Gluten Sensitive Enteropathy As A Cause Of Hartnup's Disease

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Citation

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Abstract

This clinical case report shows that Coeliac disease can lead to Hartunp's Disease. This report calls for the simultaneous screening of coeliac disease in patients being tested for Hartnup's disease. There is scope for further research on the relation between coeliac disease and Hartnup's disease and the genetic associations between the two conditions.

INTRODUCTION

Hartunp's disease was first identified in 1950's in the Hartnup's family in London. Hartnup's disease is an autosomal recessive disorder due to defective transport of Neutral aminoacids(monoamino monocarboxylic) in the small intestine and kidneys. Patients usually present with skin lesions, cerebellar ataxia and gross amino aciduria.Heterozygotes are normal. Consanguinity is common. The causative gene is on chromosome 11q 13. It is a sodium dependant and chloride independent neutral amino acid transporter seen predominantly in kidneys and intestine. It occurs when a person inherits 2 recessive genes for the disease –one from each parent. Hartnup's disease has a prevalence rate of one per 24,000 population and is one of the most common amino acid disorders in humans. Levy etal 1 found that incidence of Hartnups' disease is one per 14,219 live births in Massachusetts. The main cause of morbidity in Hartnup's is malnutrition. There is no racial or sexual predilection. Most children with Hartunp's remain asymptomatic. In United States, the disease usually does not manifest because the diet is rich in essential amino acids. Physical examination findings include vesciculo bullous lesions, photosensitivity and hyper pigmentation. The precipitating factors include malnutrition, emotional stress, infections, pyrexia and drugs like sulphonamides.

Skin- The skin reddens after exposure to sunlight. The skin changes may resemble that of chronic eczema. The changes are typically seen on light exposed areas.

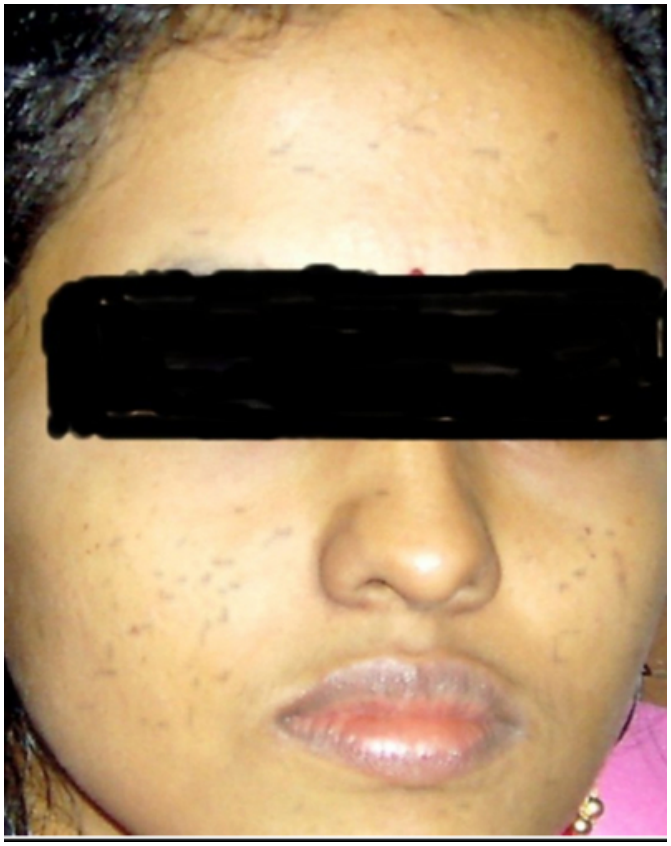
CNS- Mental retardation may be seen. In 1087 patients screened at Alexandra institute, Cape town, Hartnup's disease was found only in one person. Patients may present with fully reversible intermittent cerebellar ataxia, photophobia, nystagmus and strabismus.

There will be signs of niacin deficiency like glossitis and gingivitis. There may be episodes of diarrhoea before or after the attacks. Short stature may also be seen Wilcken etal 2 .

CLINICAL HISTORY

A 19 year old short statured girl presents with intermittent cerebellar ataxia, wide based gait,headache and tremulousness with associated double vision since the last four months. Two weeks before she had four attacks of diarrhoea. Her CNS symptoms have been progressively increasing since then. There was a history of skin reddening on exposure to sunlight. Her sister was diagnosed with coeliac disease at the age of 20. She also gave a history of migrane and personality changes.

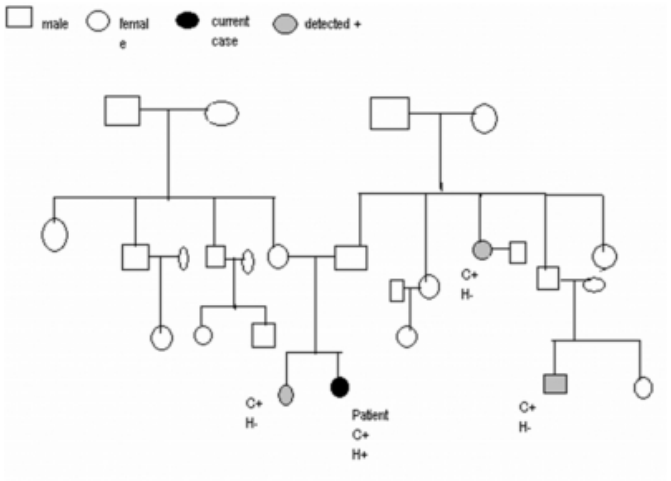
Figure 1



FAMILY HISTORY

Figure 2

Figure 2: Family tree-pic



C- coeliac disease positive
H- hartnup's disease positive

CLINICAL EXAMINATION -POSITIVE FINDINGS

Areas of hyper pigmentation and red scaly patches were seen in the peri orbital region.

Chronic eczematous changes were seen on the dorsal aspect of forearm and forehead.

CNS examinations revealed cerebellar ataxia, wide gait and intentional tremors.

THE CLINICAL PROBLEM

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findings include vesciculo bullous lesions, photosensitivity and hyper pigmentation. The precipitating factors include malnutrition, emotional stress, infections, pyrexia and drugs like sulphonamides.

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PATHOPHYSIOLOGY

The disease is caused by failure of transport of tryptophan

and other neutral amino acids in the intestine and kidneys. The retained amino acids within the intestine are converted to indolic compounds which are toxic to the neural tissue.

Following absorption, the indolic compounds formed from tryptophan are converted to 3-hydroxy indole (indican) in the liver where it undergoes conjugation with glucoronic acid and subsequently is excreted through the kidneys causing indicanuria. Other degradation products like serotonin and kynurenine are also found in the urine. Since there is a defect in tubular amino acid transport, there is gross amino aciduria. Due to the abnormality in tryptophan metabolism, there may be niacin deficiency which causes pellagra like symptoms. There may be deficiency of glutamine, phenyl alanine, leucine, isoleucine, threonine and histidine. The 2 tissue specific forms of Hartnup's disease was described by Scriver et al ($_2$).

THE DIFFERENTIAL DIAGNOSIS TO BE CONSIDERED

SKIN RASH

Xeroderma pigmentosum, Carcinoid syndrome,Seborrhoeic eczema, Pellagra, SLE, Cockayne syndrome, Infantile atopic eczema ,Pityriasis alba, Hydroa Vaccini forme

CNS

Ataxia telangiectasia-May cause difficulty in diagnosis if there is only mild skin involvement. SLE- can cause diagnostic difficulty if there is photosensitivity with neuro physchiatric symptoms. Leigh's disease, Refsum's disease, Krabbe's disease, Vitamin B 12 deficiency, Niemann Pick disease type C, Tay sach's disease.

DIAGNOSTIC WORKUP

1.Skin biopsy- changes similar to pellagra- hyperkeratosis, epidermal atrophy, parakeratosis, hyper pigmentation of basal layer, dermal lymphocytes. There were sub epidermal or intra epidermal bullae. Hyperplastic sebaceous glands were present.

2. CT scan- Normal study. No areas of focal demyelination or tumours.

3. Urine chromatography - Increased levels of neutral amino acids (glutamine, valine, phenyl alanine, asparagine, citrulline, isoleucine, threonine, alanine, serine, histidine, tyrosine, tryptophan, leucine) and indican were found in the urine examination. Urinary excretion of proline, hydroxy proline and arginine were normal (differentiates from other causes of amino aciduria).

1. Positive tryptophan loading test.
2. Plasma aminoacid levels normal.
3. Urinary indican positive (common to both coeliac and hartnup's)

4. Antiendomysial antibody - positive screening was done because sibling had coeliac disease.

5.Jejunal biopsy- Loss of villi, high cellularity of lamina propria and marked elongation of crypts with increased mitotic activity. Histopathology reported as coeliac disease.

MANAGEMENT PROTOCOL ADOPTED

Medical care-High protein diet. Avoidance of photo sensitizing drugs like sulphonamides. Daily supplementation with nicotinamide.Nicotinamide 100mg PO qid was given for three months.

Patient education- Avoid sun exposure by using protective clothings , eye ware, hats and sunscreens with skin protection factor 15 or more and to Avoid emotional stress. Patient was advised to consume a high protein gluten free diet.

Outpatient care- Severity of symptoms were assessed every week. Liver funtion tests were monitored periodically to assess liver toxicity from Nicotinamide

RESULTS

The patient improved constantly with the above management and in course of time became totally asymptomatic. CNS symptoms were totally reversed and there were no fresh skin lesions or photosensitivity rashes or areas or hyperpigmentation.

Urinary chromatography was within normal limits and indicanuria was negative. Slow tapering of Nicotinamide was done and stopped over four weeks. Patient was advised to continue high protein gluten free diet.

SUMMARY AND CONCLUSION

The patient who presented to the outpatient department with symptoms of dermatitis and nervous system symptoms without any history of dietary deficiency of niacin was screened for amino aciduria and indicanuria and a primary diagnosis was made as that of Hartnup's disease. With a positive history of coeliac disease in the family, it was decided to carry out an endomysial antibody test which turned out to be positive. Treatment was started immediately

and the patient was put on a high protein gluten free diet and precautions to avoid photo toxicity. Nicotinamide was given and gradually withdrawn over 2 months. The patient's symptoms and signs improved constantly with the therapy and continued to be so even after tapering the Nicotinamide therapy. The patient still continues to be symptom free with diet modification and is carefully monitored for signs and symptoms of Hartnup's disease. Now, after 4months of discontinuing Nicotinamide the patient continues to be totally symptom free and all her investigations are within normal limits.

AREAS OF CONCERN

Both Hartnup's disease and coeliac disease are genetically linked although they appear to be mutations in different chromosomes and differ in their patterns of inheritance. This patient with Hartnup's disease turned out to be a case of undiagnosed coeliac disease.It is suggested that all patients with Hartnup's disease be screened for coeliac disease with anti endomysial antibody test as it may be a case of misdiagnosis. Also the family members are to be screened for both the diseases as it is totally controllable with diet modification and moderate drug therapy.

SUGGESTIONS FOR THE FUTURE

This report calls for the simultaneous screening of coeliac disease in patients being tested for Hartnup's disease. There is scope for further research on the relation between coeliac disease and Hartnup's disease and the genetic associations between the two conditions.

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