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Glutamine-valine index – An aid in the detection of urea-cycle disorders

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Summary. By relating the increase in glutamine to the corresponding increase in valine following protein loading it has been possible to detect carriers of OCT deficiency.

Keywords: Amino acids – Glutamine – Urea cycle – Hyperammonaemia – Orotic acid

Introduction

Glutamine, a non-toxic carrier of ammonia is an important amino acid to measure in conditions of hyperammonaemia. Symptomatic patients with deficiencies in enzymes of the urea-cycle regularly show increased plasma levels of glutamine where this is accurately measured, (Palmer et al., 1974). Plasma glutamine tends to remain elevated even when the blood ammonia level has been reduced to normal by a low protein intake, (Palmer et al., 1974).

Measurement of ammonia, amino acids, and urinary orotic acid following a protein load is the best available method for the detection of suspected carriers of ornithine transcarbamylase, (OCT) deficiency, and the mild forms of carbamoyl phosphate synthetase (CPS) deficiency, (Batshaw et al., 1980. Haan et al., 1979).

The changes in plasma glutamine following a protein load have not been reliable in the detection of asymptomatic patients with OCT deficiency due to the wide range in reference values. Discrimination was improved by relating the change in glutamine concentration to the corresponding change in valine following protein load. The resulting "index" corrects to a large extent for variations in amount of protein and rates of absorption, correlates well with orotic acid excretion and is able to differentiate obligate carriers of OCT deficiency from controls.

Methods

Protein, 0.8–1g/kg, was given as lean ham or casein. Blood samples for amino acids and ammonia were taken fasting and two hours post protein. Urine samples were collected

fasting and for eight hours following protein. Plasma amino acids were estimated on a Locarte analyser, (Palmer et al., 1973), and urine orotic acid analysed by the method of Harris and Oberholzer, (Harris et al., 1980). The "GV index" was calculated as the quotient of the ratios of the rise in glutamine and of the rise in valine between fasting (G1;V1) and two hours (G2;V2) post protein i.e. (Gln 2/Gln 1) × (Val 1/Val 2).

Other ways of relating these glutamine and valine levels are possible but give similar discrimination (Fig. 1).

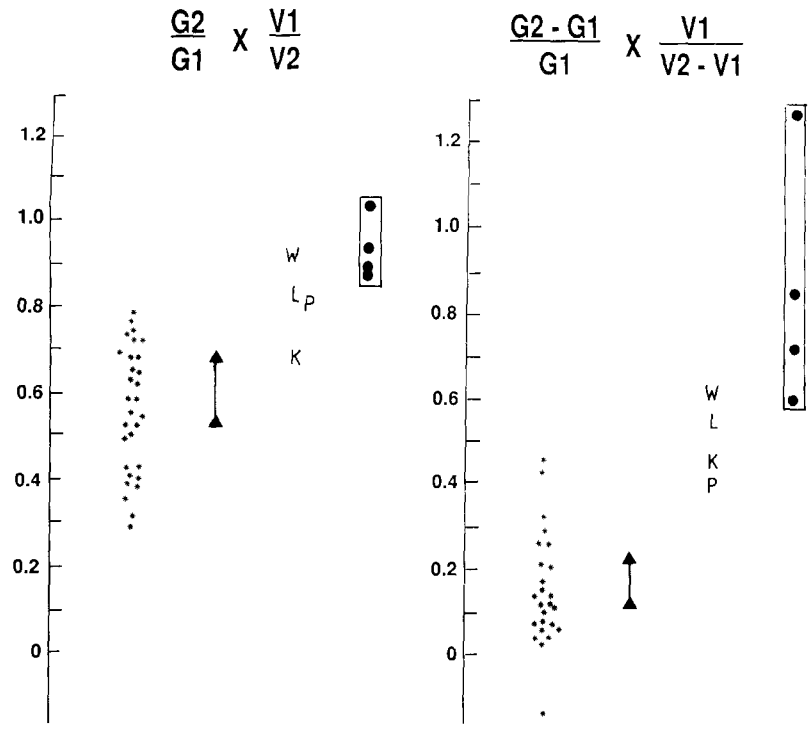

Fig. 1. Results obtained for G2/G1 × V1/V2 and also for quotient derived from proportional increases in levels: ∗; Controls; ▲; children given casein load ($n = 8$); ● mothers of affected children; *W* mother severely affected; *L* and *P* mothers orotic acid negative; *K* hepatic failure, ammonia positive, orotic acid negative

Results

After protein loading maximum levels of glutamine and valine are attained after about two and four hours respectively, (Palmer et al; 1973). In this series samples were taken after an overnight fast and two hours after protein, at about maximum glutamine level. Under these conditions 24 normal young adults and apparently healthy children gave a reference range for the GV index of 0.29 – 0.77. Mean value 0.57; (mean ± 2SD = 0.28 – 0.86).

Protein loads were done on the families of affected children with OCT deficiency to detect possible asymptomatic deficiency states. In four cases orotic acid excretion increased abnormally after protein but rises of ammonia and glutamine remained within normal limits. By applying the GV index it was possible to distinguish these cases from known normals (Table 1).

Table 1. Results of G2/G1 × V1/V2 in obligate carriers, conrol subjects and OTC deficient subjects. See text for individual comments

Patient	Glutamine (mmol/l) Fasting	2 Hours	Gln-val index	Orotic acid excretion	Plasma NH3
Mrs M	555	784	0.90	+	0
Mrs F	590	747	1.04	+	0
LF	587	820	0.95	+	0
Mrs W	649	815	0.88	+	0
EC	548	644	1.23	+	+
Mrs L	610	808	0.84	0	0
Mrs P	705	818	0.82	0	0
Controls $n = 24$	433–719	484–1096	Range = 0.29–0.77 $\bar{x} \pm 2SD$ = 0.28–0.86	0	0
Hyperammonia (OTC def)			0.94–1.75	+	+

+ abnormal response; 0 normal or nil response.

An additional patient, (E.C.), with demonstrable hyperammonaemia but apparently normal glutamine levels gave an index of 1.23. In two mothers of affected children we were unable to provoke abnormal increases in ammonia or orotic acid. In each the index was within the reference range, as defined by mean ± 2SD but slightly outside the absolute range of reference values found, (Table 1). The husband of Mrs M., (an obligate carrier of OCT deficiency), underwent an identical protein load test at the same time and gave a normal index of 0.63, as would be expected. In those cases where obvious hyperammonaemia and abnormal glutamine levels were present the index was in the range 0.94 – 1.75.

Discussion

An abnormal excretion of orotic acid following protein load presupposes a defect in ammonia metabolism affecting the substrates for carbamoyl phosphate. However, in heterozygotes with decreased OCT activity, oroticaciduria following nitrogen stress may occur in the presence of apparently normal levels of ammonia and glutamine, (Hokanson et al., 1978). In the families studied, the asymptomatic 'carriers' would not have been detected by estimation of glutamine and ammonia alone.

The assessment of glutamine levels relative to another amino acid, such as valine, helps to reduce variations in fasting level, intake, rate of protein absorption, and analytical factors. When the glutamine levels are related to a suitable 'internal control' in this way, it is possible to demonstrate an abnormal response

to protein, and also to show that glutamine levels can be a sensitive indicator of ammonia metabolism. Under the conditions of the test the index correlated with the orotic acid excretion and gave a clear differentiation between the reference range and cases with evidence of OCT deficiency. The index may be of diagnostic value in cases of CPS deficiency in which urinary excretion of pyrimidine metabolites cannot be induced.

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