Antibiotics a cure for back pain, a false dawn or a new era?

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The recent publication in this journal of papers by Albert and colleagues [1, 2] from Denmark suggesting that low grade anaerobic bacterial infection may be the underlying cause of significant persistent chronic back pain in a well-defined group of patients has precipitated an unprecedented response in the medical and lay media. In the midst of claim and counterclaim, these studies represent a significant and substantial change in our understanding of the pathophysiology of back pain in some patient groups, and the importance of this should not be lost amidst the negative, unstructured and unscientific response to this study.

The facts

The story starts in 2001 with the publication of a research letter in the *Lancet* by a group from Birmingham [3] demonstrating that 31 % of patients with sciatica tested positive to a newly developed serological test, which diagnosed deep-seated infections caused by virulent Gram-positive microorganisms. In addition, intervertebral disc material excised during microdiscectomy in a different group of patients, which was cultured in a specialist anaerobic environment, had positive cultures after long-

term incubation in 53 % of patients and of this group 84 % grew *Propionibacterium acnes*.

Following the ISSLS 2006 meeting, a collaboration developed between the Birmingham group and the group from Southern Denmark. This led to publication of a pilot study in 2008 [4] where 32 chronic low back pain patients with Modic type 1 endplate changes and a previous lumbar herniated disc were treated with amoxicillin and clavulanate for 90 days. In this uncontrolled trial, there was a clinically important and statistically significant difference in outcome at 10-month follow-up following antibiotic treatment.

In the meantime, the evidence was accumulating about the significant correlation between Modic endplate changes and back pain. Albert and Manniche [5] identified a strong association between Modic changes and non-specific low back pain, a stronger association with Modic type 1 than type 2, and that a lumbar disc herniation is a strong risk factor for developing Modic changes, especially type 1, during the following year and that these changes are strongly associated with low back pain.

A systematic review from Southern Denmark in 2008 [6] identified the prevalence of vertebral endplate signal changes as 43 % in patients with non-specific low back pain and/or sciatica, and 6 % in a non-clinical population, demonstrating that endplate changes are associated with pain. A further systematic review in the same year from Shanghai [7] identified two possible pathophysiological mechanisms for Modic changes—one biomechanical and one biochemical. A biomechanical pathway for development of Modic changes was supported by a large population MRI scan study in 2011 [8].

Against this background two key papers were then published in this journal in 2013. In one study [2] Albert and colleagues established a strong relationship between

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Modic changes type 1 adjacent to a previously herniated disc and positive microbiological culture in 46 % of patients undergoing discectomy procedures for disc herniation. Finally, the study which has triggered all of the controversy [1] was a double-blinded randomised control trial. Patients with persistent low back pain following a disc herniation in the previous year with Modic type 1 changes improve significantly following a 100-day course of antibiotic treatment.

The hype

The spinal community has significant previous experience of the outcome following lay media and commercial marketing of new treatments before these treatments are fully scientifically validated, and ultimately long-term results did not live up to the hype. Intravenous high dose corticosteroids were trumpeted in the press as a treatment for spinal cord injury shortly after the publication of the NASCIS II study [9], and this more than the scientific evidence rapidly led to corticosteroids being the standard of care for managing spinal cord injuries. The passage of time, analysis of benefits and a proper understanding of the risks led to a marked decline in the use of steroids and now recommendations are that these should not be used in spinal cord injury [10].

More recently, there has been significant controversy regarding the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) augmenting spinal fusion, leading to hostile interchanges between protagonists and antagonists both in the scientific literature [11–14] and in the lay media.

A recent Yale University open data access project led to the publication of two systematic reviews on patient level data from all clinical trials conducted by Medtronic [15, 16]. These demonstrate that there is no significant difference in pain or functional outcome for patients being treated with rhBMP-2.

Against this background, it seems that a mass media launch in the United Kingdom, Europe, and North America with the story rapidly being taken up around the world, offering a “cure” for back pain propagated from a private clinic in London, should be considered unwise (for examples see <http://www.dailymail.co.uk/health/article-2321665/From-cripple-action-man-Briton-proves-end-lifetime-pain-antibiotics.html>, <http://www.telegraph.co.uk/health/healthnews/10042211/Antibiotics-could-cure-40pc-of-chronic-back-pain-patients.html>, <http://www.express.co.uk/news/health/397889/Miracle-cure-for-back-pain-Agony-ended-by-everyday-antibiotics>, <http://www.abc.net.au/pm/content/2013/s3754841.htm>). One of the authors of the Southern Denmark papers has a commercial link with this organisation and addresses this

conflict of interest elsewhere in this edition of the European Spine Journal.

It is hard to measure the negative impact on the substantial group of chronic low back pain patients worldwide from reading in their newspaper and seeing on the television news that a new cure for back pain is available. If they understood the real outcomes from the paper [1], they would understand that at 1-year follow-up 67.5 % of the treatment group still has back pain. The treatment effect reduces the VAS for back pain from 6.7 to 3.7. This is an impressive real treatment effect, but would not be considered “a cure” by any standard. How many patients’ pain decreased to 0–2?

This mass media launch has led to a very widespread and negative feedback in the lay and specialist medical media. Obviously, this is an unregulated, opinionated repository for often extreme opinions, but there must be significant reputational risk both to the scientists, the commercial organisation in London and to the spinal community in general from some of these widely read internet resources (see <http://ferretfancier.blogspot.co.uk/2013/05/antibiotics-for-back-pain-conflicts-of.html>, and <http://theconversation.com/zit-bacteria-causing-back-pain-a-spotty-hypothesis-14060>). In addition, there has been a cynical response from the respected medical press [17] although a subsequent article gave a slightly more tempered response [18].

Response

We believe that the surgical and scientific communities should have a tempered and objective response to these publications. There was clearly a very significant and important treatment effect in this very small subgroup of patients who receive antibiotics within 1 year from a symptomatic disc herniation who develop persistent continuous back pain. It seems unlikely, however, at this stage that the majority of patients with Modic type 1 changes in the lumbar spine have an underlying infection. The tempered response in the editorial [19] in this journal flags up the need for further research.

The study of Albert [1] needs to be replicated in a different clinical and scientific setting. It was arguably underpowered and a larger study is essential. Have we satisfied Koch’s postulates or the updated criteria of Fredricks and Relman [20] for demonstrating a link between infection and the disease process? The use of Roland and Morris rather than the Oswestry Disability Index precludes comparisons with the major spinal surgery outcome studies [21–24]. We need stronger evidence that bacterial infection producing discitis and endplate changes is the cause of chronic low back pain in a significant number of patients.

Much more research is required before these results can be extrapolated to a general population of patients with chronic back pain and underlying Modic type 1 changes. On the basis of a significant but not complete resolution of back pain in the treatment group, alternative antibiotic regimens and protocols need to be explored and we need understanding of why there was no spontaneous change in clinical outcome measures in this study in the control group. It would also be interesting to see if the results could be replicated in back pain sufferers who have Modic type 1 changes, but have not had a documented disc prolapse. If we genuinely believe that there is low grade infection in Modic type 1 endplates and discs then it logically follows that we should perform biopsy and culture with subsequent treatment dictated by the results. What should our position be for patients who would normally be offered anterior lumbar interbody fusion (or similar) for discogenic back pain and Modic type 1 changes on MRI? Should conservative treatment now include 100 days of antibiotics?

At the moment, the only patients that should be considered for a course of antibiotics outside the environment of a clinical trial are those with

1. Low back pain of more than 6 months duration and has not responded to exercise therapy.
2. A symptomatic disc herniation within the previous year.
3. Modic type 1 changes at the same level as the disc herniation.

A period of reflective and scientific analysis with further high quality research may well lead to a new treatment for a small subgroup of low back pain patients being established, but it would be very wrong at this stage to give hope to the wider group of patients with chronic disabling low back pain.

Conflict of interest None.

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