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SECTION I - RESEARCH PROTOCOL

1. TITLE: History of Nightblindness: A tool for xerophthalmia screening in Bangladeshi children.

2. PRINCIPAL INVESTIGATOR: Dr. Barbara J. Stoll

CO-INVESTIGATORS: Dr. Ayesha Molla
Dr. Iqbal Kabir

3. STARTING DATE: March 1, 1982

4. COMPLETION DATE: November 30, 1982

5. TOTAL DIRECT COST: $ 3935 of which $515 is incremental cost.

6. SCIENTIFIC PROGRAM HEAD:

This protocol has been approved by the NWG

Signature of Scientific Program Head: Myra Kahrens

Date: 5/2/1982

A-031941

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Abstract Summary

Vitamin A deficiency is a major public health problem in Bangladesh. In young children, vitamin A deficiency may lead to partial or total blindness. Moreover, children with vitamin A deficiency are at increased risk for other diseases and death.

Bitot spots and conjunctival xerosis are the most widely accepted ocular manifestations of vitamin A deficiency. However, these are relatively late manifestations which require well-trained observers for detection. Nightblindness is an early, mild sign of vitamin A deficiency, but has been thought to be too subjective to be clinically useful.

This study will address the question of whether a history of nightblindness is a reliable indicator of low vitamin A status in Bangladeshi children.

One hundred Dacca Hospital Surveillance patients (ages 1-6) will be enterred into the study - 50 with a history of nightblindness and 50 age-matched controls with no history of nightblindness. A detailed history of visual problems will be taken, a physical exam performed and blood drawn for serum vitamin A level. Because of the high prevalence of vitamin A deficiency in Bangladeshi children, all study subjects will be given oral vitamin A. Vitamin A levels in the two groups of children will be compared.

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objectives

The objective of this study is to look at the reliability of a history of nightblindness to predict low vitamin A status in Bangladeshi children.

2. Background

Vitamin A deficiency is a major public health problem in several developing countries. In young children vitamin A deficiency may lead to partial or total blindness[1,2]. McLaren has estimated that 100,000 children become blind each year from vitamin A deficiency[2] and it has also been estimated that an equal number of children die each year from diseases associated with vitamin A deficiency[3]. In a national blindness survey conducted in India, keratomalacia was found to contribute to 20% of all blindness[4]. Chodpar[5] found that 29% of 5,592 preschool children in Western Orissa had ocular changes of vitamin A deficiency. Sommer et al[6] studied 5,925 preschool children in Java, Indonesia and found a prevalence of nightblindness of 4.6% and of Bitot spots of 2.2%.

For defining populations at risk for vitamin A deficiency, a lower limit of 20 ug/dl in children and adults has been used. This is primarily based on an analysis of serum vitamin A levels of 40,000 apparently healthy low income children and adults in a ten state United States survey performed in 1968-1970[7].

Bitot spots and conjunctival xerosis are the most widely accepted ocular manifestations of vitamin A deficiency[8]. However, these are relatively late manifestations which require well-trained, skilled observers for detection. Nightblindness is an early, mild sign of vitamin A deficiency, but has been thought to be too subjective to be clinically useful[6]. Nightblindness may be quantified by use of a dark adaptometer[9]. Carney and Russell[10] studied dark adaptation and vitamin A levels in adult patients with various diseases and found that a serum level of $\geq$40 ug/dl predicted normal dark adaptation 95% of the time, a level of $\geq$30 ug/dl predicted normal retinal function 68% of the time and a level of $\geq$20 ug/dl predicted normal function only 27% of the time. They concluded that 40 ug/dl is the lower limit of serum vitamin A which predicts normal dark adaptation in adults. However, use of a dark adaptometer is impractical in the field for large populations and for studying young children, those at greatest risk for ocular damage from vitamin A deficiency. Sommer et al[6] measured serum vitamin A levels in 174 Javanese children with a history of nightblindness and 164 controls without nightblindness and found that levels of vitamin A were significantly lower ($P < .001$)

in children who complained of nightblindness. They concluded that nightblindness is a sensitive sign of vitamin A deficiency in Java, but cautioned that their findings might not be valied for other cultures and might depending on the degree to which nightblindness is recognized by a community.

There is data to support a high prevalence of vitamin A deficiency among Bangladeshi children[11,12] Brown et al[12] studied 104 children with diarrhea from the Matlab hospital, independent of visual signs and symptoms, and found that 20% had low serum vitamin A levels (< 10 ug/dl). In Bengali, a specific word "ratkana" means nightblindness and is well known and widely used. In surveillance of children with diarrhea coming to ICDDR,B in Dacca, Stoll et al[13] found that in 1980 between 1 and 9% of children (0-10 years) each month complained of nightblindness (ratkana) (5% N=101, overall).

Ocular manifestations of vitamin A deficiency are difficult to use for field diagnosis because they require well trained personnel for detection. A simple screening tool, such as a history of nightblindness, would be very useful-especially in areas where doctors and other trained personnel are not available.

B. SPECIFIC AIMS

1. To address the question of whether a history of nightblindness is a reliable indicator of low vitamin A status in Bangladeshi children by comparing vitamin A levels in children who complain of nightblindness and in matched control children without nightblindness.

C. METHODS

One hundred Dacca Hospital Surveillance Study[14] children (ages 1-6) will be selected for the study. Fifty will be children who give a history of nightblindness (rat kana) and 50 will be age-matched controls who do not complain of nightblindness. If a patient or guardian agrees to participate, a consent form in Bengali will be obtained. A detailed visual history will be obtained and a physical exam will be performed by one of the investigators. One blood sample (2 cc) will be drawn for vitamin A analysis and hematocrit.

Because of the high prevalence of vitamin A deficiency in Bangladesh, all children will be given 200,000 I.U. of oral vitamin A (to be repeated once at home by the group who complain of nightblindness). If anemia is detected by hematocrit screening, further diagnostic evaluation will be performed and treatment given as necessary.

PROCEDURES

Vitamin A will be analyzed fluorometrically as described by Hansen et al[15] and as has been done previously at ICDDR,B by Dr. A. Molla.

Data Analysis

Sample tables

Table I.

Clinical Characteristics of Study Patients

		Nightblindness	No Nightblindness
Number of patients			
Age	range		
	mean		
Sex	male		
	female		
Wt/Ht	$\geq$ 80%		
	$<$ 80%		
Hct	range		
	mean		
Monthly income of family			
	range		
	mean		
No. children in family			
	range		
	mean		
Age rank of child			
	range		
	mean		
Indicators of diarrhea severity:			
	No. admitted to T.C.		
	No. admitted to ward		
	No. treated with IV		
Diarrheal etiology			
	Rotavirus		
	ETEC		
	Campylobacter		
	Shigella		

Table II

Comparison of serum vitamin A level by clinical status

		Serum Vit A level			
	n	<10ug%	10-19 ug%	≥20 ug%	mean ± S.E.
Nightblindness alone - no other clinical signs					
Nightblindness plus other clinical signs					
No nightblindness and no other clinical sign					

D. SIGNIFICANCE

Vitamin A deficiency is of major public health importance in Bangladesh. Because it may lead to partial or total blindness, vitamin A deficiency has wide social and economic implications. Simple tools to diagnose vitamin A deficiency are needed for use in field areas where doctors and other trained personnel are not available. This study will address the question of whether a simple history of nightblindness is a reliable tool for the diagnosis of vitamin A deficiency in Bangladeshi children.

E. FACILITIES REQUIRED

1. No new office or lab space or equipment is required.
2. Personnel -
   - 1 biochemistry lab technician - 20% x 9 months
   - 1 hospital physician - 10% x 9 months
3. Hospital support - none
4. Logistical support - none

F. COLLABORATIVE ARRANGEMENTS

none

Abstract Summary

1. Subjects will be Dacca Hospital Surveillance Study children 1-6 years with and without a history of nightblindness. This age group is chosen because they are at the greatest risk for ocular damage from vitamin A deficiency and are the target age group of the Bangladesh Government's Vitamin A Distribution Program.

2. The only risk to patients is mild discomfort from blood drawing in the group who will have blood drawing done.

3. Blood will be drawn by a skilled physician.

4. The confidentiality and anonymity of patients will be safeguarded. All records will be kept by the principal investigator and patients will be referred to be number rather than name.

5. After the nature of the study is explained to parents or guardians, a consent form, in Bengali, will be obtained.

6. The routine surveillance interview will be performed (about 10 minutes). An investigator will also interview the patient for an additional 5-10 minutes and perform a physical examination.

7. The potential benefits to be gained by patients are:
   1) diagnosis and treatment of vitamin A deficiency
   2) measurement of hematocrit and diagnosis and treatment of anemia
   3) more personal contact with health workers.

   If nightblindness is a reliable indicator of low Vitamin A status in Bangladeshi children, it will be useful for field diagnosis, a benefit to society in general.

8. One 2cc blood sample will be drawn from each patient.

Consent Form

Nightblindness/vitamin A level

Blindness secondary to vitamin A deficiency is a serious problem in Bangladesh. The earliest sign of vitamin A deficiency is difficulty seeing in the dark (nightblindness). Your child has diarrhea. Some children with diarrhea also have nightblindness. We are studying children with and without nightblindness to see whether the symptom of nightblindness correlates with low vitamin A in the blood.

If you agree to participate in this study, your child will receive care for diarrhea as is necessary. In addition, we will ask you some questions about your child's vision, examine him/her and draw 2 cc of blood for vitamin A level. Also, we will give your child one (two) capsule(s) of vitamin A to prevent (treat) vitamin A deficiency.

If you do not want to participate, your child will receive the same good care at ICDDR,B.

I agree that the above study has been explained to me and that I understand it and agree to participate.

_____
Subject

_____
Investigator

সম্মতি পত্র

প্রথম পর্ব - রাতকানা রোগ/"ভিটামিন এ"র মাত্রা

ভিটামিন এ'র অভাবজনিত কারণে অন্ধত্ব বাংলাদেশে একটি মারাত্মক সমস্যা। ভিটামিন এ'র অভাবে রোগীর প্রাথমিক লক্ষণ হচ্ছে, অন্ধকারে ভালভাবে দেখতে না পাওয়া (রাতকানা রোগ) আপনার শিশুর পাতলা পায়খানা হয়েছে। কিছুসংখ্যক শিশুর পাতলা পায়খানার সংগে রাতকানা রোগও হয়ে থাকে। আমরা পরীক্ষা করে দেখতে চাই, যে সব শিশুদের রাতকানা রোগ নাই বা আছে, তাদের লক্ষণ সমূহের সংগে রক্তে ভিটামিন এ'র স্বল্পতার কোন সম্পর্ক আছে কিনা ?

যদি আপনার শিশুকে এই পরীক্ষায় অংশগ্রহণে সম্মত থাকেন, তাহলে দরকার মতো আপনার শিশুর পাতলা পায়খানার চিকিৎসা করা হবে। সেই সংগে আমরা আপনার শিশুর দৃষ্টি শক্তি সম্বন্ধে কিছু প্রশ্ন করবো। তাকে পরীক্ষা করবো। এবং তার শরীর থেকে ভিটামিন এ'র মাত্রা পরীক্ষা করার জন্য ২ সি সি রক্ত নেবো। আপনার শিশুর যাহাতে ভিটামিন এ'র অভাব না হয় কিংবা অভাব থাকলে তার চিকিৎসার জন্য ভিটামিন এ ক্যাপসুল খাওয়াবো।

আপনি যদি এই পরীক্ষায় অংশ নিতে সম্মত না হোন তবুও আপনার শিশুর সুচিকিৎসা পাবেন।

আমাকে উপরোক্ত পরীক্ষা সম্পর্কে ভালভাবে বুঝিয়ে বলা হয়েছে। এবং আমি সব বুঝিয়াই পরীক্ষায় অংশ গ্রহনে সম্মত হয়েছি।

রোগীর অভিভাবকের স্বাক্ষর/টিপ সহি

তারিখ----------

গবেষকের স্বাক্ষর

References:

1. Menon, K., Vijayaraghavan, K. Sequelae of severe xerophthalmia - a follow-up study. Amer. J. Clin. Nutrit. 33: 218, 1980.

2. McLaren, D.S. Xerophthalmia and blindness. Brit. Med. J. 2: 668, 1970.

3. Vitamin A deficiency and xerophthalmia. WHO Technical Report Series, No. 590, Geneva, 1976.

4. Indian Council of Medical Research, Annual Report of the Director-General, 1974, p. 75.

5. Chodpar, A. Incidence of ocular changes due to vitamin "A" deficiency in Western Orissa. Indian Pediatrics 16: 787, 1979.

6. Sommer, A., Hussaini, M.H.S., Muhilal, M.D. Tarwotjo, I., Susanto, D., and Sulianti Saroso, J. History of nightblindness: a simple tool for xerophthalmia screening. Amer. J. Clin. Nutrit. 33: 887, 1980.

7. United States Department of Health Education and Welfare, Health Services and Mental Health Administration (1968-1970), In: Ten-State Nutrition Survey pp IV: 135-IV: 139, Atlanta Georgia.

8. Sommer, A. Field Guide to the Detection and Control of Xerophthalmia 1978 WHO Geneva, Switzerland.

9. Russell, R., Multack, R., and Smith V. Dark adaptation testing for diagnosis of subclinical vitamin A deficiency and evaluation of therapy Lancet 2: 1161 (1973).

10. Carncy, E.A. and Russell, R.M. Correlation of Dark Adaptation Test Results with Serum Vitamin A levels in Diseased Adults J. Nutr. 110:552, 1980.

11. Nutrition Survey of East Pakistan, March 1962 - January 1964. Washington D.C., 1966. Department of Health, Education, and Welfare.

12. Brown, K.H., Rajan, M.M. Chakraborty, J., and Aziz, K.M.A. Failure of a large dose of vitamin A to enhance the antibody response to tetanus toxoid in children. Amer. J. Clin. Nutrit. 33: 212, 1980.

13. Stoll, Barbara, Personal communication.

14. Stoll, B.J. Surveillance of Urban Diarrheal Patients protocol.

15. Hansen, L.G., and Warwick, W.J. An improved assay method for serum vitamin A and E using fluorometry. Am. J. Clin Pathol 70:922, 1978.

SECTION III - BUDGET

A. Detailed Budget

1. Personnel Services

Name	Position	% time used	Salary Taka	Dollar
Dr. Barbara J. Stoll	Scientist	15x9 mo		2250
Dr. Ayesha Molla	Scientist	10x9 mo		770
Dr. Iqbal Kabir	Hospital Physician	10x9 mo		400
	1 biochemistry technician	10x9 mo		132
	1 computer programmer	50x1 mo		133

2. Supplies and Materials

Item	Unit Cost	Taka	Dollar
Serum vit A assay	100 x $2		200
Vitamin A capsules	300 x $.16/25		2
1 computer diskette			8

3. Equipment

none

4. Patient hospitalization

none

5. Outpatient care

none - already budgeted on Surveillance Protocol

6. ICDDR,B - Transport

none

7. Travel and Transportation - none

8. Transportation of things - none

9. Rent, Communications, Utilities - none

10. Printing, publications - none

11. Other contractual services computer time - 2 hours x400=800 Tk= $ 40

12. Construction, renovation, alteration - none

B. Budget Summary

Category	Taka	Dollar
1. Personnel		3685
2. Supplies and Materials		210
3. Equipment		
4. Hospitalization		
5. Outpatient Care		
6. ICDDR,B Transport		
7. Travel		
8. Transport, things		
9. Rent/communication		
10. Printing Publication		
11. Contractual services		40
12. Construction		
Total		3935

of which $ 515 is incremental cost