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The clinical usefulness of adenosine deaminase measurement in cerebrospinal fluid specimens

Ekermans, Pieter Anton

2013-01-24
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DECLARATION

I, Pieter Anton Ekermans declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Clinical Pathology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…….. [Signature of candidate]

…… day of ……., 2012

Dedicated to our esteemed Professor in Chemical Pathology

Janice Paiker

PUBLICATIONS AND PRESENTATIONS

No publications and presentations have arisen from this research report at the time of submission for examination.

ACKNOWLEDGEMENTS

Professor Adriano Dusé and Dr Jaya George, supervisors of this study and research report.

Mr Floyd Olsen from the Receiving Office at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) National Health Laboratory Service (NHLS) branch.

Dr Natalie Beylis from the NHLS Mycobacteriology Referral Laboratory, Braamfontein.

Mrs Sue Candy and Mrs Alex Jennings from the Corporate Data Warehouse (CDW) of the NHLS.

Mr John Waters and his staff from the archives at CMJAH.

Dr Hendrick Emanuel Van Deventer from Lancet Laboratories.

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LIST OF ABBREVIATIONS

ADA	Adenosine deaminase
AFB	Acid-fast bacilli
AIDS	Acquired Immunodeficiency syndrome
AUC	Area under the curve
CDW	Corporate Data Warehouse
CI	Confidence interval
CLAT	Cryptococcal latex antigen test
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
CT	Computerised tomography
CXRs	Chest X-ray(s)
dx	Diagnosis
EBV	Epstein-Barr virus
ELISA	Enzyme-linked immunosorbent assay
HIV	Human Immunodeficiency virus
IQR(s)	Interquartile range(s)
JC virus	John Cunningham virus
MOTT	*Mycobacterium* other than tuberculosis
NAAT	Nucleic acid amplification techniques
NHLS	National Health Laboratory Service
PCR	Polymerase chain reaction
ROC	Receiver operating characteristic

RPR	Rapid plasma reagin
TB	Tuberculosis
TBM	Meningitis due to *Mycobacterium tuberculosis*
TPHA	*Treponema pallidum* haemagglutination
UNAIDS	Joint United Nations Programme on HIV / AIDS
VDRL	Venereal Disease Reference Laboratory
WHO	World Health Organisation

ABSTRACT

Introduction:

The diagnosis of meningitis due to *Mycobacterium tuberculosis* (TBM) in general can be extremely difficult in the absence of culture confirmation. A non-definitive test such as adenosine deaminase (ADA) could potentially assist in this regard, although its current value for the diagnosis of TBM remains unclear. The literature on the usefulness of ADA measurement in CSF to assist in the diagnosis of TBM shows inconsistencies especially from an analytical point of view regarding the actual ADA assay methodology.

Methods:

Clinical and laboratory data relating to cerebrospinal fluid (CSF) ADA requests during 2009 and 2010 at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) were extracted from patient files and the National Health Laboratory Service (NHLS) laboratory information system. An optimal cut-off for CSF ADA for the diagnosis of TBM was calculated using Receiver Operating Characteristic (ROC) curve analysis. In addition, the performance of CSF ADA in different infective and non-infective categories was assessed. Specifically the performance of CSF ADA was compared between the 'Confirmed TBM' category and the categories for 'Confirmed bacterial meningitis', 'Confirmed ventriculitis', 'Confirmed cryptococcal meningitis', and 'Confirmed viral meningitis / encephalitis'. An attempt was made to develop a prediction rule using the data collected, including the CSF ADA result, to improve the clinical diagnosis of TBM in the absence of culture confirmation.

Results:

Total CSF ADA requests considered for these 2 years amounted to 3548. Of these 1490 accounted for patients who had both a CSF ADA and a culture for mycobacteria requested. The optimal CSF ADA cut-off to assist in the diagnosis of TBM was calculated at 2.0 U/l (AUC of 0.86; 95% CI of 0.82 – 0.89; p – value of < 0.0001). The sensitivity at this cut-off was 85.9% and the specificity was 77.7%. A considerable overlap was noted in the 95% distribution of CSF ADA values as well as the outliers for each of the categories considered. No statistically significant difference was noted between the 'Confirmed TBM' and the 'Confirmed bacterial meningitis' categories as well as between the 'Confirmed TBM' and the 'Confirmed ventriculitis' categories. Stepwise logistic regression analysis failed to produce a combination of factors with appropriate performance characteristics to be used as a prediction rule.

Discussion and Conclusion:

The CSF ADA cut-off determined in this study is unusually low. This cut-off as well as those reported in other studies, in addition to the actual CSF ADA result, are of dubious value in the diagnosis of TBM and may potentially mislead clinicians. Fundamental issues of specimen integrity, ADA assay standardisation and the overlap in the performance of the assay in different diagnostic categories (especially between 'Confirmed TBM' and 'Confirmed bacterial meningitis') affect interpretation of the CSF ADA result. An inadequate number of correlations between variables chosen possibly prevented generation of an acceptable prediction rule that included CSF ADA.