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An algorithm for the clinical diagnosis of Tubercular Meningitis in the UK
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1. Background:

Tubercular meningitis (TBM) remains a significant global health problem and is on the rise in the United Kingdom (UK). Health Protection Agency (HPA) statistics have revealed 8655 cases of tuberculosis (TB) in 2008 in the UK.1Extra pulmonary tuberculosis is increasing with nearly half of the cases presenting with an exclusive extra pulmonary site 2. In 2008, there were 178 TBM cases reported in UK as compared to 140 in 20041. Diagnostic difficulties abound in TBM, particularly in distinguishing it from acute bacterial meningitis. Delayed diagnosis is associated with poor outcome. Untreated, it is universally fatal and lengthy treatment is often initiated on a presumptive diagnosis.

There are very few UK studies on TBM3, 4 Much of our information on TBM is from research conducted in countries with a high prevalence of TB. Clinicians are guided by data generated from such research. For example, the Vietnam diagnostic algorithm 5 (appendix 1) is often used to guide clinical diagnosis of TBM (the algorithm identifies parameters - age, duration of symptoms, CSF percentage of neutrophils ,CSF and Blood WBC counts which are all independently predictive of distinction between TBM and Bacterial Meningitis). However, applicability of the algorithm in the UK has not been assessed.

The prevalence of TBM in the UK is low, and the TBM population is also very different - being made up principally of people with Indian or African connections, or those among the 77,400 people in the UK who are HIV positive. Hence, there is an urgent need to not only evaluate the validity of this algorithm but also to understand the epidemiological, clinical, laboratory and radiological features of TBM *relevant to the UK population*. Quality of life after TBM has never been examined so far and there is little information regarding the economic burden of this disease.

This analysis will result in improved understanding of the diagnosis and impact of TBM in the UK and thus lead to improved management strategies.

Duration of study: 1 year

2. Question, Hypothesis, Aims & Objectives.

Question

Can a clinical algorithm be used to guide diagnosis of TB Meningitis?

Hypothesis:

The Vietnam Algorithm can reliably identify patients with clinically diagnosed TB Meningitis among all those with suspected TBM with a sensitivity and specificity of at least 80%.

Aim: We will examine the applicability of *the Vietnam algorithm* for the diagnosis of TBM in the UK population and evaluate the current state of diagnosis and management of TB Meningitis in the UK.

Objectives:
i. To examine the applicability of the *Vietnam algorithm* for the diagnosis of TBM in the UK population.
ii. To describe the *clinical* features, *laboratory* and *radiological* parameters in patients with TB Meningitis in UK.
iii. To elucidate the reasons for *diagnostic and treatment delays* in TBM.
iv. To analyze the *Quality of Life* of these patients.
v. To assess the *economic burden* of TBM in UK.

3. Outcomes:
Primary Outcome
• To assess the usefulness of the Vietnam Algorithm in guiding diagnosis of TBM in the UK population.
Secondary outcomes
• Analysis of the Clinical, Laboratory and radiological parameters of patients with suspected TB Meningitis
• Measurement of the Quality of Life of these patients by WHOQoL –Bref 6
• Resource utilization analyses for assessing the economic burden of TB Meningitis.
• Examination of factors causing diagnostic and treatment delays in this condition.
• Description of outcomes in patients with TB Meningitis.

4. Methods:
Study design
Retrospective, Multicentre, Descriptive Case Control Study.
Definitions:
• Suspected TB Meningitis
Any patient with "suspected TB Meningitis" i.e. any patient whose spinal fluid was tested for TB by means of microscopy, TB culture or Polymerase Chain Reaction).
• TBM Case
A TBM case is defined as any patient in whom TB Meningitis was confirmed by bacteriology or diagnosed by a clinician and he was treated* for TB Meningitis.
**Treated means giving a course of TB treatment for > 8 weeks or died whilst on treatment and TBM was thought to be the most likely diagnosis*
A case will be further sub - classified according to the published research consensus case definition by allocating them pre determined diagnostic scores into
• Definite
• Probable
• Possible TBM

a. Definite case of TBM
i. AFB seen in the CSF;
Or ii. *M. tb* cultured from the CSF;
Or iii. *M. tb* commercial NAAT positive from the CSF in a patient who presents with symptoms and/or signs suggestive of meningitis;
Or iv. AFB seen in the context of histological changes consistent with TB in the brain/spinal cord
b. *Probable case of TBM*
i. a total diagnostic score of _10 points (when cerebral imaging is not available)
Or ii. 12 points (when cerebral imaging is available) plus exclusion of alternative diagnoses. (At least 2 points should either come from CSF or cerebral imaging criteria.)
c. Possible TBM.
i. a total diagnostic score 6-9 points (when cerebral imaging is not available)
Or *ii.* 6-11 points (when cerebral imaging is available) plus exclusion of alternative diagnoses.

Control
A control is defined as any patient with "suspected TB Meningitis whose spinal fluid was tested for TB Meningitis however he/she was not commenced on anti - TB treatment or was given a course of treatment for _ 8 weeks and TB was not thought to be the most likely diagnosis.For every 1 case we aim to identify 1 control. These will be patients who fulfil the definition of a control .i.e. any patient with "suspected TBM" who was not commenced on anti TB treatment and are closest in time and immediately prior to the case.

Site Eligibility
This is a *multicentre* study with the main centre at the University of Liverpool. Hospitals have been identified through the Health Protection Agency, the UK Brain Infections Network and the Infectious Diseases Research Network (www.idrn.org). TB Meningitis is a notifiable disease and every case of TB meningitis is reported to the Health Protection Agency where data is maintained. This data will be examined to identify any hospital which has reported more than 5 cases of TB Meningitis in the years 2006 – 2008

Additional hospitals which have expressed an interest in being a part of the UK Brain Infections Network and from the Infectious Diseases research network will also be invited to take part in the study.

Inclusion criteria

- Age >18 years
- Both males and females
- Any patient with suspected TB Meningitis i.e. any patient whose spinal fluid was tested for TB by means of either microscopy / PCR / TB culture will be included in the study.

Exclusion criteria

- Paediatric patients will be excluded (<18 years old)

Initial screening and Recruitment –

• We will examine the Health Protection Agency's data and identify hospitals which will take part in the study. These will be hospitals who have reported more than 5 cases of TBM in the years 2006-2008. We will then invite clinicians (General physicians, TB Leads, Infectious Disease specialists, neurologists, microbiologists, , elderly care physicians, Intensive care specialists) from these hospitals as well as clinicians who have expressed an interest in being a part of the UK-BIN and members of the Infectious Diseases Research network (IDRN) to take part in the study and offer them local collaborator status.

• The local collaborator will liaise with the HPA to obtain a list of cases of TB Meningitis and will also assess the medical records of their own hospital to add any cases that may not have been notified to the HPA. They will also evaluate the electronic microbiology records in their hospitals to identify the controls as per above definitions. Data will be evaluated for cases and controls between the dates 01/01/2006 and 31/06/2010

Data Collection

This will be done for each objective as follows:

Objective 1 - To **examine the applicability of the Vietnam algorithm** for the diagnosis of TBM in the UK population

• Case notes of all "suspected TB Meningitis" patients will be evaluated. We will apply the Vietnam Algorithm to all the patients of "suspected meningitis" by giving them a Vietnam Algorithm score of >4 (hence non TBM) or _ 4 (TBM)

• *Validation of the algorithm* will be done by calculating the Sensitivity, Specificity, Positive and Negative Predictive values.

• Comparison will be made between the diagnosis of TBM / Non TBM using the Vietnam Algorithm and the clinician diagnosis.

Objective 2, 3 & 5 - To **describe** the **clinical features, laboratory and radiological parameters** in patients of TB Meningitis in UK **,** elucidation of the reasons for diagnostic & treatment delays in TBM as well as **analysis of** the **economic burden** of TBM in UK.

• Case notes of all cases and controls will be reviewed and information regarding clinical, laboratory and radiological features, duration of hospital stay, time taken to diagnose and initiate treatment will be abstracted by local clinical teams.

• The data will be entered on an electronic form which will ensure anonymity for the patients and sent electronically to the main centre at Liverpool where it will be analysed in a coded anonymous format in accordance with the national guidelines (Data Protection Act)

Objective 4 – Analysis of the Quality of Life of these patients

• All patients with "suspected TB Meningitis" will receive a quality of life questionnaire – the WHOQoL- Bref. A patient information leaflet and consent form along with a reply paid envelope will be provided as well. If they fail to respond to the questionnaire a second reminder will be sent to the patients after 3 weeks. No further reminders will be sent. Analysis will be done by use of SPSS and software designed specifically to analyze the WHOQoL group of instruments.

Statistical considerations:

Hospitals with _ 5 cases of TB Meningitis in the years 2006 – 2008 (England and Wales) reported 344 cases of TB Meningitis to the Health Protection Agency.

We will validate the Vietnam Algorithm in patients of Suspected TB Meningitis from these hospitals by comparing the diagnosis of TBM using the Vietnam Algorithm criteria with the Clinician diagnosis. The Vietnam Algorithm has been shown to have a variable sensitivity and specificity in different settings and populations (Vietnam - sensitivity 88% and specificity of 79%; Malawi sensitivity 78% and specificity of 43%; Turkey- sensitivity 95.6% and specificity of 70.8%).

We will determine the sensitivity, specificity, positive and negative predictive values in the UK population of suspected TBM.

If the sensitivity / specificity levels of the scale in a UK population are 85% or greater, 150 cases and controls will be needed to estimate the true sensitivity / specificity levels to a precision (measured using 95% confidence intervals) of, at worst, ±5.7%.

If the sensitivity / specificity levels of the scale in a UK population are found to be less than 85%, data will be collected to try to identify potential risk factors (e.g. travel history to the Asian subcontinent) that could be usefully added to the existing version of the Vietnam Algorithm to improve its psychometric properties. A total sample of 150 cases and 150 controls will be sufficient to identify risk factors that increase the odds of a positive diagnosis by a factor of between 2 and 3 with between 80% and 90% power (assuming the prevalence of the risk factor in the control group is 15% or greater).

In order to avoid bias, each control will be selected closest in time to the corresponding case *prior* to the case diagnosis.

Data entry and monitoring

Data entry will be done electronically and will be password protected. Data monitoring for this study will be arranged through the University of Liverpool.

5. Confidentiality and Data Protection:

All personal information regarding study participants will be confidential. Personal identifiable information will only be accessed by the clinical team (local collaborator) responsible for the care of the patient. The local collaborator will assign a unique identifier number that will encode the local site as well to each participant. A copy of the participant's name and number will be kept securely by the local collaborator at the local recruitment site in a password protected electronic document as well as a

hard copy (stored securely) in the participant's medical records. All information will be anonymised prior to transfer and transferred to the central site (University of Liverpool) securely (using nhs.net). Imaging will be transferred by CD's which will also be anonymised and password protected.
Investigators at the Central site will not have access to any personal identifiable information and will only be able to identify participants by the unique identifier numbers allocated to them.

6. **Safety:**

There is no intervention in this study as this is a retrospective study.
Some patients may experience anxiety on completing their quality of life form as they reflect on their illness affecting their quality of life; however this risk is extremely low. There are benefits of participation for the volunteers as they may feel that their disease is being researched and their view on how their illness has affected their life is being looked into.

7. Consent:

Consent will be taken from patients taking part in the quality of life questionnaire by post. A detailed patient information leaflet will be provided. Since the data collection will be done by local clinical teams, postal consent will be taken in order to maintain confidentiality. The questionnaire (and a reminder to non responders) will be mailed by the clinical team looking after the patient. A copy of the consent will be filed in the patient's clinical notes.
Patients who lack capacity will also be included in the study because TB meningitis can result in an impairment of the brain which may be temporary, permanent or may even fluctuate. It is particularly important to include the patients who have been more severely affected as we presently have inadequate information on the impact of TBM on sufferers in the UK. As the risks involved in completing this questionnaire are very small, it is unnecessary for capacity to be formally assessed by a physician. Since assessment of capacity is specific to the time it needs to be made, the capacity assessment for this study can be done by the carer/relative who is with the participant at that time and is opening and acting on the mail received by the participant. The consent and Consultee declaration form have been worded to account for the two possibilities of the participant consenting for themselves or the Consultee advising on whether the person question should take part in the project. If the participant is able to open their mail, read the letter, complete the questionnaire and post it back it may reasonably be assumed that they have capacity to consent, particularly in view of the low risk posed by a questionnaire. A cover letter will also be sent along with the Consultee Declaration Form.

8. Indemnity:

The University of Liverpool's professional indemnity and clinical trials insurances will apply.

9. Publication and dissemination of results

The results of these studies will be published in the medical and scientific literature. Results will also be presented at local level and national and international conferences. Participants will not be identified in any publication or presentation. All authors of publications will give written consent to publication prior to submission for publication. Results will also be disseminated on charity websites

10. Potential Impact:

This study will result in improved understanding of TBM in the UK. It will help us to identify the usefulness of an algorithm which is being used without having been validated hence lead to better management strategies. Health economics and quality of life study will inform policy. It will set up a national TB meningitis network where future collaborations can lead to further studies

11. Role of the funding source. The funding source has no involvement in the study design, collection, analysis or interpretation of the data, writing of the report, or the decision to submit for publication.

References:

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<u>COMMENT: RECRUITED STUDY SUBJECTS WERE LATER RE-CLASSIFIED AS *CONFIRMED* TBM, *UNLIKELY* TBM OR *TREATED AS* TBM</u>

***Confirmed TBM (Target condition positive)*:** Patients had positive Mycobacterium Tuberculosis (Mtb.) diagnostics (Mtb. culture, or Mtb. specific NAAT or microscopy for Mtb) in CSF or brain tissue.

Unlikely TBM (Target condition negative): Patients had negative Mtb. diagnostics in CSF or brain tissue, and either had an alternative diagnosis at discharge/death , were never treated with anti-TB therapy but had a good outcome, or were exposed to a sub-therapeutic course of anti-TB therapy (under 21 days) with a good outcome. Good outcome was defined as no or light disability, not limiting return to work, based on the Glasgow Outcome Scale).

Treated as TBM (Target condition inconclusive): Patients treated as TBM with anti-TB therapy for over two months, with negative Mtb. diagnostics in CSF or brain tissue.