Metabolic Studies of Mongoloids

Stanley N. Gershoff, ph.d.,* D. Mark Hegsted, ph.d., † and Martha F. Trulson, d.sc.†

During the hundred years that mongolism has been recognized as a medical entity, many studies of the disease have been made. The epidemiology of this condition has received considerable attention and much emphasis has been placed on the anthropometric, physical, and mental characteristics of the mongoloid. There is, however, a marked lack of data concerning the metabolism of mongoloids and those which exist, for the most part, do not show mongoloids to be particularly abnormal in their metabolic patterns.

The present study is the result of the common observations that as mongoloids age, their skins become rough, dry, and exzematous. Fissures of the lips and corners of the mouth are also frequently seen. These types of lesions are also found in individuals deficient in the B vitamins.

This study is an attempt to determine whether the metabolism of vitamins by mongoloids is abnormal.

METHODS

The subjects used in these experiments were either mongoloids or mentally deficient patients without other obviously abnormal characteristics. During these studies the subjects ate their usual diets in the dining rooms of the Wrentham State School. In the first two studies all food served was weighed and the nutrient intakes calculated from tables of food consumption. The subjects were under continuous supervision to assure complete collections of urine and accurate estimates of food intake.

In the first study, in which subjects aged 10 to 12 years were used, 24-hour urine collections were made for five days. On the sixth day each subject received 2.5 mg thiamine hydrochloride, 2.5 mg riboflavin, 25 mg niacinamide, 50 mg ascorbic acid, 25 mg calcium pantothenate and 2.5 mg pyridoxine hydrochloride. Following the load test two 4-hour urine collections were obtained. In the second study in which older subjects were used, urine was collected every two hours day and night during an experimental period of five days. The purpose of the short collection periods was to study the variation in vitamin excretion. This has been reported in part elsewhere.[1] On the morning of the third day a test dose of 2.5 mg thiamine, 2.5 mg riboflavin, 25 mg niacinamide and 20 mg ascorbic acid was given orally.

In the third experiment, 17 mongoloids and 13 non-mongoloids were given 100 mg of niacinamide at midnight, approximately six hours after their evening meal, and urines were collected during the next six hours. Three weeks later the same groups were given test doses of 5 g of DL-tryptophan at midnight and urines were collected during the next thirty hours. The unsolicited assistance of one of the subjects resulted in the loss of the urine obtained during the six-hour period following the load test.

At various times during these studies urine samples were analyzed for thiamine,[2] riboflavin,[3] niacin,[4] N-methylnicotinamide,[5] xanthurenic acid,[6] creatine,[7] creatinine,[7] and ascorbic acid.[8]

RESULTS

Tables I and II present the results of urine

From the Department of Nutrition, Harvard School of Public Health and the Department of Biochemistry, Harvard Medical School, Boston, Massachusetts.

* Assistant Professor of Nutrition; † Associate Professors of Nutrition, Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts.

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TABLE I
Vitamin Intake and Excretion Data, Young Subjects

	Mongoloids				Non-mongoloid				Average	
	1	2	3	4	5	6	7	8	Mongoloids	Non-mongoloids
Age, years	11	12	13	12	12	10	13	11		
Weight, kg	33.6	28.6	28.6	29.0	33.6	27.2	25.0	27.2	30.0	28.3
Height, in.	50	50.5	50	53	55.4	54.2	52	53.7	50.9	53.8
Riboflavin										
Average intake, mg/day	2.9	2.3	2.7	2.3	2.4	2.2	2.4	2.4	2.55	2.35
Average urinary excretion, mg/day	0.65	0.65	1.15	0.96	0.90	0.61	0.92	1.32	0.85	0.94
4 hours after load, total mg	1.35	1.49	0.90	2.15	1.36	0.95	1.91	1.70	1.47	1.48
*Recovery, % of dose	50	55	28	80	49	34	70	63	53	54
Thiamine										
Average intake, mg/day	1.6	1.4	1.5	1.1	1.3	1.5	1.6	1.3	1.40	1.42
Average urinary excretion, mg/day	0.20	0.20	0.25	0.17	0.25	0.38	0.24	0.26	0.21	0.28
4 hours after load, total mg	0.27	0.22	0.17	0.30	0.23	0.08	0.18	0.21	0.24	0.18
*Recovery, % of dose	9.6	7.6	5.2	10.3	7.6	0.8	5.6	6.8	8.2	5.5
Niacin										
Average intake, mg/day	11.3	11.2	9.7	9.6	9.3	11.4	9.9	10.1	10.45	10.17
Average urinary N-Me nicotinamide, mg/day	2.02	2.70	4.31	4.35	3.61	4.70	2.89	3.81	3.34	3.75
4 hours after load, total N-Me nicotinamide, mg	1.10	1.90	1.32	2.96	2.41	3.47	1.47	2.24	1.82	2.40
*Recovery, % of dose	3.2	5.8	2.4	8.9	7.2	10.7	4.0	6.4	5.1	7.1
Average urinary niacin, mg/day	0.32	0.43	0.43	0.46	0.44	0.61	0.29	0.41	0.41	0.44
4 hours after load, total mg	0.16	0.18	0.18	0.24	0.16	0.19	0.21	0.31	0.19	0.22
*Recovery, % of dose	0.44	0.44	0.44	0.64	0.36	0.36	0.64	0.24	0.49	0.40
Ascorbic Acid										
Average intake, mg/day	49	56	47	34	48	54	38	30	47	43
Average urinary excretion, mg/day	5.9	5.8	6.9	6.3	7.5	6.0	6.6	6.7		
4 hours after load test, total mg	1.23	1.13	0.81	2.31	1.72	0.90	1.23	1.09		
*Recovery, % of dose	0.48	0.32	None	2.52	0.96	None	0.28	None		
Creatinine, mg/kg/day	19.2	18.1	19.3	20.6	17.4	19.6	19.4	20.3	19.3	19.2
Creatine, mg/kg/day	2.3	3.3	1.9	1.5	4.5	3.4	2.9	4.7	2.3	3.9

* Excess over the amount expected in the sample as estimated from the previous mean rate of excretion.

TABLE II
Vitamin Intake and Excretion Data, Older Subjects

	Mongoloids		Non-mongoloids	
	1	2	3	4
Age, years	43	20	20	25
Weight, kg	73.6	60.5	70.5	61.4
Height, in.	63.7	58.5	69	65
Riboflavin				
Average intake, mg/day	2.96	2.80	3.09	2.64
Average urinary excretion, mg/day	0.75	0.62	1.14	0.78
4-hour excretion after load, mg	1.46	1.29	1.12	0.80
4-hour excretion, % of dose	53	48	37	67
Thiamine				
Average intake, mg/day	1.74	1.80	1.98	1.72
Average urinary excretion, mg/day	0.38	0.28	0.37	0.14
4-hour excretion after load, mg	0.25	0.39	0.24	0.25
4-hour excretion after load, % of dose	7.16	13.2	7.2	9.2
Niacin				
Average intake, mg/day	19.9	18.1	23.1	20.9
Average urinary N-Me nicotinamide, mg/day	11.71	4.80	10.19	5.46
4-hour urinary N-Me nicotinamide after load, mg	1.59	0.87	2.19	1.75
% of dose	None	0.3	2.0	3.4
Average urinary niacin, mg/day	1.36	0.67	1.24	1.14
4-hour niacin after load, total mg	0.24	0.16	0.24	0.16
4-hour urinary niacin, % of dose	0.05	0.2	0.1	None
Creatinine, mg/kg/day	22.2	24.4	28.5	19.7

analyses made on the subjects of the first two studies prior to the load tests and for four hours after the vitamin supplementation. Nutrient intakes, except for ascorbic acid, approximated or were above recommended allowances[9] for subjects of the ages and sex used. While the ascorbic acid intakes were considerably below the amounts recommended by the Food and Nutrition Board of the N.R.C., they are as high as the amounts considered adequate in Britain[10] and are thus considerably above deficiency levels. The intakes of calories, protein, calcium, phosphorus, iron and vitamin A were also calculated from the food intake data and found to be more than adequate.

There is considerable literature concerned with the excretion of vitamins by subjects fed diverse diets and following load tests varying in amounts and methods of administration. The general methods and findings have been summarized by Unglaub and Goldsmith.[11] Since in this paper we are primarily interested in comparing mongoloids with non-mongoloids, it is not particularly useful to review such material at this time except to point out that, with the exception of ascorbic acid, the excretion values of the subjects used in these experiments reflect the generous nature of the diets fed. The low levels of urinary ascorbic acid before and after the load tests are indicative of the low level of intake of ascorbic acid.

It is apparent from Tables I and II that although considerable individual variation in urinary excretion values was observed, relatively little differences were seen between the mongoloid and non-mongoloid patients. The only apparent differences encountered in these studies were in creatine excretion (Table I) and in N-methylnicotinamide excretion following the load tests (Tables I and II). In both instances excretion values were higher for non-mongoloids than mongoloids. A tendency towards greater excretion of thiamine by mongoloids following the load tests was also observed.

Methylation reactions are involved in the production of N-methylnicotinamide, creatine, and creatinine. The third test in which loads of 100 mg of niacinamide were given was designed to see if there might be a difference in the methylating ability of mongoloids and non-

TABLE III

The Effect of Niacinamide on Urinary Metabolites

	Mongoloids	Non-mongoloids
Number of subjects	16	13
Urine volume, ml	238 ± 28	302 ± 29
Creatinine, mg	247 ± 18	347 ± 30 p < .05
N-Methylnicotinamide, mg	12.9 ± 1.3	19.1 ± 0.7 p < .005
Xanthurenic acid, mg	6.7 ± 1.1	7.2 ± 0.4
Niacin, γ	294 ± 27	371 ± 68

Figures include standard error of the mean.

mongoloids. The results presented in Table III show that mongoloids excrete significantly less N-methylnicotinamide and creatinine than non-mongoloids, but not of niacin or xanthurenic acid, following a load test of niacinamide.

The relationship between niacin and tryptophan metabolism led to the fourth study in which each subject received 5 g of DL-tryptophan.

TABLE IV

Effect of DL-Tryptophan on Urinary Metabolites

	Mongoloids	Non-mongoloids
Number of subjects	17	13
Urine volume, ml	1239 ± 46	1166 ± 156
Creatinine, mg	830 ± 44	916 ± 27
N-Methylnicotinamide, mg	11.2 ± 2.9	13.1 ± 1.5
Xanthurenic acid, mg	26.2 ± 2.3	38.4 ± 5.6

Figures include standard error of the mean.

The results shown in Table IV do not show a statistically significant difference in the excretion of creatinine and N-methylnicotinamide by mongoloids and non-mongoloids following a tryptophan load test although more of these metabolites were excreted by the non-mongoloids. In this study the excretion of xanthurenic acid was significantly ($p = 0.05$) greater in non-mongoloids than in mongoloids.

DISCUSSION

Since no other explanation is available, it would seem certain that metabolic changes must underlie the marked abnormalities which occur in mongolism. Those metabolic changes which result in epithelial abnormality may be relatively specific for the tissue affected and at the tissue level, or they may be more general in nature and contribute to other phases of the over-all picture of mongolism. Although the present studies do not indicate any difference in the way that riboflavin is handled by mongoloids and non-mongoloids and the differences observed in thiamine excretion are not marked, it cannot be concluded that the requirements and metabolism of these two vitamins are the same for mongoloids and non-mongoloids. Vitamin excretion tests are relatively noncritical particularly when intakes are high. For the purposes of these studies more limited vitamin intakes would have been advantageous.

The difference in excretion of N-methylnicotinamide following niacinamide administration is interesting. It is impossible at this time to evaluate the significance of this observation with regard to the pathology of mongolism. It may be unrelated to the physical manifestations of the disease or may represent a basic difference in the metabolism of niacin related to the epithelial and other abnormalities of mongolism.

It is generally considered that creatinine excretion is more closely correlated with active muscle mass than with body weight. The weights of the large groups of subjects used in the third and fourth studies were essentially the same averaging with standard deviations 53.4 $\pm$ 7.6 kilos for the mongoloids and 53.7 $\pm$ 6.8 kilos for the non-mongoloids. Although mongoloids are generally thought to be more obese than non-mongoloids, the creatinine coefficients (mg of creatinine/kilo body weight/24 hr) of the two groups obtained from 24-hour control urine collections were not significantly different statistically, being with standard errors of the mean 23.7 $\pm$ 1.8 mg for the non-mongoloids and 20.2 $\pm$ 1.1 mg for the mongoloids. Nevertheless these values which are in the normal range may represent the trend towards increased obesity in the mongoloids. During the six hours following the 100 mg niacinamide load test, the differences in creatinine excretion of the two groups were increased to statistical significance (Table III). The lower excretion of both N-methylnicotinamide and creatinine by mongoloids following the niacinamide load test suggest the possibility of a defect in the methylating ability of mongoloids since both these compounds are end products of methylation reactions. It is possible that the lowered creatinine values in the mongoloids reflect a low B.M.R. and that the decreased N-methylnicotinamide excretion of mongoloids is indicative of a generally limited metabolic capacity. However, the B.M.R. of mongoloids has been reported normal[12] or only slightly reduced.[13,14] Furthermore, serum protein-bound iodine levels between mongoloid children and controls of the same age have been found to be similar.[15]

The significance of the difference in xanthurenic acid excretion following tryptophan administration (Table IV) needs further study. Usually in tests of this kind two times as much tryptophan are used as in this experiment. In view of the recent interest in the role of tryptophan metabolism in mental disease,[16] extension of these studies to include other tryptophan metabolites would appear worthwhile.

SUMMARY

The metabolism of a number of water-soluble vitamins by mongoloid and non-mongoloid, all mentally deficient children, has been studied. Relatively little differences in the excretion of thiamine, riboflavin, niacin, N-methylnicotinamide and vitamin C were observed prior to vitamin load tests. Following the load tests no significant difference was observed in the excretion of riboflavin by mongoloids and non-mongoloids and the excretion of thiamine although slightly greater in mongoloids was not marked. The administration of 100 mg of nicotinamide resulted in significantly less excretion of N-methylnicotinamide and creatinine by mongoloids than non-mongoloids. The possibility of a defect in the methylating ability of mongoloids has been suggested. Following the feeding of 5 g of DL-tryptophan, significant differences in N-methylnicotinamide and creatinine excretion were not observed, but the excretion of xanthurenic acid was lower in mongoloids than non-mongoloids.

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