Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases

Second Edition

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Editors

with CD-ROM

Springer

Physician's Guide
to the Laboratory Diagnosis
of Metabolic Diseases

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(Eds.)

Delay and mistakes in the diagnosis of inherited metabolic diseases may have devastating consequences. Reference laboratory data are scattered and clinical descriptions of rare conditions are hard to locate. This book describes 298 disorders, grouped into 35 chapters according to the type of condition. Within each group of disorders, chapters provide tables of pertinent clinical findings as well as reference and pathological values for crucial metabolites. Relevant metabolic pathways and diagnostic flow charts are included. There are three indices to make the book as user-friendly as possible: *Disorders index*, *Signs and symptoms index*, and *Tests index*. *The Physician's Guide* provides paediatricians and other physicians with a unique aid to help them select the correct diagnosis from a bewildering array of complex clinical and laboratory data.

This book includes a bonus CD-ROM further facilitating access to the content by means of a full-text search function.

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With 100 Figures and 270 Tables

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11 Inherited Hyperammonemias

CLAUDE BACHMANN

11.1 Introduction

Hyperammonemia (systemic venous or arterial plasma ammonia >80 in newborns or >50 μmol/L after 28 days postnatally) is due either to an increased production exceeding the capacity to detoxify (as in colonization with urease containing microorganisms in an intestinal loop, a neurogenic bladder or with a ureterosigmoidostomy), or to a decreased detoxification capacity. Among the latter causes are primary or secondary defects of enzymes involved in ammonia detoxification or a deficiency of intermediates needed as substrates for a functional urea cycle, such as a nutritional, enzyme, or transport defect, or to interference with portal circulation so that portal blood does not reach the hepatocytes (a portacaval bypass or a patent ductus), which can cause "transient hyperammonemia of the premature". Ammonia detoxification is reduced in deficiencies of urea cycle enzymes, transport proteins (estimated incidence 1:30000 newborns, [1]) in conditions where glutamate or acetyl CoA is decreased (valproate therapy and organic acidurias), with carnitine and CoA (sequestered by pathological acyl moieties) and defects of mitochondrial beta-oxidation or carnitine metabolism. These lead to a deficient formation of N-acetylglutamate (NAG), an obligate activator of the first step of ammonia detoxification, and thus to a functional NAGS deficiency. An acetyl CoA deficiency further reduces pyruvate carboxylase, which blocks gluconeogenesis. These two effects of an acetyl CoA deficiency lead to a Reye syndrome. Today, because more specific etiological diagnoses can be made, the Reye Syndrome is disappearing.

The actual enzyme activity in urea cycle disorders (UCD) in vivo is only partially assessed by in vitro assays (artificial conditions). It is a problem and must always be viewed in respect to the nitrogen load entering the pathway (Fig. 11.3). This depends as well on the exogenous nutritional supply or bacterial ammonia production in the gut as on the endogenous balance or imbalance between protein synthesis and catabolism. The clinical heterogeneity of the disorders and any prognostic predictions will thus only partly depend on the genetic background if residual protein is present. "Mild" leaky variants (unstable enzymes in vitro or residual enzyme activ-

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