Molecular Genetics and Metabolism Reports 12 (2017) 103–109

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

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

Adrien Bigot[a,j,k], Paul Brunault[b,c], Christian Lavigne[d], François Feillet[e], Sylvie Odent[f], Elsa Kaphan[g], Christel Thauvin[h], Vanessa Leguy[i], Pierre Broué[j], Michel C. Tchan[k], François Maillot[a,l,*]

[a] CHRU de Tours, Médecine interne, Tours, France
[b] CHRU de Tours, Clinique Psychiatrique Universitaire, Tours, France
[c] CHRU de Tours, Équipe de Liaison et de Soins en Addictologie, Tours, France
[d] CHRU d'Angers, Service de médecine interne, Angers, France
[e] CHRU de Nancy, Centre de références des maladies héréditaires du métabolisme, Nancy, France
[f] CHRU de Rennes, Service de génétique, Rennes, France
[g] CHRU de Marseille, Service de neurologie, La Timone, Marseille, France
[h] CHRU de Dijon, Service de génétique, Dijon, France
[i] CHRU de Dijon, Service de Médecine Interne, Dijon, France
[j] CHRU de Toulouse, Service de pédiatrie, Toulouse, France
[k] Genetic Medicine, Westmead Hospital, NSW, Australia
[l] Université François-Rabelais, INSERM 1069, Tours, France

ARTICLE INFO

Keywords:
Urea cycle disorders
Ornithine transcarbamylase deficiency
Hyperammonemia
Valproate
Psychiatric decompensations
Late-onset
Adults

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 µmol/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

* Corresponding author at: Service de Médecine Interne, Hopital Bretonneau, 2bd Tonnellé, 37044 Tours CEDEX 9, France.
E-mail address: francois.maillot@univ-tours.fr (F. Maillot).

http://dx.doi.org/10.1016/j.ymgmr.2017.07.001
Received 27 March 2017; Received in revised form 2 July 2017; Accepted 2 July 2017
Available online 06 July 2017

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 bioclinical 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 valpromide 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^2).

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

Table 1
Characteristics of the patients.

N	Sex	Age (yrs)	Way of life	Evocative obstetrical history	Evocative familial history	Evocative psychiatric history	Evocative neurologic history	History evocative of UCD	Acute symptoms	Dietary eviction	Defectuous enzyme	Trigger	Macimal NH3 + / Gln (μmol/L)	Biology	Acute treatment	Outcome
1	M	52	NA		Y	Y	Confusion	Y	Agitation, Stereotypies Hallucinations, Fluctuations	N	CPS1	Infection	715/1062	NTS	Scavengers Precursors MV, HD	DC
2	F	14,5	NA	N	N	N	N	Y	Agitation, Mydriasis, Fluctuations, Vomiting	Y	OTC	N	302/981	NTS Hepatic Alcalosis	Regimen	Favourable
3	F	44	Married Reclusive life	G3P2, IUFD	N	Y	Epilepsy	N	Agitation, Delirium, Hallucinations Ataxia, Fluctuations, Language	N	OTC	enema fasting	276/623	NTS Hepatic	Regimen Scavengers Precursors	Psychiatric follow-up
4	F	20	Nurse student	N	N	N	Epilepsy	Y	Delirium, Stereotypies, Mydriasis, Language, CC, Somnolence, Fluctuations; Vomiting	N	OTC	Infection	180/NA	NTS Hepatic	Regimen	Cognitive sequelae
5	F	23	Seller A-level	N	Y	N	Coma	Y	Agitation, Stereotypies, Coma Vomiting	Y	OTC	Alim. CTCD	267/876	Alcalosis Hepatic	Scavengers Precursors, PTN, HD, MV	Favourable
6	F	57	NA	G4P4	Y	N	Confusion	Y	Agitation, Language, Somnolence, Coma, CC	N	OTC	N	327/NA	NTS	Scavengers Precursors, HD, PTN, MV	Favourable
7	F	20	Student	N	NA	N	Ataxia	Y	Delirium, Language, Ataxia, Somnolence, Coma, Mydriasis, CC; Vomiting	Y	OTC	Infection	510/NA	Alcalosis	Scavengers Precursors, HD, PTN, MV	Cognitive sequelae Epilepsy
8	F	35	Teacher	G2P1	NA	N	N	N	Agitation, Stereotypies, Somnolence, Coma, Mydriasis	N	OTC	Pregnancy	600/1941	NTS Hepatic	Regimen Scavengers, HD Precursors, MV	DC
9	F	23	Student	N	Y	Y	N	Y	Agitation, Hallucinations Ataxia, Fluctuations, Somnolence Vomiting	Y	OTC	Alim.	477/NA	Alcalosis Hepatic	Regimen, Scavengers, Precursors, PTN	Cognitive sequelae
10	M	35	GP, Married		Y	Y	Ataxia	Y	Agitation, Disinhibition, Hallucinations, Somnolence, Coma, Fluctuations	N	OTC	Infection, CTCD	190/1075	NTS	Regimen Scavengers, MV Precursors, PTN	Visual sequelae
11	F	19	Secretary student	N	N	Y	N	N	Agitation, disinhibition, stereotypies, delirium, Coma, fluctuations	N	OTC	Stress	NA/NA	NTS Hepatic	Aspecific, MV	DC
12	F	20	Cashier	N	Y	N	N	Y	Agitation, Disinhibition, Fluctuations, Somnolence, Coma, CC, Language	N	OTC	N	606/1750	NTS	Regimen, HD Scavengers, MV Precursors, PTN	DC
13	M	55	Children		N	Y	N	N	Coma Vomiting	O	OTC	Valproate,	273/351	NA	Scavengers,	DC

(continued on next page)

Table 1 (*continued*)

N	Sex	Age (yrs)	Way of life	Evocative obstetrical history	Evocative familial history	Evocative psychiatric history	Evocative neurologic history	History evocative of UCD	Acute symptoms	Dietary eviction	Defectuous enzyme	Trigger	Macimal NH3 +/ Gln (μmol/L)	Biology	Acute treatment	Outcome
												alim.			Precursors, HD, MV	
14	F	55	Married	NA	N	Y	Epilepsy	N	Language, Ataxia, CC, Coma Vomiting	N	CPS1	Valproate, alcohol	451/609	NTS	Regimen, HD Scavengers, MV Precursors, PTN	Favourable

M: male; F: female; yrs.: years; NA: non-assessed; A-level: graduated French Baccalauréat; G: gravidity; Gln: glutamine; GP: general practitioner; P: parity; IUFD: intrauterine fetal demise of a male fetus; UCD: urea cycle disorder; Y: yes; N:no; language: language disorder; CC: convulsive crisis; CPS1: Carbamoyl Phosphate Synthase 1; OTC: ornithine transcarbamylase; Alim.: exogenous protidic charge; CTCD: corticosteroids; NTS: negative toxicology screening; Hepatic: abnormalities of hepatic enzymes or of haemostasis; Alkalosis: respiratory alkalosis; MV: mechanical ventilation; HD: Haemodialysis; PTN: parenteral nutrition; DC: death.

one case, of unexplained post-surgery coma in the mother in one another case, and of meat avoidance in the daughters in one case. In 2 cases, some members of the family were aware of a metabolic disease in some close relatives. One patient had a female cousin deceased from unexplained encephalopathy.

Overall, 9 patients had a previous personal or familial history suggestive of UCD.

3.6. Triggers

Triggers were reported in 11 patients, including 4 infections such as gastroenteritis, rhinitis, or upper respiratory tract infections. In 2 patients, the use of corticosteroids was reported. In one case, the inaugural coma occurred after an enema in a dehydrated patient. In 2 patients, an unusual amount of protein in a meal was reported shortly before the clinical onset. In one of the patients, β-HCG were positive, but with uterine vacuity suggesting miscarriage. In one case, the only trigger reported was psychological, while the patient was preparing for a school examination; she had similar episodes of agitation and stereotypies previously during periods of stress (exams, death of a relative). In patients 13 and 14 the trigger was the recent introduction of valproate, associated in one patient with a meat meal.

3.7. Investigations

All patients had cerebral imaging. In most patients (10 each), drug screening and lumbar puncture were performed given suspicion of intoxication and/or meningoencephalitis. Non-convulsive status epilepticus was also frequently considered.

Hepatic abnormalities were reported in most patients (8/14): steatosis on imaging, or moderate elevation of liver enzymes were described, contrasting with sometimes (6/14) decreased prothrombin times. Post-mortem hepatic biopsies, performed in 3 cases, showed macro and micro steatosis.

At the time of diagnosis, ammonia was elevated (13/14 cases), with values ranging from 180 to 600 μmol/L. AAC was performed in all but two patients with OTC defect, and were indicative of an underlying UCD (see Fig. 1 for representative results). Glutamine was normal or high in most patients. All three patients with Glutamine over 1000 μmol/L (patients 1, 8, 20) did not survive the acute episode, these patients also all had ammonia > 600 μmol/L. Respiratory alkalosis was reported in 3 patients.

3.8. Diagnosis

Overall, the diagnosis of OTC defect was considered in 11 patients and proven in 10, by enzymatic activity measurement or DNA analysis. In one patient, the diagnosis was obtained retrospectively when her female cousin died from hyperammonemic encephalopathy. The remaining two patients were proven to have a CPS1 defect. Three patients had post mortem liver enzymatic activities measured. Patient 1 (CPS1 activity 0.06, N > 1.84); patient 12 (OTC activity 0.15 μmol/H/mg, N 33.5 ± 9.6), and patient 13 (OTC activity 3.1 μmol/h/mg, N 14–52). These enzymatic activities remained detectable, which is consistent with late onset urea cycle disorders. In patient 13, activity was 10% of mean activity, which is more elevated than in patients 1 and 12 and may account for a valproate induced onset. Despite a very low activity (0.5% of normal), patient 12 experienced late onset OTC deficiency. No inactivation studies were available.

3.9. Treatment and outcome

All but one patient (whose diagnosis was posthumouse) received a high calorie and low protein diet. Sodium phenylbutyrate or sodium benzoate was administered in 9 patients, urea cycle precursors (arginine or citrulline) in 11. Haemodialysis was required in 8/14, and

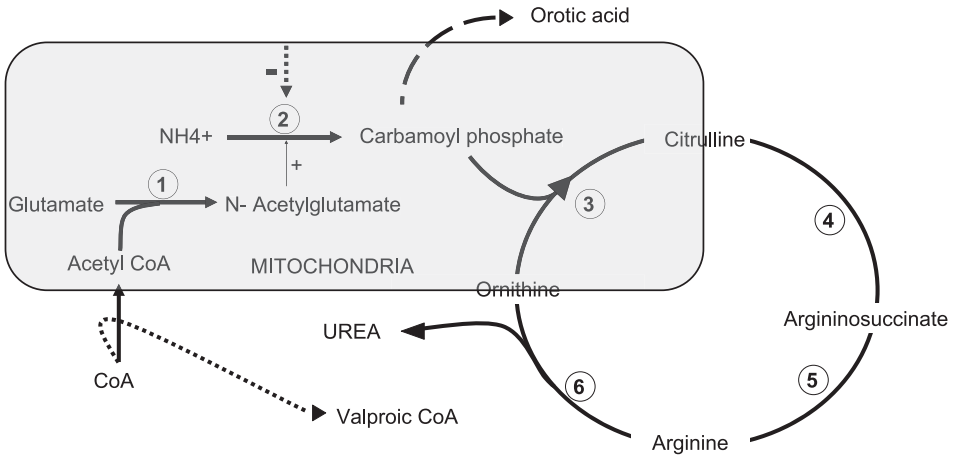

Fig. 1. Urea cycle and related diseases in case of enzymatic defect.
1. *N*-Acétylglutamate Synthase (NAGS) → Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome.
2. Carbamoylphosphate Synthetase 1 (CPS1).
3. Ornithine transcarbamylase (OTC).
4. Argininosuccinate Synthetase (ASS) → Type 2 Citrullinemia.
5. Argininosuccinate Lyase (ASL) → Argininosuccinic aciduria.
6. Arginase.
▬▬▬▶ Valproate interferences with urea cycle.
▬ ▬▶ Pyrimidine synthesis alternate metabolic pathway.

mechanical ventilation in 9/14 patients.

Mortality was high, with 5 patients dying. Survival without sequelae was reported in 4 patients. Cognitive (n = 3), visual (n = 1), or neurological (epilepsy, n = 1) sequelae were frequent in survivors. One patient (no 3) required psychiatric follow up.

4. Discussion

In the present study, we report 14 cases of adult onset UCD presenting with psychiatric symptoms. A multitude of psychiatric symptoms have been reported in children as well as in adults in the literature [13], such as features suggestive of psychotic disorder or schizophrenia [6,7,9]. However, in this series, the heterogeneous clinical presentation frequently misled the physicians in charge, thus delaying the diagnosis. The outcomes were severe, with only 4 patients surviving without sequelae. As the prognosis of acute UCD is linked to the extent and to the duration of hyperammonemia [13,14], an earlier diagnosis is therefore essential.

Most of the psychiatric symptomatology was non-specific in our series. In keeping with previous reports [5,21–24] agitation and perseveration or automatism were the most frequently reported signs. Delirium was also reported in several patients. Unexpectedly, behavioural disinhibition, sometimes under the form of encopresia, was reported in 3 patients. Numerous reports of UCDs masquerading as post-partum psychosis [16,18,25,26], none of our patients was misdiagnosed as such. On the other hand, in keeping with previous reports (7, 24), spontaneous protein restriction and vomiting episodes were suggestive of anorexia nervosa in two of our patients. Psychiatric symptoms could have the same physiopathological basis as cognitive abnormalities in UCDs, including ammonia and glutamine toxicity, as well as neurotransmitters abnormalities [27].

Of note, the association of neurologic with psychiatric symptoms was very evocative, as all patients experienced various neurologic symptoms ranging from confusion to coma, with frequently reported ataxia, dysarthria or seizures. Those symptoms have regularly been described in adult-onset UCDs [21,25,28]. Of note, neither asterixis nor flapping tremor was reported in this series of patients. Therefore, its absence on clinical examination in the psychiatric setting should not rule out hyperammonemic encephalopathy. Fluctuations of consciousness or the alternance of somnolence with agitation were reported in most patients. To our knowledge, these variations in consciousness are not described in the literature. The selection of patients with psychiatric symptoms may have induced a recruitment bias by selecting, among encephalopathic patients, those more susceptible to be agitated, raising the need for a psychiatric evaluation. Nevertheless, we believe fluctuations of consciousness in a psychiatric setting should urgently lead to screening for UCD. Finally, it is interesting to highlight that besides the exclusion of infectious, vascular or neoplastic causes to the clinical features presented, the vast majority of our patients had toxicology screening at some point. This indicates that in trained physicians, the picture of an acute psychiatric UCD can be evocative of intoxication. We strongly recommend, in keeping with international guidelines [13], that in unexplained intoxication presentations an endogenous intoxication (i.e. metabolic diseases) should be considered in the same timeframe as usual toxicology screening.

Apart from the aforementioned, other clinical features should also prompt a metabolic screening. Overall, the vast majority of our patients had a personal or familial history suggestive of UCD, or a diet restricted in protein [29], which underlines the crucial importance of a full clinical history in these situations. Additionally, the identification of a trigger to the episode can be strongly evocative of a metabolic condition.

These triggers cluster in 3 categories. The first is an exogenous protein load, which can be nosocomial during artificial nutrition [30,31]. The second are hypercatabolic states such as infections, fasting, corticosteroids, pregnancy or surgery [21,32]. Pregnancy is a classical trigger to late-onset UCDs [16,18,25]. Here, one of our patients had likely undergone recent miscarriage (no 8: positive β HCG and uterine vacuity), while another had psychiatric troubles which had started after her first pregnancy. The third trigger is valproate-induced hyperammonemia [22], due to the inhibition of the urea cycle (Fig. 1). Of note, some other drugs such as PEG-asparaginase can trigger hyperammonemic decompensations [13]. Finally, we also report here a hyperammonemic crisis seemingly triggered by psychological stress. This trigger has been rarely described in adult-onset UCD [22,33].

Once an acute decompensation of a UCD has been suggested, an ammonia should be taken without delay, and seems to have an excellent predictive value [13], both positive and negative, for acute onsets of UCD. Ammonia should be taken on Lithium Heparin, put immediately on ice and processed as soon as possible [34], in the same timeframe as the exclusion of more frequent diagnosis such as cerebrovascular causes or encephalitis. Cerebral CT scanner and MRI are usually normal until the onset of cerebral oedema; respiratory alkalosis may be observed on blood gas. Interestingly, the majority of our patients had elevated hepatic enzymes, with sometimes lowering of PT. Consistent with our data, UCDs are currently thought to be associated to several chronic and acute hepatic diseases [13,35–38]. In any case, acute liver failure and low PT should not rule out acute-onset UCD.

Overall, psychiatric late-onset UCD are rare, and their clinical variability frequently leads to delayed diagnosis and treatment, with possible dramatic consequences. Some elements of the clinical picture are suggestive and may raise a suspicion of the correct diagnosis. The psychiatric symptoms are non-specific, but usually include agitation and stereotypic behaviour. Aggressiveness, visual hallucinations, delirium or disinhibition can also be part of the picture. A personal or familial history of specific diet restrictions, inebriation-like, confusional

or cyclic digestive disorders episodes, as well as unexplained coma should trigger the suspicion of a UCD. Triggers such as exogenous protein load, hypercatabolic states stress or recent valproate introduction are also strongly evocative. The clinical presentation is usually atypical, but some elements are suggestive, particularly the association of psychiatric symptoms with neurologic symptoms.

Once raised the possibility of a UCD, it should be immediately assessed by measuring a blood ammonia. If elevated, specialised metabolic advice should be seeked and treatment should be started without delay [13]. Suggested care for adult-onset UCD are summarized.

Our study has some strengths and limitations. First, this is to the best of our knowledge the first series to date investigating psychiatric adult-onset UCDs to date. A key message is that all patients had neurological signs associated to psychiatric symptoms. All psychiatric patients presenting neurological signs should have a thorough clinical examination and a workout including ammonia. Second, we have shown that psychiatric presentations of late onset UCDs are as severe if not worse as non-psychiatric onsets or childhood onsets. This severity makes it essential to evoke the diagnosis precociously. Third, some of the cases reported in this study raise the possibility of chronic psychiatric manifestations in adults, together with other reports from the medical literature [39–42] suggests the hypothesis of psychiatric chronic expression of UCDs, which should be taken into account when valproate therapy is considered. Fourth, the fact that a vast majority of patients were screened for drugs should raise the possibility to include ammonia in toxicology screenings in emergency or psychiatry departments. Our study has some limitations, the principal being its retrospective case series design. However, in the absence of Case Report Forms, the clinical elements written down in medical notes were spontaneously considered as relevant by physicians unaware of a metabolic condition at the time of the decompensation. Therefore we think they should be relied on when raising awareness of UCDs in emergency and psychiatry physicians. Another bias is the small number of observations that were gathered. Therefore, generalization of these results will need to be comforted by other studies. Particularly, the constant association to neurological signs may have resulted from a selection bias, and could only be confirmed by prospective screenings in adult psychiatry emergency departments. Third, there was missing data in the notes we gathered. Therefore, IQ, neuropsychological assessments, relevant psychiatric scales could not be provided, and future study should focus on these gaps.

5. Conclusions

The present study underlines the ability of late-onset UCDs to mimic psychiatric diseases, always associated with neurological symptoms. The association of neurological or digestive signs with an atypical psychiatric picture should raise the diagnosis of UCD, especially when a trigger is highlighted. A familial history or a specific diet can also be suggestive of UCD. In this situation, ammonia should be measured and treatment started without delay, to prevent the onset of cerebral edema and further neurological damage.

Disclosures/competing interests

The authors declare no competing interests.

Acknowledgements

Contributorship statement: FM and AB designed the study and collected the data, AB wrote the manuscript. PB, FM and MT reviewed the manuscript. FM, CL, PK, SO, EK, CT, VL, PB provided scientific data for the study. CL, SO, EK, CT, VL, PB approved the final version.

Guarantor author: Pr. François Maillot

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics: Given the methodology of retrospective extraction of data from paper files exclusively, no consent or ethics approval was required under French Law.

References

[1] F. Maillot, H. Blasco, B. Lioger, A. Bigot, C. Douillard, Diagnosis and treatment of urea cycle disorders in adult patients, Rev. Med. Interne 37 (2016) 680–684, http://dx.doi.org/10.1016/j.revmed.2016.02.011.

[2] M.L. Summar, S. Koelker, D. Freedenberg, C. Le Mons, J. Haberle, H.-S. Lee, B. Kirmse, European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD). Electronic address: http://www.e-imd.org/en/index.phtml, Members of the Urea Cycle Disorders Consortium (UCDC). Electronic address: http://rarediseasesnetwork.epi.usf.edu/ucdc/, The incidence of urea cycle disorders, Mol. Genet. Metab. 110 (2013) 179–180, http://dx.doi.org/10.1016/j.ymgme.2013.07.008.

[3] M. Yazaki, M. Kinoshita, S. Ogawa, S. Fujimi, A. Matsushima, A. Hineno, K. Tazawa, K. Fukushima, R. Kimura, M. Yanagida, H. Matsunaga, T. Saheki, S. Ikeda, A 73-year-old patient with adult-onset type II citrullinemia successfully treated by sodium pyruvate and arginine, Clin. Neurol. Neurosurg. 115 (2013) 1542–1545, http://dx.doi.org/10.1016/j.clineuro.2012.12.027.

[4] T. Rohininath, D.J. Costello, T. Lynch, A. Monavari, M. Tuchman, E.P. Treacy, Fatal presentation of ornithine transcarbamylase deficiency in a 62-year-old man and family studies, J. Inherit. Metab. Dis. 27 (2004) 285–288.

[5] M.C. Nassogne, B. Héron, G. Touati, D. Rabier, J.M. Saudubray, Urea cycle defects: management and outcome, J. Inherit. Metab. Dis. 28 (2005) 407–414, http://dx.doi.org/10.1007/s10545-005-0303-7.

[6] M. Walterfang, O. Bonnot, R. Mocellin, D. Velakoulis, The neuropsychiatry of inborn errors of metabolism, J. Inherit. Metab. Dis. 36 (2013) 687–702, http://dx.doi.org/10.1007/s10545-013-9618-y.

[7] C. Demily, F. Sedel, Psychiatric manifestations of treatable hereditary metabolic disorders in adults, Ann. General Psychiatry 13 (2014) 27, http://dx.doi.org/10.1186/s12991-014-0027-x.

[8] O. Bonnot, H.H. Klünemann, F. Sedel, S. Tordjman, D. Cohen, M. Walterfang, Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: a systematic review, Orphanet J. Rare Dis. 9 (2014) 65, http://dx.doi.org/10.1186/1750-1172-9-65.

[9] O. Bonnot, P.M. Herrera, S. Tordjman, M. Walterfang, Secondary psychosis induced by metabolic disorders, Front. Neurosci. 9 (2015), http://dx.doi.org/10.3389/fnins.2015.00177.

[10] S. Nia, Psychiatric signs and symptoms in treatable inborn errors of metabolism, J. Neurol. 261 (Suppl. 2) (2014) S559–S568, http://dx.doi.org/10.1007/s00415-014-7396-6.

[11] I. Görker, Ü. Tüzün, Autistic-like findings associated with a urea cycle disorder in a 4-year-old girl, J. Psychiatry Neurosci. 30 (2005) 133–135.

[12] M. Serrano, C. Martins, B. Pérez-Dueñas, L. Gómez-López, E. Murgui, C. Fons, A. García-Cazorla, R. Artuch, F. Jara, J.A. Arranz, J. Häberle, P. Briones, J. Campistol, M. Pineda, M.A. Vilaseca, Neuropsychiatric manifestations in late-onset urea cycle disorder patients, J. Child Neurol. 25 (2010) 352–358, http://dx.doi.org/10.1177/0883073809340696.

[13] J. Haberle, N. Boddaert, A. Burlina, A. Chakrapani, M. Dixon, M. Huemer, D. Karall, D. Martinelli, P.S. Crespo, R. Santer, A. Servais, V. Valayannopoulos, M. Lindner, V. Rubio, C. Dionisi-Vici, Suggested guidelines for the diagnosis and management of urea cycle disorders, Orphanet J. Rare Dis. 7 (2012) 32, http://dx.doi.org/10.1186/1750-1172-7-32.

[14] H.A. Sloas 3rd, T.C. Ence, D.R. Mendez, A.T. Cruz, At the intersection of toxicology, psychiatry, and genetics: a diagnosis of ornithine transcarbamylase deficiency, Am. J. Emerg. Med. 31 (2013) 1420e5–6, , , http://dx.doi.org/10.1016/j.ajem.2013.05.010.

[15] S. Kölker, V. Valayannopoulos, A.B. Burlina, J. Sykut-Cegielska, F.A. Wijburg, E.L. Teles, J. Zeman, C. Dionisi-Vici, I. Barić, D. Karall, J.-B. Arnoux, P. Avram, M.R. Baumgartner, J. Blasco-Alonso, S.P.N. Boy, M.B. Rasmussen, P. Burgard, B. Chabrol, A. Chakrapani, K. Chapman, E. Cortès, I. Saladelafont, M.L. Couce, L. de Meirleir, D. Dobbelaere, F. Furlan, F. Gleich, M.J. González, W. Gradowska, S. Grünewald, T. Honzik, F. Hörster, H. Ioannou, A. Jalan, J. Häberle, G. Haege, E. Langereis, P. de Lonlay, D. Martinelli, S. Matsumoto, C. Mühlhausen, E. Murphy, H.O. de Baulny, C. Ortez, C.C. Pedrón, G. Pintos-Morell, L. Pena-Quintana, D.P. Ramadža, E. Rodrigues, S. Scholl-Bürgi, E. Sokal, M.L. Summar, N. Thompson, R. Vara, I.V. Pinera, J.H. Walter, M. Williams, A.M. Lund, A. Garcia Cazorla, The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype, J. Inherit. Metab. Dis. 38 (2015) 1059–1074, http://dx.doi.org/10.1007/s10545-015-9840-x.

[16] G.M. Enns, W.E. O'Brien, K. Kobayashi, H. Shinzawa, J.E. Pellegrino, Postpartum “psychosis” in mild argininosuccinate synthetase deficiency, Obstet. Gynecol. 105 (2005) 1244–1246, http://dx.doi.org/10.1097/01.AOG.0000157769.90230.24.

[17] D. Brajon, P. Carassou, L. Pruna, F. Feillet, P. Kaminsky, Ornithine transcarbamylase deficiency in adult, Rev. Médecine Interne Fondée Par Société Natl. Francaise Médecine Interne. 31 (2010) 709–711, http://dx.doi.org/10.1016/j.revmed.2010.02.008.

[18] T. Fassier, N. Guffon, C. Acquaviva, T. D'Amato, D.V. Durand, P. Domenech, Misdiagnosed postpartum psychosis revealing a late-onset urea cycle disorder, Am. J. Psychiatry 168 (2011) 576–580, http://dx.doi.org/10.1176/appi.ajp.2010.10071032.

[19] A. Legras, F. Labarthe, F. Maillot, M.-A. Garrigue, A. Kouatchet, H. Ogier de Baulny,

Late diagnosis of ornithine transcarbamylase defect in three related female patients: polymorphic presentations, Crit. Care Med. 30 (2002) 241–244.
[20] S. Rimbaux, C. Hommet, D. Perrier, J. Cottier, A. Legras, F. Labarthe, L. Lemarcis, A. Autret, F. Maillot, Adult onset ornithine transcarbamylase deficiency: an unusual cause of semantic disorders, J. Neurol. Neurosurg. Psychiatry 75 (2004) 1073–1075, http://dx.doi.org/10.1136/jnnp.2003.026542.
[21] J. Lien, W.L. Nyhan, B.A. Barshop, Fatal initial adult-onset presentation of urea cycle defect, Arch. Neurol. 64 (2007) 1777–1779, http://dx.doi.org/10.1001/archneur.64.12.1777.
[22] M.L. Summar, D. Dobbelaere, S. Brusilow, B. Lee, Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes, Acta Paediatr. Oslo Nor. 1992 (97) (2008) 1420–1425, http://dx.doi.org/10.1111/j.1651-2227.2008.00952.x.
[23] P.C. Rowe, S.L. Newman, S.W. Brusilow, Natural history of symptomatic partial ornithine transcarbamylase deficiency, N. Engl. J. Med. 314 (1986) 541–547, http://dx.doi.org/10.1056/NEJM198602273140903.
[24] M. Yoshino, J. Nishiyori, F. Yamashita, R. Kumashiro, H. Abe, K. Tanikawa, T. Ohno, K. Nakao, N. Kaku, H. Fukushima, Ornithine transcarbamylase deficiency in male adolescence and adulthood, Enzyme 43 (1990) 160–168.
[25] G. Eather, D. Coman, C. Lander, J. McGill, Carbamyl phosphate synthase deficiency: diagnosed during pregnancy in a 41-year-old, J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas. 13 (2006) 702–706, http://dx.doi.org/10.1016/j.jocn.2005.07.014.
[26] M.C. Tonini, V. Bignamini, M. Mattioli, Headache and neuropsychic disorders in the puerperium: a case report with suspected deficiency of urea cycle enzymes, Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol. 32 (Suppl. 1) (2011) S157–S159, http://dx.doi.org/10.1007/s10072-011-0518-3.
[27] A.L. Gropman, M.L. Batshaw, Cognitive outcome in urea cycle disorders, Mol. Genet. Metab. 81 (Suppl. 1) (2004) S58–S62, http://dx.doi.org/10.1016/j.ymgme.2003.11.016.
[28] P.H. Arn, E.R. Hauser, G.H. Thomas, G. Herman, D. Hess, S.W. Brusilow, Hyperammonemia in women with a mutation at the ornithine carbamoyltransferase locus. A cause of postpartum coma, N. Engl. J. Med. 322 (1990) 1652–1655, http://dx.doi.org/10.1056/NEJM199006073222307.
[29] F. Maillot, P. Crenn, Urea cycle disorders in adult patients, Rev. Neurol. (Paris) 163 (2007) 897–903.
[30] D.M. Felig, S.W. Brusilow, J.L. Boyer, Hyperammonemic coma due to parenteral nutrition in a woman with heterozygous ornithine transcarbamylase deficiency, Gastroenterology 109 (1995) 282–284.
[31] U. Pillai, R. Kahlon, J. Sondheimer, P. Cadnapaphorncai, Z. Bhat, A rare case of hyperammonemia complication of high-protein parenteral nutrition, JPEN J. Parenter. Enteral Nutr. 37 (2013) 134–137, http://dx.doi.org/10.1177/0148607112447815.
[32] W.T. Hu, O.H. Kantarci, J. Merritt IIet al., Ornithine transcarbamylase deficiency presenting as encephalopathy during adulthood following bariatric surgery, Arch. Neurol. 64 (2007) 126–128, http://dx.doi.org/10.1001/archneur.64.1.126.
[33] S. Sakamoto, H. Shinno, M. Ikeda, H. Miyoshi, Y. Nakamura, A patient with type II citrullinemia who developed refractory complex seizure, Gen. Hosp. Psychiatry 35 (2013) 103e1–3, , , http://dx.doi.org/10.1016/j.genhosppsych.2012.03.019.
[34] N. Nikolac, J. Omazic, A.-M. Simundic, The evidence based practice for optimal sample quality for ammonia measurement, Clin. Biochem. 47 (2014) 991–995, http://dx.doi.org/10.1016/j.clinbiochem.2014.05.068.
[35] A. Zimmermann, C. Bachmann, R. Baumgartner, Severe liver fibrosis in arginino-succinic aciduria, Arch. Pathol. Lab. Med. 110 (1986) 136–140.
[36] K. Badizadegan, A.R. Perez-Atayde, Focal glycogenosis of the liver in disorders of ureagenesis: its occurrence and diagnostic significance, Hepatol. Baltim. Md. 26 (1997) 365–373, http://dx.doi.org/10.1002/hep.510260217.
[37] R.C. Gallagher, C. Lam, D. Wong, S. Cederbaum, R.J. Sokol, Significant hepatic involvement in patients with ornithine transcarbamylase deficiency, J. Pediatr. 164 (2014) 720–725e6, , , http://dx.doi.org/10.1016/j.jpeds.2013.12.024.
[38] J.M. Wilson, O.A. Shchelochkov, R.C. Gallagher, M.L. Batshaw, Hepatocellular carcinoma in a research subject with ornithine transcarbamylase deficiency, Mol. Genet. Metab. 105 (2012) 263–265, http://dx.doi.org/10.1016/j.ymgme.2011.10.016.
[39] L. von Wendt, S. Similä, A. Ruokonen, M. Puukka, Argininosuccinic aciduria in a Finnish woman presenting with psychosis and mental retardation, Ann. Clin. Res. 14 (1982) 145–147.
[40] M.Y. Chang, J.T. Fang, Y.C. Chen, C.C. Huang, Continuous venovenous haemofiltration in hyperammonaemic coma of an adult with non-diagnosed partial ornithine transcarbamylase deficiency, Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc. 14 (1999) 1282–1284.
[41] C. Largillière, Psychiatric manifestations in girl with ornithine transcarbamylase deficiency, Lancet 345 (1995) 1113.
[42] M.J. Blans, P.E. Vos, H.J. Faber, G.H. Boers, Coma in a young anorexic woman, Lancet 357 (2001) 1944, http://dx.doi.org/10.1016/S0140-6736(00)05067-4.