MEA PURPLE BOOK, 2017 EDITION

PRINCIPAL TEXT CHANGES

PAGE 16 – NEW SECTION 4.3

Mortality in people with ME/CFS:

There is very little research examining mortality in ME/CFS. Anecdotal information, as well as some research studies, indicates that there is an increased risk of suicide.

McManimen *et al* (2016) have examined whether people with ME/CFS are dying earlier than the overall population from the same cause. This was done through analyzing data on cause and age of death from 56 people with ME/CFS. The findings from this very small study suggest that there is a significantly increased risk of earlier all-cause and cardiovascular related mortality along with a lower age of suicide and cancer. As the authors point out, this is a small study with over-representation of people with severe ME/CFS. So these findings cannot be regarded as conclusive evidence.

PAGE 24 – IN SECTION 5.3

New penultimate paragraph

Rutherford *et al* (2016) have produced a comprehensive review of muscle and mitochondrial research findings in ME/CFS.

PAGE 33 – line 3, add:

….feature of this illness. See also recent research findings by Nguyen *et al* (2016) on calcium mobilization from natural killer cells in ME/CFS.

PAGE 38 – final paragraph added

The Biobank Protocol paper has now been published in *Open Journal of Bioresources* (Lacerda *et al* 2017).

PAGE 39 – new material in shaded box

2017 Research Update

Researchers in the UK (Professor Tom Wileman *et al*) and the USA (Professor Mauren Hanson *et al*) are investigating the role of the **microbiome** in ME/CFS (Navaneetharaja *et al* 2016). Professor Hanson's group results

indicate that there is gut dysbiosis in ME/CFS with an increased incidence of microbial translocation, and this may play a role in the development of inflammatory symptomatology (Giloteaux *et al* 2016).

The collection of 'big data' involves epigenetics, metabolomics and proteomics being applied to blood, saliva and possibly other tissue samples from large numbers of people with ME/CFS. Preliminary results from a small pilot study being carried out by Professor Ron Davies in the USA have already been reported. A UK 'Grand Challenge' initiative – the MEGA study - is being developed by Professor Stephen Holgate and a group of experts from a wide range of scientific disciplines. This will involve detailed phenotyping and genetic analysis of blood and saliva samples from around 10,000 people with ME/CFS.

Further information on microbiome studies and some preliminary findings from Professor Ron Davis, can be found in an MEA website conference report:
http://www.meassociation.org.uk/2016/06/iime-conference-another-important-day-for-sharing-ideas-on-research-20-june-2016/

MEGA study website:
http://www.megaresearch.me.uk

Following on from research by Naviaux *et al* (2016) involving **metabolomics** - which found abnormalities in 20 metabolic pathways along with a metabolic response that was chemically similar to the dauer response - the MEA Ramsay Research Fund is funding the first UK metabolomics research study at the University of Oxford. More information on the MEA website:
http://www.meassociation.org.uk/2017/02/m-e-biomed-research-its-like-buses-you-wait-years-then-five-come-along-at-once-2-february-2017/

Further evidence on **energy metabolism and mitochondrial function** comes from Lawson *et al* (2016) who found that ATP levels are higher and mitochondrial cristae are more condensed in ME/CFS compared to their paired controls. However, mitochondrial crista length, mitochondrial size, shape, density, membrane potential, and enzymatic activities of the complexes in the electron transport chain remain intact. They also reported that the increased ATP largely comes from non-mitochondrial sources.

Ciregia (2016) have recently analysed **mitochondrial proteins** in a couple of monozygotic twins who are discordant for ME/CFS and found upregulation of ATP synthase subunit beta (ATPB) and aconite hydratase (ACON).

Fluge *et al* (2016) analysed **amino acids** in 200 ME/CFS patients and 102 healthy controls. They found an amino acid pattern suggestive of a functional impairment of **pyruvate dehydrogenase.** This is consistent with inadequate ATP generation by oxidative phosphorylation and excessive lactate generation upon exertion.

A **longitudinal MRI study** from Shan *et al* (2016) has investigated progressive brain changes in ME/CFS. They reported on inferior fronto-

occipital fasciculus white matter deficits which continued to deteriorate at an abnormal rate.

Mitochondrial research: Shoeman *et al* (2017) examined complete mitochondrial DNA (mDNA) sequencing of 93 ME/CFS patients and found no evidence of clinically proven mDNA mutations.

PAGE 45: Table 7

Under ENDOCRINE add:

Hyperparathyroidism – where a raised level of calcium may be quite small

Under GYNAECOLOGICAL add:

Premature ovarian insufficiency

Under NERVE AND MUSCLE add:

Macrophagic myofasciitis

PAGE 49: Table 9

Penultimate para: Add after Kavi et al (2016)

The ME Association has a new information leaflet covering PoTS and ME/CFS

PAGE 50

Add to bullet point 6/IBS:

…and back pain. Consider bile acid diarrhoea if diarrhoea is prominent.

PAGE 53

Biochemical panel, line 4:

..hypocalcaemia, hyperparathyroidism with hypercalcaemia, and sarcoidosis with hypercalcaemia and chest symptoms (Sharma 1999).

PAGE 80: Table 12

Link to House of Lords debate now removed, and final paragraph now reads:

Following the outcome of a Freedom of Information Tribunal, which resulted in release of unpublished data from the PACE trial, the data on recovery has been re-analysed by Wilshire *et al* (2017) who concluded: *The claim that patients can recover as a result of CBT and GET is not justified by the data, and is highly misleading to clinicians and patients considering these treatments.*

PAGE 93

New shaded box inserted at foot of page.

2017 updates:

Hepatitis B vaccine: This vaccine has recently been linked to macrophagic myofasciitis - a condition with very similar symptoms to ME/CFS (Rigolet *et al* 2016)

Midodrine: Results from a phase 4, double-blind, placebo-controlled, randomized tilt-table study indicate that midodrine can be of benefit in symptomatic orthostatic hypotension (Smith *et al* 2016).

Rintatolimod (Ampligen) Mitchell (2016) has reviewed the current evidence relating to chemistry, mechanism of action, clinical trial data, and current regulatory status for the use of Ampligen in ME/CFS.

Ubiquinol-10 (Co-enzyme Q10): Results from a small randomized controlled trial found that a 10 to 12 week course of ubiquinol-10 is effective in improving several CFS symptoms (Fukuda *et al* 2016).

Anakinra: Roerink *et al* (2017) carried out a four week randomised, placebo-controlled trial to assess the value of subcutaneous anakinra - a drug which inhibits interleukin 1, an important pro-inflammatory cytokine that has been linked to ME/CFS. Anakinra failed to produce any reduction in fatigue severity in 50 females with more severe ME/CFS.

PAGE 98

New material inserted in shaded box

Education and Child care proceedings

The 2002 Chief Medical Officer's Report on ME/CFS has an excellent chapter covering Children and Adolescents with ME/CFS. The report can be downloaded from the document archive section of the MEA website. As disputes relating to education and child protection are still quite common, the CMO guidance is also included here:

5.2.6 Education

Nearly all children who are severely affected and many who are moderately affected will require the provision of home tuition and/or distance learning. A critical element of the child's management is assessment and provision of educational needs. An educational plan is not an optional extra but an integral part of therapy, just as play is for the younger child. A young person who is likely to have special needs, including home tuition, should be identified early in the diagnostic process, preferably by a GP or paediatrician.

The co-ordinating clinician is then responsible for early referral to the Education Welfare Service to ensure that education is minimally disrupted. Adequate provision of continuing education needs close liaison between GP, community paediatric services, education services, the young person, and their family.

Some young people will be too severely affected by their illness to participate in any form of education, even at home. A resumption of education, in whatever form, should be managed in keeping with the general principles of activity management as outlined in Chapter 4 and Annex 6. Specifically, a young person with CFS/ME should never be forced to study but instead should be encouraged to set a pace that is likely to be sustainable, then have their progress regularly reviewed.

With support and reassurance, both schools and families can reach a position where the child is attending their school for short periods, is working in a separate area quietly if need be, can rest or work as their ability to concentrate fluctuates through the day, and can maintain some contact with their peers. Gradually they can be reintegrated into the mainstream education system. The advantage of this approach is that it minimises the isolation of the child once he or she is able to get out of the house. It does require sensitive negotiation with the school and a tolerance on all sides.

Some more severely disabled children may need home tuition and/or distance learning on a longer-term basis. In addition to the time of a tutor or therapist, this may require information and communications technology, which can also hel improve social contact.

5.2.8 Child protection

On occasions, families of child sufferers with more severe CFS/ME have been the subject of child protection concerns. The Working Group notes that neither the fact of a child or young person having unexplained symptoms nor the exercising of selective choice about treatment or education for such a patient by the parents/carers and/or young person constitutes evidence of abuse.

Nonetheless, children with CFS/ME may suffer harm, and this is part of the differential diagnosis. It is important to listen to the child, as well as to family members and parents/carers, to respect their experiences, and to give due weight to their views, especially the child's. The young person should be given the opportunity to speak with the clinician, with or without their parents/carers.

In cases of CFS/ME, evidence clearly suggestive of harm should be obtained before convening child protection procedures or initiating care proceedings in a family court – Social Services should be made aware that medical opinion in this area is divided, and consideration should be given to obtaining a further opinion from an expert medical practitioner with a specialist knowledge of CFS/ME. Working together to safeguard children, issued jointly by the Department of Health, the Department for

Education and Skills, and the Home Office, sets out the interagency arrangement to protect and safeguard children's welfare. This should be followed when there are concerns that a child may be or is likely to suffer significant harm.

Page 99

New final paragraph inserted

2017 Update: NICE is currently carrying out a surveillance review of new and relevant evidence relating to clinical trials and management of ME/CFS. This could then form the basis to a formal review of the NICE guideline later in 2017.

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