Case Report

The use of Neurobion® Forte in the Treatment of Pellagra in an adult on anti-TB treatment: A case report from Lusaka, Zambia

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ABSTRACT

The deficiency of Niacin and/or its precursor amino acid, Tryptophan can result in a disease called Pellagra. Isoniazid (INH), a key drug used in tuberculosis (TB) treatment has been associated with pellagra particularly in developing nations where poor nutritional status is highly prevalent among its people.We report a case of pellagra with classical dermatological manifestations (hyperpigmented skin lesions around the neck), on the face, and external surfaces of the upper limbs) in a black African HIV negative adult female, on TB treatment for 11 weeks managed with a combo of Vitamin B1 - 10mg, Vitamin B2 - 10mg, Vitamin B3 - 45mg, Vitamin B5 - 50mg, Vitamin B6 - 3mg and Vitamin B12 - 15mcg (Neurobion® Forte) with noticeable response to the treatment within one week.

INTRODUCTION

Pellagra is a disease caused by the deficiency of niacin (Vitamin B-3) or its precursor amino acid tryptophan.[1] It is characterized by a triad of symptoms; dermatitis, diarrhea and dementia. The typical skin manifestation is in sun exposed areas such as the dorsum of the hands and feet, neck area and upper chest.[2] Primary vitamin B-3 deficiency occurs as a result of inadequate amounts of niacin in their everyday diet. This is commonly seen in countries with maize meal as their staple food.[3] Maize meal has a combination of low levels of niacin and tryptophan.[4,5] The body is not able to absorb vitamin B-3 in the maize unless it has been treated with an alkali.[6] Secondary deficiencies are due to an underlying medical condition such as adrenal pheochromocytoma, liver cirrhosis, malignant carcinoid tumor, Hartnup disease, disorders such as ulcerative colitis, Crohns disease, abuse of alcohol or drug therapies for example isoniazid.[3]

Dermatitis is reported in 33% of the patients with pellagra.[7] The majority of the affected population are women compared to men.[8] It has been shown that certain sex hormones such as oestrogen inhibit the biochemical conversion of the essential amino acids, tryptophan to the B-vitamin niacin when diets are minimally adequate for tryptophan.[8] Matapandeu *et al*, in 2017 reported a pellagra outbreak in Malawi in which about 60% of affected people were females. Resource limited countries with social inequality and unrest are more at risk of pellagra than developed countries.[9]

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In resource limited settings, Niacin assay is not a routine investigation for patients with suspected Vitamin B3 deficiency as it is expensive. Furthermore, treatment with niacin supplement is a challenge due to its high cost. Therefore, the diagnosis is often made clinically, and most patients are treated with vitamin B complex. Each tablet of Vitamin B complex contains B1 1.5mg, B2 1.7mg, B3 20mg, B5 10mg, B6 2mg, B7 300mcg, B9 400mcg, B12 6mcg.[10] We report on the use of Neurobion® Forte for treatment of pellagra. Neurobion® Forte is a combination of six Vitamins, 1 tablet contains: Vitamin B1 - 10mg, Vitamin B2 - 10mg, Vitamin B3 - 45mg, Vitamin B5 - 50mg, Vitamin 6 - 3mg and Vitamin B12 - 15mcg.

CASE REPORT

We report on the case of a 23-year-old HIV negative, black African adult female, being managed for bacteriologically confirmed tuberculosis for 11 weeks on standard World Health Organisation (WHO) recommended first line anti-TB treatment.

The patient presented to the TB clinic with a one-week history of rash on the face, neck and upper limb. The rash was described as itchy, had a painful burning sensation with some parts peeling off especially areas exposed to the sunlight. The rash was not affecting her daily routine, but the appearance was disturbing to her. The use of paracetamol to relieve the pain only gave temporal relief. She had no history of diarrhea or dementia, no jaundice or abdominal pain. Her past medical history was unremarkable. There was no history of alcoholism, use of anti-convulsant or use of tobacco products. A dietary history collected revealed that she consumed maize meal frequently as the main staple food that was often accompanied with other relish as available mainly vegetables rarely meat and fish . She regularly consumed tea without milk, often accompanied by wheat bread and sweet potatoes.

On clinical examination, the woman was lean in appearance with weight of 40kg and height of 153cm giving a body mass index (BMI) of 17. She had a hyper-pigmented lesion surrounding the neck, on the extensor surfaces of both upper limbs and around the eyes. The rash appeared dry and scaly (Fig1). Other physical findings were normal. A clinical diagnosis of Pellagra with adult malnutrition was made based on the classic dermatological appearance, low BMI, and drug history. For Laboratory tests and results conducted see Table.1.

Fig.1 A taken at the time of diagnosis of Pellagra

*Figure.1 A shows the dry, scaly and hyper-pigmented Rash on the dorsum of forearm **1** and the Neck. **2** (note these are all sun exposed areas). JPG file*

The patient was started on the combo of Vitamin B1 -10mg, Vitamin B2 -10mg, Vitamin B3 -45mg, Vitamin B5 - 50mg, Vitamin B6 - 3mg and Vitamin B12 - 15mcg (Neurobion® Forte 1 tablet three times daily) and continued the fixed dose of Rifampicin and Isoniazid for the tuberculosis treatment. The patient was advised to take a diet high in niacin (such as meat, eggs, peanuts, poultry, bran, legumes, fish etc.).[11] There was improvement after one week of treatment. The patient was reviewed weekly for the first 3 weeks then twice weekly and after about 6 weeks of treatment the symptoms had resolved. All rashes had cleared by the seventh week and BMI had improved to 17.5. Treatment was extended for a week then stopped. She reported no new complaints at the end of the treatment period for pellagra although she still had dietary challenges. At no point was the TB medication withdrawn during the time of assessment

Fig. 2A taken at the time of diagnosis of Pellagra

Figure.2 A shows the patient has recovered after treatment with a combo of Vitamin B1, B2, B3, B5, B6 and B12. JPG file

Table 1: Baseline Laboratory Results at Diagnosis of Pellagra

	Result	Reference interval/SI Units	
FULL BLOOD COUNT			
WBC	5.4	4-11.0	10^9/L
RBC	5.04	3.8-5.8	10^{12}/L
HCT	37	0.37-0.47	L/L
HB	11.9	11.5-16.5	g/L
MCV	73	80.0-100	fl
MCH	23.5	27.0-32.0	pg
MCHC	27	32.0-36.0	g/l
PLT	462	150-450	10^9/L
RDW	15.2	12.2-16.2	%
LIVER AND KIDNEY FUNCTION			
Creatinine	37	88.0-128	mL/min
urea	Not done	No Reagents	
AST	23.7	0-35	units/l
URINALYSIS			
Specific gravity	1.010	Normal	
Leukocytes	trace	Normal	
Nitrates	Negative	Normal	
Protein	Negative	Normal	
Bilirubin	Negative	Normal	
Glucose	Negative	Normal	
Ketones	Negative	Normal	
Blood	Negative	Normal	

DISCUSSION

In this report, the pellagra developed 11 weeks after being started on standard anti-TB medication (ATT), thereby making the association in causality of the pellagra to Isoniazid. Isoniazid induced pellagra has been reported in some studies due to the competitive binding effect of Isoniazid and tryptophan on the active site.[12] Decreased tryptophan serum levels in nutritional deficiency accelerate the development of isoniazid induced pellagra. Malnourishment determinants coupled with TB therapy are confounding factors in this patient. We cannot completely rule out pre-existing niacin deficiency in our patient as routine testing for Niacin and other B vitamins is not part of standard practice and was not done in this patient.

The rash is described as appearing symmetrically on both upper limbs on the extensor surfaces, a butterfly-shaped lesion on the face and a necklace

lesion on the neck. Very typical distribution of the hyper-pigmented lesions in pellagra.[10] However, the patients did not have any other features such as dementia or diarrhea. The diet of this patient also predisposed her to pellagra as it consisted mostly of maize meal and less protein; her sex was also a predisposing factor.

Testing of the actual levels of niacin or tryptophan was neither feasible nor easily accessible. The results of this patient also suggest there was no underlying medical condition like liver or kidney disease, and she had never taken alcohol before thereby ruling them out as possible causes. Of note is the low levels of creatinine in the blood presumably suggestive of a diet low in protein and decreased body mass.

WHO recommended treatment for pellagra is 300mg of nicotinamide daily and a maintenance dose of 50-100mg daily for three to four weeks.[3] The average cost of a 100mg 30 tablet pack is $5 to $10. Vitamin B complex is often used as an alternative due to its low cost of less than $1to $5 per 100 tablets pack; however, it only contains 20mg of niacin which is inadequate to replenish the loss and therefore treatment takes longer. Much as Neurobion® Forte is more expensive than Vitamin B complex, as it costs $2.5 to $9 per 30 tablet pack, it is a better alternative to Vitamin B complex because it has higher levels of both Vitamin B3 and necessary cofactors in the synthesis of Vitamin B3. Vitamin B2 and B6 are essential cofactors for two key enzymes in the synthesis of the niacin from the amino acid tryptophan through the kynurenine pathway.[13] Therefore, adequate availability of these vitamins improves the status of niacin in the body. Additionally, it has higher levels of Vitamin B12 which is essential to produce DNA which tends to be damaged at a skin cellular level in pellagra.[11]

There is scarcity of literature on time to resolution of dermatitis in patients with pellagra that are treated with Vitamin B complex. However, given the low concentration of the various vitamins in relation to Neurobion® Forte, it is expected to be longer.

CONCLUSION

Neurobion® Forte, a vitamin B1, B2, B3, B5, B6 and B12 combo, is effective and can be used for the treatment of pellagra in resource limited settings. As the uptake of Isoniazid for treating latent TB Infection increases in Low-middle income countries, the cases of isoniazid induced pellagra in the face of poor nutrition are expected to increase. Research studies are required to fully understand the cost effectiveness studies of Neurobion Forte in treatment of pellagra in resource limited settings.

Limitations

Photos taken initially were not of good quality and could not be re-taken at review as the rash had started clearing.

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Authors Contributions:

Patient review and follow up was done by Sarah Nyangu and Lophina Chilukutu

Script write up and revisions were done by Sarah Nyangu, Monde Muyoyeta, Kelvin Zimba, Patrick Lungu and Mary Kagujje

Declaration of conflict of interest

We the authors declare that we are free of any conflict of interest and have not been funded by the manufactures of the drugs used in this case report. This work is purely novel and has not been published elsewhere.

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