Journal of Inherited Metabolic Disease (2018) 41:689–698
https://doi.org/10.1007/s10545-018-0157-4

ORIGINAL ARTICLE

The impact of ammonia levels and dialysis on outcome in 202 patients with neonatal onset urea cycle disorders

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Received: 22 November 2017 / Revised: 19 January 2018 / Accepted: 6 February 2018 / Published online: 8 March 2018

Abstract

Neonatal onset hyperammonemia in patients with urea cycle disorders (UCDs) is still associated with high morbidity and mortality. Current protocols consistently recommend emergency medical and dietary management. In case of increasing or persistent hyperammonemia, with continuous or progressive neurological signs, dialysis is performed, mostly as ultima ratio. It is presently unknown whether the currently defined ammonia threshold (e.g., at 500 μmol/L) to start dialysis is useful to improve clinical outcome. A systematic review of clinical and biochemical data from published neonatal onset UCD patients was performed to identify factors determining clinical outcome and to investigate in which clinical and biochemical setting dialysis was most effective. A total of 202 patients (118 proximal and 84 distal UCDs) described in 90 case reports or case series were included according to predefined inclusion/exclusion criteria. Median age at onset was three days and mean ammonia that triggered start of dialysis was 1199 μmol/L. Seventy-one percent of all patients received any form of dialysis. Total mortality was 25% and only 20% of all patients had a "normal" outcome. In general, patients with higher ammonia levels were more likely to receive dialysis, but this had for most patients no influence on outcome. In conclusion, in severe neonatal onset hyperammonemia, the current practice of dialysis, which effectively clears ammonia, had no impact on outcome. It may be essential for improving outcome to initiate all available treatment options, including dialysis, as early as possible.

Introduction

Urea cycle disorders (UCDs) are inherited conditions affecting ammonia detoxification (Brusilow and Horwich 2001; Häberle and Rubio 2016). In the mammalian organism, the urea cycle, located exclusively in periportal hepatocytes, is responsible for ammonia detoxification and arginine biosynthesis (Häussinger 1990).

Five enzymes and two transporters form the urea cycle. Of these, carbamoyl phosphate synthetase 1 (CPS1, MIM *608307) and ornithine transcarbamylase (OTC, MIM *300461) are located in the mitochondrial matrix; and argininosuccinate synthetase (ASS, MIM *603470), argininosuccinate lyase (ASL, MIM *608310) and arginase 1 (ARG, MIM *608313) in the cytosol. Regarding the transporters, the ornithine/citrulline antiporter (ORNT 1, MIM *603861) is responsible for exchange of ornithine and citrulline across the mitochondrial membrane, while the aspartate/glutamate antiporter citrin (MIM *603859) transports aspartate (a substrate of ASS) from the mitochondrion into the cytosol (Palmieri 2008). In addition, the urea cycle requires the activity of N-acetylglutamate synthase (NAGS, MIM *608300) to produce the allosteric activator of CPS1, N-acetylglutamate (NAG) (Sancho-Vaello et al 2016), and intramitochondrial supply of bicarbonate by carbonic

Martina Huemer and Johannes Häberle contributed equally to this work.

Responsible Editor: Carlo Dionisi-Vici

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10545-018-0157-4) contains supplementary material, which is available to authorized users.

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anhydrase Va (CAVA, MIM *114761) (Häberle and Rubio 2016; van Karnebeek and Häberle 2015).

Dysfunction of any of these enzymes or transporters results in primary hyperammonemia (Häberle 2013). Except for the most common UCD, OTC deficiency (OTCD, MIM #311250), which is X-linked, all UCDs are autosomal recessive disorders (Ah Mew et al 1993). The incidence has been estimated to 1/35,000 but is variable in different populations (Jalan et al 2016; Keskinen et al 2008; Summar et al 2013).

Even though patients can present first symptoms at any age, about half of the UCD patients present neonatally (Bachmann 2003; Nassogne et al 2005). Disease manifestation beyond 28 days is classified as late onset (Burgard et al 2016).

Long-term treatment of UCDs is based on a low-protein diet supplemented with essential amino acids, vitamins, and trace elements (Häberle et al 2012; Leonard and Morris 2002). In addition, nitrogen scavengers, such as sodium benzoate and/or sodium or glycerol phenylbutyrate, provide an alternative pathway for nitrogen removal (Batshaw 1983; Batshaw et al 2001; Berry et al 2014; Brusilow et al 1979; Diaz et al 2013). L-arginine and/or L-citrulline are applied in all UCDs deficient of these intermediary urea cycle metabolites (Brusilow 1984). Liver transplantation is recommended for patients with severe disease and a high risk for recurrent metabolic crises (Häberle et al 2012; Morioka et al 2005).

In the event of acute life- or brain-threatening hyperammonemia, extracorporeal detoxification is the treatment of choice. Of the different techniques available, hemodialysis or hemo(dia)filtration, at times combined with extracorporeal membrane oxygenation (Summar et al 1996), are superior to peritoneal dialysis in eliminating blood ammonia (Schaefer et al 1999). The current European UCD guidelines recommend to start extracorporeal detoxification as soon as plasma ammonia levels exceed 500 μmol/L; this threshold, however, was based on expert opinion rather than on systematic research or specific scientific evidence (Häberle et al 2012).

The recommendation to use a threshold for starting dialysis is challenged by a recent meta-analysis which could not detect significant improvement of survival in UCD patients over more than three decades (Burgard et al 2016). Furthermore, in a Japanese cohort of 177 patients (including 77 cases of neonatal-onset UCDs), investigated between 1999 and 2009, low peak ammonia levels strongly correlated with improved survival and neurological outcome (Kido et al 2012). Based on this, the authors suggested that patients with a peak ammonia level > 180 μmol/L should receive hemodialysis (Kido et al 2012).

In conclusion, while the efficacy of dialysis to remove ammonia is unquestioned, the optimal approach to apply this method is still unclear. The aim of this study is to add information on the optimal starting point for extracorporeal detoxification in neonatal onset UCDs. To do so, we performed a systematic review of clinical and biochemical data from published neonatal onset UCD patients to identify factors with an impact on outcome and to investigate in which clinical and biochemical setting dialysis was most effective.

Aims and hypotheses

Specific research questions were:

- Does the diagnosis or the diagnosis-group (proximal versus distal UCD) have an impact on outcome and especially on mortality?
- Was there a change of outcome or treatment modalities over recent decades?
- What is the influence of the ammonia level that triggers start of dialysis on outcome and especially on mortality?
- Does the use of dialysis vary between disorders or between diagnosis-groups (proximal versus distal UCD)?
- Are patients with higher trigger ammonia levels more likely to receive dialysis?
- What is the influence of dialysis on outcome?
- Is it possible to define a threshold of ammonia to guide initiation of dialysis?

Methods

Literature search

MEDLINE was searched for publications (https://www.ncbi.nlm.nih.gov/pubmed) until 24 January 2016 using the following search terms: “UCD”, “urea cycle disorder”, “urea cycle defect”, “carbamoyl-phosphate synthetase deficiency 1”, “carbamylphosphate synthetase deficiency 1”, “CPS1”, “ornithine transcarbamylase deficiency”, “OTCD”, “argininosuccinate synthetase deficiency”, “ASS”, “CTLN1”, “citrullinemia”, “argininosuccinate lyase deficiency”, “argininosuccinic aciduria”, “ASL”, “ASA”, “arginase deficiency”, “argininemia”, “hyperargininemia”, “ARG”, “N-acetylglutamate synthase deficiency” or “NAGS”, together with “hyperammonemia”, “hyperammonaemia” and “neonat*” or “newborn”. The list of references of all retrieved articles were searched for further suitable studies and an additional 17 publications describing 36 patients were added during the review process of this paper. In one case, we got in contact with the corresponding author of a publication (Choi et al 2015) to include unpublished additional data into our database.

Inclusion and exclusion criteria

All publications in English or German reporting patients with a neonatal onset (≤28 days) UCD (namely defects of NAGS, CPS1, OTC, ASS, ASL, and ARG1) were included, evaluated and screened for relevant data. We did not include patients with defects in either of the transporters.

Information on blood ammonia levels, details on use and method of extracorporeal detoxification, and basic outcome data including survival was required for inclusion in the study. In most publications only one blood ammonia level (either peak ammonia or ammonia at presentation) was reported. When additional ammonia levels were described, we either entered the maximum level during the initial presentation or the ammonia value that reportedly had triggered the initiation of dialysis ("trigger ammonia"). Exclusion criteria were non-human reports, other diagnoses, late onset disease, missing of any of the above listed data, prenatal diagnosis of a UCD or patients who remained asymptomatic after birth. The selection process is summarized in Fig. 1.

Data analysis

All relevant data of the 202 included patients were complete with the exception of missing information on exact age at onset in five patients (McBride et al 2004).

First, a descriptive analysis was performed with regard to medical characteristics of the cohort. This included the exact diagnosis, age at onset (days), age at follow up (days), trigger ammonia, and the therapeutic modality (hemodialysis/hemofiltration, peritoneal dialysis, or no dialysis). Data analysis was done separately for single disorders and for the groups "proximal UCD" (comprising deficiencies of NAGS, CPS1, and OTC) and "distal UCD" (comprising deficiencies of ASS, ASL, and ARG) (Ah Mew et al 2013). Further, we analyzed the entire cohort but also divided in arbitrarily defined groups according to their level of trigger ammonia (group 1: ≤350 μmol/L, group 2: 351–500 μmol/L, group 3: 501–750 μmol/L, group 4: 751–1000 μmol/L, group 5: >1000 μmol/L). The main outcome parameters studied were "normal outcome" (according to the description of the patient in the respective paper), "deceased", "handicapped" (if any signs of physical or cognitive impairment due to hyperammonemia were reported), and "alive but with no further information" (alive-no-info) according to the classification in (Kido et al 2012).

Data were analyzed using the IBM SPSS Statistical Software Package for Macintosh (version 21). All variables were descriptively reviewed, and wherever needed, grouped for further analyses. Fisher's exact tests were used to compare categorical variables. Student's t-tests and one-way ANOVAs were computed to compare means of ammonia levels across different groups and decades. Mann-Whitney test was used to compare groups with regard to ordinal variables. All analyses were performed with two-sided tests; an alpha of .05 or a p-value <.05 were considered significant, correspondingly.

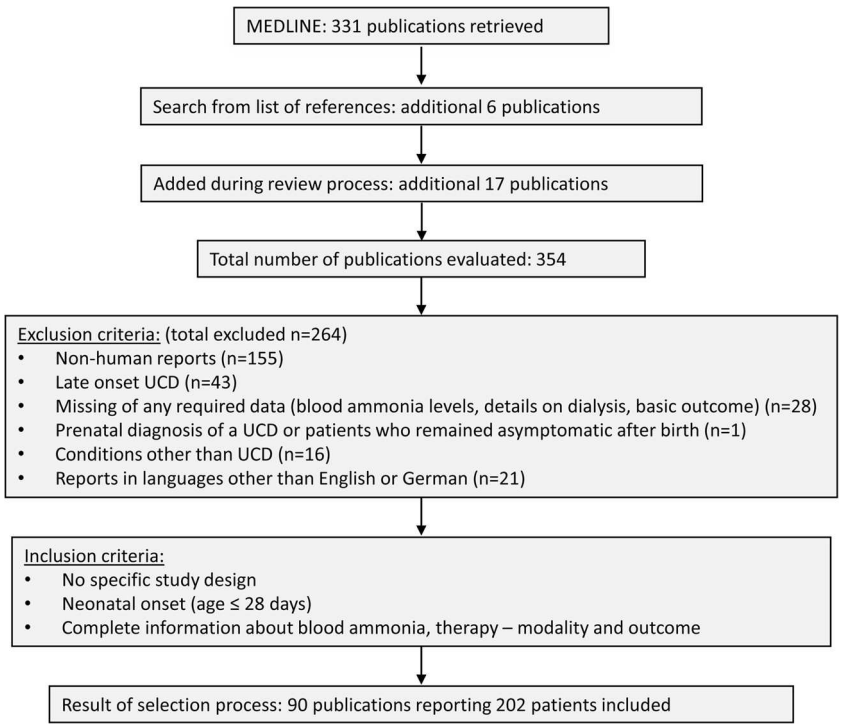


Fig. 1 Diagram schematizing the steps of the selection process of patients for this study. The criteria for inclusion and exclusion of patients are listed

Results

Study selection and patient cohort

The search in MEDLINE identified 331 manuscripts published between July 1971 and January 2016. In addition, six reports were found by reference search (Go et al 2012; Hanudel et al 2014; Jorda et al 1986; Picker et al 2003; Takahashi et al 2015; Woo et al 2013) and 17 publications were added during the review process. Finally, 202 patients with neonatal onset UCD were considered eligible. The process of inclusion or exclusion is summarized in Fig. 1.

Of the selected 90 publications, 39% had been published between 2001 and 2010 and 38% had been published between 2011 and 2016. Thirty-seven reports were from Europe, 28 from North America, 24 from Asia, and one report from Australia.

Basic characteristics of the included cases

Clinical and biochemical details of the 202 patients, dialysis modality, and the outcome of the patients are listed in Suppl. Table 1. The majority of patients in this study ($n = 118$, 58%) were affected by a proximal UCD; 84 patients (42%) suffered from a distal UCD. The most frequent disorder was OTCD ($n = 66$, 32%) followed by ASSD ($n = 54$, 27%) (Fig. 2a). Of the 66 OTCD cases, the vast majority ($n = 59$) were male and only two were female (plus five with no information on the gender) rendering a separate gender specific analysis not useful.

Basic data of the cohort including median age at onset and at follow-up as well as mean trigger ammonia and outcomes are included in Table 1. Of the total 202 patients, 75% were reported to be alive at the time of the report. There was a significant association between outcome and types of UCDs ($\chi^2(5) = 13.471$, $p = .013$). Proximal UCDs were associated with a significantly higher mortality: 33% of these patients died compared to 14% with a distal UCD ($\chi^2(1) = 9.155$, $p = .003$). Figure 2b illustrates outcome categories specific for the different UCDs.

Trigger ammonia and mortality

The trigger ammonia of deceased patients (mean = 1501 μmol/L, SD = 1052) was significantly higher (t = −2.530; df = 68.604; $p = .014$) than in survivors (mean = 1097 μmol/L, SD = 762) (Suppl. Table 1).

Use of dialysis

A total of 143 patients (71%) received either peritoneal dialysis or hemodialysis (Suppl. Table 1). Dialysis was similarly often performed in proximal ($n = 79$, 70%) and distal ($n = 64$, 76%) UCDs ($\chi^2(1) = 2.027$; $p = .155$) (Fig. 2c). In OTCD patients, who had a mean trigger ammonia of 1298.6 μmol/L (SD = 876.3; $n = 66$), 40 (61%) received dialysis. In contrast, the vast majority of patients with CPS1D (86%, $n = 37$; mean trigger ammonia = 1312.9 μmol/L; SD = 912.9) and ASSD (89%, $n = 48$; mean trigger ammonia = 1054.7 μmol/L; SD = 797.9) were treated with dialysis (Fig. 2C). Remarkably, only 22% of the NAGS patients received dialysis.

Effect of dialysis on the outcome of patients

The main aim of this study was to estimate the effect of dialysis on outcome in neonatal hyperammonemia as analyzed for the entire cohort and for groups according to their level of trigger ammonia (Fig. 3a).

Trigger ammonia level (as divided into five groups) had no statistically significant impact on outcomes "deceased" ($\chi^2(4) = 6.971$; $p = .137$), "normal" ($\chi^2(4) = 2.523$; $p = .641$), "alive-no-info" ($\chi^2(4) = 5.426$; $p = .246$), and "handicapped" ($\chi^2 = (4)\ 2.005$; $p = .735$). In each of the groups defined according to trigger ammonia, there was no significant association between the use of dialysis and outcome categories (group ≤350 μmol/L: $\chi^2(3) = 1.302$; $p = 1.00$; $n = 15$), (group 351–500 μmol/L: $\chi^2(3) = 3.881$; $p = .237$; $n = 17$), (group 501–750 μmol/L: $\chi^2(3) = 2.154$; $p = .578$; $n = 36$), (group 751–1000 μmol/L: $\chi^2(3) = 0.673$; $p = .937$; $n = 44$), (group >1000 μmol/L: $\chi^2(3) = 11.982$; $p = .005$; $n = 90$) (Fig. 3a, b). Ammonia levels were not significantly related to the use of dialysis in subgroups "normal" (U = 127.0; $p = .376$) and "alive-no-info" (U = 165.0; p = 1.0). In contrast, deceased patients (U = 168.0; $p = .007$) and handicapped patients (U = 226.5; $p = .001$) showed a significant association between higher ammonia levels and more frequent use of dialysis (Fig. 3a).

Patients with trigger ammonia ≥1000 μmol/L ($n = 95$) were significantly more frequently (81%, $n = 77$) treated with dialysis ($\chi^2(1) = 9.132$; $p = .003$) than patients with a trigger ammonia <1000 μmol/L (62%, $n = 66$) (Fig. 3b).

Development from 1971 to 2016

The percentage of deceased patients decreased continuously over time from 50% ($n = 10$) in publications between 1971 and 1990 to 20.8% ($n = 16$) reported between 2011 and 2016 ($\chi^2(3) = 11.353$; $p = .01$) (Fig. 3d). The proportion of handicapped and patients with normal outcome remained virtually unchanged: handicapped 20% ($n = 4$) in 1971–1990 and 37.7% ($n = 29$) in 2011–2016 ($\chi^2(3) = 2.69$; $p = .442$); normal outcome 20% (n = 4) in 1971–1990 and 14.3% ($n = 11$) in 2011–2016 ($\chi^2(3) = 6.750$; $p = .080$) (Fig. 3d). Mean trigger ammonia was not significantly different between the four

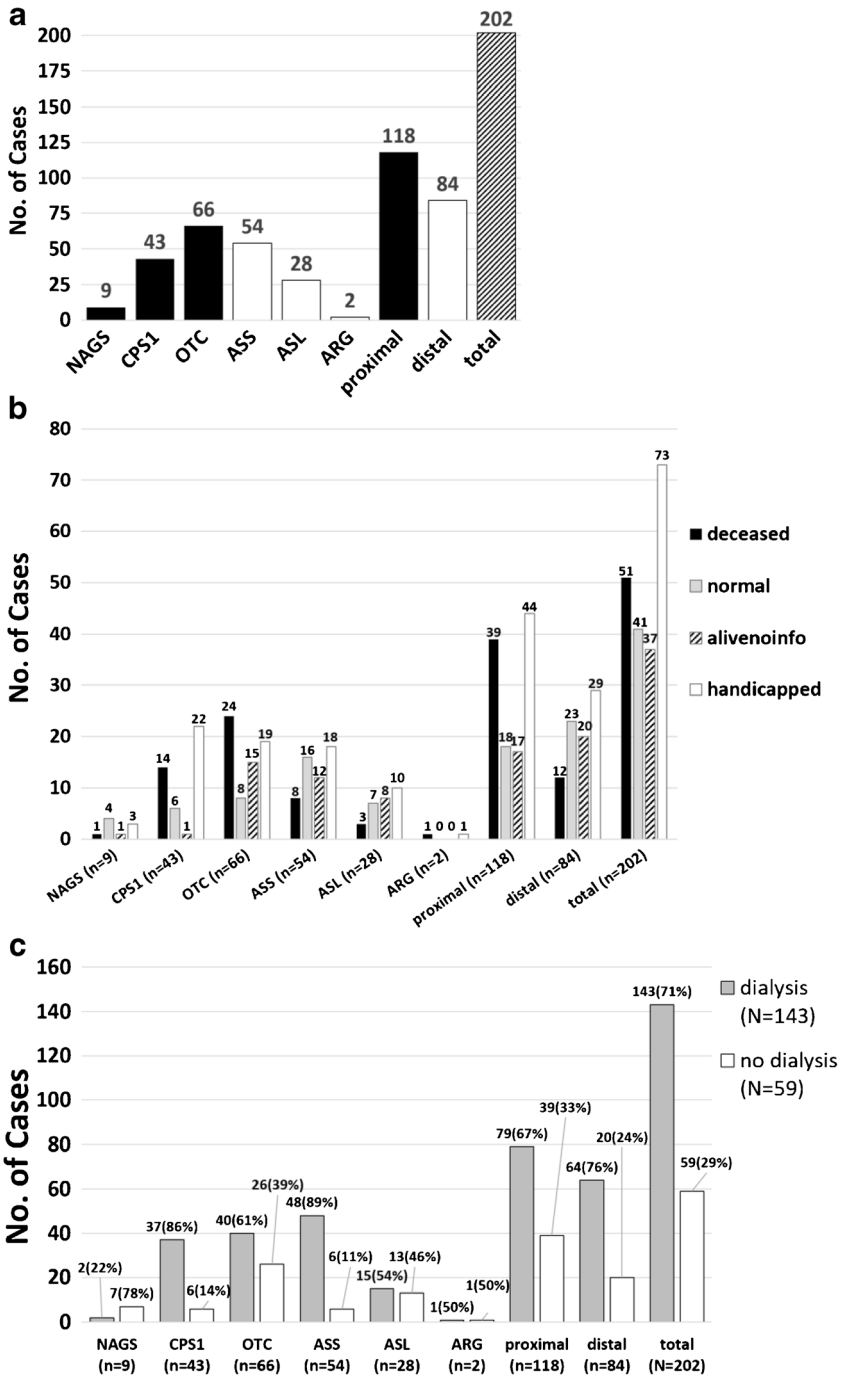


Fig. 2 Distribution of number of cases according to UCD, outcome of the patients and the use of dialysis. a) Distribution of UCDs in the study cohort specified for single UCDs or grouped as either proximal UCDs (including NAGS, CPS1, and OTC deficiencies), distal UCDs (including ASS, ASL, and ARG deficiencies) or total (including all patients). b) Relation between the main outcome parameters classified as "normal outcome", "deceased", "handicapped", and "alive but with no further information" (alive-no-info) specified for single and grouped UCDs (labeled as in a). Absolute case numbers are given above each column. c) Distribution of the use of dialysis in single and grouped UCDs (labeled as in a). Absolute numbers are given above the columns, corresponding percentages in brackets

investigated decades (range, 1109–1226 μmol/L; F = 0.221, $p = .882$) (Fig. 3d).

Practice of dialysis changed in the study period: while total use of dialysis dropped (70% ($n = 14$) in 1971–1990 and 56% ($n = 43$) in 2011–2016) ($\chi^2(3) = 15.316$, $p = .002$), use of hemodialysis significantly increased from 20% (n = 4) in the first period to 26% ($n = 20$) in the last period ($\chi^2(3) = 24.175$, p = <.001) after reaching a maximum value of 61% in period 3. Use of peritoneal dialysis continuously decreased significantly from about 50% ($n = 10$) to 14% (n = 11) ($\chi^2(3) = 14.497$, p = .002) (Fig. 3d). Data on dialysis should, however, be interpreted with caution due to incomplete data ($n = 13$).

Discussion

This study aimed at extracting all available information from published cases to elucidate whether a specifically defined ammonia threshold for extracorporeal detoxification in neonatal hyperammonemia is justified. Current guidelines

Table 1 Basic data of the cohort studied here including mean age at onset and at follow up, mean trigger ammonia, and outcomes

	Proximal UCDs ($n = 118$)	Distal UCDs ($n = 84$)	Total ($N = 202$)
age at onset (days), mean (SD)	3.5 (2.8), n = 118	4.0 (3.3), n = 84	3.7 (3.0), $n = 202$
age at follow up (days), mean (SD)	510.1 (735.2), $n = 98$	1045 (1325.9), $n = 76$	743.7 (1065.8), $n = 174$
trigger ammonia (μmol/L), mean (SD)	1285 (882.4)	1079.2 (818.8)	1199.4 (860.5)
≤ 350 μmol/L, n (%)	8 (6.8)	7 (8.3)	15 (7.4)
351–500 μmol/L, n (%)	7 (5.9)	10 (11.9)	17 (8.4)
501–750 μmol/L, n (%)	18 (15.3)	18 (21.4)	36 (17.8)
751–1000 μmol/L, n (%)	29 (24.6)	15 (17.9)	44 (21.8)
>1000 μmol/L, n (%)	56 (47.4)	34 (40.5)	90 (44.6)
Outcome, n (%)			
normal outcome	18 (15.3)	23 (27.4)	41 (20.3)
handicapped	44 (37.3)	29 (34.5)	73 (36.1)
alive-no-info	17 (14.4)	20 (23.8)	37 (18.3)
deceased	39 (33.1)	12 (14.3)	51 (25.2)

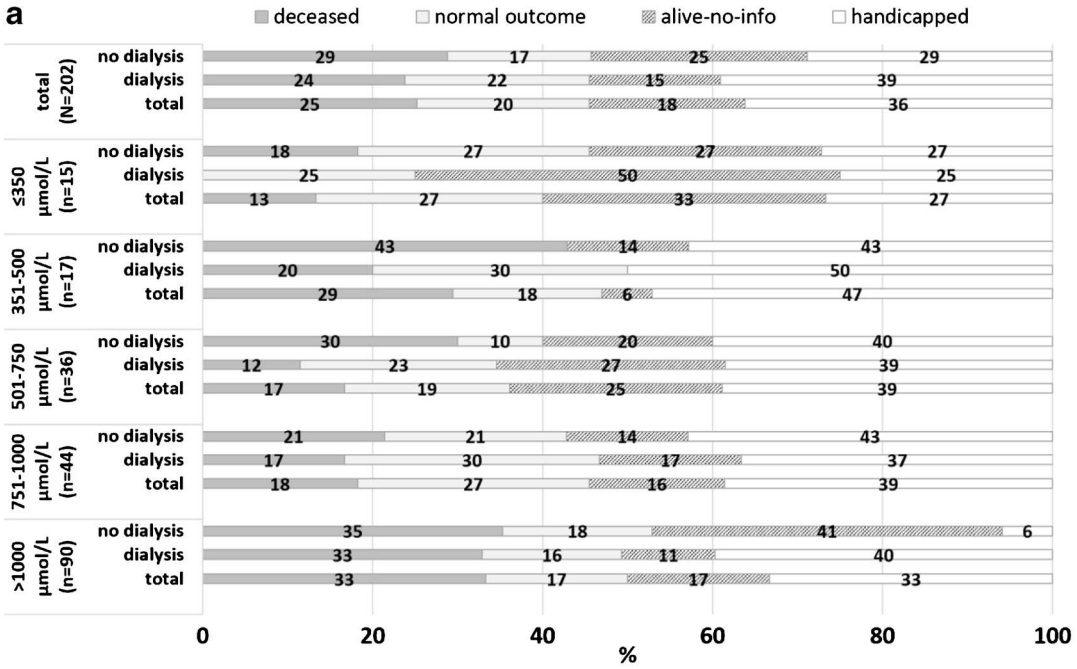
recommend initiation of dialysis when ammonia levels exceed 400 or 500 μmol/L (Alfadhel et al 2016; Häberle et al 2012). This recommendation is however challenged by data from a Japanese cohort, in which only patients with a peak ammonia level <180 μmol/L had a good outcome (Kido et al 2012). Therefore, it seems of utmost importance to either substantiate or discard the guidelines' recommendations.

After our systematic literature review 28 case series, cohort studies or reports from registries (Ah Mew et al 2013; Brassier et al 2015; Burgard et al 2016; Enns et al 2007; Kido et al 2012; Kölker et al 2015; Martin-Hernandez et al 2014; Nakamura et al 2014; Picca et al 2015; Uchino et al 1998) that addressed neonatal hyperammonemia could not be included because key data (blood ammonia levels, modality of extracorporeal detoxification, basic outcome data including survival) were fragmentary.

From the 202 patients included, OTCD patients ($n = 66$) formed the largest subgroup, followed by ASSD ($n = 54$ of 84 patients with a distal UCD). While this corroborates the data from UCD registries (Batshaw et al 2014; Kölker et al 2015; Summar et al 2013), we included an unexpectedly large number of 43 patients with CPS1D (21% of total cohort), a subtype that comprises ≤5% of patients in other case series, cohorts or registries (Batshaw et al 2014; Kölker et al 2015). This distribution may reflect a publication bias in favor of CPS1D compared to more common UCDs. Additionally, our study includes fewer OTCD cases compared to other reports (Batshaw et al 2014; Kölker et al 2015; Martin-Hernandez et al 2014) but as a result of the larger number of CPS1D cases, the proportion of proximal and distal UCDs as reported both by the US-based UCDC registry (Batshaw et al 2014) and the European registry (Kölker et al 2015) is maintained and supports the representative composition of our cohort.

We could confirm that neonatal onset UCDs are burdened by high mortality (25% deceased in our cohort), as observed in most studies (Burgard et al 2016). Outcome in proximal UCDs (33% mortality), and especially in OTCD (36% mortality), was less favorable than in distal UCDs (14% mortality). Only 41 patients (20% of total), mainly with distal UCDs, had a normal outcome. Our results contrasted with a recent study performed in 103 patients ($n = 38$ CPS1D or OTCD), which showed no

Fig. 3 Relation between trigger ammonia levels, outcome of the patients, and the use of dialysis with time. a) Classification of patients according to trigger ammonia levels (group 1: ≤350 μmol/L, group 2: 351–500 μmol/L, group 3: 501–750 μmol/L, group 4: 751–1000 μmol/L, group 5: >1000 μmol/L), outcome (deceased, normal, handicapped or alive with no information), and the use of dialysis. Each bar fragment includes the corresponding percentage of patients per category with numbers rounded up/down to facilitate reading. b) Distribution of patients according to trigger ammonia and outcome. Each individual patient is indicated with either a circle (if no dialysis was used as treatment) or a triangle (if the patient received dialysis). c) Classification of patients according to the trigger ammonia level (either < or ≥1000 μmol/L) and the use of dialysis as treatment. Absolute numbers are given above each column, percentages in brackets. d) Overview of the distributions of outcome, mean trigger ammonia, and use of hemodialysis or peritoneal dialysis in relation to publication date. Black continuous line represents the mean trigger ammonia levels (referenced to the left axis), exact values are underlined and given above. Bar fragments correspond to the distribution of each outcome category (corresponding percentages are indicated in black) along four time periods (1971–1990, 1991–2000, 2001–2010, and 2011–2016). Dotted lines represent the percentage of patients (right axis) that received dialysis: total patients receiving dialysis are represented by dark gray triangles, patients receiving hemodialysis by light gray rhombus, and patients receiving peritoneal dialysis by white circles


a
deceased
normal outcome
alive-no-info
handicapped
total (N=202)
≤350 µmol/L (n=15)
351-500 µmol/L (n=17)
501-750 µmol/L (n=36)
751-1000 µmol/L (n=44)
>1000 µmol/L (n=90)
no dialysis
dialysis
total
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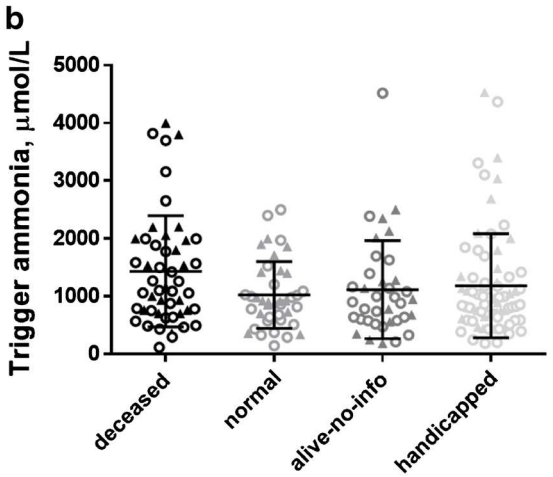
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Trigger ammonia, µmol/L
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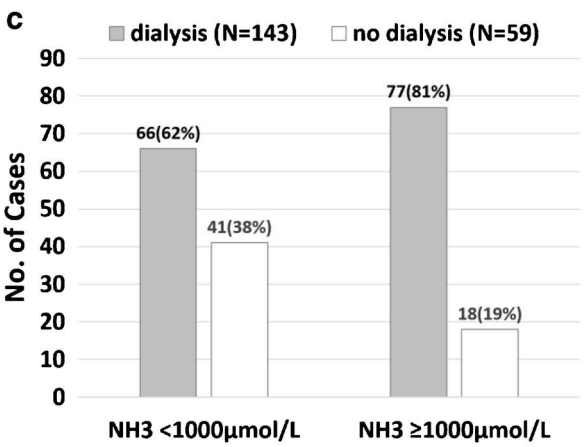
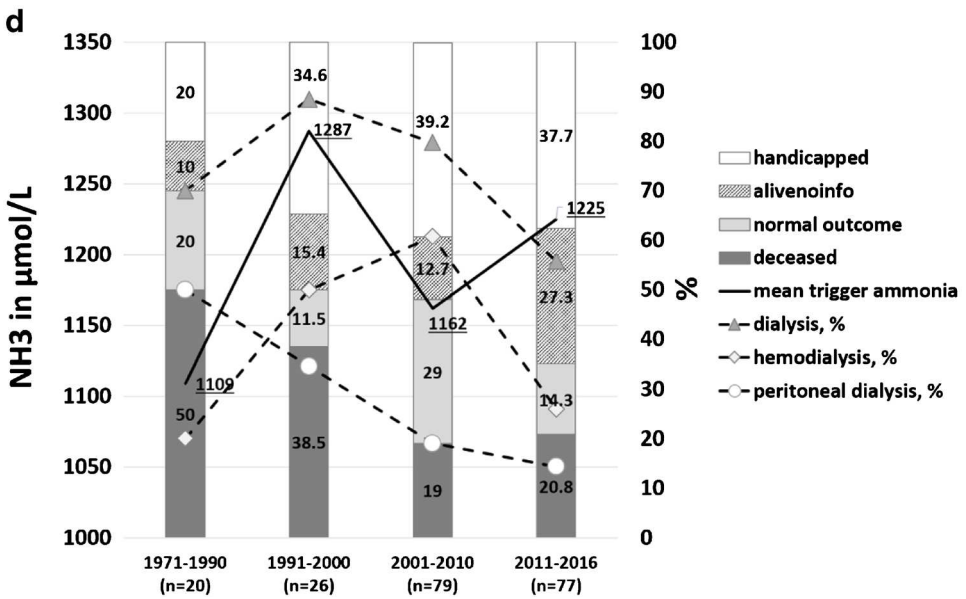

c
dialysis (N=143)
no dialysis (N=59)
No. of Cases
66(62%)
41(38%)
77(81%)
18(19%)
NH3 <1000µmol/L
NH3 ≥1000µmol/L


d
NH3 in µmol/L
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normal outcome
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mean trigger ammonia
dialysis, %
hemodialysis, %
peritoneal dialysis, %
1971-1990 (n=20)
1991-2000 (n=26)
2001-2010 (n=79)
2011-2016 (n=77)

difference in mortality and neurodevelopmental outcome between proximal and distal UCDs (Ah Mew et al 2013). However, in this sample, mortality was exceptionally low with only 4%.

It is generally accepted that neonatal brain damage is determined by degree and duration of hyperammonemia (Häberle et al 2012; Msall et al 1984; Picca et al 2001). Based on lack of data, we cannot comment on the impact of the duration of coma on outcome in our cohort. However, we assume that the less favorable outcome in patients with proximal UCDs in our study may be due to the higher trigger ammonia in this subgroup, possibly indicating a more severe phenotype. This assumption is also supported by the significantly higher trigger ammonia levels in deceased subjects compared to survivors (Fig. 3a). Based on this, an earlier start of ammonia detoxification would be desirable.

Regarding use of dialysis, numbers in our study are similar to the recent Japanese study (Kido et al 2012), underlining that neonatal UCD patients have a high likelihood to be treated with dialysis during their initial metabolic crisis.

In our study, dialysis had, irrespective of the trigger ammonia level, no relevant impact on outcome (total mortality rates 28.8% and 23.8% in dialyzed and not dialyzed patients, respectively; Fig. 3a). Interestingly, in the subgroup of patients with the lowest trigger ammonia (<350 μmol/L, $n = 4$ patients), all patients survived when treated with dialysis (vs. 18% that died when no dialysis was applied) (Fig. 3a). This is in perfect accordance with the findings from the Japanese cohort (Kido et al 2012), but relies on a number of cases too small for meaningful interpretation.

We found a relevant overlap between the outcomes (deceased, normal, alive-no-info, handicapped) in patients who did or did not receive dialysis in all subgroups (Fig. 3b). Additionally, significantly more patients with trigger ammonia >1000 μmol/L had been treated with dialysis (81% versus 62% if ammonia was <1000 μmol/L) (Fig. 3c). Thus, we hypothesize that the high ammonia levels determined the poor outcome which could not be improved by dialysis (Fig. 3a, b).

In current practice, dialysis is started when conservative treatment has failed and ammonia levels are exceedingly high. Dialysis is considered predominantly as a last resort given its invasiveness and technical challenges. The European guidelines also reflect this approach, by recommending extracorporeal detoxification when plasma ammonia levels exceed 500 μmol/L (Häberle et al 2012). Recommendation of such a precise threshold was based on common clinical practice and expert opinion but is not supported by any systematic study. In this study, it was observed that lower ammonia levels at start of dialysis lead to a better outcome. Thus, whenever hyperammonemia in a neonatal onset UCD is detected, all available therapeutic options, including dialysis, should be initiated without delay. Ideally, this conclusion would be investigated in a prospective study addressing the efficacy of dialysis dependent on ammonia levels. However, various objections can be raised against a prospective design: the low number of patients in single centers will inevitably result in a multi-center setting, which will have an impact on the uniformity of clinical practice; it will take a long time to recruit sufficient numbers of patients to allow reliable conclusions; it may be regarded unethical to postpone dialysis since lower ammonia levels at start of dialysis allow better outcome. As an alternative, we propose an observational study with clearly defined core set variables reflecting ammonia kinetics, and the effect of dialysis on ammonia and short- and long-term outcome.

Although this is the first systematic review aiming to describe the efficacy of the current practice of dialysis in neonatal hyperammonemia, some limitations need to be discussed. Pooling data from case studies to evaluate treatment efficacy is hazardous (Vandenbroucke 2001) due to lack of standardization. With this in mind, we applied strict inclusion and exclusion criteria (Fig. 1) to create a study population as homogenous as possible. Even then, the publication bias with underreporting of "classical" and more likely publication of unusual patients (such as CPS1D cases in our cohort) must be considered. As well, patients with specific characteristics that justified their description in the medical literature may have been preferentially selected. Moreover, treatments are very dependent on local practices and outcomes are influenced by the experience of local physicians. Another limitation is the retrospective character of the study and the inclusion of patients over a long period. For instance, patients reported in the first two decades of this study had a higher risk to die. As well, the total number of patients in the first decades are lower, probably due to a reduced diagnostic rate. As another limitation, modalities of dialysis changed over the years with a decreasing proportion of patients being treated with peritoneal dialysis. Finally, even with a sample size of 202 patients, some subgroups included only a few patients.

In summary, outcome in neonatal onset UCD patients, and especially in proximal defects, is still overall poor with only 20% of 202 patients being reported with a normal outcome. Dialysis, if performed in the way it is currently practiced, does not improve this situation. One reason for this lack of efficacy, which is not understandable from a biochemical perspective on the method, is the use of an arbitrarily defined threshold for plasma ammonia. The key to success definitely remains early diagnosis followed by initiation of all available treatment options, including dialysis, as fast as possible.

Acknowledgements This study was supported by the Swiss National Science Foundation (grant 310030_153196). The authors are grateful to Jin-Ho Choi & Han-Wook Yoo, MD, PhD, Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, who helped to complete missing data.

Compliance with ethical standards

None.

Studies with human or animal This article does not contain any studies with human or animal subjects performed by the authors.

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