access to sodium benzoate, although the child already had severe limitation of joint movements.

The parents did not return to France until the child was nearly 6 years old. During the 2-year interval, spasticity of the lower limbs had considerably increased and he could no longer stand up. Upper limb spasticity had become apparent. The child was apathetic and lacked expression; he no longer spoke but understood. The clinical course deteriorated rapidly and at 6 years he was bed-ridden. Ammonia was only moderately elevated (53 μmol/L) under treatment with sodium benzoate (4 × 1 g before each meal), but argininaemia was extremely high (456 μmol/L) despite protein restriction. At 6.5 years, the ammonia level was normal and argininaemia had decreased to 264 μmol/L, but there was no clinical improvement.

Case 2: Amadou K. was born at term when his brother Idi was 6 years 9 months of age. He weighed 2820 g at birth and presented an OB-incompatibility but did not require blood exchange transfusion. At the age of 6 days the arginine level was 88 μmol/L, which can be considered normal (normal values for the age group are 35–92 μmol/L), but assay of erythrocyte arginase revealed severely decreased enzymatic activity: 4% of the control values.

At 1 month of age the ammonia level was below 40 μmol/L; glutamate–glutamine was normal, but argininaemia was 159 μmol/L and citrulline was at the upper limit of normal (38 μmol/L). The child vomited often and presented tremor and hypertonia. A protein-restricted diet administered at regular intervals was initiated, but was rendered difficult by the family context and the stays in Africa. The boy was breast-fed, and at 4 months he was hospitalized in France for gastroenteritis (Rotavirus). The ammonia level was slightly elevated, argininaemia (200 μmol/L) was accompanied by a rise in methioninaemia (306 μmol/L). Sodium benzoate supplementation was added to the diet. At 5 months of age, despite the difficulties with administration of the diet, psychomotor development and growth in height and weight were correct. Moderate hypertonia affected all four limbs but tremor and vomiting were absent. Ammonaemia was 65 μmol/L after 3 h fasting, but arginine was 153 μmol/L.

At the age of 9 months 22 days Amadou weighed 8.1 kg and measured 72 cm; head circumference was 45.5 cm. He was able to sit up and stand up unassisted, crawled, and showed satisfactory psychomotor development. Neurological evaluation failed to detect any tendinous retraction or hypertonia, reflecting satisfactory development on the low-protein diet. Electroencephalogram patterns showed improvement. Ammonia was 110 μmol/L although arginine was 120 μmol/L. Anaemia with hypo-sideraemia was noted. Amadou is now 15 months old; he walks, has started to talk, and no longer vomits.

Genetic expression of arginase deficiency is heterogeneous, and many affected patients go undiagnosed, having only nonspecific symptoms. This progressive disease characterized by mental retardation and spastic tetraplegia can be treated with a low-protein diet and addition of sodium benzoate to reduce blood arginine and ammonia levels (Cederbaum et al 1982). While the exact mechanism responsible for neurological damage remains unknown, arginine and its guanidino metabolites may be neurotoxins (Marescau et al 1990). Although several teams have observed

improvements under metabolic control, other authors report severe developmental delays with spastic diplegia.

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CASE REPORT

Tyrosinaemia type Ia without excess of urinary succinylacetone

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Tyrosinaemia type I (McKusick 276700) (Kvittingen 1991) is an autosomal recessively inherited metabolic disorder due to two enzymatic deficiencies: fumarylacetoacetase (FAH) (type Ia) and maleylacetoacetate isomerase (type Ib) (Berger et al 1988).

Elevation of urinary succinylacetone (SA) is usually deemed to be specific for tyrosinaemia type I. Diagnosis is made by assessing plasma tyrosine levels and urinary SA and by determining the activity of FAH in fibroblasts or lymphocytes. We report the case of a 3-year-old female child affected by tyrosinaemia type Ia, with persistent low levels of plasma tyrosine and no excess of urinary SA.

Maria M. was born to first-degree cousins; the postnatal period is reported as uneventful. At 7 months of age hepatomegaly was noted and the child was hospitalized. At that time plasma tyrosine was slightly elevated (425 μmol/L by ion exchange chromatography), with moderate tyrosinuria. No excess of SA was detectable in urine by GC-MS. α-Fetoprotein serum level was >300 IU/ml. Liver ultrasound and CT scans showed hepatomegaly and multifocal micronodular structural abnormalities. Tyrosinaemia type I was then suspected despite the absence of SA and a dietary regimen with low phenylalanine and tyrosine intake (25 mg/kg per day) was

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introduced. One month later, plasma tyrosine level was in the normal range (100 μmol/L).

The clinical picture has always been good, including adequate psychomotor development, except for a marked hepatomegaly (4 cm below the costal arch); plasma tyrosine was steadily below 110 μmol/L with only a slight elevation of plasma methionine; a major biochemical abnormality was α-fetoprotein 4232 IU/ml (normal 0.01–7.00). On the basis of the good metabolic control, diet was then progressively relaxed in order to assess her dietary tyrosine tolerance (up to 100 mg/kg per day). Plasma tyrosine levels remained constantly below 160 μmol/L, even 3 h after a meal. Urinary SA was still absent. Tyrosinaemia was then monitored for 1 year on a relaxed diet, being continuously below 110 μmol/L even after a protein load test providing 100 mg/kg body weight, with no detectable urinary SA and only slight increase of δ-aminolaevulinic acid (600 μmol/L; normal < 500 μmol/L). Hepatomegaly was the only clinical abnormality ever reported. The child stayed on a relaxed diet until the diagnosis of tyrosinaemia type Ia was confirmed by enzymatic activity determination on cultured skin fibroblasts (FAH 0.19 nmol/min per mg protein; normal 0.67) performed at Professor R. Berger's Metabolic Laboratory, Wilhelmina Kinderziekenhuis, Utrecht.

In the meantime her younger sister, aged 2 months, was admitted to another centre for recurrent vomiting, diarrhoea and jaundice. She had hepatomegaly (4 cm below costal arch) and elevation of serum total and conjugated bilirubin, ammonia, AST and ALT. Plasma tyrosine was 510 μmol/L. In 24 h her clinical picture worsened acutely with occurrence of seizures, dyspnoea, cyanosis and haematemesis, until death. Post-mortem liver histology showed a diffuse cirrhosis and features suggestive of tyrosinaemia type I.

Maria was referred again to our department for progressive restriction of the dietary tyrosine intake. At that time liver ultrasound scan showed no modification of the previous picture of cirrhosis. Serum α-fetoprotein level was 795 IU/ml.

Three months later she remained in very good clinical condition, with adequate psychomotor development; plasma tyrosine was 70 μmol/L and urinary SA still present in undetectable or trace amounts.

We report this case of tyrosinaemia type Ia to encourage consideration of this disease even when the biochemical picture is not properly suggestive of it. Furthermore, the family history confirms the possible occurrence of acute and chronic forms of this disease in one family. Also, we believe that it demonstrates that no biochemical parameter by itself is pathognomonic for this disease, and that any slight elevation of plasma tyrosine levels even without SA urinary excess is worth further investigation.

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CASE REPORT

Pseudodeficiency of α-iduronidase

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Mucopolysaccharidosis type I (Hurler syndrome, Scheie syndrome; McKusick 252800), a lysosomal storage disease, results from the deficiency of α-iduronidase. Patients who are homozygous for the Hurler allele are unable to hydrolyse dermatan and heparan sulphates that result in the characteristic phenotype of lumbar gibbus, corneal clouding, stiff joints, short stature, hepatosplenomegaly, coarse facies, hernias and progressive mental retardation.

When patients are homozygous for the Scheie allele, a milder phenotype occurs with the onset of symptoms generally in later childhood. Scheie syndrome features include claw hand deformity, corneal clouding, coarse facies and aortic valve stenosis. In contrast to Hurler syndrome, there is no mental retardation and height is usually normal in Scheie syndrome.

The compound heterozygote, Hurler/Scheie, i.e. those individuals having a Hurler allele and a Scheie allele at the iduronidase locus, results in a phenotype intermediate between Hurler syndrome and Scheie syndrome.

We report the finding of deficiency of α-iduronidase in a clinically normal individual. The initial finding was in leukocytes. Using 4-methylumbelliferyl-iduronide as the substrate, the activity was 2.5 nmol/h per mg protein (controls, 49.5 ± 15). All other enzymes assayed were normal. The sample was sent as an assay control in a Hurler syndrome family study. To rule out the possibility that samples had been mixed up, a second sample from the 'control' was requested and similar results were obtained. A skin biopsy was requested, fibroblasts were grown, and iduronidase activity was assayed in two laboratories. Iduronidase activity was 9.3 nmol/h per mg protein from fibroblasts when assayed with the 4-methylumbelliferyl-iduronide (controls, 93 ± 22; obligate heterozygotes, 25 ± 11). When [^{35}S]sulphate incorporation–turnover studies were done, which is an indirect measure of iduronidase activity (and glycosaminoglycan turnover in general) in the natural state, the pseudodeficient cells behaved normally with 82% correction (control, 84% correction; mucopolysaccharidosis type I, 38% correction), which would be predicted in a pseudodeficiency situation.

To our knowledge only two other instances of pseudodeficiency of iduronidase have been reported (Gatti et al 1985; Whitley et al 1987). Those cases involved obligate heterozygotes for Hurler syndrome, having one Hurler allele and presumably one pseudodeficiency allele. Obviously, prenatal diagnostic studies would need to be interpreted with caution in cases of heterozygotes having a pseudodeficiency allele.

The present case is not an obligate heterozygote for Hurler syndrome nor is there any family history of a mucopolysaccharide storage disorder. The alleles in this

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