

(seven partial or complete responses, four stable disease for more than 6 months), while 12 (52%) did not. The median time to progression for responding patients was 11 months (range 5–29) and for non-responding patients 3 months (range 0–6). The rate of response did not depend on the type of chemotherapy given. There was no difference between responders and non-responders in age, lymph node status, or recurrence-free period. Two of eight (25%) postmenopausal patients responded, compared with nine of 15 (60%) premenopausal patients. The incidence of MRP-positive tumours was not different for patients with soft tissue (one of three), bone (two of eight), or visceral metastases (five of twelve) as predominant site of relapse. In patients receiving first-line chemotherapy, MRP was more often positive in non-responding tumours (50%) than in responding tumours (18%). Only one of eight (13%) MRP-positive tumours had an objective response (5 months), compared with six of 15 (40%) MRP-negative tumours. Analysing for overall response, including stable disease, two of eight (25%) MRP-positive tumours responded, compared with nine of 15 (60%) MRP-negative tumours (odds ratio: 0.22; 95% CI 0.03–1.49). Patients with MRP-positive tumours showed a shorter time to progression on first-line chemotherapy than those with MRP-negative tumours (Cox proportional hazard model, $p=0.006$, figure). The relative hazard rate for time to progression in patients with MRP-positive tumours, compared with MRP-negative tumours, was 4.08 (95% CI 1.50–11.12). At 9 months, all eight patients with MRP-positive tumours showed disease progression, while seven of 15 of those with MRP-negative tumours did not (four objective responses, three stable disease). In Cox multivariate analysis for time to progression, MRP was the only significant variable in the model.

Of the 41 patients who received chemotherapy after one or more lines of hormonal therapy, 19 (46%) responded (seven partial responses, 12 stable disease), whereas 22 (54%) did not. In these patients, there was no significant difference in the rate or duration of response, or in the time to progression between patients with MRP-positive and MRP-negative tumours, suggesting differences in tumour cell biology. Metastatic breast cancer patients who receive chemotherapy as the first choice of treatment usually are premenopausal, are oestrogen-receptor and progesterone-receptor negative, and may have visceral metastases. These are all unfavourable prognostic factors. Women first treated with hormonal therapy are usually postmenopausal, have receptor positive tumours, and have bone rather than visceral metastases. We conclude that MRP expression is an

important predictor of poor prognosis in patients with breast cancer who were treated with chemotherapy as first-line systemic therapy for recurrence.

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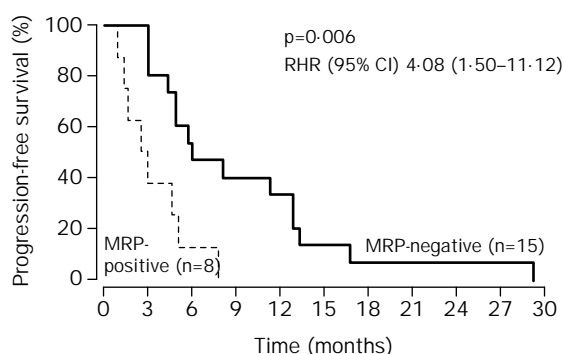
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Complement C3 and factor B cerebrospinal fluid concentrations in bacterial and aseptic meningitis

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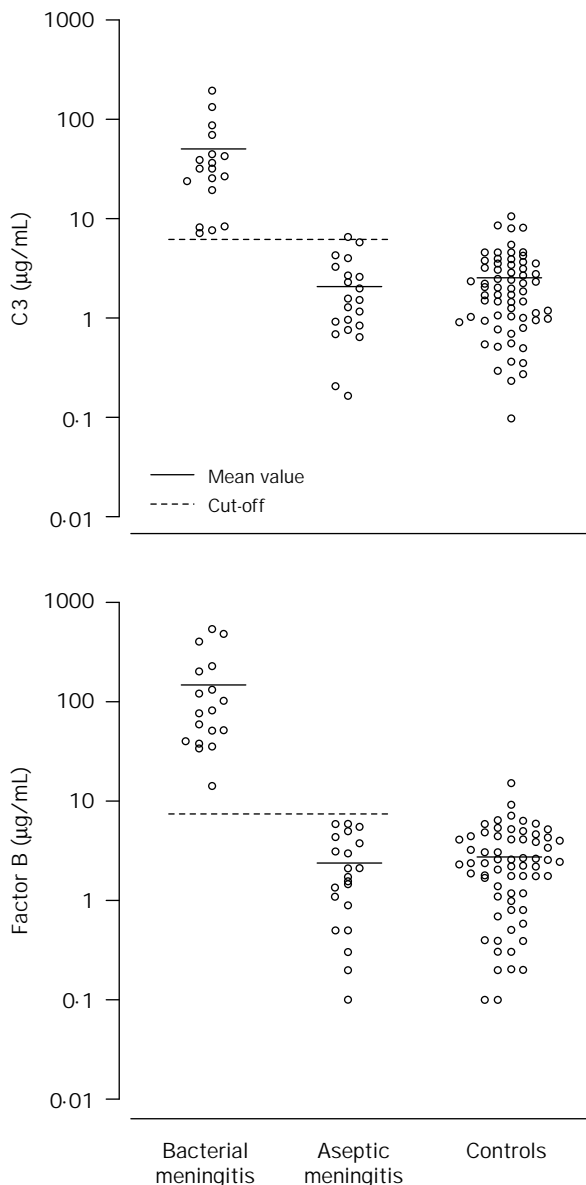
Establishing a diagnosis is difficult in most cases of acute meningitis, since its clinical signs are non-specific, and laboratory examination of cerebrospinal fluid (CSF) often does not accurately differentiate between bacterial and aseptic meningitis.^{1,2} Therefore the identification of a discriminating parameter, which might lead to a rapid and accurate clinical test, would be of value in the differential diagnosis of acute meningitis.

Several studies have suggested that the complement system contributes to intrathecal inflammation in bacterial meningitis.³ In a retrospective analysis, we measured the concentrations of the alternative pathway complement components C3 and factor B in CSF samples obtained by lumbar puncture from 39 patients with clinically suspected acute infectious meningitis, and from 64 controls without central nervous system infection, with an ELISA developed in our laboratory. 18 patients (median age 40 years; range 14–67 years; 9 female) were diagnosed as having bacterial meningitis, on the basis of positive bacterial culture or on detection of bacterial antigen in CSF. The pathogens were *Streptococcus pneumoniae* (n=10), *Haemophilus influenzae* (3), *Neisseria meningitidis* (3), *Listeria monocytogenes* (1), and *Streptococcus bovis* (1). 21 patients were diagnosed as having aseptic meningitis (median age 8 years; range 2 months to 13 years; 6 female) on the basis of CSF pleocytosis with a predominance of mononuclear cells, negative bacterial and fungal CSF and blood cultures, negative results on CSF antigen detection tests for *S pneumoniae*, *H influenzae*, and *N meningitidis*, and full recovery without antibiotic treatment. No patient had received antibiotics or steroids before diagnostic lumbar puncture, and all CSF samples were obtained on admission. The mean C3 concentration in the CSF of patients with bacterial meningitis (48.32 [SD 50.74] $\mu\text{g/mL}$) was significantly higher than in aseptic meningitis (2.16 [1.82] $\mu\text{g/mL}$; $p<0.001$, Wilcoxon rank sum test) or in controls (2.49 [2.18] $\mu\text{g/mL}$; $p<0.001$). Similarly, factor B CSF concentrations were significantly raised in patients with bacterial meningitis (15.89 [17.36] $\mu\text{g/mL}$) compared with those with aseptic meningitis (0.25 [0.20] $\mu\text{g/mL}$; $p<0.001$) or controls (0.29 [0.26] $\mu\text{g/mL}$; $p<0.001$). C3 and factor B CSF concentrations in bacterial meningitis did not correlate



MRP-negative	15	12	7	6	5	2	1	1	1	0
MRP-positive	8	3	1	0	0	0	0	0	0	0

Time to progression for patients treated with first-line chemotherapy for recurrence as a function of MRP status. Patients at risk at start and at every 3 months are indicated
RHE=relative hazard rate.



Complement C3 and factor B concentrations in the CSF of patients with infectious meningitis and controls

Each point represents the mean of duplicate sample analysis. Cut-off level=mean of aseptic meningitis group+2 SD for differentiation between bacterial and aseptic meningitis.

with CSF total white blood cell counts or CSF protein concentrations ($r < 0.6$, Spearman's rank correlation coefficient).

We found that complement concentrations in the CSF may be of clinical value in distinguishing bacterial from aseptic meningitis. With cut-off levels of the mean value +2 SD for the aseptic meningitis population (5.8 µg/mL for C3 and 0.65 µg/mL for factor B; figure), C3 and factor B CSF concentrations were highly sensitive (both 100%) and highly specific (95.2% and 100%, respectively) tests for the diagnosis of bacterial meningitis, and associated with a negative predictive value of 100%, and a positive predictive value of 94.7% (C3) and 100% (factor B). Quantification of C3 and factor B CSF concentrations can be completed within 3–4 hours. We plan to test these preliminary results in a multicentre prospective study.

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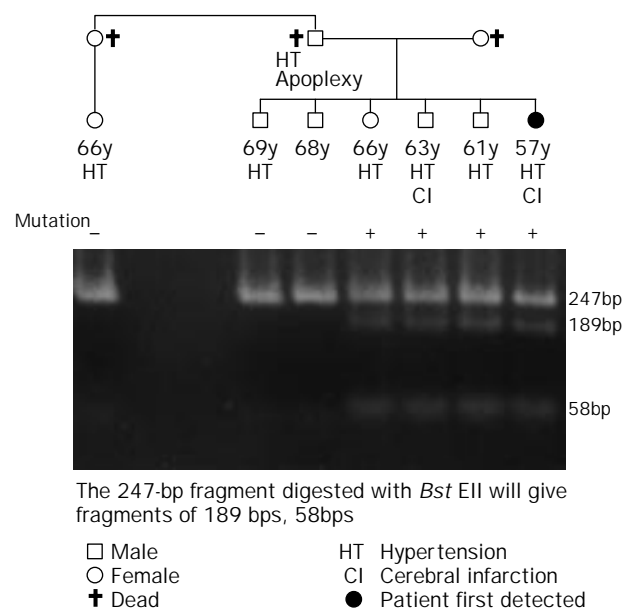
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Nonsense mutation of prostacyclin synthase gene in a family

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We found a nonsense mutation in exon 2 of the human prostacyclin-synthase gene in a family with essential hypertension and cerebral infarction. Prostacyclin (PGI₂) is an inhibitor of platelet aggregation, smooth muscle cell proliferation, and vasoconstriction. Prostacyclin synthase (PGIS), which catalyses the formation of PGI₂ from prostaglandin H₂, is widely distributed, predominantly in vascular endothelial and smooth muscle cells. We have reported the organisation of this gene.¹

We searched for possible point mutations in the exons using peripheral blood from 100 patients with essential hypertension by PCR and single strand conformation polymorphism (PCR-SSCP) analysis. One patient had an abnormally migrating band on exon 2. Sequencing of this exon showed a nonsense mutation in codon 26 (CGA/TGA). This nucleotide change makes *Bst* EII the restriction site. 300 people (150 with essential hypertension and 150 healthy controls) were screened by PCR and *Bst* EII digestion. The mutation was found in one patient with essential hypertension and in none of the controls. The patient was shown to be heterozygous for this mutation. This mutation of the stop codon is 76 bp downstream from ATG, the start codon in cDNA, thus a large part of mRNA,



Family tree and PCR