

pond seems to be the only one not frequented by the birds and is in some areas densely overgrown with the aquatic weed *Potamogeton pusillus* which in our experience is closely associated with *B. pfeifferi* habitats elsewhere. It should be interesting to see what happens to the *B. pfeifferi* population if the birds could be lured to this pond by means of a feeding trough similar to those installed in adjacent ponds. If after 2 - 3 years the birds do not control the snails successfully, regular mollusciciding could then be undertaken as a control measure. In addition, it is necessary to identify the unknown trematode parasite transmitted by these snails, since this uncommon association with *B. pfeifferi* needs to be pursued.

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The simultaneous determination of cerebrospinal fluid and plasma adenosine deaminase activity as a diagnostic aid in tuberculous meningitis

P. R. DONALD, CHRISTINA MALAN, ADRI VAN DER WALT, J. F. SCHOEMAN

Summary

The simultaneous determination of cerebrospinal fluid (CSF) and plasma adenosine deaminase (ADA) activity was evaluated as a diagnostic aid in tuberculous meningitis (TBM). CSF and plasma ADA activity were determined in four groups of patients: (i) a 'no meningitis' group of 174 children investigated for possible meningitis, but found to be uninfected; (ii) an aseptic meningitis group of 40 children; (iii) a bacterial meningitis group of 31 children; and (iv) a TBM group of 27 patients (24 children and 3 adults). CSF ADA alone was determined in a further 23 children with aseptic meningitis, 19 with bacterial meningitis and 13 children and 7 adults with TBM. Both the CSF/plasma ADA ratio and the absolute CSF ADA activity were raised in TBM (mean values

0,24 and 12,61 U/l respectively) and bacterial meningitis (mean values 0,59 and 15,43 U/l respectively), but not in the aseptic meningitis group (mean values 0,06 and 2,00 U/l) or the 'no meningitis' group (mean values 0,04 and 1,51 U/l). Both values will distinguish TBM from aseptic meningitis, but do not appear to hold any marked advantages over conventional CSF criteria in the diagnosis of TBM.

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Cerebrospinal fluid (CSF) adenosine deaminase (ADA) levels are known to be raised in tuberculous meningitis (TBM) and their use has been suggested to help differentiate TBM from other forms of meningitis.¹⁻³ CSF ADA levels are, however, frequently raised in bacterial meningitis before the initiation of therapy and the value of the test may thus be limited to differentiating TBM from aseptic meningitis.⁴

An investigation of ADA levels in pleural fluid in cases of pleural effusion suggested that determination of the pleural fluid/plasma ADA ratio improved the accuracy of the test.⁵ The value of the CSF/plasma ADA ratio as an aid in the diagnosis of TBM was therefore investigated and is reported together with further experience with the absolute CSF ADA level in the diagnosis of TBM.

Departments of Paediatrics and Chemical Pathology, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

P. R. DONALD, F.C.P. (S.A.), M.R.C.P., D.T.M. & H.

CHRISTINA MALAN, F.C.P. (S.A.)

ADRI VAN DER WALT, B.S.C. HONS, M.MED. (PAED.)

J. F. SCHOEMAN, M.MED. (PAED.), F.C.P. (S.A.)

Patients and methods

This study was approved by the Ethical Committee of the Faculty of Medicine of the University of Stellenbosch.

Simultaneous plasma and CSF ADA activity was determined in four groups of patients: (i) a 'no meningitis' group; (ii) an aseptic meningitis group; (iii) a bacterial meningitis group; and (iv) a TBM group.

All patients were 13 years of age or younger with the exception of the TBM group which included 10 adults. All CSF specimens were obtained for normal clinical indications.

'No meningitis' group

This consisted of 174 children who presented to the Paediatric Outpatient Department of Tygerberg Hospital with symptoms and signs suggestive of meningitis, but who were subsequently found not to be suffering from this disease. No more than $5 \times 10^6/l$ lymphocytes were present in their CSF, Gram staining of the CSF revealed no organisms and no organisms were cultured from the CSF. The median age of these children was 19 months.

Aseptic meningitis group

This was made up of 63 children whose CSF contained more than $10 \times 10^6/l$ leucocytes. They received no antibiotic treatment before or after diagnostic lumbar puncture (LP). No bacteria were grown from the CSF and Gram staining of the CSF revealed no organisms. Viral culture was not routinely undertaken. The median age of these children was 53 months. In 40 cases simultaneous CSF and plasma ADA activity was determined and in 23 cases CSF ADA activity alone.

Bacterial meningitis group

The diagnosis in this group of 50 patients was confirmed by culture of the relevant organism from the CSF: *Neisseria meningitidis* (30 cases), *Haemophilus influenzae* (11 cases), *Streptococcus pneumoniae* (5 cases), group B β -haemolytic streptococcus (3 cases) and *Proteus mirabilis* (1 case). The CSF specimens evaluated were those obtained on admission from which the causative organism was grown. The median age of these children was 10 months. In 31 cases simultaneous CSF and plasma ADA activity was determined and in 19 cases CSF ADA activity alone.

Tuberculous meningitis group

This group of 47 patients included 37 children and 10 adults. The diagnosis of TBM was confirmed by culture of *Mycobacterium*

tuberculosis (MTB) from the CSF in 18 cases (4 adults and 14 children). In the remaining 29 cases (6 adults and 23 children) the diagnosis was made on clinical grounds — compatible history, course and CSF findings, chest radiographic changes suggestive of pulmonary tuberculosis, culture of MTB from sputum or gastric washings and tuberculin test results. Some of the diagnostic criteria for the whole group are summarized in Table I.

In 27 patients (3 adults and 24 children) simultaneous CSF and plasma ADA levels were determined, before starting therapy in 10 cases and within 1 week of the initiation of therapy in the remainder. In 20 cases (7 adults and 13 children), CSF ADA levels only were determined, before therapy in 9 cases and within 1 week in the remainder. The median age of all the children with TBM was 19 months.

In addition to the four groups described above, CSF ADA levels only were determined in two other small groups of patients: (i) a group of 7 adults with meningovascular syphilis, the diagnosis being confirmed by positive serological tests in both blood and CSF; and (ii) a group of 5 adults and 1 child with malignant involvement of the meninges.

ADA activity was assayed according to the method of Giusti⁶ as described previously.⁴

Results

The CSF/plasma ADA ratios and CSF ADA levels obtained in the different groups of patients are set out in Figs 1 and 2. In Fig. 1 ratios of 0,10 and 0,15 have been selected as decision points above which TBM (or bacterial meningitis) should be suspected. In Fig. 2 6 U/l, 5 U/l and 4 U/l have been similarly indicated.

In Table II the sensitivity and specificity of these values in detecting TBM are set out. The greatest sensitivity was achieved by a CSF ADA value of 4 U/l and the greatest specificity by a CSF/plasma ADA ratio of 0,15.

It had been previously noted that adults with TBM had considerably higher CSF ADA levels than children.⁴ In this series the mean CSF protein level in the paediatric TBM patients was 1,7 g/l and in the adults 6,73 g/l and the mean CSF ADA level in the same groups 10,38 U/l and 20,85 U/l respectively.

Meningovascular syphilis. CSF ADA levels only were determined in 7 adult patients and varied from 0,6 U/l to 12,2 U/l (mean 5,2 U/l). In 2 patients levels above 6 U/l were obtained — 12,2 U/l and 7,8 U/l.

Malignant involvement of meninges. The following CSF ADA values were obtained in the presence of meningeal malignant involvement; lymphoma 9,5 U/l, meningioma 0,5 U/l, acute myeloid leukaemia 8 U/l, chronic myeloid leukaemia 2,2 U/l, acute lymphatic leukaemia 5,8 U/l, and breast carcinoma metastases 6,9 U/l.

TABLE I. DIAGNOSTIC CRITERIA

	Tuberculin test		XRC indicative of PTB	GW or sputum positive on culture for MTB
	Done	Positive		
Confirmed TBM (18 cases)	13	8	15	7
Clinical TBM (29 cases)	25	12	24	10

XRC = chest radiograph; PTB = pulmonary tuberculosis; GW = gastric washing; MTB = *Mycobacterium tuberculosis*.

TABLE II. SENSITIVITY AND SPECIFICITY OF SUGGESTED UPPER LIMITS OF NORMAL CSF ADA IN DETECTION OF TBM

	CSF ADA (%)			CSF/plasma ADA ratio (%)	
	4 U/l	5 U/l	6 U/l	0,10	0,15
Sensitivity	85,1	70,2	63,8	81,5	63
Specificity	81,2	85,7	87,1	81,6	88,6

Sensitivity and specificity determined by conventional statistical methods.⁷

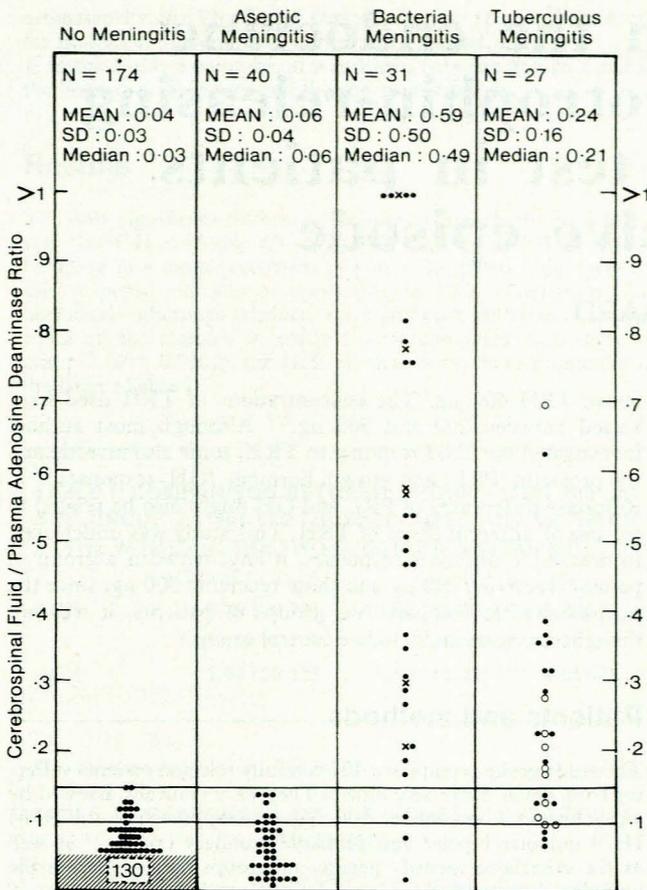


Fig. 1. CSF/plasma ADA ratio in the four study groups (o = confirmed TBM; x = bacterial meningitis — CSF cell count < 500 x 10⁶/l):

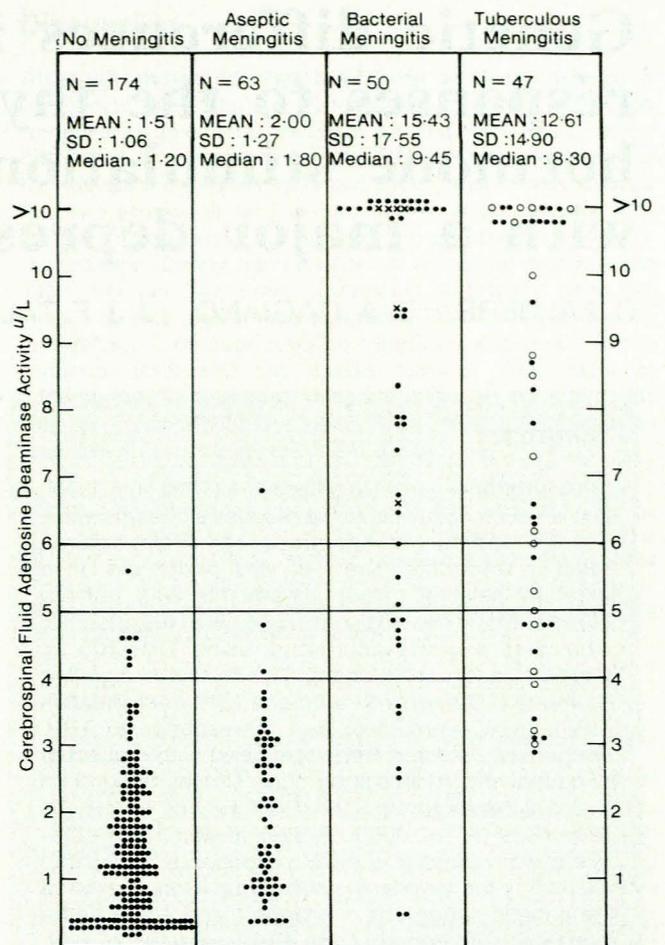


Fig. 2. CSF ADA levels in the four study groups (o = confirmed TBM; x = bacterial meningitis — CSF cell count < 500 x 10⁶/l):

	Plasma ADA values (U/l)		
	Mean	SD	Median
No meningitis	42,16	16,04	40,30
Aseptic meningitis	36,72	12,08	35,50
Bacterial meningitis	27,23	11,00	25,50
TBM	40,44	21,47	36,70

Discussion

Figs 1 and 2 demonstrate that neither the CSF/plasma ADA ratio nor CSF ADA levels are of value in differentiating TBM from other forms of bacterial meningitis. Even in the presence of a low cell count, CSF ADA levels and the CSF/plasma ratio may be markedly elevated in bacterial meningitis.

CSF/plasma ADA ratios and CSF ADA levels are, however, clearly different in TBM and aseptic meningitis cases. If the bacterial meningitis group is omitted and a CSF ADA level of 5 U/l is taken as the upper limit of normal, then a sensitivity of 70,2% and a specificity of 99,2% is achieved in the detection of TBM. Similarly, if a ratio of 0,10 is taken as the upper limit of normal, sensitivity will be 81,5% and specificity 92,6%. To compare the above results with conventional CSF criteria, a CSF protein level of 1 g/l was selected as a point above which TBM should be suspected rather than aseptic meningitis. In the TBM group 34 patients had CSF protein values above 1 g/l — a sensitivity of 72,3% — while in the 'no meningitis' group and the aseptic meningitis group no patients had a CSF protein in excess of 1 g/l — a specificity of 100%.

Our experience in this and in a previous series of cases indicates that a CSF ADA value greater than 6 U/l is not seen in 'no meningitis' cases and is very unusual in aseptic meningitis cases.⁴ Values above this level may indicate the presence of TBM, bacterial meningitis or some other malignant or infec-

tious involvement of the central nervous system.^{1,4,8} In individual cases of TBM, CSF ADA activity > 6 U/l and CSF/plasma ADA ratio > 1,5 were encountered while the results of conventional CSF investigations fell within normal or 'aseptic' limits. As with conventional CSF chemistry, CSF ADA levels and the CSF/plasma ADA ratio should be interpreted in the light of the patient's clinical condition. Normal CSF ADA levels do not exclude TBM.

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