



## Psychiatric adult-onset of urea cycle disorders: A case-series



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### ABSTRACT

Adult onset urea cycle disorders (UCD) may present with psychiatric symptoms, occasionally as the initial presentation. We aimed to describe the characteristics of patients presenting with a psychiatric adult-onset of UCDs, to discuss which signs could suggest this diagnosis in such a situation, and to determine which tests should be conducted. A survey of psychiatric symptoms occurring in teenagers or adults with UCD was conducted in 2010 among clinicians involved in the French society for the study of inborn errors of metabolism (SFEIM). Fourteen patients from 14 to 57 years old were reported. Agitation was reported in 10 cases, perseveration in 5, delirium in 4, and disinhibition in 3 cases. Three patients had pre-existing psychiatric symptoms. All patients had neurological symptoms associated with psychiatric symptoms, such as ataxia or dysmetria, psychomotor slowing, seizures, or hallucinations. Fluctuations of consciousness and coma were reported in 9 cases. Digestive symptoms were reported in 7 cases. 9 patients had a personal history suggestive of UCD. The differential diagnoses most frequently considered were exogenous intoxication, non-convulsive status epilepticus, and meningoencephalitis. Hyperammonemia (180–600  $\mu\text{mol/L}$ ) was found in all patients. The outcome was severe: mechanical ventilation was required in 10 patients, 5 patients died, and only 4 patients survived without sequelae. Adult onset UCDs can present with predominant psychiatric symptoms, associated with neurological involvement. These patients, as well as patients presenting with a suspicion of intoxication, must have UCD considered and ammonia measured without delay.

### 1. Introduction

Urea cycle disorders (UCDs) are rare genetic diseases of human metabolism [1,2]. They are usually diagnosed in neonates, but late-onset UCDs have also been reported in children and in adult patients of any ages [3–5]. Late-onset UCDs may be as severe as in neonates, in the form of life-threatening hyperammonemic encephalopathy. Clinical manifestations usually include neurological and gastrointestinal symptoms. Similar to other inborn errors of metabolism [6–10], psychiatric symptoms may also be present at UCD onset, in children as well as in

adults [11–15], and may be at the forefront of acute symptoms [5,7,16,17]. According to the 2012 UCDs guidelines [13], UCD diagnosis should be systematically considered as a differential diagnosis in patients presenting (at any age) with an acute psychiatric disorder [13].

Such psychiatric adult-onsets have only occasionally been described in the medical literature [16,18], and it is not known what are the most frequent psychiatric symptoms associated with UCD, and in which clinical situations a UCD diagnosis should be suspected. The early recognition of psychiatric symptoms suggestive of UCD is fundamental (7), because effective therapies must be started on an emergency basis

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in order to prevent the onset of cerebral edema [13].

This study aimed to describe the clinical and psychiatric characteristics of patients presenting with a psychiatric adult-onset of UCDS, and to discuss other clinical characteristics that could suggest this diagnosis in such a situation, and to determine which clinical and laboratory tests should be conducted to diagnose UCD in these cases.

## 2. Materials and methods

A national retrospective observational study was conducted between January 2010 and December 2010 among the members of the French national society for the study of IEMs (SFEIM). Through an email survey, we asked members to report late-onset UCD cases with psychiatric manifestations. A specific case report form was designed for the study. Inclusion criteria were cases describing a post-pubertal onset of UCD involving psychiatric symptoms, and to have had a clinical assessment by a psychiatrist (or admission in a psychiatric unit). We also selected observations of patients with a past psychiatric history, in whom a triggering factor led to an acute revelation of UCD. Exclusion criteria were patients with hyperammonemic encephalopathy not related to UCD, pre-puberty onsets of UCD, imprecise observations, observations with incomplete biochemical data, observations without psychiatric symptomatology. Cases of patients diagnosed with UCD through family screening were not considered.

Diagnosis criteria for UCD relied on a specific measure of the deficient enzyme or the presence of pathogenic sequence variation(s) in an enzyme of the urea cycle. In the absence of such enzymologic or molecular data, the presence of hyperammonemia at onset along with a consistent amino acid chromatography pattern (AAC) or a proven diagnosis in a close relative with a similar clinical presentation were considered.

### 2.1. Data selection

We extracted the following data: age at diagnosis, gender, occupation, obstetrical history, personal and familial medical history, treatments at onset, presence of dietary eviction, acute psychiatric neurological and digestive symptoms, suspected initial diagnosis, highest ammonia and glutamine, results of AAC, investigations and imaging, therapeutic management and outcome.

### 2.2. Statistical analysis

Descriptive statistics were used. Results are presented as percentages.

## 3. Results

Overall, we collected 19 cases, among which 5 were not included in the study because of pre-pubertal diagnosis ( $n = 1$ ), non-psychiatric symptomatology ( $n = 1$ ), missing data ( $n = 1$ ), or diagnosis of UCD through familial screening ( $n = 2$ ). The remaining 14 cases consisted of 12 ornithine transcarbamylase (OTC, MIM 311250) deficiency and 2 Carbamoyl Phosphate Synthetase 1 (carbamoylphosphate synthetase 1, MIM 237300) deficiency. Among those, two patients with psychiatric manifestations experienced an UCD related hyperammonemic encephalopathy after the introduction of valproate. Data are summarized in Table 1. Among our series, cases 7 and 9 have been previously published as case reports [17,19,20].

### 3.1. Epidemiology

The age at onset ranged from 14.5 to 57 years old (mean 30, SD 13.6).

The two patients with valproate-triggered onsets (no 13 and 14) were diagnosed at 55 years old.

### 3.2. Psychiatric symptoms

All non-valproate patients were described as agitated, or having delirium. Overall, 10 patients (71%) were reported to be agitated, or had to be restrained or sedated. Other symptoms were verbal or motor perseverations or automatisms (5), delirium or nonsense speech (4), delusions (3), behavioural or verbal disinhibition (3) including sexual disinhibition (2), and encopresia (2). One patient with a history of psychiatric symptoms (patient no 3) awoke from a coma with symptoms that included delusions, emotional lability and impulsivity. She later underwent psychiatric assessment: a personality disorder *with histrionic* and schizoid features was diagnosed which responded partially to olanzapine 15 mg and tiapride 200 mg daily.

Patients 13 and 14 had treated bipolar disorder, and a history of alcohol use disorder suicide risk and mood disorder requiring constraint hospitalisation in psychiatry. Both experienced coma after initiation of valproate. Patient 14, for example had been taking 600 mg of valproate daily for 4 months when she was admitted in psychiatry, which was then replaced by valproate 500 mg daily, 3 days before she became comatose.

Psychiatric diagnoses considered by the patients' initial primary care units prior to confirmation of a UCD included anorexia nervosa, major depressive disorder, factitious disorder (Munchausen's syndrome), somatization disorder, and anxiety disorder.

### 3.3. Neurological symptoms

Neurological symptoms were associated with psychiatric symptomatology in all patients. Ataxia or cerebellar symptoms such as dysmetria were reported 5 patients. In patients not sedated, lethargy or slow ideation was reported in 8 patients, evolving towards coma or alternating with agitation. Fluctuating mentation was common, being reported in nine patients (64%). Seizures were reported 5 patients. Coma occurred in 9 (64%) patients. Other neurological symptoms reported were hallucinations (3) language or elocution disorder (5), and mydriasis (4), sometimes occurring before the onset of intracranial hypertension. Asterixis or flapping tremor was not reported.

### 3.4. Gastrointestinal symptoms

Nausea or vomiting was reported in 7 patients. Some of them had been diagnosed as cow's milk protein intolerance during childhood. One of the patients – considered as having anorexia nervosa - (case 10) had severe malnutrition at the time of diagnosis (Body Mass Index 12.4 kg/m<sup>2</sup>).

### 3.5. Medical history

Information about patient's way of life is provided in Table 1. Overall, all patients were autonomous prior to the onset of their urea cycle disorder, and had normal development. Several had cognitively demanding occupations (nurse student, teacher, general practitioner...).

A past history of psychiatric disorder was reported in 7 patients, such as behavioural disorder, episodic or chronic feeding disorders, depression, personality disorder, bipolar psychosis and mood disorder. Two patients (cases 9, 10) had been diagnosed with anorexia nervosa during adolescence. Eight patients had a neurological history such as epilepsy, unexplained coma, ataxic episodes or mental confusion episodes, which in one patient occurred with bulimic episodes. A story of chronic vomiting or nausea, or of "acetonic crisis" was reported in 3 patients. Dietary protein avoidance was reported in 5 patients. One woman had a history of in utero fetal death of a male fetus, other had normal pregnancies.

Familial inquiry revealed a story of peripartum death in the sister of an index case, of deaths tagged as "cerebral aneurysm" in two uncles in

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