Improving early diagnosis of tuberculous meningitis in children

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SUMMARY

Due to the sub-optimal performance of definite diagnostic tests, the early identification of paediatric TBM suspects relies on a thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations. Rapid diagnosis is needed for early treatment initiation but microbiological confirmation is difficult at stage 1 disease because a lumbar puncture is generally only done once signs of meningitis have developed (stage 2 and 3 TBM). With this thesis, we aim to investigate mechanisms of improving the early and/or more accurate diagnosis of childhood TBM.

Part I

In chapter 2 we provide an update on the diagnosis and management of TBM in children, based on local experience, which can be transposed to similar settings. Highlights include firstly that short (6 months) intensified therapy in children with drug susceptible TBM is safe and effective, with a good outcome and low mortality. Secondly, home-based TBM treatment after initial in-hospital stabilization is feasible in carefully selected patients under close supervision. Thirdly, treatment of tuberculous hydrocephalus depends on the level of cerebrospinal fluid (CSF) obstruction. Communicating hydrocephalus can be successfully treated with medical therapy with normalization of intracranial pressure occurring within days in the majority children and non-communicating hydrocephalus requires neurosurgical intervention. Fourthly, thalidomide is the local drug of choice in children who develop life-threatening TB mass lesions (IRIS) despite corticosteroids.

Part II

In clinical practice, TBM diagnosis is most often based on a combination of clinical, laboratory and radiological findings. A uniform research case definition utilizing these criteria was proposed by an international panel of experts as a means of improving diagnostic standardization in order to answer critical research questions, categorizing patients as definite, probable, or possible TBM. Part 2 of the thesis focuses on the diagnostic utility of the uniform research case definition criteria for TBM. In chapter 3.1 we retrospectively evaluate the diagnostic performance of probable and possible TBM criteria in children with culture-confirmed TBM and culture-confirmed bacterial meningitis. The proposed uniform research case definition provided excellent diagnostic accuracy compared to microbiologically-confirmed TBM, when a 'probable' TBM score was used. When a 'possible' TBM score was used, not a single TBM case would have been missed, but clinical utility was minimal given the low specificity achieved. In order to strengthen our findings we prospectively assessed the diagnostic

accuracy of the uniform TBM research case definition (see chapter 3.2). Excellent diagnostic accuracy was obtained for a diagnosis of TBM when compared to bacterial and viral meningitis controls. The high specificity of a probable TBM score justifies its use as an alternative reference standard to microbiological confirmation in future studies. In both studies poor sensitivity was obtained when a probable TBM score was used to diagnose early (stage 1) TBM, emphasizing a very high clinical index of suspicion of TBM in young children with recent TB exposure and persistent non-specific signs.

CSF findings are essential to early diagnosis of TBM. Cut-off values for CSF glucose in TBM lack evidence. A CSF protein cut-off of >1g/L (100mg/dL) differentiated between cases of TBM and other forms of meningitis. Our study on the diagnostic value of cerebrospinal fluid chemistry results in childhood TBM found that the optimal lower limit of CSF glucose concentration as a diagnostic aid for TBM was 2.2 mmol/L (see chapter 3.3). Absolute CSF glucose differentiated non-TBM from TBM cases with sensitivity of 68% and specificity of 96%, excluding its use as a 'rule-out' test. Simultaneous determination of serum and CSF glucose was seldom performed but my findings suggest that the CSF:serum glucose ratio may further improve diagnostic sensitivity. CSF protein cut-off of >1g/L as well as CSF macroscopic appearance, cell counts and the presence of lymphocyte predominance are required to assist the distinction between TBM and bacterial meningitis.

Previous studies suggest that chest X-ray findings consistent with active pulmonary TB are observed in 70% to 84% of children with TBM. In our study (chapter 3.4) only 46% of cases with TBM had chest radiograph findings highly suggestive of pulmonary TB. A need to treat calculation showed that only 1 in 4.39 children ≤3 years of age with TBM are likely to have 'certain TB' on chest X-ray.

Part III

Microbiological confirmation of TBM remains the gold-standard of diagnosis, but is challenging in young children due to the paucibacillary nature of disease, low CSF volumes available for diagnostic analysis and sub-optimal sensitivity of direct microscopy for acid-fast bacilli and *M.tuberculosis* culture on CSF. Several new commercially available NAA tests have been developed for the rapid diagnosis of TB. In part III of the thesis our meta-analysis of newer commercial NAA tests found a summary sensitivity of 69% and specificity of 98%. Summary sensitivity of commercial NAA tests remains suboptimal and is unlikely to greatly enhance early accurate diagnosis. However, the excellent specificity suggests that commercial NAA tests may be regarded as definitive in the correct clinical setting. In 2013, the WHO

recommended Xpert MTB/RIF® as the preferential initial investigation in all adults and pediatric TBM suspects. Our sub-analysis of 5 studies reporting Xpert MTB/RIF® on CSF, found summary sensitivity of 70% and specificity of 97%.

In chapter 4.2 we aim to assess the utility of MTBDR*plus*® and Xpert MTB/RIF® to diagnose TBM in a clinical setting, alone and/or in combination. The main finding was the incremental increase in diagnostic accuracy achieved with combined use of these commercial NAA tests performed on CSF. Although both NAA tests were superior to liquid culture, sensitivity remained low compared to a rigorous predefined clinical case definition. The MTBDR*plus*® assay performed with sensitivity of 33% (98% specificity), Xpert MTB/RIF® was 26% sensitive (100% specificity) and combining positive results from both these tests provided a sensitivity of 49% (98% specificity) against a TBM case definition. This is insufficient to serve as a rule-out test and provides limited clinical guidance. However, microbiological confirmation provided by a positive test prevents unnecessary treatment delay and potential life-threatening consequences. The additional advantage of a positive NAA test is that of early detection of mycobacterial resistance.

A major limitation of this study was the failure to improve diagnosis of stage 1 childhood TBM, mainly because it was hospital-based. Good surveillance at primary healthcare level, identifying children with poor weight-gain (or weight loss) and persistent non-remitting cough for longer than 2 weeks, could improve the detection of both childhood TB and early TBM. IMCI is potentially a valuable tool to increase awareness of TBM among healthcare workers, and in detecting early TB and TBM, as it is practiced at the healthcare level of first contact. Household contact-tracing and prophylaxis with isoniazid therapy, as well as more general measures such as improving nutrition, housing and poverty relief, are valuable measures in preventing TBM in young children.