Library (2)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. M. S. Akbar

*Trainee Investigator (if any) ____

Application No. Bacterial Corpus

Supporting Agency (if Non-ICDDR,B) ____

Title of Study of a hypoglycaemic syndrome with high mortality (Pilot)

Project status:
( ) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes No
   (c) Minors or persons under guardianship — (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects — Yes (No)
   (b) Social Risks — Yes (No)
   (c) Psychological risks to subjects — Yes (No)
   (d) Discomfort to subjects — (Yes) No
   (e) Invasion of privacy — Yes No
   (f) Disclosure of information damaging to subject or others — Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) — Yes (No)
   (b) Use of fetal tissue or abortus — Yes (No)
   (c) Use of organs or body fluids — (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study — (Yes) No
   (b) Procedures to be followed including alternatives used — (Yes) No
   (c) Physical risks — (Yes) No
   (d) Sensitive questions — (Yes) No
   (e) Benefits to be derived — (Yes) No
   (f) Right to refuse to participate or to withdraw from study — (Yes) No
   (g) Confidential handling of data — (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — NA (No)
5. Will signed consent form be required:
   (a) From subjects — Yes No
   (b) From parent or guardian (if subjects are minors) — Yes No
6. Will precautions be taken to protect anonymity of subjects — Yes No
7. Check documents being submitted herewith to Committee:
   ✓ Umbrella proposal - Initially submit a overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   X Informed consent form for subjects
   ✓ Informed consent form for parent or guardian
   ✓ Procedure for maintaining confidentiality
   X Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Principal Investigator — 8 OCT 1984 — Trainee

84-043P
2/10/84

SECTION I - RESEARCH PROTOCOL

1. Title : BIOCHEMICAL BASIS OF A HYPOGLYCEMIC SYNDROME WITH HIGH MORTALITY.

2. Principal Investigator: Dr. M.S. Akbar, Dhaka Shishu Hospital

Co-Investigators :
1. Dr. A.N. Alam
2. Dr. Zulfiquar (DSH)
3. Dr. Samsuzzoha (DSH)
   Dr. Waker Khan (DSH)
4. Dr. M.M. Rahaman (ICDDR,B)
5. Dr. Sayeedul Huq (BCSIR)

Consultants :
1. Dr. Moinul Islam (ICDDR,B)
2. Dr. Tofayel Ahmed (DSH)
3. Dr. S.F. Rubbi (BCSIR)
4. Dr. W.B. Greenough III (ICDDR,B)

3. Starting Date : 15 November 1984

4. Completion Date : 14 May 1985

5. Total Direct Cost : US$.2900.00

6. Scientific Programme : This protocol has been approved by the Nutrition Working Group.

Signature of Scientific Programme Head: M Akbar

Date: Sept 20, 1984

7. Abstract Summary

During the last winter, patients between 4 to 12 years of age and coming from poor families were admitted to Dhaka Shishu Hospital with a short history of convulsion and coma. Death occured in seventy-five per cent cases. Almost all of them had some degree of undernutrition and gave a history of vomiting and Diarrhoea.

Patients with similar presentation and high mortality were also reported from Chittagong and Mymensingh Medical College Hospital during the same period. Similar patients are being admitted this year.

It is planned to carry out a prospective study to evaluate the biochemical, clinical and post mortem histological changes in such a fatal syndrome.

8. REVIEWS:

(a) Ethical Review Committee: _____

(b) Research Review Committee: _____

SECTION II - RESEARCH PROTOCOL

A. INTRODUCTION

1. Objectives: To investigate the probable biochemical basis of a syndrome featuring hypoglycemia associated with unconsciousness, convulsion, vomiting and/or diarrhoea and high mortality in malnourished children following ingestion of a green leafy vegetable.

2. Background: Convulsion in patients with diarrhoea and vomiting is not infrequent finding, particularly in malnourished children. Cases have been reported by Hirschhorn et al (1) and Molla et al (2) where they found hypoglycaemia as a complication of diarrhoeal diseases. The pathogenesis of hypoglycaemia in these cases were obscure. In a retrospective study, Alam et al (3) reported 12 cases of diarrhoea with convulsion and 11 cases with vomiting and convulsion. All These patients had hypoglycaemia. In the vomiting group, no pathogens could be isolated from blood, stool, or CSF. All showed polymorphonuclear leukocytosis with high PNMs. In the diarrhoea group, shigella flexneri was isolated in half of the cases. Patients in both groups show high mortality (7 out of 11 in vomiting group and 6 out of 12 in diarrhoea group died). Some of the patients gave the history of taking a green leafy vegetable called "Ghagra shag." Two other patients reported to have "Ghagra" and developed vomiting, convulsion and unconsciousness without hypoglycaemia both, however, expired in the hospital.

In the last 12 weeks, 24 patients with similar presentations were admitted into Dhaka Shishu Hospital. Eight of these patients gave history of taking "Ghagra Shag", out of which six patients expired. All these patients were usually admitted with short history of convulsion and unconsciousness

followed by [illegible] cases signed out of the hospital at a critical [illegible] and in all probability they died at home. [illegible] also gave history of diarrhoea and vomiting. Eighty-five percent patients had hypoglycaemia (with mean value 40 gm%). Serum bilirubin, SGOT, SGPT and blood urea were found to be raised. All of these patients also showed leukocytosis with high PMN count. CSF showed no abnormality. Blood culture and stool examination, X-ray chest could not be doen due to lack of facilities and rapid fatal outcome. Liver biopsy (done in two cases) showed no significant changes by light microscopic examination.

The clinical presentation in many ways resemble Reye's syndrome (4,5) since its recognition in 1963. It is an acute illness which may develop in the course of a non specific viral infection (upper) resp. tract, gastrointestinal) and occurs frequently in association with varicella, influenza A + B, echovirus 2, xoxsachi A, rotavirus and Epstein-Barr virus. Cases have also been reported with aflatoxin poisoning from Thailand and warfarin poisoning from Israel, Jamaican vomiting sickness. An illness which resembles Reye's sundrome, is produced by ingestion of hypoglycin A contained in the unripe fruit of ackee tree. In Reye's syndrome, altered liver function tests, and occasionally with hypoglycaemia, high BUN and elevated blood ammonia are common findings. There were striking histopathological changes in brain, liver and kidney. Brain showed loss of neurons and fatty vacuolation around small vessels. The liver showed diffu micro-vesicular steatosis with minimal inflammatory changes. Ultra-structural changes were metochondrial. The kidney consist, principally of swelling and fatty degenaration of tubules.

3. Rationale: Cases have been reported from Dhaka Shishu Hospital Mymensingh and Chittagong Medical Colleges recently, who were admitted with hypoglycaemia, convulsion, unconsciousness,

followed by [illegible] cases signed out of the hospital at a critical state and in all probability they died at home. [illegible] had history of diarrhoea and vomiting. Eighty-five percent patients had hypoglycaemia (with mean value 40 gm%. Serum bilirubin, SGOT, SGPT and blood urea were found to be raised. All of these patients also showed leukocytosis with high PMN count. CSF showed no abnormality. Blood culture and stool examination, X-ray chest could not be doen due to lack of facilities and rapid fatal outcome. Liver biopsy (done in two cases) showed no significant changes by light microscopic examination.

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3. Rationale: Cases have been reported from Dhaka Shishu Hospital Mymensingh and Chittagong Medical Colleges recently, who were admitted with hypoglycaemia, convulsion, unconsciousness,

vomiting and diarrhoea. These cases were associated with high mortality. A prospective study to evaluate the clinical patterns and biochemical basis of this syndrome will help in the better management of these patients.

B. SPECIFIC AIMS:

(1) To establish a biochemical basis of this syndrome.

(2) To carry out a prospective study of the clinical pattern of these fatal syndrome..

(3) If possible, to carry out a study of post-mortem histological changes in liver, kidney and brains.

C. METHODS OF PROCEDURE:

1. Patient Selection - Any patient, between 3-14 years of age, who will be admitted at Dhaka Shishu Hospital with short history of convulsion, vomiting and/or diarrhoea and coma will be selected for the study. Patients with meningitis and febrile convulsions will be excluded. Patients in ICDDR,B presenting with similar complaints will also be included. A total of 25 such patients will be recruited for this study. A limited number of patients with this syndrome will be transferred to ICDDR,B for better investigation and management.

2. Informed Consent - Attendants of selected patients will be explained the nature of the study and be told that they are free not to enroll. Those who agree will be asked to sign the informed consent form.

3. On admission, a detailed clinical history will be obtained from the patients' attendant including history of taking any kind of indigenous vegetable, drugs, chemicals, insecticides etc. Preceding the illness.

4. The patients will be kept in the Intensive care units of the respective hospitals and will be provided standard treatment and adequate nursing care.

5. Laboratory investigations: Routine investigations on admission will include :-

(a) Complete blood picture and M.P.

(b) Blood-sugar, urea, creatinine, electrolyte, ammonia, S. bilirubin, SGOT, SGPT, culture. 6 - 7 ml. of venous blood will be required.

(c) Stool-M/E and culture.

(d) Urine - analysis and culture.

(e) CSF - Cytology, Bacteriology and Biochemical.

(f) Trachael aspirate - Gram Stain + Culture.

(g) Acute and convalescent sera will be kept for future (e.g. influenza, arbo, Japanese B viruses) analyses.

(h) Liver and Renal biopsy (if possible and if attendants agree). For both light and E.M. examination and mycotoxin assay in these patients. Besides, attempts will be made to do other investigations.

Outcome - The patients will be discharged when they get well. The parents of the expired patients will be approached for permission to do autopsy and if permitted, autopsy will be carried out by a qualified pathologist obtaining a written informed consent. This will be done in about five cases.

D. SIGNIFICANCE:

Patients with short history of convulsions and unconsciousness and having high mortality have been reported from Dhaka Shishu Hospital and ICDDR,B. Many of them had vomiting and diarrhoea. Understanding the clinical pattern, as well as cause and pathogenesis of this syndrome will help in developing an optimum

management of these critically ill patients and hopefully significantly reduce the high mortality.

E. FACILITIES REQUIRED:

Patients will be kept in the intensive care units of ICDDR,B and Dhaka Shishu Hospital. Existing laboratory facilities of these institutes will be utilised.

F. COLLABORATIVE ARRANGEMENTS:

This will be a collaborative study between Dhaka Shishu Hospital and ICDDR,B. Principal Investigator Dr. ~~K. Azad~~ Mis. Akter and Co-Investigators - Drs. Ashraf, Waseem, Tofayel Ahmed are collaborating from Dhaka Shishu Hospital. Dr. Sayeedul Huq and Dr. S.F. Rubbi from BCSIR will also collaborate in the study.

REFERENCES

1. Hirschhorn N, Lindenbaum J, Greenough WB III, Alam SM. Hypoglycaemia in Children with Acute Diarrhoea. Lancet 1966; 2:128-132.

2. Molla AM, Hossain M, Islam R, Bardhan PK, Sarker SA. Hypoglycaemia: A Complication of Diarrhoea in Children. Indian Paediatrics 1981; 18:181-85.

3. Alam AKMJ, Islam R, Sultana N, Rahaman MM. Vomiting and Hypoglycaemia. Proceeding of the 9th Meeting of the Scientific Review and Technical Advisory Committee of CRL 1974 pp 131-139.

4. Reye's Syndrome. M. Michael Thaler. In Nelson Text book of Paediatrics. 12th Ed. 1983. pp 973-75 WB Saunders Company.

5. Reye's Syndrome. Arnold Sulverman & Claude C. Roy. In Current Paediatric Diagnosis and Treatment. 7th Ed. 1982 pp 491-92, Large Medical Publications.

ABSTRACT SUMMARY FOR ERC

1. Twentyfive malnourished children, between 3-14 years admitted into Dhaka Shishu Hospital and the treatment Centre of ICDDR,B having short history of convulsion, unconsciousness, features of hypoglycaemia, vomiting and/diarrhoea following intake of green leafy endegenous vegetables will be taken for the study.

2. There is no potential risk involved in this study.

3. Not applicable.

4. All records will be kept strictly confidential with principal investigator. If data are put on computer tapes, study patients will be referred to by number only.

5. Informed consent (signed or thumb impression) from the guardians will be obtained prior to the study. There is no procedure in this study which may unmask the privacy of the subject.

6. Interview will be taken from guardians only related to their medical history.

7. Understanding the clinical pattern, as well as cause and pathogenesis of this unknown syndrome will help in developing an optimum maangement of these critically very ill patients and hopefully significantly reduce the high mortality and this study may help to prevent this disease in the community in future.

8. 6-7 ml venous blood, stool, urine, treacheal aspirate, usual small quantity of CSF, liver, andrenal biopsy material (if possible and guardians agree) at 0 hour and 2 cc convulescence serum during discharge. Autopsy will be done if patient dies and guardians agree.

BUDGET

		% Effort	Project Requirement
		30%	–
		10%	Tk. 9,000.00
		10%	–
		10%	–
		–	–
	BCSIR	–	–
	DSH	–	–
Dr.	ICDDR,B	–	–
Dr.	BCSIR	–	–

Lab. Technician (Microbiology)	month	Tk. 4,000.00
	month	Tk. 4,000.00
	month	Tk. 4,000.00
	month	Tk. 3,000.00
	10 days	Tk. 1,000.00
		Tk.20,000.00

TWBC,

Serum glucose, urea creatinine, electrolyte, lever

Will be done at DSH

To be done at ICDDR,B Tk. 2,500

(at IPH)

toxin assays (at BCSIR)

Nil

DDR,B Tk. 2,000.00

5.	Patient hospitalisation .10x200x10		Tk. 20,000.00
6.	Outpatient.care	Nil	
7.	Transportation of things and patients		Tk. 5,000.00
8.	Travel	Nil	
9.	Rent, Communication, Utilities	Nil	
10.	Printing & Publication		Tk. 2,000.00
11.	Other contractual services	Nil	
12.	Construction	Nil	

Increamental Cost 81,500 --9,000

72,500

(US$ 1 = Tk.25) = 2,900

fs

CONSENT FORM

Dhaka Shishu Hospital and ICDDR,B are jointly working to find out the cause and proper treatment of "unknown and deadly disease" with which your child is suffering. We have found that mortality rate is extremely high when a child is attacked by this "unknown disease." We would like you and/or your child to participate in this study, the purpose of which is to determine the cause and treatment of this "unknown disease" and thus a service to the society and mankind.

If you/your child decide to participate you can expect the following :

1. Your child will be provided with all possible medical care and treatment .

2. We will collect samples of urine, stool, cough and about 2-3 ml of C.S.F. for different investigation and laboratory examination.

3. If necessary, we will do X-ray of any parts of the body and chest.

4. We will collect only once 6-7 ml of blood by venepuncture for different investigation. This amount of blood is generally taken from children patients for diagnosing the diseases and is considered as usual and harmless procedure.

5. A small piece of tissue will be taken from liver or kidney for biopsy. This is a general and established procedure for the diagnosis of many diseases.

6. We always pray to almighty God or the uneventful recovery of your sick child. If, however, inspite of our all efforts, your child expires, an autopsy will be carried out in order to find the real the cause of death. Autopsy will be completed within shortest possible time and thereafter, the dead body will be handed over to you with due solemnity.

7. If necessary and for the better treatment, your child may be transferred from DSH to ICDDR,B and vise versa with our own cost.

8. Your child will be discharged from the hospital after the complete recovery from the disease. In case you decide not to join the study, you will still be eligible for care at DSH. You may also decide to withdraw after entering the study and this will not affect any medical care you might require now or later on.

I agree to participate and co-operate with the study on my own/my child's behalf :

Signature of Staff:

Signature .....

.....

Date .....

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র এবং ঢাকা শিশু হাসপাতাল

সম্মতি পত্র

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র এবং ঢাকা শিশু হাসপাতাল আপনার শিশু যে ধরণের এক অজ্ঞাত ও জটিল রোগ দ্বারা আক্রান্ত হয়েছে তার কারণ ও যথোপযুক্ত চিকিৎসা উদ্ভাবনের জন্য যৌথভাবে কাজ করে যাচ্ছে। এই অজ্ঞাত রোগে শিশুদের মৃত্যুর হার খুবই বেশী। আমরা চাই সমাজ ও মানবতার বৃহত্তর স্বার্থে ও প্রয়োজনে আপনি আপনার রোগাক্রান্ত শিশুকে এই রোগের কারণ ও চিকিৎসা উদ্ভাবনের জন্য প্রয়োজনীয় গবেষণায় অংশ গ্রহণ করতে অনুমতি দিবেন।

আপনি যদি স্বেচ্ছায় রাজী থাকেন তাহলে আমরা নিম্নলিখিত ব্যবস্থাদি নিব :-

১) আপনার শিশুর জরুরী চিকিৎসার প্রয়োজন সাপেক্ষে জরুরী ভিত্তিতে সম্ভাব্য সুচিকিৎসা দেওয়া হবে।

২) আপনার শিশুর প্রস্রাব-পায়খানা, গলার কফ ও শিরদাড়া থেকে ২-৩ সি সি রস বিভিন্ন পরীক্ষার জন্য নেওয়া হবে।

৩) প্রয়োজনবোধে বুকের বা শরীরের যে কোন অংশের এক্সরে করা হবে।

৪) শিরা থেকে মাত্র একবারের জন্য মোট ৬-৭ সি সি রক্ত বিভিন্ন পরীক্ষার জন্য নেওয়া হবে। এই পরিমান বা তার বেশী রক্ত অনেক ধরণের রোগে আক্রান্ত শিশুদের রোগ নির্ণয়ের জন্য স্বাভাবিক ভাবে নেওয়া হয়ে থাকে।

৫) যকৃত ও মূত্রাশয় হতে অতি ক্ষুদ্র পরিমান টিস্যু বায়োপসির জন্য আপনার অনুমতিক্রমে নিতে পারে। রোগ নির্ণয়ের জন্য এই ধরণের পরীক্ষা একটি স্বাভাবিক ও প্রতিষ্ঠিত পদ্ধতি।

৬) আমরা পরম করুণাময়ের নিকট আপনার আক্রান্ত শিশুর আরোগ্য কামনা করি। সবার সমস্ত প্রচেষ্টা সত্ত্বেও যদি আপনার শিশু মারা যায় তবে মৃত্যুর প্রকৃত কারণ অনুসন্ধানের জন্য স্বাভাবিক ভাবে শবব্যবচ্ছেদ করা হবে। শবব্যবচ্ছেদ অত্যন্ত দ্রুত ও অল্প সময়ে সমাধা করা হবে এবং মৃতদেহ যথাযোগ্য মর্যাদার সংগে ফেরত দেওয়া হবে।

৭) সুব্যবস্থা ও সুচিকিৎসার জন্য প্রয়োজনে আপনার শিশুকে শিশু হাসপাতাল হতে উদরাময় হাসপাতালে অথবা উদরাময় হাসপাতাল হতে শিশু হাসপাতালে আমাদের খরচে স্থানান্তরিত করা হতে পারে।

৮) আপনার শিশুকে সম্পূর্ণ সুস্থ হওয়ার পর হাসপাতাল ত্যাগের অনুমতি দেওয়া হবে।

আপনি যদি গবেষণায় অংশ গ্রহণ করতে রাজী না হন, তবুও আপনার শিশুকে প্রথামত সকল চিকিৎসা দেওয়া হবে।

গবেষণা চলাকালীন যে কোন সময়ে আপনি ইচ্ছা করলে আপনার শিশুকে প্রত্যাহার করে নিতে পারেন। এতে আপনার শিশুর চিকিৎসার কোন ত্রুটি হবে না।

উপরোক্ত বিষয়গুলি সজ্ঞানে বিবেচনা করে আপনি যদি রাজী থাকেন তাহলে নীচে আপনার স্বাক্ষর কিংবা বাম হাতের বৃদ্ধাংগুলের ছাপ দিন।

গবেষকের স্বাক্ষর ও তারিখ

অভিভাবকের স্বাক্ষর ও তারিখ