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Significant Hepatic Involvement in patients with Ornithine Transcarbamylase Deficiency

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Abstract

Objective—To determine the frequency of significant liver injury and acute liver failure (ALF) in patients with ornithine transcarbamylase deficiency (OTCD), the most common urea cycle defect (UCD).

Study design—A historical cohort study was performed. Charts were reviewed at two centers to assess the proportion of 71 individuals with OTCD who had evidence of ALF (INR ≥ 2.0), liver dysfunction (INR 1.5–1.99), or hepatocellular injury (AST/ALT≥ 250 IU/L).

Results—57% of the 49 patients with symptomatic OTCD had liver involvement: 29% met the criteria for ALF, 20% had liver dysfunction, and 8% had isolated hepatocellular injury. The proportion with ALF was greatest in those with more severe OTCD, including neonates with markedly elevated ammonia levels (> 1,000 μmol/L). Some patients with severe liver involvement

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Portions of the study have been presented at the annual Meeting of the Urea Cycle Disorder Consortium <<>>, as well as a poster at the meet of the Society for Inherited Metabolic Disease, March 2012.

(INR ≥ 2.0 and AST/ALT > 1,000 IU/L) had only moderate hyperammonemia (100 – 400 μmol/L). ALF was the initial presenting symptom of OTCD in at least 3 of 49 symptomatic OTCD patients.

Conclusions—Episodes of hepatocellular injury, liver dysfunction, and ALF were identified in a high proportion of individuals with symptomatic OTCD. The more severely affected OTCD patients had a higher likelihood of ALF. The diagnosis of a UCD should be considered in unexplained ALF, liver dysfunction or hepatocellular injury.

Keywords

Urea cycle defects; hyperammonemia; acute liver failure; elevated AST/ALT; Reye syndrome; orotic acid

Accurate diagnosis of an underlying etiology is crucial to outcome in acute liver failure (ALF)[1]. Up to 50% of children with ALF[2], and ~15% of adults with ALF[1], are of "indeterminate" cause. Genetic metabolic disorders are an important cause of ALF in children, comprising 9.7% of final diagnoses in a large international multi-site observational study[2], and 42.5% of final diagnoses in patients presenting at less than one year to a single center[3]. Metabolic disorders presenting with ALF include galactosemia, tyrosinemia type 1, fatty acid oxidation defects, Wilson disease, mitochondrial hepatopathies, and others[4,5]. Narkewicz et al[2] emphasized that a systematic evaluation for treatable causes in children with ALF, including metabolic diseases, does not occur routinely in many centers.

Urea cycle defects (UCDs) occur in approximately 1/30,000 live births[6]. These disorders are not considered prominent among metabolic diseases that cause severe hepatic dysfunction and ALF[4,5], despite past reports of hepatocellular injury and ALF in individuals with ornithine transcarbamylase deficiency (OTCD)[7–11]. OTCD is the most common UCD, and is an X-linked genetic disorder that affects both males and females. Severely affected males present with marked hyperammonemia in the newborn period. There is variable clinical expression in heterozygote females and in males with residual OTC enzyme activity; individuals of either sex may remain asymptomatic throughout their lifetime with no episodes of hyperammonemia, and symptomatic individuals, with at least one episode of hyperammonemia, can present at any age[12]. Hepatic histology in OTCD may show microvesicular steatosis, focal cell necrosis, aggregates of clear hepatocytes, portal to portal bridging fibrosis, abnormal mitochondria, abnormal peroxisomes, or may appear normal[13–19]. Other UCDs have been associated with hepatocellular injury and liver failure as well[20–28]. Sundaram et al[29] reported that 2 of 148 infants less than 3 months of age (1.4%) with ALF were diagnosed with a UCD, one with OTCD. Despite these reports, OTCD and other UCDs are rarely considered in children and adults presenting with severe liver injury or ALF unless profound hyperammonemia is present; this has resulted in delayed or post-mortem diagnosis[11]. The goal of this study was to determine the frequency of significant liver injury and ALF in patients with OTCD.

An illustrative case is a 19-month-old female who was transferred to UCLA Medical Center for evaluation for liver transplant because of ALF of unknown origin. She had presented to an outside hospital with fever, vomiting, and lethargy, and was found to have an ALT of 906

IU/L, an INR of 3.9, a PTT of 46, and ammonia of 161 μmol/L. Evaluation for infectious hepatitis, autoimmune hepatitis, Wilson disease, and acetaminophen toxicity was negative. Liver biopsy showed acute hepatocellular injury with mild lobular necrosis. Upon further testing it was noted that orotic acid and uracil were elevated in the patient's urine. Pharmacologic treatment of OTCD was initiated on day 10 of hospitalization. Laboratory abnormalities normalized after treatment (Figure 1). The diagnosis of OTCD was confirmed by genotyping which identified a heterozygous c.67C>T (p.R23X) mutation. Liver tissue was not available for enzyme analysis (part 2, case 8, Table III; available at www.jpeds.com).

METHODS

A historical cohort study was conducted at two large metabolic disease centers (Children's Hospital Colorado and UCLA Medical Center). The study was approved by the Institutional Review Board at each center. Records were reviewed of all individuals with OTCD who were followed at these centers between the years 2000 and 2011. They were identified by site records and ongoing clinical care, and through enrollment in the NIH funded, multi-site Longitudinal Study of Urea Cycle Disorders at these two centers, which is an IRB approved, natural history study[30], for which written informed consent was obtained. Many individuals followed clinically for OTCD were also subjects in the NIH study, some asymptomatic individuals were not seen clinically, but were subjects in the NIH study. These two groups constituted all known individuals followed for OTCD at the two centers. OTCD was established in each subject by biochemical test results, molecular diagnosis, or by enzymology. For each subject the following historical information was recorded: age at presentation, sex, OTC mutation if known, clinical presentation, OTC enzyme activity in liver, and liver histology. To assess liver injury the following tests were recorded at least once for every subject: AST, ALT, prothombin time (PT), PTT, and INR. Values were obtained from clinic visits, Longitudinal Study research visits, or hospitalizations. If available, concurrent total and direct bilirubin, Factor V, Factor VII, Factor VIII, D-dimers and fibrinogen were also recorded, as was plasma ammonia. For each subject the time point at which the available liver injury related laboratory results were collected was at the time of the highest recorded PT or INR (or AST/ALT if PT/INR was not performed). Some of the recorded tests may have been obtained at an earlier or later time point that same day. Liver injury related tests were also recorded on every identified occasion that the AST/ALT or PT/INR values met the criteria defined in this study for ALF, liver dysfunction or hepatocellular injury, see below. When possible, outside medical records, including evaluations prior to the identification of a UCD, were reviewed.

For the purposes of this study, *acute liver failure* (ALF) was defined as acute liver injury with an INR ≥ 2.0, or PT ≥ 20 seconds in the absence of disseminated intravascular coagulation[2,29]; *liver dysfunction* as INR ≥ 1.5 and < 2.0 or PT ≥ 15 seconds and < 20 seconds; and *hepatocellular injury* as AST or ALT ≥ 250 IU/L. Lack of response of elevated INR or PT to vitamin K was not included as a criterion for ALF, as this is a retrospective study and vitamin K was not given uniformly.

For the purposes of this study individuals were placed in one of five groups of clinical severity with respect to their urea cycle defect. Individuals were considered to be *Asymptomatic* with respect to OTCD if they had not had episodes of hyperammonemia requiring medical intervention. Individuals with symptomatic OTCD were classified into four groups: *Neonatal Males* who lack residual enzyme activity are the most severe and developed symptoms of hyperammonemia in the first two days of life; *Severe* males and females developed symptoms of hyperammonemia after two days of life, required maximal medical and dietary therapy, and had frequent hospitalizations; *Moderate* males and females required medical and/or dietary therapy, and had less frequent hospitalizations; *Mild* males and females did not have recurrent hyperammonemia after establishment of the diagnosis of OTCD.

Statistical Analyses

A two sample test of proportions was performed comparing the proportion of symptomatic versus asymptomatic OTCD subjects who had ALF, liver dysfunction, or hepatocellular injury. Descriptive statistics (mean, standard deviation, and range for AST, ALT, ammonia, PT and INR) were performed using the STATA program.

RESULTS

Charts of 89 subjects were reviewed from the two centers, and 71 subjects were included in the analysis; 18 subjects were excluded due to lack of sufficient laboratory data, 12 of thom were asymptomatic (Table III; online). For each of the 71 subjects, available liver injury related laboratory tests were recorded at least once. Additional events of ALF, liver dysfunction or hepatocellular injury were observed in several cases and these data were recorded on separate rows. For each individual the most severe liver injury identified (ALF> liver dysfunction>hepatocellular injury) was used for Tables I and II); each individual is included only once in the summary tables.

In this historical cohort of 71 individuals with OTCD, the severity of hepatic synthetic dysfunction, reflected by the PT and INR, correlated with the severity of the OTCD (Table I). The mean PT and INR were higher in *Neonatal Males* and *Severe Females* than in those classified as *Moderate* and *Mild*. Markedly elevated AST (1,063 ± 1,405 IU/L) and ALT (923 ± 828 IU/L) were identified in individuals classified as *Severe*, all of whom were female. Elevations of AST and ALT were moderate in *Neonatal Males* (AST 151 ± 151, ALT 109 ± 86). Mild elevations of ammonia, minimal elevations of AST and ALT, and mild elevations of PT and INR were identified in *Asymptomatic* individuals. Symptomatic individuals classified as *Moderate* or *Mild* had intermediate elevations of ammonia, ALT, AST, PT and INR.

The risk of ALF, liver dysfunction and isolated hepatocellular injury varied with OTCD clinical severity (Table II); 75% of *Neonatal Males* and 67% of *Severe* females showed evidence of liver involvement. Those with less severe OTCD had lower frequencies of liver involvement. ALF was identified most often in individuals classified as *Neonatal Male* (7/12, 58%), or *Severe* (5/9, 56%). Almost half of individuals classified as *Mild* OTCD showed evidence of liver dysfunction or isolated hepatocellular injury at least once in their

clinical course. In some cases ALF or liver dysfunction was associated with hepatocellular injury as defined for this study. All six *Severe* females with ALF or liver dysfunction had concurrent elevated AST or ALT ≥ 250 IU/L and met criteria for hepatocellular injury. Two of nine *Neonatal Males*, with ALF or liver dysfunction had concurrent elevated AST or ALT ≥ 250 IU/L. The two *Moderate* individuals with ALF met had concurrent elevated AST or ALT ≥ 250 IU/L, as did one of three with liver dysfunction. *Mild* individuals with liver dysfunction did not have concurrent AST or ALT ≥ 250 IU/L.

Type of liver injury in symptomatic versus asymptomatic individuals with OTCD is shown in Figure 2. In those individuals with liver injury, serum bilirubin was normal for age, or only mildly elevated (Table III). The proportion of OTCD subjects who had ALF, liver dysfunction or hepatocellular injury was significantly higher in the symptomatic (28 of 49) compared with the asymptomatic (2 of 22) group (p=0.0002).

ALF was the initial clinical presentation of at least three individuals (part 1, cases 7 and 8; part 2, case 8; Table III). ALF was documented to be recurrent in five individuals (part 1, cases 8, 9 and 13; part 2, cases 7 and 8; Table III). Liver dysfunction and hepatocellular injury were also recurrent in some cases. Liver laboratory abnormalities were not always recurrent in subsequent episodes of hyperammonemia, though this was not formally assessed in this study. Two females with severe OTCD had recurrent hyperammonemia, but never had documented liver test abnormalities using the criteria established for this study. Notably, liver histology was abnormal in these two subjects (part 1, cases 11 and 12; Table III).

DISCUSSION

We report the results of a historical cohort study conducted at two large genetic metabolic disease centers, which has identified the presence of significant liver injury and dysfunction in over 50% of individuals with symptomatic OTCD at some time in their clinical history. This report represents a systematic investigation of this association and suggests that a clinical liver presentation, including ALF, is not uncommon among patients with OTCD.

The most severe clinical presentations of UCDs occur in the newborn period, and later-onset presentations may be precipitated by infection, the post-partum period, valproate therapy, or corticosteroid use[12,24,31,32]. As these are treatable conditions in which delay of treatment can result in irreversible neurologic injury or death, testing for UCDs is critical when indicated. Although the urea cycle enzymes are active in the liver, standard liver function has generally been considered to be largely unaffected in UCDs[4,5,33]. However, elevated AST and ALT and coagulopathy were identified in the first reported cases of OTCD in the 1960s and 1970s[34–38], and a Reye syndrome presentation of OTCD was recognized in the 1970s and 1980s[39–42] (Table IV; available at www.jpeds.com). In the late 1980s and early 1990s, neurologic presentations of OTCD were emphasized, with little focus on hepatic injury[43–47]. Since the 1990s there have been rare reports of significant clinical liver disease in patients with OTCD[8,10,48].

As in the case presented here, liver injury in OTCD is often seen in association with elevated ammonia levels (Figure 1). Our study, therefore, required review of the highest recorded liver laboratory tests (AST, ALT, PT, PTT and INR) during hyperammonemic episodes. These data were not collected through the Longitudinal Study, and required local chart review. A limitation of this study is that liver tests were collected for some subjects during hospitalizations, and for others, largely those asymptomatic with respect to OTCD, at study visits in the outpatient setting. This is due to the fact that asymptomatic individuals were not hospitalized frequently, therefore, in some cases the only available liver test results were obtained during study visits. However, in symptomatic individuals, many of whom who were hospitalized, the highest mean PT and INR were in those more severely affected, and the frequency of liver test abnormalities correlated with the severity of OTCD (Tables I and II). This suggests the underlying OTCD as the cause of, or a predisposing factor to, the liver injury. The pathogenesis of liver injury in OTCD is unknown and this study suggests that further work is indicated. It is possible that the liver injury is caused by direct toxicity of ammonia; toxicity of carbamoyl phosphate has been proposed, but this is speculative[49,50].

The observation that liver blood tests may be elevated in individuals with OTCD raises the question of whether regular assessment of liver tests, especially during episodes of hyperammonemia, should be performed. These abnormal tests may resolve with treatment (Figure 1)[25] and may not change initial care, however, in at least one reported case urgent liver transplantation for acute liver failure in OTCD was performed[10]. In addition, the finding of histological abnormalities on liver biopsy[13–19] and reports of hepatocellular carcinoma (HCC) in OTCD patients[49] suggest that recurrent liver injury and chronic inflammation could predispose to the development of HCC, as in other genetic metabolic liver diseases[51]. An increased risk of HCC has implications for long-term treatment and monitoring of patients with OTCD[49]. There are currently no recommendations for HCC screening in OTCD.

The finding of an ALF presentation in OTCD raises the question as to whether undiagnosed OTCD may be responsible for a significant number of indeterminate pediatric ALF patients. In the past decade, a renewed interest in pediatric ALF revealed that an appropriate evaluation to define treatable underlying genetic and metabolic etiologies is not completed for most patients[2]. As a result, patients with metabolic disorders, such as UCDs, may have gone undiagnosed and labeled indeterminate ALF. Indeed, in the Pediatric ALF Study Group registry, only 1 of 148 infants less than 3 months of age had the diagnosis of OTCD (another had an unspecified urea cycle defect) and 56 (38%) were labeled indeterminate[29]. However, OTCD was not investigated in the majority of the indeterminate cases. OTCD can also be a cause of liver failure in adults[11]. Therefore, the current study suggests that OTCD should be considered in all patients with indeterminate ALF, especially those with normal, or mildly elevated, serum bilirubin concentration.

In conclusion, this study demonstrates that clinical hepatic presentations of OTCD may include ALF, liver dysfunction and hepatocellular injury as defined in this report, which may be associated with only moderate elevations of blood ammonia levels that may not call attention to a UCD. To investigate a UCD in a patient with ALF, laboratory evaluation should be expedited[6]. Initial testing should include quantitative plasma amino acids, urine

organic acids and a quantitative urine orotic acid. Specific metabolic treatment can be life-saving, and may reverse ALF, obviating consideration of emergency liver transplantation[23]. The failure to correctly diagnose and treat OTCD may result in irreversible neurologic disability or death, and is a lost opportunity to evaluate family members and to provide genetic counseling[52].

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Appendix

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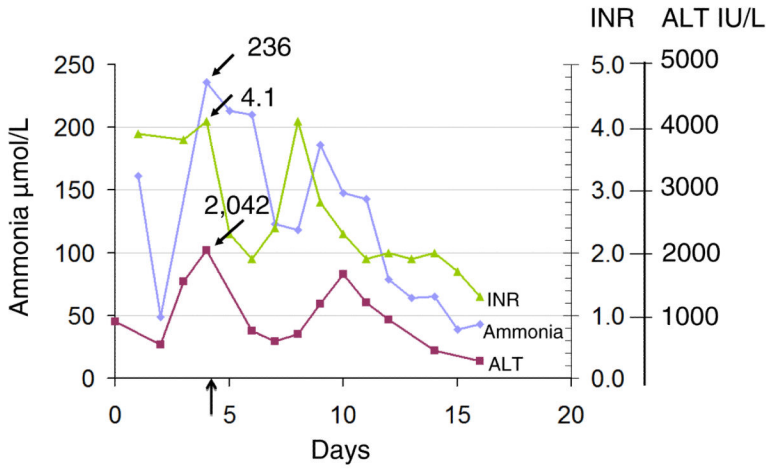

Figure 1.

Time course of plasma ammonia, ALT, and INR in a severe OTCD female during her initial hospitalization at 19 months of life. Dietary treatment was instituted on day 7, and full medical therapy on day 10. The vertical black arrow indicates the time point collected for the chart review in this hyperammonemic episode (part 2, case 8; Table III).

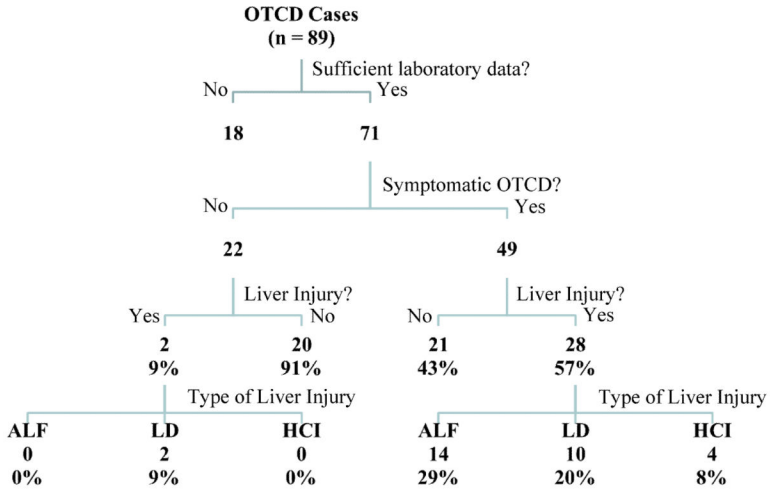

Figure 2.

Summary of types of liver injury present in cases of OTCD followed at the two metabolic disease centers.

Table 1

Liver Laboratory Values in 71 Individuals with OTCD

Clinical Classification (N)	Ammonia µmol/L			ALT IU/L			AST IU/L			PT seconds			INR		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Neonatal Male (12)	1232	817.6	41.1, 2634	109	85.6	22, 256	151	151	25, 467	23	9.8	8.6, 37.6	2.48	1.64	0.9, 6.41
Severe (9)	202	92.1	106, 410	923	827.6	16, 2089	1063	1405	16, 4139	32	19.4	10.6, 63.7	2.92	1.64	1.0, 5.7
Moderate (12)	155	92.4	37.6, 332	331	467.1	13, 1223	137	236	11, 785	14.8	7.4	10.4, 34.9	1.48	0.62	1.0, 3.1
Mild (15)*	72.2	79.7	9, 297	102	187.6	10, 689	71.1	129	14, 519	13	2.4	10.4, 17.6	1.15	0.14	0.95, 1.4
Asymptomatic (22)	39	22.97	9, 104.5	19	10.04	11, 49	23	13.5	10, 62	12	1.8	10.1, 16.2	1.04	0.09	0.92, 1.27

Normal values: Ammonia: < 50 µmol/L (< 80 µmol/L in Neonates); ALT: 10 – 35 IU/L; AST: 15 – 40 IU/L; PT: 12.0 – 15.0 seconds; INR: < 1.5

*One individual was classified as mild but did not survive the initial presentation, his values are not included here.

Table 2

Acute Liver Failure, Liver Dysfunction, and Hepatocellular Injury in 71 Individuals with OTCD

Clinical Classification (N)	Acute Liver Failure	Liver Dysfunction	Hepatocellular Injury Only	No Known Liver Lab Abnormality	Percent with either ALF/LD/HCI
Neonatal Male (12)	58%	17%	0%	25%	75% (9/12)
Severe (9)	56%	11%	0%	33%	67% (6/9)
Moderate (12)	17%	25%	8%	50%	50% (6/12)
Mild (16)	0%	25%	19%	56%	44% (7/16)
Asymptomatic (22)	0%	9%	0%	91%	9% (2/22)

ALF: Acute Liver Failure: INR ≥ 2.0, or PT ≥ 20 **LD:** Liver Dysfunction: INR ≥ 1.5 and < 2.0, or PT ≥ 15 and < 20 **HCI:** Hepatocellular Injury: AST or ALT ≥ 250 IU/L

Table 3

Part 1 OTCD Cases at Children's Hospital Colorado

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
Neonatal Males																
1 Deceased **ALF**	M	4 d	3 day h/o increased RR, progressive encephalopathy	104	81	37.6	3.83	65	6.0	2634	ND	ND	ND	ND	71	5.73
2 Deceased **ALF**	M	2 d	Increased RR, jitteriness, progressive encephalopathy	91	22	35.6	3.3	>250 Dialysis	10.0	2125	ND	ND	ND	ND	119	1.62
3 Deceased **ALF**	M	2 d	Respiratory distress, lethargy	ND	ND	24.3	ND	39.3	5.1	1398	ND	ND	ND	Normal	140	ND
4 Deceased **ALF**	M	2 d	Increased RR, twitching, apnea	45	32	24.0	2.1	45	8.4	1308	ND	ND	ND	OTC enzyme activity 2%. Microvesicular steatosis, mild cholestasis	112	3.64
5 Deceased **LD**	M	2 d	Poor feeding, lethargy	37	130	17.0	1.57	109	3.1	24 (peak 1939)	ND	ND	ND	ND	108	1017
6 Tx **LD HCI**	M	2 d	Emesis	467	256	17.8	1.43	39	5.4	1152	ND	ND	ND	Unremarkable	214	1.79
Severe OTCD																
7 Tx **ALF HCI**	F	1 year	Liver failure, h/o emesis, “reflux” (Had multiple later HA events without LF)	4139	2089	63.7	5.7	49.9	0.4	207	ND	ND	ND	Microvesicular steatosis, mild inflammation, mild portal fibrosis	ND	ND
8 Tx **ALF HCI**	F	Prenatal	Known family history, liver failure at 2 years	2232	2127	23.8	2.52	45	0.8	49 (was > 100)	55 (low)	9.2 (low)	230	OTC enzyme activity 4% Increased glycogen, no fibrosis, diffuse microvesicular steatosis	263	333
ALF HCI	Same pt as above	Same pt as above	Same pt as above	1538	1165	21.5	1.8	45.4	1.2/0.5	40 (was 178)	ND	ND	ND	Same pt as above	ND	ND

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
ALF HCI	Same pt as above	Same pt as above	Same pt as above	2401	1692	23.6	1.97	43.6	0.5	216	39.9 (low)	17.7 (low)	130.2	Same pt as above	ND	< 200
ALF HCI	Same pt as above	Same pt as above	Same pt as above	74 (went up to 869)	178 (went up to 997)	52.3	3.76	58.5	0.4	171	60.4 (low)	<4.0 (low)	192	Same pt as above	227	< 230
9 Tx **ALF HCI**	F	5 years	Emesis, lethargy with UTIs	377	1083	19	2.4	ND	ND	ND	ND	ND	ND	OTC enzyme activity 7.8% Diffuse glycogenation of hepatocytes with minimal portal fibrosis	ND	ND
ALF HCI	Same pt as above	Same pt as above	Same pt as above	57	446	18.8	2.66	ND	ND	ND	ND	ND	ND	Same pt as above	ND	ND
ALF HCI	Same pt as above	Same pt as above	Same pt as above	1212	1749	28.4	ND	ND	1.1/0.4	41 (was 167)	49 (low)	19 (low)	ND	Same pt as above	ND	ND
LD	Same pt as above	Same pt as above	Same pt as above	ND	ND	15.7	1.52	ND	ND	88 (was 118)	ND	ND	ND	Same pt as above	ND	ND
10 Diet/Bu/Cit **LD HCI**	F	3 years	2 year h/o emesis, AMS, recurrent vision loss	2039	1605	17.5	1.39	40	0.8	111 (was 410)	ND	ND	ND	ND	227	1.09
11 Tx No liver injury	F	4 years	Mother died of OTCD	20	41	14.9	1.29	37.3	0.4	106	ND	ND	ND	Path at tx – mild peripoprtal fibrosis, patchy centrilobular architectural collapse	ND	ND
12 Tx No liver injury	F	3 d	Lethargy and poor feeding, progressive encephalopathy	80	169	ND	ND	ND	0.4	192	ND	ND	ND	OTC activity very low Ballooning hepatocytes, multinucleation granular cytoplasm, minimal periportal fibrosis	ND	ND
Moderate OTCD																
13 Diet/Bu/Arg **ALF HCI**	M	3 years	Recurrent emesis	615	1938	22.8	1.84	38	0.2/0.0	46 (was 160)	ND	ND	ND	OTC activity 10% Patchy ballooning hepatocytes, glycogneated nuclei	ND	ND

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
ALF **HCI**	Same pt as above	Same pt as above	See above	ND	1088	ND	2.1	ND	ND	ND	ND	ND	ND	Same pt as above	ND	ND
HCI	Same pt as above	Same pt as above	See above	ND	1530	ND	ND	ND	ND	ND	ND	ND	ND	Same pt as above	ND	ND
14 Diet/Bu/Arg **ALF** **HCI**	M	3 years	Illness, affected sib	785	1223	34.9	3.1	48	0.3	108	ND	ND	ND	ND	ND	ND
Mild OTCD																
15 Diet/Be/Cit **LD**	F	2 years	Altered mental status	41	67	17.6	1.4	55	0.4	198	ND	ND	ND	ND	ND	ND
16 **LD** Arg	M	11 y	Valproate induced hyperammonema h/o autism, delay, recurrent emesis	14	14	15.6	1.21	29	0.1	144	ND	ND	ND	ND	ND	ND
LD	Same pt as above	Same pt as above	Same pt as above	23	10	16	1.28	33	0.4	<9	ND	ND	ND	Same pt as above	232	ND
17 Cit **LD**	F	NA	Family history, brother with neonatal OTC	18	27	15.4	1.16	30	0.6	91	ND	ND	ND	ND	ND	ND
LD	Same pt as above	Same pt as above	Same pt as above	17	27	15.8	1.28	32	0.7	99	ND	ND	ND	Same pt as above	236	ND
LD	Same pt as above	Same pt as above	Same pt as above	21	28	15.3	1.18	31	0.9	35	ND	ND	ND	Same pt as above	ND	ND
LD	Same pt as above	Same pt as above	Same pt as above	26	43	15.6	1.22	30	1.2	ND	ND	ND	ND	Same pt as above	281	ND
18 Bu/Cit **LD**	F	2 y	Intermittent ataxia, abnormal eye movements, family history, brother with neonatal OTC	43	31	15.1	1.16	39	0.3	48	ND	ND	ND	ND	ND	ND
LD	Same pt as above	Same pt as above	Same pt as above	25	18	15.2	1.14	33	0.5	56	ND	ND	ND	Same pt as above	ND	ND
LD	Same pt as above	Same pt as above	Same pt as above	26	14	15.4	1.19	37	0.4	36	ND	ND	ND	Same pt as above	175	ND
19 Arg **HCI**	M	1st year	Recurrent emesis, increased AST/ALT	519	689	ND	ND	ND	0.2/0.8	ND	ND	ND	ND	Scattered individual hepatocytes with nonspecific degeneration	ND	ND

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
20 No Rx **HCI**	M		Neonatal presentation, suspected mosaic due to current status	150	317	13.6	1.26	35	0.5	33	ND	ND	ND	ND	ND	ND
21 Bu/Arg No liver injury	F	27 y	Son with neonatal OTCD	30	14	14.0	1.04	28	0.6	23	ND	ND	ND	ND	208	ND
22 No current Rx, was on Bu/Arg No liver injury	F	37 y	Family history, possible seizures	23	39	13	0.95	29	0.2	29	ND	ND	ND	ND	271	ND
No Symptoms/Treatment																
23 No Rx **LD**	F	NA	Family history	12	14	16.2	1.27	32	0.4	57	ND	ND	ND	ND	195	ND
24 No Rx **LD**	F	NA	Family history	51	44	15.6	1.21	33	0.4	40	ND	ND	ND	ND	201	ND
25 No Rx No liver injury	M	10 y	Brother with hyperammonemia	37	19	14.2	1.09	32	0.7	22	ND	ND	ND	ND	252	ND
26 No Rx No liver injury	F	NA	Family history	34	49	13.3	0.98	30	0.3	<9	ND	ND	ND	ND	304	ND
27 No Rx No liver injury	F	NA	Family history	19	11	12.7	0.92	29	0.3	13	ND	ND	ND	ND	369	ND
28 Cit since birth, Asx No liver injury	F	NA	Affected brother	62	21	13.4	0.98	30	1.2	20	ND	ND	ND	ND	249	ND
29 No Rx No liver injury	F	NA	Three affected children	20	12	13.1	0.96	32	0.5	57	ND	ND	ND	ND	351	ND
30 No Rx No liver injury	F	37	Affected son	34	19	13.6	1.01	29	0.5	39	ND	ND	ND	ND	285	ND
31 No Rx No liver injury	F	21	Affected son	15	12	12.8	0.94	29	0.4	< 9	ND	ND	ND	ND	342	ND

Table 3 Part 2. OTCD Cases at UCLA.

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
Neonatal Males																
1 Deceased **ALF**	M	2 d	Poor feeding, lethargy, then seizure, then apnea, and then NH_3 = 1734.	202	188	32.9	3.2	151.2	14.1/1.9	1293	ND	ND	ND	ND	67	ND
2 Deceased **ALF**	M	9 d	Pulmonary hemorrhage on DOL 3, hyperammonemia on DOL 9.	138	94	22.8	2.3	38.7	25.2/14.6	1744	19.9% act.	19.6% act.	ND	Hepatomegaly, splenomegaly; green, homogeneous liver parenchyma, geographic fibrosis with bile stasis noted.	158	ND
3 Tx **ALF** HCI	M	1 d	Brother had passed away of OTC, lethargy on DOL 1, needed hemodialysis.	406	242	32.6	6.4	>180	8.2/5.8	256	ND	ND	ND	Diffuse macro and micro vesicular steatosis, moderate cholestasis, no evidence of hepatitis.	66	ND
4 Tx No Liver Injury	M	2 d	Poor feeding, irritable, hyperammonemia, coma by 36 hours of life	93	93	14.3	1.1	41	4.3	143	ND	ND	ND	ND	ND	ND
5 Diet/Bu/Be No Liver Injury	M	prenatal	Diagnosed *in utero* (mother is OTC carrier), neonatal seizures.	49	39	10.8	1.1	31.3	0.6	41	ND	ND	ND	ND	159	ND
6 Tx No Liver Injury	M	1 d	Poor feeding and lethargy at 24–30 hours of life.	25	22	8.6	0.9	26	2.2/1.0	754	ND	ND	ND		233	ND
Severe OTCD																
7 Diet/cit/arg/Be/Ac **ALF** **HCI**	F	5 y	Increased irritability with ketosis.	419	900	37.7	3.5	62	0.6	133	ND	ND	ND	ND	ND	ND
ALF **HCI**	Same pt as above	Same pt as above	See above	3204	4407	26.3	2.4	43	1.4	492	ND	ND	ND	ND	176	2
8 Diet/Bu/Cit **ALF** **HCI**	F	1 yo 7 m	Presented with h/o chronic n/v, with acute fever, vomiting, seizures found to be in acute liver failure.	1932	2042	39.5	4.1	39.9	0.4/0.1	220	70%	11% act.	211% act	Acute hepatocellular injury with mild lobular necrosis, paucity of inflammatory infiltrate.	245	ND

Table 3 Part 2. OTCD Cases at UCLA.

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
ALF HCI	Same pt as above	Same pt as above	Same pt as above	6299	5519	21.4	2.1	35.1	0.3	443	39%	13%	ND	ND	228	ND
9 Diet/Bu/Arg Carnitine No Liver Injury	F	6 y	Reccurent abd pain/n/v/ataxia.	16	16	10.6	1	27.8	0.4	174	ND	ND	ND	ND	242	ND
Moderate OTCD																
10 Diet/Bu/Cit **HCI**	F	3 yo 7 m	AGE with persistently elevated AST/ALT	59	216	11.9	1.2	31.3	0.5	253	ND	ND	ND	ND	236	ND
HCI	Same pt as above	Same pt as above	Same pt as above	309	65	ND	ND	ND	0.6	ND	ND	ND	ND	ND	ND	ND
11 Diet/Be **LD)**	F	12 m	Lethargy, hyperammonemia, left sided weakness, multiple, bilateral foci of stroke R>L.	123	167	17.5	1.8	30.2	0.5	97	ND	ND	ND	ND	181	ND
12 Diet/Bu **LD**	M	20 m	Chronic emesis, elevated ammonia.	21	25	15.2	1.5	26	0.5	235	ND	ND	ND	ND	206	ND
13 Diet/Be/Cit **LD HCI**	F	13 m	Fever, emesis × 5 mo, lethargy, irritability, elevated liver enzymes, coagulopathy.	337	959	16.6	1.7	53	0.2	159	ND	ND	ND	ND	305	ND
14 Diet/Bu No Liver Injury	F	4 y	N/v + FH of OTC. in brother	11	13	11.6	1.1	26.3	0.4	213	ND	ND	ND	ND	192	ND
15 Diet/Bu No Liver Injury	M	9 y	Occasional lethargy and inability to function, hyperammonemia.	14	25	10.6	1	27.2	0.6	132	ND	ND	ND	ND	222	ND
16 Diet No Liver Injury	M	13 m	URI + lethargy, hyperammonemia.	102	191	11.4	1.1	28	0.5	214 (later 332)	ND	ND	ND	ND	198	ND
17 Diet/Cit No Liver Injury	M	12 y	Hyperammonemia with coma.	18	28	11.4	1.1	30	0.8	55	ND	ND	ND	ND	165	ND
18 Diet/BuCit No Liver Injury	F	ND	ND	20	13	10.4	1	26	0.4	38	ND	ND	ND	ND	226	ND
19 Diet/Cit/Arg Carnitine No Liver Injury	F	16–20 m	Hyperammonemia and coma.	14	21	10.8	1.1	29.6	ND	86	ND	ND	ND	ND	285	ND

Table 3 Part 2. OTCD Cases at UCLA.

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
Mild OTCD																
20 Diet/Bu **HCI**	F	7 yo 2 m	Frank confusion and hyperammonemia with h/o intermittent abdominal pain and nausea.	97	252	11.3	1.1	ND	0.3	27 (was 297)	ND	ND	ND	ND	ND	ND
21 Diet/Be/Cit No Liver Injury	F	1 y	Nausea/vomiting + FH with sister with OTC.	41	14	ND	ND	ND	0.4	35	ND	ND	ND	ND	226	ND
22 Diet/BuArg No Liver Injury	F	2 m	FH of brother with OTC	25	20	11.3	1.2	ND	ND	55	ND	ND	ND	ND	ND	ND
23 Diet/Be/Cit/Carnitine No Liver Injury	M	3 y 2 m	Lethargy, hyperammonemia, nausea, vomiting, and history of headache head hitting and decreased attention.	24	11	10.7	1	29.6	0.7	42	ND	ND	ND	ND	253	ND
24 Deceased No Liver Injury	M	13 y 11 m	H/o learning disabilities, and schizoaffective disorder, lethargy, coma, hyperammonemia, brain herniation	78	63	13.4	1.4	43	0.4/0.1	2372	ND	ND	ND	Hepatomegaly (3030g), diffuse micro and macrovesicular steatosis.	ND	ND
25 Diet/Bu No Liver Injury	F	9 m	Stroke and hyperammonemia	14	10	ND	ND	ND	0.3	63	ND	ND	ND	ND	ND	ND
26 No Rx No Liver Injury	M	30 y	Coma with Meclizine + FH (brother with OTC)	14	22	10.4	1	30.5	ND	32	ND	ND	ND	ND	335	ND
27 Diet/Cit No Liver Injury	F	ND	Infrequent irritability, + FH (3 sisters with OTC)	23	18	11.8	1.1	30.5	2.1	60	ND	ND	ND	ND	ND	ND
No Symptoms/Treatment																
28 No Rx No Liver Injury	F	N/A	Family History	12	11	10.8	1.1	27	0.4	65	ND	ND	ND	ND	282	ND
29 No Rx No Liver Injury	F	N/A	Family History	15	15	10.4	1	27.9	0.4	39	ND	ND	ND	ND	245	ND
30 No Rx No Liver Injury	F	N/A	Family History	12	13	10.4	1	25.9	0.4	43	ND	ND	ND	ND	319	ND
31 No Rx	F	N/A	ADHD and Family History	17	26	10.6	1	28	0.7	49	ND	ND	ND	ND	249	ND

Table 3 Part 2. OTCD Cases at UCLA.

Case No. Current status/Rx Liver Injury	Gender	Age	Presentation	AST IU/L	ALT IU/L	PT sec	INR	PTT sec	Bili	NH_3 umol/L	V	VII	VIII	Liver histology	Fibrinogen	D-dimers
No Liver Injury																
32 No Rx No Liver Injury	F	N/A	Family History	10	11	11	1.1	29.1	0.5	40	ND	ND	ND	ND	230	ND
33 No Rx No Liver Injury	F	N/A	Family History	21	18	10.1	1	28.3	0.5	37	ND	ND	ND	ND	298	ND
34 No Rx No Liver Injury	F	N/A	Family History	10	11	10.7	1	28.9	0.3	23	ND	ND	ND	ND	341	ND
35 No Rx No Liver Injury	F	N/A	Family History (son)	14	17	11	1.1	27.5	0.5	26	ND	ND	ND	ND	310	ND
36 No Rx No Liver Injury	F	N/A	Family History (son)	24	22	10.5	1	25.9	0.5	34	ND	ND	ND	ND	217	ND
37 No Rx No Liver Injury	F	N/A	Family History	20	16	11.2	1.1	24.5	0.6	25	ND	ND	ND	ND	142	ND
38 No Rx No Liver Injury	F	N/A	Family History	14	12	10.8	1	26.7	0.5	105	ND	ND	ND	ND	250	ND
39 No Rx No Liver Injury	F	N/A	Family History	20	20	10.6	1	28.7	1.1	32	ND	ND	ND	ND	256	ND
40 No Rx No Liver Injury	M	N/A	Family History (daughters)	24	25	11.7	1.2	29.4	1	78	ND	ND	ND	ND	212	ND

Legend: **LF:** Acute liver failure. **LD:** Liver dysfunction. **HCI:** Hepatocellular injury. **RR:** Respiratory rate. **Rx:** Treatment. **Tx:** Liver transplant. **ND:** Not done. **AMS:** Altered mental status. **Diet:** Dietary therapy, restriction of natural protein +/− use of essential amino acids. **Arg:** Arginine therapy. **Cit:** Citrulline therapy. **Bu:** Sodium phenylbutyrate. **Be:** Sodium benzoate. **Asx:** Asymptomatic. **NH_3:** Ammonia. **HA:** Hyperammonemic.

Legend: **ALF:** Acute liver failure. **LD:** Liver dysfunction. **HCI:** Hepatocellular injury. **RR:** Respiratory rate. **Rx:** Treatment. **Tx:** Liver transplant. **ND:** Not done. **AMS:** Altered mental status. **Diet:** Dietary therapy, restriction of natural protein +/− use of essential amino acids. **Arg:** Arginine therapy. **Cit:** Citrulline therapy. **Bu:** Sodium phenylbutyrate. **Be:** Sodium benzoate. **Asx:** Asymptomatic. **NH_3:** Ammonia. **HA:** Hyperammonemic. **N/v:** Nausea and vomiting. **DOL:** day of life. **FH:** Family History. **URI:** Upper respiratory tract infection. **ADHD:** Attention deficit hyperactivity disorder.

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Table 4

Twenty-Four Literature Cases of OTCD with Acute Liver Failure, Liver Dysfunction or Hepatocellular Injury

Sex Liver Injury	**Age**	**Presentation**	**AST IU/L**	**ALT IU/L**	**PT**	**INR**	**PTT**	**Bili**	**NH_3 μmol/L**	**V**	**Author**	**Year**
F **HCI**	4 y	Recurrent emesis, lethargy, hemiparesis stupor (Case 10 in literature)	2,232	2,610	NR	NR	NR	NR	658	NR	Sunshine38	1972
M **HCI**	10 m	Emesis, hypotonia, brother died at 7 months	1,590	740	NR	NR	NR	NR	NR	NR	Van der Heiden53	1978
F **HCI**	14 m	Episodic emesis, loss of milestones	600	NR	NR	NR	NR	NR	Unknown (later 315 and 407)	NR	La Brecque13	1979
M **HCI**	15 m	Recurrent “Reye syndrome”	542	481	NR	NR	NR	NR	29	NR	Yokoi41	1981
M **ALF HCI**	9m	Emesis, seizures, encephalopathy	NR	1,200	28%	NR	NR	NR	406	NR	Landrieu15	1982
M **HCI**	21 y	Emesis, nausea, progressive encephalopathy, death, brother died at 10 years	720	561	NR	NR	NR	Nl	1,012	NR	Tallan16	1983
F **HCI**	2 y	Emesis, lethargy, “Reye syndrome”	679	976	NR	NR	NR	NR	113	NR	Hayasaka54	1987
M **HCI**	6 m	Emesis, episodic lethargy, Coagulation “severely disturbed”	900	600	NR	NR	NR	NR	NR	NR	Wendel55	1989
M **LD**	12.5 years	Emesis, lethargy, altered mental status – combative	90	86	17.2	NR	NR	6.4	282	NR	Capistrano-Estrada56	1994
F **HCI**	23 m	Recurrent emesis, lethargy,	777	1,213	NR	NR	NR	NR	1026	NR	Pridmore46	1994
		extensor plantar reflexes										
F **HCI**	22 m	Recurrent emesis, lethargy, delay, acute cerebellar ataxia with increased AST/ALT, “atypical Reye syndrome”	1,052	275	NR	NR	NR	NR	218	NR	Pridmore46	1994
M **HCI LD**	13 y	Emesis, ataxia, altered mental status, clonus	68	347	16.5	NR	NR	2.4 (0.1)	408	NR	Myers47	1995
F **HCI**	3 y	Emesis	1,206	1,663	42%	NR	43	NR	294	NR	Zammarchi48	1996
F **ALF HCI**	5 m	Emesis	1,692	2,328	18%	NR	48	NR	150	NR	Zammarchi48	1996

Sex Liver Injury	Age	Presentation	AST IU/L	ALT IU/L	PT	INR	PTT	Bili	NH_3 µmol/L	V	Author	Year
F **LD**	3 y	Coma in illness	187	114	17.6	NR	NR	NR	343	NR	Inui57	1996
F **ALF**	3 d	Hypoglycemia, lactic acidemia, seizures, hypotonia	NR	NR	NR	NR	NR	NR	2301	10%	Klowsowski58	1998
F **HCI**	3 y	Aggression, confusion, abnormal movements	NR	299	NR	NR	NR	NR	NR	NR	Schultz59	2000
F **HCI**	28 y	GI bleed	196	466	15	1.3	NR	1.1	247	NR	Trivedi7	2001
M **HCI**	15 m	Recurrent emesis, elevated AST/ALT, FTT, normal ammonia, Gln, orotic, possible HFI	300	1,727	NR	NR	NR	NR	40	NR	Burlina60	2006
F **ALF** **HCI**	14 m	Emesis	2,212	3,609	NR	5.1	67 s	Nl	74	NR	Mustafa8	2006
M **HCI**	36 y	Lethargy post steroid treatment	295	317	NR	1.1	NR	3.1/0.9	494	NR	Atiq9	2008
F **ALF** **HCI**	3 y	Emesis, lethargy, aggression	7,900	5,000	NR	3.1	NR	NR	161	25%	Teufel10	2009
M **ALF**	24 y	Emesis, hallucinations, h/o ADHD, growth retardation	114	NR	NR	2.7	NR	Nl	348	Low	Thurlow11	2010
F **ALF**	1.5 y	Cyclic vomiting, lethargy	NR	3,500	55	NR	NR	NR	207	NR	Mira61	2011

Legend: **ALF:** Acute liver failure. **LD:** Liver dysfunction. **HCI:** Hepatocellular injury. **V:** Factor V. **RR:** Respiratory rate. **Rx:** Treatment. **Tx:** Liver transplant. **ND:** Not done. **AMS:** Altered mental status. **HFI:** Hereditary fructose intolerance. **ADHD:** Attention deficit hyperactivity disorder. **FTT:** Failure to thrive. **NR:** Not recorded. **Gln:** Glutamine **F:** Female. **M:** Male, **m:** Months old. **y:** Years old. **Nl:** Normal