Matters Arising

HM MEINCK
Section of Clinical Neurophysiology, Rupeke-Karls-Universitats-Heidelberg, Germany


Matte et al reply:
We thank Dr Meinck for his comments and the presentation of two additional cases of isolated muscle hypertrophy. However, comparing his and our cases, the EMG results were substantially different. As Dr Meinck states, both his patients showed intramuscular areas which were silent on EMG close to areas with diffuse spontaneous activity. Silent EMG areas were not present in our patients. We intended our cases to make a contribution to the understanding of the neuropathology of isolated muscle hypertrophy after peripheral nerve or root lesions. We showed that this phenomenon is not restricted to the calves and may affect other muscles as well, where the stretch hypothesis for generation of muscle hypertrophy might be un true and the diffuse spontaneous activity of the muscle fibres might have caused hypertrophy. We agree that tumours are much more common causes of muscle masses and might cause spontaneous activity on EMG when invading terminal nerve branches. However, as stated, there are silent EMG areas within tumours. In these and doubtful cases we also perform MRI.

MATTLE
Department of Neurology, Inselspital, CH-3010 Bern, Switzerland

Iron and Akathisia

The report by O’Loughlin et al on the serum iron status of patients with acute neuroleptic-induced akathisia is of interest to us as our own similar investigation revealed no associated between the two. Since the publication of our findings, we have repeated the study on a further 50 patients recently started on neuroleptic medication, with further negative results (unpublished). Studies of serum iron status in “chronic akathisia” have reported similarly conflicting findings. It would therefore be worthwhile at this stage to re-examine the rationale and the methodology of the studies. We commend Dr O’Loughlin and colleagues for their attention to detail, except for the following points: 1) The definition of akathisia used in their study was based on scale scores. Not only have the psychometric properties of this scale not been published, it was also designed to rate and not “diagnose” akathisia. As we point out elsewhere, the issue of appropriately defining akathisia is of paramount importance. 2) The small number of patients with akathisia involved; 3) The failure of the authors to report the differential neuroleptic doses of the two groups. The dose can be an overriding factor that can obscure the contribution of any other factors difficult to determine; 4) The lack of any correlation between Simpson and Angus scores and akathisia scores is surprising, suggesting that their patients may not have typical acute akathisia.

There are some important theoretical considerations. What constitutes iron deficiency, and whether serum biochemical measures accurately reflect the state of brain iron, is debatable. While transferrin is important for the exchange of iron between tissues, its saturation in the serum fluctuates between 20-50% in normal subjects (due to mono- and dimeric forms), and small variations in saturation seen in the above study are unlikely to affect iron delivery. The most important determinant of tissue iron delivery is the total number of transferrin receptors, and an efficient hematocrit mechanism exists to maintain the rate of iron transported to the tissues. The turnover of iron in the brain is low, and it has a tendency to resist iron depletion, raising further doubts about the pathophysiological significance of the reported findings. It is also possible that neuroleptic drugs either mobilise iron from peripheral tissues into the brain, or decrease the turnover in the brain, making peripheral measures of iron status even more sus-pect in revealing the iron status in the brain. MRI may be one method of overcoming this problem, but only good animal models are likely to provide the final answer.

Despite these objections, we feel that there are compelling reasons to study the interaction of iron and neuroleptic drugs. The fall in serum iron and transferrin in the patients with akathisia reported by O’Loughlin et al is intriguing, even though its significance for the development of akathisia is questionable. Rosebush and Mazurek reported somewhat similar findings for patients with drug-induced neuroleptic malignant syndrome. Little is known about the effect of neuroleptics on ferro-kinetics. Clearly this area needs further informed investigation.

PERMINDE SACHDEV
Neuropsychiatric Institute, St John’s Hospital, Anzac Parade, Little Bay, NSW 2036, Australia.


Iron and Akathisia

The report by O’Loughlin et al on the serum iron status of patients with acute neuroleptic-induced akathisia is of interest to us as our own similar investigation revealed no associated between the two. Since the publication of our findings, we have repeated the study on a further 50 patients recently started on neuroleptic medication, with further negative results (unpublished). Studies of serum iron status in “chronic akathisia” have reported similarly conflicting findings. It would therefore be worthwhile at this stage to re-examine the rationale and the methodology of the studies. We commend Dr O’Loughlin and colleagues for their attention to detail, except for the following points: 1) The definition of akathisia used in their study was based on scale scores. Not only have the psychometric properties of this scale not been published, it was also designed to rate and not “diagnose” akathisia. As we point out elsewhere, the issue of appropriately defining akathisia is of paramount importance. 2) The small number of patients with akathisia involved; 3) The failure of the authors to report the differential neuroleptic doses of the two groups. The dose can be an overriding factor that can obscure the contribution of any other factors difficult to determine; 4) The lack of any correlation between Simpson and Angus scores and akathisia scores is surprising, suggesting that their patients may not have typical acute akathisia.

There are some important theoretical considerations. What constitutes iron deficiency, and whether serum biochemical measures accurately reflect the state of brain iron, is debatable. While transferrin is important for the exchange of iron between tissues, its saturation in the serum fluctuates between 20-50% in normal subjects (due to mono- and dimeric forms), and small variations in saturation seen in the above study are unlikely to affect iron delivery. The most important determinant of tissue iron delivery is the total number of transferrin receptors, and an efficient hematocrit mechanism exists to maintain the rate of iron transported to the tissues. The turnover of iron in the brain is low, and it has a tendency to resist iron depletion, raising further doubts about the pathophysiological significance of the reported findings. It is also possible that neuroleptic drugs either mobilise iron from peripheral tissues into the brain, or decrease the turnover in the brain, making peripheral measures of iron status even more sus-pect in revealing the iron status in the brain. MRI may be one method of overcoming this problem, but only good animal models are likely to provide the final answer.

Despite these objections, we feel that there are compelling reasons to study the interaction of iron and neuroleptic drugs. The fall in serum iron and transferrin in the patients with akathisia reported by O’Loughlin et al is intriguing, even though its significance for the development of akathisia is questionable. Rosebush and Mazurek reported somewhat similar findings for patients with drug-induced neuroleptic malignant syndrome. Little is known about the effect of neuroleptics on ferro-kinetics. Clearly this area needs further informed investigation.

PERMINDE SACHDEV
Neuropsychiatric Institute, St John’s Hospital, Anzac Parade, Little Bay, NSW 2036, Australia.

Disturbances of C-fibre-mediated sensibility in lumbar sacral disc disease

I was interested to read the communication by F Strian et al.1 There is difficulty, however, in accepting that heat pain threshold is lowered in the foot contralateral to the sciatic root compression, rather than raised in the foot ipsilateral to the lesion (as is the warmth threshold).

With JA Campbell, AW Chan, G Leijon and T Nurmikko, thresholds to most somatosensory stimuli have been measured by the method of limits, at five body sites on each side in a large number of volunteers, as well as in patients with neurogenic pain conditions. In the case of the foot, a Marstock Peltier thermode measuring 25.0 × 50.0 mm (12.5 cm²) was applied just below the medial malleolus, where the skin is neither thickened nor hairy. Our results for warmth and heat pain in (1) the normal foot; (2) the diabetic foot; (3) postherpetic neuralgia; and (4) central post-stroke pain ("thalamic syndrome") are shown in table 1. In cases 3 and 4, comparison is made (paired t test) with normal immediately applied to the other side of the body, while in (2) age-matched normal subjects were used (unpaired t test). Our results suggest that while there is a large rise in the warmth threshold (average about 6°C), or warming rate, for the warm-cold limen, on the affected side, there is only a very small (average about 2°C), but significant, rise in the heat pain threshold, also on the affected side.

Strian et al used a thermode measuring 6 cm². With J Giewal, we have performed experiments using both large (12.5 cm²) and small (1-3 cm²) thermodes, and found that while warmth thresholds vary according to the surface area of the thermode, heat pain thresholds do not. We find the ipsilateral mean (SD) heat pain threshold of 48.1 (1-6°C) to be significantly higher compared with our normal thresholds (see table 2) and those found by others, and would suggest that the ipsilateral heat pain threshold in the patients of Strian et al may be raised.

It would be helpful to know how many of their 9 patients had L5 root lesions and how many S1; where on the foot they measured heat pain thresholds for the two roots; and whether there is any difference according to

disturbances of C-fibre-mediated sensibility in lumbar sacral disc disease.

Table 1 Mean warmth and heat pain thresholds (°C) in normal feet

| Age (mean) | 17-30 (22-1) | 31-45 (35-1) | 46-60 (54-1) | 61-74 (68-7) | 75+ (72-7) |
| Number     | 28           | 28           | 28           | 28           | 28         |
| Warmth threshold (SD) | 36-75 (3-22) | 37-65 (2-89) | 37-75 (2-88) | 39-4 (4-03) | 38 (3-2)  |
| Heat pain threshold (SD) | 41-5 (2-7)   | 41-75 (2-4)  | 43-0 (3-3)   | 43-1 (2-5)  |

Table 2 Mean (SD) warmth thresholds, warm-cold limen, and heat pain thresholds (°C) in neurogenic pain conditions

<table>
<thead>
<tr>
<th>Painful diabetic neuropathy</th>
<th>Warm Pain Threshold: 46-2 (2-6)</th>
<th>Warm Pain Threshold: 43-0 (3-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Warmth threshold (SD)</td>
<td>37-75 (2-88)</td>
<td>39-4 (4-03)</td>
</tr>
<tr>
<td>Heat pain threshold (SD)</td>
<td>41-75 (2-4)</td>
<td>43-1 (2-5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postherpetic neuralgia</th>
<th>Warm Pain Threshold: 45-8 (0-5)</th>
<th>Warm Pain Threshold: 43-1 (0-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>69-5</td>
<td>69-5</td>
</tr>
<tr>
<td>Warmth threshold (SD)</td>
<td>37-75 (2-88)</td>
<td>39-4 (4-03)</td>
</tr>
<tr>
<td>Heat pain threshold (SD)</td>
<td>41-75 (2-4)</td>
<td>43-1 (2-5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Central post-stroke pain</th>
<th>Warm Pain Threshold: 43-8 (0-4)</th>
<th>Warm Pain Threshold: 42-7 (0-45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Warmth threshold (SD)</td>
<td>37-75 (2-88)</td>
<td>39-4 (4-03)</td>
</tr>
<tr>
<td>Heat pain threshold (SD)</td>
<td>41-75 (2-4)</td>
<td>43-1 (2-5)</td>
</tr>
</tbody>
</table>


Strain et al reply: We found the comments of Dr Bowsher on our article very informative, and a suitable starting point for a discussion on the diagnostic value of heat pain sensitivity testing. His main concern was that the mean heat pain threshold in the dermatome ipsilateral to the chronic nerve root compression was 48.1°C, which he found unaccountably high. We wish to point out that our controls' value was 47-3°C in this study and that we had obtained a value of 46-5°C at the same sites in a much younger group of healthy subjects. We therefore think the question is why our values consistently higher than those reported by Bowsher, which are in the range of 41°C to 43°C.

Even with contact thermodes, the heat pain threshold cannot be considered as a physiological constant given in °C. It is clearly dependent on the physical characteristics of the thermode and the measurement procedures. We will give some examples of our experience. We recently changed from Marstock type thermodes (used also in the study under discussion) to a more advanced model with the same surface area (6 cm²).

Because of the different characteristics of these thermodes that is, the isolation layer between the Peltier elements and the thermode surface - an average lowering of the heat thresholds of about 1°C occurred.2 The heat pain thresholds of the affected site measured at the lateral dorsum media pedis were 44-9 (1-5°C) (17-29 years), 44-8 (1-9°C) (30-44 years) and 45-7 (1-2°C) (45-63 years). These values are still considerably higher than those given by Bowsher. We think that there may be two reasons.

First, threshold estimates in the early trials were lower and more variable than in the later ones. For example, the difference between the first and the eighth trial was a measure- ments on the foot was found to be -1°C.3 We therefore disregard the first three trials in evaluation. Second, with the traditional Marstock procedures the temperature increases start from temperatures around 30°C and may lead to what we would call "premature pain responses" at temperatures well below 40°C. This can again be clearly seen in a very recent study by Jensen et al.4 To avoid this, we set the base temperatures to 38°C or 40°C, which is levels that have not been felt painfully by any of our patients or control subjects.

Considering these factors, we think that the pain threshold values we reported, although different from those of Bowsher, should be considered valid and that it is very unlikely that the difference between the pain thresholds reported in our study and the contralateral decrease as a result of the nerve root compression is the consequence of an ipsilateral threshold increase rather than a contralateral threshold decrease. (As a reminder, the contralateral value was 45-8°C and significantly smaller than the value of the health controls).

We read the findings of Bowsher on heat pain and warmth sensitivity in different patient groups with interest and have no difficulty agreeing with them. However, hypalgesic phenomena in diabetic, postherpetic and post-stroke patients do not exclude the possibility of hyperalgesic phenomena in
Iron and akathisia.

P Sachdev

*J Neural Neurosurg Psychiatry* 1992 55: 1221-1222
doi: 10.1136/jnnp.55.12.1221-a

Updated information and services can be found at:
[http://jnnp.bmj.com/content/55/12/1221.2.citation](http://jnnp.bmj.com/content/55/12/1221.2.citation)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)