1 Disorders of Phenylalanine and Tetrahydrobiopterin Metabolism

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1.1 Introduction

Patients with disorders described in this chapter present either with or without hyperphenylalaninemia (HPA). In those presenting with HPA (1.1–1.5 in the table below), the main goal of treatment is to reduce or normalize blood phenylalanine levels. This can be done either by introduction of the low-phenylalanine or low-protein diet or by administration of the synthetic cofactor tetrahydrobiopterin (BH₄). The mode of treatment depends on the type of disease and may differ with the patient’s age, and the policies are different in different countries. In addition, patients with HPA due to a cofactor defect need more strict plasma phenylalanine control and additional supplementations with neurotransmitter precursors L-dopa and 5-hydroxytryptophan in a combination with the peripheral decarboxylase inhibitor carbidopa. Patients with dihydropteridine reductase (DHPR) deficiency (disorder 1.4) need additional folinic acid substitution. In patients revealing levodopa-induced peak-dose dyskinesia, slow-release forms of drugs can be used, and reaching the upper therapeutic limits of L-dopa may be an indication for the use of monoamine oxidase (MAO) and/or catecholamine-O-methyl transferase (COMT) inhibitors.

Patients with dopa-responsive dystonia (DRD, dominant GTP cyclohydrolase I (GTPCH I) deficiency; disorder 1.6) and sepiapterin reductase (SR) deficiency (disorder 1.7) respond to low-dosage L-dopa/carbidopa therapy, and patients with SR deficiency need additional supplementation with 5-hydroxytryptophan and probably also BH₄.

Prognosis and outcome strongly depend on the age when the diagnosis is made and treatment introduced, but also on the type of mutation.

Recommendations for treatment and monitoring are not completely uniform worldwide. Therefore, where possible and necessary, recommendations have been combined and ranges of values indicating lower and upper limits are reported (Fig. 1.1).
Fig. 1.1. Management of plasma phenylalanine concentrations