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Correspondence to Professor T Meloni, Clinica Pediatrica dell'Università, Viale San Pietro 12, 07100 Sassari, Italy.

Hydroxyprolinaemia with normal development

MICHAEL J ROBINSON, IAN S MENZIES, AND IAN SLOAN

Department of Child Health, Department of Chemical Pathology, and Department of Obstetrics and Gynaecology, St Thomas's Hospital Medical School, London

SUMMARY A 6th case of hydroxyprolinaemia is described. The response to an oral hydroxyproline load failed to demonstrate an abnormal response in a presumed heterozygote. The infant is developing normally at age 36 months and we agree with others that this aminoacidaemia is benign.

Hydroxyprolinaemia is a metabolic disorder, characterised by an increase in free hydroxyproline in plasma and urine with a normal excretion of peptide-bound hydroxyproline. The disorder was first described in 1962 in a 12-year-old girl investigated for mental retardation.¹⁻² Two further cases (a 7-year-old girl³ and an 8-year-old boy⁴) in which the condition was also associated with mental retardation were described subsequently. The discovery of the disorder in 2 adult siblings of normal intelligence⁵ refuted the initial suggestion that mental retardation was a necessary feature of the disorder. This 6th case of hydroxyprolinaemia was diagnosed in a 6-week-old boy who has shown normal development subsequently. This supports the idea that the condition due to deficiency of hydroxyproline oxidase is benign; if mental retardation is present, it is likely to be due to other causes.

Case report

Our patient was the first child of a healthy 13-year-old girl of West Indian extraction. The father was the girl's brother. The baby was born at term weighing 2.86 kg after a normal pregnancy. Examination showed bilateral single palmar creases and a soft apical systolic murmur. Amino-acid chromatography performed because of consanguinity showed a high level of plasma hydroxyproline. Quantitative analysis using a TSM amino-acid analyser* showed a plasma hydroxyproline level of 300 $\mu\text{mol/l}$; 3.4 mg/100 ml (normal, <20 $\mu\text{mol/l}$; <0.23 mg/100 ml). Urine hydroxyproline excretion was 2000 $\mu\text{mol/24h}$; 262 mg/24h (normal, up to 180 $\mu\text{mol/24h}$; 23.6 mg/24h). There was no microscopical haematuria and the serum creatinine level was 50 $\mu\text{mol/l}$; 0.56 mg/100 ml (normal, 60-120 $\mu\text{mol/l}$; 0.68-1.36 mg/100 ml). The chromosome complement was 46XY.

An oral hydroxyproline load of 200 mg/kg was given to the patient at age 2 months, and also to the mother and to 2 healthy adult female volunteers. The patient excreted 77% of the load in his urine during

* Technicon Instruments Company Ltd., Hamilton Close, Houndmills, Basingstoke, Hants R921 2YE, England.

the next 24 hours. His mother, who was presumed to be heterozygous, excreted 6% of the oral load. This did not differ significantly from the two control subjects and the proportion excreted was similar to that described in a previous case.⁵

There was no increase in urine metabolites of hydroxyproline (Figure) either in the patient or his mother during this period. Urine and plasma analysis of 9 members of the patient's family failed to demonstrate any further raised hydroxyproline levels. The patient's plasma hydroxyproline concentration was 431 $\mu\text{mol/l}$ (4.8 mg/100 ml) at 11 months, and at 36 months was still raised (293 $\mu\text{mol/l}$); 3.4 mg/100 ml), while both physical and mental development remained normal.

Our patient smiled socially at 5 weeks, sat at 7 months, and walked unsupported at 9½ months. He was uttering single words at 14 months and at age 3 years was speaking in sentences. He is a very lively child with normal vision and hearing, and his comprehension is normal.

Discussion

Hydroxyproline is a nonessential amino-acid most of which is formed in the body from proline, probably by hydroxylation of proline residues attached to polysomes during the synthesis of collagen.⁶ This hydroxylation is catalysed by a specific enzyme, proline hydroxylase. Biosynthesis of free hydroxyproline also occurs from glyoxalate and pyruvate.⁷ Free hydroxyproline is catabolised by a well-defined pathway (Figure) that has been demonstrated in human liver and kidney. Some 80% of human hydroxyproline disposal occurs via the kidney pathway, the remainder being excreted in the urine largely as a peptide-bound derivative of collagen. In

the plasma, peptide-bound hydroxyproline accounts for only 2% of the total, but in the urine it constitutes up to 95% of the total.⁸ Renal clearance of free hydroxyproline is low, reabsorption occurring by a tubular transport system shared partly by proline and partly by glycine.⁹⁻¹⁰

When the condition was first described¹⁻² mental retardation was thought to be an essential feature, presumed to be the effect of raised hydroxyproline levels on the developing nervous system. Indeed, familial encephalitis associated with hydroxyprolinaemia resulting in early death has been described.¹¹ Methods for reducing plasma hydroxyproline concentration were therefore considered. Dietary restriction of hydroxyproline, which is synthesised within the body, has little effect on plasma concentration, but administration of oral glycine and proline was found to reduce plasma levels by saturating the tubular reabsorptive mechanism and thereby increasing loss in the urine.³ Cooke and Raine³ did not mention if there was any beneficial effect on their patient's developmental progress with this form of treatment.

The fortuitous discovery of 2 adults of normal intelligence with hydroxyprolinaemia in 1969 showed that the condition can be benign.⁵ The child we describe is now 39 months old and is developing normally despite continued raised levels of plasma hydroxyproline. We therefore suggest that it is not necessary to control the raised plasma hydroxyproline levels in this condition.

Previous authors found an increase in free/bound urine hydroxyproline ratio in a 2-year-old heterozygote.⁵ We were unable to detect any hydroxyproline in the urine of the mother of our patient while on a normal diet, and her urinary hydroxyproline excretion was similar to that of 2 healthy control adults after oral loading. The consanguinity in this family supports the suggestion that this condition has a recessive inheritance.

Increased renal excretion of hydroxyproline and glycine due to transport pathway saturation is a well recognised feature in hyperprolinaemic subjects.⁹ The fact that proline and glycine excretion were normal in our patient, despite pronounced hydroxyprolinuria, is interesting and may imply that hydroxyproline has a relatively lower affinity than proline for the transport pathway. Scriver¹⁰ suggested that hydroxyproline was less effective at inhibiting the renal tubular transport of proline than vice versa.

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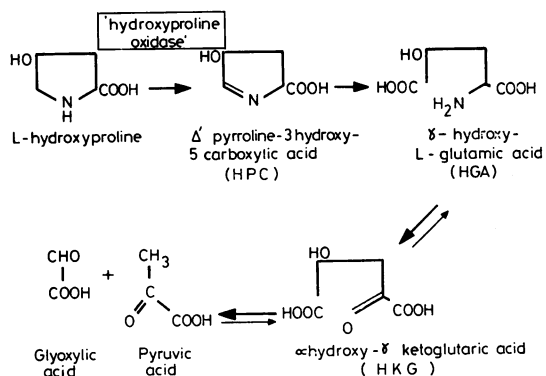


Figure Degradative pathway of hydroxyproline. (After Goldstone and Adams.)⁷

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Correspondence to Dr M J Robinson, Department of Paediatrics, St Thomas's Hospital, Lambeth Palace Road, London SE1 7EH.

Brucellosis treated with rifampicin

J LLORENS-TEROL AND R M BUSQUETS

Department of Paediatrics, Universidad Autónoma de Barcelona, and Hospital Nuestra Señora del Mar, Barcelona, Spain

SUMMARY 14 children, aged between 15 months and 14 years, with brucellosis were treated with oral rifampicin only (20 mg/kg per day) for 3 weeks. Laboratory diagnosis depended on blood culture (positive for *Brucella melitensis* in 11 of the cases), serum agglutination, complement-fixation test, and Coombs's test. Response was good in each child, with fever clearing between the 2nd and 8th day. 2 children relapsed, but one relapse was probably a reinfection from contaminated cheese. Both children were given a further course of treatment (rifampicin and co-trimoxazole) which was successful. Despite the reasonably good results with rifampicin alone, it is advisable to combine the drug with co-trimoxazole when treating brucellosis.

In Spain, brucellosis is still endemic and constitutes a major public health problem.¹ Treatment of this infection has been unsatisfactory,² despite the use of such drugs as sulphonamides and streptomycin, and broad spectrum antibiotics—such as chloramphenicol, chlortetracycline, oxytetracycline.³⁻⁴

Rifampicin is a broad spectrum antibiotic with potent antibrucellar activity *in vitro*. It has been reported to be effective in the treatment of experi-

mental brucellosis.⁵ Rifampicin is rapidly absorbed by the bowel to give high plasma levels, spreading widely through the body. Because of its neutral molecule it penetrates into the interior of cells and so reaches the reticuloendothelial system, where the brucellar organisms persist, thus causing relapses and chronic illness.⁶

Materials and methods

We have studied 14 cases of brucellosis in children (9 boys and 5 girls); their ages ranged between 15 months and 14 years. Most came from country areas: 9 from villages, 2 from suburban areas, and only 3 from the city. Except in three cases, the source of infection was almost certainly attributable to the consumption of contaminated milk or cheese.

The variety of symptoms (Table 1) was wide. Fever was present initially, often associated with articular and muscular pains. Sweats and weakness were present in half of the children, but not necessarily together. The fever sometimes took an undulant form, but was more often a constant low fever. Splenomegaly was observed in 11 patients and hepatomegaly in 9.

A clinical diagnosis of brucellosis was made in