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ORIGINAL PAPER

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Outcome and survival of 88 patients with urea cycle disorders: a retrospective evaluation

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Abstract This paper presents data obtained by questionnaires sent to local hospitals and metabolic centres in Germany, Austria, Italy and Switzerland concerning the survival and outcome of patients with urea cycle disorders treated between 1975 and 1986. A total of 130 questionnaires were sent out of which 88 questionnaires of patients were returned. This study compares results of conservative long-term management using protein restriction versus protein restriction combined with more extensive treatment (arginine/citrulline, essential amino acid supplements and sodium benzoate as alternate pathway therapy). While survival was improved in neonates receiving extensive therapy, there was an increased risk of mental retardation on long-term follow-up in this group. The time at which the first symptoms of hyperammonaemia appeared, the age at diagnosis, and the time of delay in diagnosis after the first symptom were not helpful in predicting outcome; however, when plasma ammonia concentrations exceeded 300 μmol/l initially or 480 μmol/l at its peak, none of the patients had a normal cognitive outcome. *Conclusion*: There is a need to establish improved treatment approaches and a network of ''rare disease'' centres to assure the rapid diagnosis and effective treatment and follow-up of affected children. This should precede any consideration of neonatal screening for urea cycle disorders.

Keywords Hyperammonaemia · Inborn errors of metabolism · Neonatal screening · Urea cycle disorders

Abbreviation *UCD* urea cycle disorders

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Introduction

Innovative techniques such as tandem mass spectrometry allow high throughput quantification of an increasing number of metabolites in neonatal blood spots. As some, but not all, of the metabolites that are needed or potentially useful in detecting urea cycle disorders (UCD) can be assayed by this method, it is tempting to recommend neonatal population screening for these disorders. Before this is considered, however, certain generally accepted criteria should be met [3, 4, 10, 14, 17, 18, 21]. There is actually a lack of evidence on the effectiveness of treatment in an unselected population by comparison with the natural history of the disorders and on the presence of a functioning decentralised network of specialised metabolic centres that can rapidly confirm the diagnosis and treat effectively, in the long term, infants with positive screening test results [4].

This paper presents data on the survival and outcome of patients with UCD treated before and after the introduction of alternate pathway therapy in 1980 [6, 7]. The effect of extensive chronic treatment (''new therapy'') on outcome is compared to the ''old therapy'' of UCD involving protein restriction, approximating the ''untreated'' natural history that can serve as a baseline for assessing the effectiveness of the new therapy. This retrospective study indicates that extensive treatment has not been effective in preventing mental retardation in affected children. It emphasises the importance of continuing to learn more about the pathogenesis of UCD and of pursuing innovative treatment methods, including liver transplantation and gene therapy. This study also suggests caution in considering implementation of neonatal screening in advance of improved treatment approaches and an effective network of diagnostic/treatment centres.

Subjects and methods

A retrospective questionnaire was sent out from the Central Laboratory of Clinical Chemistry, Inselspital, Berne, Switzerland to

Table 1 Disorders of the patients in the questionnaires sent out compared to those returned

Disorder	OMIM	Abbreviation	All questionnaires (*n*)	Returned (*n*)
Carbamoyl phosphate synthetase I deficiency	237300	CPS	13 (10%)	8 (9%)
Ornithine transcarbamylase deficiency (hemizygous)	311250	OTCm	30 (23%)	18 (20%)
Ornithine transcarbamylase deficiency (heterozygous)	311250	OTCf	26 (19%)	18 (20%)
Citrullinaemia type I	215700	CIT	17 (13%)	14 (16%)
Argininosuccinic aciduria	207900	ASA	25 (19%)	14 (16%)
Argininaemia (arginase 1 deficiency)	207800	ARG	6 (4%)	4 (5%)
Other:				
Lysinuric protein intolerance	222700/603593	LPI	5 (4%)	2 (2%)
Hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome	238970/603861	HHH	4 (3%)	4 (5%)
Transient hyperammonaemia of the premature newborn		THPN	6 (4%)	4 (5%)
N-acetylglutamate synthetase deficiency	237310	NAGS	2 (1%)	2 (2%)

colleagues in regional hospitals of varying size as well as metabolic centres who had sought laboratory diagnostic help or counselling concerning children with UCD between 1975 and 1986. Some data from these questionnaires related to ornithine transcarbamylase deficiency have already been published [1] and are included. A total of 134 questionnaires were sent out and 90 (67%) were returned. Some 88 questionnaires of patients born between 1946 and 1986 (none prospectively treated) contained sufficient information for estimating survival and outcome. The chronic treatment of 44 patients (19 female; 25 male) was protein restriction alone (''old therapy''), while 44 patients (22 female; 22 male) received extensive treatment (''new therapy''). The modifications consisted in supplementing arginine or citrulline, with or without essential amino acid mixtures, and sodium benzoate in addition to the protein restriction. Specific treatment/dosage depended on the diagnosis and severity of illness.

Some of the patients were initially treated by exchange transfusions (old therapy $n=17$; new therapy $n=11$), peritoneal dialysis (7; 5 respectively) and haemodialysis (0/1). Among these, six survived on long term (two with normal outcome assessment on ''old therapy'' with hyperornithinaemia-hyperammonaemia-homocitrullinaema syndrome; four retarded on ''new therapy'' with argininosuccinic aciduria).

There was no statistical difference (Mann Whitney test) between the new and old therapy groups with respect to the age at which the first symptoms appeared, age at diagnosis, or initial/maximal ammonia value during the first hospitalisation. The specific diagnoses were made either by metabolite quantification or enzyme assay according to an algorithm described elsewhere [2].

Table 1 compares the UCD diagnoses for all questionnaires sent out to those returned. It shows that the sample of questionnaires returned does not differ significantly from the spectrum of questionnaires sent out.

Statistical comparisons on outcome were done by Fishers exact test; the relatively small number of patients could result in our missing minor effects.

Results

Our data (Fig. 1) show that the overall mortality was 85% 10 years after diagnosis. If the data are truncated and neonatal presentation is excluded, mortality decreased to 60% at 10 years in all instances. There was no difference whether the truncation occurred at 15 or 23 or 28 days of life. This percentage of mortality is comparable to the more recent literature from large clinical centres where neonates up to 15 or 23 days have been excluded from mortality assessment [8, 9, 18].

The mortality rate was higher in patients manifesting their first symptoms as neonates (i.e. before 28 or even 15 days of age) than with later presentation ($P=0.002$). ''Old therapy'' was associated with a higher mortality rate than ''new therapy'' in patients with neonatal presentation ($P=0.045$); but survival rate did not differ between ''new'' and ''old'' therapy in post-neonatal presentation (Table 2).

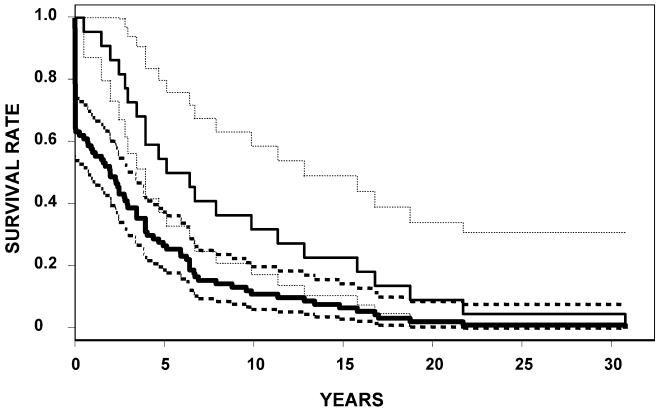

Fig. 1 Survival curve (Kaplan-Meier) of 88 patients with UCD with 95% confidence limits (*dotted lines*) taking into account all patients (*thick lines*) or after truncation excluding neonatal presentation (*thin lines*)

As shown by Saudubray et al. [18], quality of life can be as much of a concern as survival. Our data on the outcome of surviving neonates show (Table 2) a significantly higher rate of mental retardation in patients receiving ''new therapy'' as compared to ''old therapy'' ($P=0.0325$). This difference was not significant for post-neonatal presentation. Where indicated in the questionnaires the IQ/DQ of patients varied between 40 and 71 in individuals with mental retardation; if the psychomotor development was described as borderline it was included in the normal category.

Fig. 2, Fig. 3, Fig. 4 and Fig. 5 illustrate the outcome found at the indicated age of assessment as a function of factors which could be predictive of outcome, and thus be useful for decision making and counselling. Since these variables were not independent of each other, we did not calculate correlation coefficients. There was a major overlap between patients with mental retardation versus normal outcome in terms of age at which the first

Table 2 Outcome of patients with neonatal or post-neonatal first symptom treated either with conservative protein restricted diet (“old” therapy) or with arginine/citrulline and essential amino acids and benzoate depending on severity (“new” therapy)

First symptom	Neonatal age ≤ 28 days		Neonatal age > 28 days		Total	
Therapy	“New”	“Old”	“New”	“Old”	“New”	“Old”
Total (*n*)	28	26	16	18	44	44
Outcome						
Dead	13	22	3	5	16	27
Survived	15	4	13	13	28	17
Normal	5	4	7	4	12	8
Retarded	10	0	6	9	16	9

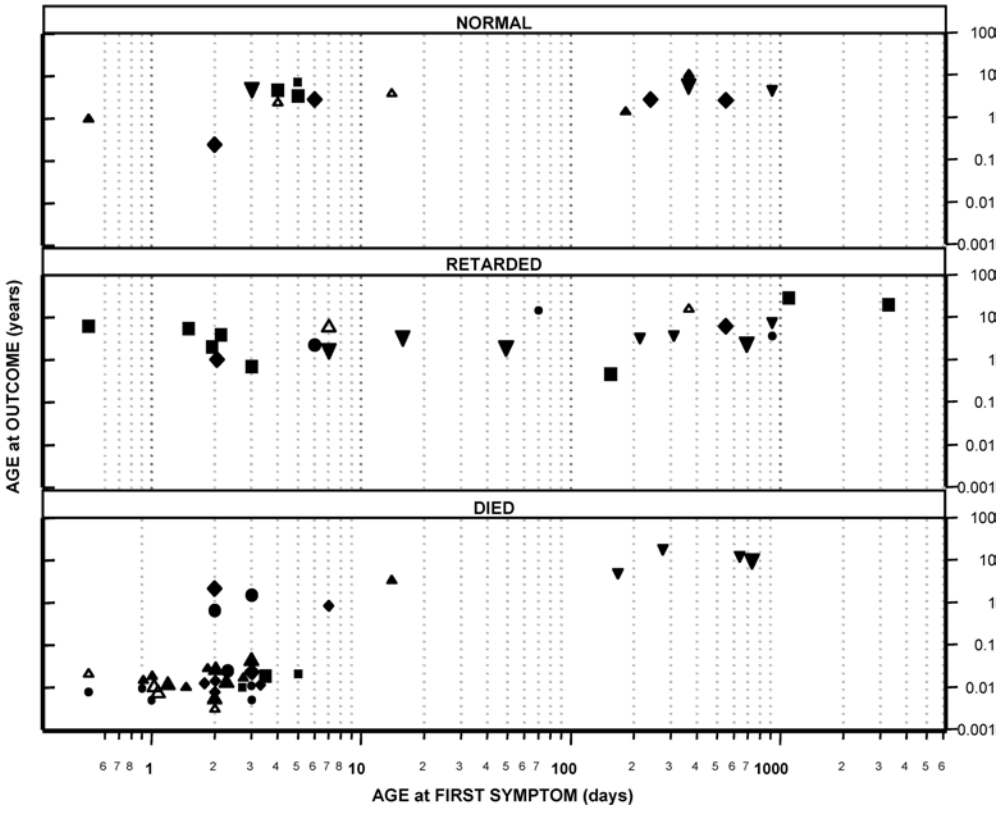

Fig. 2 Outcome of patients (panels: normal psychomotor development/ retarded/ dead) at age of assessment (years; log scale) versus recorded age (days; log scale) at first symptom. Despite the presence of neonatal clinical symptoms, nine patients have a normal long-term outcome; normal and retarded outcome overlap with respect to manifestation of the first symptom. Thus for individual cases, the age at which the first symptom is noted does not allow prediction of outcome, neither with “old” nor with “new therapy”. The large symbols show patients on “new” therapy, the small symbols those on “old” therapy. CPS deficiency (*closed circles*); OTC deficiency (*closed triangles*) (▲: males, ▼: females); citrullinaemia (*diamonds*); argininosuccinic aciduria (*closed squares*); argininaemia (*open circles*); other (*open triangles*)

symptoms were observed (Fig. 2), the age at diagnosis (Fig. 3), and the delay in diagnosis after the first symptom appeared (data not shown). There was no significant difference in the rate of normal development versus mental retardation depending on whether the diagnosis was made rapidly. Our data show, however, that all patients with normal developmental outcome had initial ammonia concentrations < 300 μmol/l (Fig. 4) and peak ammonia concentrations < 480 μmol/l (Fig. 5).

Discussion

Survival of patients with UCD has been assessed in the past primarily in groups of patients treated and followed by major metabolic centres with well-defined protocols [11, 13, 18]. Such patients probably are more likely to reach these centres if they have survived the neonatal period (or at least 15 days of age), unless they have been treated prospectively. Critically ill patients below 2–3 weeks of age might well be underrepresented in large centres. Consequently, a truncation of survival data has been used in the literature (starting after 3 or 4 weeks of life [8, 9]) which improves the survival results artificially. Fig. 1 illustrates this point by comparing survival in our data set including all patients with the survival curve after exclusion of the neonatal cases. Furthermore, the inclusion of patients into prospective clinical programmes in metabolic centres might improve compliance with treatment and rapid intervention in the case of metabolic crises. These factors might lead to a more pronounced ascertainment bias than in our retrospective data which were based on diagnostic laboratory requests.

Ideally one would wish a prospective research programme encompassing all neonates to assess prevalence,

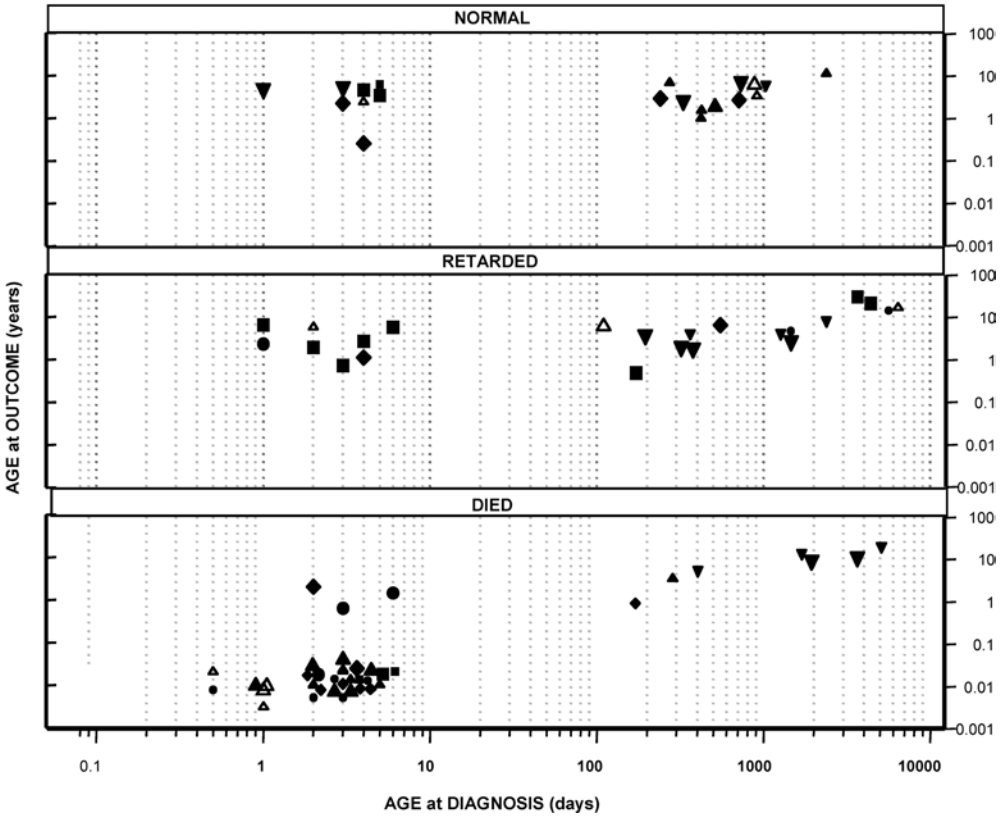

Fig. 3 Outcome of patients versus age at diagnosis. In surviving patients normal and retarded outcome overlap widely with respect to age at the diagnosis (and thus start of the therapy). The age at diagnosis does not allow prediction of a favourable or fatal outcome. Symbols are as in Fig. 2

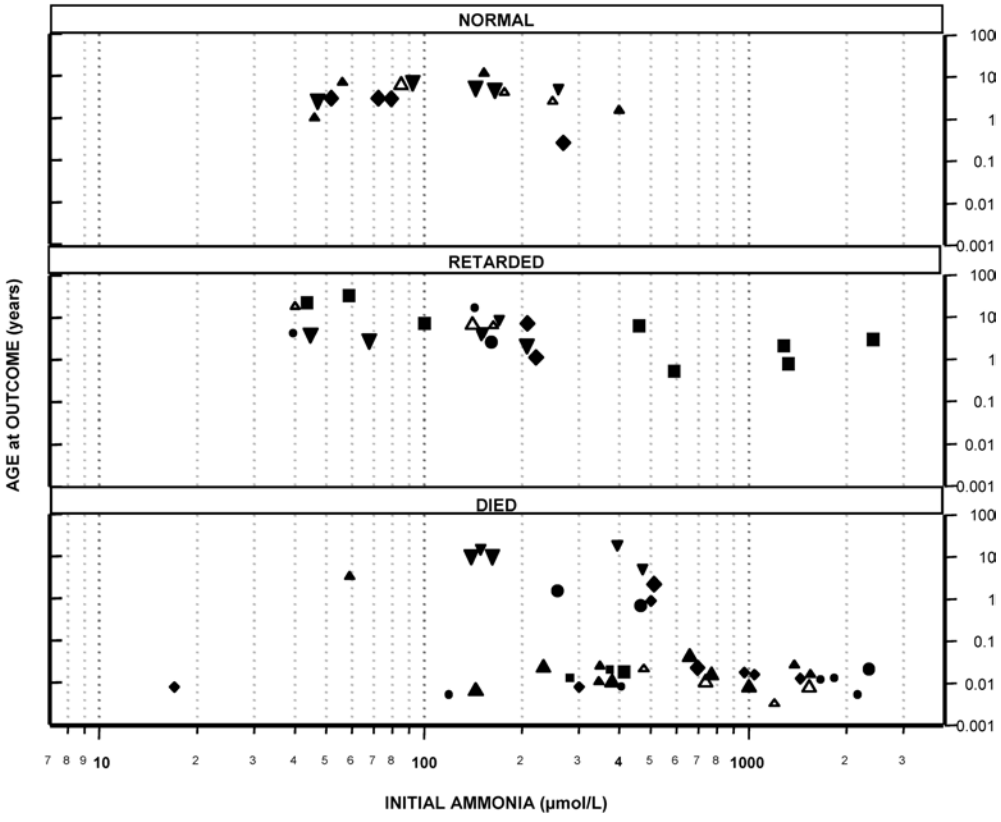

Fig. 4 Outcome versus initial plasma ammonium concentration at time of diagnosis. None of the surviving patients with an initial ammonia >300 µmol/l at the time of diagnosis had a normal outcome. Symbols are as in Fig. 2

as has been done for argininosuccinic aciduria in Austria [20]. However, a screening programme covering all the UCD would require the assay of ammonia in every newborn infant; this does not seem feasible at present. Glutamine screening as an alternative would be problematic as well.

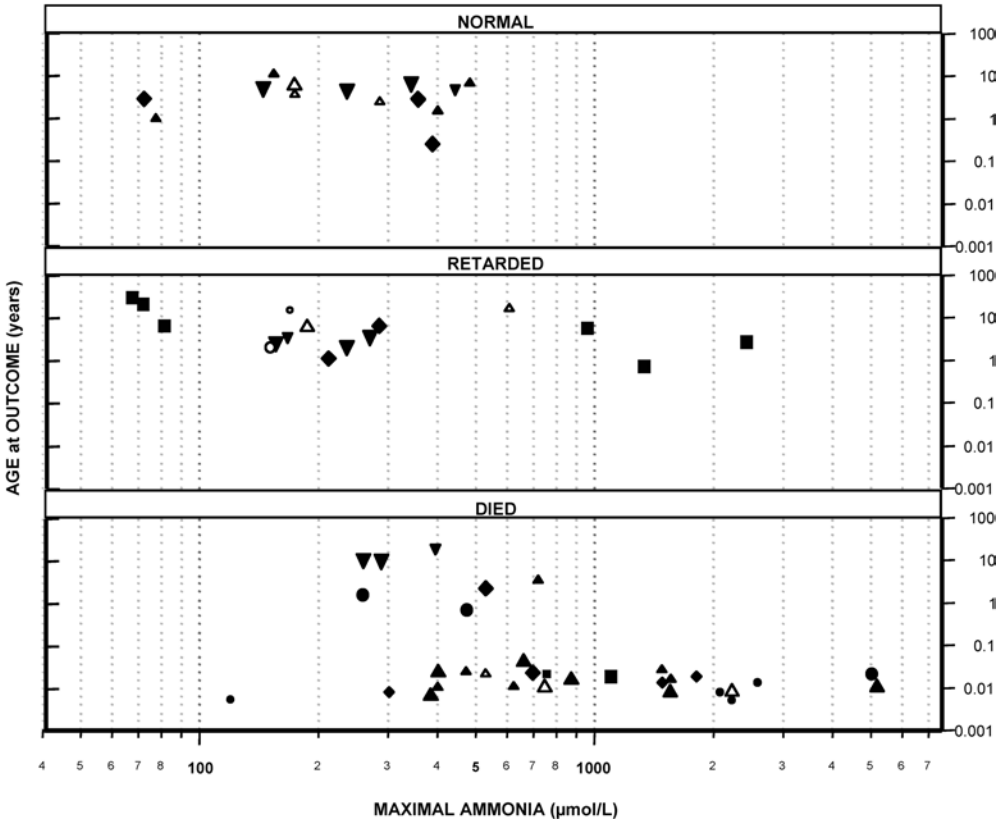

Fig. 5 Outcome versus maximal recorded value of plasma ammonium concentration. None of the surviving patients with a peak ammonia level >480 µmol/l had a normal outcome with respect to psychomotor development. Symbols are as in Fig. 2

Our retrospective data, gathered mostly from Germany, Austria, Italy and Switzerland, reflect a situation where there is less centralisation of treatment. Much of the treatment is done in peripheral hospitals with a diversity of diagnostic procedures and follow-up plans, often based on sending samples to specialised laboratories, with a resultant delay in intervention. The ammonia concentrations were uniformly assayed enzymatically in Europe at the time the patients were diagnosed. Pre-analytical and analytical inter-laboratory variance is certainly higher than in a centralised study; thus the ammonia limits for decisions should be used with care. All these uncontrolled variables contribute to increased variance and less discrimination between the therapy groups.

Nevertheless, this reflects more likely the real situation that one would actually face with population screening than a centralised well controlled investigation. It cannot be excluded that improvements in treatment (liver transplantation or the use of combined sodium benzoate/sodium phenylbutyrate) has nowadays improved the outcome. Surprisingly, the survival rates 10 years after presentation shown here are not significantly different from data published previously from metabolic centres [8, 9]. Similar to previous studies, we found a high percentage of mental retardation in children who received ''new therapy'' [12, 15]. The present study does not include patients of affected families which have been treated prospectively. Knowing the genotype and/or biochemical phenotype could in some instances allow counselling of the parents more precisely as to the risks of nitrogen overload.

The poor association of outcome with age at occurrence of the first symptom or age at diagnosis indicates that clinical data alone are not good predictors of outcome. It should especially be stressed that even with neonatal presentation there are patients who develop without retardation and conversely that among patients with late manifestation there is a significant risk of death or disability. The classification of UCD into neonatal, classical, and adult forms does not appear to be of much help in establishing a prognosis in individual cases.

The time at which the first symptom occurs is usually thought to reflect the residual enzyme activity in vivo. The clinical manifestations of the disease, however, depend only in part on the gene defect and residual enzyme activity; additional factors intervene to reduce the prognostic value of the residual enzyme activity. Our results on the association of outcome with initial or maximal recorded ammonia concentration confirm, in principle, the data of Msall et al. [15] and of Uchino et al. [19], although our cut-off limits for ammonia are slightly higher than those proposed by the latter. Our results indicate that the maximal ammonia levels might more directly influence the outcome than the inherited defect alone. This is, in fact, not a surprise, as the extent of hyperammonaemia not only depends on the capacity of the organism to detoxify ammonia but also on the exogenous and endogenous nitrogen load. The detoxifying capacity will be exceeded in situations of increased

catabolism or impaired protein synthesis (e.g. in newborns, with infections; when there is insufficient supply of calories or of essential amino acids as compared to their utilisation, often found in patients treated with phenylacetate or phenylbutyrate [12]; and in the presence of excessive stimulation of alternate pathways), nutritional excess, or bacterial overgrowth. Because these situations are rarely predictable, outcome will depend on how well the parents understand the disease if well instructed; how rapidly they react to vomiting and loss of appetite as early signs of hyperammonaemia; and how close they live to a centre with competent interventional resources for such patients. Strict control of the concentrations of essential amino acids and arginine is also necessity for avoiding nutritional imbalance, not only when initiating treatment but also during long-term follow-up.

Recently, Picca et al. [16] stressed the impact of rapid intervention on medium term outcome in hyperammonaemic patients. Using the data given in that pilot study, we found that discrimination between the risk of mental retardation versus normal development in medium-term outcome can be improved by using the combination of peak ammonia concentration (in mmol/l) and duration of coma (in days) as compared to each parameter separately. Cut-off values of approximately 2.5 or 4.2 days x peak mmol ammonia/l are found depending on whether one takes the coma duration before or including haemodialysis. In addition to this concentration over time effect of hyperammonaemia, the age at which the patient is exposed to hyperammonaemia (i.e. the stage of brain maturation) might further influence the outcome [5] and should probably be taken into account.

These data taken together with more recent assessments stress the importance of assaying ammonia at a very early stage in sick neonates or in patients with loss of appetite, vomiting and affected consciousness or irritability. Means of assaying ammonia should be available around the clock, even in small hospitals, as well as the availability of rapid transportation of patients to metabolic centres. Since unpredictable factors appear to have an important impact on outcome, there is a need not only for educating neonatologists and paediatricians to increase their index of suspicion for hyperammonaemic conditions, but also to pay special attention to establishing and guaranteeing a functioning network of centres for the long-term treatment of patients with UCD. Such a network should be sufficiently dense to avoid long travelling distances. The task of such centres for treatable metabolic disorders should be to establish or confirm, rapidly and independently of the screening centres, the definite diagnosis; to institute effective, accepted treatment; to manage crisis situations; to follow, control and adapt long-term treatment so as to avoid malnutrition or metabolic imbalance situations; and to inform, counsel and support parents of affected children.

In contrast to the age of disease manifestation or diagnosis, the degree of hyperammonaemia and the duration of coma appear to be helpful in deciding whether or not to start or to consider discontinuation of treatment in patients with urea cycle disorders (except for argininaemia); however these parameters do not ensure a favourable long-term prognosis. Before population screening for UCD is recommended, a network of rare disease centres should be established which can assure a rapid diagnosis, provide close control of treatment, and avoid protein malnutrition and hyperammonaemic crises. Pilot research programmes that investigate prospectively long-term outcome including both survival and cognitive impairment should then be encouraged.

We conclude that, in contrast to phenylketonuria, the influence of unavoidable external and unpredictable endogenous factors leading to nitrogen overload (''environome'') seems to play a more important role in affecting the outcome of patients with UCD than the constitutional defect resulting from the genome. Thus, assuring specialised follow-up and efficient support is as important for improving the outcome as is detection of the disorder. Uncritical extrapolations from existing, successful screening programmes for other inborn errors should be avoided.

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