Inborn Errors of the Urea Cycle and Other Hyperammonemias

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Descriptions and studies of inborn errors of urea metabolism (Fig. 1) have greatly contributed to the knowledge of the regulation and gene expression of the enzymes involved in the urea cycle (1). Recent progress in this field has included new therapeutic approaches, a better knowledge of the mechanism of post-translational process of mitochondrial enzyme proteins, and DNA cloning of genes. For most of urea cycle enzymes, the gene for the protein has been cloned and characterized, opening up the possibility of analysis of the molecular basis for defects and new approaches to the diagnosis by DNA analysis.

However, from a medical point of view, hyperammonemia requires a rapid diagnosis workup, which is essential for instituting an adequate therapy (2). The aim of this chapter is to review recent data on the diagnosis and treatment of hyperammonemia.

CIRCUMSTANCES OF DIAGNOSIS

In urea cycle defects the signs usually appear between 2 and 4 days of age. It is likely that the rapid fatal outcome in undiagnosed patients underestimates the real incidence of urea cycle enzymopathies. Besides the classical forms with rapid onset and severe metabolic disorder, there is a wide variation in both the time of presentation and the symptoms, which may initially suggest a neurological, behavioral, or gastroenterological problem. In such cases recognition of the early symptoms of the disease is often delayed. Consequently, a family history of children dying of a metabolic disorder in the newborn period, or any history of recent alteration in diet or of unusual food avoidance, should reinforce the search for a urea cycle defect.

DIAGNOSTIC WORK-UP

Symptomatic hyperammonemia is a medical emergency demanding early recognition, specific diagnosis, and aggressive therapy. The first symptoms are feeding
FIG. 1. The urea cycle and its defects. CPS activity deficiency can result from a lack of the carbamylphosphate synthetase I apoenzyme (EC 6.3.4.16) (2) or, more rarely, a deficiency in N-acetylglutamate synthetase (1). Ornithine transcarbamylase (OTC) deficiency (EC 2.1.3.3) (3) is the most frequent of inborn errors of urea cycle and is an X-linked disease. Citrullinemia is characterized by deficient argininosuccinate synthetase (ASS) (EC 6.3.4.5) (4) Argininosuccinate lyase (ASL) (EC 4.3.2.1) (5) deficiency is the second most common of the urea cycle disorders. Hyperargininemia is characterized by a hereditary deficiency of arginase (EC 3.5.3.1) (6).

difficulties, hypotonia, vomiting, lethargy, grunting respiration, and seizures; this progresses rapidly to coma and early death. The clinical presentation is associated with plasma ammonium levels in the range of 500–2,000 µmol/liter (normal <35). A small number of routine laboratory tests can then be used to establish the diagnosis (Table 1) by excluding other metabolic situations that can be associated with hyperammonemia (Fig. 2).

Upon the discovery of symptomatic hyperammonemia, immediate therapeutic measures should be taken. Peritoneal dialysis (or hemodialysis) should be started to remove accumulated nitrogen rapidly, and sufficient energy (above 120 cal/kg-day) should be supplied to suppress endogenous proteolysis. In the meantime, the measurement of plasma amino acids and urinary orotate should differentiate the various possibilities (Fig. 2).

Once a provisional diagnosis of urea cycle enzymopathy has been made (apart from hyperargininemia), intravenous arginine supplementation (4 mmol/kg-day) and sodium benzoate (250 mg/kg-day) should be started. Final diagnosis is obtained from enzymatic investigations (Table 2).
Differential Diagnosis

The prominent biochemical abnormality in urea cycle disorders is the hyperammonemia; however, many situations can be associated with hyperammonemia (Fig. 2). The identification of the underlying cause influences the prognosis for recovery and recurrence of symptoms.

1. Transient Neonatal Hyperammonemia

Batshaw et al. (4) reported that plasma ammonium levels are elevated in more than 50% of premature infants. Levels are approximately twice those noted in term

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**TABLE 1. Routine tests for the diagnostic approach to hyperammonemia**

<table>
<thead>
<tr>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>pH</td>
</tr>
<tr>
<td>Glucose</td>
<td>Ketone bodies</td>
</tr>
<tr>
<td>Acid-base (anion gap)</td>
<td>DNPH test</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>(aliquot at -20°C)</td>
</tr>
<tr>
<td>Lactate</td>
<td>Orotic acid</td>
</tr>
<tr>
<td>Amino acids</td>
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**FIG. 2.** Diagnostic scheme of hyperammonemias.
infants and high levels persist for 4–8 weeks. Although they are not associated with clinical symptoms or with long-term neurologic deficits, an arginine supplementation is recommended (4,5). However, on some occasions symptomatic hyperammonemia is observed and requires aggressive therapy (6) since neurologic symptoms correlate well with levels of ammonia. There is marked central nervous system depression and most of these infants require ventilatory assistance. No specific biochemical alterations other than the hyperammonemia are noted; the plasma amino acid chromatogram is normal, and activities of urea cycle enzymes in liver are unmodified (6). The etiology of this syndrome is unknown, but it is generally attributed to a developmental delay in regulation of one of the enzymes required for urea synthesis or to a nonadaptation to nitrogen load (7). Mild hyperammonemia may also be seen during parenteral alimentation in premature infants; but differential diagnosis from “transient hyperammonemia” in sick preterm infants is not certain.

2. Hyperammonemia and Organic Aciduria

Hyperammonemia has been reported in several disorders of branched-chain amino acid metabolism, in pyruvate carboxylase deficiency (8), and in the most severe form of pyruvate dehydrogenase deficiency (9). A significant correlation between ammonia concentration and organic acid accumulation is observed (10). The secondary inhibition of ureogenesis in organic aciduria appears to be due to a functional deficiency of carbamylphosphate synthetase activity (11).

3. Reye Syndrome

Reye syndrome is probably the best situation mimicking inborn errors of the urea cycle (12); this explains the controversial reports about its pathogenesis in late 1970s. Nowadays, this syndrome should be considered a diagnosis of exclusion. Reye syndrome is generally seen in otherwise healthy children older than 2 years of age, but
many cases have been reported in early infancy (13). A history of viral illness (e.g., chickenpox) and exposure to salicylates approximately 2 weeks before presentation is often found.

4. Iatrogenic Hyperammonemia

It has been stated that 20% of epileptic children treated with valproic acid can develop hyperammonemia (>60 μmol/liter) (14). In rats (15), valproic acid produces a marked reduction in hepatic CPS I activity; an inhibition of the N-acetylglutamate synthesis was also hypothesized (16). However, Morgan et al. (17) recommended that urea cycle defects should be sought in the diagnosis of patients with seizures and mental retardation of undetermined etiology who develop hyperammonemia after valproic acid treatment.

A syndrome of idiopathic hyperammonemia has also been described in patients who have received high-dose chemotherapy for the treatment of hematologic malignancies. It is characterized by abrupt alteration in mental status and respiratory alkalosis associated with markedly elevated ammonium levels in the absence of any identifiable cause, and frequently results in coma and death (18).

5. Dibasic Aminoaciduria

The impaired ammonia metabolism (postprandial hyperammonemia) in lysinuric protein intolerance is attributed to low plasma arginine and ornithine levels (19). Hyperornithinemia, hyperammonemia, and homocitrullinuria syndrome (HHH) is presumably due to an impairment of the transport of citrulline across the inner mitochondrial membrane.

LONG-TERM TREATMENT

It is not clear how close to normal the levels of ammonium and other metabolites must be kept to prevent mental retardation and acute episodes. The most important point is the rapidity with which infants develop symptomatic hyperammonemia at times of infection, stress, or excessive protein intake.

The morbidity remains high, presumably due to the degree of brain damage correlated with duration of neonatal hyperammonemic coma (20). Msall et al. (21) pointed out that even prospective treatment may not prevent cognitive impairment and suggested that asymptomatic hyperammonemia may have subtle effects on intellect. This point is illustrated by the spectrum of manifestations among female OTC heterozygotes, ranging from asymptomatic illness to recurrent episodes of coma and death, as predicted by Lyon’s hypothesis (random inactivation of the X chromosomes). More frequent than initially believed are the manifestations of protein intolerance, including recurrent migraine headaches, cyclical vomiting episodes, ir-
ritability, ataxia, and seizures (22). Even in asymptomatic carriers, intellectual deficits have been noticed, perhaps a result of unrecognized episodic hyperammonemia (23).

The therapeutic measures include the following (Table 3 and Fig. 3):

1. **Protein restriction combined with supplements of essential amino acids (EAA) or their nitrogen-free analogues.** The need for EAA supplementation is self-evident. In addition, arginine becomes an EAA for infants with inborn errors of ureogenesis (apart from arginase deficiency). For patients with deficiencies of argininosuccinate synthetase and argininosuccinate lyase deficiency, dietary arginine supplementation promotes the synthesis of citrulline and argininosuccinate which, respectively, serve as waste nitrogen products (24). However, long-term effects of arginine therapy on chronic stimulation of growth hormone and insulin have not been evaluated. In patients with partial forms, the requirement for substrate may have a different mechanism. Wendel et al. (25) have recently observed a better metabolic control in a patient with a partial defect of OTC by supplying arginine in order to increase the mitochondrial ornithine to achieve critical substrate concentration for the kinetically abnormal OTC.

The keto analogs of amino acids offer at least two potential advantages. First EAA can be supplied without giving nitrogen. Second, since ketoacids are transaminated and ultimately incorporated into protein, nitrogen will be used.

2. **Stimulation of alternative pathway of waste nitrogen excretion has been extensively investigated.** This approach usually employs sodium benzoate to acylate glycine forming hippurate and sodium phenylacetate to acetylate glutamine forming phenylacetylglutamine, both of which are readily excreted in the urine (26). At a dose of 250 mg benzoate/kg·day, glycine availability seems not to be limiting for the synthesis of hippurate (27). A note of caution was raised since it has been shown in animals that benzoate potentiates ammonia toxicity. Acute benzoate toxicity can occur inadvertently, leading to irritability and vomiting mimicking hyperammonemia. At therapeutic dose, the paradoxical effect of benzoate is counterbalanced by a significant increase in waste nitrogen excretion. Nevertheless, periodical measurement of benzoate levels in plasma seems highly recommended.
FIG. 3. Metabolic ways used to limit nitrogen accumulation according to the localization of the enzyme defect. A: CPS and N-acetylglutamate synthetase deficiency; B: OTC deficiency; C: argininosuccinate synthetase deficiency; D: argininosuccinate lyase deficiency. PAA, phenylacetic acid; GFR, glomerular filtration rate; OA, oxaloacetate; +, enzymatic activation.
FIG. 3. Continued.
In N-acetylglutamate synthetase deficiency and partial CPS deficiency, administration of carbamylglutamate has been suggested (28). Because of its structural analogy with N-acetylglutamate, the physiologic allosteric activator of CPS, and its easy entry in mitochondria, carbamylglutamate may substitute for the decreased or non-existent N-acetylglutamate in the first case, while in the second, stimulation of the remaining CPS may increase the rate of urea synthesis.

In argininosuccinate lyase deficiency, argininosuccinic acid, the substrate of the defective enzyme, is ideally suited as a waste nitrogen product. It contains the two nitrogen atoms destined for excretion as urea and has a renal clearance equal to glomerular filtration rate. Argininosuccinic acid is not toxic (29) and is dependent on the provision of adequate arginine and citrulline carbon skeletons. An arginine supplement of 3–4 mmol/kg·day is sufficient to meet these needs. With arginine supplementation, a high protein intake is expected to be well tolerated (30) and avoids the deleterious effects of severe protein restriction (29). Citrate supplementation has also been used successfully to improve waste nitrogen excretion. Indeed, citrate is cleaved in the cytosol to oxaloacetate, which is transaminated to aspartate at the expense of glutamine. Aspartate is required as substrate with citrulline to form argininosuccinic acid. Aspartate becomes an “essential” substance in this disease.

Hyperargininemia represents a different situation since elevated levels of arginine or its metabolites [guanidino compounds (31)] are thought to lead to a progressive neurologic disorder characterized by epilepsy, pyramidal spasticity, and mental retardation, which gives the disease a particular clinical picture. Hyperammonemia may be absent, but intercurrent hyperammonemia can result in episodes of vomiting and lethargy. Therapy has been directed at reducing hyperammonemia and hyperargininemia by protein restriction or by an arginine-free diet. However, the addition of benzoate has also been suggested (32) to permit a more varied diet than is possible with an amino acid mixture alone.

3. Protective effect of L-carnitine has been evoked by several authors (33,34). Ohtani et al. (34) reported data suggesting that OTC-deficient patients had a secondary carnitine deficiency and O’Connor et al. reported that L-carnitine prevents the paradoxical effect of benzoate on ammonia toxicity (35). Oral administration of L-carnitine (50–100 mg/kg·day) was proposed.

Other Therapeutic Problems

A side effect of the dietary treatment is anorexia and food refusal, often observed in such patients, which may necessitate nasogastric or gastrostomy tube feeding. Generalized food aversion is often observed. Hyman et al. (36) have suggested that an increased serotonin turnover secondary to either hyperammonemia or high-carbohydrate low-protein diets can explain a serotonin-dependent appetite suppression.

The Future

Liver transplantation is the only available form of enzyme replacement therapy for patients with severe defects in the urea cycle. However, new problems may
appear which may clarify some physiologic aspects of the urea cycle. For example, Tuchman (37) reported a case of CPS deficiency who underwent a successful liver transplantation. Interestingly, citrulline levels failed to increase, confirming that citrulline probably originates from the gut, the only organ other than the liver that has CPS and OTC activities. Consequently, citrulline supplementation was continued in this case.

In the future, gene therapy may become possible. Cloned genes can be transferred into cells. Transgenic mouse is a model for the study of tissue specificity of gene expression; OTC deficiency in mouse (sfp-ash) has been corrected by gene transfer (38).

CONCLUSION

Although screening methods have been developed using blood or urine specimens, the cost-benefit ratio of mass screening for urea cycle disorders is particularly unfavorable. “The patients with neonatal onset will become ill before routine screening is performed. On the other hand, the patients with late onset forms of urea cycle disorders may escape screening in the neonatal period” (39). Clinical information and simple routine laboratory tests, including ammonia determination, allow rapid orientation of the diagnosis to enable the patient to be managed correctly initially. Final diagnosis is a matter of more sophisticated investigation not immediately necessary for the institution of the treatment. In summary, the crucial point remains that the possibility of hyperammonemia should be considered at all.

Whatever the defect, variability in residual enzyme activity and clinical presentation (lethal neonatal or delayed onset form) points toward a variety of mutations in the enzyme molecule. Recent developments in molecular genetics will provide new tools for the diagnosis of these diseases. However, correct identification of the index case and the preservation of tissue for DNA extraction are prerequisites for optimal utilization of these new techniques.

REFERENCES


DISCUSSION

Dr. Wang: We are concerned about detection of carriers and about prenatal diagnosis of urea cycle abnormalities, but we have some difficulties just using enzyme determination. What is your comment about this kind of determination? Can detection of carriers with enzyme determinations be useful for heterozygote detection or even for prenatal diagnosis?

Dr. Dhondt: Phenomenal advances in molecular biology have changed the way in which we obtain the diagnosis and, of course, the detection of carriers has also improved. About the detection of carriers for OTC deficiency, the main problem is to have the index case very well documented, because the DNA analysis looks for the polymorphism. Since all the mutations are probably different, it is not possible to search directly for the abnormal gene. Without documentation of the index case, DNA analysis is informative in only 10% of the carriers, except where other biochemical investigations are taken in account (i.e., protein loading test). Consequently, tissue samples have to be taken from any patients who die with a suspected metabolic disease, for eventual DNA analysis.

Dr. Endres: I would like to take the opportunity to advertise some enzymatic methods of my co-worker Dr. Shin. With these more sensitive methods it is possible to use blood cells and chorionic villi for the postnatal and prenatal diagnosis of urea cycle disorders (UCD) (1). Concerning postnatal diagnosis activities of the two mitochondrial enzymes, carbamylphosphate synthetase and ornithine transcarbamylase, are measurable in leukocytes. In contrast, the argininosuccinate synthetase activity is not detectable in blood cells but can be detected in cultured fibroblasts. The determination of the argininosuccinate lyase and arginase activity in red blood cells is an excellent method for diagnosing the respective homozygotes as well as the heterozygotes. Concerning prenatal diagnosis, application of these methods to chorionic villi demonstrated that they might be suitable for the antenatal detection of all five urea cycle disorders.

Dr. Hobbs: I have a question concerning the white cell and red cell content of the other two enzymes. Do you think there is sufficient content of enzyme to detoxify patients if we exchange transfuse their blood with normal white and red cells, which is very easy.

Dr. Endres: I am afraid that the enzyme content is not high enough for sufficient ammonia detoxication.

Dr. Hobbs: The red cell mass is enormous, and might detoxify the blood sufficiently to save the brain. The other question is: your colleagues in Paris have described cellular immune deficiency with orotic aciduria because of an associated defect in nucleic acid synthesis. Have you encountered this, and do you know the frequency with which it occurs among all orotic aciduria?

Dr. Endres: I have no idea at all.

Dr. Saudubray: I can give a short comment because it was my friend Claude Griscelli who published this case. This is a completely different inborn error due to a specific defect in orotic acid catabolism: hereditary orotic aciduria. In orotic aciduria secondary to urea cycle defects, as in OTC deficiency, there is no immune deficiency.
Dr. Jaeken: Let me tell you something about our experience with the transient neonatal hyperammonemia syndrome. We have seen 13 patients during the last 10 years, all preterm neonates, from 31 to 36 weeks of gestational age. All had a respiratory distress syndrome and went into deep coma with complete apnea and required ventilatory support; only some spinal reflexes remained. Eight died due to cerebral hemorrhage and the others survived, four of them with completely normal development and one with cerebral palsy. We have evidence that in this disorder there is hepatic hyperperfusion. There is no enzymatic deficiency or developmental delay in enzymatic activity of the urea cycle. In our experience this disease is even more frequent than congenital urea cycle defects.

Dr. Dhondt: I am glad to have this information because the explanation of a delayed maturation of enzymes was not very good. What is really important to remember is that in transient neonatal hyperammonemia, if the child survives, there is no severe long-term effect from the hyperammonemia itself. The reverse situation occurs in heterozygotes for OTC, where the chronic hyperammonemia has subtle effects on brain development. I think this is one of the reasons why we need to use very aggressive therapy like liver transplantation as early as possible in urea cycle disorders to prevent such developmental problems.

Dr. Van den Bergh: Maybe I missed the point, but you said that you did not find data concerning the amount of amino nitrogen that was accounted for by the excretion of orotate. This surprises me since one molecule of carbamyl phosphate, synthesized from ammonia in the mitochondria but flowing over in the cytoplasm in urea cycle disorders, and one molecule of aspartate yield one molecule of orotic acid.

Dr. Dhondt: Perhaps I did not explain myself enough. I never found any evaluation of orotate as a waste nitrogen compound.

Dr. Saudubray: Sodium benzoate therapy has been advocated as a good method of detoxication in the acute phase of hyperammonemia, but I am not sure that it really works. Consider from a quantitative point of view the catabolism of 6 g protein and 1 g nitrogen: 1 g of nitrogen is 71 mmol; when you give sodium benzoate at a dose of 250 mg/kg, it means that in a 3- to 4-kg neonate you give a total amount of approximately 12 to 14 mmol. So when you compare 70 mmol from the catabolism of 30 g of muscle to 14 mmol of sodium benzoate I can’t understand how this therapy can work. It is the same kind of question you stressed. Do you have some comments?

Dr. Dhondt: I agree with you and for this reason I was very interested in the recent report from Batshaw about the use of phenylacetate or phenylbutyrate because it looks from these data better than the benzoate therapy.

Dr. Vis: You claim that high blood levels of ammonia, either permanent or transient, are toxic for the brain. What level do you think may be tolerated by premature newborns over a period of several weeks without deleterious effects? The question is of importance because premature babies receiving parenteral amino acid mixtures sometimes present very high levels of ammonia in blood. I don’t think this problem has been given enough attention in the literature.

Dr. Dhondt: We don’t know exactly what ammonia level is toxic in the long term. Even in asymptomatic transient hyperammonemia it has been proposed that arginine should be added to prevent such an effect.

Dr. Jaeken: I think that below 150 μmol/l there is no clinical problem at all, but there is probably no clear cutoff value.

Dr. Schaub: You recommend peritoneal dialysis. In many hospitals this technique is not available in newborns. Is there another form of treatment like exchange transfusion for newborns in hyperammonemnic crisis?
Dr. Dhondt: The Johns Hopkins hospital group has shown that peritoneal dialysis is the most effective system for clearing ammonium, more effective than exchange transfusion.

Dr. Endres: Sometimes you can even increase the level of ammonium by exchange transfusions because the blood you give contains a lot of ammonium.

Dr. Saudubray: I have observed more than 70 patients with urea cycle defects in the neonatal period. My policy now is not to treat such patients. I disagree completely with Batshaw’s treatment policy in neonates because more than 80% of their patients are very severely mentally retarded. Therefore, it is not reasonable to treat a neonate who will spontaneously die within 3 days of life. This is my policy. It does not seem reasonable to me to treat patients with urea cycle defects presenting with the very severe neonatal form.

Dr. Sokal: The liver enzymes are heterogeneously distributed across the liver acinus. The urea cycle enzymes are located in the perportal zone, whereas other ammonium detoxification systems, such as glutamine synthetase, are located in the perivenular zone. Ammonium ions “escaping” the urea cycle are detoxified by glutamine synthetase in the perivenular zone. It is likely that in urea cycle enzyme defects, the latter system has an enhanced activity. Is there any evidence that this could lead to a secondary lack of glutamate which is the substrate for this reaction, and would it help the patient to give additional glutamate or α-ketoglutarate?

Dr. Wanders: Carbamyl glutamate could be used in the urea cycle defects, because in these conditions limited amounts of protein are given and hence intramitochondrial glutamate levels will be low; consequently, the N-acetylglutamate levels will also be low, because N-acetylglutamate arises from glutamate and acetyl-CoA. So by giving carbamyl glutamate you might speed up CPS to the greatest degree and so effectively remove ammonia. I would therefore suggest that in the other enzyme deficiencies it would also be good to use carbamyl glutamate.

Dr. Dhondt: This should be a possibility, similar to arginine supplementation since arginine stimulates carbamyl phosphate synthesis.

Dr. Wanders: With regard to the stimulation by arginine, it is very doubtful whether this also happens in vivo because the $K_i$ of arginine is in the micromolar range and the normal concentration in mitochondria is far above this $K_i$.

Dr. Dhondt: However, carbamyl glutamate is an analog and we are always a little anxious about using nonnatural products.

Dr. Roe: I just want to elaborate on a point and also ask a question. My comment is related to our experience with ASL deficiency and citrate administration. We know that in that ASL deficiency, plasma citrulline levels are extremely high, aspartate levels low, and ASA is high. With the administration of citrate the citrulline level drops and ASA levels go up. But more important one can see the resolution of hepatomegaly in that disease and appetite returns. This all suggest a very fundamental problem with intermediary metabolism and the TCA cycle that may apply to several disorders. We agree with the importance of the use of arginine. I am not so convinced about benzoate, phenylacetate, and phenylbutyrate. One of my concerns is there seems to be no documentation in the literature regarding the dose of arginine used for supplementation.

Dr. Widhalm: Dr. Thalammer introduced the modified Murphy test for arginine-succinate deficiency into the Austrian screening program. By means of this test about 14 patients have been detected with arginine-succinate lyase deficiency but without or with only mild hyperammonemia. These patients had been treated for several years with arginine and within the last year with citric acid. I would like to ask if anybody has experience with mild hyperammonemia and a definite-succinate lyase deficiency.
Dr. Baerlocher: We have observed two children with argininosuccinic aciduria and only slight hyperammonemia. They have grown up with no special problems. May I ask Dr. Saudubray if he includes argininosuccinic aciduria among the disorders of the urea cycle in which he would not begin any treatment. My experience is not so bad with this disorder. We recently observed a child with a severe neonatal form of argininosuccinic aciduria and severe hyperammonemia. We started peritoneal dialysis on the third day without any effect on the hyperammonemia. Only when arginine was given 12 h later did the hyperammonemia rapidly diminish and finally normalize. The child is at the moment quite well. On the third day, ultrasonography revealed dense kidney parenchyma reflecting nephrocalcinosis. Orotic acid was very high in the urine at this time but diminished under treatment with arginine. We therefore suggest that orotic acid crystals may have been responsible for the ultrasonographic findings.

Dr. Saudubray: I agree. Maybe argininosuccinic aciduria is a little bit different from the other urea cycle defects because you have a very effective way of nitrogen clearance through argininosuccinic acid excretion itself. But until now if you consider the Johns Hopkins group's long-term results there is no 10-year-old patient with normal psychomotor development having presented with a urea cycle defect in the neonatal period. The true problem in the neonatal period confronted with hyperammonemia is to separate the following three conditions rapidly: transient hyperammonemia, urea cycle defect, and organic aciduria. In the first condition (transient hyperammonemia) you have to treat, of course, because the patient can die but he can also improve and develop normally afterward. In this condition the clinical context is evident: it is a clinical diagnosis, not a biological one. As stated by Dr. Jaeken, all the patients affected with transient hyperammonemia are premature babies. This is not a clinical condition encountered in full-term neonates. Patients with organic acidurias also have to be treated, whereas those with urea cycle defects do not have to be.

Dr. Dhondt: I cannot totally agree on an ethical point of view because it is difficult to refuse treatment in such patients. I remember our first OTC-deficient patient, who was in poor condition at the start but now is totally normal. Of course, that will represent only 5-10% of patients, but how can one refuse the possibility of treatment even if only a few patients will have normal development?

Dr. Krywawych: My comment is an addition to the points raised on argininosuccinic aciduria. In our patient with argininosuccinic acid lyase deficiency a diagnosis was made at 48 h after birth and treatment was started within 3 days after birth. During the neonatal period this child was treated with arginine supplements and citrate to replenish the oxaloacetate which was being excreted and lost as part of the argininosuccinic acid. In later life benzoate supplements were also included in the treatment regime. Since that time, this patient has experienced only three crisis periods but was promptly treated and the plasma ammonia was rapidly brought under control. His plasma ammonia levels have generally been maintained below 100 μmol/liter. He is now 6 years old and is neurologically delayed. We do not know whether this has been caused by some toxic properties of argininosuccinic acid, by the chronically mildly raised plasma ammonia levels, or whether this patient may have suffered some degree of neurological damage during the three brief crisis periods. I would like to ask whether anyone here has any experience of children with argininosuccinic aciduria presenting with an acidosis. In the three cases we have seen profound acidosis was present with only a mildly raised lactate and some indication of a raised plasma chloride. I would also wish to ask whether the administration of benzoate to these patients could lead the formation of benzoyl carnitine, carnitine loss, and interference with fatty acid metabolism.
Dr. Roe: In response to the question about whether benzoyle carnitine is formed, this is apparently not a substrate for carnitine acyltransferase, as we are completely unable to identify any benzoyle carnitine in patients on benzoate therapy.

REFERENCE