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Malnutrition with hypoaminoacidemia in a 22-year-old pregnant patient masking a likely ornithine transcarbamylase deficiency

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SUMMARY

Background: Symptoms and clinical presentations of OTC deficiency vary widely according to the remaining activity of the enzyme. Three factors determine the residual enzyme activity. First, as the OTC gene is carried on the X chromosome, a complete inactivation of this enzyme in a newborn boy results an acute ammonia intoxication. Second, the female mosaicism due to lyonization (differential randomized X-inactivation) leads to differential OTC expression in hepatocytes. Third, the degree of severity depends on the mutation and the level of remaining activity it leaves to the protein. Published cases of OTC deficiency during pregnancy are scant. Most often, diagnosis of the metabolic disease is made before pregnancy or during the post-partum period.

Methods: We report the case of a 22-year-old woman's successful pregnancy with a moderate form of ornithine transcarbamylase (OTC) deficiency, unsuspected before pregnancy, biochemically consistent with plasma aminoacidogram and orotic acid analysis, and initially masked by malnutrition.

Results - conclusion: Although maternal ammonia was subnormal and the neonate was safe, an OTC deficiency was revealed by stress factors such as the pregnancy itself and infection, and associated with uncontrollable maternal vomiting and psychiatric syndrome. However, this metabolic disease, revealed by aminoacidogram and urine orotic acid analysis, fortunately did not prevent a successful pregnancy. Even if infrequent, this situation deserves to be highlighted.

1. Introduction

The metabolism of nitrogen derived from protein intake and catabolic breakdown of endogenous protein is regulated by biochemical pathways that convert toxic ammonia into non toxic water-soluble urea which is released in the blood, and excreted by the kidneys. To ensure this nitrogen homeostasis, the complete urea cycle, strictly located in periportal hepatocytes, involves a series of four enzyme-mediated reactions that detoxify ammonia [1]. Transporters such as ornithine transporter-1 are also involved in the urea cycle (Fig. 1).

Ornithine transcarbamylase (OTC) deficiency, though uncommon (estimated incidence: 1/14000), is the most frequent inborn urea cycle disorder (UCD) [2]. OTC catalyzes one of the mitochondrial steps of this cycle, transferring a carbamoyl group from the carbamyl-phosphate to ornithine to form citrulline, thus introducing the first nitrogen atom into the cycle. A scavenging pathway can also convert carbamyl-phosphate into orotate, an intermediate in pyrimidine base biosynthesis. Profiling plasma amino acid concentrations is the first step in diagnosing the malfunctioning enzyme in UCD, as summarized in Table 1; of note, variations of amino acids (e.g. alanine, lysine) are not systematically observed [3]. The citrullinemia values can be used in order to distinguish proximal from distal urea cycle deficiency. The citrullinemia levels are low in OTC and in carbamoyl phosphate synthetase (CPS-1) deficiency. Plasma concentration of arginine is reduced in every type of UCD, except in arginase deficiency, and are sometimes normal in late-onset or partial defects. Urine concentrations of orotic acid can help to distinguish between certain UCDs such as CPS-1 deficiency (low) and OTC deficiency (high) [4].

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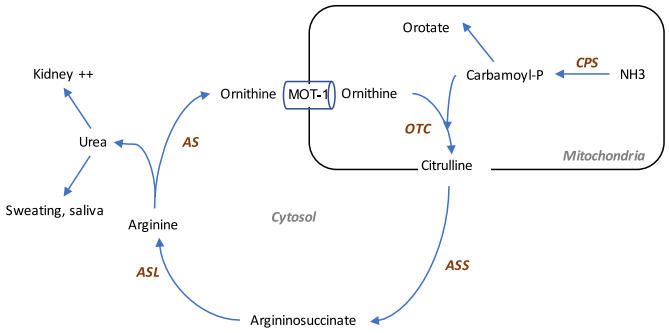

Fig. 1. Periportal hepatocyte ureogenesis: a simplified view of the urea cycle. CPS: Carbamyl phosphate synthetase, *OTC*: Ornithine transcarbamoylase, *ASS*: Argininosuccinate synthetase, *ASL*: Argininosuccinate lyase, *AS*: Arginase, MOT-1: Mitochondrial ornithine transporter 1.

Symptoms and clinical presentations of OTC deficiency vary widely according to the remaining activity of the enzyme. Three factors determine the remaining enzyme activity. First, as the OTC gene is carried on the X chromosome, a complete inactivation of this enzyme in a newborn boy results in acute ammonia intoxication with digestive disorders, acid-base deregulation and progressive coma [5]. Second, the female mosaicism due to lyonization (differential randomized X-inactivation) leads to differential OTC expression in hepatocytes. Third, the degree of severity depends on the mutation and the level of remaining activity it leaves to the protein [4]. Hence partial deficiency of the urea cycle can leave the patient symptom-free, without hyperammonemia. Symptoms are delayed, usually triggered by metabolic decompensation related to high protein intake, acute catabolic stress or illness, such as sepsis, surgery, trauma, or drugs (e.g. valproic acid). In most of these episodes, patients can present with vomiting, loss of appetite, lethargy and neuropsychological abnormalities. Prompt recognition and treatment of these late-onset manifestations is crucial to improve the poor prognosis.

Published cases of OTC deficiency during pregnancy are scant. Most often, diagnosis of the metabolic disease is made before pregnancy or in the postpartum period. To our knowledge, the present case is one of only seven published reports of an OTC diagnosed in this setting (Table 2) [6–11]. Hence despite specific guidelines [9], little is known about these patients. Mainly asymptomatic before pregnancy, all late-onset metabolic manifestations correspond to heterozygous mutation for the *OTC* gene. The common symptom shared by these heterozygous parturients seems to be disturbance of consciousness. Indeed, Schimanski et al. [11] suggest that OTC deficiency should be suspected in any hyperammonemic patient, albeit with normal hepatic function.

2. Results

The patient, a 22-year-old nulliparous woman, with an unremarkable medical history (including no documented intolerance or self-imposed dietary restriction), had been hospitalized seven times for uncontrollable cyclical vomiting from 9 weeks of gestation (GW). The prescribed antiemetic medications, such as metoclopramide and ondansetron, were ineffective.

At 26 GW, the patient was admitted to the obstetric ward at Cochin Hospital for pelvic pains. She had received no prenatal care as a result of her precarious socioeconomic status.

On admission, the patient presented uncontrollable vomiting with hematemesis, esophagitis and gastritis, and deterioration of general status. She suffered from a severe hypokalemia (1.8 mmol/L), signs of discrete hepatic cytolysis (ASAT at 66 IU/L and ALAT at 48 IU/L), dehydration and moderate-acute renal failure (creatinine clearance by the Cockroft-Gault formula at 49 mL/min).

She also presented psychomotor slow down and an episode of acute psychomotor agitation treated with chlorpromazine, with no underlying psychosis.

An echography showed an intrauterine growth restriction (IUGR) with a broken curve on cephalic and femoral parameters. Despite the risk of genetic abnormalities of the karyotype associated with IUGR, the patient refused amniocentesis.

For an unrecorded reason, a plasma aminoacidogram prescription was given at 26 GW by a gastroenterologist. Amino acids were measured by ion exchange chromatography using an Aminotac® instrument (Jeol, Japan). The assay revealed overall hypoaminoacidemia (1551 μmol/L, N: 2242–3610 μmol/L) and a ratio of non-essential AAs to essential AAs close to 2 (Table 3). Urinary aminoacidograms were also performed (Table 4).

At 29 GW, enteral nutrition by nasogastric tube was refused by the patient. At 30 GW, her weight had decreased by 29% compared with pre-pregnancy weight. During progressive oral refeeding, from 29 to 32 GW, the patient took two food supplements (Fortimel Compact Protein®), with ingestas estimated at 1300 kcal/day including 450 kcal of sodas according to the nutritionist (32 GW). At this moment, we did not know that protein intake was deleterious; anyway, dietitian mentioned that she did not take always the two food supplements (lack of compliancy? Hidden protein-intolerance?). Most amino acids returned to normal levels, except for citrulline, ornithine and arginine, which remained at low levels (Table 3), suggesting a UCD. Moreover, a characteristic hyperorotaturia (14.7 μmol/mmol of creatinine, N < 6 μmol/mmol of creatinine) associated with mild hyperammonemia (64 μmol/L, N < 26 μmol/L) [12] at 34 GW evoked an ornithine transcarbamylase (OTC) deficiency. It was managed by initiation of parenteral nutrition and close ammonemia monitoring. Administration of glucose 10% and Intralipid 20% was prescribed in order to forestall metabolic decompensations. Some differential diagnosis, such as a mitochondrial disorder or abnormalities in the β-oxydation, could be ruled out, since plasma lactate and plasma acylcarnitine patterns were normal (data not shown).

A severe sepsis occurred at 31 GW, involving the enterobacterium *Klebsiella pneumomiae*, an opportunistic pathogen taking advantage of the physiological immunodepression associated with pregnancy [11]. This infection was treated with antibiotics

Table 1
Biological differential diagnosis of urea cycle disorders (UCD) associated with hypocitrullinemia.

UCD	Protein involved	Ala	Arg	Lys	Orn	Urinary orotate
OTC	Ornithine transcarbamoylase	↑	↓	↑	↓	↑↑
NAGS	N-Acetylglutamate synthetase	↑	↓	↑	↓	N
CPS	Carbamoyl phosphate synthetase	↑	↓	↑	↓	N or ↓
HHH	Mitochondrial ornithine transporter 1	↑	↓	N or ↓	↑	N or ↑
P5CS	Pyrolline-5-carboxylate synthetase	N	↓	N	↓	N

Ala: alanine; Cit: citrulline; Arg: arginine.
HHH: Hyperornithinemia – Hyperammonemia – Homocitrullinemia
N: normal; ↑: increased compared to normal value: ; ↓ decreased compared to normal value.
Adapted from [3]

Table 2
Literature review of late-onset OTC deficiency diagnosed during pregnancy or shortly post-partum.

Authors	Age and GW	Clinical outcomes	Biology
Bailly [6]	32 18–20 G1, P1	- progressive neuropsychological and behavior disorders, coma - improvement of consciousness with therapy, but persistent mild cognitive impairment persistent - female infant had no sequelae at 11 months	- Biochemistry: hyperammonemia (173 μmol/L), glutamine chromatographic peak, increased urinary orotate excretion - DNA analysis: novel heterozygous mutation c.626C > A/p.Ala209Glu in *OTC* gene for both mother and female infant
Nakajima [7]	28 G1	- chief complaint: disturbance of consciousness - *hyperemesis gravidarum*	- Biochemistry: hyperammonemia at admission: 268 μmol/L; Gln elevated, Cit, Orn, Arg low, high orotic acid excretion - DNA analysis: OTC mutation (829 C > T/R277W) c.829C > T/p.Arg277Trp
Celik [8]	31 G1, P2	- admission for mental confusion - epileptic seizures for 15 years, - vaginal delivery of a viable, unaffected male infant	- Biochemistry: hyperammonemia (179 μmol/L), normal plasma aminoacidogram, increased urinary orotate excretion - DNA analysis: heterozygous for three polymorphisms (K46R, Ivs3-8A4 T, Q27OR)
	23 Uncertain G2, P1	- the patient has two maternal half- sisters found to be OTC deficiency carriers - lifelong history of migraine headaches, self-imposed restricted protein diet - the patient remained asymptomatic postpartum	- Biochemistry: prenatal and postpartum serum amino acid profiles all within normal limits. Ammonia levels remained within normal limits, except for one value after an unauthorized snack - DNA analysis: heterozygous c.122A > G (p.D41G) mutation for both mother and male fetus c.122A > G/p.Asp41Gly
	28 35 G2, P0	- positive family history of OTC deficiency - lifelong history of migraine headaches after high-protein meals - vaginal delivery a viable female infant	- Biochemistry: ammonia level of 98 μmol/L on admission for induction of labor, levels then remained normal 4 months postpartum. - DNA analysis: heterozygous OTC mutation for the mother
Mendez-Figueroa [9]	16 36 G1	- gestational diabetes - vaginal delivery of a viable male infant - postpartum day 3: hypoxic episode for the infant	- Biochemistry: all results at admission within normal limits, but serum ammonia level not obtained. Hyperammonemia in postpartum. - DNA analysis: c.122A > G (p.D41G) mutation for the mother c.122A > G/p.Asp41Gly
	18 36 G1	- preterm premature rupture of membranes - nausea and vomiting early in pregnancy - forceps-assisted vaginal delivery - postpartum day 8: lethargic infant	- Biochemistry: hyperammonemia for the infant at day 2 - DNA analysis: hemizygous mutation c.904C > T (p.H302Y) for both mother and infant c.904C > T/p.Cys302Tyr
Quintero-Rivera [10]	35 G1, P0	- self-chosen vegetarian diet - mother and two male infants died of OTCD	- One infant was demonstrated likely to be OTC deficient. - DNA analysis: exon 1 deletion of *OTC* gene
Shimanski [11]	2410 G2P0	- *hyperemesis gravidarum*, severe malnutrition - encephalopathy, mental confusion, cerebral edema, death	- Biochemistry: hyperammonemia (380 μmol/L), massive excretion of orotic acid, normal OTC activity in biopsy - DNA analysis: deletion T892 and G893 of *OTC* gene

GW: Weeks of gestation; G: Gravidity P: Parity.

Table 3
Plasma amino acids (μmol/L) at admission (25 GW) and during hospitalization.

Amino acid	25 GW	29 GW	30 GW	31 GW	32 GW	Reference range [29]
Taurine	45	49	89	56	78	42–68
Aspartic acid	3	4	7	4	5	2–14
Hydroxyproline	24	38	55	59	72	0–37
Threonine	95	121	115	100	140	107–173
Serine	75	119	123	117	135	95–133
Asparagine	29	48	49	54	63	36–60
Glutamic acid	37	78	59	45	64	30–80
Glutamine	415	590	595	630	616	500–670
Proline	104	183	297	300	322	108–228
Glycine	139	219	253	221	278	178–282
Alanine	189	225	507	405	308	286–416
Citrulline	6	6	6	8	11	30–46
2-Aminobutyric acid	4	7	8	8	9	9–29
Valine	75	93	75	87	102	190–276
Cystine	13	15	26	15	22	55–109
Methionine	11	10	14	12	15	21–29
Isoleucine	22	18	26	18	27	48–76
Leucine	37	46	42	46	53	98–148
Tyrosine	22	17	25	20	25	47–71
Phenylalanine	26	31	33	32	36	48–66
Ornithine	19	13	18	13	18	39–74
Lysine	75	114	82	98	108	156–220
Histidine	51	70	69	63	86	72–92
3-Methylhistidine	2	3	2	4	3	1–5
Tryptophane	16	5	9	4	8	10–40
Arginine	17	18	15	15	19	60–80
Total aminoacidemia	1551	2140	2599	2434	2623	2242–3610

including gentamicin, amoxicillin, cefotaxime. Simultaneously, there was a risk of pre-term delivery, addressed by Atosiban injection. A *Clostridium difficile* nosocomial infection also occurred, which was treated with metronidazole. Also at 31 GW, the nutritional markers were decreased and the inflammation marker was increased (Table 5).

The neonate was a premature hypotrophic boy (1.4 kg at birth at 32 GW, < 3rd percentile,). While awaiting genetic confirmation, normal blood ammonia levels (<94 μmol/L) [13] during the first week, and normal orotic acid urine levels (2.5 μmol/mmol creatininuria) suggest that the neonate did not inherit the disease. Finally, the newborn gained weight normally, and after one week, ammonia monitoring was stopped. Mother and child were discharged one month after delivery.

3. Discussion

Here we report an OTC deficiency masked by hypoaminoacidemia that can be explained by either two hypotheses. The most consistent one is a state of malnutrition. However, despite knowledge of the consequences of malnutrition on both mother and child, few guidelines and little consensus have been established to estimate the exact nutritional status of pregnant women [14]. Biological markers such as albumin and transthyretin (prealbumin) are difficult to interpret. Albumin tends to decrease throughout pregnancy due to physiological haemodilution and a

Table 4
Urinary aminoacidogram

Amino acid/creatinine (μmol/mmol)	29 GW	30 GW	31 GW	Reference range [29] (μmol/mmol)
Taurine	16	17	23	16–180
Hydroxyproline	3	2	2	<13
Threonine	**186**	22	**40**	7–29
Serine	**381**	**75**	**122**	21–50
Asparagine	**183**	17	**46**	<23
Glutamate	1	4	4	<12
Glutamine	**509**	70	**134**	20–76
Proline	1	4	32	<9
Glycine	**764**	**273**	**517**	43–173
Alanine	**76**	**69**	**129**	16–68
Citrulline	0	0	0	<4
2-Aminobutyric acid	**4**	2	**32**	<4
Valine	9	3	4	3-13
Cystine	5	**6**	4	6-34
Methionine	3	4	5	2-16
Isoleucine	3	2	2	<4
Leucine	10	3	3	2–11
Tyrosine	**29**	10	**14**	2–23
Phenylalanine	18	6	Interference*	2–19
Ornithine	4	0	1	<5
Lysine	30	4	8	7–58
Histidine	**453**	**99**	**189**	26–153
3-Methylhistidine	38	24	8	19–47
Arginine	1	1	1	<5
Total aminoaciduria/creatinine	2718	717	1320	

*Likely by antibiotics.
Bold characters correspond to amino acid for which there are values upper to reference range.

possible down-regulation of α-foetoprotein on maternal albumin production [15]. Concerning transthyretin, the literature is conflicting: some authors report that transthyretin levels remained unchanged throughout pregnancy [16] while others found that they decreased [17]. Here, hypoalbuminemia and hypotransthyretinemia must be interpreted cautiously because of a biological inflammatory syndrome [18]. Hypoaminoacidemia could be caused by protein-energy malnutrition, due to decreased food intake and increased amino acid catabolism. Despite an initial severe obesity (BMI: 37.7 kg/m^2), the patient suffered an unintended loss of weight of more than 10% in 6 months (usual pre-pregnancy weight: 87 kg; weight at 30 GW: 62 kg). This weight loss could have been caused by anorexia, nausea and vomiting during pregnancy.

Another hypothesis is an excessive amino acid urinary loss. Indeed, a selective hyperaminoaciduria pattern evoked a Hartnup disorder (an inherited disorder of renal and intestinal amino acid transport [19], consistent with the patient's dermatitis and neurological problems. Organic kidney failure with tubulopathy (persistent proteinuria >1 g per day, urinary ratio Na/K < 1, β2-microglobulinuria at 200 μg/g creatinine) and urinary amino acid loss could also have contributed to amino acid blood depletion. This hypothesis could be ruled out since urinary amino acids levels returned partially to normal (Table 4) with refeeding and improvement of the patient's kidney function.

Little is known about the influence of malnutrition and pregnancy on the amino acid profile during OTC deficiency and the interaction between parameters could explain why the biological profile observed in our patient was atypical. Hypoaminoacidemia during pregnancy can be driven by three processes: lower protein catabolism, higher gluconeogenesis from amino acids and active transport through the placenta. Previous experimental [20] or clinical reports [21] found a selective hypoaminoacidemia (mostly concerning non-essential amino acids), whereas all amino acids were decreased in the present case.

Stress factors can trigger acute metabolic decompensations in the case of incomplete enzymatic deficiency with potentially lethal fetal hyperammonemic encephalopathy [8] which is explained by multiple biochemical disturbances in brain cells. The main features are edema, probably secondary to disruption of the aquaporin system and brain electrolyte homeostasis, increase in astrocytes glutamine synthesis, and swelling of astrocytes in response to the osmotic effect of glutamine, resulting in higher intracranial pressure [22].

In the present case, a remaining enzymatic activity could have prevented an acute metabolic decompensation that was triggered by hyperemesis, pregnancy and infection. The disease outcomes appear during decompensation episodes, thus contributing to a delayed diagnosis, from infancy to adulthood. The psychiatric symptoms mentioned might conceivably have resulted from a chronic moderate ammoniemic neurointoxication. Maternal vomiting, absent before the pregnancy continued after birth with severe hypokalemia, and might be possibly be linked to a psychiatric condition, with pathomimetic skin scratching, anxiety, obsessive-compulsive disorder and depressive syndrome. These symptoms are frequently described during the *hyperemesis gravidarum* syndrome [23], along with pernicious vomiting, hydroelectrolytic disorders or kidney damage. The moderate elevation of ammonia level can be explained by a detoxification by the healthy fetal liver [24], in addition to the increased nitrogenous conservation [25]. Though at risk of elevation due to the collagen breakdown theory during uterine involution, ammoniemia remained normal during post-partum period [26]. Indeed, catabolism of uterine extracellular matrix compounds, via metalloproteinase [27], releases nitrogen and permits the physiological post-partum involution (loss of size and weight).

The limitation of our study is that we were not able to get a genetical proof due to the lack of compliancy of the patient who refused repeatedly to consent to a genetic analysis. Another limitation is that the patient's protein intake during refeeding is not indicated in her files. However, measurement of plasma amino acids was performed at the post-absorptive state; therefore, protein intake did not affect the plasma amino acids pattern [28]. A third limitation is that we were unable to obtain a plasma aminoacidogram at discharge.

To sum up, OTC deficiency was masked in this case by hypoaminoacidemia and the relative normalization of amino acids levels with spontaneous refeeding, associated with persistent low citrulline and arginine levels, have revealed this urea cycle disorder. In conjunction with the amino acid profile, urinary orotate elevation, though unspecific, and hyperammonemia highlighted this potential OTC deficiency.

This form of enzyme deficiency, unsuspected before pregnancy, was revealed by stress factors – such as pregnancy itself, infection, uncontrollable vomiting, psychiatric syndromes – and was masked by malnutrition. However, this metabolic disease, revealed by aminoacidogram and urine orotic acid analysis, fortunately did not prevent a successful pregnancy.

Table 5
Biological nutritional assessment at 31 GW.

	Level	Reference range
Albuminemia	**22 g/L**	35–52 g/L
Transthyretinemia	**0.10 g/L**	0.20–0.40 g/L
CRP	**40 mg/L**	<5 mg/L

Bold characters correspond to pathological values.

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