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Research Paper

Diagnostic and Prognostic Significance of Urinary Xanthurenic Acid Excretion in Tuberculosis

Medical Science

KEYWORDS : Urinary xanthurenic acid, Excretion, Tuberculosis, Tryptophan

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ABSTRACT

Objective: To assess the diagnostic and prognostic significance of the test in tuberculous patients.

Methods: Xanthurenic acid excretion in urine was measured before and after an oral load of 5 gm tryptophan in 10 healthy individuals and 24 patients of tuberculosis (pulmonary, lymph glandular and osteocarticular). Xanthurenic acid excretion estimation was done again after 3 months of successful antituberculosis chemotherapy in pulmonary tuberculosis cases only.

Results: The mean excretion values before and after load in the tuberculosis patients were found higher as compared to control subjects. These values came down significantly after successful chemotherapy of 3 months.

Conclusion: We found that altered tryptophan metabolic pathway did operate in tuberculosis patients, being maximum in pulmonary followed by lymph gland and osteo-articular tuberculosis respectively.

INTRODUCTION

Xanthurenic acid, or xanthurenate, is a chemical shown to induce gametogenesis of Plasmodium falciparum, the parasite that causes malaria (Billker et al, 1998; Garcia et al, 1998). It is found in the gut of the Anopheles mosquito.

Xanthurenic acid is a metabolic intermediate that accumulates and is excreted by pyridoxine (vitamin B_6) deficient animals after the ingestion of tryptophan. Xanthurenic acid is suspected to be an endogenous agonist for Group II metabotropic glutamate receptors in humans (Copeland et al, 2013). It is also known to be a potent VGLUT inhibitor, thereby preventing the movement of glutamate from the cytoplasm into synaptic vesicles, an action that it mediates via competitive blockade of vesicular glutamate transporters (K_i = 0.19 mM) (Bartlett et al, 1998). In 2015, researchers reported a marked reduction of xanthurenic acid levels in the serum of patients with schizophrenia, describing this phenomenon as a potential trait marker for schizophrenia (Fazio et al, 2015).

In 1901, Hopkins discovered that tryptophan (Trp) was an amino acid contained in proteins. The mean Trp protein content in the human body is 1.2 g/100g of protein, which is much lower than that of other essential amino acids such as lysine (7.6%), leucine (7.1%) and threonine (4.0%(Mahan and Shields, 1998).

Under normal circumstances a very small amount of xanthurenic acid is formed, which excreted (1-3 mg/24 hrs) in the urine. Altered tryptophan metabolism has been found when there is vitamin B6 deficiency in the body or when there is a metabolic pathway block of vitamin B6 because of any cause and in certain diseases of varied etiology including tuberculosis. In all these circumstances, an unusual large amount of xanthurenic acid is excreted in the urine. The excretion of this acid increases manifold if the test is performed after an oral load of tryptophan.

The present work is a modest attempt to assess the diagnostic and prognostic significance of the test in tuberculous patients. The study is also important in the sense that probably no work of this kind has been done in India and only a preliminary report exclusively on pulmonary tuberculosis appeared in foreign literature.

MATERIAL AND METHODS

This was a prospective follow-up study conducted in a tertiary care teaching hospital in north India on newly diagnosed out patients and indoor patients attending/admitted in the hospital. Cases were diagnosed on clinical, radiological, bacteriological and histopathological basis. The study included 10 cases of pulmonary tuberculosis, 7 each of osteoarticular & glandular tuberculosis and 10 controls. The study was approved by the Ethical Committee of the Institute. The consent was taken from each subject before enrolling in the study.

Patients who had any apparent clinical signs and symptoms suggestive of vitamin B6 deficiency and those who were actually ill or had any concomitant disease were excluded from the study. The patients of pulmonary tuberculosis were followed up for three months, and only those patients were selected who could be put on a drug regimen devoid of isoniazid, because isoniazid is known to interfere with the vitamin B6 metabolism with irregular appearance of abnormal amounts of xanthurenic acid in urine following a test dose of tryphothan (Biehl and Vilter, 1954). Due to this reason, these patients were not given isoniazid during the study period.

Specimen estimation

Twenty four hours urine collection was made in a glass container from 8 am to 8 am next day. Subsequent to the first collection. 5 gm tryptophan was given orally and again samples were collected in the same way. The total output was measured and examined on the same day.

For controls, urine samples were collected from amongst healthy volunteer doctors, nurses, medical students and hospital staff in the same way as for the other patients after ascertaining that they did not suffer from any systemic or metabolic disorders.

A green colour producing material with ferric iron by reduction to ferrous iron has been defined as xanthurenic acid. This green colour essentially is not due to pure xanthurenic acid but also to other xanthurenic acid like substances. Estimation of xanthurenic acid was therefore, separately done by colorimeteric method of Rosen et al (1951).

RESULTS

Xanthurenic acid excretion was measured in patients of pulmonary, glandular and osteo-articular tuberculosis before and after a load of 5 gms Tryptophan. The mean xanthurenic acid excretion level before tryptohan load was found to be 31.3 mg/24hrs, 20.7 mg/24hrs and 11.5 mg /24 hrs in pulmonary, glandular and osteoarticular tuberculosis respectively and these levels increased to 81.3 mg/24hrs, 48.6 mg/24 hrs and 23.6 mg/24 hrs respectively after the tryptophan load. The increase was found to be statistically significant (p=0.0001). In control subjects, however, the mean xenthurenic excretion levels before and af-

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ter tryptophan load was only 3.1 mg/24hrs and 10.9 mg/23hrs respectively with statistically significant difference (p=0.0001). There was significant (p<0.0001) difference in Xanthurenic acid excretion levels between pulmonary, glandular & osteoarticular tuberculosis with controls at without and with load (Table 2).

In order to ascertain the prognostic value of the test, an attempt was made to estimate xanthurenic acid excretion levels patients of pulmonary tuberculosis after 3 months of anti-tubercular therapy (Table 3). It was interesting to note that there was a significant drop in the xanthurenic acid excretion level after 3 month of treatment when compared with the excretion levels at the time of admission (initiation of therapy). The decrease in xanthurenic acid excretion levels from admission to 3 month was statistically significant (p=0.0001).

DISCUSSION

The products of vitamin B_6 metabolism are excreted in the urine, the major product of which is 4-pyridoxic acid. An estimated 40–60% of ingested vitamin B_6 is oxidized to 4-pyridoxic acid. Several studies have shown that 4-pyridoxic acid is undetectable in the urine of vitamin B_6-deficient subjects, making it a useful clinical marker to assess the vitamin B_6 status of an individual (Combs, 2008). Other products of vitamin B_6 metabolism excreted in the urine when high doses of the vitamin have been given include pyridoxal, pyridoxamine, and pyridoxine and their phosphates. In a study, the xanthurenic acid excretion of patients with active tuberculosis was found to be consistently higher than in normal control subjects. The xanthurenic acid excretion decreased to normal values as the patients improved clinically and the tuberculosis process became inactive (Nair and Baron, 1973).

In the study of Biehl and Vilter (1954), the administration of large doses of isoniazid resulted in a considerable increase in urinary excretion of vitamin B6 ,about 40 percent incidence of clinical evidence for pyridoxine deficiency,but an irregular elevation of xanthurenic acid excretion following a tryptophan Load.

Xanthurenic acid excretion in normal healthy subjects was measured without and after a load of 10 gm. Our patients developed nausea, vomiting, diarrhoea and vague abdominal discomfort with 10gm. Therefore, the load was reduced to 5 mg in this study.

In the present study, the pre and post load xanthurenic acid excretion values were comparable with that of Wachestein and Label (1956) but were lower than that of Nair and Baron (1973). This difference might be because of the smaller load (5 mg), difference in dietary habits, the radial patterns and methodology of estimation and therefore, only the pattern of excretion was comparable.

Xanthurenic acid excretion in eclamptic and pre-eclamptic women and other diseases had been measured by various workers, but probably no report appeared in the literature which gave any information regarding excretion of xanthurenic acid in extra pulmonary tuberculosis i. e. lymph gland and osteoarticular tuberculosis. In the present study, the xanthurenic acid excretion before and after tryptophan load in lymph gland and osteo-articular, tuberculosis has been found to be 20.7 mg/24hrs and 48.6mg/24 hrs, 11.5 mg/24hrs and 23.6 mg/24 hrs respectively.

Prognostic value or the test has probably been first shown by Nair and Baron (1973). We too, in the present study observed a significant fall (p=0.003) in the xanthurenic acid excretion after 3 month of successful anti tubercular chemotherapy of pulmonary tuberculosis patients.

CONCLUSION

We found that altered tryptophan metabolic pathway did operate in tuberculosis patients being maximum in pulmonary followed by lymph glandular and osteo-articular tuberculosis respectively. The metabolism of tryptophan is definitely altered in tuberculosis, and the recognition of this alteration might be of value in the diagnosis of the disease.

CONFLICT OF INTEREST: None

FUNDING: None

Table-1: Distribution of patients according to site of lesion

	No. (n=24)	%
Pulmonary	10	100.0
Lymph nodes	7	100.0
Cervical	4	57.1
Axillary	2	28.6
Generalised	1	14.3
Osteo-articular	7	100.0
Spine	5	71.4
Knee joint	1	14.3
Hip joint	1	14.3

Table-2: Xanthurenic acid excretion in control and tuberculous patients on admission

Groups	No. of subjects	Xanthurenic acid Excretion (mg/24hrs)				
		Without load		After load		p-value[1]
		Mean±SD	Range	Mean±SD	Range	
Control	10	3.1±0.7	2.0-4.2	10.9±1.5	8.6-13.2	0.0001*
Pulmonary tuberculosis	10	31.1±6.3[a]	19.0-40.0	81.3±14.2[a]	59.6-98.0	0.0001*
Glandular tuberculosis	7	20.7±6.1[a]	12.0-30.0	48.6±14.2[a]	21.6-61.4	0.0001*
Osteo-articular tuberculosis	7	11.5±1.7[a]	9.6-14.0	23.6±6.8[a]	15.0-31.7	0.0001*

[a]p<0.0001 (Unpaired t-test, between tuberculosis and controls)

Table-3: Xanthurenic acid excretion in pulmonary tuberculosis patients on admission and after chemotherapy

Time period	Xanthurenic acid Excretion (mg/24hrs)				
	Without load		After load		p-value[1]
	Mean±SD	Range	Mean±SD	Range	
On Admission	31.3±6.3	19.0-40.0	81.3±14.2	59.6-98.0	0.0001*
After 3 months	22.3±6.5	12.0-34.0	56.3±51.1	32.2-73.5	0.0001*
p-value[1]	0.0001*		0.0001*		

[1]Paired t-test

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