Biochemical Abnormalities in Children with ME/CFS

Illness in youngsters has a particular poignancy; the transformation of a bright, active child into one who is unable to go to school or play with friends is something that touches us all. Estimates of the numbers of children affected by ME/CFS vary, but with prevalence figures of 60–70 cases per 100,000, it is likely that around 9,000 people under the age of 16 in the UK have this diagnosis. As the report to the Chief Medical Officer in 2002 made clear, this illness "represents a substantial problem in the young" and "potentially threatens physical, emotional, and intellectual development of children and young people, and can disrupt education and social and family life, at a particularly vulnerable time of life".

In a previous issue of Breakthrough (issue 11, Spring 2010), we reported the results of a study on the quality of life of children with ME/CFS, recently published in Pediatrics by Dr Gwen Kennedy at the Vascular and Inflammatory Diseases Research Unit in the University of Dundee. In parallel with this work, Dr Kennedy and her colleague Dr Faisel Khan have been investigating biochemical and vascular abnormalities in children with the disease, and their results have just been published in the US journal Archives of Pediatrics & Adolescent Medicine. Like the previous study, this work was supported financially by ME Research UK, The Young ME Sufferers (Tymes) Trust and Search ME (see Box A).

The Dundee group had previously reported a number of biochemical and vascular abnormalities in adults with ME/CFS. These mainly involve the immune and cardiovascular systems, and include an increase in the programmed death (apoptosis1) of white blood cells, raised levels of oxidative stress which can damage blood vessels and other organs, increased markers of inflammation, and abnormalities in blood vessel function. All of these are potentially associated with a future risk for cardiovascular problems such as heart disease and stroke.

Drs Kennedy and Khan wanted to investigate whether these abnormalities were also present in children with ME/CFS, given the potential long-term consequences for cardiovascular risk. Risk factors such as high cholesterol and increased blood pressure, which are usually associated with adult diseases, have also been found in children and can progress into adulthood as hypercholesterolaemia and hypertension, so it is important that risks are identified as early in life as possible.

Twenty-five children with ME/CFS (all between the ages of 10 and 18 years) and 23 healthy children matched for age, gender and stage of puberty were recruited from throughout the UK. The diagnosis of ME/CFS had been made according to a revised version of the CDC-1994 case definition, and was confirmed by the researchers from a clinical examination.

A blood sample was taken from each child (using an anaesthetic cream to minimise their discomfort), and this was then subjected to a battery of tests in Dr Kennedy's laboratory (see Box B). The child's blood pressure was measured, and then the pulse at their wrist was detected using a special pen-like probe applied lightly to the skin. This records the fluctuations in pressure as each pulse travels along the artery, and is exactly what you feel with your finger when you take your own pulse. This recording of the pulse is then analysed on a computer to give information on how flexible the artery is, which gives an indication of its health and function.

Overall, compared with healthy control children, the young people with ME/CFS had:

1. Higher levels of oxidative stress, manifested as elevated levels of isoprostanes
2. Reduced levels of vitamins C and E
3. A greater percentage of white blood cells undergoing apoptosis.
4. A trend towards increased arterial stiffness, although this was not statistically significant.

Dr Kennedy suggests that the increased oxidative stress may be due to a deficiency of antioxidants in the diet (such as vitamins C and E, which were found to be reduced here). However, she feels it is more likely to have been caused by white blood cells releasing an excessive amount of highly reactive free radicals, possibly from exercising muscle. This would tie in with the finding of increased white cell apoptosis, and Dr Kennedy has previously reported increased oxidative stress following exercise in adults with ME/CFS. She does emphasise, however, that more studies, perhaps including an assessment of diet, are needed to determine this mechanism.

The increased apoptosis (or programmed cell death) may be caused by a number of factors, including a persistent viral infection or toxic agent, or an abnormal immunological response. This finding is particularly intriguing given that many patients, including most children in this study, report that their disease started following a viral infection of some kind. At present, however, there is insufficient evidence to make a causal link between infection and increased apoptosis, though the finding is tantalising.

Although there were no other statistically significant changes in the children with ME/CFS, there was a clustering of markers such as arterial stiffness and cholesterol that showed small changes which may indicate the possibility of future cardiovascular risk. This type of clustering has been shown before in healthy children and in young people with diabetes. Although it should be stressed that children with ME/CFS are at no immediate risk of developing cardiovascular problems, these changes to become greater (closer to the adult pattern) as the children grow older and have been ill for longer.

Dr Kennedy and her team conclude their report by saying that the findings show that many children with ME/CFS “have an underlying, detectable abnormality in the behaviour of their immune cells, consistent with an activated inflammatory process”, and provide evidence of “a persistent or reactivating viral infection triggering apoptosis of white blood cells with an increased production of free radicals”.

To date, aside from symptomatic treatments, no specific therapy is available for children or adults with ME/CFS, and there is an urgent need for intervention trials, which could include both pharmacological and non-pharmacological strategies (such as for the dysautonomia reported in ME/CFS patients including children), or antioxidant or antiviral interventions.

Box A - Financial support

The Young ME Sufferers (Tymes) Trust is the longest-established UK service for children and young people with ME and their families. It is a respected national charity whose entire team give their time free of charge. It runs an Advice Line, provides access to ME experts for doctors, teachers and social workers, and produces a magazine for children, families and professionals. The Trust played a major role in producing the children's section of the Department of Health Report on CFS/ME (2002). It promotes interactive virtual education for children with ME, and provides the Tymes Trustcard — a pass card for children in school, endorsed by the Association of School and College Leaders. See their website www.tymestrust.org for details and free publications.

Search ME
Search ME, based at Rosyth in Fife, was founded in 2002. Its aims are to improve the lives of people with ME and to provide them with a voice on the Cross Party Group for ME in the Scottish Parliament. The charity has raised the bulk of its donations through organising rock and pop concerts. Search ME became an early supporter of the work at the University of Dundee and helped fund the research carried out there, of which the members are very proud. Further information can be found on their website www.search-me.org.uk.

Box B - Biochemical measurements

Oxidative stress
Oxidative stress is damage caused by highly reactive molecules called free radicals. They are normally kept under control by natural processes which remove them from the circulation, but when an imbalance occurs they can be left to cause damage unchecked. In particular, free radicals can change our normal "good cholesterol" into something more harmful, leading to heart and circulation problems. This "bad cholesterol" is known as oxidised low density lipoprotein. The reaction of free radicals with essential fatty acids (which are important substances obtained from the diet) produces compounds called isoprostanes, which act as another marker of oxidative stress. Other signs of oxidative stress include low levels of vitamin C and vitamin E.

Inflammation
Inflammation is a complex set of immunological and vascular processes which occur in response to injury or infection. Although it is a vital part of our body's defence mechanism, prolonged inflammation can be harmful to otherwise healthy tissue, and causes diseases such as rheumatoid arthritis. In particular, it can cause damage to blood vessels leading to cardiovascular disease. C-reactive protein is found in the blood and its levels rise in response to inflammation, making it a useful marker.

1Apoptosis
Apoptosis is the programmed destruction of unwanted cells in the body. It is an important process removing cells that have reached the end of their natural life, as well as controlling infections. Apoptosis is carried out by white blood cells called neutrophils, which are part of the immune system. Increased apoptosis can be a sign of abnormalities in the immune system, and may be caused by a persistent viral infection or quicker-than-normal turnover of neutrophils. Apoptosis can be measured by looking at the expression of the protein annexin V and other substances on the surface of neutrophils. This gives an indication of what

proportion of these cells are healthy, dead because of external factors, or dead because of apoptosis.

Pain in ME/CFS

Pain is a very common symptom in ME/CFS; it tends to be experienced in the muscles and/or joints, but it can often be widespread and changeable in location and intensity. In one survey, quoted in the Chief Medical Officer's report, 79% of patients said that they had severe pain sometimes, much of the time, or all of the time, and between 84 and 94% of patients in formal research studies report some degree of muscle or joint pain. Importantly, 53% of unemployed people surveyed recently by the campaigning charity Action for ME said that chronic pain was one of the greatest barriers to their obtaining paid employment.

Despite this, there is very little scientific information about the specific pain characteristics of ME/CFS patients – what kind of pain is it? where is it localised? what strength is it? To explore such questions, ME Research UK provided part-funding for a PhD studentship, under the supervision of Prof Lorna Paul and Dr Les Wood (pictured), at Glasgow Caledonian University. The student, Rebecca Marshall, has now submitted her thesis, and the first scientific paper from her work has just been published in the Journal of Musculoskeletal Pain.

For the investigation, 50 people with ME/CFS and painful symptoms were recruited from support groups across Scotland; all had previously been diagnosed by a consultant or general practitioner, and all met the CDC-1994 and Canadian Guideline symptom criteria. No participants had any psychiatric illness or any other serious conditions such as cancer, rheumatoid arthritis or multiple sclerosis (which would have affected their experience of pain). The investigators visited the patients in their own homes to conduct their interviews, which allowed the participation of those who were so severely affected that they would not have been able to make a trip to the hospital. This was particularly important in this study since the researchers wanted to ensure that the findings represented the full spectrum of ME/CFS. Between 10% and 25% of ME/CFS sufferers fall into the "severe" category, so 10 of the 50 patients interviewed by Dr Paul's team were either housebound or bedbound and had been recruited via the national charity, the "25% ME Group" which caters for severely ill patients.

Overall, the 50 patients had been ill for an average of 12.6 years (range 1.3 to 27.4), and only one was working full time, and two part-time. A number of tools and questionnaires were used to evaluate participants' experience of pain, and these consisted of a visual analogue scale, the Margolis Body Chart, the McGill Pain Questionnaire, the Pain Anxiety Symptoms Scale-20 and the Medical Outcome Survey Short Form-36 (see box 1 for more detailed descriptions of each of these).

The results revealed that pain is indeed an important symptom of patients with ME/CFS. The most common painful symptom was muscle pain, which was reported by over two thirds of patients. The average intensity of pain at the time of the interview was reported to be around 43 out of a maximum of 100 mm on the visual analogue scale (see box 1), while the average intensity over the previous 24 hours was higher at around 58 mm. The investigators suggest that this latter value may be a more accurate reflection of patients' experiences, particularly if pain fluctuates. Significantly, ME/CFS patients reported worse pain than did patients with rheumatoid arthritis or multiple sclerosis in previous studies, both

conditions in which pain is recognised as a major symptom.

Patients used words such as “throbbing”, “aching”,” tender”, “gnawing” and “burning” to describe the pain they experienced, while those with more severe illness also used “exhausting” and “nagging”. In fact, as the graph shows, only the severe patients chose the word “gruelling” while none chose the less emotive words “tight” or annoying” – indicating a more severe quality of pain, as well as intensity, in the most severely affected group. These descriptions may give clues as to the mechanisms causing pain in ME/CFS; in particular, “burning” pain is often associated with neuropathic conditions in which the nerves have been damaged. Also, they may help in assessing any change in the quality of pain over time, such as after treatment, as Dr Paul’s group suggests. Despite this burden of pain, most participants described their mood as generally positive, although those with more intense pain tended to describe a lower mood.

The most common locations of pain were the cervical spine (66%), the anterior thighs (44 to 46%), the lumbar spine (42%) and the posterior calves (38%), and most participants had pain in more than one location. Nearly a third of patients said they experienced their most severe pain in the area of the cervical spine/upper trapezius, while 20% reported the scapular/upper thoracic area and another 20% reported the right lumbar spine as the most painful regions. Twenty-eight participants said they experienced the worst pain in the morning, while it was the afternoon for four individuals, the evening for ten and the night for eight.

The results of the Pain Anxiety Symptoms questionnaire suggest that the study participants were not overly anxious or fearful because of their pain, although the most severely affected were more susceptible. When considering quality of life, Dr Paul’s findings were similar to those of Dr Gwen Kennedy’s study from 2004 (published in the Annals of Epidemiology). Patients tended to have reduced physical functioning and vitality (but not emotional or mental health), and again this was more pronounced in those with more severe illness.

This is the first major study to document and categorise the pain experienced by people with ME/CFS, and to provide sound, objective, scientific support to their anecdotal and clinical reports of painful symptoms. As the authors say, “This study has emphasized that the problem of chronic pain in CFS needs to be treated as seriously as the pain experienced in other conditions such as rheumatoid arthritis and MS”.

Box 1

Visual analogue scale

Participants are asked to indicate their current pain intensity on a visual scale from 0 mm, representing “no pain”, to 100 mm, representing “most pain ever experienced”.

Margolis Body Chart
Participants use a diagram of the human body to indicate the areas in which they experience the most pain. This is then matched to a chart which divides the body into 45 sections, in order to identify the locations of most pain.

McGill Pain Questionnaire
Participants are asked to describe their pain using words from a standard list of 78, grouped into 20 subcategories. Numerical values are assigned to each word, and a Pain Rating Index is calculated as the total of the values for each word chosen. This provides a measurement of the pain itself (sensory component), as well as unpleasant feelings and emotions (affective component), and how it is judged by the sufferer (evaluative component).

Pain Anxiety Symptoms Scale-20
Participants are asked to score their experience of 20 psychological aspects of pain, such as anxiety, fearful thinking, feelings of wanting to escape or avoid a situation, and physiological responses. Each item is scored from 0 (never) to 5 (always), and the total is calculated out of a maximum of 100.

Medical Outcome Survey Short Form-36
A questionnaire consisting of thirty-six questions examining physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. The participant's answers to each question are translated into a total score from 0, representing poor health, to 100, representing good health.