

**RESEARCH BULLETIN 33:
April 2004**



This bulletin provides a short summary of the research relating to MS and other neurological diseases in the following major scientific journals:

Archives of Neurology	February 2004
British Medical Journal	March 2004
Journal of Neurology, Neurosurgery and Psychiatry	April 2004
Neurology	April 2004
Multiple Sclerosis	April 2004

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FATIGUE

Relating fatigue to nerve fibre loss

Title: The Relationship Between Diffuse Axonal Damage and Fatigue in Multiple Sclerosis.

Authors: M Tartaglia, S Narayanan, S Francis, A Santos, N De Stefano, Y Lapierre & D Arnold.

Place of Report: Quebec, Canada.

Journal Reference: Archives of Neurology, 2004. Vol. 61, pages 201-207.

Research Summary

Fatigue is a common symptom of MS and is often described as one of the most disabling - it is one of the major reasons for unemployment amongst people with MS. The biological basis of fatigue is not well understood and a number of processes have been investigated. Previous studies have hinted that the widespread nerve fibre loss that occurs in MS, rather than the number or position of specific areas of damage (called lesions) in the brain and spinal cord (central nervous system), may be responsible or closely linked with fatigue. This study aimed to investigate the possible link between widespread nerve fibre loss, by measuring levels of markers associated with nerve loss, and fatigue.

60 people with relapsing remitting and secondary progressive MS took part in the study. All participants were asked to self-rate their fatigue after completion of an MRI scan designed to measure nerve fibre loss. On the basis of this, participants were divided into two groups – those who reported low levels of fatigue (26 participants) and those with high levels of fatigue (34 participants). In addition, levels of disability were assessed by a neurologist.

Results showed that nerve fibre loss was significantly associated with increased fatigue in people with MS. This result was independent of disability levels, age, disease type or duration. This study found no correlation between the number (or type) of lesions and the perception of fatigue.

The report highlights that the mechanisms behind fatigue are unknown, but that it is increasingly likely that it is related to the nerve fibre loss and dysfunction which occurs in MS. Nerve fibre loss in the brain and spinal cord means that messages passing to the rest of the body need to be “re-routed” The authors suggest that this may cause an increase in the nervous system “effort” necessary to perform the same task and this may result in the perception of fatigue. The results from this study imply that therapies aimed at protecting nerves maybe beneficial in delaying or preventing the development of fatigue.

Key messages

- Fatigue is a common and disabling symptom of MS.
- The biological basis of fatigue is not well understood although it is possibly linked to widespread nerve fibre loss in the brain.
- 60 participants took part in a study to investigate whether self-assessed fatigue was related to nerve fibre loss.
- Participants who rated their fatigue as high were more likely to have more widespread nerve fibre loss.
- This effect was independent of other variables such as age, disability level or number of localised areas of nerve damage (called lesions).
- It’s suggested that nerve fibre loss may increase the nervous system “effort” necessary to perform the same task, possibly resulting in fatigue.
- Therapies aimed at protecting nerves may be beneficial in delaying or preventing the development of fatigue.

EXPERT PATIENT

Reaction to the term “Expert Patient”

Title: “Expert patient” – dream or nightmare? (Editorial).

Author: J Shaw.

Place of Report: London, UK.

Journal Reference: British Medical Journal, 2004. Vol. 27, pages 723-724.

Research summary

The “Expert Patient” programme is a course for people with long-term diseases, (originally developed in the US) which is run by trained volunteer tutors. It places emphasis on giving people the necessary skills and confidence to deal with their condition and work in partnership with health professionals, to improve their quality of life. The Programme has now been running for two years, in a number of different long-term diseases, including MS, but reactions from health professionals are mixed.

This report highlights that many doctors believe the term “expert” patient is associated with demanding, unreasonable or time-consuming patients. From a survey conducted by the pharmaceutical industry, over half of doctors believed expert patients would increase GP workloads, with over 40% believing it would increase NHS costs.

Research, however, shows that people who have attended expert patient courses actually take up less time and make fewer visits to health professionals, than those who haven't. For example, a trial assessing the impact of a self-management course for people with arthritis, found that participants showed consistent improvements in knowledge, self-dependence and “health promoting behaviours”, in particular exercise. The report identifies that doctors need to act on what they already know – that by understanding patient's views and concerns they are better able to identify solutions likely to lead to more successful outcomes.

The report concludes that the term “expert patient” is unhelpful in developing relationships between patients and healthcare professionals and should be

replaced with a simple, understandable phrase that is less likely to provoke the hostility that “expert patient” currently often does. The terms “autonomous” (as an opposite of a dependant patient) and “involved” patient are both put forward as possible replacements for the term “expert patient”.

Key messages

- The chronic disease self-management programme or “expert patient” programme enables people to develop skills to deal with their condition, in partnership with health professionals.
- Reactions from health professionals are mixed but many believe expert patients may be time-consuming or demanding.
- A large percentage of GPs believe that expert patients increase GP workloads and NHS costs.
- Research shows expert patients make fewer visits to GPs and have increased knowledge, self-efficacy and “health promoting behaviours”.
- Many GPs recognise that patients are experts in their own conditions and have valuable input into managing their conditions.
- The term expert patient is identified as unhelpful and suggestions for a better description include “autonomous” and “involved”.

NERVE FIBRE LOSS

Linking inflammation to nerve fibre loss.

Title: Brain tissue loss occurs after suppression of enhancement in patients with multiple sclerosis treated with autologous haematopoietic stem cell transplantation.

Authors: M Inglese, G Mancardi, E Papani, M Rocca, A Murialdo, R Saccardi, G Comi, M Filippi & The Italian GITMO-NEURO Intergroup on Autologous Hematopoietic Stem Cell Transplantation.

Place of Report: Milan, Italy.

Journal Reference: Journal of Neurology, Neurosurgery and Psychiatry, 2004. Vol. 75, pages 643-644.

Research summary

In MS, a number of events occur including inflammation, damage to myelin (the protective sheath surrounding nerve fibres) and nerve fibre loss. The link between these processes is not fully understood although it's known that substantial inflammation is associated with a greater number of damaged nerve fibres. The purpose of this study was to assess whether widespread nerve fibre loss (a process called atrophy) occurs, even when areas of inflammation in the brain and spinal cord (as visualised by MRI) have been suppressed.

Ten participants with severe, rapidly progressing secondary progressive MS took part in a study which involved treatment with stem cells (unspecialised cells which have the capacity to develop into lots of cell types). This procedure is known to cause a dramatic and sustained decrease in inflammation. The amount of atrophy was assessed at the start of the study, monthly for three months and then every three months until 24 months after the start of the study.

Results showed that only five new lesions were seen in two participants during the first three months following treatment, then no further new lesions were seen for the remainder of the 24-month follow up period. No new lesions were found in any of the other participants. This indicates that there was a

substantial suppression of inflammation. Despite this, the average rate of atrophy was about 1.9%

The authors acknowledge that they do not know the rate of atrophy of each of the participants prior to starting the study - all had aggressive MS, which may explain the large loss. However, these findings support the idea that nerve fibre loss in MS is likely to be triggered by a large amount of inflammation but proceeds even when the inflammation has been effectively suppressed. It is suggested that this might possibly be caused by a reduced ability of the body to repair damaged myelin, after inflammation.

Key messages

- In MS a number of events occur including inflammation, damage to myelin and nerve fibre loss.
- The link between these processes is not clear although inflammation appears to impact on nerve fibre loss (a process called atrophy).
- This study assessed whether atrophy continued, when inflammation was effectively suppressed (as a result of treatment with stem cells).
- Results showed that despite effective inflammation suppression, atrophy continued.
- The authors suggest that atrophy is likely to be triggered by a large amount of inflammation but proceeds independently even without continued inflammation.

CANNABIS

Cannabis for tremor?

Title: The effect of cannabis on tremor in people with multiple sclerosis.

Authors: P Fox, P Bain, S Glickman, C Carroll & J Zajicek.

Place of Report: Plymouth, UK.

Journal Reference: Neurology 2004. Vol. 62, pages 1105-1109.

Research summary

Tremor is a common symptom of MS and produces significant disability in over a quarter of people affected. It typically affects the arms and hands and does not tend to respond well to medication. It is estimated that up to 8% of people with MS use cannabis (privately) and anecdotal reports suggest that it may have a beneficial effect on a range of symptoms including pain, nausea, muscle spasms, bladder problems and tremor. However, there is little scientific evidence to support these findings, Therefore, this study aimed to investigate the effect of a cannabis extract (in tablet form) on tremor in a controlled clinical trial.

13 people took part in the study. All had moderate tremor and moderate disability levels. Tremor was objectively assessed in all participants prior to the start of the trial and then every two weeks for six weeks. All participants took either cannabis extract or placebo (a control substance known to cause no effect), for two weeks, then after a two-week gap, participants “swapped over” for the final two weeks. Assessments included an overall objective measurement of tremor using specialised measurement scales and a range of tasks designed to test tremor in functional situations.

Results showed that the oral cannabis extract was not effective in reducing tremor in the upper limbs and had no beneficial effect on functional activities. Side effects reported during the study were however, minimal.

The authors highlight that previous studies have shown some beneficial effects of cannabis extract on tremor, although this study did not. Possible reasons for this discrepancy include the lack of comparison with no treatment

during earlier studies. As participants knew they were taking cannabis extract, this may have introduced bias into the results. The dose and means of administration of the cannabis extract (orally, rather than inhaled) may also be a reason for this. The report concludes that oral cannabis does not appear to be beneficial in treating tremor and is unlikely to become an important treatment for tremor.

Key messages

- Tremor is a common symptom of MS and is difficult to treat.
- Anecdotal reports suggest that cannabis may be effective in relieving tremor (and other symptoms in people with MS).
- This study tested the effectiveness of oral cannabis extract in treating tremor by objective assessment and completion of a number of functional activities.
- No beneficial effect on tremor was reported from any of the measurements, although side effects were minimal.
- These results are in contrast to some other studies, which have shown a beneficial effect of cannabis on tremor.
- Oral cannabis does not appear to be beneficial in treating tremor and this report suggests it is unlikely to become an important treatment for tremor in the future.

STRESS

Does stress trigger relapses?

Title: Association between stressful like events and exacerbation in multiple sclerosis: a meta-analysis.

Authors: D Mohr, S Hart, L Julian, D Cox & D Pelletier.

Place of Report: California, USA.

Journal Reference: British Medical Journal, 2004. Vol. 328, pages 731-733.

Research summary

Relapsing remitting MS is the most common form of MS and is characterised by periods of relapse (“attacks”) followed by periods of recovery (remission). There are a number of theories as to what triggers relapses, and viruses have been implicated. Many people with MS also report that relapse onset is linked to stressful life events, although there is little research based evidence to back this up. This report comprises an analysis of studies (of various quality) which have investigated psychological stress and relapse onset, to clarify any possible relationship.

14 studies, which took place between 1965 and 2003, were analysed together. In all studies, the participants have a definite diagnosis of MS and all relapses were confirmed by a neurologist. All stressful events were recorded through the administration of questionnaires and/or interviews.

Results showed that psychological stress was associated with a risk of relapse, although this could not be linked to any specific type of stress. The authors also acknowledge that any link is small and not conclusive. There does not appear to be a consistent association between stress and relapse onset. Similarly, psychological stress appears to have no impact on triggering a relapse for some people. However, the authors acknowledge that stress is an individual thing and a stressful event is unlikely to affect many different people in the same way.

Scientists have previously used animal models of MS to study the effect of stress and have found that moderate stress is associated with a worsening of

symptoms. The stress may cause changes in the way the immune system responds, increasing the risk of inflammation in the brain and spinal cord. This theory has not however, been tested in people with MS. This study concludes that specific relapses cannot be linked to a specific type of stress. The potential differential effects of various types of stress or the mechanism by which stress affects inflammation in people with MS are not known.

Key messages

- Relapsing remitting MS is characterised by “attacks” (relapses) followed by periods of recovery (remission).
- There are a number of theories as to what triggers relapses and stress has been implicated.
- This study analysed the results from 14 studies which investigated the possible link between stress and relapses onset.
- Results showed psychological stress was linked to relapse onset although the association was small and not consistent.
- Stress is acknowledged to be an individual experience and is unlikely to affect everyone in the same way.
- The mechanism by which stress may be associated with relapses in people with MS is not known.

CARERS

Support for carers

Title: Caregivers of people with multiple sclerosis: evidence of support.

Authors: L McKeown, A Porter-Armstrong & G Baxter.

Place of Report: Northern Ireland.

Journal Reference: Multiple Sclerosis, 2004. Vol. 10, pages 219-230.

Research summary

MS is an unpredictable disease and its severity, progression and symptoms can vary greatly over time. There is often disability progression and effects on daily living and subsequently care needs, can change over time. Many people with MS rely on some level of assistance from an "informal" carer (e.g. a family member) to remain in their own home. However, for many people, providing care for a person with MS can affect their own quality of life, well-being and career. Studies have also shown that carers often perceive that they have low levels of support and do not take up formal community support services. The purpose of this study was to examine the experiences of a group of carers for people with MS.

The study used group interviews (3-5 carers per group) to examine the experiences of 16 carers. All carers were over 18 years old, had been caring for a person with MS for over a year and had required (at some point) at least one hour of assistance with personal care, per week. Each focus group lasted two hours and participants were free to discuss any aspect of caring (i.e. the interviews were not structured).

Results showed that in the early stages of caring neither the carer nor recipient wanted support, possibly due to a desire "not to want to know what might happen" or to "maintain normality". As time progressed, many carers appeared to become aware they needed support but were unwilling to ask for it. Carers reported a sense of responsibility that "it was their job and they shouldn't ask for help", or that people providing the help wouldn't do as thorough a job as they did. Most carers expressed a strong desire to care for their loved one without formal assistance.

Some carers reported reaching a crisis point, after which they felt forced to seek support from formal care support services. Barriers to obtaining formal care included a lack of information about available services, long waiting times and inflexibility. Once formal support was sought, which was perceived as suitable, carers reported reaching a stage where they could accept the support service offered, although frequently carers felt that these services did not meet their needs or those of the care recipient.

This study concludes that carers appear to experience an "inner conflict" between desiring independence in their role as a carer and wanting support. The balance of this appears to shift over time with carers accepting that they may need some degree of formal support. The report highlights that the acceptance of support is a fluid, changing process and provides an insight for healthcare professionals into peoples attitudes about caring and acceptance of support over time.

Key messages

- MS is an unpredictable disease and people's needs can vary significantly over time.
- Many people with MS have an "informal" carer.
- This study examined the experiences of a group of informal carers by using group interviews.
- During the early stages of MS, carers were reluctant to accept help with caring, and felt it was "their job".
- This study found that over time carers experienced a shift in opinion (sometimes after a crisis point) and often sought formal support.
- Barriers to obtaining help with caring included a lack of information about available services, long waiting times and inflexibility.
- This study highlights that acceptance of support for carers is a fluid process and provides an insight into people's attitudes to caring.

OSTEOPOROSIS

Bone loss in men with MS

Title: Risk of bone loss in men with multiple sclerosis.

Authors: B Weinstock-Guttman, E Gallagher, M Baier, L Green, J Feichter, K Patrick, C miller, K Wrest & M Ramanathan.

Place of Report: New York, USA.

Journal Reference: Multiple Sclerosis, 2004. Vol. 10, pages 170-175.

Research summary

Osteoporosis is a disease of the bones characterised by reduced bone density and bone deterioration. This in turn leads to "fragile bones" and increases the risk of fractures. Traditionally it was thought to be a disease which affects women primarily, although research has now shown that it also occurs in men, with effects evident during their 60s and 70s. A recent study of women with MS found that they have a higher risk of osteoporosis, than women of the same age who don't have MS. This study investigated the prevalence of reduced bone density in men with MS.

The strength of the bones (bone mass density: BMD) was analysed in 40 men with MS, with moderate levels of disability. Results were compared to 93 women with MS of a similar age. 25% of the men had primary progressive MS, 60% had secondary progressive, and just over 15% had relapsing remitting MS. The average age of the men in this study was 52 years.

Results showed that 80% of the men examined had some degree of reduced BMD. This could be defined as osteopenia (low bone density) in just over half, and osteoporosis in the remaining 38%. This was similar to the percentage of women who were affected, with 82% having some degree of reduced bone density. The study acknowledges there was no comparison made with men of a similar age who did not have MS. The authors highlight that these results suggest that osteoporosis and loss of bone density is a potentially serious health problem in males with MS, that is under recognised.

Limited walking has been implicated as an important contributor to reduced BMD, particularly in the femur (thigh bone), although wheelchair users appear to maintain some bone density possibly through positioning in the chair. Other possible contributory factors to reduced BMD include steroid use. Reduced BMD in people with MS is a particularly important issue as people may be more prone to falls due to potential problems with balance, weakness and mobility. This study suggests that increased awareness and bone screening of people with MS over the age of 40 may be warranted.

Key messages

- Osteoporosis is a disease of the bones characterised by reduced bone density and bone deterioration, which can lead to fractures.
- Women with MS have been shown on average to have lower bone density than women of the same age without MS.
- This study investigated the prevalence of low bone density in 40 men with MS.
- Results showed 80% of men had some degree of low bone density, with 38% diagnosed with osteoporosis.
- Limited walking and steroid use are both thought to contribute to low bone density.
- Loss of bone density appears to be a serious problem in people with MS, particularly those more prone to falls.
- This study suggests that bone screening of people with MS over 40 may be warranted to target this potential problem.

BETA INTERFERON

Long term follow up of different doses of Avonex

Title: Interferon beta-1a in relapsing multiple sclerosis: four-year extension of the European Interferon Beta-1a Dose-Comparison Study.

Authors: M Clanet, L Kappos, H-P Hartung, R Hohlfeld and the European IFN Beta-1a Dose-Comparison Study Investigators.

Place of Report: Toulouse, France.

Journal Reference: Multiple Sclerosis, 2004. Vol. 10, pages 139-144.

Research summary

There are currently two different types of beta interferon (beta IFN) available – beta IFN-1a (Avonex, Rebif) and beta IFN-1b (Betaferon). These are available for people with relapsing remitting MS and secondary progressive MS with relapses. All have been shown to reduce the relapse rate by around a third, although effects on disease progression are limited.

Avonex is given as an injection into the muscle once a week. This study reports on the four year extension of an original three year study to establish whether a higher dose of Avonex (60 micrograms: mcg), rather than the standard 30mcg dose, could impact on disease progression.

A total of 446 participants with relapsing forms of MS completed the full four year monitoring period. On average, participants had fairly mild disability at the start of the trial, with an average relapse rate of 1.3 per year. The major aim of this trial was to assess the effect of both doses on disability progression, therefore disability levels were assessed every 3 months.

Results showed that after four years the rate of disability progression was not significantly different between the two doses. By the end of the study the disability levels of 30% of participants (in both groups) were more advanced and 22% were assessed as having moderate disability. Similarly, there were no differences in the self-reported relapse rates of both groups over the study period, with both groups having an average of 0.75 relapses per year. Side

effects in both groups were generally mild, and included flu-like symptoms, depression and headache.

In summary, results showed that the effectiveness of 30mcg and 60mcg Avonex is equivalent and this effect is sustained for the four year period of monitoring. This study adds important information about the safety and effectiveness of Avonex over a longer treatment period.

Key messages

- Avonex is a type of beta interferon-1a, which is available for people with relapsing remitting MS and secondary progressive MS with relapses.
- It has been shown to reduce relapse rates by a third although effects on disability progression are limited.
- 30mcg of Avonex was compared with a 60mcg dose to assess impact on disability levels.
- Results after four years showed no difference in the rate of disability progression or reduction in relapses, between the doses.
- Side effects of both doses were generally mild.
- 60mcg Avonex offers no advantage over 30mcg although this study provides important information about the long-term safety and effectiveness of Avonex.

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