SYMPOSIUM

Long-term Outcome of Urea Cycle Disorders

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Abstract

Evaluation of long-term outcome of patients with urea cycle diseases (UCD) is needed for medical decisions and counselling. Own data comparing outcome of UCD patients with the old treatment limited to protein restriction (i.e. close to the natural history) with that of patients on the modern conservative treatment have shown that gains in survival occur at the cost of more mentally retarded surviving patients. We discuss the possible bias in long-term outcome studies of those rare inheritable disorders where non-predictable environmental factors leading to catabolic crises have a crucial impact on prognosis. A combination of peak or initial ammonia value combined with the duration of coma is discussed as a criterion for prognosis of handicap. The neglect of dietary compensation of branched chain amino acid deficiency worsened by phenylbutyrate treatment in some published protocols could well be an additional cause of the non satisfactory long-term results of conservative treatment which – in our view - mainly aim at bridging optimally the period of late neonatal presentation until liver transplantation in patients with CPS and OTC deficiency (except for mild forms).

Introduction

Knowledge about outcome of patients with UCD is necessary for medical decisions on choice of treatment, for informing patients or their parents on prognosis, for prenatal diagnosis, for the assessment of treatments, and for development and research of relevant markers and their validation (1,2). Last but not least, outcome assessment is an integrating part of the natural history of disease which is required for pilot programs addressing the issue whether neonatal population screening is desirable, useful and allows prevention.

Data on the outcome of UCD in the literature are scarce (2-10). Very few data exist on the natural history of UCD. All data published are from retrospective studies mainly aimed at showing the outcome with selected treatments and for trying to delineate predictive markers for irreversible developmental handicap in disorders with hyperammonemia.

Some studies have been focussed on survival as the main outcome parameter measured without asking the question of the quality of life of the surviving patients and without taking into account the burden of restrictions in daily life, handicap or suffering for the surviving patients and consequences for their family. Such questions should not be neglected since they might be considered useful for decisions by some or then unethical by others depending on the patients or parents values and beliefs. Since many centuries it is accepted that our main medical duty is to prevent or alleviate suffering, not death at the cost of suffering.

Bias in outcome evaluation

When using published data of outcome studies of UCD different factors leading to bias should be recognized : Underreporting : Any collection of cases reported in the literature will be biased by the fact that negative data, treatment failures or disasters are less published than short term success.

Analytical systematic differences of quantification : Biochemical data obtained in collaborative studies in different laboratories which are then used as markers of disease severity or course are prone to gross interlaboratory variation disallowing the pooling of results. Data from European quality assessment schemes illustrate this problem which might be underestimated by clinicians. There are also systematic differences between research laboratories and general laboratories in the same institution (e.g. for ammonia) and even more with data obtained by self-monitoring of patients.

Ascertainment bias by specialized centres : The patients studied in major specialised clinical centres are not representative for the whole population by the fact that patients (be it newborns, children or adults) whose first clinical manifestation of disease occurs mainly in peripheral hospitals with a life threatening metabolic crisis. Such patients might not reach the centre before death and/or then not be diagnosed as UCD in a peripheral hospital.

Bias by research protocols with high quality information and follow-up : Outcome studies aiming at assessment of treatment are based on protocols. Patients or their parents are thus better informed about the disease than patients out of protocol and followed much more carefully than in average regional hospitals ; they might benefit from more rapid adequate interventions in metabolic crises. The aim to limit the variables in a study leads to a selection of the patients. Exclusion and inclusion criteria are not always well defined. Generalisation of conclusions might thus be overoptimistic.

Of course financial interests in the treatment (e.g. patents, licence fees) of organisers of scientific protocols should been transparent to the reader.

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Own data

Our retrospective evaluation on the outcome with respect to survival and neuro-developmental handicap (mental retardation and other disabilities) in urea cycle disorders has shown that the age of first manifestation does not allow to predict outcome, except for extremely severe neonatal presentations (1, 2). This is in contrast to several other inborn errors of the metabolism of essential amino acids. In UCD the extent of hyperammonemia depends on the imbalance between the metabolising capacity and the exogenous and endogenous load not only of one essential amino acid, but of all amino acids ; thus in situations of a predominant catabolism there are not a few percent of the metabolised (muscle) protein nitrogen which add to the pool of the "toxin", but the whole amount of protein catabolised. It is thus no surprise that – except for very severe deficits - the clinical outcome of UCD reflects not so much the enzyme defect but probably much more the impact of *individual* situations like exposure to infections, dietary changes rapidity of intervention, geographic proximity of a competent centre, information and awareness of the parents or patients of the imminent crisis. Thus general statistical predictions have not much prognostic value for individuals. Most often outcome of UCD depends less on the inherited enzyme or transport protein defect than on the environmental factors which lead to catabolic crises. The outcome of UCD is less predictable than that of PKU; models and procedures imprinted in our mind from PKU cannot be transferred in all instances to our way of reasoning about UCD.

Prognostic factors

In the literature two prognostic factors for outcome prevail : Msall *et al*. had emphasized the duration of coma as prognostic factor (3). Uchino *et al*. documented the prognostic value of ammonia measurements (7). In addition we suggest that in some cases acute or chronic amino acid imbalance and malnutrition must be considered as (iatrogenic) confounding factor in some patients (see below).

Initial and maximal plasma ammonia at first hospitalisation and duration of coma

We have tried to estimate up to which limits of blood ammonia concentration uncompromised neurodevelopmental outcome is found (approx. 300 µmol/L and 500 µmol/L for first and maximal value during first hospitalisation respectively (2)). The data of Picca *et al*. (11) allowed to include tentatively also the duration of coma before haemodialysis or haemofiltration for this guess; we estimated that normal outcome in neonates was found if the product of duration of coma times ammonia at entry into the hospital was below 4'200 days * µmol/L. Such findings integrating the apparent contradictions in the literature ((3, 7) could be useful in the complex decision for liver transplantation in mitochondrial defects of the urea cycle which should be encouraged in view of the uncertainty of prognosis of other treatments.

Excessive treatment

Nowadays with the internet and excessively schematic guidelines - followed by some to the letter, apparently without understanding of the background - another factor should not be neglected : Excessive treatment (focussed only on keeping blood ammonia low) could also lead to iatrogenic protein malnutrition and thus to fall into the trap of the vicious cycle of inhibiting anabolism and thus increasing nitrogen load. This can occur on one hand by excessive restriction of natural protein and/or absence of adequate supplementation of essential amino acids. On the other hand the use of phenylbutyrate (PBA), as alternate pathway substrate, has worsened the situation. The main part of the nitrogen excreted (1.1 mol of nitrogen per mol of PBA given, not 2.0 (12)) originates from glutamate and glutamine formation, unlike benzoate therapy where nitrogen is drained from glycine. The glutamine synthesis pathway uses preferentially branched chain amino acids and alanine as nitrogen donors. It is thus no surprise that branched chain amino acids are further depleted under PBA treatment (5, 6, 13). If not supplemented this leads to a inhibition of translation i.e. anabolism, not only because the essential amino acid substrates are missing but as shown in recent years also because leucine acts as intracellular signal molecule for protein synthesis (14-17). Amino acid imbalance and inhibited protein synthesis with prevailing protein breakdown leads to acute or chronic nitrogen overload and malnutrition.

We could not evaluate the plasma amino acid concentrations in our study because the systematic bias between different laboratories is such that we would not have been able to interpret the findings. This is clearly a draw-back of our study which was based on questionnaires and data obtained from various small and big hospitals which had sent us samples for establishing or confirming the enzyme defect.

Benefice of treatment ?

Our study compared outcome of hyperammonemic patients with UCD (no prospective treatment) treated solely by protein restriction (~natural history of UCD) with the outcome of UCD patients treated in addition with benzoate and/or supplemented with essential amino acids and arginine (1, 2). The results have shown that the outcome with respect to survival per se is improved in neonatal onset patients by using the actual therapy i.e. with added benzoate and supplements ($p = 0.035$), but not in patients with later onset. It should be emphasized that survival data of others with phenylbutyrate (PBA)

treatment (if corrected for selection) fit our data closely. However, the improved survival in neonatal patients by modern conservative treatment shown in our study is obtained at the cost of increasing significantly the number of mentally retarded surviving patients. There is experimental evidence in brain cell aggregates that the inhibition of axonal development is limited to a time window which corresponds roughly to the first two years of life in humans (18). The main conclusions of our investigation have recently been confirmed by Nassogne *et al*. (10).

Take home message

In order to prevent timely the toxic effects of hyperammonemia the clinician should order and obtain without delay (24/24h) a blood ammonia value in any newborn or baby for whom he orders a septicaemia work-up.

Conclusions

In our view there is still room for improvements in the treatment of UCD. A tight control of fasting plasma amino acids with frequent adaptation of essential amino acids (mainly branched chain and arginine/citrulline) is needed. For mitochondrial urea cycle disorders liver transplantation must be considered in order to replace often predictable disorders by a more predictable one. A cure of UCD by gene replacement is still far from mature for general application since the control of the synthesis, transport, assembly and degradation of the gene products is not mastered.

The long term outcome of liver transplantation for defects of enzymes located in the cytosol is less certain since we don't know if the deficiency of this part of the urea cycle in brain cells (used for recycling citrulline to arginine for NO and creatine synthesis) and kidney (arginine and creatine synthesis) which persist after liver transplantation will lead to functional consequences.

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