Ki-67 labelling indices in human malignant gliomas according to the intensity of staining with the anti-TN mAb BC-4

	Anaplastic astrocytomas (n = 48) % (SD)	Glioblastomas (n = 27) % (SD)
Group 1 (strong staining)	16.3 (8.3) (n = 26)	15.7 (6.8) (n = 14)
Group 2 (weak to moderate staining)	15.5 (6.7) (n = 22)	16.1 (9.4) (n = 13)

There were no significant differences between groups (Student's *t* test).

gliomas, but failed to show a correlation with cell proliferation. Nor was the occasional enhancement of staining in perivascular conglomerates of cells related to either TN expression in the stroma, or endothelial proliferation. It must be stressed that TN is actually represented by different isoforms, with the primary transcript being dependent on the cell cycle, and that the role of TN in tumour progression is regarded as being primarily related to the actively remodelling extracellular matrix on proliferating cells. Furthermore, TN has been shown to play a part in epithelial–mesenchymal interactions, cell spreading and adhesion, and postanoxic and post-traumatic gliosis.³ The variety of factors related to and affecting the TN expression in various tissues might account for the different outcomes resulting from clinical trials. Intracavitary administration of radiolabelled anti-TN monoclonal antibody after debulking of glioblastomas, resulted in some complete remissions with a median follow up of 18 months.¹ In several patients, however, anti-TN treatment was not able to affect the progression of growth, with early recurrences after surgery and immunotherapy. Further testing has been advocated, to select those patients in whom a TN related immunotherapy can be expected to provide beneficial effects. All the more so as TN expression in malignant gliomas is related neither to the cell type, nor to the cell proliferation. Evidence of a widespread distribution of TN in the white matter at the periphery of malignant gliomas, irrespective of its actual expression within the bulk of the tumours, limits the use of cerebral immunoscintigraphy with anti-TN monoclonal antibodies⁵ as a guideline for subsequent immunotherapy. Despite the intrinsic limitations of findings obtained on surgical specimens, a preliminary immunohistochemical screening aimed to the evaluation of the behaviour of both the tumorous stroma and the glial components possibly represents a necessary prerequisite of clinical trials testing the potential benefits of TN related immunotherapy.

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Spontaneous intracranial hypotension: MRI and radionuclide cisternography findings

Spontaneous intracranial hypotension (SIH) is a rarely reported syndrome of spontaneous postural headache associated with low CSF pressure. Although postural headache usually occurs after a dural puncture,¹ a spontaneous form of the syndrome does exist. Its characteristic headache is elicited or exacerbated by the upright position and is relieved when the patient is recumbent.² There is no history of previous dural puncture and, in most cases, the aetiology remains obscure.³ The similarity of SIH to the postdural puncture headache syndrome supports the notion that a CSF leak may be the cause of SIH, but this has rarely been demonstrated.^{2–4}

We present a patient with SIH whose gadolinium enhanced MRI disclosed bilateral subdural hygroma and thin diffuse meningeal enhancement. The clinical symptoms were spectacularly resolved when a CSF leak at the dorsal level, shown by radionuclide cisternography, was closed after an epidural blood patch. This case is unusual because meningeal enhancement persisted on the brain MRI at three month follow up whereas the patient was clinically asymptomatic.

Figure 1 Initial brain MRI. Coronal T1 weighted after gadolinium injection, showing bilateral extra-axial fluid collections and thin, intense, and diffuse meningeal enhancement.

Figure 2 Radionuclide cisternography six hours after injection of tracer. Anterior projection of the thoracic spine showing diffusion of the radionuclide into the extra-arachnoid space. The isotope is seen outlining the spinal roots, predominantly left sided (image of "christmas tree").

A 32 year old previously healthy man developed a sudden severe frontal headache with vertigo and vomiting. The headache appeared after a sneezing crisis accompanied by bright rhinorrhea, while he was travelling in a 14 hour plane journey. The headache subsided when the patient lay down. He was admitted to our hospital two days later. General physical examination was normal, there was no meningeal signs, and he was afebrile. Unenhanced brain CT and routine biological examination were normal. Lumbar puncture yielded a clear CSF with no red blood cells, and 1 white blood cell/mm.³ The protein concentration in CSF was slightly raised at 0.92 g/l (normal 0.2–0.4 g/l). All cultures were negative.

The patient was treated symptomatically with bed rest and analgesics and discharged. He was readmitted three weeks later because of continuing and incapacitating postural headache associated with vomiting, anorexia, and vertigo. His clinical examination was unchanged. Brain MRI disclosed bilateral subdural hygroma, small thin ventricles, and thin linear meningeal gadolinium enhancement including membranes along cerebral and cerebellar convexities, inter-hemispheric fissure, and tentorium (fig 1). There was no mass effect. Two blood patches were carried out at 24 hour intervals with epidural injection at the level L4 of 15 ml autologous blood. These were unsuccessful. Because of a doubt about the diagnosis, radionuclide cisternography was performed 10 days later, consisting of an injection at the lumbar level L4–L5 of Indium111-DTPA. It was suggestive of a CSF leak, showing early appearance of activity in the bladder, slow ascent along the spinal axis, no activity over the cerebral convexities after 24 hours, and appearance of extra-arachnoid radioactivity at the dorsal level six hours after injection, visualised as a double straight line (fig 2). A magnetic resonance myelogram did not show any abnor-

malities; in particular there was no arachnoid cyst. Consequently, a third blood patch (20 ml) was carried out at a higher level (L2) than the previous one, guided by the radionuclide cisternography findings. The patient was headache free a few minutes later and able to ambulate the next day. Postural headache had not recurred within 12 weeks of follow up and the patient returned to work full time. Follow up brain MRI with gadolinium showed complete resolution of the subdural hygroma but persistence of thin meningeal enhancement. However, its intensity was smaller than that seen on the MRI at admission.

Intracranial hypotension associated with postural headache is a common clinical phenomenon after lumbar puncture, but it may also occur spontaneously; a more rarely reported syndrome.^{1,2} Our patient fits well with the typical description of SIH—namely, spontaneous frontal headache exacerbated by erect posture and relieved by supine position. It may be associated with nausea and vomiting; less commonly, patients experience vertigo, diplopia, photophobia, or neck stiffness.² If the SIH is unrecognised, evaluation of the patient's headache may include lumbar puncture that may allow measurement of the CSF pressure. This was not performed in our patient but it is usually low, less than 60 mm H₂O. Because the CSF in SIH sometimes contains an abnormal number of white blood cells, or high protein content, or both,² suspicion of meningeal infection or tumour may lead to further evaluation, including a contrast enhanced MRI.

Several recent reports¹⁻³ have shown subdural hygromas and diffuse meningeal enhancement on MRI with gadolinium associated with this syndrome. In all reported cases, the enhancement disappeared as clinical symptoms resolved. This may be related to inflammation of the pachymeninges secondary to reversible disturbance of the choroid plexus,¹ to a dural venous dilatation in response to low CSF pressure,³ or to a fibrocollagenous proliferation of the leptomeninges.⁵ The last is consistent with our finding because of the persistence of enhancement three months after disappearance of clinical symptoms. Such an enhancement can lead to diagnostic confusion. However, the clinical presentation should be sufficient to make the distinction in most cases.

Spontaneous spinal CSF leaks are now increasingly recognised as a cause of postural headache associated with intracranial hypotension.^{1,2,6} However, in most of the cases, the site of the CSF leak may be difficult to determine and will remain unknown.² It has been reported that small dural tears can occur at the nerve roots from even minor trauma; indeed, there is often a history of a trivial fall, vigorous exercise, or violent coughing preceding the onset of the headache in many cases of SIH.² The sneezing and the altitude with possible depressurisation may have been a promoting circumstance for our patient.

Radionuclide cisternography has been used to visualise CSF leaks in SIH,²⁻⁴ showing early accumulation of radioactivity in the bladder and less activity than expected over the cerebral convexities, suggestive of unusually rapid uptake of the tracer into the circulation.^{2,4} The characteristic finding is the diffusion of tracer into the extra-arachnoid space, outlining the spinal roots.

The headache in SIH usually resolves spontaneously with strict bed rest, some-

times with analgesics and antiemetics. More aggressive treatment may be necessary when the headache persists or is incapacitating. According to therapies for postdural puncture headache, an autologous epidural blood patch is often used.^{1-3,6} Pain relief is often immediate but sometimes several blood patches are needed, as we found. It is now recommended that the precise level of the leak is identified with contrast or isotope cisternography in patients in whom blood patch therapy has failed.

In conclusion, SIH features are well established. Misleading MRI findings should suggest the diagnosis, and a search for a cryptic CSF leak should be considered in patients with unexplained postural headache, especially when treatment has failed. It is important to bear in mind that several blood patches are often needed.

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Transient multiple cranial nerve involvement as a first sign of macrophage activation syndrome

In 1979, Risdall *et al*¹ described a disorder characterised by histiocytic hyperplasia, preponderant hemophagocytosis, and proliferation of macrophage cells. The term macrophage activation syndrome was proposed. Clinical symptoms are heterogeneous and not specific.² Neurological signs are rare. We report a man with macrophage activation syndrome in whom the first signs were multiple cranial nerve involvement.

A 43 year old man developed left peripheral facial nerve palsy. Three days later, intrabuccal dysaesthesia associated with hypoaesthesia in the second branch of the trigeminal nerve occurred. Eight days later, he developed left hypoacusia and a right T8 band of hypoaesthesia. At this point, laboratory tests, CT, and cerebral MRI were normal; a CSF examination disclosed normal protein concentrations and 10 lymphocytes/ μ l. In the third week, the signs disappeared, but left optic neuritis occurred. Antibacterial and antiviral, including HIV, serologies were negative except for Epstein-Barr virus suggesting a latent infection. Although Borrelia serology was negative, ceftriaxone (2 g/day) was given for three weeks. Two months after the onset of the symptomatology, left eye

vision had improved but right optic neuritis appeared. He lost 8 kg over two months; his temperature was 38°C. Neurological examination showed only a bilateral asymmetric visual loss. Laboratory test results were white blood cells $6.4 \times 10^9/l$, haemoglobin 13.4 g/dl, platelets $200 \times 10^9/l$, fibrinogen 2.30 g/l. Electrolytes, renal, and hepatic variables, and lactate dehydrogenase were normal. Systemic lupus erythematosus, rheumatoid arthritis serologies, and biological variables of sarcoidosis were all negative. A second CSF examination and another cerebral MRI with gadolinium injection were normal. A few days later an erythematous skin rash occurred on his legs; biopsy showed leukocytoclastic vasculitis. His fever increased and corticosteroid therapy was started. Temperature returned to normal. However, in the third month fever reappeared, with weight loss and liver failure. Pancytopenia appeared, platelets decreased to $20 \times 10^9/l$, white blood cells to $3.5 \times 10^9/l$, haemoglobin to 8.1 g/dl, and triglyceridaemia increased to 7 mmol/l. Serum tumour necrosis factor α (TNF α) concentrations were six times higher than normal. Finally, bone marrow aspiration established the diagnosis of macrophage activation syndrome. Macrophage cytoplasm contained erythroblasts, neutrophils, and platelets (fig 1). Atypical lymphocytes were also present (fig 2), suggesting malignant T lymphoma. This was confirmed by marrow biopsy. Subsequently, hepatomegaly and splenomegaly occurred. Despite aggressive therapy with bolus steroids, the patient died from myocardial incompetence and bilateral lung infiltration. Postmortem examination was not performed.

Diagnosis of macrophage activation syndrome may be evoked in the presence of heterogeneous non-specific clinical symptoms and biological abnormalities. Asthenia, weight loss, sweating, and fever can be the first signs of the disease.² But what clearly indicates macrophage activation syndrome onset is a rapidly deteriorating clinical status. Pancytopenia, regenerative anaemia, severe thrombocytopenia, hypertriglyceridaemia, and hyperferritinaemia usually occur.² Diagnosis is established by bone marrow examination showing the most characteristic signs—that is, clearly differentiated macrophages presenting abnormal signs of active haemophagocytosis. No clear aetiopathogenic explanation exists for the occurrence of macrophage activation syndrome but it can occur after infections (Epstein-Barr virus, HIV, bacterial and parasitic pathogens),² in patients with an underlying disease: immune deficiency, solid tumours, inflammatory diseases, haemopathies,² lymphomas.⁶ Macrophage activa-

Figure 1 Macrophages containing numerous erythroblasts and platelets. Myelogram (originally $\times 100$).