J. Fernandes J.-M. Saudubray G. Van den Berghe (Eds.)

Inborn Metabolic Diseases

Diagnosis and Treatment

3rd, Revised Edition

With 66 Figures and 57 Tables

Springer

C

Dr. JOHN FERNANDES
Professor Emeritus of Pediatrics
Veldweg 87
8051 NP Hattem, The Netherlands

Professor JEAN-MARIE SAUDUBRAY
Hospital Necker-Enfants Malades
149 Rue de Sevres
75743 Paris Cedex 15, France

Professor GEORGES VAN DEN BERGHE
Christian de Duve
Institute of Cellular Pathology
Université Catholique de Louvain
Avenue Hippocrate 75
1200 Brussels, Belgium

Cover Illustration: Putti by della Robbia at Spedale degli Innocenti, Firenze, Italy

ISBN 3-540-65626-X Springer-Verlag Berlin Heidelberg New York

ISBN 3-540-58546-X, 2nd edition, Springer-Verlag Berlin Heidelberg New York

Library of Congress Cataloging in Publication Data applied for.
Die Deutsche Bibliothek – CIP-Einheitsaufnahme
Inborn metabolic diseases: diagnosis and treatment/J. Fernandes... – 3., rev. ed. – Berlin; Heidelberg; New York; Barcelona; Hong Kong; London; Milano; Paris; Singapore; Springer, 2000.
ISBN 3-540-65626-X

Cover Design: Springer-Verlag, E. Kirchner
Production: Pro Edit GmbH, 69126 Heidelberg, Germany
Typesetting: Scientific Publishing Services (P) Ltd, Madras

Printed on acid-free paper SPIN: 10708260 22/3134/göh - 5 4 3 2 1 0

The Urea Cycle

The urea cycle which, in its complete form, is only present in the liver, is the main pathway for the disposal of excess of ammonium nitrogen. This cycle sequence of reactions, localised in part in the mitochondria and in part in the cytosol, converts the toxic ammonia molecule into the non-toxic product, urea, which is excreted in the urine. There are genetic defects of each of the enzymes of the urea cycle which lead to hyperammonaemia. Some genetic defects of other important metabolic pathways may lead to secondary inhibition of the urea cycle. Alternative pathways for nitrogen excretion, namely conjugation of glycine with benzoate and of glutamine with phenylacetate can be exploited in the treatment of patients with defective ureagenesis.

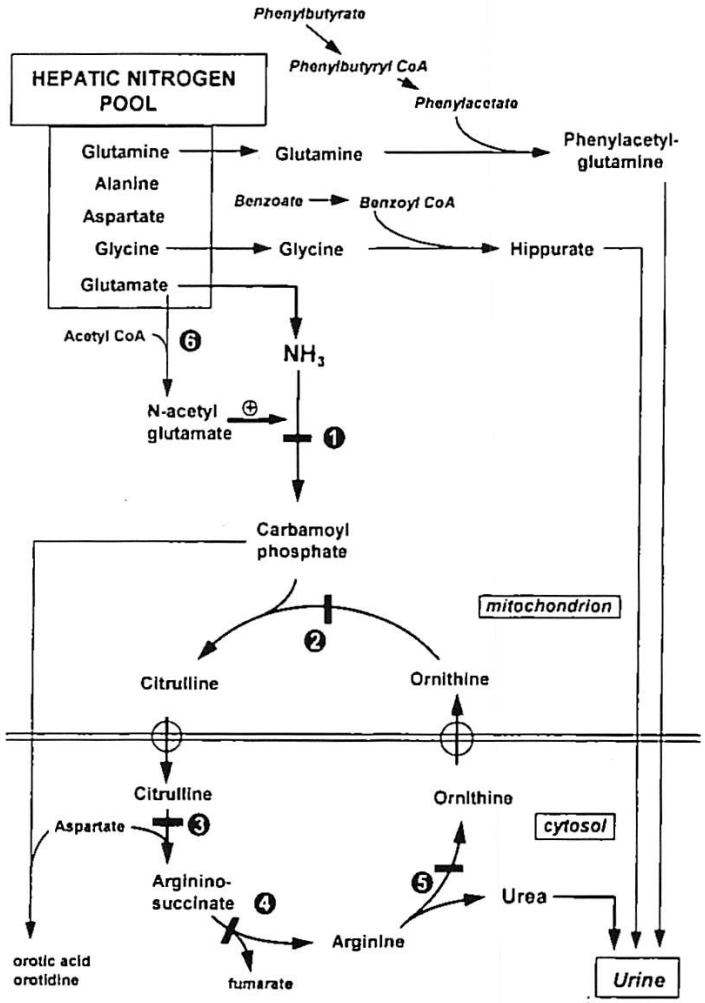

Fig. 17.1. The urea cycle and alternative pathways of nitrogen excretion. Enzymes: 1, carbamoyl phosphate synthetase; 2, ornithine transcarbamoylase; 3, argininosuccinate synthetase; 4, argininosuccinate lyase; 5, arginase; 6, *N*-acetylglutamate synthetase. Enzyme defects are depicted by *solid bars* across the arrows

CHAPTER 17

Disorders of the Urea Cycle

J.V. Leonard

CONTENTS

Five inherited disorders of the urea cycle are now well described. These are characterised by hyperammonaemia and disordered amino-acid metabolism. The presentation is highly variable: those presenting in the newborn period usually have an overwhelming illness that rapidly progresses from poor feeding, vomiting, lethargy or irritability and tachypnoea to fits, coma and respiratory arrest. In infancy, the symptoms are less severe and more variable. Poor developmental progress, behavioural problems, hepatomegaly and gastrointestinal symptoms are usually observed. In children and adults, chronic neurological illness is characterised by behavioural problems, confusion, irritability and cyclic vomiting, which deteriorates to acute encephalopathy during metabolic stress. Arginase deficiency shows more specific symptoms, such as spastic diplegia, dystonia, ataxia and fits. All urea-cycle disorders have autosomal-recessive inheritance except ornithine carbamoyl transferase deficiency, which is X-linked.

Clinical Presentation

Patients with urea-cycle disorders may present at almost any age. However, there are certain times at which they are more likely to develop symptoms because of metabolic stress, such as infection precipitating protein catabolism. These are:

- The neonatal period.
- During late infancy. Children are vulnerable during this period because of the slowing of growth, the change to cow's milk and weaning foods and the declining maternal antibody and consequent development of intercurrent infections.
- Puberty. The changing growth rate and psychosocial factors may precipitate decompensation.

However, it must be emphasised that many patients may present outside these periods. The patterns of the clinical presentation of hyperammonaemia are rather characteristic and are broadly similar for all the disorders except arginase deficiency, which is discussed separately. The early symptoms are often non-specific and initially, therefore, the diagnosis is easily overlooked. The most important points in diagnosing hyperammonaemia are to think of it during diagnosis and to measure the plasma ammonia concentration.

Neonatal Presentation

Most babies with urea cycle disorders are of normal birthweight and are initially healthy but, after a short interval that can be less than 24 h, they become unwell. Common early symptoms are poor feeding, vomiting, lethargy and/or irritability and tachypnoea. The initial working diagnosis is almost invariably sepsis. Rather characteristically, these babies may have a transient mild respiratory alkalosis, which can be a useful diagnostic clue at this stage. Usually, they deteriorate rapidly, with more obvious neurological and autonomic problems, including changes of tone with loss of normal reflexes, vasomotor instability and hypother-

mia, apnoea and fits. The baby may soon become totally unresponsive and may require full intensive care. Untreated, most babies will die, often with complications, such as cerebral or pulmonary haemorrhage, the underlying metabolic cause for which may not be recognised. Some survive neonatal hyperammonaemia but are invariably handicapped to some degree.

Infantile Presentation

In infancy, the symptoms are generally rather less acute and more variable than in the neonatal period and include anorexia, lethargy, vomiting and failure to thrive, with poor developmental progress. Irritability and behavioural problems are also common. The liver is often enlarged but, as the symptoms are rarely specific, the illness is initially attributed to many different causes that include gastrointestinal disorders (gastro-oesophageal reflux, cow's milk protein intolerance), food allergies, behaviour problems or hepatitis. The correct diagnosis is often only established when the patient develops a more obvious encephalopathy with changes in consciousness level and neurological signs (see below).

Children and Adults

At these ages, the patients commonly present with a more obviously neurological illness.

ACUTE ENCEPHALOPATHY. Whilst older patients often present with episodes of acute metabolic encephalopathy, they may also have chronic symptoms. Usually, symptoms develop following metabolic stress precipitated by infection, anaesthesia or protein catabolism, such as that produced by the rapid involution of the uterus in the puerperium [1]. However an obvious trigger is not always apparent. The patients first become anorexic, lethargic and unwell. Sometimes they are agitated and irritable, with behaviour problems or confusion. Vomiting and headaches may be prominent, suggesting migraine or cyclical vomiting. Others may be ataxic as though intoxicated. On examination, hepatomegaly may be present, particularly in those with argininosuccinic aciduria. The patients may then recover completely but, if not, they may then develop neurological problems, including a fluctuating level of consciousness, fits and (sometimes) focal neurological signs, such as hemiplegia [2] or cortical blindness. Untreated, they continue to deteriorate, becoming comatose, and they may die. Alternatively, they may recover with a significant neurological deficit. The cause of death is usually cerebral oedema.

Between episodes, the patients are usually relatively well, although some, particularly younger ones, may continue to have problems, such as vomiting or poor developmental progress. Some patients may voluntarily restrict their protein intake. In addition to those disorders already mentioned, the illness may be attributed to a wide variety of other disorders, including Reye's syndrome, encéphalitis, poisoning and psychosocial problems.

CHRONIC NEUROLOGICAL ILLNESS. Learning difficulties or more obvious mental retardation are common, and some patients, particularly those with argininosuccinic aciduria, may present with relatively few symptoms apart from mental retardation and fits. About half the patients with argininosuccinic acid have brittle hair (trichorrhexis nodosa). Patients may present with chronic ataxia, which is worse during intercurrent infections [3].

ARGINASE DEFICIENCY. Arginase deficiency commonly presents with spastic diplegia and, initially, a diagnosis of cerebral palsy is almost always suspected. However, the neurological abnormalities appear to be slowly progressive, although it may be difficult to distinguish this from an evolving cerebral palsy. During the course of the disease, fits, ataxia and dystonia may develop. Occasionally, patients may present with an acute encephalopathy or anticonvulsant-resistant fits [4].

Metabolic Derangement

The urea cycle is the final common pathway for the excretion of waste nitrogen in mammals. The steps in the urea cycle are shown in Fig. 17.1. Ammonia is probably derived principally from glutamine and glutamate and is converted to carbamoyl phosphate by *carbamoyl phosphate synthetase* (CPS). This enzyme requires an allosteric activator, *N*-acetylglutamate, for full activity. This compound is formed by the condensation of acetyl coenzyme A (acetyl CoA) and glutamate in a reaction catalysed by *N-acetyl glutamate synthetase*. Carbamoyl phosphate condenses with ornithine to form citrulline in a reaction catalysed by *ornithine transcarbamoylase*. The product, citrulline, condenses with aspartate to produce argininosuccinate in a reaction catalysed by *argininosuccinate synthetase*, and the arginosuccinate is then hydrolysed to arginine and fumarate by *argininosuccinate lyase*. The arginine is itself cleaved by *arginase*, releasing urea and re-forming ornithine. Within the urea cycle itself, ornithine acts as a carrier; it is neither formed nor lost.

Each molecule of urea contains two atoms of waste nitrogen, one derived from ammonia and the other from aspartate. Regulation of the urea cycle is not fully understood, and it is likely that there are several mechanisms controlling flux through this pathway [5].

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.