Clinical course and biochemistry of sialuria

G. M. Enns1,2*, R. Seppala3,4, T. J. Musci5, K. Weisiger2, L. D. Ferrell6, D. A. Wenger7, W. A. Gahl3 and S. Packman2

1 Division of Medical Genetics, Department of Pediatrics, Stanford University, California; 2 Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco, California; 3 Section on Human Biochemical Genetics, Heritable Disorders Branch, National Institute of Child Health and Human Development, National Institutes of Health, Maryland, USA; 4 Department of Pathology, Oulu University, Oulu, Finland; 5 Department of Obstetrics and Gynecology, 6 Department of Pathology, University of California, San Francisco, California; 7 Department of Neurology, Jefferson Medical College, Philadelphia, Pennsylvania, USA

* Correspondence: Stanford University, Division of Medical Genetics, Department of Pediatrics, 300 Pasteur Drive, H-315, Stanford, CA 94305-5208, USA. E-mail: greg.enns@stanford.edu

MS received 12.09.00   Accepted 26.10.00

Summary: Sialuria is a rare inborn error of metabolism in which excessive free sialic acid (N-acetylneuraminic acid, NeuAc) is synthesized. A defect in the feedback inhibition of UDP-N-acetylglucosamine (UDP-GlcNAc) 2-epimerase by the end-product of the sialic acid synthetic pathway, CMP-NeuAc, is the mechanism underlying this overproduction. Recent evidence suggests that sialuria is an autosomal dominant disorder. Only five patients have been documented to have such an enzymatic defect. We report a longitudinal study of one of the original sialuria patients, to age 11 years. Although he has coarse features and massive hepatomegaly, he has shown normal growth and relatively normal development. Pulmonary function testing showed minimal small airway obstruction. At 11 years, he developed intermittent abdominal pain and transient transaminase elevation above his baseline. Sialuria should be considered in the differential diagnosis of a patient with a phenotype suggestive of a mucopolysaccharidosis or oligosaccharidosis in the absence of developmental regression or prominent dysostosis multiplex. We recommend close monitoring of liver and pulmonary function in sialuria patients.

Sialuria (MCKusick 269921) is a rare inborn error of metabolism in which excessive free sialic acid (N-acetylneuraminic acid, NeuAc) is synthesized and stored
within the cytoplasm (Seppala et al 1991; Thomas et al 1985; Weiss et al 1989). A defect in the feedback inhibition of uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) 2-epimerase (EC 5.1.3.14) by the end-product of the NeuAc synthetic pathway, cytidine monophosphate-N-acetylneuraminic acid (CMP-NeuAc), is the mechanism underlying this overproduction (Seppala et al 1999). UDP-GlcNAc 2-epimerase catalyses the first committed step of NeuAc synthesis, converting UDP-N-acetylglucosamine (UDP-GlcNAc) to N-acetylmannosamine (ManNAc) (Kornfeld et al 1964; Sommar and Ellis 1972) (Figure 1). Sialuria should be distinguished from sialidosis (McKusick 256550), in which there is dysfunction of lysosomal α-neuraminidase, and from Salla disease/infantile sialic acid storage disease (ISSD) (McKusick 269920), in which there is defective transport of unconjugated NeuAc out of lysosomes (Gahl et al 1996; Renlund et al 1986; Tietze et al 1989).

Only five patients with sialuria have been reported (Don and Wilcken 1991; Ferreira et al 1999; Fontaine et al 1968; Krasnewich et al 1993; Montreuil et al 1968; Seppala et al 1991; Wilcken and Don 1987). Missense mutations in the allosteric binding site for CMP-NeuAc have been found in four of the patients, including the child of the present report. The second UDP-GlcNAc 2-epimerase alleles in these patients did not harbour a mutation, leading to the suggestion that sialuria is an

Figure 1 The N-acetyleneuraminic acid (NeuAc) synthetic pathway, showing feedback inhibition of UDP-GlcNAc 2-epimerase by CMP-NeuAc

*J. Inherit. Metab. Dis.* 24 (2001)