Misdiagnosed Postpartum Psychosis Revealing a Late-Onset Urea Cycle Disorder

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Case Presentation

"Mrs. G," a 35-year-old married mother of three healthy children, including a newborn, was referred to the inpatient obstetric unit for management of an acute onset of fever. She had been diagnosed as having postpartum psychosis and had been hospitalized on the psychiatric unit for the past 16 days after a postpartum psychotic episode.

Mrs. G previously worked as a journalist but had been unemployed for several years. Her medical history was marked by two similar episodes of agitation, confusion, and mystic delusions starting on day 3 after each delivery, which required her immediate transfer to a psychiatric hospital and treatment with antipsychotic medication. The outcome of each episode was favorable, with a weaning from antipsychotics within 4 to 6 weeks postpartum and no psychiatric symptoms between episodes. Mrs. G reported no medical family history and denied use of alcohol, tobacco, or other drugs. The current episode began suddenly on postpartum day 3. Although midwives initially reported only an anticipatory anxiety focused on the possible recurrence of postpartum psychosis, by midday they noticed an increased level of anxiety and a mild obnubilation (mental clouding). Within hours, Mrs. G became confused, agitated, and violent, and verbal contact with her quickly became impossible as she aimlessly shouted her husband's name while trying to leave her room. After placement of physical restraints and an intramuscular injection of loxapine (100 mg), the patient was immediately transferred to a psychiatric hospital. Initial medical reports indicated normal results on physical examination and laboratory tests (complete electrolyte panel, CBC, liver function tests, and ECG).

On postpartum day 16, Mrs. G presented with fever (40°C [104°F]) and leukorrhea. Endometritis was sus-pected. On readmission to the obstetric ward, her treatment included risperidone (2 mg/day), alprazolam (1.5 mg/day), the phenothiazine antipsychotic cyamemazine (62.5 mg/day), and the anticholinergic tropatepine (10 mg/day). Antibiotic treatment was started to treat a possible infection.

Unlike in her previous postpartum episodes, Mrs. G's mental status responded only partially to antipsychotic treatment. A liaison psychiatry consultation was requested. The liaison psychiatrist found a mildly agitated and disoriented young woman who had wet herself and was circling around her bed. The patient was logorrheic, and her speech, which was mostly incoherent, revealed memory impairment. Strikingly, this mild state of confusion fluctuated during the interview, confirming midwives' reports of hourly changes in the patient's behavior. Mrs. G anxiously expressed feelings of guilt toward her newborn and the belief that her diagnosis of postpartum psychosis made her less able to take care of her children. She displayed no anger toward her children and no ideas of persecution, infanticide, or suicide. She also expressed the belief that "God talks to humankind through premonitory dreams or providential meetings," a claim that had previously been interpreted as a mystic delusion. However, it appeared that this view was part of her cultural and religious background, as was later confirmed by her husband, who reported that she had held this belief for a long time and that it was shared by her relatives.

Overall, Mrs. G was more confused and less delusional than one would have expected in a typical postpartum psychosis. Puzzled by this clinical picture, the psychiatrist reconsidered the diagnosis of postpartum psychosis and extended his examination to assess the differential diagnosis. He found that Mrs. G had chronic headaches and a habitual reluctance to consume meat. His clinical examination revealed little; the patient had a well-tolerated fever, stable blood pressure and pulse, and no signs of severe sepsis. A neurological examination was unremarkable. The psychiatrist ordered immediate blood tests, including ammonia levels.

Within an hour, hyperammonemia was confirmed (224 µmol/liter, controls <50 µmol/liter), along with a respiratory alkalosis and a marked inflammatory syndrome. Results of liver function tests, as well as all the other blood tests, were normal. The psychiatrist contacted the internal medicine fellow, who confirmed the need for an immediate multidisciplinary management of a probable late-onset urea cycle disorder. He decided to transfer the patient to the intensive care unit (ICU), despite the reluctance of the obstetrical team, who felt that the patient should instead be in a secure psychiatric facility. In the ICU, an etiologic treatment of urea cycle disorder-induced hyperammonemia was immediately started un-

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der the guidance of a metabolic physician. It combined intravenous sodium benzoate, sodium phenylbutyrate (each at a loading dose of 10 g, then 2 g five times per day), citrulline (2 g five times per day), and protein-free hypercaloric nutrition delivered through a nasogastric tube. Antibiotic treatment was continued with co-amoxiclav (amoxicillin trihydrate and potassium clavulanate), and the differential diagnosis workup was completed. CT imaging of the brain was unremarkable. Blood and CSF cultures were sterile. During the night, the patient's neuropsychiatric status improved in conjunction with a drop in her ammonia level (her ammonia level fell to 64 µmol/liter the day after initiation of treatment and to 19 µmol/liter the following day). The diagnosis of urea cycle disorder was substantiated by plasma amino acid chromatography showing high glutamine-glutamate and low citrulline concentrations.

Within 5 days, this treatment yielded a complete and stable normalization of both Mrs. G's neuropsychiatric status and her ammonia plasma level. Weaned from antipsychotics and asymptomatic, she was discharged 13 days after the diagnosis of urea cycle disorder was made, with instructions for a protein-restricted diet and prescriptions for oral sodium benzoate, sodium phenylbutyrate, and citrulline. The diagnosis of urea cycle disorder was secondarily confirmed by molecular analysis. Ornithine transcarbamylase and N-acetyl glutamate synthase deficiency were ruled out. Carbamyl phosphate synthase (CPS) gene analysis found two mutations (p.P87S and p.R803C), confirming CPS1 deficiency.

Six months after discharge, Mrs. G remained free of psychiatric symptoms on a regimen of sodium benzoate, sodium phenylbutyrate, and citrulline (each at 2 g three times per day). Her cerebral MRI was unremarkable. However, neuropsychological tests revealed an IQ in the lower normal range (verbal IQ=77, performance IQ=84), restricted working memory, and mild attention deficit, which contrasted with the fact that she had worked as a journalist several years ago. Further investigations of Mrs. G's family history revealed that her mother had 11 pregnancies with six miscarriages. One boy died unexpectedly at 2 days of life and one girl died at age 4 after measles. Mrs. G's sister also had a postpartum acute confusion, and her brother, who is also reluctant to eat meat, had several episodes of acute ataxia associated with strange behaviors.

Postpartum Psychosis: Avoiding Diagnostic Pitfalls

The typical presentation of postpartum psychosis is a complex mixture of mood disorders (ranging from mania to depression), psychotic symptoms, and confusion, usually occurring within the first 2 weeks after delivery. Baby-related delusions of persecution are common and underlie homicidal and suicidal ideation, although Schneiderian symptoms, such as thought broadcasting, feeling of being controlled by outside forces, and imperative auditory hallucinations, may be present. Switches between mood states are frequent, sometimes presenting as severe mood lability. Cognitive impairments associated with confusion lead to memory and attention impairments, an inability to maintain a coherent stream of thought or actions, distractibility, and disorientation. Finally, a personal or family history of postpartum psychosis or postpartum bipolar disorder is strongly suggestive of the diagnosis (1).

However, the postpartum period is also associated with an elevated risk for numerous medical conditions that may be misdiagnosed as postpartum psychosis: bromocriptine side effects, postpartum thyroiditis, acute porphyria, stroke, central venous thrombosis, meningioma, and hyperammonemia induced by a late-onset urea cycle disorder have all been reported (2–6). Meticulous interviewing and examination are critical in the differential diagnostic process for postpartum psychosis, as they may reveal atypical features that should direct the psychiatrist's attention toward another diagnosis (6). In the case of Mrs. G, atypical features led the psychiatrist to doubt previous reports of mystical delusions and the diagnosis of postpartum psychosis, to critically assess causes of postpartum confusion with headaches, and to gather key information that suggested a urea cycle disorder.

A review of published reports of late-onset urea cycle disorders revealed by psychiatric symptoms outlines some common features among the clinical cases available (3–5). In the context of postpartum onset, the patient generally becomes confused 2–4 days after delivery. Confusion becomes more severe within hours, is associated with aggressive behaviors, and may evolve to coma (5). Delusions, sensorium distortions, and cognitive impairments reflect a state of delirium and do not fit well with the typical psychiatric symptomatology of postpartum psychosis. Similar puerperal episodes are likely to be found in the patient's personal or family history and may have been misdiagnosed or gone unnoticed (3). Symptoms associated with cerebral hypertension, although not constant, must always be assessed because of their value in helping to substantiate the diagnosis and to assess the level of urgency of transfer to an ICU (headache, nausea and vomiting, or ocular paresis) (4).

Urea Cycle Disorders: Definition and Physiopathology

The urea cycle disorders that are due to an enzymatic defect include six inherited metabolic diseases (Table 1) with an estimated overall prevalence of about 1/8,200 (7). Each disease corresponds to genetic defects in one of the six genes coding the enzymes of the urea cycle (8). About half of urea cycle disorders are diagnosed within the first month of life. These early-onset urea cycle disorders are associated with complete enzyme deficiency and are characterized by poor feeding, vomiting, irritability, tachypnea, and lethargy or coma (9). Late-onset urea cycle disorders, by contrast, are associated with partial enzyme deficiencies and usually are asymptomatic or evolve chronically with mild symptoms until a first acute hyperammonemic

TABLE 1. Main Characteristics of Urea Cycle Defects

Defective Enzyme and Disease Name	Estimated Prevalence	Gene, Locus, and Genetic Transmission	Plasma Quantitative Amino Acid Analysis and Urinary Orotic Acid Measure
N-acetyl glutamate synthase (NAGS); NAGS deficiency	Unknown (rare)	NAGS; 17q21.31; autosomal recessive	Elevated glutamine-alanine, low citrulline-arginine; normal urinary orotic acid
Carbamyl phosphate synthetase 1 (CPS1); CPS1 deficiency	1/62,000	CPS1; 2q35; autosomal recessive	Elevated glutamine-alanine, low citrulline-arginine; normal urinary orotic acid
Ornithine transcarbamylase (OTC); OTC deficiency	1/14,000	OTC; Xp21.1; X-linked	Elevated glutamine-alanine, low citrulline-arginine; markedly elevated urinary orotic acid
Argininosuccinic acid synthetase (ASS); ASS deficiency or citrullinemia	1/57,000	ASS; 9q34.1; autosomal recessive	Elevated glutamine-alanine, markedly elevated citrulline, normal or low arginine; elevated urinary orotic acid
Argininosuccinic acid lyase (ASL); ASL deficiency or argininosuccinic aciduria	1/70,000	ASL; 7q11.21; autosomal recessive	Elevated glutamine-alanine, elevated citrulline, markedly elevated argininosuccinic acid, low arginine; elevated urinary orotic acid
Arginase (ARG); ARG deficiency or argininemia	1/350,000	ARG1; 6q23.2; autosomal recessive	Markedly elevated arginine; elevated urinary orotic acid

episode is triggered, which can occur at any time in the patient's life, from the first months of life to age 60 (9, 10).

The urea cycle's main function is to produce urea from ammonia through a sequence of biochemical reactions. Under physiological conditions, a tightly regulated balance between ammonia production and degradation maintains plasma levels under 35 μmol/liter (9). Ammonia comes mainly from protein digestion, through either amino acid deamination or bacterial metabolism in the digestive tract and is degraded in the liver through the urea cycle and then excreted in urine (11). Another key organ of ammonia homeostasis is the kidney, which adjusts its own ammonia production and urinary ammonia excretion in response to changes in plasma ammonia concentration (11).

An enzymatic defect at any point in the urea cycle will result in a deficit in all the metabolites downstream from the blockade and an accumulation of all the metabolites upstream from the blockade (Table 1) (7). Ammonia and glutamine plasma levels are always elevated, irrespective of the specific enzymatic defect involved, as they are the first metabolites of the urea cycle. Thus, measuring the plasma ammonia level effectively screens for all urea cycle disorders (8). In the setting of acute hyperammonemia, the brain contributes to ammonia homeostasis by converting ammonia to glutamine. However, ammonia detoxification by the brain hijacks a neurotransmitter synthesis pathway, which disrupts astrocyte/neuron metabolic coupling, leading to astrocyte loss by osmotic cell swelling and apoptosis (11, 12). This astrocyte loss results in seizures, cerebral edema, intracranial hypertension, brainstem herniation, and eventually death (11, 12).

By contrast, hyperammonemia-induced neuropsychiatric symptoms, especially those seen in patients with late-onset urea cycle disorders, are still poorly understood and may involve NMDA and AMPA receptors (12).

Clinical Course of Late-Onset Urea Cycle Disorders

Late-onset urea cycle disorders are either asymptomatic or mildly symptomatic outside acute hyperammonemic episodes (13, 14). Because symptoms, when present, are subtle, nonspecific, and often misattributed to neurological or psychiatric pathologies, diagnosis of a urea cycle disorder during the chronic phase is difficult and delayed (14, 15). The clinical presentation includes neurological, digestive, and psychiatric symptoms, isolated or in association, on a chronic, acute, or mixed course, as illustrated in Table 1 (3–5, 13–19).

In late-onset urea cycle disorders, hyperammonemia occurs whenever there are acute stresses on the balance between the urea cycle's inputs and outputs (11). Acute variations in metabolic demand burden a partially deficient urea cycle. Its functional capacity is exceeded, resulting in acute ammonia accumulation. Thus, all instances of higher protein intakes (initiation of enteral or parenteral nutrition, gastrointestinal bleeding, changes in medication regimen) and hypercatabolic stresses (pregnancy, childbirth, trauma, surgery, sepsis, unusual physical activity) can potentially trigger hyperammonemic episodes. However, the most common triggers of acute hyperammonemia are diet changes and infections (8). It is noteworthy that even minor infections can cause decompensation in

Clinical Picture, Illustrated by Selected Case Reports

Case: a 12-year-old boy with acute headache, vomiting, and confusion, then coma; previous history of attention deficits, learning disabilities, anxiety, and irritability with misdiagnosis of psychosis; ammonia level on diagnosis, 350 µmol/liter (13)

Case: a 41-year-old woman with subacute confusion, headache, and ataxia, then coma during pregnancy; previous recurrent headaches, confusion, and "strange behavior" with discussed diagnoses of migraine with seizure or psychiatric causes; self-selected low-protein diet; ammonia level on diagnosis, 520 µmol/liter (14). Case: a 26-year-old woman with postpartum (day 1) acute disorientation and agitation, then coma and death; previous history of self-selected meat restriction and misdiagnosis of "complex partial seizures"; ammonia level on diagnosis, 1,000 µmol/liter (15)

Case: an 8-year-old girl with acute confusion, blindness, vomiting, then coma with pyramidal tract signs; previous admission in psychiatric hospital for personality disorders and possible psychosis; ammonia level on diagnosis, 239 µmol/liter, then 1,270 µmol/liter (16). Case: a 20-year-old woman with acute delirium hospitalized in the psychiatric unit; disorientation, lethargy, hypotonia, and walking difficulties, then seizures and coma; previous headaches, recurrent vomiting, vegetarian diet; ammonia level on diagnosis, 510 µmol/liter (17). Case: a 28-year-old woman with postpartum (day 3) acute mental status change with emesis, headache, confusion, lethargy, delirium, decorticate and decerebrate posturing, and delirium, then coma; previous history of "pseudoseizures" and behavioral problems; anorexia for meat; ammonia level on diagnosis, 180 µmol/liter (4)

Case: an adult woman with postpartum (day 2) acute confusion and lethargy; previous misdiagnosis of postpartum psychosis, then coma; ammonia level on diagnosis, 422 µmol/liter (3). Case: a 31-year-old woman with postpartum (day 4) headaches, dizziness, and disorientation, initially misdiagnosed as postpartum depression; then generalized tonic seizures and coma; ammonia level on diagnosis (day 14), 800 µmol/liter (5)

Case: a 49-year-old woman with ataxia and tremor; previous schizophrenia (since age 26) and mental retardation (18)

Case: an 11-year-old girl with somnolence and confusion; previous history of learning disabilities, spastic diplegia, vomiting, and self-selected low-protein diet (19)

late-onset urea cycle disorders. Finally, it is crucial to emphasize that valproates—which are widely used as mood stabilizers—are likely to trigger acute hyperammonemia at treatment initiation in patients with an underlying urea cycle disorder (10).

Acute episodes of a late-onset urea cycle disorder can resolve spontaneously or lead to death within hours (3, 15). Epidemiological data are lacking to assess mortality rate and prognostic factors. However, misdiagnosis and delayed treatment of an acute urea cycle disorder-related hyperammonemic coma seem to be associated with an unfavorable outcome (15, 17). Among surviving patients, some will be symptom free (4, 14) and others will have sequelae such as ataxia (3) and deficiencies in memory, understanding, and expression (17). Recurrent symptomatic hyperammonemia episodes associated with nonoptimal disease control appear to underlie neurocognitive sequelae (8), which underscores the need for long-term, standardized, multidisciplinary management for patients with urea cycle disorders (20).

Conclusions

Hyperammonemia is a life-threatening complication revealing a late-onset urea cycle disorder. Because the postpartum period is a clearly identified trigger for late-onset hyperammonemia related to a urea cycle disorder, routine monitoring of plasma ammonia levels in women with postpartum psychosis, a severe mood disorder, or delirium is recommended. Multidisciplinary management must be started immediately once hyperammonemia is confirmed.

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Clinical Guidance: Persistent Postpartum Psychosis Because of Unrecognized Urea Cycle Disorder

Fassier et al. describe a woman with apparently persistent postpartum psychosis that was caused by an initially unrecognized genetic deficit in the urea cycle. The biological stress of pregnancy may have brought this indolent condition to symptomatic significance.