Steroid response

Predicting steroid response in muscle disease

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Granulysin expression or glucocorticoid receptor polymorphisms may be factors underlying the variable steroid response in patients with myopathies

Idiopathic inflammatory myopathies and genetic muscular dystrophies are distinct and well-recognised clinical entities. However, it is increasingly evident that there is overlap in both the clinical presentation¹ and the pathophysiology² of the two groups.

The preferred management of polymyositis and dermatomyositis has traditionally been with corticosteroids and, although controlled clinical trial data to support this are lacking, the efficacy of these drugs has long been established in clinical practice. However, not all patients respond to steroids.

Non-response rates of up to 40% have been reported, but it has become increasingly clear in recent years that polymyositis in particular has been overdiagnosed, and many of these patients actually had inclusion-body myositis (IBM), for which there is no strong evidence of a response to steroids, or a form of muscular dystrophy. The classical Bohan and Peter criteria for the diagnosis of polymyositis have been modified to include other criteria, such as the presence of CD8+ T cell infiltration along with expression of major histocompatibility class I molecules on muscle biopsy specimens, but this is not completely specific.³

Clearly, it is important to revisit the diagnosis in the steroid-unresponsive patient with presumed idiopathic inflammatory myositis.¹ Nonetheless, there remains a subset of patients with proved disease who do not respond to treatment. However, at present, corticosteroid treatment in inflammatory myopathy remains empirical.

Inflammation also has a role in the pathophysiology of most muscular dystrophies, including the dystrophinopathies, facioscapulohumeral dystrophy and the dysferlinopathies. Since the 1960s, evidence has been accumulating that treatment with corticosteroids improves muscle strength and function in Duchenne muscular dystrophy (DMD) over the shorter term (up to 2 years), although the effects of longer-

term treatment are less clear cut and need to be balanced against major adverse effects resulting from their use.⁴ Recent evidence has also thrown into question whether the observed benefits relate directly to the immunosuppressive effects of steroids. Furthermore, as with polymyositis and dermatomyositis, there is considerable variability in the clinical response of each patient to treatment.

In both idiopathic inflammatory myopathy and DMD, there is presently no way of predicting steroid responsiveness and avoiding unnecessary exposure to drugs with major adverse effects. Two studies in this issue of the *Journal of Neurology, Neurosurgery and Psychiatry* attempt to tackle this problem by considering the mechanisms that may underlie steroid resistance in patients. In the first of these studies, Ikezoe *et al* (see page 1187) examine the expression of granulysin, a protein present in the cytotoxic granules of cytotoxic T cells and natural killer cells. They show that granulysin expression in CD8+ lymphocytes is markedly higher in pre-treatment muscle biopsy specimens from patients subsequently found to have steroid-resistant polymyositis than in those who respond to standard corticosteroids. However, levels of perforin, which is expressed in the same granules, were not considerably different in the two groups, although there was again a trend to higher expression in steroid-resistant polymyositis. Interestingly, expression levels of both proteins were lower in IBM than in all cases of polymyositis. This study raises interesting questions about the differing mechanisms of muscle damage in polymyositis and IBM. Perforin and granulysin may be differentially expressed in immune cells in response to particular insults, and it is possible that this may reflect the different pathophysiology of the two conditions. As Ikezoe *et al*⁵ point out, granulysin expression in serum peripheral blood lymphocytes can act as a marker for steroid resistance in patients who undergo renal transplantation. It may be possible to

exploit these differences to predict steroid response in patients with polymyositis, although clearly new large prospective studies will be required to evaluate this.

In a second study, Bonifati *et al* (see page 1177) examine glucocorticoid receptor polymorphisms as a possible factor underlying the variable steroid response in patients with DMD. Bonifati *et al*⁶ carried out a survival analysis examining the effect of the N363S glucocorticoid receptor polymorphism, which has previously been shown to increase sensitivity to exogenous glucocorticoids. In 48 patients with DMD, despite identifying only three patients with the polymorphism, there was a trend to later ambulation, although this did not reach statistical significance. However, there was no difference between the two groups in functional tests after 1 year of treatment. Longer-term studies in larger groups will be necessary to clarify whether this polymorphism truly improves response to treatment. However, although the presence of the N363S polymorphism is a plausible hypothesis to explain a better response to steroids in some patients, as the frequency of the polymorphism is only 6% in the general population, it cannot explain the profound variability in steroid response in patients with DMD. In keeping with previous studies, the authors also found that earlier age at initiation of treatment and duration of treatment markedly increased the age at loss of ambulation.

There remains little research into the treatment of patients with primary muscle disease with corticosteroids, particularly with regard to predicting response to treatment. It is to be hoped that the two small studies published in this issue will spur more active research on this topic. A clearer understanding of the factors that underlie steroid resistance in the inflammatory myopathies and DMD will deepen our understanding of their pathophysiology and may, in the longer term, permit prognostication of treatment response, considerably improving the experience of some patients with these conditions.

J Neurol Neurosurg Psychiatry 2006;**77**:1104–1105.

doi: 10.1136/jnnp.2006.087874

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Competing interests: None.

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Head injury

Patients after a head injury face an uncertain long-term future

S Fleminger

Long-term changes in patients after head injury: for better or for worse?

After a head injury, it is sometimes assumed that once the first 2–3 years of recovery have passed, any impairment and disability remaining is fairly fixed. There will be little further improvement and in the unlikely event of any subsequent deterioration, the clinician should expect to be able to find a specific cause—for example, hydrocephalus—for the decline. However, longer-term follow-up studies suggest that in fact a fair proportion of patients change, some for the better and some for the worse.

The last time the Journal considered this issue was in 2003.¹ Millar *et al*² found that at 18 years follow-up after a head injury, twice as many patients had deteriorated (32%) as improved (15%) compared with how they were 6 months after the injury. There was no evidence that a biological marker, APOE ε4 status, could predict who would deteriorate. Since then, another group from Glasgow, again using the Glasgow Outcome Scale, has compared disability at a year after injury with that about 5 years later.³ Most patients had mild head injury. At follow-up, using a conservative estimate of change, as many had deteriorated (12%) as had improved (13%). Those who deteriorated were more depressed and anxious, had lower self-esteem and had more problems with alcohol.

Neuropsychological test performance can also be used to measure change over time. A recent study compared scores on tests of memory and IQ at first assessment, in most cases within 2 years after the injury, with test performance almost 30 years later. In more than half the cases the patients had deteriorated.⁴ Men and those who were older when injured were more at risk. On the other hand, Wood and Rutherford⁵ (*see p 1180*) using very similar methods come to a more optimistic conclusion. On the whole the patients' scores on measures of IQ at 16-year follow-up were better than those within a few years after injury. More patients improved than deteriorated. Excluding those who were first assessed within 2 years of injury made no difference. Thus, there was no evidence that the good outcome was simply because of continuing spontaneous recovery early after the first assessment. About half the patients had their first assessment as part of a medicolegal assessment for compensation. Perhaps because they were claiming compensation they had underperformed when first assessed and this explained why they did better when retested many years later. However, in a separate analysis, the authors found no effect of status at first assessment, medicolegal versus routine NHS clinic, on the outcome.⁶

Wood and Rutherford's study is not the first to suggest that the long-term outlook is good. Across all studies the evidence is ambiguous and conflicting.¹ It is difficult to discern any convincing explanations for the differences between studies. It has been suggested that cohorts recruited from rehabilitation units may do better, and that the observed outcome in studies with a high drop out rate is also likely to be better. Other factors to be considered are the age of the cohort when injured, the length of the follow-up period and the method used to reliably detect change over time. For the time being, the evidence suggests that in those with milder injuries adverse psychosocial factors are associated with deterioration. For those with more severe injuries who deteriorate, it will be interesting to see if biological effects are found.

J Neurol Neurosurg Psychiatry 2006;77:1105.
doi: 10.1136/jnnp.2006.099697

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Published Online First 17 July 2006

Competing interests: None declared.

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