HYPER PROLINURIA AND HYPER-HYDROXY PROLINURIA IN CHILDREN WITH MENTAL RETARDATION

M. Swarna, A. Jyothy, P. Usha Rani and P.P. Reddy

Institute of Genetics and Hospital for Genetic Diseases, Begumpet, Hyderabad-500 016, A.P., India.

ABSTRACT

Three thousand cases with mental retardation referred from different hospitals were screened for aminoacid disorders. Among them one case of hyperprolinuria and another case of hyperprolinuria with hyper hydroxyprolinuria were detected. These are the first cases to be reported from the state of Andhra Pradesh.

KEYWORDS

Mental retardation, Hyperprolinuria, Hyperhydroxyprolinuria.

INTRODUCTION

Hyperprolinemia is a rare autosomal recessive disorder of proline metabolism resulting from the deficiency of proline oxidase enzyme. Screening for metabolic disorders in man, reported cases of hyperprolinemia in association with diseases (1,2,3,4). Recently, in the year 2000, Shivananda et al. (5) reported a case of hyperprolinemia from Karnataka state. However, no cases of hyperprolinuria and hyperprolinuria with hyperhydroxyprolinuria were reported from India. We have screened 3000 individuals with mental retardation during the last two decades in Andhra Pradesh and detected one case of hyperprolinuria and another case of hyperprolinuria with hyperhydroxyprolinuria. The details of these rare cases are presented in this report.

MATERIALS AND METHODS

The cases were referred to the Institute of Genetics, Hyderabad from government hospitals. The children were clinically examined and the details of the case histories were recorded in a standard proforma. Pedigrees of the patients were obtained by direct interrogation of the parents of the patients. Psychometric and cytogenetic investigations were carried out in all the patients.

Twenty four hours urine and heparinized blood samples were collected from the patients for biochemical analysis. Urine samples were subjected to a battery of chemical tests to detect metabolic disorders.

The aminoacids were separated by the paper chromatography technique of Sharma and Zweig (1971) (6) for qualitative analysis. Quantitation of amino acids in urine was done on automatic amino acid analyser (LKB4400 model) using lithium buffer system.

CASE REPORTS:

Case No. 1:

A 3 year old male child was referred to the Institute with complaints of mental retardation and convulsions. History revealed that he was normal at birth and was born after full-term pregnancy. The mother had no complaints during her pregnancy. His parents were non-consanguineous. Elder brother of the patient survived for one year and he also had the complaint of convulsions and delayed milestones.

Height was 82.5cm, weight 11.8kgs, head circumference 47.5cm and chest circumference 52.5cm. He has squint on left eye and low set ears. Psychometric analysis showed that the patient is mentally handicapped (moderate) and able to say only mono syllables. He is unable to walk without support. No cardiovascular, respiratory and nervous system abnormalities were observed. Preliminary analysis of urine and serum was done by paper chromatography. The results indicated that proline

Author for correspondence:

Prof. P.P. Reddy
Director,
Institute of Genetics &
Hospital for Genetic Diseases,
Begumpet,
Hyderabad-500 016.
Email: redypp@rediffmail.com

was elevated in urine whereas in serum, amino acid levels were found normal. Further for quantification of urine amino acid levels, the sample was run on amino acid analyzer using lithium buffer. The concentration of each amino acid is given in table-1. Since, serum amino acid levels were normal using paper chromatography, we have not analysed serum on amino acid analyzer. In urine, proline was elevated but the other amino acids like phosphoserine, taurine, glutamine, alanine, glycine, cystathionine and tyrosine were within the normal limits. The quantity of amino acids is expressed as mg/g creatinine. Cytogenetic analysis showed normal karyotype of 46, XY.

Case No. 2:

A 2 years old female child was referred to the Institute with the complaint of delay in developmental milestones. The history revealed that she was normal at birth and born after a full-term pregnancy. She had parental consanguinity of uncle niece type. She had one elder sister who also had complaints of mental retardation and convulsions.

Height was 70cm, weight was 7kgs, head circumference was 37.5cm and chest circumference was 5cm. Psychometric analysis revealed low developmental quotient. She was unable to walk without support. Anterior fontanelle was closed. Spasticity of all the limbs was observed. No cardiovascular, respiratory and nervous system abnormalities were observed. Preliminary analysis of urine and serum was done by paper chromatography. The results indicated elevated levels of proline and hydroxyproline in urine but in serum amino acid levels were found normal. The quantification of amino acids in urine was carried out on amino acid analyzer and the results are given in table-2. In urine, proline and hydroxyproline were elevated whereas other amino acids like threonine, serine, glutamic acid, alanine and histidine were within the normal limits. Cytogenetic analysis of the patient showed normal karyotype of 46, XX.

DISCUSSION

So far more than 7,000 genetic disorders have been identified. Approximately 1 in 1500 children are born with defective enzymes resulting in inborn errors of metabolism (7). Earlier studies have reported cases

of hyperprolinemia in association with other disorders such as renal diseases (1), aniridia and ocular dystrophy (2) and mental retardation and convulsions (3,4). From India, the first case of type I hyperprolinemia was reported recently from Bangalore, a city in South India by Shivananda *et al.* (2000) (5) in an individual with mental retardation and convulsions.

Reports on hyperprolinuria with hyperhydroxyprolinuria are very rare. As early as in 1968, Rokkens and Loken (8) from Europe reported a case of renal dysplasia and mental retardation, who had an increased excretion of proline and hydroxyproline in urine, while plasma levels of these amino acids were normal. This patient died at the age of 6 years and 5 months. In our screening programme, we have detected a similar case for the first time in South India.

Scriver *et al.* (1961) (9) observed that hydroxyproline and glycine share the common transport system with proline in the kidney and the gut and that in hydroxyprolinemia, the active transport system is 'saturated' with proline so that hydroxyproline, glycine as well as proline cannot be efficiently reabsorbed and are excreted in excess in urine.

In our cases also, urinary excretion of proline and hydroxyproline clearance rates were greatly increased while their own plasma concentrations remained normal. These results imply that proline and hydroxyproline reabsorption in the renal tubule is impaired. Clearance rates of other amino acids were unaffected.

The results also suggest that proline and hydroxyproline share a common transcellular transport system in the renal tubule and the system has higher preference for these two amino acids than for glycine.

The cases reported so far with hyperprolinemia mostly presented hereditary nephrities, congenital renal anomalies, deafness, epilepsy or mental retardation with seizures. Hence, screening of these cases for hyperprolinuria and Hyperhydroxyprolinuria is worthwhile to undertake. The early diagnosis not only helps in the better management of the cases but also helps to prevent the birth of such cases by offering genetic counseling.

Table 1

Aminoacid concentration in the urine of case No. 1

Aminoacid	mg. of AA/gm. Creatinine	
	Patient	Normal Range
Taurine	48.58	85 - 300
Glutamic acid	21.25	10 - 100
Alanine	20.01	10 - 100
Glycine	83.42	Traces – 400
Tyrosine	51.02	10 – 60
Proline	27.91	Traces

Table 2

Aminoacid concentrations in the urine of case No. 2

Aminoacid	mg. of AA/gm. Creatinine	
	Patient	Normal Range
Threonine	2.13	10 - 60
Serine	3.9	25 – 75
Glutamic acid	10.17	10 – 100
Alanine	2.8	10 – 100
Histidine	26.5	50 – 500
Hydroxyproline	209.6	Traces
Proline	95.59	Traces

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