CMHI after sudden deterioration related with the first feeding with respiratory distress, expiratory groans, increased muscle tone, generalized seizures and lockjaw. Laboratory data showed persistent hyperammonemia. Despite treatment with low protein diet, ammonia scavengers, l-arginine and hemodiafiltration, he died from multiple organ failure aged 14 days. Urinary orotic acid excretion was within normal range and Sanger sequencing of the OTC gene did not show pathogenic alterations.

The younger sister, patient 4, was diagnosed prenatally. The pregnancy and delivery were uneventful. On treatment with low-protein diet and ammonia scavengers initiated at birth she was doing well. Only four mild decompensation episodes were observed up to the age of six months when she received a living-related liver transplantation. The girl is currently aged 14.5 months, her psychomotor development is age-appropriate.

3.3. Family 3 (patient 5)

Patient 5 was born as first child to healthy unrelated Malaysian parents. The pregnancy had been complicated by gestational diabetes mellitus. Poor feeding and lethargy were recognized from day 2 onwards and treated as sepsis. At day 3 she developed encephalopathy with progressive respiratory distress and was referred to a tertiary hospital. She had hypertonic limbs with normal reflexes and showed jerky movements. Laboratory investigations revealed lactic acidosis, organ failure at the age of 11 days under suspicion of sepsis. No specific metabolic laboratory tests or autopsy were performed.

This patient, suddenly deteriorated after several hours with irritability, screaming, convulsions and bradycardia, metabolic acidosis was recorded (no details available). Despite resuscitation and artificial ventilation he died on the second day of life in a local hospital. Autopsy showed fatty liver degeneration.

In both siblings no specific investigations had been performed during life, e.g. no ammonia levels were determined. Blood of both children and a urine sample of patient 1 were sent to Children's Memorial Health Institute (CMHI), Warsaw, Poland following the national protocol for unexplained neonatal death.

3.2. Family 2 (patients 2, 3 and 4)

The patient 1, second child of unrelated, healthy Polish parents born apparently healthy at term. His older sister was born prematurely, had suddenly deteriorated after the first breast feeding and died of multiple

2. Patients and methods

2.1. Metabolic and genetic investigations

Blood gas analysis; serum lactate, plasma ammonia, serum or plasma amino acid analysis; urinary organic acid and purines/pyrimidines analysis were performed using standard methods. Exome sequencing in patients 2, 4 and 6 was performed as described before [7,8]. The DNA of P7, P8 and P9 underwent high-throughput sequencing by TruSight One panel (Illumina, San Diego, CA) [9] Patient 10 underwent solely Sanger Sequencing of the CPS1 gene. Sanger sequencing was used to confirm all mutations and verify their segregation in the parents (details are available upon request).

2.2. Patients

The patients were treated by the contributing authors at three tertiary metabolic centres (Warsaw, Poland; Kuala Lumpur, Malaysia; Rome, Italy) and gave written informed consent for the genetic studies. All clinical, metabolic and genetic data are summarized in Table 1. The detailed case reports of patients 1–10 are shown below.

3. Case reports

3.1. Family 1 (patient 1)

The patient 1, second child of unrelated, healthy Polish parents born apparently healthy at term. His older sister was born prematurely, had suddenly deteriorated after the first breast feeding and died of multiple...
Table 1
Urinary 3-MGA excretion and other biochemical and molecular data of ten neonates with CPS1 deficiency.

<table>
<thead>
<tr>
<th></th>
<th>F1, P1, m (Polish)</th>
<th>F2, P2, m (Polish)</th>
<th>F2, P3, m (Polish)</th>
<th>F2, P4, f (Polish)</th>
<th>F3, P5, f (Malaysian)</th>
<th>F4, P6, m, (Italian)</th>
<th>F5, P7, m, (Italian)</th>
<th>F6, P8 m, (Italian)</th>
<th>F7, P9, m (Italian)</th>
<th>F8, P10, f (Italian)</th>
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<tbody>
<tr>
<td>Complications during pregnancy, weeks of gestation at delivery</td>
<td>Uneventful, 39</td>
<td>Uneventful, nd</td>
<td>Uneventful, nd</td>
<td>Uneventful, 40</td>
<td>Gestational diabetes mellitus, 39</td>
<td>Uneventful, 39</td>
<td>Uneventful, NA</td>
<td>Uneventful, CS, 39</td>
<td>Uneventful, 40</td>
<td>Hypercholesterolemia, CS, 40</td>
</tr>
<tr>
<td>Birth weight g; Apgar score</td>
<td>4190; 10</td>
<td>3380; 9</td>
<td>4000; 10</td>
<td>2940; 10</td>
<td>3115; 8(1'), 9 (5')</td>
<td>3500; 9(1'), 10(5')</td>
<td>2850; 9(1'), 9(5')</td>
<td>2950; 9(1'), 9(5')</td>
<td>3750; na</td>
<td></td>
</tr>
<tr>
<td>Age at onset; age deceased</td>
<td>1; 2 d</td>
<td>2; 2 d</td>
<td>3; 14 d</td>
<td>2 d; 11 m</td>
<td>4; 7 d; 3; 5 d</td>
<td>2 d; 8 d</td>
<td>4 d; 8 y</td>
<td>4 d; alive age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical course</td>
<td>Fulminant</td>
<td>Fulminant</td>
<td>Fulminant</td>
<td>Mild, treatment from birth</td>
<td>Severe</td>
<td>Pulminant</td>
<td>Fulminant</td>
<td>Pulminant</td>
<td>Severe</td>
<td>Mild (LTX 2014 age?)</td>
</tr>
<tr>
<td>Specific treatment*</td>
<td>No</td>
<td>no</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Autopsy finding</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Max. NH₃ (ref. 35-76) μmol/L</td>
<td>ND</td>
<td>ND</td>
<td>2142</td>
<td>337</td>
<td>808</td>
<td>2727</td>
<td>2727</td>
<td>5697</td>
<td>1571</td>
<td>714</td>
</tr>
<tr>
<td>Plasma lactate (ref. &lt; 1.8) mmol/L</td>
<td>ND</td>
<td>ND</td>
<td>3.1-5.3</td>
<td>2.1</td>
<td>3.2</td>
<td>9.2</td>
<td>50</td>
<td>15.0</td>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>glutamine (ref. 538-958) μmol/L</td>
<td>4860</td>
<td>ND</td>
<td>17.37</td>
<td>1167</td>
<td>3105</td>
<td>1651</td>
<td>3200</td>
<td>3750-4800</td>
<td>992-1050</td>
<td>1129</td>
</tr>
<tr>
<td>Glutaminic acid (ref. 0-50) μmol/L</td>
<td>604</td>
<td>ND</td>
<td>67</td>
<td>99</td>
<td>125</td>
<td>125</td>
<td>987</td>
<td>383-780</td>
<td>154-169</td>
<td>NA</td>
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<tr>
<td>Alanine (ref. 236-410) μmol/L</td>
<td>1891</td>
<td>ND</td>
<td>ND</td>
<td>391</td>
<td>895</td>
<td>1285</td>
<td>2416</td>
<td>2380-4000</td>
<td>588-965</td>
<td>NA</td>
</tr>
<tr>
<td>Citrulline (ref. 8-28) μmol/L</td>
<td>3.5</td>
<td>ND</td>
<td>ND</td>
<td>2.4-5</td>
<td>0</td>
<td>7</td>
<td>15</td>
<td>3-7</td>
<td>15-21</td>
<td>0</td>
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<tr>
<td>Ornithine (ref. 49-151) μmol/L</td>
<td>250</td>
<td>ND</td>
<td>333</td>
<td>58</td>
<td>154</td>
<td>491</td>
<td>1285</td>
<td>1206-1700</td>
<td>27-243</td>
<td>NA</td>
</tr>
<tr>
<td>Urinary orotic acid (ref. 0.08-1.08) μg/μmol creat</td>
<td>ND</td>
<td>ND</td>
<td>1.3</td>
<td>ND</td>
<td>0</td>
<td>4.5</td>
<td>0.7</td>
<td>0.5</td>
<td>0.3</td>
<td>ND</td>
</tr>
<tr>
<td>Urinary 3-MGA (ref. &lt; 20) mmol/mol creat.</td>
<td>46</td>
<td>+ + +</td>
<td>88</td>
<td>&lt; 20</td>
<td>75-210</td>
<td>147-304</td>
<td>182-248</td>
<td>109</td>
<td>+ +</td>
<td>157</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other urinary organic acid findings</th>
<th>LA, KB</th>
<th>LA, KB</th>
<th>LA, KB</th>
<th>LA, KB</th>
<th>LA, KB</th>
<th>LA, KB</th>
<th>LA, KB</th>
<th>LA, KB</th>
<th>none</th>
<th>none</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS1 allele 1 (NM_001875.4)</td>
<td>c.1837-8A &gt; G (p.7)</td>
<td>c.1289C &gt; G; p.Ser430*</td>
<td>c.1289C &gt; G; p.Ser430*</td>
<td>c.1289C &gt; G; p.Ser430*</td>
<td>c.3980G &gt; A; p.Cys1327Tyr</td>
<td>c.1263 + 5G &gt; C; p.?</td>
<td>c.2440C &gt; T; p. (Arg814Trp)</td>
<td>c.3136C &gt; T; p. (Gln1046?)</td>
<td>NA</td>
<td>c.850delA. p. (Ser284Val18*15)</td>
</tr>
<tr>
<td>CPS1 allele 2 (NM_001875.4)</td>
<td>c.3691G &gt; C; p.Ala1231Pro</td>
<td>c.1289C &gt; G; p.Ser430*</td>
<td>c.3972de; p.Leu1325*</td>
<td>c.3972de; p.Leu1325*</td>
<td>c.3980G &gt; A; p.Cys1327Tyr</td>
<td>c.1923,1925delTA; p. (Arg642del)</td>
<td>c.3940C &gt; T; p. (Arg814Trp)</td>
<td>c.3136C &gt; T; p. (Gln1046?)</td>
<td>NA</td>
<td>c.2339G &gt; A; p. (Arg780His)</td>
</tr>
</tbody>
</table>

3-MGA = 3-methylglutaconic acid, +++ very high, ++ high (not quantified), CS = cesarean section, HCM = hypertrophic cardiomyopathy, HSM = hepatosplenomegaly, KB = ketone bodies, LA = lactic acid, PVL = periventricular leucomalacia, ND = not determined, NA = not available, * low protein diet, sodium benzoate, sodium phenylbutyrate, L-arginine, hemodialfiltration etc. **Novel mutations in bold.**
arginine, citrulline and L-carnitine. She initially stabilized but subsequently had frequent recurrent unprovoked episodes of hyperammonemia necessitating repetitive hemodialfiltration. MRI showed bilateral basal ganglia lesions. She died at 11 months of age due to septicemia.

3.4. Family 4 (patient 6), family 5 (patient 7), family 6 (patient 8)

These three patients were born from healthy unrelated Italian parents and were referred to the Bambino Gesù Children’s Hospital (BGCH), Rome for severe neonatal hyperammonemia. Despite intensive ammonia detoxification treatment, including ammonia scavengers and dialysis, the three patients died within a few days after admission.

3.5. Family 7 (patient 9)

Patient 9, male, was the first born of healthy Italian parents. On the 4th day of life he presented with hypotonia, lethargy, seizures and coma and was referred to the BGCH, laboratory investigations showed hyperammonemia. He was successfully treated with HD combined with ammonia scavengers and i.v. arginine. Despite appropriate treatment he showed a severe clinical course with progressive cerebral atrophy. The patient died at the age of seven years during an intercurrent episode of hyperammonemia.

3.6. Family 8 (patient 10)

Patient 10, female, is the first child born to healthy unrelated Italian parents. Lethargy and vomiting begun on the 4th day of life and laboratory investigations revealed increasing hyperammonemia. She was referred to the BGCH where she was successfully treated with HD, ammonia scavengers and i.v. arginine. The therapy was maintained with a low-protein diet combined with ammonia scavengers and arginine/citrulline supplementations. At follow-up she presented with feeding difficulties and experienced repeated episodes of mild hyperammonemia requiring frequent hospitalization. At the age of 9.5 years she successfully received a living-related liver transplantation. After 11 months, she is doing well on a low protein diet and presents an age-appropriate intellectual development.

4. Results

4.1. Laboratory investigations (summarized in Table 1)

Newborn screening was reported unremarkable in all patients.

3-MGA-uria levels were available for all patients and were significantly increased to up to 10 × of the upper normal range (range 46–304, reference range < 20 mmol/mol creatinine) in all symptomatic patients. In the patients with multiple measurements available, this was a consistent finding. Only the prenatally diagnosed patient 4 did not show excretion of this metabolite in four urine samples. In the patients 1, 4 and 6 the 3-MGA-uria was rated as dominant metabolic finding that lead to exome sequencing.

Ammonia levels were unavailable for patients 1 and 2. All other patients showed hyperammonemia with maximum levels between 277 and 4685 (ref. 35–76) μmol/L.

Plasma amino acid profile was unavailable for patient 2. Citrulline was decreased in patients 1, 4, 5, 6, 8, 10 and normal in patient 7 and 9; glutamine was elevated in all patients measured. Notably, ornithine levels were found elevated in seven out of eight patients (median 291.4, range 27–1700; ref. 49–151 μmol/L).

4.2. Retrospective analysis of urinary organic acid profiles of patients with different urea cycle disorders

In a retrospective analysis of 19 patients with urea cycle disorders (2 × Argininosuccinate Lyase Deficiency, 2 × Lysinuric Protein Intolerance, 13 × Ornithine Transcarbamylase Deficiency, 2 × Citrullinemia) 3-MGA-uria was only found in one patient with a complete deletion of the OTC gene.

4.3. Molecular studies

Exome sequencing of the patients 1, 3 and 5, and TruSight One panel analysis of patients 6, 7, 8 revealed rare biallelic alterations in CPS1 (NM_001122633.2). No other potentially or known pathogenic variants were found in the genes known to be related with 3-MGA-uria (AUH, TAZ, OPA3, SERAC1, AGK, TMEM70, CLPB) and in nuclear genes known to be related with mitochondrial disorders.

Patient 1 carried one reported clinically relevant near splice variant c.1837-8A > G (p.?) [10] and missense variant c.3691G > C, (p.Ala1231Pro) [6]. The missense variant is predicted to change an evolutionarily highly conserved amino acid of the phosphorylation domain of CPS1 [10]. In patient 3 two nonsense variants were found, c.1289C > G (p.Ser430*) and c.3972delT (p.Leu1325del*) [6]. Both variants are predicted to lead to a premature stop and result in a truncated protein lacking evolutionarily highly conserved regions of CPS1.

In patient 5, a previously unreported homozygous c.3980G > A, (p.Gly1327Tyr) missense variant was found. In silico prediction programs (PolyPhen 2, SIFT, CADD) rate this change of an evolutionarily highly conserved amino acid as damaging. Patient 6 was compound heterozygous for the known mutation c.1263 + 5G > C (p.?) and the unreported c.1923_1925delTGA, p.(Asp642del) [11]. Patient 7 was homozygous for the previously reported missense mutation c.2440C > T, p.(Arg814Trp) [10]. Patient 8 was homozygous for the novel nonsense mutation c.3138C > T, p. (Gln1046*). No molecular diagnosis was available in patient 10. Sanger sequencing confirmed the same alterations in the affected sibs (sister of patient 1, patient 2 and patient 4 respectively) and carrier status in all parents with exception of patient 6 (parental DNA unavailable).

5. Discussion

Making the correct and timely diagnosis in an encephalopathic neonate is key, both for effective treatment but also for counseling with regards to end of life decisions.

For many classical intoxication type inborn errors of metabolism this is possible based on characteristic metabolic profiles in blood and urine [13]. However, diagnostic delay can occur if local diagnostic possibilities are limited and/or if the metabolic profile is dominated by a certain marker misleading the diagnostic team.

Here, we present a case series of 10 patients with neonatal hyperammonemia due to CPS1 deficiency treated and/or diagnosed at three international metabolic centres.

Due to limited local diagnostic possibilities in the patients 1 and 3 neither ammonia levels nor extensive metabolic screening had been performed during the short life of the patients. The significant 3-MGA-uria, the dominating metabolic marker, lead the diagnostic team to perform exome sequencing given the heterogeneity of inborn errors of metabolism with 3-MGA-uria as discriminating feature or general towards mitochondrial disorders [5,14]. The finding of biallelic CPS1 mutations was unexpected, but retrospectively supported/confirmed by additional investigations (retrospectively low citrulline level in newborn screening, family linkage studies).
A similar diagnostic journey took place in patient 5 who showed several unprovoked metabolic deteriorations and bilateral basal ganglia lesions questioning the presumed diagnosis of a urea cycle disorder and raising the suspicion of SERAC1 defect, as (sole or) additional diagnosis.

Additionally, significant 3-MGA-uria was found dominating the metabolic profiles of the five Italian CPS1 deficient patients from five unrelated families (Table 1, patients 6–10). The exact origin of 3-MGA-uria is unknown, there is however a strong coincidence with primary or secondary mitochondrial dysfunction, a new theory proposes that it arises in three steps from mitochondrial acetyl CoA [5,14,15]. The findings of 3-MGA-uria in association with metabolic deterioration in this case series of 10 patients with CPS1 deficiency cannot be easily explained. Our limited retrospective survey in 19 patients with other urea cycle disorders did only show it in one patient with complete deletion of the OTC gene. Previously, in patients with urea cycle disorders (two carbamoylphosphatase synthetase 1 deficiency, two argininosuccinate lyase deficiency, two ornithine transcarbamylase deficiency) two ornithine transcarbamylase deficiency were reported to have shown 3-MGA-uria upon disease presentation or metabolic deterioration during the course of disease [5]. This study also did not focus on the occurrence of 3-MGA-uria in urea cycles disorders, however these data suggest, that 3-MGA-uria is occurring significantly more frequently in CPS1 deficiency (12 patients), than in other urea cycle disorders (five patients). This may display the severity of CPS deficiency comparing to e.g. OTC deficiency with regards to life threatening illness leading to a secondary mitochondrial dysfunction.

The data presented here are important for the differential diagnosis in severely ill neonates with clinical signs of intoxication accompanied by hyperammonemia and 3-MGA-uria and lactic acidosis. Based on our data we conclude the following.

1) We here present four new mutations in relation with CPS1 deficiency.
2) 3-MGA-uria is a frequent finding in CPS1 deficiency and seems less frequent in other urea cycle disorders. This is important for counseling as the prognosis of CPS1 deficiency is associated with an overall poorer outcome quad vitam and concerning neurological sequelae than other urea cycle disorders (e.g. ASL or OTC deficiency) [16].
3) The combination of hyperammonemia, 3-MGA-uria and lactic acidosis is also a typical combination of laboratory findings in neonates with SERAC1 and TMEM70 defects [2,17–19]. These can clinically be difficult to distinguish if they do not exhibit the classical clinical symptoms (hypoglycemias and/or liver failure (SERAC1), cardiomyopathy/cardiac rhythm abnormalities (TMEM70)) which distinguish them from CPS1 defect. However, thorough metabolic profiling in blood and urine will lead to the correct diagnosis. The correct and timely diagnosis of these disorders is important as the course of disease can vary significantly with TMEM70 probably the most favorable of the three disorders.
4) Interestingly, most of our CPS1 deficient patients showed elevated plasma ornithine levels, with some values in the range observed in Hyperornithinemia-Hyperammonemia-Homocitrullinuria syndrome, a urea cycle defect caused by mutations in the SLC25A15 gene, which encodes for the mitochondrial ornithine carrier ORC1, allowing the exchange of cytosolic ornithine with mitochondrial citrulline [20]. The severe mitochondrial citrulline depletion due to CPS deficiency, may impair the exchange with cytosolic ornithine, leading to hyperornithinemia. It is likely that a similar mechanism may be the cause of hyperornithinemia in a patient with fatal neonatal OTC deficiency, another enzyme defect of the urea cycle impairing citrulline synthesis in mitochondria, with full gene deletion (C. Dionisi-Vici, personal communication). However this theory has to be examined in more detail, especially to exclude preanalytical influences (e.g. hemolysis).

Taken together, the main purpose of this short report is to increase the awareness to the finding of 3-MGA-uria as a frequent finding in CPS1 deficiency and should help to avoid diagnostic delay in these critically ill patients. We therefore suggest to add this novel finding to the diagnostic algorithm for urea cycle disorders.

Conflict of interest

All authors declare no conflict of interest.

Informed consent/compliance with ethical standards

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Animal rights

This article does not contain any studies with human or animal subjects performed by the any of the authors.

Author contribution statement

1/ Conception and design: EP, SBW
2/ Analysis and interpretation of data: EP, CDV, SBW
3/ Drafting the article: EP, CDV, SBW
4/ Revising article critically for important intellectual content: all authors

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References


