Radiculopathy associated with disc herniation

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Should we treat it with anti-TNF α agents or is TNF α only one piece of the puzzle?

The treatment of radiculopathy associated with disc herniation by anti-tumour necrosis factor α (TNF α) agents is currently being examined.¹⁻³ However, although the rationale appears to be sound, there is no proof of the efficacy of such a treatment and its use still has not been validated.

HAS THERE BEEN PROGRESS IN THE PHYSIOPATHOLOGY OF DISC HERNIATION ASSOCIATED RADICULOPATHY?

Since 1934, when a link was demonstrated between disc herniation and sciatica,⁴ it has been accepted that compression of the nerve root by disc herniation explained the sciatica. Surgical treatment therefore became standard when medical treatment failed. It now seems that "chemical" factors have a central role in sciatica.

The clinical arguments supporting the "chemical" theory are numerous. Laminectomy is sometimes ineffective, the long term success rate being 40–80%,⁵ and reintervention rates are reported to be 5–25%.⁶ A considerable amount of asymptomatic disc herniation⁷ and severe sciatica without visible root compression has been reported⁸; there is poor correlation between the severity of symptoms and the extent of the disc herniation⁹; and the outcome, frequently favourable, is similar after conservative and surgical treatment.^{10 11}

"Chemical factors may play a part in sciatica"

The role of a chemical component is supported by experimental findings. The spontaneous resorption of disc herniation, dependent on metalloproteinases and neo-vascularisation¹² and demonstrated by longitudinal computed tomography and magnetic resonance imaging (MRI) studies, appears to be more marked for large or extruded herniation.¹³ Immunogenicity of intervertebral discs has been proposed,¹⁴ and the *nucleus pulposus* (NP), isolated from the immune system after its embryological

formation, might secrete substances which can induce an autoimmune reaction in cases of disc herniation, particularly those that are extruded.¹⁴ Mediators of inflammation and metalloproteinases have been identified in disc tissue.^{15 16} It has been shown in animal models that radicular compression cannot explain sciatica, the mechanical compression of a healthy nerve causing dysaesthesia or motor deficit.¹⁷ Mechanical stimulation of a nerve root not exposed to disc herniation in volunteers operated on under local anaesthesia for disc herniation produced simple discomfort, whereas stimulation of a nerve root in contact with disc herniation reproduced sciatic pain.¹⁸

However, several studies have demonstrated that the mechanical and chemical components each play a part, acting synergistically, with the chemical component having a dominating effect at an initial stage.² It thus appears that, even in the absence of mechanical compression, substances secreted by the NP can provoke functional and structural abnormalities of the nerve root, with pain probably being felt only when the nerve root has been previously or simultaneously affected by a mechanical factor.

WHICH OF THE CHEMICAL SUBSTANCES IS SECRETED BY THE NP?

The chemical theory was confirmed by an animal model, which showed for the first time that the NP could cause radicular abnormalities without compression.¹⁹ Indeed, epidural application of the NP in the pig, without radicular compression, decreased the nerve conduction velocity (NCV) with histological changes, compared with retroperitoneal fat used as control.¹⁹ High doses of corticosteroids re-established the NCV²⁰ and had beneficial effects on the increase in endoneurial vascular permeability induced by the NP.²¹ These experiments thus indicate the proinflammatory nature of the substances secreted by the NP and their ability to

induce electrophysiological changes. Other experiments have suggested that the origin of the biological effects is situated on the NP cell membrane.²²

The NP can cause damage to axons and the myelin sheath, increasing the vascular permeability and intravascular coagulation and reducing the intraneural blood flow. These effects can be inhibited by methylprednisolone and non-steroidal anti-inflammatory drugs and are generated by NP cells.² These properties of the NP are fairly similar to those of TNF α .²³ Indeed, TNF α can cause nerve damage, particularly to myelin, very similar to that seen after application of NP, with increased vascular permeability and coagulation disorders, and can be inhibited by corticosteroids and ciclosporin.² The reduction in NCV after application of the NP was completely blocked by doxycycline (a powerful inhibitor of TNF α) and partially blocked by anti-TNF α monoclonal antibodies.²⁴

"Some of the properties of the nucleus pulposus are similar to those of TNF α "

These results are interesting because doxycycline inhibits not only TNF α , but also interleukin (IL) 1, interferon γ , and nitric oxide synthetase, which act in synergy with TNF α , have neurotoxicity potential, and are inhibited by corticosteroids.² Thus several substances may explain the effects occurring after application of the NP, although the most well documented is TNF α .

EXPERIMENTAL FINDINGS SUPPORTING THE PARTICIPATION OF TNF α

Proinflammatory cytokines (IL1 β , IL6, and particularly, TNF α) are secreted in neurological disorders. Plasma levels of cytokines are increased after nerve compression, and endoneurial injections of TNF α cause thermal hyperalgesia and mechanical allodynia, oedema of the nerve root, damage to Schwann cells, and activation of macrophages.³ Endogenous TNF α causes pain related behaviour in models of nerve dysfunction. Thus applications of exogenous TNF α cause neuronal excitation and pain, and thalidomide, a selective inhibitor of TNF α , reduces hyperalgesia in animal models of sciatica.³ Finally, TNF α appears to be able to sensitise the nerve root to pain when the latter has previously been subjected to mechanical stress, a hypothesis which is compatible with current understanding of the physiopathology of disc-induced sciatica.

Cell culture experiments have shown that TNF α , which has been detected by immunohistochemistry in NP cells, is a

major component of the NP.²⁴ In the rat chronic constriction injury (CCI) model the number of TNF α reactive cells detected by immunohistochemistry clearly increased after sciatic compression compared with non-compressed nerves, and in situ hybridisation showed that Schwann cells could produce TNF α in vivo.³

When exogenous TNF α was applied to the nerve roots in the rat it caused significantly greater neuropathological damage than saline solution, and these abnormalities were similar to those recorded after application of the NP.²⁵ Endoneural injection of TNF α into the sciatic nerves of rats caused painful neuropathy and histological changes identical to those of experimental models.²⁶ Olmarker's model was used and pigs were given an application of NP, retroperitoneal fat, interferon γ , IL1 β or TNF α ; of these, only TNF α caused changes in the NCV similar to those produced by application of the NP.²⁷

When small doses of TNF α were applied to the ganglion of the dorsal root of L5 in healthy rats, or after ligature of the spinal nerve, they provoked earlier allodynia and behavioural abnormalities after ligature.³ Application of TNF α to the normal dorsal root ganglia in the rat provoked persistent allodynia, which lasted beyond the duration of the application, and when there had been prior nerve compression the allodynia was more marked and more prolonged than that provoked by compression alone.³ Immunohistochemistry showed that the endoneural activity of endogenous TNF α was only accentuated during the first few days after compression.³

To extrapolate these findings to humans it is necessary to demonstrate that TNF α can induce sciatica. TNF α provokes pain and hyperalgesia in animals, particularly when combined with mechanical stress, and has a role in the behavioural changes related to pain in these animals.³

Thalidomide attenuates thermal hyperalgesia and mechanical allodynia in animal models, probably by inhibiting the endogenous production of

TNF α .³ In a model of CCI, the use of a polyclonal anti-TNF α antibody and/or an IL1 receptor showed that the combination had a more marked effect on thermal hyperalgesia and mechanical allodynia.³ Etanercept (a soluble receptor of TNF α) had a beneficial effect on thermal hyperalgesia and mechanical allodynia in a mouse model of CCI compared with human immunoglobulins; the effect of a local application of 87.5 μ g etanercept was greater than the systemic administration of 100 μ g.³ In one study, pigs received an application of NP and then an infusion of 100 mg infliximab, or a subcutaneous injection of 12.5 mg etanercept, or 0.3 ml heparin or 0.3 ml saline solution.³ NCV was restored only in the infliximab and etanercept groups.

"TNF α provokes pain and hyperalgesia in animals particularly when combined with mechanical stress"

Although the animal model experiments are sometimes contradictory, they have identified the role of TNF α : (a) it is involved in the physiopathology of nerve dysfunction and sensitises roots previously exposed to mechanical stress; (b) it has been identified in the NP and Schwann cells; (c) it causes electrophysiological, histological, and behavioural abnormalities similar to those seen after application of NP, and these are more pronounced when there is mechanical compression; (d) local production of endogenous TNF α occurs at an early stage in the disease process and is short lived; (e) TNF α blocking agents reduce or inhibit abnormalities induced by NP; (f) local and systemic administration of TNF α may have similar efficacy; (g) cytokines other than TNF α may also be involved.

USE OF ANTI-TNF α IN DISC HERNIATION ASSOCIATED RADICULOPATHY IN HUMANS

One open study evaluated the effects of infliximab infusion (3 mg/kg) in 10 patients with sciatica (2–12 weeks' duration, disc herniation on MRI).²⁸

The initial pain intensity of the sciatica (mean (SD) 78.7 (18.7) mm) was reduced by 49% 1 hour after infusion; after 1 week it was 26.0 (21.2) mm, at 2 weeks 19.1 (20.2) mm, at 1 month 16.8 (19.3) mm, and at 3 months 5.2 (6.6) mm. Evolution of low back pain, straight leg raising test and Oswestry Index scores were similar. These 10 patients returned to work at 4 weeks and no patient required surgery or had untoward effects from the infliximab.

Another open study evaluated the efficacy of etanercept (25 mg subcutaneous injection on days 1, 4, and 7) in 10 patients with sciatica (<8 weeks' duration, radicular pain >50 mm).²⁹ Radicular pain, Oswestry Index, and Rolland-Morris scores had improved significantly at day 10 in all patients, and 9/10 patients continued to improve between day 10 and week 6 (table 1).

The results of the first randomised, controlled, double blind trial comparing infliximab (5 mg/kg) and placebo (40 patients, disc herniation on MRI, 7 $\pm$ 3 weeks' duration) were disappointing, although we do not know the full details (unpublished).³⁰ Infliximab was not shown to have a greater effect than placebo on the pain symptoms or functional handicap.

The methodology of this trial has been criticised (heterogeneous population, small group size, only one infusion) and several questions remain unanswered. The response might have been influenced by the intensity of the radicular pain, the duration of evolution, or the anatomical localisation of the disc herniation. The concept of inhibition of TNF α is perhaps a false dawn and although TNF α may have a central role a number of questions remain:

- How can we explain the fact that only a few patients have sciatica that resists conservative treatment?
- Are the symptoms linked to the degree of electrophysiological abnormalities induced by TNF α or to a genetic predisposition?
- Might TNF α be only one of the pieces in the puzzle, and might anti-TNF α

Table 1 Evolution of 10 patients with sciatica treated with etanercept²⁹

	T0	Day 10	Week 6
Radicular pain (VAS, 0–100 mm)	74.4 (12.9)	20.2 (16.6)	12.4 (13.2)*
Low back pain (VAS, 0–100 mm)	36.4 (39.8)	8.4 (11.9)	7.4 (10.8)**
Oswestry Index (0–100)†	75.4 (19.4)	33.9 (25.4)	17.3 (13.1)***
Rolland-Morris (0–24)‡	17.8 (3.3)	9.8 (7.8)	5.8 (5.5)****

The results are given as mean (SD).

*p<0.001; **p=0.002; ***p<0.05; ****p=0.1 v T0.

†The Oswestry Index consists of 10 items assessing the level of pain interference with physical activities and incorporates a measure of pain as well as physical function.

‡The Rolland-Morris Disability Questionnaire measures 24 activity limitations due to back pain and is mostly a measure of function.

be beneficial only if used in combination with drugs blocking other cytokines?

- Might TNF α only have a role in the initial stages of sciatica, and might anti-TNF α only be effective at an early stage?
- Should administration of anti-TNF α be systemic or local?

CONCLUSION

It might be beneficial to treat disc-induced sciatica resistant to medical treatment with anti-TNF α drugs. Although their use appears premature for this indication, it cannot be denied that the abundant findings of animal experiments and the rationale are appealing. The results of current controlled studies (one with adalimumab in progress in Switzerland, one with adalimumab in France by 2006) are therefore eagerly awaited.

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