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ORIGINAL ARTICLE

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Adult-onset diagnosis of urea cycle disorders: Results of a French cohort of 71 patients

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Abstract

Urea cycle disorders (UCD) are rare diseases that usually affect neonates or young children. During decompensations, hyperammonemia is neurotoxic, leading to severe symptoms and even coma and death if not treated rapidly. The aim was to describe a cohort of patients with adult onset of UCDs in a multicentric, retrospective and descriptive study of French adult patients with

Marta Spodenkiewicz, Claire Douillard, and François Maillot contributed equally to this work.

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a diagnosis after 16 years of age of UCDs due to a deficiency in one of the 6 enzymes (arginase, ASL, ASS, CPS1, NAGS, OTC) or the two transporters (ORNT1 or citrin). Seventy-one patients were included (68% female, 32% male). The diagnosis was made in the context of (a) a metabolic decompensation (42%), (b) family history (55%), or (c) chronic symptoms (3%). The median age at diagnosis was 33 years (range 16-86). Eighty-nine percent of patients were diagnosed with OTC deficiency, 7% CPS1 deficiency, 3% HHH syndrome and 1% argininosuccinic aciduria. For those diagnosed during decompensations (including 23 OTC cases, mostly female), 89% required an admission in intensive care units. Seven deaths were attributed to UCD—6 decompensations and 1 epilepsy secondary to inaugural decompensation. This is the largest cohort of UCDs diagnosed in adulthood, which confirms the triad of neurological, gastrointestinal and psychiatric symptoms during hyperammonemic decompensations. We stress that females with OTC deficiency can be symptomatic. With 10% of deaths in this cohort, UCDs in adults remain a life-threatening condition. Physicians working in adult care must be aware of late-onset presentations given the implications for patients and their families.

KEYWORDS

adults, hyperammonemia, inherited metabolic diseases, late-onset diagnosis, urea cycle disorders

1 | INTRODUCTION

Urea cycle disorders (UCD) are a group of inherited metabolic diseases caused by a deficiency of one of the six enzymes or two transporters involved in the urea cycle.[1] The urea cycle is necessary to detoxify ammonia, otherwise toxic, and for the endogenous synthesis of arginine.[2] Three of these enzymes are mitochondrial: N-acetylglutamate synthase (NAGS, EC 2.3.1.1), carbamoyl phosphate synthetase I (CPSI, EC 6.3.4.16) and ornithine transcarbamylase (OTC, EC 2.1.3.3); and three cytoplasmic: argininosuccinate synthetase (ASS, EC 6.3.4.5), argininosuccinate lyase (ASL, EC 4.3.2.1) and arginase 1 (ARG1, EC 3.5.3.1). Two transporters are necessary to link the mitochondrial and cytoplasmic compartments: the mitochondrial ornithine transporter 1 (ORNT1 also named solute carrier family 25, member 15 SLC25A15) which carries ornithine into the mitochondria, and the mitochondrial aspartate/glutamate transporter (citrin, transporter SLC25A13).

In most cases, UCDs are diagnosed in the first months of life but late-onset forms have been reported.[3-7] The phenotypic differences between pediatric vs adult onset are not well understood.[8] Furthermore, no cohort exclusively focused on adult-onset patients has been published to date. The aim of this paper is to describe a large French cohort of adult-onset UCD patients.

2 | MATERIALS AND METHODS

2.1 | Patients

This study was multicentric, retrospective and observational. French metabolic specialists were contacted by e-mail through the mailing list of the Adult group of the French Society for the Study of Inherited Metabolic Diseases (SFEIMA) and data were collected through a questionnaire. Inclusion criteria were: (a) patients with UCD: NAGS deficiency (OMIM 237310), CPSI deficiency (OMIM 237300), OTC deficiency, (OTCD, OMIM 311250), citrullinemia type I or ASS deficiency (OMIM 215700), argininosuccinic aciduria or ASL deficiency (OMIM 207900), argininemia or ARGI deficiency (OMIM 207800) or diseases caused by deficiency in one of the two transporters envolved in HHH syndrome (Hyperornithinemia-Hyperammonemia-Homocitrullinuria syndrome, OMIM 238970), either ORNT1 deficiency or citrullinemia type II (OMIM 605814, 603 471) due to citrin deficiency; and (b) diagnosis after 16 years of age.

Collected data included diagnosis, clinical signs (neurological, psychiatric or gastrointestinal symptoms), previous clinical symptoms that could be related to former decompensations (noticed by the patient or family and reported in the patient's chart), biological analyses (ammonia, plasma aminoacids, urinary orotic acid), long-term

treatment, diets and genetic pathogenic variants. Data were collected by metabolic specialists using patients' records as the source of information. An anonymized database was constituted in accordance with the reference methodology MR004 of the "Commission Nationale de l'Informatique et Libertés" (N° 2 206 749, 13/09/2018).

2.2 | Statistics

Collected data were expressed as mean, median and range for quantitative variables and as percentage for qualitative variables.

3 | RESULTS

Eighty-five patients were screened for this study: they were diagnosed between 1997 and 2017, except two mothers of OTC deficient patients diagnosed in 1973 and 1980. Four patients were excluded because diagnosis was made during childhood; in 9 cases the data were missing and in one case the final diagnosis was not confirmed (Figure 1). We included 71 patients described in Table 1,[9-12] Table 2,[9-12] Table 3 and Table 4,[9] from 12 centers: Paris (17 patients), Lille (16), Tours (10), Rennes (9), Bordeaux (7), Lyon (4), Strasbourg (3) and one patient from each of the other centers (Angers, Montpellier, Reims, Grenoble). Forty-eight patients were female (68%) and 23 were male (32%). The diagnosis was made at the time of an acute decompensation for 30 patients (42%), in the context of chronic symptoms for 2 patients (3%) or through family screening for 39 patients (55%). Mean age at diagnosis was 37 years (median age 33 years, range 16-86). Sixty-three patients were diagnosed with OTC deficiency (89%), 5 with CPS1 deficiency (7%), 2 with HHH syndromes (3%), and one with argininosuccinic aciduria (1%). At inclusion, 9 patients were already deceased: 7 deaths were related to UCD (6 patients from hyperammonemic decompensations and one neurologic sequelea following inaugural crisis), whereas one patient died during follow-up (unknown cause). All patients who died from hyperammonemia were diagnosed concomitantly to metabolic decompensations: 3 patients had OTC deficiency (2 men and one woman), 2 had CPS1 deficiency, and one had HHH syndrome.

3.1 | Patients diagnosed during acute decompensation

This group comprises 30 patients (Table 1 and 2)[9-12] :16 were female (53%) and 14 were male (47%). Mean age at diagnosis was 39 years (median age 35 years, range 18-69). Ten patients did not have any comorbidity (missing data for one patient). Medical history was otherwise notable for 2 patients with surgical procedures, 2 patients treated for depression and 8 patients with neurological symptoms (developmental delay, migraines, seizures, episodes of confusion and capsulo-thalamic stroke). During this hyperammonemic decompensation, 16 patients (53%) displayed gastrointestinal problems: 15 (50%) with nausea or vomiting, 4 (13%) with anorexia and 4 (13%) with abdominal pain. Ten patients (34%) displayed psychiatric symptoms: delirium, puerperal psychosis, catatonic depression, behavioral disturbance or visual hallucinations. Twenty-eight patients (93%) had neurological symptoms: coma (19 patients, 63%), lethargy or drowsiness (14 patients, 47%), confusion (14 patients, 47%), agitation (8 patients, 27%), seizures (8 patients, 27%), ataxia (7 patients, 23%), slurred speech (6 patients, 20%), increased or decreased muscle tone (6 patients, 20%), headaches (5 patients, 17%), brain oedema (5 patients, 17%), pseudo strokes (3 patients, 10%), and acute loss of vision (1 patient, 3%). Four patients (13%) died during this first decompensation including one female with OTC deficiency, whereas 2 other patients died after diagnosis during a subsequent decompensation. One patient died because of neurologic sequelae following his first decompensation (status epilepticus without hyperammonemia) whereas another patient died of hepatocarcinoma.

Twenty-three patients (77%) were diagnosed with OTC deficiency (14 women and 9 men), 5 (17%) with CPS1 deficiency, one (3%) with HHH and one (3%) with ASL deficiency.

A precipitating factor was found in 23 cases (77%), and among them 7 patients (23%) had two precipitating factors (Table 1). The most frequent factor was increased protein intake (7 patients, 23%). Other factors were sodium valproate (4 patients, 14%), pregnancy and/or delivery, surgery, infections, fasting, high-protein diet (exceeding normal dietary recommendations) to lose weight, intense exercise, psychological stress and immunotherapy for hepatocarcinoma.

In this group, chronic symptoms, prior to diagnosis, were identified in 24 patients (80%)—including 12 OTC deficient female: spontaneous low-protein or vegetarian diet (13 patients, 43%), psychiatric symptoms (11 patients, 37%), chronic headaches (10 patients, 33%), recurrent episodes of nausea or vomiting (8 patients, 27%), episodes of confusion (7 patients, 23%), learning disabilities (4 patients, 14%), seizure or epilepsy (4 patients, 14%) and anorexia (2 patients, 7%). Five patients did not have any chronic symptom before their first hyperammonemic crisis and data were missing for 1 patient.

Hyperammonemia was found in all patients, with a mean initial level of 275 μmol/L (median 218, range

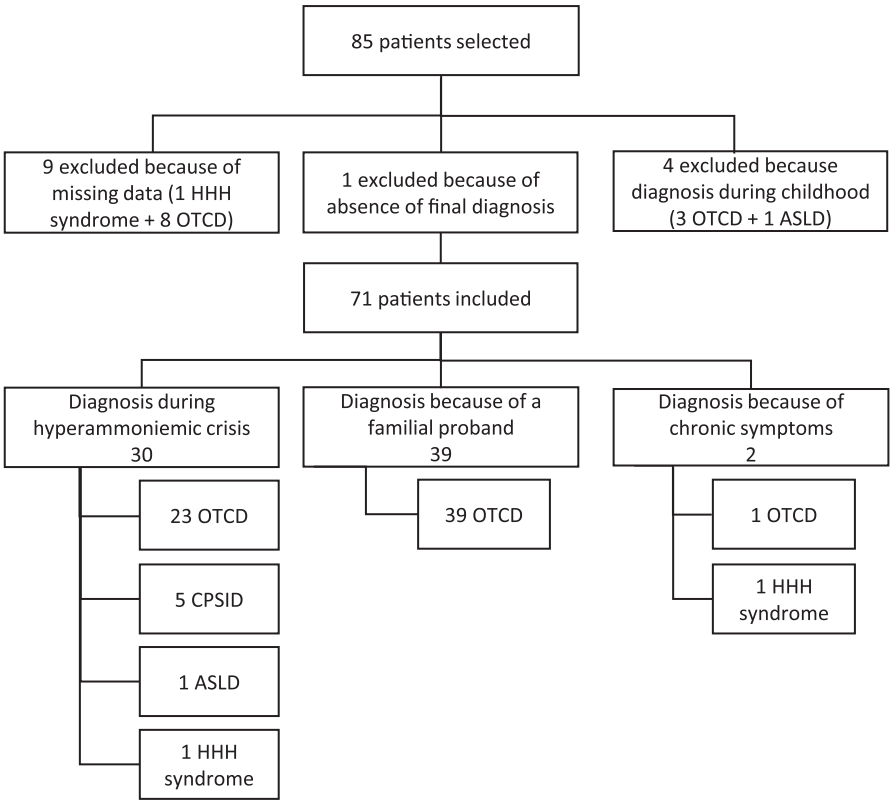

FIGURE 1 Flow chart.
Figure explaining the inclusion of all patients in this study, the reason of the diagnosis and the final diagnosis with the number of patients by diagnoses. ASLD, argininosuccinate lyase deficiency; CPSID, carbamoylphosphate synthetase deficiency; HHH syndrome, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome; OTCD, ornithine transcarbamylase deficiency

45-1254), and a mean peak of 414 μmol/L (median 268, range 75-2500). Mean glutamine level was 924 μmol/L (median 862, range 250-1941). For patients with OTC deficiency, plasma ammonia was high at 262 μmol/L (median 175, range 45-1254), with a peak of 418 μmol/L (median 267, range 75-2500), as well as glutamine at 955 μmol/L (median 862, range 250-1941) and urinary orotic acid at 204 μmol/mmol of creatinine (median 122, range 1,6-579). All patients had a genetic analysis with available results for 28 patients (93%). Pathogenic variants were identified in 25 patients (89%).

Eighty-six percent of patients (25/29) required an admission in intensive care units (data not available for one patient). Hemodialysis was performed in 50% (15 patients). Noticeably, one patient presented with central pontine myelinolysis following hemodialysis, possibly related to a rapid change in serum tonicity with prompt correction of ammonia.[10] Nitrogen scavenger drugs were used in 72% (21 patients)—benzoate in 18 patients (64%), phenylbutyrate in 14 patients (50%) and both in 11 patients (39%). Carglumic acid was used in 4 patients (14%), including two CPS1 deficient patients, and 3 patients (12%) received antiepileptic drugs. Long-term treatment of the 26 remaining patients included low-protein diet (22 patients, 85%) with a median protein restriction of 0.7 g/kg/day (range 0.4 to 1 g/kg/day), nitrogen scavengers (21 patients, 81%), citrulline and/or arginine supplementation (17 patients, 65%). The median dose required for stability was 6 g/day (range 3-15, 11 patients) for phenylbutyrate and 5 g/day of benzoate (range 2-12; 12 patients). Glycerol phenylbutyrate was prescribed for two patients (9.9 and 17.6 g/day, respectively).

Long-term follow-up for these patients—except for 3 patients lost during follow-up—were: return to baseline for 11 patients (including 3 patients with previous intellectual disability and/or epilepsy), neurological sequelea for 7 patients, psychiatric symptoms for 2 patients, subsequent decompensations for 6 patients including 2 patients who died.

3.2 | Patients diagnosed following chronic symptoms

Two men were diagnosed because of chronic symptoms (Table 3). One patient (16 years old) was diagnosed with OTC deficiency because of abdominal pain along with headaches, drowsiness, and dizziness, with episodes of agitation and aggressive behavior that required a psychiatric follow-up, without other comorbidities. After diagnosis, he was treated with a low-protein diet, sodium benzoate and arginine supplementation. The other patient (26 years old) was diagnosed with HHH syndrome after recurrent episodes of drowsiness, lethargy and aphasia. He also had intellectual deficiency. He was

TABLE 1 Characteristics of patients diagnosed during their first hypermmoniemic decompensation. Epidemiological, clinical and biological data as well as initial treatment

			During first hyperammonemic crisis					Ammonia level		Treatment of first decompensation		
Number of patients	Sex	Age at diagnosis (years)	Triggering factors	Gastro intestinal symptoms	Neurologic symptoms	Psychiatric symptoms	Death	Initial level (μmol/L)	Peak (μmol/L)	Intensive care units	Hemo(dia) filtration	Nitrogen scavengers
Patients diagnosed with OTCD												
1	F	18	NA	×	×			High	NA	×	NA	NA
2	M	18	Diabetic ketoacidosis	×	×			113	272	×	×	×
3[9]	F	21	Valproate		×	×		510	510	×	×	×
4	F	21	Increased protein intake		×			High	NA			×
5	F	22	Increased protein intake	×	×			267	267	×	×	×
6	F	23	increased protein intake + valproate	×	×	×		106	161	×		×
7	M	27	Immunotherapy		×			144	687	×	×	×
8	M	27	NA		×		×	1254	2500	×	×	×
9[10]	F	29	Pregnancy (9 WA) + fasting	×	×	×		150	281	×	×	×
10	F	31	Infection + high-protein diet (exceeding normal dietary recommendations)	×				45	75	×		
11	F	33	Pregnancy (20 WA)		×	×		173	173	×		×
12[11]	M	35	Intense physical effort	×	×			256	256	×		
13	M	36	Infection	×	×	×		190	190	×		×
14	F	37	Psychological stress	×	×	×	×	600	NA	×	×	×
15	F	43	Increased protein intake		×			78	78	×		
16	F	44	Increased protein intake + valproate	×	×	×		290	290	×	NA	NA
17	M	49		×	×			176	794	×	×	×
18	F	52	Surgery		×			high	NA	NA	NA	NA
19	M	54	Psychological stress	×	×			120	120	×		×
20	M	55		×	×	×	×	270	700	×	×	

(Continues)

TABLE 1 (Continued)

Number of patients	Sex	Age at diagnosis (years)	During first hyperammonemic crisis					Ammonia level		Treatment of first decompensation		
			Triggering factors	Gastro intestinal symptoms	Neurologic symptoms	Psychiatric symptoms	Death	Initial level (μmol/L)	Peak (μmol/L)	Intensive care units	Hemo(dia) filtration	Nitrogen scavengers
			Increased protein intake + valproate									
21	F	57			×			327	327	×	×	×
22	F	59	Surgery			NA		65	105			
23	M	64	Increased protein intake	×	×			114	155			×
Patients diagnosed with CPS1D												
24	F	21	Cesarean section		×			268	268	×	×	×
25[12]	F	35	Infection + postpartum		×	×		high	224	×		×
26	M	46	Surgery	×	×			800	800	×	×	×
27	M	52	Infection		×	×	×	218	715	×		×
28	M	68			×			329	329	×	×	×
Patient diagnosed with ASLD												
29	M	22		×	×			101	237	×	×	×
Patient diagnosed with HHH syndrome												
30	M	69			×			235	235			

Note: References of primary publications where these patients were previously published.[9-12]

Abbreviations: ASLD argininosuccinate lyase deficiency; CPS1D, carbamoylphosphate synthetase deficiency; F, female; HHH syndrome, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome; M, male; NA, not available; OTCD, ornithine transcarbamylase deficiency; WA, weeks of amenorrhea.

TABLE 2 Characteristics of patients diagnosed during their first hyperammonemic decompensation: presence of chronic symptoms, genetic data and long-term treatment (after acute decompensation)

	Chronic symptoms before diagnosis				Genetic results (verified with mutalyzer 2.0.32 and varsome)		Long-term treatment				
Number of patients	**Gastro intestinal**	**Neurologic**	**Psychiatric**	**Spontaneous restricted protein diet**	**Pathogenic variants**	**Type of variants**	**Restricted protein diet**	**Arginine and/or citrulline**	**Nitrogen scavengers drugs**	**Current status at last follow up**	
Patients diagnosed with OTCD					***OTC*, transcript NM_000531.6**						
1	×	×			exon 2 c.119G>A, p. Arg40His	Missense	×	×	×	Alive	Headaches and decompensations
2					exon 8 c.817_819del, p. Glu273del	Deletion	×	×	×	Alive	Stable
3[9]	×	×		×	exon 6 c.583G>A p. Gly195Arg	Missense	×	×	×	Alive	Neurological and psychiatric sequelae and decompensations
4		×			exon 2 c.119G>A, p. Arg40His	Missense	×			Alive	Stable
5				×	exon 10 c.1052del, p. Lys351Serfs*44	Frameshift	×	×	×	Alive	Stable
6	×	×		×	exon 1 c.3G>A, p.?	Misense (start-loss)			×	NA	NA
7	×	×			Not found		×	×	×	Deceased	
8	NA		NA	NA	exon 2 c.119G>A, p. Arg40His	Missense				Deceased	
9[10]					exon 9 c.919A>G, p. Lys307Glu	Missense		×		Alive	neurological sequelae
10	×	×		×	exon 3 c.275G>A, p. Arg92Gln	Missense				Alive	other decompensation
11		×		×	exon 6 c.626C>A, p. Ala209Glu	Missense	×	×	×	Alive	neurological sequelae
12[11]					exon 9 c.903A>T, p. Leu301Phe	Missense	×	×		NA	NA
13	×		×	×	exon 2 c.119G>A, p. Arg40His	Missense	×	×	×	Alive	neurological sequelae
14	NA	NA	NA	NA	exon 6 c.622G>A, p. Ala208Thr	Missense				Deceased	

(Continues)

TABLE 2 (Continued)

Number of patients	Chronic symptoms before diagnosis				Genetic results (verified with mutalyzer 2.0.32 and varsome)		Long-term treatment				
	Gastro intestinal	Neurologic	Psychiatric	Spontaneous restricted protein diet	Pathogenic variants	Type of variants	Restricted protein diet	Arginine and/or citrulline	Nitrogen scavengers drugs	Current status at last follow up	
15		×			exon 2 c.119G>A, p. Arg40His	Missense	×	×		Alive	Stable
16	×	×	×	×	exon 6 c.638T>A, p. Met213Lys	Missense	×	×	×	Alive	Stable
17					exon 6 c.622G>A, p. Ala208Thr	Missense	×	×	×	Deceased	
18	×	×			Not found		×	×	×	Alive	neurological and psychiatric sequelae and decompensations
19		×			exon 6 c.653C>T, p. Ala218Val	Missense		×	×	Alive	Stable
20			×	×	exon 2 c.214G>A, p. Glu72Lys	Missense				Deceased	
21		×			NA		×		×	Alive	Neurological sequelae
22				×	exon 8 c.740C>G, p. Thr247Arg	Missense	×		×	Alive	Stable
23					exon 2 c.206A>T, p. Gln69Leu	Missense				Alive	Stable
Patients diagnosed with CPS1D					***CPS1*, transcript NM_001875.5**						
24		×		×	exon 38 c.4451A>T, p. Asp1484Val[a]	Missense	×	×	×	Alive	Stable
25[12]		×	×	×	exon 3 c.259C>T, p. Pro87Ser; exon 20 c.240C>T, p.Tyr80-	Missense; silent	×	×	×	Alive	Stable
26		×		×	c.1201G>C, p.Gly401Arg; c.2810T>A, p.Ile937Asn; c.3097G>T, p.Glu1033*	Missense; missense; nonsense	×	×	×	NA	NA
27		×	NA		NA					Deceased	
28					exon 28 c.3464C>A, p. Ala1155Glu[a]	Missense	×	×	×	Deceased	

TABLE 2 (Continued)

Number of patients	Chronic symptoms before diagnosis				Genetic results (verified with mutalyzer 2.0.32 and varsome)		Long-term treatment				
	Gastro intestinal	Neurologic	Psychiatric	Spontaneous restricted protein diet	Pathogenic variants	Type of variants	Restricted protein diet	Arginine and/or citrulline	Nitrogen scavengers drugs	Current status at last follow up	
Patient diagnosed with ASLD					***ASL*, transcript NM_000048.4**						
29	×			×	intron 6 c.446+1G>A; exon 8 c.566A>G, p. Glu189Gly	Splicing; missense	×	×	×	Alive	stable
Patient diagnosed with HHH syndrome											
30	×				Not found		×	×	×	Deceased	

Note: References of primary publications where these patients were previously published.[9-12]

Abbreviations: OTCD ornithine transcarbamylase deficiency, ASLD argininosuccinate lyase deficiency, CPS1D carbamoylphosphate synthetase deficiency, HHH syndrome hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, NA not available.

[a]Homozygote mutation.

treated with a low-protein diet, sodium phenylbutyrate, citrulline supplementation and antiepileptic drugs. Both patients had hyperammonemia at diagnosis.

3.3 | Patients diagnosed from family screening

Thirty-nine patients were screened because of a familial proband: 32 women (82%) and 7 men (18%) (Table 4). All of them were diagnosed with OTC deficiency and we observed clear differences in clinical presentations within members of the same family. Mean age at diagnosis was 37 years (median 32 years, range 17-86). For 7 patients, clinical or biological data were not available. Seven patients did not have any comorbidity, whereas 11 patients had surgical comorbidities, 3 patients had migraines or chronic headaches and 2 were depressive. All patients had a genetic test. Forty-four percent of patients (14/32) had symptoms that could be related to chronic or recurrent hyperammonemia: 11 patients (34%) were spontaneously avoiding proteins, 7 patients (22%) had chronic episodes of nausea or vomiting, 6 patients (19%) reported chronic headaches, 3 patients had previous episodes of drowsiness, 2 patients had a psychiatric disorder, and one patient had an episode of confusion. Fourteen patients (44%) had never experienced symptoms before diagnosis.

After diagnosis, only 4 patients (3 men and 1 woman) presented with metabolic decompensations, including one severe hyperammonemic crisis leading to coma and hospitalization in the ICU. Fourteen patients initiated a restricted protein diet, 5 patients were put on nitrogen scavenger drugs and 7 patients on arginine, citrulline and/or carnitine. Two patients died from causes unrelated to OTC deficiency.

4 | DISCUSSION

Our study describes the largest cohort of 71 patients with adult-onset UCD. First, we confirmed the clinical spectrum previously described for late-onset UCDs with three major symptom categories: neurological, gastrointestinal and psychiatric. Second, we observed that a large proportion of OTC deficient patients with acute decompensations in adulthood were women, which underlines that heterozygous females can have life-threatening onset in adulthood. This suggests that DNA testing should be considered for females at risk for OTC deficiency as they can appear asymptomatic for decades before presenting in hyperammonemic crisis during adulthood. Third, we emphasized that UCDs are life-threatening conditions,

with mortality or neurologic sequelae if not rapidly treated and/or prevented.

Unlike most previous cohorts of UCD patients where late-onset was defined as onset after the first month of life,[4-6,13-21] we specifically included patients with adult-onset (after 16 years of age). Not surprisingly, the most frequent diagnosis in our cohort was OTC deficiency (89%), as previously reported.[5,6,13-16,18,21] Our cohort also comprised two patients with HHH syndrome, which is in line with a literature review of all cases of HHH syndrome, in which Martinelli et al showed that more than 30% of patients are diagnosed during adulthood.[22] A triggering factor of decompensation was found in 80% of patients, which is comparable to children's cohorts, but some factors were specific to adults such as increased protein intake (7 patients) or high-protein diet (exceeding normal dietary recommendations) (patient 10) and pregnancy or post-partum for 5 women. Infection was present in only 4 patients although this is the most common triggering factor during childhood.

Three studies[4-6] have reported adult patients with UCDs. In one study, 3 patients were diagnosed during adulthood.[6] In another study, 26 patients were older than 16 years at diagnosis—including 14 females with OTC deficiency and one patient with arginase deficiency—but without clinical and biochemical data.[4] In the third study,[5] 105 patients (50%) were older than 16 years at the time of inclusion (74 with OTC deficiency, 17 with ASL deficiency, 8 with ASS deficiency, 4 with arginase deficiency, one patient with CPS1 deficiency and one patient with NAGS deficiency), but no information was provided about their age at diagnosis. Nevertheless, some of their results were comparable to our patient's cohort: (1) 52% of patients presented one episode of symptomatic hyperammonemia, vs 51% in our cohort, (2) 58% of patients followed a restricted protein diet, vs 53% in our cohort, (3) 69% of patients with OTC deficiency were female, vs 63% in our cohort. Brassier et al. also described 11 OTC deficient patients (5 males, 6 females) with a median age at diagnosis of 28 years of age, which is younger than our OTC deficient patients (mean age 37 years),[7] but similar findings in terms of symptoms during acute decompensations, preexisting history in some patients, triggering factors and death rate. Noticeably, 3 pathogenic variants of *OTC* were frequent in our cohort: c.622G>A (p.Ala208Thr)[23] in 12 patients (4 male; 8 female) from 4 families, c.119G>A (p.Arg40His)[24] in 8 patients (5 male, 3 female) from 6 families and c.350A>G (p.His117Arg) in 5 women from 3 families. These variants are known to be associated with late-onset presentation.[7,25]

In our study, hemo(dia)filtration was used in 50% of symptomatic patients, whereas no clear data are reported in other cohorts. If we consider the 2012 UCD guidelines[26] and their revision[27] as a reference, hemo(-dia)filtration should be started immediately in an undiagnosed patient if ammonia level is above 500 μmol/L. Between 250 and 500 μmol/L, it should be used only if there is no improvement in the ammonia levels with nitrogen scavenging drugs. These recommendations were established for all patients including neonates. In our cohort, the mean peak of ammonia level was 414 μmol/L, and 50% of our patients (all of them receiving nitrogen scavenging drugs) were under hemofiltration. This is in agreement with the only recommendations for adults that suggest treating all patients with ammonia levels higher than 200 μmol/L with extra-renal filtration.[28] Management of patients was decided following local protocol, in district or university hospital, and one center followed international guidelines. There were no differences regarding availability of nitrogen scavenger drugs or hemofiltration in the various centers, except for one patient who died after being treated with only hemofiltration as nitrogen scavengers were not available (ammonia level around 600 μmol/L). In our cohort, patients who died exhibited the highest levels of peak ammonia (mean 753 μmol/L), which could explain their poor prognosis. Peak ammonia above 500 μmol/L has been associated with a poor neurological outcome.[29] Similarly, two other patients (patients 17, 26) with high peak ammonia at initial presentation (around 800 μmol/L) survived but manifested poor neurological outcomes. Overall, a third of our patients presented with neurologic and/or psychiatric manifestations following their initial metabolic crisis. It appeared that patients who died despite being diagnosed with UCD had very low treatment and diet compliance related to the complex psychosocial issues of their social and/or cognitive disabilities. Notably, 3 patients presented stroke-like episodes during their inaugural decompensation. Brain MRI was available for one patient and showed slight hypersignal of the white matter (internal capsule and semiovale center) initially, with persistent signal abnormality at 4 months follow-up but without neurologic sequelae.

Based on our patient cohort and data from the literature, we recommend searching for UCDs in all adult patients presenting with unexplained encephalopathy, especially when they are associated with gastrointestinal and/or psychiatric symptoms. The diagnosis of UCD may be further supported by the identification of triggering factors—for example, infection, medication or recent increase of protein intakes—, and/or evocative chronic symptoms—for example, vomiting, headaches, protein-restricted diet, episodes of unexplained neurological and/or psychiatric symptoms. Ammonia should be measured immediately in these patients. Hemo(dia)filtration in association with nitrogen scavenger drugs should be

TABLE 3 Characteristics of patients diagnosed because of chronic symptoms. Epidemiological data, clinical description, biological data and treatment

			Chronic symptoms before diagnosis				Ammonia level		Genetic results (verified with mutalyzer 2.0.32 and varsome)		Long-term treatment			
Number of patients	Sex	Age at diagnosis (years)	Gastro intestinal	Neurologic	Psychiatric	Spontaneous restricted protein diet	Initial level (µmol/L)	Peak (µmol/L)	Pathogenic variants	Type of variants	Restricted protein diet	Arginine and/or citrulline	Nitrogen scavengers drugs	Current status at last follow up
Patient diagnosed with OTCD									***OTC*, transcript NM_000531.6**					
31	M	16		×	×		167	276	exon 6 c.622G>A, p. Ala208Thr	missense	×	×	×	alive
Patient diagnosed with HHH syndrome														
32	M	26		×			100	100	NA		×	×	×	alive

Abbreviations: F, female; HHH syndrome, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome; M, male; NA not available; OTCD, ornithine transcarbamylase deficiency.

TABLE 4 : Description of OTC deficient patients diagnosed because of a familial proband. Epidemiological, clinical and genetic data

					Chronic symptoms				Genetic results (verified with mutalyzer 2.0.32 and varsome)		
Number of patient	Sex	Age at diagnosis (years)	Index case (age at diagnosis)	Number of family	Gastro intestinal	Psychiatric	Neurological	Spontaneous restricted protein diet	Pathogenic variants of *OTC*, variant NM_000531.6	Type of variants	Current status at last follow up
33	M	26	Brother	1			×	×	exon 2 c.119G>A, p.Arg40His	Missense	Alive
34	M	32	Brother	1	NA	NA	NA		exon 2 c.119G>A, p.Arg40His	Missense	NA
35	M	36	Brother	1	×		×	×	exon 2 c.119G>A, p.Arg40His	Missense	Alive
36	F	38	Son (3d)	2				NA	exon 6 c.608C>T, p. Ser203Phe	Missense	Alive
37	F	61	Grandson (3d)	2	×		×	×	exon 6 c.608C>T, p. Ser203Phe	Missense	Alive
38	F	23	Son (15d)	3					exon 5 c.422G>A, p. Arg141Gln	Missense	Alive
39	F	NA	Grandson (15d)	3					exon 5 c.422G>A, p. Arg141Gln	Missense	Alive
40	F	24	Son (birth)	4	NA	NA	NA	NA	exon 4 c.386G>A, p. Arg129His	Missense	NA
41	F	NA	Brother	4					exon 4 c.386G>A, p. Arg129His	Missense	Alive
42	F	21	Father (49y)	5	NA				exon 6 c.622G>A, p. Ala208Thr	Missense	Alive
43	M	21	Uncle (49y)	5		NA	NA	NA	exon 6 c.622G>A, p. Ala208Thr	Missense	Alive
44	M	27	Uncle (49y)	5					exon 6 c.622G>A, p. Ala208Thr	Missense	Alive
45	F	83	Son (49y)	5					exon 6 c.622G>A, p. Ala208Thr	Missense	Alive
46	F	NA	Brother (49y)	5	Deceased before investigations				exon 6 c.622G>A, p. Ala208Thr	Missense	Deceased
47	F	33	Nephew	6		NA			exon 4 c.386G>A, p. Arg129His	Missense	Alive
48	F	NA	Cousin	6		NA			exon 4 c.386G>A, p. Arg129His	Missense	Alive
49	F	33	Son (10m)	7	NA	NA	NA	NA		Missense	NA

TABLE 4 (Continued)

Number of patient	Sex	Age at diagnosis (years)	Index case (age at diagnosis)	Number of family	Chronic symptoms				Genetic results (verified with mutalyzer 2.0.32 and varsome)		Current status at last follow up
					Gastro intestinal	Psychiatric	Neurological	Spontaneous restricted protein diet	Pathogenic variants of *OTC*, variant NM_000531.6	Type of variants	
									exon 4 c.350A>G, p. His117Arg		
50	F	43	Nephew (10m)	7					exon 4 c.350A>G, p. His117Arg	Missense	NA
51	F	NA	Son (18m)	8	NA	NA	NA	NA	exon 4 c.350A>G, p. His117Arg	Missense	Alive
52	F	NA	Brother (18m)	8	NA	NA	NA	NA	exon 4 c.350A>G, p. His117Arg	Missense	Alive
53	F	32	Cousin	9		×			exon 6 c.622G>A, p. Ala208Thr	Missense	NA
54	F	42	Sister	9					exon 6 c.622G>A, p. Ala208Thr	Missense	NA
55	F	60	Daughter	9	NA	NA	NA	NA	exon 6 c.622G>A, p. Ala208Thr	Missense	NA
56[9]	F	28	Sister (21y)	10					exon 6 c.583G>A, p. Gly195Arg	Missense	NA
57[9]	F	52	Daughter (21y)	10	×		×	×	exon 6 c.583G>A, p. Gly195Arg	Missense	Alive
58	F	17	Mother				×	×	exon 6 c.638T>A, p. Met213Lys	Missense	NA
59	F	23	Son (8d)		×		×	×	Not found		Alive
60	F	25	Son (1m)		×		×		exon 6 c.584G>C, p. Gly195Ala[a]	Missense	Alive
61	F	27	Son						exon 3 c.269G>A, p.Ser90Asn	Missense	NA
62	F	29	Daughter (9m)					×	exon 9 c.996G>A, p.Trp332*	Nonsense	Alive
63	F	29	Nephew (2y)		×			×	exon 2 c.158T>C, p.Ile53Thr	Missense	Alive
64	F	30	Son (18m)				×	×	NA		Alive
65	F	30	Son						exon 5 c.533C>T, p. Thr178Met- polymorphism	Missense; missense	NA

(Continues)

TABLE 4 (Continued)

Number of patient	Sex	Age at diagnosis (years)	Index case (age at diagnosis)	Number of family	Chronic symptoms				Genetic results (verified with mutalyzer 2.0.32 and varsome)		Current status at last follow up
					Gastro intestinal	Psychiatric	Neurological	Spontaneous restricted protein diet	Pathogenic variants of *OTC*, variant NM_000531.6	Type of variants	
									exon 2 c.137A>G, p. Lys46Arg		
66	F	32	Son (13m)						exon 4 c.350A>G, p. His117Arg	Missense	alive
67	F	33	Son			×			exon 6 c.622G>A, p. Ala208Thr	Missense	NA
68	F	46	Grandson (5d)		×			×	NA		Alive
69	M	64	Nephew						Exon 8 c.817_819del, p. Glu273del	Deletion	NA
70	M	86	Niece				×	×	Not done		Deceased
71	F	NA	Brother			NA			NA		Alive

Note: Reference of primary publication where these patients were previously published.[9]

Abbreviations: d, days; F, female; M, male; m, months; NA, not available; OTC, ornithine transcarbamylase; y, years.

[a]Homozygote mutation.

performed as soon as hyperammonemia is confirmed in patients with neurologic signs and/or if level of ammonia is greater than 200 μmol/L.[28] In our study, adult patients diagnosed with OTC deficiency during an acute metabolic decompensation were mostly female. Hence, we stress the importance of extended family screening that includes OTC women. All situations that put adult UCD patients at risk of metabolic decompensation should be anticipated. All patients, even asymptomatic individuals should be issued with emergency certificates or cards. These patients should be made aware of factors that could trigger metabolic decompensations (prolonged fasting, anesthesia, infection), with specific triggers for women such as pregnancy and post-partum.

Our study has some limitations: this is a retrospective analysis, and patients from this cohort were ascertained thanks to a collaboration, which might not be exhaustive for all French patients. However, this is the first study focusing on adult patients that highlights the need to educate clinicians working in adult care about UCD decompensation first occurring in adulthood (with neurologic, gastro-intestinal and sometimes psychiatric symptoms), as well the importance of prompt management of acute metabolic crisis to avoid neurologic damage. We also insist on the importance of family screening, especially for OTC women who may be symptomatic.

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CONFLICT OF INTEREST

None of the authors have conflicts of interest.

AUTHOR CONTRIBUTIONS

Ségolène Toquet: conception and design of the study. Design of the questionnaire. Statistical analysis and interpretation of data. Drafted and extensively revised the article. Marta Spodenkiewicz, Fanny Mochel, Claire Douillard, François Maillot: recruited patients into the study, provided clinical and biological data, revised the article critically for important intellectual content. Jean-Baptiste Arnoux, Lena Damaj, Sylvie Odent, Caroline Moreau, Isabelle Redonnet-Vernhet, Samir Mesli, Aude Servais, Esther Noel, Sybill Charriere, Christian Lavigne, Vincent Rigalleau, Elsa Kaphan, Agathe Roubertie, Gérard Besson, Adrien Bigot, Amélie Servettaz: recruited patients into the study and as well as provided clinical and biological data. Fanny Mochel: recruited patients into the study, provided clinical and biological data, drafted and extensively revised the article. Roselyne Garnotel: conception and design of the study. Revision of the article for important intellectual content.

ETHICS STATEMENT

The study was performed in accordance with the Helsinki declaration. Since the study was based on systematic medical data records, as authorized by the French "Commission Nationale Informatique et Liberté" (N° CNIL 1118523) and because no supplementary procedure was performed and no additional biological samples collected, the study did not require approval by an ethic committee according to "French legislation on human research (reference methodology CNIL n°2206749, 13/09/2018)."

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