SERUM LEVELS OF FOLATE AND VITAMIN B_{12} IN PATIENTS WITH BILATERAL OPTIC NEUROPATHY ATTENDING THE EYE CLINIC AT MUHIMBILI NATIONAL HOSPITAL

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By

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A Dissertation Submitted in (Partial) Fulfillment of the Requirement for the Degree of Master of Medicine (Ophthalmology) of Muhimbili University of Health and Allied Sciences

October, 2017

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation titled **"*Serum folate and vitamin B_{12} levels in patients with bilateral optic neuropathy attending the eye clinic at Muhimbili National Hospital*",** in (partial) fulfillment of the requirement for the degree of Master of Medicine (Ophthalmology) of the Muhimbili University of Health and Allied Sciences.

_____

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(Supervisor)

Date_____

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Dr: John Kisimbi

(Co Supervisor)

Date_____

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DEDICATION

This work is dedicated to my parents, brothers, sisters, nephews and nieces.

ABSTRACT

Background

Optic neuropathy is a unilateral or bilateral disease of the optic nerve characterized by damage of the optic nerve (cells and sheath) anywhere between the ganglion cell layer and lateral geniculate body. It has different etiologies like ischemia, inflammation, pressure effect, infiltrative, traumatic, nutritional, toxic and hereditary causes. Patients with optic neuropathy usually have visual loss and defective color perception which can affect quality of life. In Tanzania, bilateral optic neuropathy has been reported to be epidemic and the proportion is estimated to be 0.3 to 2.4%.

Objective

The aim of this study was to determine the serum levels of folate and vitamin B_{12} in patients with bilateral optic neuropathy attending the eye clinic at Muhimbili National Hospital.

Methodology

A cross sectional study was conducted at Muhimbili National Hospital eye clinic in Dar es Salaam from July 2016 to February 2017, where 93 patients with bilateral optic neuropathy were recruited by consecutive sampling method. Patients were examined in the eye clinic and best corrected visual acuity was taken, intraocular pressure was taken and color vision test was done. The anterior segment was examined using a slit lamp biomicroscope. Fundoscopy was examined using slit lamp biomicroscope with 78D and 90 D lenses after full dilation of the pupil. Blood was taken for measurement of folate and vitamin B_{12}serum levels. Data were analyzed using computer software SPSS version 20 and results summarized using frequency tables, and pie charts.

Results

Ninety three patients with bilateral optic neuropathy were recruited. There were slightly more males (51.6%) than females and the mean age was 29±3.4years. Low serum levels of folate were found in 60.6% of the patients, while 4.3% of the patients were found to have low serum levels of vitamin B_{12}. About 48.3% of patients had moderate visual impairment of which 66.6% of these patients had low levels of serum folate. The commonest ocular feature was temporal pallor (92.5%) followed by color vision defect (83.9%).

Conclusion and Recommendations

More than a half of the patients with optic neuropathy had low levels of folate while few had low levels of vitamin B_{12} and moderate visual impairment was a common feature found in patients studied.

Measurement of serum folate and vitamin B_{12} levels before initiating treatment for optic neuropathy in order to ascertain the cause of optic neuropathy is proposed.

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ABBREVIATIONS

AIDS:	Acquired Immune Deficiency syndrome
AION:	Arteritic Ischemic Optic Neuropathy
CDR:	Disc Cup Ratio
DOA:	Dominant Optic Atrophy
ESR:	Erythrocyte Sedimentation Rate
HIV:	Human Immunodeficiency Virus
IOP:	Intra Ocular Pressure
LP:	Light Perception
LHON:	Leber Hereditary Optic Neuropathy
MNH:	Muhimbili National Hospital
MS:	Multiple Sclerosis
MUHAS:	Muhimbili University of Health and Allied Sciences.
NAION:	Non Arteritic Ischemic Optic Neuropathy
NLP:	No Light Perception
OCT:	Ocular Coherence Tomography
ON:	Optic Neuropathy
RAPD:	Relative Afferent Pupillary Defect
SPSS:	Statistical Package for Social Sciences

DEFINITION OF KEY TERMS

Anterior segment of the eye: The front third of the eye that includes the structures in front of the vitreous humour: the cornea, iris, ciliary body and lens.

Folate: Vitamin B_9 or its synthetic folic acid is a water soluble vitamin which is essential for numerous metabolic functions such as synthesis of RNA and DNA.

Vitamin B_{12}: Also called cobalamin is a water-soluble vitamin important for the normal formation of red blood cells and the health of the nerve tissues.

Optic disc: or optic nerve head is the point of exit for ganglion cell axons leaving the eye.

Optic neuropathy: Disease that damages nerve cells anywhere between the retinal ganglion cells and the lateral geniculate body.

Posterior segment of the eye: The posterior two-thirds of the eye that includes the anterior hyaloid membrane and all of the optical structures behind it: the vitreous humor, retina, choroid and optic nerve.

Refraction: A test to detect problems of focusing light to the retina and to find correction to the problems.

Snellen chart: An eye chart that is be used to measure visual acuity.

Slit lamp biomicroscope: An instrument consisting of a high-intensity light source that can be focused to shine a thin sheet of light into the eye. It is used in conjunction with a biomicroscope.

Tonometer: An instrument for measuring Intra Ocular Pressure.

Visual acuity: Sharpness of vision, measured by the ability to discern letters or numbers at a given distance according to a fixed standard.

Fundoscopy: is a test that allows a health professional to see inside the fundus of the eye.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Optic neuropathy is a unilateral or bilateral disease of the optic nerve characterized by damage of the optic nerve (cells and sheath) anywhere between the ganglion cell layer and lateral geniculate body. It has different etiology like Ischemia, inflammation, pressure effect, infiltrative, traumatic, nutritional, toxic and hereditary origin.[1]Depending on the cause, the optic nerve disorders can manifest as isolated episodes or epidemic outbreaks. Nutritional deficiencies resulting from poor economic status, political instabilities and natural calamities (drought, storm, and flood) were postulated as the main causes contributing to such high number of cases of Optic neuropathy.[2]Some geographical regions, such as Cuba, Tanzania, Gambia, Somalia, Nigeria, and Papua New Guinea, are characterized by high incidence of this neuropathy.[3,4,5]

Nutritional optic neuropathy is a functional disorder of the optic nerve resulting from the dietary deficiency of certain nutrients like vitamin B group required for normal functioning of nerve fibers.[6]Rarely, the neuropathy can develop due to copper deficiency.[7]The exact mechanism of neuropathy development associated with the vitamin deficiency has not been completely understood, but it is postulated that the deficiency impairs biochemical processes at a cellular level. The inadequate intake of vitamin B_{12} and/or folic acid promotes synthesis and accumulation of toxic formate, which block the process of oxidative phosphorylation in mitochondria. This leads to the decreased synthesis of adenosine triphosphate(ATP), excessive accumulation of reactive oxygen species, and disorders of axonal transport in the optic nerve fibers.[5,8]

Nutritional optic neuropathy is characterized by painless, gradually progressing, bilateral decrease in visual acuity, which can be accompanied by color vision dysfunction. However, patients with deficit of central vision are likely to notice poor vision early, but in case of early peripheral visual loss, patients are commonly not aware of their condition, because they still have intact central vision. Subtle impairment of pupillary light reflexes may also be present which can be misinterpreted as normal due to their symmetric nature. Wide, non-reactive pupils are observed at the terminal stages of the condition after the complete atrophy of the optic nerves has

occurred. Fundus abnormalities depend on the stage of the disease. At initial stages of the neuropathy, the optic discs can appear normal, sometimes slightly swollen and/or hyperemic with small hemorrhages. Neuropathy progression is associated with optic nerve atrophy, manifesting as temporal disc pallor or at the terminal stage, as complete disc pallor. Visual field testing usually shows specific central or centrocecal scotoma with periphery sparing.[7]

Vitamin B_{12}, also known as Cobalamin, is a water soluble vitamin which is synthesized by certain bacteria (Propionibacterium and Lactobacillus) in the gastrointestinal tract of animals and is then absorbed by the host animal. It is concentrated in animal tissues; hence, vitamin B_{12} is found only in foods of animal origin and cannot be synthesized in the human body thus must be supplied in the diet.DNA synthesis and neurological function depends on vitamin B_{12}. Adequate serum levels are necessary for nervous system maintenance and the development of normal red blood cells.[7,9]

Folate, vitamin B_9 or its synthetic folic acid is a water soluble vitamin which is essential for numerous metabolic functions such as synthesis of RNA and DNA as well as DNA repair. It is mostly found in cereals and vegetables. It has several functions including acting as a cofactor in many vital biological processes and is important during periods of rapid cell division and growth.[10,11,12]

Muhimbili National hospital is a tertiary hospital where patients with different eye conditions including bilateral optic neuropathy are treated. It is important for the clinician to narrow down the long list of causes of bilateral optic neuropathy to find the cause. Since folate and vitamin B_{12} are not measured routinely this study aimed to exhort clinicians to measure folate and vitamin B_{12} for an adequate management of optic neuropathy.

1.2 LITERATURE REVIEW

Optic neuropathy is a unilateral or bilateral disease of the optic nerve characterized by damage of the optic nerve (cells and sheath). It has multiple causes and can affect people of different age groups.

Epidemiology

Epidemics of optic neuropathy have been reported primarily during wartime, especially among prisoners of war in Asia during World War II.[13] A three-year data from Ministry of Public Health of Cuba (MINSAP), found the incidence of optic neuropathy to be 462 per 100,000among residents of Cuba. Tobacco use and vitamin B complex deficiency was associated with the increased risk of optic neuropathy .[14]

In Nigeria, Osuntokun et al in 1969 reported the prevalence of ataxic polyneuropathy associated with optic neuropathy to be 22 per 1000 in Ososa,[15] while in 1998 Oluwole et al using the same case definition of the 1960s found a prevalence of 60 per 1000 in the same area.[16] The incidence of 64 per 10 000 person–years was found in 2003 by Oluwole et al**.**[17]

First described in 1988, several studies done in Dar es Salaam reportedas bilateral optic neuropathy to be epidemic disease affecting people aged between 10 and 40 years of age with a prevalence of 2.4%.[18,19,20]A study done in Dar es salaam by Bourne et al among primary school children aged 10 to 16 years in 1997,reported a prevalence of 1%.[21].

Another study in Dar es Salaam, Tanzania between July 2003 and September 2004 by Bowman et al estimated the prevalence to be 0.3% among 10892 students aged between 12 and 22 years.[22]

Folate and vitamin B_{12} deficiencies

Vitamin B_{12}

Vitamin B_{12}, is a complex organometallic compound found only in foods of animal origin and cannot be synthesized in the human body thus must be supplied in the diet. The acidic environment of the stomach enables the release of vitamin B_{12} bound to food then it binds to intrinsic factor secreted by gastric parietal cells in the stomach. The binding takes place in the duodenum and absorbed in the terminal ileum.[23]Adequate serum levels are necessary for nervous system maintenance and the development of normal red blood cells.[9,23]

In a National Health and Nutrition Examination Surveys among United States of America population, prevalence of vitamin B_{12} deficiency (serum vitamin B_{12}< 148 pmol/L) varied by age group where deficiency was found in ≤3% of those aged 20–39 years, 4% of those aged 40–59 years, and 6% of persons aged ≥70 years. Deficiency was also found in <1% of children and adolescents but was ≤3% in children aged <4 years (the youngest age group reported). Marginal depletion (serum vitamin B-12: 148–221 pmol/L) was more common and occurred in 14–16% of those aged 20–59 years and >20% of those >60 years.[24,25]

A review of studies done across Latin America reported that 40% of children and adults had vitamin B_{12} deficiency or marginal status.[26]The reported prevalence of deficient and marginal values is much higher in African and Asian countries, where in Kenya it was found in 70% of Kenyan school children,[27,28] 35% in Indian pre-schoolers,[29] and 50% in Indian adults.[30]

Optic neuropathy was reported in patients with vitamin B_{12} deficiency by Foulds et al in 1969,[31]in Cuba study done by CDC reported that the risk of optic neuropathy was significantly lower among the subjects who reported higher consumption of two groups of nutrients: those related to animal products and the group of B-complex vitamins, notably vitamin B_{12}.[14]

Folate

Folate, vitamin B_9 or its synthetic folic acid is a water soluble vitamin which is essential for numerous metabolic functions such as synthesis of RNA and DNA, repair of DNA, acts as cofactor in many vital biological processes and it is important during periods of rapid cell division and growth.[10,11]

In the diet, folates exist as polyglutamates and need to be enzymatically converted into folate monoglutamates by folate reductase in the jejunal mucosa in order to be absorbed. Natural food folates are quite unstable compounds, so that losses in vitamin activity can be expected during food processing. In vegetables, up to 40 per cent of folates can be destroyed by cooking and in grains/cereals, up to 70 per cent of folates can be destroyed by milling and baking.[11, 32]

Folate deficiency is most frequently due to very low dietary folate intake but may alsobe caused by impaired folate absorption due to gastrointestinal diseases or genetic defects in the absorption mechanisms. Severe folate deficiency has serious consequences and may cause megaloblastic, macrocytic anaemia, polyneuropathy, diarrhea, cognitive impairment and behavioral disorders.

Low levels of blood folate lead to increased plasma homocysteine, impaired DNA synthesis and DNA repair.[33, 34]

In Venezuela, the main groups affected were preschool children (33.8%) and pregnant women (25.5%), while in Costa Rica 48.8% of pregnant women were affected. In the United Kingdom, deficiency was found in elderly (15.0%). In the United States, folate deficiency was present in school-age children (2.3%), adults (24.5%), and the elderly (10.8%).[27]In India a study done by Taneja et al reported that 5-20% of children had low plasma level of folate.[29]In a study done in Ethiopia by Haidar et al among women of reproductive age,46.1% had severe folate deficiency of $\leq$ 4 ng/mL, 21.2% had marginal folate deficiency> 4–6.6 ng/mL while only 32.7% had optimal levels of serum folate> 6.6 ng/mL.[35]

Studies done in Cuba by CDC and in Tanzania by Hodson et al reported that a higher folate status was significantly associated with a reduced risk of optic neuropathy.[14, 36]

Clinical presentation

Toxic/nutritional optic neuropathy often presents as a painless, progressive, bilateral decrease of vision, deficiency in color vision with variable optic nerve pallor. Pallor in the temporal quadrant (**Figures 1,2**) is most common with this condition. The patient may manifest reduction in visual acuity (20/50- 20/200), loss of central visual field (usually relative cecocentral scotoma) and reduced color perception[7,37]. Because of bilaterality, RAPD is not common.[38] Hearing loss and peripheral neuropathy with numbness of limbs have also been reported.[4,18]

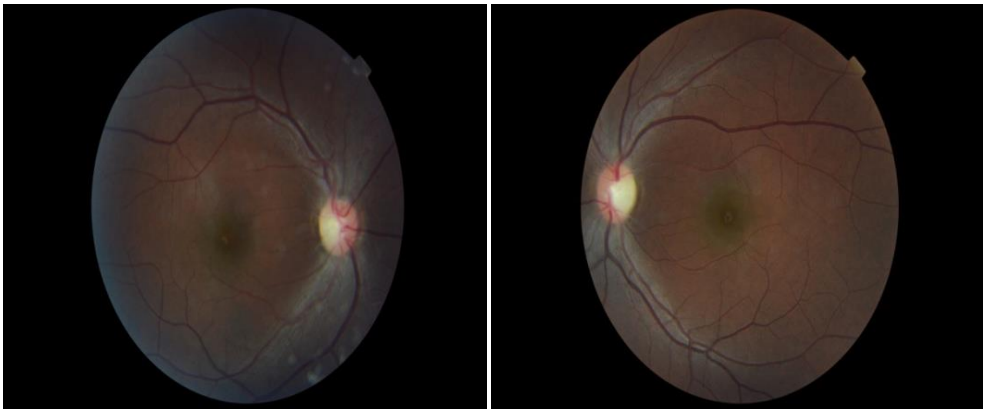


Figure 1: **Right eye optic disc temporal pallor** Figure2: **Left eye optic disc temporal pallor**

Laboratory tests

Vitamin B_{12}

Depending on the technique used in measurement, the lower limit of normal for serum vitamin B_{12} is variable whereby; it is usually set at about 148 pmol/L (200 pg/mL). Published estimates of the sensitivity and specificity of the test in the diagnosis of vitamin B12 deficiency vary widely. This relates in part to the lack of a consistently defined gold standard for the diagnosis and in part to varying study designs.[39]The sensitivity of the test is estimated to be 90% to 95%.However, there has been a concern that the use of metabolite assays as a gold standard for the diagnosis of vitamin B_{12}deficiency may lead to overdiagnosis and overtreatment.The reported specificity of a low serum vitamin B_{12} level in predicting deficiency is also variable 60% to 90%.[40]

Folate

The lower limit of the reference range for serum folate varies depending on technical factors but is usually set at about 6.8 nmol/L (3 ng/mL). Serum folate levels decrease within a few days of dietary folate restriction, [41] although tissue stores may be normal. Serum folate levels increase with feeding, and the use of fasting determinations has been recommended.[42]Folate concentrations within erythrocytes are much higher than in serum, and even a slight degree of hemolysis will cause a falsely elevated serum folate level. The sensitivity of serum folate measurement for the diagnosis of folate deficiency is uncertain.[43]Serum folate assay has been advocated as method of diagnosing folate deficiency, as it gives equivalent information as red blood cell folate and it is easier to perform.[44]

1.3 PROBLEM STATEMENT

Nutritional optic neuropathy which commonly presents with decreased vision has been reported in various studies. Epidemic optic neuropathy in Tanzania has been documented since 1988, which was described to predominantly occur in young people.[18,19,36]Some researchers thought of it being nutritional related with strong suspicion of vitamin B complex deficiency while others thought of cyanide intoxication related to cassava eating.[18,19,36]

Optic neuropathy was found to be the leading cause of low vision among patients that attended Muhimbili National Hospital in the year 2011, [45] though the causes were not well elicited.

The only study that delivered information about the levels of folate and vitamin B_{12} among patients with optic neuropathy was done in 2009 by Hodson et al among 57 patients aged between 12 and 25 years.[36]There was a need to study the serum levels of folate and vitamin B_{12} in patients with optic neuropathy extending the age limit.

1.4 RATIONALE

The results of this study are expected to provide information about bilateral optic neuropathy and the role of low serum levels of folate and vitamin B_{12} as one of the causes of bilateral optic neuropathy, therefore raising awareness when dealing with differentials. Since there is no declared hunger in the country, and neither social nor economical crisis this study will reveal existing neuropathy due to folate and vitamin B12 deficiencies amid stable food availability in the country.

Again this study will provide the avenue that accelerates researching at the level of the community in order to design guidelines for prevention and treatment for nutritional optic neuropathy related to the nutritional deficiencies.

RESEARCH QUESTIONS

1. What are the serum levels of folate and vitamin B_{12} in patients diagnosed with optic neuropathy attending the eye clinic at Muhimbili National Hospital?
2. What are the variations of visual acuity according to levels of folate and vitamin B_{12} in patients with optic neuropathy?

1.5 CONCEPTUAL FRAMEWORK

Folate and vitamin B_{12} deficiencies are among the known causes of optic neuropathy; this study was looking for serum levels of folate and vitamin B_{12} in patients with optic neuropathy, variations of visual acuity and the serum levels of folate and vitamin B_{12}.

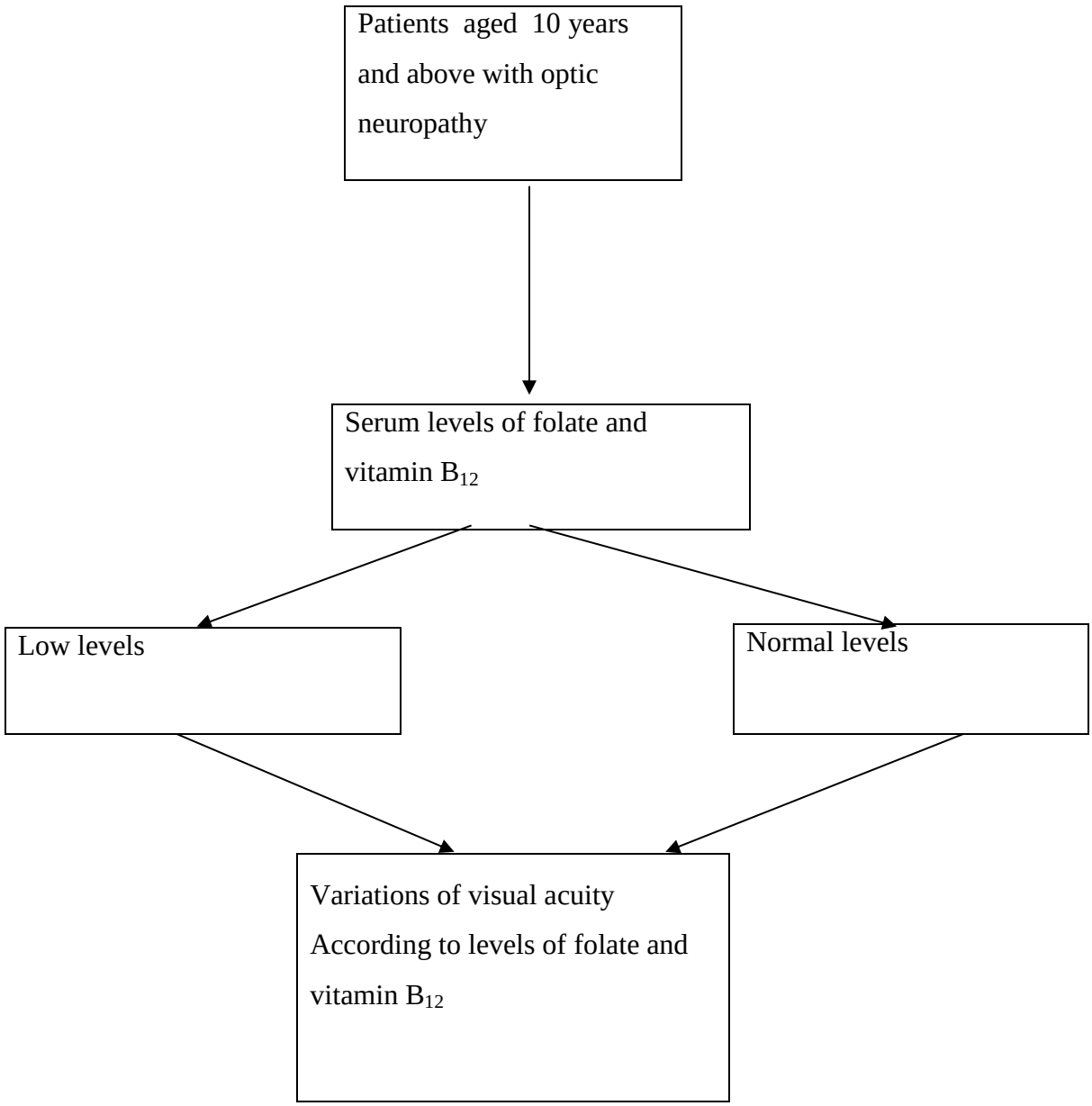


Figure 3: Conceptual framework

1.6 OBJECTIVES

Broad Objective

To determine the serum levels of folate and vitamin B_{12}in patients with bilateral optic neuropathy attending eye clinic at Muhimbili National Hospital.

Specific objectives

1. To determine levels of folate in patients with optic neuropathy.
2. To determine levels of vitamin B_{12} in patients with optic neuropathy.
3. To determine visual acuity according to levels of folate and vitamin B_{12} in patients with optic neuropathy.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 Study design

A hospital based cross-sectional descriptive study.

2.2 Study period

The study was conducted from July 2016 to February 2017.

2.3 Study area

This study was carried out at Muhimbili National Hospital eye clinic (adult and pediatric clinics). Muhimbili National Hospital is situated in Dar es Salaam, Tanzania. It is a tertiary hospital serving in-patients as well as out-patients from all over the country and a teaching hospital for the Muhimbili University of Health and Allied Sciences.

The ophthalmology department provides tertiary eye services to a catchment population of more than10 million in the regions of Dar es Salaam, Coast, Morogoro, Zanzibar and all patients referred from other regions of Tanzania. This department works every day, Monday to Friday from 0900 to 1600 for out- patients and 24 hours for emergency cases. Adult out patients are attended at the adult clinic from Monday to Friday starting from 0900 to 1600, and the pediatric out patients eye clinic operates on Monday and Friday, from 0900 to 1600. Each eye clinic serves between 45 and 60 patients per day.



Figure 4: Tanzania map

2.4 Study population

Patients who attended Muhimbili National Hospital eye clinic (adult and pediatric) aged 10 years and above with the diagnosis of bilateral optic neuropathy during the study period were recruited to participate in this study.

2.5 Sampling technique

Consecutive sampling technique was used, where patients who attended the eye clinic at Muhimbili National Hospital and diagnosed with optic neuropathy were recruited.

2.6 Sample size

With the proportion of about 1% patients with optic neuropathy obtained from a study done by Bourne et al.[21], the sample size was estimated as follows:

$$\frac{n=Z^2P(100-P)}{\varepsilon^2}$$

Where:

n= sample size

P= estimated prevalence 0.01.

1-p=Expected proportion of subjects without the disease

Z= Z statistic for the level of confidence, i.e. 1.96= 95% CI

ε=Maximum likely error/ margin of error 0.021

$n = \frac{1.96^2 * 0.01 * 0.99}{0.021^2}$

n = 86, hence an estimated sample size was expected to be not less than 86 patients

2.7 Inclusion criterion

1. All patients who attended Muhimbili National Hospital (MNH) eye clinic diagnosed with optic neuropathy aged 10 years and above from July 2016 to February 2017.
2. Patients with the criteria above, who had signed an informed consent form themselves or their next of kin for the patients who could not consent.

2.8 Exclusion criteria

1. Patients below 10 years of age since some of the tests involved subjective answers from patients like color vision test.
2. Patients diagnosed with glaucoma, diabetes and hypertension and traumatic optic neuropathy.
3. Patients with unilateral optic neuropathy since nutritional optic neuropathy is bilateral.
4. Patients who were under long term treatment using drugs known to cause optic neuropathy.
5. Patients with haze media that could not permit the fundus examination.
6. Patients with neurological deficit suggesting of brain lesion confirmed by MRI or CT Scan.

2.9 Data collection procedures

Data was collected for a period of 8 months starting from July 2016 to February 2017.Patients were recruited on every Tuesday and Thursday for adult eye clinic and on every Friday for pediatric eye clinic. All ophthalmologists working at the eye clinic on the mentioned days were informed about the study and participated in identifying the new patients with optic neuropathy. All patients who were clinically diagnosed to have optic neuropathy were reviewed by the

researcher under supervision of the ophthalmologists in order to confirm the diagnosis then recruited to participate in the study. Patients and/or their next of kin were informed about the study and a consent form was signed by the patient (if >18years) or by the parent/guardian (if <18years) before participating in the study. Data sheets were used to obtain information from patients or care takers by the investigator.

Clinical examination and investigation

A medical history was taken from patients and their next of kin by the investigator reporting decrease of vision and the duration of the symptom. Information about past medical history concerning systemic disease such as diabetes, hypertension, surgical history and medications known to cause optic neuropathy was gathered for the purpose of this study.

Case definition: Patient was considered to have bilateral optic neuropathy if presented with bilateral decrease of vision which did not improve with correction, and having one of the following features: color vision deficiency, optic disc temporal pallor or generalized disc pallor after exclusion of other causes of decreased vision**.**

Complete ocular examination was conducted as follows:

Visual Acuity and IOP measurement

VA test was performed using Snellen's chart/illiterate E-chart. With the patient seating at 6 metres from the Snellen chart, the examiner showed the patient letters in decreasing order of the size first with the right eye while the left eye was covered then with the left eye while the right eye was covered. The examiner moved closer to the patient by 1 metre if the patient was not able to read at 6 metres. If the patient was unable to read the letters at 1 metre, finger counting close to the patient's face was done, followed by testing for ability to discern hand movement or perceive light.Refraction was done using a streak retinoscope followed by subjective refraction for refinement and best corrected visual acuity for each eye was then recorded.Visual acuity of 6⁄ 6 to 6⁄ 18 was considered normal, below 6⁄18 to 6⁄60 was considered as moderate visual impairment, below 6⁄60 to 3⁄60 was considered as severe visual impairment and below 3⁄60 was considered as blindness. IOP was measured using rebound tonometer (Icare), normal IOP was taken as 10 to 21 mmHg, low IOP as < 10mmHg and high IOP as > 21mmHg.

Anterior Segment Examination

Examination of the eyelids, conjunctiva, cornea, anterior chamber, iris, pupil reaction, lens and anterior vitreous was done by a pen torch and slit lamp biomicroscope for all patients and findings were recorded in the data sheet.

Posterior segment examination

Fundus examination was performed with the use of 78 D and 90DVolk lenses after pupil dilatation with tropicamide 0.5%eye drop. Appearance of the optic disc was recorded as normal, hyperemic, presence of temporal pallor or total pallor of the optic disc.

Color vision test

Ishihara plates were used to test the color vision, where 21 plates were presented to the patient. Each plate was held at 75cm from the patient eyes and read for 3 seconds for each eye while the other eye is occluded then results were recorded and compared with the normal values. Patients who managed to read correctly 13 plates or less were considered to have color vision deficiency and those who managed to read 14 and above were considered to have normal color vision.

Laboratory tests

Laboratory evaluation included serum folate and vitamin B_{12} levels. Patients were sent to the laboratory where 5ml of venous blood were drawn from the patients and collected in vacutainers with no additives where serum was obtained after centrifugation. ARCHITECT folate assay and ARCHITECT B_{12} assay were done to obtain serum levels of folate and vitamin B_{12}. Ranges of 200-900pg/ml for vitamin B_{12} were considered normal and low levels were considered to be less than 200pg/ml while folate levels of 7.2 -15.5 ng/ml were considered normal and values less than 7.2 ng/ml were considered to be low. Full blood picture and ESR were done routinely to rule out anemia and inflammation. The tests were run in the Central Pathology Laboratory of Muhimbili National Hospital.

Data management and Analysis

Data was entered into the Statistical Package for Social Sciences (SPSS) software version 20.0 and before entering the data, the forms were checked again for completeness and consistency. Univariate analysis was done to assess characteristics of the study population. Any association

was considered significant at 95% confidence interval. Descriptive statistics such as frequency, percentage, mean, standard deviation were used to summarize and describe the data.

Ethical Consideration

Ethical clearance to conduct the study was granted from Ethics and Research Committee of MUHAS, and permission to conduct the study was granted by Muhimbili National Hospital. Informed consent was obtained from the patient or patient's care taker. Refusal to be enrolled in the study did not affect patient treatment quality. Registration numbers instead of names were used for confidentiality. Patients with optic neuropathy associated with non-ocular features were referred to appropriate disciplines for further management.

CHAPTER THREE

3.0 RESULTS

During the study period, we recruited 93 patients with bilateral optic neuropathy. The mean age of the patients with optic neuropathy was 29.0 ±3.4years at 95% CI with the age of the patients varying from 10 to 86 years. The duration of the symptoms was reported to be ranging from 3 months to more than 5 years.

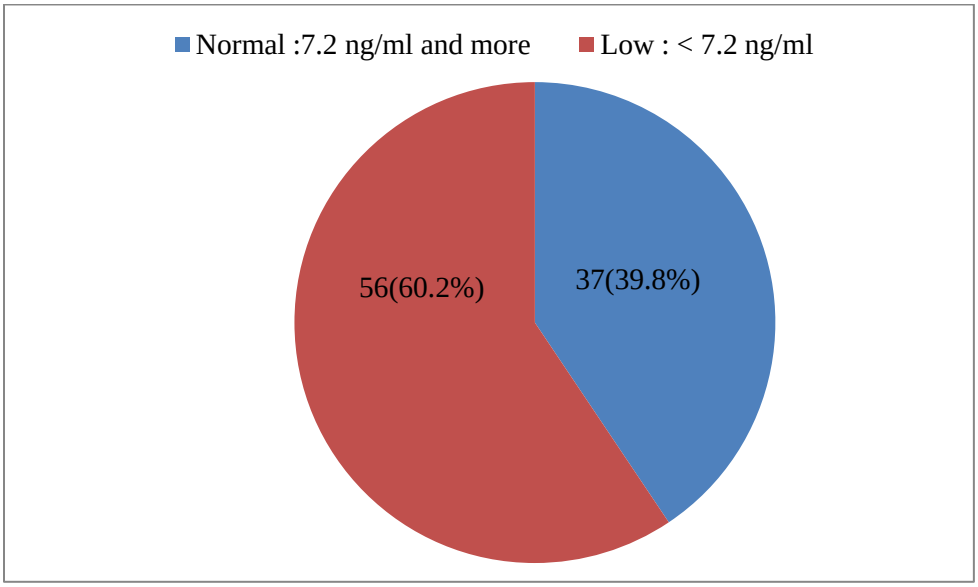
Table 1. Demographic characteristics of patients with bilateral optic neuropathy

Characteristics	**Number of patients n:93**	**%**
Age group		
<18	27	29
18-33	43	46.2
34-49	13	14
50+	10	10.8
Sex		
Male	48	51.6
Female	45	48.4
Occupation		
Peasant	10	10.7
Self employed	17	18.3
Student/pupil	50	53.7
Employed	12	13
Retired	4	4.3
Living community		
Family	71	76.3
institutionalized	22	23.7
Residency		
Dar es Salaam	86	92.5
*Others	7	7.5

**Others: Morogoro,Dodoma,Iringa and Mbeya*.

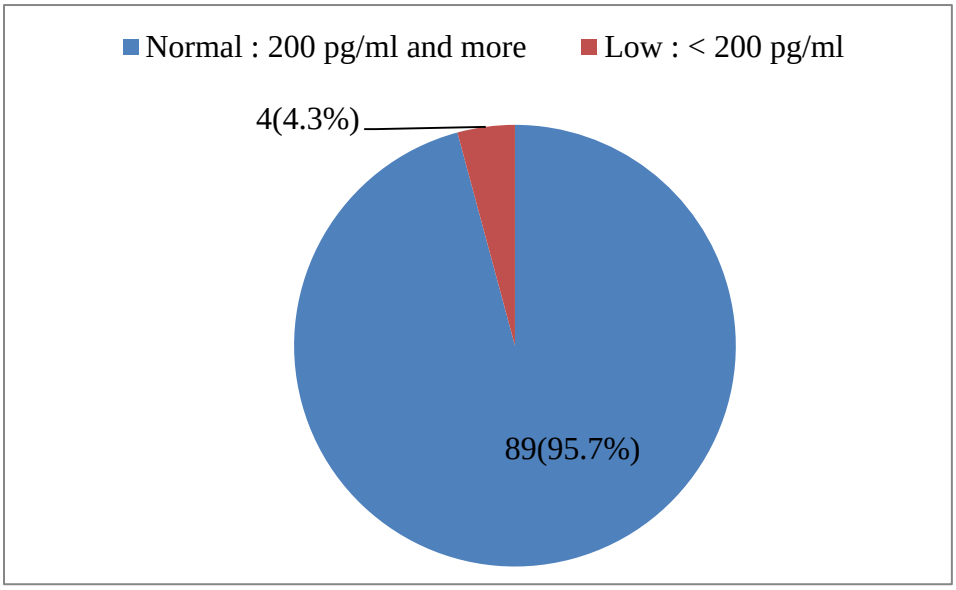
The male to female ratio was 1.06:1. Most of the patients were in the age group of 18-33 years of age (46.2%) and majority were students (53.7%). Most of the patients (92.5%) were residents of Dar es Salaam (**Table 1**).

Figure 5: Distribution of serum folate levels



More than a half 56(60.2%) of the patients had low serum levels of folate.

Figure 6: Distribution of serum vitamin B_{12} levels



Minority of the patients 4(4.3%) had low serum levels of vitamin B_{12}.

Table 2: Demographic factors associated with low folate levels among patients with bilateral optic neuropathy

Factor	Total, n(%)	Low levels of folate, n(%)	OR, 95%CI	P-value
Age group				
<32	63(67.7)	47(73.4)	6.1(2.4-15.4)	<0.0001
32+	30(32.3)	10(31.2)	1	
Sex				
Female	45(48.2)	22(47.8)	1	
Male	48(51.6)	35(61.4)	2.5(1.1-5.9)	0.029
Occupation				
Employed/self employed	29(31.2)	16(51.6)	1	
Others (students, retired, peasant etc)	64(68.8)	41(63.1)	1.6(0.7-3.8)	0.286
Living community				
Family	71(76.3)	42(57.5)	0.7(0.3-1.9)	0.514
Others(camps, boarding)	22(23.7)	15(26.3)	1	

Patients less than 32 years of age were 6 times more likely to get low serum levels of folate (**Table 2**).

Table 3: Eye examination findings

Examination	RE, n(%)	LE, n(%)	Total eyes, n(%)
IOP			
<10 mmHg	3(3.2)	2(2.2)	5(2.7)
10-21 mmHg	90(96.8)	91(97.8)	181(97.3)
RAPD			
Present	10(10.7)	12(12.9)	22(11.7)
Absent	83(89.2)	81(87.1)	164(88.2)
Color vision test			
Normal	17(18.3)	13(13.9)	30(16.1)
Abnormal	76(81.7)	80(86.1)	156(83.9)
Optic disc appearance			
Pale	7(7.5)	7(7.5)	14(7.5)
Temporal pallor	86(92.5)	86(92.5)	172(92.5)

Out of 186 eyes, 22(11.7%) were found to have Relative afferent papillary defect. More than a three quarter of the eyes 156 (83.9%) had color vision deficiency and majority of the eyes were found to have temporal pallor 172 (92.5. %) (**Table 3**).

Table 4: Disc appearance and serum levels of folate

Optic disc appearance	(<7.2ng/ml)	(>7.2ng/ml)	Total
Pale	1(7%)	13(93%)	14
Temporal pallor	111(64.5%)	61(35.5%)	172

Most of the eyes with temporal pallor 111(64.5%) were found in patients with low serum folate levels (**Table 4**).

Table 5: Disc appearance and serum levels of vitamin B_{12}

Optic disc appearance	Low levels (<200 pg/ml)	Normal (200+pg/ml)	Total
Pale	0	14(100%)	14
Temporal pallor	8(4.7%)	164(95.3%)	172

The majority of eyes with temporal pallor 164(95.3%) were found in patients with normal levels of vitamin B 12 (**Table 5**).

Table 6: Best corrected visual acuity in the better eye and serum levels of folate and vitamin B_{12}

Variable	Total, n(%)	6/6-6/18	<6/18-6/60	<6/60 – 3/60	<3/60-NPL
Serum folate					
Low levels (<7.2 ng/ml)	56(60.2)	20(35.7)	30(51.8)	5(8.9)	1(1.8)
Normal (7.2-15 ng/ml)	37(39.8)	20(54.1)	15(40.5)	1(2.7)	1(2.7)
Serum vitamin B_{12}					
Low levels (<200pg/ml)	4(4.3)	1(25)	1(25)	1(25)	1(25)
Normal (200+pg/ml)	89(95.7)	39(43.8)	44(49.4)	5(5.6)	1(1.1)

Among patients with low serum folate levels, 53.6% had moderate visual impairment (**Table 6**).

Table 7: Association between best corrected visual acuity in the better eye with serum levels of folate and vitamin B_{12}

Variable	Total, n(%)	With moderate/Severe Visual impairment/blindness, n(%)	OR, 95%CI	P-value
Serum folate				
Low levels (<7.2 ng/ml)	56(60.2)	35(62.5)	1.6(0.7-3.8)	0.286
Normal (7.2-15 ng/mg)	37(39.8.)	17(45.9)	1	
Serum vitamin B12				
Low level (<200pg/ml)	4(4.3)	3(75.0)	1.5(0.2-14.6)	0.751
Normal (200+ pg/ml)	89(95.7)	50(56.1)	1	

Among patients with low levels of serum folate, 62.4% had visual impairment however the difference is not statistically significant (**Table 7**).

CHAPTER FOUR

4.0 DISCUSSION

Most of the patients recruited during the study were between 18 and 33 years, which resembles with what was reported in Tanzania in a study which was done by Mtanda et al on epidemic optic neuropathy where patients were between 10 and 40 years of age.[18]This trend is probably related to the disease being common among school age, therefore by the second decade of life there is a relative high cumulative number of the patients as some patients might have had the disease from early teenage. Conversely after school age, the number of patients decrease as most of them had probably attended hospital for a long time and had either improved from the condition or had already been given low vision aid as rehabilitation. There was no sex differences among the patients in this study, this was also reported in other previous studies.[7, 46]

The study found that more than a half of the study participants had low folate levels while almost all of the patients had normal levels of vitamin B_{12}. This result has close similarity with other studies done in Cuba and Tanzania on optic neuropathy where low folate levels were high risk for optic neuropathy.[14,36]

Similar trend of folate and Vitamin B_{12} levels were reported in other studies where folate was predominantly found to be low as compared to vitamin B_{12}.[36, 37, 48]Furthermore there is likelihood that most of the patients are treated empirically based on clinical diagnosis and therefore the exact levels of the folate and vitamin B_{12} cannot be established in advance.

Though several studies have reported low folate and vitamin B_{12} levels in optic neuropathy with wide spread age of the patients, this study has revealed age among other demographic factors as an important factor associated with optic neuropathy. In this case low folate was found to have significant statistical association with patients under 32years (p value< 0.0001). This may be explained by the food preferences and could be also due to the reason that young people do not pay much attention on the diet. Folate acts as cofactor in many vital biological processes and it is important during periods of rapid cell division and growth.[10,11]

The reasons for nutritional deficiencies were out of the scope of this study however famine is unlikely the reason as no critical shortage of food across the country has been reported. We think life style and preference of unhealthy food and high metabolic demand for growth among young

adult may be held responsible for this problem. None of the patients reported gastrointestinal diseases or surgery which may impair vitamin absorption to be accounted for the deficiencies.

This study found that majority of patients had moderate visual impairment (48.3%). Among patients with moderate visual impairment 66.6% had low serum levels of folate. This is similar to what has been reported by Sethi et al, which stated that patients with toxic/nutritional optic neuropathy presented with visual acuity between 6/15 and 6/60.[37]Among patients who had low serum levels of folate, 51.8% had moderate visual impairment and this tallies with the predominantly low serum folate levels as discussed above. Nutritional optic neuropathy being an insidious progressive disease, patients are likely to seek for medical attention when their vision is significantly altered, therefore vitamin supplements may not help to recover lost vision completely.

Blindness was found in 2% of patients with bilateral optic neuropathy. This is almost similar to what has been reported in a school based study in Tanzania where no patient was found to have severe visual impairment or blindness.[21]This could be explained by the fact that pupils (students) with poor vision might have dropped out of the school. In our study the fewer number of patients with blindness may be due to the fact that most patients with the late stage of the disease could have been treated and counseled hence were no longer attending the eye clinic.

Relative afferent pupillary defect (RAPD) is not known to be common in bilateral and symmetric optic neuropathy however asymmetrical manifestation of the disease has been reported in other studies.[7,47] This also tallies with our study findings that only few eyes were found to have RAPD. This could be related to late presentation of our patients to the hospital whereby they come with significant loss of nerve fiber layer in one eye compared to the other.

It is known that color vision is affected in patients with optic neuropathy. We found that more than three quarter of the eyes had color vision deficiency which resemble to what has been reported in other studies.[36, 37]The difference with other studies could be explained by the difference in testing color vision methods. Previous studies considered a patient to have color vision deficiency when using Ishihara plates, there was a failure to read 1 plate out of 15,[49] or when using Tokyo Medical College plates, there was a failure to read 1 plate out of 8.[21] For this

study color vision was considered deficient when a patient could manage to read 13 plates or less using Ishihara plates.

Optic disc temporal pallor is an important sign which is known to be found in patients with nutritional optic neuropathy. In this study it was found that out of 186 eyes, more than three quarters had temporal pallor. Among those who had temporal pallor, 111eyes (64.5%) were found in patients with low folate levels. This shows that folate has a role in the health and normal function of the optic nerve. Loss of nerve fiber layer in the papillomacular bundle evidenced by OCT scan was reported by Kisimbi et al in which severe nerve fiber loss were related to severe temporal pallor.[20]Therefore those patients with well- established temporal pallor might have no significant visual changes even after treatment is given as they already have significant loss of the papillomacular bundle nerve fiber layer.

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATION

5.1 Conclusion

Majority of patients with optic neuropathy in the age group 18-33 had low levels of folate and were found to have moderate visual impairment, while few patients were found to have low serum levels of vitamin B_{12}. Defective color vision and temporal pallor were the common ocular findings in patients with bilateral optic neuropathy.

5.2 Recommendation

To Measure the serum folate and vitamin B_{12} levels before initiating treatment for optic neuropathy in order to ascertain the cause of optic neuropathy and to treat adequately.

5.3 Study limitation

Being a hospital based study it may not give the exact picture of optic neuropathy in the community.

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APPENDICES

Appendix I: Questionnaire

Serum Folate and Vitamin B_{12} Levels in Patients with Bilateral Optic Neuropathy Attending the eye clinic at Muhimbili National Hospital

1. Patient Identification No._____ 2. Date of an interview:___/____/_____

3. Hosp. Reg. No._____

SECTION A: DEMOGRAPHIC INFORMATION

S/N	Question Code	
4.	**District**_____	N/A
5.	**Region**_____	N/A
6.	**Age (in years)**_____	
7.	**Sex:** 1. Male 2. Female	
8.	**Education level:** 1. None 2. Primary 3. Secondary 4. Tertiary	
9.	**Marital status:** 1. Single 2. Married 3. Widowed 4.Divorced 5. Cohabiting 6. Separated	
10.	**Occupation:** 1. Peasant 2. Student/pupil 3.Self employed 4. Employed	
11.	**Living community:** 1. Family 2. Institutionalized 3. Specify_____	

SECTION B: CLINICAL MANIFESTATIONS

S/N Question Code

12. Complaints:

a) Decreased vision: 1. Yes 2. No

b) Ocular pain: 1. Yes 2. No

c) Tearing: 1. Yes 2. No

d) Photophobia: 1. Yes 2. No

e) Hearing loss: 1. Yes 2. No

f) Numbness of limbs: 1. Yes 2. No

g) Others_____

13. Duration of symptoms. 1. 3months- < 1 year

2. 1year -<2 years

3. 2years -< 5 years

4. > 5 years

S/N Code

14. Underlying conditions

a) Pregnant: 1. Yes 2. No

b) Breastfeeding : 1. Yes 2. No

c) Diabetes: 1. Yes 2. No

d) Hypertension: 1. Yes 2. No

e) HIV infection : 1. Yes 2. No

f) Tuberculosis: 1. Yes 2. No

g) Others_____

15. Past surgical history

a) Intraocular: 1. Yes 2. No

b) Intracranial : 1. Yes 2. No

c) Others_____

16. Nutritional habits

a) Vegetarian: 1. Yes 2. No

b) Non vegetarian: 1. Yes 2. No

c) Cassava: 1.Yes 2. No

17. Alcohol drinking: 1. Current drinker 2. Ex-drinker 3. Non drinker

18. Smoking status: 1. Current smoker 2. Ex-smoker 3. Non smoker

19. Medication; Use of:

a) Anti TB drugs: 1.Yes 2. No

b) Antimalaria drugs: 1.Yes 2. No

c) Amiodarone: 1.Yes 2. No

d) Multivitamin: 1.Yes 2. No

e) Anticonvulsants: 1.Yes 2.No

f) Other_____

20. History ocular of injury:

a) Blunt: 1.Yes 2. No

b) Penetrating: 1.Yes 2. No

SECTION C: EYE EXAMINATION

S/N	Part/question	RE	LE
21.	**Best Corrected Visual acuity**	1.6/18-6/6	1.6/18-6/6
		2.<6/18-6/60	2.<6/18-6/60
		3.<6/60 -3/60	3.<6/60 -3/60
		4.NPL-<3/60	4.NPL-<3/60
22.	**IOP**	1.<10mmHg	1.<10mmHg
		2. 10-21 mmHg	2. 10-21 mmHg
		3.>21 mmHg	3.>21 mmHg

23.	**Abnormality noted in the examination of anterior segment?**	**RE**	**LE**
		a) Iritis	a) Iritis
		b) Cyclitis	b) Cyclitis
		c) Cataract	c) Cataract
		d) Others	d) Others
24.	RAPD: (*circle the correct answer*)	1. Present	1. Present
		2. Absent	2. Absent
		3. N/A	3. N/A
25.	**Color vision test:**	1. Normal	1. Normal
		2. Abnormal	2. Abnormal
26.	**Optic disc appearance:**	**RE**	**LE**
	a) Normal	1. Yes 2. No	1. Yes 2. No
	b) Pale	1. Yes 2. No	1. Yes 2. No
	c) Swollen	1. Yes 2. No	1. Yes 2. No
	d) Hemorrhagic	1. Yes 2. No	1. Yes 2. No
	e) Hyperemic	1. Yes 2. No	1. Yes 2. No
	f) Temporal pallor	1. Yes 2. No	1. Yes 2. No
	g) Papilledema	1. Yes 2. No	1. Yes 2. No
	h) New vessels	1. Yes 2. No	1. Yes 2. No
	i) Other		

27. Other retina Signs

a) Maculopathy	1. Yes	2. No	1. Yes	2. No
b) Retinal edema	1. Yes	2. No	1. Yes	2. No
c) Arteriolar Narrowing	1. Yes	2. No	1. Yes	2. No
d) AV nipping	1. Yes	2. No	1. Yes	2. No
e) Haemorrhage	1. Yes	2. No	1. Yes	2. No
f) Cottonwool spots	1. Yes	2. No	1. Yes	2. No
g) Microaneurysms	1. Yes	2. No	1. Yes	2. No
h) New vessels	1. Yes	2. No	1. Yes	2. No
i) Normal	1. Yes	2. No	1. Yes	2. No
j) Other				

SECTION D: LAB TEST RESULTS

28. Part/question

a) Serum folate: 1.<7.2 ng/ml 2. 7.2 ng/ml and more

b) Serum vitamin B_{12}: 1. <200 pg/ml 2. 200 pg/ml and more

Appendix II: Informed Consent Form (English Version)

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

School of Medicine, Department of ophthalmology

Informed Consent Form

ID-NO | | | | | | | | | | |

Consent to participate in a research study about serum folate and vitamin B_{12} levels in patients with bilateral optic neuropathy attending the eye clinic at Muhimbili National Hospital.

Introduction and Purpose of the study

I am Dr. Michel KABANO, a postgraduate student, doing masters of medicine in ophthalmology at MUHAS. I am conducting a research on serum folate and vitamin B_{12} levels in patients with optic neuropathy attending the eye clinic at Muhimbili National Hospital. Optic neuropathy is known to affect the optic nerve and is associated with decreased vision. The purpose of this research is to determine the levels of folate and vitamin B_{12} in patients with optic neuropathy.

How to participate in the study

If you have agreed to participate in this study, the researcher will interview you and perform thorough ocular examinations, blood will be taken to tests folate and vitamin B_{12} levels and information will be recorded into the structured questionnaire.

Confidentiality

Researcher-patient confidentiality will be observed throughout the study. There will be no use of names but serial numbers. All the information gathered from patients will be used for the purposes of this study ONLY.

Risk No harm is expected to occur because of participating in the study.

Benefits

The results of this research will help to improve the quality of care of optic neuropathy.

The participants will benefit from complete eye checkup and treatment of any eye disorder discovered in the course of the research.

Right to withdrawal

It is your complete decision to participate in the study. You have the right to withdraw at any particular moment. You will continue to receive treatment and care similar to other patients. No conditions shall be imposed on you for the purpose of pressurizing you to participate in the study.

Whom to contact

Feel free to contact us in case of any concern or question about the study. You can contact

1. Dr Michel KABANO,
   The principal researcher (0712601219), or by email, michelkabano@gmail.com,
2. Dr Suzan MOSENENE (0689527952)
   Supervisor
   Lecturer MUHAS
3. Dr John KISIMBI (0773391114 or 0689093844)
   Co supervisor
   Lecturer MUHAS
4. Prof Mainen J. Moshi
   Chairperson, Muhimbili University Research and Publications Committee,
   P.O.BOX 65001, Dar es Salaam.

Declaration

I ……..have read and understood the contents in this consent form. My questions have been sufficiently answered and I agree to participate in this study.

Signature of interviewee…….. Date……..

Signature of interviewer…….. Date……..

Appendix III: Informed consent (Swahili version)

Kibali cha kushiriki kwenye utafiti

Utangulizi

Jina langu ni Dk.Michel KABANO. Ni mwanafunzi wa shahada ya uzamili,Idaraya macho,chuo kikuu cha Afya na sayansi shirikishi Muhimbili. Ninafanya utafiti kuhusu viwango vya vitamini B_{12} na folic acid kwenye damu kwa wagonjwa wenye ugonjwa wa mshipa wa fahamu wa kuonea wanaokuja Hospitali ya taifa ,Muhimbili. Magonjwa ya mshipa wa fahamu wa kuonea husababisha uoni hafifu.

Lengo kuu la utafiti huu ni kujua viwango vya vitamini B_{12} na folic acid kwa wateja wenye ugonjwa wa mshipa wa fahamu wa kuonea.

Jinsi ya kushiriki katika utafiti huu

Ukikubali kushiriki, utahojiwa kwa kutumia dodoso kwa lugha ya kiswahili. Na pia utafanyiwa vipimo vya macho. Damu itachukuliwa kupima viwango vya vitamin B_{12} na folic acid kisha taarifa zitajazwa kwenye dodoso.

Usiri

Usiri baina ya mgonjwa na mtafiti utahakikihwa kipindi chote cha utafiti. Majina hayatatumina bali namba. Taarifa zitakazo kusanywa zitatumika kwa madhumuni ya utafiti huu tu.

Madhara

Hakuna madhara yoyote yanayotegewa kujitokeza kwa kushiriki kwako. Kutakuwa na maumivu kidogo wakati wa kuchukua damu ya kipimo.

Haki ya kushiriki

Hakuna shuruti yoyote juu ya ushiriki wako katika utafiti huu. Una uwezo wa kukubali ama kukataa bila kutoa sababu zozote za kufanya hivyo. Na ukikubali, unaweza kubadili uamuzi wako ukijisikia kufanya hivyo wakati wowote. Utaendelea kupatiwa matibabu na huduma kama wagonjwa wengine.

Faida za kushiriki

Ushiriki wako utasaidia kuboresha huduma kwa wagonjwa wenye ugonjwa wa mshipa wa fahamu wa kuonea. Pia utafaidika kwa kupata huduma ya kuchunguzwa macho yako na kutibiwa tatizo lolote la macho litakalogunduliwa wakati wa utafiti huu.

Mawasiliano

Endapo utakuwa na maswali au maoni yoyote juu ya utafiti huu tafadhali wasiliana na:

1. Dr Michel KABANO (0712601219) michelkabano@gmail.com,
2. Dr Suzan MOSENENE (0689527952)
   Msimamizi wa utafiti
3. Dr John KISIMBI (0773391114 au 0689093844)
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4. Mwenyekiti, Kamati maalumu ya Muhimbili inayo shughulika na tafiti na maadili yake, Prof. Mainen J Moshi,
   S.L.P 65001, Dar es Salaam.
   Simu 022 2150302-6

Kama umekubali kuhojiwa, tafadhali saini hapa:

Mimi……., nimesoma/nimesomewa na kuelewa kilichoelezwa kwenye fomu hii na maswali yangu yamejibiwa kiufasaha. Hivyo ninakubali kuhojiwa kwa ajili ya utafiti huu.

Sahihi ya mhojiwa …….. Tarehe ……..

Sahihi ya mhoji…… Tarehe……