



Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study

Guy E Thwaites, Jeremy Macmullen-Price, Tran Thi Hong Chau, Pham Phuong Mai, Nguyen Thi Dung, Cameron P Simmons, Nicholas J White, Tran Tinh Hien, David Summers, Jeremy J Farrar

Summary

Background Adjunctive dexamethasone increases survival from tuberculous meningitis, but the underlying mechanism is unclear. We aimed to determine the effect of dexamethasone on cerebral MRI changes and their association with intracerebral inflammatory responses and clinical outcome in adults treated for tuberculous meningitis.

Methods Cerebral MRI was undertaken, when possible, at diagnosis and after 60 days and 270 days of treatment in adults with tuberculous meningitis admitted to two hospitals in Vietnam. Patients were randomly assigned either dexamethasone (n=24) or placebo (n=19) and received 9 months of treatment with standard first-line antituberculosis drugs. We assessed associations between MRI findings, treatment allocation, and resolution of fever, coma, cerebrospinal fluid inflammation, and neurological outcome.

Findings 83 scans were done for 43 patients: 19 given placebo, 24 given dexamethasone. Basal meningeal enhancement (82%) and hydrocephalus (77%) were the most common presenting findings. Fewer patients had hydrocephalus after 60 days of treatment with dexamethasone than after placebo treatment ($p=0.217$). Tuberculomas developed in 74% of patients during treatment and in equal proportions in the treatment groups; they were associated with long-term fever, but not relapse or poor clinical outcome. The basal ganglia were the most common site of infarction; the proportion with infarction after 60 days was halved in the dexamethasone group (27% vs 58%, $p=0.130$).

Interpretation Dexamethasone may affect outcome from tuberculous meningitis by reducing hydrocephalus and preventing infarction. The effect may have been under-estimated because the most severe patients could not be scanned.

Introduction

More than half of patients with tuberculous meningitis are disabled by or die from the disease, but the underlying mechanisms responsible for the poor outcome are not well understood.¹ The disease is characterised by a necrotising granulomatous inflammatory response, which predominantly affects the structures of the midbrain and the hindbrain.² Inflammatory exudate can obstruct the flow of cerebrospinal fluid (CSF) and cause hydrocephalus. Adhesions can compromise cranial nerves and an obliterative vasculitis of both large and small vessels can result in infarction and stroke syndromes. Granulomas can coalesce to form tuberculomas, causing diverse clinical problems depending on their size and location.

There are few interventions available to prevent or treat these life-threatening complications. We undertook a controlled trial³ of dexamethasone in 545 Vietnamese adults with tuberculous meningitis. The findings showed that dexamethasone improved survival but did not prevent severe disability. To determine how dexamethasone exerted its effect we examined the kinetics of the inflammatory response in peripheral and CSF specimens from 87 adults recruited to the trial. Dexamethasone did not seem to improve outcome by

attenuating immunological mediators of inflammation in the subarachnoid space or by suppressing peripheral T-cell response to mycobacterial antigens.⁴ These findings challenged previously held theories of corticosteroid action in this disease, although the study was limited to sampling blood and CSF at infrequent timepoints and these data were not linked to the presence or development of inflammatory exudates, hydrocephalus, infarction, and tuberculomas.

The effect of dexamethasone on these common complications of tuberculous meningitis has not been well studied. Schoeman and colleagues⁵ did a randomised controlled trial of adjunctive corticosteroids in South African children with the disease and assessed the effect of these drugs on direct measurements of intracranial pressure, serial cerebral CT, and clinical outcome. The trial showed improved survival in the corticosteroid group, but no difference in intracranial pressure, ventricular size, or extent of infarction between those treated with or without corticosteroids. The authors postulated that corticosteroids exerted a beneficial effect by reducing basal meningeal inflammation and associated brain-stem encephalopathy, but suggested that the drugs did not modify infarct-causing periarthritis.

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See [Reflection and Reaction](#)

page 203

Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam

(G E Thwaites MRCP,

C P Simmons PhD,

N J White FRCP, J J Farrar FRCP);

Centre for Molecular

Microbiology and Immunity,

Imperial College, London, UK

(G E Thwaites); Department of

Neuroradiology, Western

General Hospital, Edinburgh,

UK (J Macmullen-Price FRCP,

D Summers FRCP); Hospital for

Tropical Diseases, Ho Chi Minh

City, Vietnam

(T Thi Hong Chau MD,

P Phuong Mai MD,

N Thi Dung MD, T Tinh Hien MD);

and Centre for Tropical

Medicine, Nuffield Department

of Clinical Medicine, John

Radcliffe Hospital, Oxford, UK

(C P Simmons, N J White,

J J Farrar)

Correspondence to:

Dr Guy E Thwaites, Centre for

Molecular Microbiology and

Immunity, Flowers Building,

Imperial College, London

SW7 2AZ, UK

guy.thwaites@btinternet.com

To further examine the mechanism of action of dexamethasone in the treatment of tuberculous meningitis we undertook serial MRI on a cohort of adults with the disease recruited consecutively to our controlled trial of dexamethasone. These patients also had serial measurements of CSF inflammatory mediators. Our aim was to describe the cerebral MRI changes seen in adults treated for tuberculous meningitis and to determine the effect of dexamethasone on those changes and their association with intracerebral inflammatory responses and clinical outcome.

Methods

Participants

A randomised, double-blind, placebo-controlled trial of adjunctive dexamethasone for the treatment of tuberculous meningitis was undertaken in 545 adults between April, 2001, and April, 2003, according to methods described previously.³ Two centres in Ho Chi Minh City, Vietnam, recruited patients to the study: Pham Ngoc Thach Hospital for tuberculosis and lung disease (n=452) and the Hospital for Tropical Diseases (n=93). Randomisation was stratified according to hospital of entry and disease severity grade. The effects of dexamethasone on intracerebral immune response and cerebral MRI appearances were studied in all adults recruited at the Hospital for Tropical Diseases from January, 2002, onwards (n=50). Adults (>14 years) with definite, probable, or possible tuberculous meningitis were eligible to enter the trial, as defined previously.³

The ethical and scientific committees of the hospitals, the health services of Ho Chi Minh City, and the Oxford Clinical Research Ethics Committee approved the study protocols. Written informed consent to participate in the study was obtained from all patients or their relatives.

Procedures

All patients received standard first-line antituberculosis drugs for 9 months.³ Additionally, patients were randomly allocated to start dexamethasone sodium phosphate or placebo as soon as possible after the start of antituberculosis treatment. Those with a Glasgow coma score less than 15 or focal neurological deficit at the start of treatment received intravenous drugs for 4 weeks (0.4 mg/kg per day for week 1, 0.3 mg/kg per day week 2, 0.2 mg/kg per day week 3, 0.1 mg/kg per day week 4) followed by 4 mg total of oral drug, reduced each week by 1 mg until zero was reached. Those without coma or neurological signs received intravenous drug for 2 weeks (0.2 mg/kg per day week 1, 0.1 mg/kg per day week 2), followed by the same oral reducing course described above. None of the patients received antiretroviral drugs or any second-line antituberculosis drugs and ventricular-peritoneal shunting was not offered to any of the patients.

Serial paired CSF and peripheral blood samples were obtained from all patients before and after starting the

study drug (days 3, 7, 30, 60, and 270) as part of normal clinical care. CSF concentrations of leucocytes, lactate, glucose, and protein were measured by standard methods. All other measurements were done on aliquots of CSF supernatant frozen at -70°C. All patients were tested for antibodies to HIV-1 and HIV-2, although antiretroviral drugs were not available at the time of the study.

Cerebral MRI was undertaken on a 1.5T MR system (General Electric, USA) at the start of treatment and as close as possible to 60 days and 270 days thereafter. The scanner was located outside the hospital and patients could only be scanned if medically stable and fit for transfer to this facility. The reasons for missed scans were not recorded. The principal MRI sequences included T1 and T2 axial and post-contrast axial T1 cranial imaging. The scans were reviewed by two experienced neuroradiologists unaware of treatment allocation and patient outcome.

Systematic assessment of the imaging studies was undertaken with discrepancies between reviewers agreed by consensus. The features recorded were the abnormal enhancement of the leptomeninges (basal, sylvian fissure, convexity and ependymal), the presence, number, and distribution of tuberculomas (defined as a focal punctate area of parenchymal, ependymal, or leptomeningeal enhancement), hydrocephalus (pan-ventricular or localised, communicating or non-

	Placebo (n=19)	Dexamethasone (n=24)	Total (n=43)
Male sex	12 (63%)	15 (63%)	27 (63%)
Age (years)	32 (18–66)	24 (15–59)	31 (15–66)
Weight (kg)	49 (33–61)	47 (43–73)	47 (33–73)
HIV infection	1 (5%)	0	1 (2%)
Duration of symptoms (days)	17 (5–60)	18 (5–45)	17 (5–60)
Tuberculous meningitis diagnosis			
Definite	12 (63%)	15 (63%)	27 (63%)
Probable	3 (16%)	4 (17%)	7 (16%)
Possible	4 (21%)	5 (21%)	9 (21%)
BMRC grade			
I	6 (32%)	8 (33%)	14 (33%)
II	11 (58%)	8 (33%)	19 (44%)
III	2 (11%)	8 (33%)	10 (23%)
Temperature (°C)	38.6 (37.0–40.0)	39.0 (37.0–41.0)	38.9 (37.0–41.0)
Cerebrospinal fluid			
Opening pressure (cm H ₂ O)	18 (5–40); [n=18]	25 (7–40); [n=23]	22 (5–40); [n=41]
White cell count (× 10 ⁶ /mL)	275 (51–1120); [n=18]	240 (10–1880)	260 (10–1880); [n=42]
% neutrophil	29 (2–80); [n=18]	32 (2–90)	30 (2–90); [n=42]
% lymphocytes	71 (20–98); [n=18]	68 (10–98)	70 (10–98); [n=42]
Total protein (mg/L)	1980 (500–5710)	2000 (840–7200)	2000 (500–7200)
Lactate (mmol/L)	6.1 (2.3–13.5); [n=16]	5.9 (2.8–15.1); [n=20]	6.2 (2.3–15.1); [n=36]
CSF:plasma glucose	0.28 (0.06–0.72)	0.25 (0.04–0.45)	0.25 (0.04–0.72)

Data are number (%) or median (range). Number and denominator given only when there are missing values.

Table 1: Baseline characteristics of patients with one or more MRI scans

	MRI (n=22)	No MRI (n=28)	p
BMRC grade			0.604
I	7 (32%)	7 (25%)	
II	10 (46%)	11 (39%)	
III	5 (23%)	10 (36%)	
Cranial nerve palsy	9 (41%)	12 (43%)	>0.999
Hemiplegia	4 (18%)	7 (25%)	0.734
Glasgow coma score	14 (6–15)	13 (3–15)	0.603
Glasgow coma score <11	5 (23%)	10 (36%)	0.367
Dead after 9 months of treatment	3 (14%)	9 (32%)	0.186

Data are number (%) or median (range).

Table 2: Comparison of disease severity at start of treatment in patients with or without cerebral MRI at baseline

	Placebo (n=10)	Dexamethasone (n=12)	Total (n=22)
Enhancement	8 (80%)	10 (83%)	18 (82%)
Basal meninges	5 (50%)	7 (58%)	12 (55%)
Sylvian fissure	4 (40%)	9 (75%)	13 (59%)
Convexity	5 (50%)	8 (67%)	13 (59%)
Posterior fossa	0	0	0
Ventricular	1 (10%)	1 (8%)	2 (9%)
Hydrocephalus	7 (70%)	10 (83%)	17 (77%)
Communicating	6 (60%)	7 (58%)	13 (59%)
Infarction	1 (10%)	1 (8%)	2 (9%)
Tuberculoma	5 (50%)	9 (75%)	14 (64%)
Parenchymal	3 (30%)	5 (42%)	8 (36%)
Ependymal	0	3 (25%)	3 (14%)
Meningeal	2 (20%)	3 (25%)	5 (23%)

Data are number (%) or median (range).

Table 3: MRI characteristics at baseline

communicating), and the presence, number, and distribution of infarcts. Hydrocephalus was defined as the presence of dilated temporal horns, or dilated lateral and third ventricles with or without a dilated fourth ventricle (the fourth ventricle is usually the last ventricle to dilate). Communicating hydrocephalus was defined as enlargement of the ventricles, without evidence of an obstructing lesion along the intraventricular CSF pathways down to the level of C1, including the fourth ventricular outflow tracts and the cerebral aqueduct.

The primary clinical outcome was death or severe disability 9 months after randomisation, assessed by methods described elsewhere.³ The results of a neurological examination were also recorded at this time. Secondary outcome measures included time to fever and coma resolution. The time to coma resolution was defined as the interval (days) from randomisation to the time when a Glasgow coma score of 15 was reached and sustained for more than 2 consecutive days. Only patients who entered with a Glasgow coma score of less than 15 could enter the analysis. Fever clearance time

was defined as the interval from randomisation to observe a maximum daily temperature of less than 37.5°C for more than 5 consecutive days. All patients were febrile (temperature >37.5°C) at randomisation. Neurological relapse was also documented, defined as the onset of new focal neurological signs or a fall in Glasgow coma score of 2 points or more for 2 or more days, following greater than 7 days clinical stability or improvement at any time after randomisation. All definitions were set a priori.

Local and peripheral immune responses were assessed blind to clinical outcome and treatment allocation by methods previously described.⁴ Briefly, CSF cytokines (interferon γ , interleukin 6, interleukin 10, interleukin 1 β , tumour necrosis factor, interleukin 8, interleukin 12p70) and chemokines (interferon-inducible protein 10 [IP 10], monocyte-chemotactic protein 1 [MCP 1], regulated on activation normal T expressed and secreted [RANTES], and monokine induced by interferon γ [MIG]) were measured using a cytometric bead array assay (Becton Dickinson, San Diego, USA). Blood–brain barrier integrity was assessed by measurement of paired CSF and plasma albumin concentrations by standard methods with calculation of the albumin index using the formula $[\text{albumin}_{\text{csf}}]/[\text{albumin}_{\text{plasma}}]$.

Statistical analysis

The methods for primary and stratified subgroup analysis of death and disability are reported elsewhere.³ Continuous variables were compared by the Student's *t* test if normally distributed and the Mann-Whitney *U* test if not normally distributed. Categorical variables were compared by the χ^2 test (or Fisher's exact test when appropriate). A 5% level of significance was used in all analyses. Multiple univariate comparisons using the tests described above were made to investigate associations between MRI findings and clinical and inflammatory parameters. Nine clinical variables entered the analysis (age, sex, disease severity grade, duration of symptoms, weight, Glasgow coma score, body temperature, and the presence of cranial nerve palsies and hemiplegia) and 13 CSF parameters (white-cell count, concentrations of neutrophils, lymphocytes, and total protein, CSF: blood glucose concentration, interferon γ , tumour necrosis factor, interleukin 6, interleukin 10, interleukin 8, MCP 1, RANTES, and albumin index). Results of this analysis were interpreted with caution because of the multiple comparisons and the increased probability of associations occurring by chance. Bonferroni adjustments were not used for reasons discussed by Perneger.⁶ Time to fever clearance, resolution of coma, and neurological relapse were summarised using Kaplan-Meier estimates and compared between patients with different MRI appearances using the log-rank test. All *p* values were two sided. All analysis was undertaken using SPSSv10 (SPSS, Chicago, IL, USA).

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

83 scans were available for analysis from 43 patients (19 given placebo, 24 given dexamethasone). Seven patients died before any scans could be taken (two given dexamethasone, five given placebo) and five patients died after one or more scans had been undertaken (three given placebo, two given dexamethasone). More scans were available from patients given dexamethasone ($n=46$) than placebo ($n=37$) because of the better outcome in the dexamethasone group. In total, 18 patients had one scan (two scanned at day 0, five scanned at day 60, and 11 scanned at day 270 of treatment); 11 patients had two scans (three scanned at days 0 and 60, three scanned at days 0 and 270, and five scanned at days 60 and 270); and 14 patients were scanned on days 0, 60, and 270. Only one patient was infected with HIV (all patients were tested). All patients received a full course of study drug started on the same day as the anti-tuberculosis drugs.

Table 1 shows the baseline clinical variables of the 43 patients with one or more MRI scans for analysis. 22 patients had a scan at the start of treatment; 28 patients were not able to be scanned at this time. A comparison of disease severity of those scanned and not scanned is presented in table 2 and shows that higher proportions of the unscanned group had more severe disease and were less likely to survive 9 months of treatment than the scanned group, although the differences were not significant ($p>0.05$).

Baseline MRI revealed that meningeal enhancement and hydrocephalus were common features at diagnosis, whereas infarction was rare (table 3). One or more tuberculoma were reported in nearly two-thirds of patients, most of which were seen within the cerebral parenchyma. Figure 1 shows examples of common MRI findings.

Univariate analysis was done to assess whether MRI findings on admission were associated with any of the nine presenting clinical features and 13 CSF inflammatory parameters. Hydrocephalus was associated with long median duration of symptoms before treatment (hydrocephalus 20 days, range 5–60; no hydrocephalus 10 days, range 7–13; $p=0.005$). Tuberculomas were associated with high median bodyweight (tuberculomas 50 kg, 45–73; no tuberculomas 45 kg, 33–60; $p=0.006$). No other significant associations ($p<0.05$) were found.

Figure 2 shows the effect of dexamethasone on the proportion of patients with enhancement, hydrocephalus, infarction, and tuberculoma during the 270 days of treatment. A significant number could not be scanned at each timepoint. Recovery was assessed at days 60 and 270

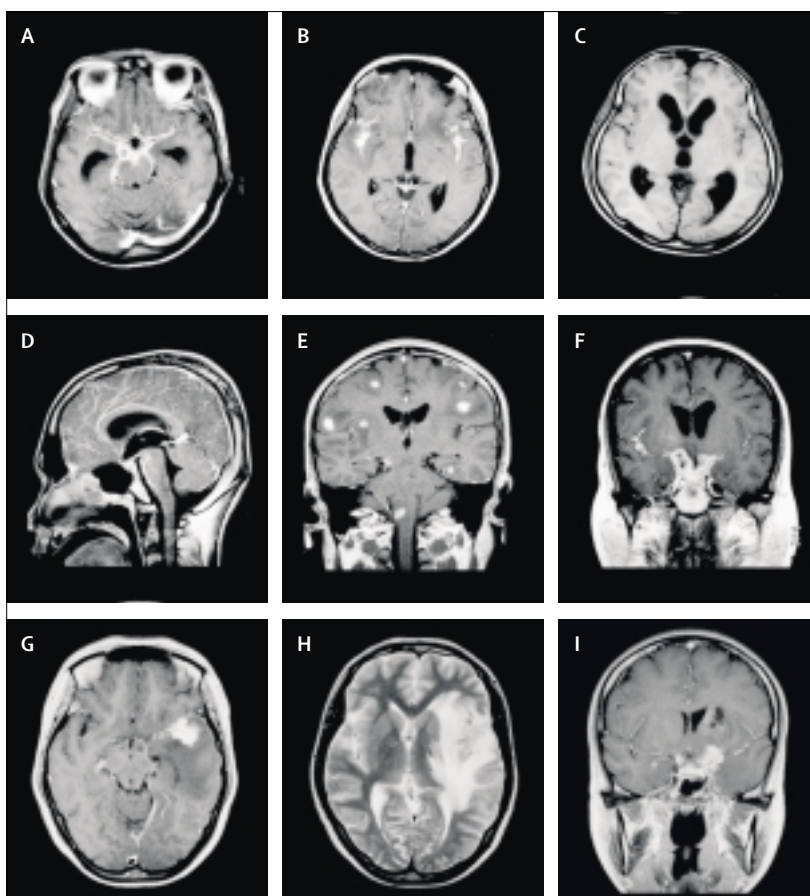


Figure 1: Common MRI findings in adults with tuberculous meningitis

A: Contrast enhanced axial T1-weighted image reveals thick leptomeningeal enhancement in suprasellar cistern extending into sylvian fissures and ambient cisterns. Temporal horns are also dilated. B: Contrast enhanced axial T1-weighted image reveals leptomeningeal enhancement within cortical sulci and sylvian fissures. Diffuse low signal around sylvian fissures suggests oedematous change. C: Axial T1-weighted image reveals hydrocephalus with dilated lateral and third ventricles. D: Sagittal T1-weighted image following intravenous contrast administration. There is prominent enhancement in the pituitary fossa and along the hypothalamus. The aqueduct of sylvius is clearly patent and third ventricle is dilated. E: Contrast enhanced coronal T1-weighted image. Multiple enhancing nodules, principally parenchymal but also ependymal and leptomeningeal. F: Contrast enhanced coronal T1-weighted image. Marked basal and right sylvian fissure leptomeningeal enhancement is present. Lateral ventricles are dilated. G: Enhanced axial T1-weighted image. There is a large nodular focus of enhancement within the left sylvian fissure extending into the left temporal lobe associated with substantial low-signal change. H: Axial T2-weighted image reveals extensive high signal within left cerebral hemisphere with large heterogeneous signal tuberculoma in sylvian fissure. I: Gadolinium-enhanced T1 coronal imaging showing extensive basal meningeal enhancement and established left capsulostriate lacunar infarct.

by the modified Rankin disability score (mRS).³ Only one of 23 (4%) patients not scanned had recovered completely by day 60 compared with seven of 27 (26%) who were scanned. Furthermore, 13 of 22 (59%) not scanned were either dead or severely disabled at day 60 compared with eight of 27 (30%) who were scanned. All survivors were scanned at day 270, apart from four patients who did not attend the MRI appointment. These four patients all made a complete recovery (mRS=1).

There was no significant reduction in the proportion of patients with meningeal enhancement or hydrocephalus at days 60 or 270 of treatment in those given dexamethasone compared with placebo (figure 2). The basal meninges

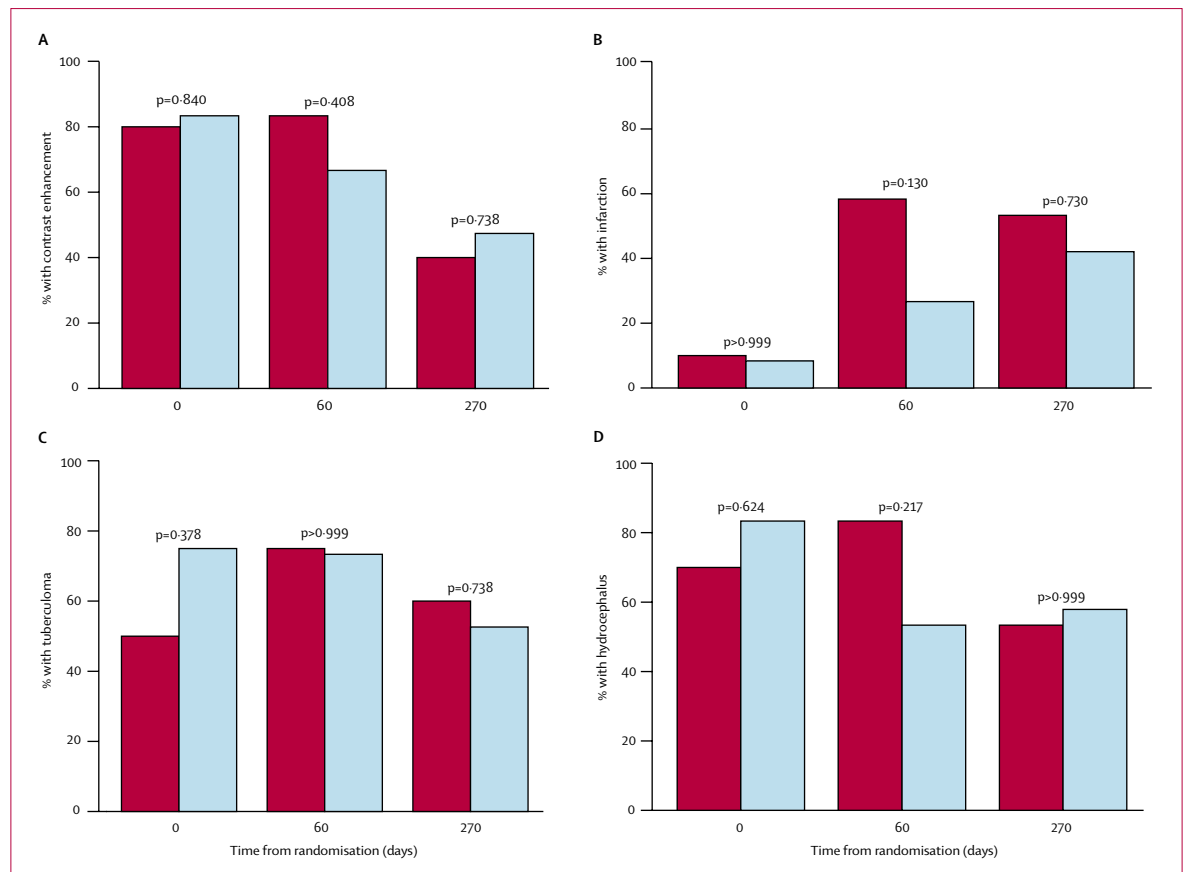


Figure 2: Effect of dexamethasone on MRI appearances of tuberculous meningitis during treatment

Proportions of patients with post-contrast enhancement (A), cerebral infarcts (B), tuberculomas (C), and hydrocephalus (D) before and after treatment with dexamethasone (blue bars) or placebo (red bars).

and the sylvian fissure were the most common structures to enhance throughout treatment, although dexamethasone did not seem to affect the site, degree, or duration of enhancement (data not shown). Hydrocephalus was identified in 17 of 22 (77%) patients at baseline and 18 of 27 (67%) on day 60; the proportion with communicating hydrocephalus fell from 13 of 17 (77%) at baseline to five of 18 (28%) after 60 days of treatment. There was no significant difference between the treatment groups.

The proportion of patients with one or more tuberculomas rose after the start of treatment from 14 of 22 (64%) before treatment to 20 of 27 (74%) after 60 days. The location of the tuberculomas changed during treatment from predominantly affecting the cerebral parenchyma before treatment (eight of 14 [57%]) to mostly affecting the meninges after 60 days (19 of 20 [95%]) and 270 days (14 of 19 [74%]) of treatment. Dexamethasone did not affect the site or the total numbers of tuberculomas reported (data not shown) or the proportion of patients with one or more tuberculoma at days 60 or 270 of treatment (figure 2).

Although infarction was rare at presentation (two of 22 [9%]) it was reported in 11 of 27 (41%) after 60 days of

treatment. A smaller proportion occurred in those treated with dexamethasone (27%) than in those treated with placebo (58%, $p=0.13$; figure 2). Infarction predominantly involved the basal ganglia and the internal capsule. All of the infarcts reported on day 0 (two of two) and at day 60 (11 of 11) involved the basal ganglia; three of 11 patients also had internal capsule infarction at day 60 of treatment. Infarcts of the corpus callosum ($n=1$) and the cerebral cortex supplied by the middle cerebral artery ($n=1$) were also reported. Dexamethasone did not seem to affect the location of the infarcts (data not shown).

After 60 days of treatment, associations were sought between enhancement, hydrocephalus, infarction, and tuberculomas seen on MRI and nine clinical features and 13 CSF inflammatory parameters. Significant associations ($p<0.05$) are presented in tables 4–6. Hydrocephalus was associated with a persistent inflammatory response with raised CSF concentrations of protein, interferon γ , interleukin 10, and interleukin 6. The presence of tuberculomas was also associated with increased numbers of white cells in the CSF, a higher proportion of which were neutrophils, and increased concentrations of protein, interleukin 6, and

interleukin 10. Infarction was associated with reduced CSF:plasma glucose ratio, increased concentrations of interleukins 8 and 10 in CSF, and greater impairment of blood–brain barrier dysfunction (as assessed by albumin index). No significant associations were shown between contrast enhancement on MRI and any of the clinical or CSF parameters.

Multivariate analysis of variables independently associated with MRI appearances at baseline and after 60 days of treatment was attempted, but was impossible because the number of observations was fewer than the number of parameters in the model.

MRI appearances at diagnosis or after 60 days of treatment were not associated ($p > 0.05$) with death or disability after 9 months of treatment (data not shown). 34 patients were scanned and examined at the end of treatment. 14 recovered without any neurological sequelae, although MRI revealed meningeal enhancement in one, hydrocephalus in three, infarction in five, and tuberculoma in seven. 16 patients were left with some neurological symptoms but could live independently; their MRI revealed enhancement in seven, hydrocephalus in 13, infarction in eight, and tuberculoma in nine. Four patients were severely disabled at the end of treatment and MRI showed enhancement in two, hydrocephalus in three, infarcts in three, and tuberculoma in three.

Although there were no significant associations with fever clearance or coma resolution and MRI findings at diagnosis, median fever clearance times were significantly longer in those with tuberculoma seen on MRI at day 60 of treatment (median time 6 vs 12 days, $p = 0.018$) than in those without tuberculoma. Only hydrocephalus seen on day 60 was clearly associated with prolonged coma resolution (median 16 vs 4 days, $p = 0.004$). Tuberculosas seen at day 60 had no significant effect on coma resolution times. Seven patients relapsed neurologically during treatment, but there were no significant associations between MRI findings at baseline or 60 days and relapse (data not shown).

Discussion

The results provide important clinical data for use of MRI to assess treatment responses in tuberculous meningitis and important pathophysiological data for how dexamethasone might act to improve outcome from tuberculous meningitis by reducing hydrocephalus and preventing infarction.

There are some important limitations to the study. In particular, there were a large number of missing scans, predominantly from patients with more severe disease. As a result, comparisons of the MRI findings between the two treatment groups were not based on the same group of patients at each timepoint. This scenario is especially problematic when comparing data across timepoints. Additionally, more patients in the placebo group than in the dexamethasone group did not complete the study because of death. Consequently, the effect of

	Hydrocephalus (n=18)	No hydrocephalus (n=9)	p
Protein (mg/L)	2100 (360–5500); [n=17]	800 (270–2470)	0.009
Interferon γ (pg/mL)	312.1 (14.6–12074.2); [n=16]	38.4 (0.1–163.5); [n=8]	0.002
Interleukin 10 (pg/mL)	30.3 (14.6–133.7); [n=16]	9.2 (0.1–14.4); [n=8]	0.006
Interleukin 6 (pg/mL)	408.9 (35.9–1429.0); [n=16]	89.6 (9.9–340.1); [n=8]	0.004

Number and denominator given only when there are missing values.

Table 4: CSF variables significantly ($p < 0.05$) associated with hydrocephalus on MRI after 60 days of treatment

	Tuberculoma (n=20)	No tuberculoma (n=7)	p
Total white cell count ($\times 10^6$ /mL)	120 (24–600)	30 (4–180)	0.040
Percent neutrophils/lymphocytes	10 (2–39) / 90 (61–98)	2 (0–20) / 98 (80–100)	0.025
Protein (mg/L)	1980 (600–5500)	700 (270–2260)	0.030
Interleukin 10 (pg/mL)	27.9 (0.1–133.7); [n=16]	7.6 (0.1–21.9); [n=6]	0.042
Interleukin 6 (pg/mL)	325.7 (14.3–1429.0); [n=18]	89.6 (9.9–490.9); [n=6]	0.004

Number and denominator given only when there are missing values.

Table 5: CSF variables significantly ($p < 0.05$) associated with tuberculoma on MRI after 60 days of treatment

	Infarction (n=11)	No infarction (n=16)	p
CSF:plasma glucose	0.37 (0.28–0.52)	0.43 (0.32–0.84)	0.038
Interleukin 10 (pg/mL)	46.2 (6.6–133.7); [n=8]	14.2 (0.1–36.6); [n=12]	0.040
Interleukin 8 (pg/mL)	1219.5 (187.3–2280.5); [n=8]	312.8 (36.9–1589.9); [n=12]	0.026
Albumin index	2.70 (1.10–11.02); [n=7]	0.62 (0.04–2.43); [n=11]	0.004

Number and denominator given only when there are missing values.

Table 6: CSF variables significantly ($p < 0.05$) associated with infarction on MRI after 60 days of treatment

dexamethasone on the major complications of tuberculous meningitis (infarction and hydrocephalus) might have been under-estimated as only survivors with less severe disease tended to be scanned.

The MRI appearances described at baseline of patients in this study are similar to those reported in previous studies.⁷ Hydrocephalus and basal meningeal enhancement were the most common presenting findings, with hydrocephalus occurring most often in those with a long duration of symptoms. Hydrocephalus seen after 60 days of treatment was associated with long-term coma and a protracted inflammatory response within the CSF, although conclusions from this analysis must be interpreted with caution in view of the multiple comparisons undertaken.

The role of dexamethasone in treating hydrocephalus is uncertain. Analysis from all patients recruited to the trial showed that dexamethasone was associated with faster defervescence but not with reduced coma resolution times³ and this study did not show dexamethasone to significantly reduce hydrocephalus at days 60 and 270 of treatment. Many authorities advocate ventricular–peritoneal shunts for the treatment of hydrocephalus associated with tuberculous meningitis, especially in

those with non-communicating hydrocephalus or in those with persistent coma.⁸ Neurosurgical intervention was not available to our patients, which affects the generalisability of the controlled trial results. However, these MRI data do not suggest dexamethasone's effect on survival occurs primarily by treating and preventing hydrocephalus. Indeed, the increased proportion of patients with non-communicating hydrocephalus between baseline and 60 days of treatment (28% to 72%) suggests that ventricular–peritoneal shunting should be considered in all those with hydrocephalus who do not respond to medical treatment.

Tuberculomas have been considered a well-described but relatively rare complication of tuberculous meningitis. Indeed, their occurrence has been the subject of several case reports, often under the headline of paradoxical treatment reactions.⁹ Therefore, to find 74% of patients had tuberculomas evident on MRI after 60 days of treatment was surprising. To the best of our knowledge this is the first published prospective study to report serial MRI in a cohort of patients with tuberculous meningitis. Previous MRI studies have only scanned selected symptomatic patients (deteriorating on treatment, for example). Our data suggest tuberculomas form in most patients during treatment, predominantly within the meninges, and could be a typical rather than a paradoxical aspect of disease resolution. Their presence was associated with a prolonged fever clearance time and inflammation in the CSF, but in most patients they seem to be asymptomatic. Indeed, half of those who made a complete recovery after 270 days of treatment had tuberculomas seen on MRI. Dexamethasone seemed to have no effect on their incidence or resolution. Whether tuberculomas cause clinical problems is probably dependent on their size and anatomical location, but further research is needed to address these issues and the role of corticosteroids in their management.

Cerebral infarction is an important complication of tuberculous meningitis and this study, like others, confirms that the perforating vessels to the basal ganglia are most commonly occluded.¹⁰ Most infarcts seemed to occur after starting treatment, although the proportion with infarction at this time was probably an underestimate because the more seriously ill at baseline could not be scanned. However, after 60 days of treatment more than double the proportion of patients had had an infarct in the placebo group compared with in the dexamethasone group ($p=0.130$).

In summary, hydrocephalus was the most common serious complication of tuberculous meningitis and was strongly associated with long-term coma. Tuberculomas developed in most patients during treatment, which suggests that they are part of the normal pathological response to treated infection. Infarctions were often

multiple and always affected the basal ganglia. The effect of dexamethasone on these complications is unclear in view of the numbers of missing scans, although the proportions of patients with hydrocephalus and infarctions in the dexamethasone group could have been even smaller had the most severe patients from the placebo group been scanned. Therefore, dexamethasone might improve survival from tuberculous meningitis by reducing the incidence of infarction and speeding the resolution of hydrocephalus, but the anti-inflammatory mechanisms for doing so remain obscure. Other extracerebral effects of dexamethasone might be equally important. In particular, dexamethasone might protect against severe drug-related liver toxicity and prevent life-threatening interruptions in anti-tuberculosis chemotherapy.³

Contributors

Guy Thwaites, Nicholas White, Tran Tinh Hien, and Jeremy Farrar designed the study. Tran Tinh Hien, Tran Thi Hong Chau, Pham Phuong Mai, and Nguyen Thi Dung were responsible for recruiting the patients and caring for them whilst in hospital. Jeremy Macmullen-Price and David Summers reported all of the MRI scans. Cameron Simmons performed the assays assessing CSF inflammatory response. The paper was written by Guy Thwaites, Jeremy Farrar, and Jeremy Macmullen-Price with review and comment from all authors.

Conflicts of interest

We have no conflicts of interest.

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