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Clinical Practice

Radioactive Bromide Partition Test in Differential Diagnosis of Tuberculous Meningitis

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Summary

In 19 cases of lymphocytic meningitis, the radioactive bromide partition test showed that four were tuberculous and 15 viral in origin. In all the tuberculous cases the serum/cerebrospinal fluid bromide ratio was below a critical value of 1·6, and in all the cases of viral meningitis the ratio was above this value. The test may be particularly helpful when diagnosis is difficult. The test may prove to be a valuable and justified additional procedure in the early diagnosis of tuberculous meningitis.

Introduction

Tuberculous meningitis may still pose considerable diagnostic difficulties, particularly during the earlier stages of the illness, when effective therapy offers the greatest chance of success. In a high proportion of cases the initial diagnosis depends on the clinical findings and cerebrospinal fluid (C.S.F.) changes. In general acid-fast bacilli are found in the C.S.F. in only a minority of cases[1] and culture of *Mycobacterium tuberculosis* takes several weeks. The presence of abnormalities suggestive of tuberculosis in other systems of the body is helpful but is not present in every case. The disease often presents in an unfamiliar way in non-European immigrants, as emphasized by Wiseman and Mahmood[2] and Kocen and Parsons[3]. Too much reliance cannot be placed on a low sugar level in the C.S.F. as this may be normal in the early stages of tuberculous meningitis, whereas depressed levels may be found in viral meningitis.[4 5]

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In view of the serious consequences associated with a delay in instituting treatment any test which can help to establish the diagnosis is particularly welcome. As far back as 1929 Walter[6] showed that the permeability of the blood-brain barrier could be measured by estimating the partitioning of administered bromide between blood and C.S.F., expressing this as the *serum* C.S.F. bromide ratio. He found that in normal subjects the ratio remained within the range 2·9 to 3·5 (mean 3·1), whereas in cases of tuberculous meningitis it fell towards unity, indicating an increase in the permeability of the blood-brain barrier. In the 1950s several groups of workers[7–9] confirmed the value of the bromide partition test in the differential diagnosis of lymphocytic meningitis by showing that in almost all patients with tuberculous meningitis, the bromide ratio remained below 1·6, whereas higher values were found in patients with non-tuberculous lymphocytic meningitis.

The chemical method of bromide estimation used by these workers however, was cumbersome, time consuming, and gave occasional false positive results. In 1960, Crook *et al.*[10] described a simple method of estimating the bromide ratio by using ^{82}Br (radioactive bromide partition test), and the bromide ratio thus measured clearly separated two patients with tuberculous meningitis from five other patients with non-tuberculous meningitis. Despite the claimed simplicity and accuracy of the radioactive bromide partition test it remained generally unknown and no further account of its use appeared in the English medical literature, although its application and usefulness have been described in France.[11]

During 1971 we used the radioactive bromide partition test in a series of tuberculous and non-tuberculous meningitis patients to assess its value as an early diagnostic test, and our experience is described below.

Patients and Methods

Non-pregnant patients admitted to the department of infectious diseases, Monsall Hospital, with infections of the central nervous system of the lymphocytic meningitis type were included in the study. The radioactive isotope used was ^{82}Br, which has a half-life of 35·4 hours and emits beta rays of maximum energy 0·4 meV and gamma rays with energies in the

range 0·55-1·48 meV. With the modifications that radioactive ammonium bromide was used instead of sodium bromide and that children were included in the study with a dosage schedule based on body weight, the method used was otherwise similar to that described by Crook *et al.*[10] Patients over 18 years of age received a dose of 50 μCi, whereas patients below that age were given a dose of 0·6 μCi/kg body weight up to a maximum of 50 μCi.

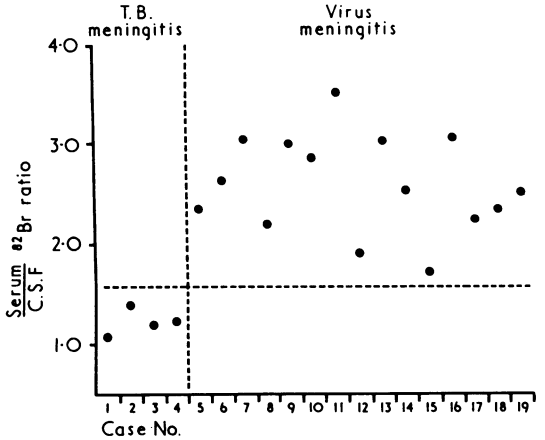
The calculated amount of radioactive ammonium bromide was given by mouth in 50 ml of water. Forty-eight hours later lumbar puncture was performed and the first 5 ml of C.S.F. and also 5 ml of clotted blood were taken for analysis. Two millilitre samples of C.S.F. and serum were pipetted into counting vials. The vials were placed in turn in a soduim iodide well scintillation counter and each sample was counted for 20 minutes. The background count was measured using an empty vial. The serum and C.S.F. counts were corrected by subtracting the background count and the ratio of corrected serum counts to corrected C.S.F. counts was calculated.

Results

The bromide ratio was measured in a total of 19 patients (Table). Four of the patients were later confirmed as suffering from tuberculous meningitis and the other 15 patients from aseptic meningitis of presumed or confirmed viral aetiology. The bromide ratio was below 1·6 in each of the tuberculous meningitis cases (range 1·1 to 1·4, mean 1·24, S.D. 0·13) but above this figure in patients with viral meningitis (range 1·7 to 3·5, mean 2·59 SD 0·49) (see Chart).

C.S.F. Findings and ^{82}Br Ratio in 19 Patients with Lymphocytic Meningitis

Case No.	Age	Sex	C.S.F. Cell	C.S.F. Protein	C.S.F. Sugar	^{82}Br Ratio	Acid-fast Bacilli in C.S.F. Smear	Guinea-pig Inoculation	Diagnosis
1	19	F.	77	410	32	1·10	−	+	T.B. meningitis
2	42	M.	230	100	44	1·40	−	−	T.B. meningitis
3	36	M.	91	100	24	1·20	−	+	T.B. meningitis
4	17	F.	153	50	39	1·25	+	+	T.B. meningitis
5	27	M.	187	73	55	2·36			Virus meningitis
6	29	F.	31	65	50	2·65			Virus meningitis
7	29	F.	8	106	75	3·07			Virus meningitis
8	19	M.	145	158	42	2·20			Virus meningitis
9	31	M.	66	82	68	3·0			Virus meningitis
10	37	F.	6	50	53	2·86			Virus meningitis
11	30	M.	285	175	65	3·50			Virus meningitis
12	26	F.	33	97	—	1·90			Virus meningitis
13	19	M.	185	100	67	3·03			Virus meningitis
14	16	M.	187	200	33	2·51			Virus meningitis
15	46	M.	285	142	42	1·70			Virus meningitis
16	14	M.	468	90	61	3·04			Virus meningitis
17	34	F.	70	60	77	2·23			Virus meningitis
18	12	M.	87	32	39	2·36			Virus meningitis
19	23	M.	120	95	65	2·50			Virus meningitis



Results of radioactive bromide partition tests in 19 patients.

Of the four tuberculous meningitis patients only Case 1 presented with typical clinical and C.S.F. pictures but, even so, gave a negative tuberculin reaction, and no acid-fast bacilli could be shown in the C.S.F. The other three patients presented varying diagnostic problems, and to illustrate the practical value of the bromide test, their cases are described in detail.

Case 2.—Male Kenyan Asian aged 42, resident in U.K. five years. This patient had been in good health apart from bilateral chronic otitis media. He presented with a six-day history of persistent headache associated with vomiting and signs of meningitis. Admission C.S.F. contained 205 white cells/mm^3 (94% lymphocytes), 40 mg sugar 100 ml, and 94 mg/100 ml protein but no demonstrable acid-fast bacilli. Although he felt somewhat better over the next two days a repeat C.S.F. examination on the third day still showed a mildly depressed sugar level of 44 mg /100 ml, 230 white cells/mm^3 (80% lymphocytes), and 100 mg protein/100 ml. Despite the absence of demonstrable acid-fast bacilli in the C.S.F. the possibility of tuberculous meningitis was entertained and triple antituberculous therapy was started. The radioactive bromide partition test at this stage gave a ratio of 1·4 and the chemotherapy was continued. A repeat test in the eighth week of treatment still showed a low value of only 1.49. Although no mycobacteria were isolated on culture or guinea-pig inoculation from the C.S.F. he later developed an enlarged left supraclavicular gland, which showed the typical histological picture of tuberculosis, thus helping to establish the diagnosis. The ultimate response to treatment was satisfactory.

Case 3.—Male Pakistani aged 36, resident in U.K. 10 years. This patient was transferred from another hospital for further diagnostic studies. Eight weeks previously he was admitted to the referring hospital with a fortnight's history of fever, shivering attacks and headache. He was regarded as a possible case of tuberculosis meningitis on the basis of suggestive C.S.F. findings. On triple antituberculous chemotherapy along with corticosteroid, he improved rapidly, but three weeks later when corticosteroids were discounted he again became unwell with a return of pyrexia and doubt arose about the original diagnosis. After his transfer to Monsall Hospital, however, the radioactive bromide partition test gave a ratio of 1.2, supporting the diagnosis, which was finally confirmed by positive results from guinea-pig inoculation. At the 14th week of treatment the ratio had risen to 2.1, by which time he was quite well.

Case 4.—East African Asian girl aged 17. This patient was transfered from another hospital as a possible case of tuberculous meningitis. She presented with a 10-day history of fever, vomiting, and headache. Admission C.S.F. contained 60 white cells/mm^3 (80% polymorphs), 60 mg sugar/100ml, 60 mg protein/100 ml; no acid-fast bacilli were seen. Initially regarded as a case of virus meningitis the possibility of tuberculous infection was considered when she remained ill after two days in hospital. Repeat C.S.F. showed 153 white cells/mm^3 (60% polymorphs, 40% lymphocytes), 39 mg sugar/100 ml, and 50 mg/100 ml, with two doubtful acid-fast bacilli in the stained smear. She was put on antituberculous chemotherapy, and on transfer to Monsall Hospital the radioactive bromide partition test gave a ratio of 1.25, supporting the diagnosis. Guinea-pig inoculation was later positive. The ratio was still low (1.39) in the sixth week of treatment.

In these four cases of tuberculous meningitis acid-fast bacilli could be shown in stained films in only one (Case 4), although guinea-pig inoculation was eventually positive in three patients (Cases 1, 3, and 4). No bacteriological confirmation was forthcoming in Case 2, the diagnosis being supported by subsequent lymph node biopsy findings. In this case measurement of the bromide ratio gave valuable support to the early clinical suspicion of tuberculosis based chiefly on the racial origin of the patient and the mildly depressed C.S.F. sugar levels. The value of the test was all the more evident in view of the subsequent negative guinea-pig inoculation.

The observation by earlier workers that the use of antituberculous chemotherapy did not affect the ratio in the early stages of treatment[9 10] was supported by the finding of persistently low values of the bromide ratio in Case 3 on the 37th day of treatment, in Case 2 in the eighth week of treatment, and in Cise 4 in the sixth week of treatment. In Case 3 the

ratio had returned to normal by the 14th week of treatment.

The value of the radioactive bromide partition test in excluding tuberculous meningitis is illustrated by the following three cases.

Case 13.—This 19-year-old English man was admitted to hospital with a five-day history of sore throat, headache, vomiting, and meningism. He was ill-looking, anaemic, and had signs of meningitis. C.S.F. on admission showed 36 white cells/mm^3 (70% polymorphs 30% lymphocytes) and 53 mg/100 ml sugar and 80 mg/100 ml protein. He remained ill and febrile, and a repeat C.S.F. a week later showed some deterioration, with 145 white cells/mm^3 (90% lymphocytes) and 42 mg/100 ml sugar and 158 mg/100 ml protein. The possibility of tuberculous meningitis was then considered, but as the bromide ratio at that time was 2·2 chemotherapy was withheld, and thereafter he improved rapidly. An echovirus type 4 was later isolated from the C.S.F. and guinea-pig inoculation was negative.

Case 14.—A 16-year old English boy was admitted with a two-week history of backache, headache, vomiting, and abdominal pains. He had signs of meningitis. C.S.F. on admission contained 245 white cells/mm^3 (84% lymphocytes) and 49 mg/100 ml sugar and 146 mg/100 ml protein. Although initially regarded as a case of virus meningitis, the possibility of tuberculosis infection arose when he remained ill and febrile after five days in hospital. Repeat C.S.F. showed a further rise in protein (200 mg) and a depression of the sugar level (33 mg/100 ml). The bromide ratio, however, was 2.5 and antituberculous treatment was withheld. He then recovered rapidly and uneventfully.

Case 15.—A 46-year-old Pakistani man was admitted with a six-day history of headache, vomiting, and photophobia. He also complained of persistent cough for seven months. Admission C.S.F. showed 285 white cells/mm^3 (90% lymphocytes), 42 mg/100 ml sugar and 142/100 ml protein. The possibility of tuberculous infection was considered but a radioactive bromide partition test gave a ratio of 1.7. No treatment was given and he made a rapid and complete recovery.

Each of the above three patients gave rise to diagnostic difficulty because of such features as persistent illness and fever, usually high C.S.F. protein levels, or depressed C.S.F. sugar levels, and all illustrate the value of the radioactive bromide partition test in helping to exclude the possibility of tuberculous meningitis.

Conclusions

Our findings illustrate the value of the radioactive bromide partition test in the differential diagnosis of lymphocytic meningitis. Using the figure of 1·6 as the critical bromide ratio value we found the test 100% accurate in both the tuberculous and non-tuberculous groups, though admittedly the numbers of cases were not large. The test is simpler and seems to be more accurate than the time-consuming chemical method of bromide estimation, with which Taylor *et al.*[7] and Nicol and Fawns[9] obtained 7% and 10% false-positives respectively in patients with non-tuberculous lymphocytic meningitis. Since treatment with antituberculous drugs does not affect the bromide ratio in the early stages chemotherapy can begin immediately in highly suspicious cases without affecting the diagnostic value of the test. Hence we think that the radioactive bromide partition test is a valuable additional procedure for the early diagnosis of tuberculous meningitis and merits further study and wider application.

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Mayhew's Medicine

Arthritis as an Engineering Problem: Leeds and London

FROM A SPECIAL CORRESPONDENT

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This is the first of an occasional series of articles in which a special correspondent will describe the work of units in which medical research is closely combined with other scientific disciplines.

The bones and joints are the most obviously mechanical parts of the body, so that orthopaedics and rheumatology are logical points of contact between mechanical engineering and medicine. Indeed the early research done in the Biomechanics Unit at Imperial College, London, was on the strength and stiffness of the metal fixation devices used by orthopaedic surgeons in the management of fractures. This work was then extended to a study of the mechanical properties of bone, including its fatigue characteristics but—as was perhaps inevitable in a unit whose medical partner spends so much time dealing with patients with arthritis—the current major preoccupation at the Imperial College unit is a hypothesis of the pathogenesis of osteoarthritis.

Dr. S. A. V. Swanson and Mr. M. A. R. Freeman—respectively engineer and surgeon—take the view that the primary defect in degenerative arthritis is a disturbance in the load-carrying function of the articular cartilage. It has been known for many years that there is a reduction in the mucopolysaccharide content of cartilage in arthritic joints, and it may be, they suggest, that this biochemical change occurs early on. Whatever the cause of the mucopolysaccharide depletion, it is accompanied by a reduction in the mechanical strength and stiffness of the cartilage. Another possibility, now being examined in the Unit, is that the cartilage suffers fatigue failure