

Dr Charles Shepherd

HOT TOPICS!

Presentation to West London Network MESH on Tuesday 23rd October
2012

Chalford Hill donkey delivery

.....



Royal Free disease 1955 and the Lancet editorial: ME



and Beard, BMJ 1970 >>
mass hysteria



How I got involved in this subject...



CV

- Personal experience of all aspects of ME/CFS
- Hon medical adviser to ME Association and Ramsay Research Fund
- MRC Expert Group on ME/CFS Research
- DWP Fluctuating Conditions Group
- CMO/DoH Working Group >> CMO Report on ME/CFS

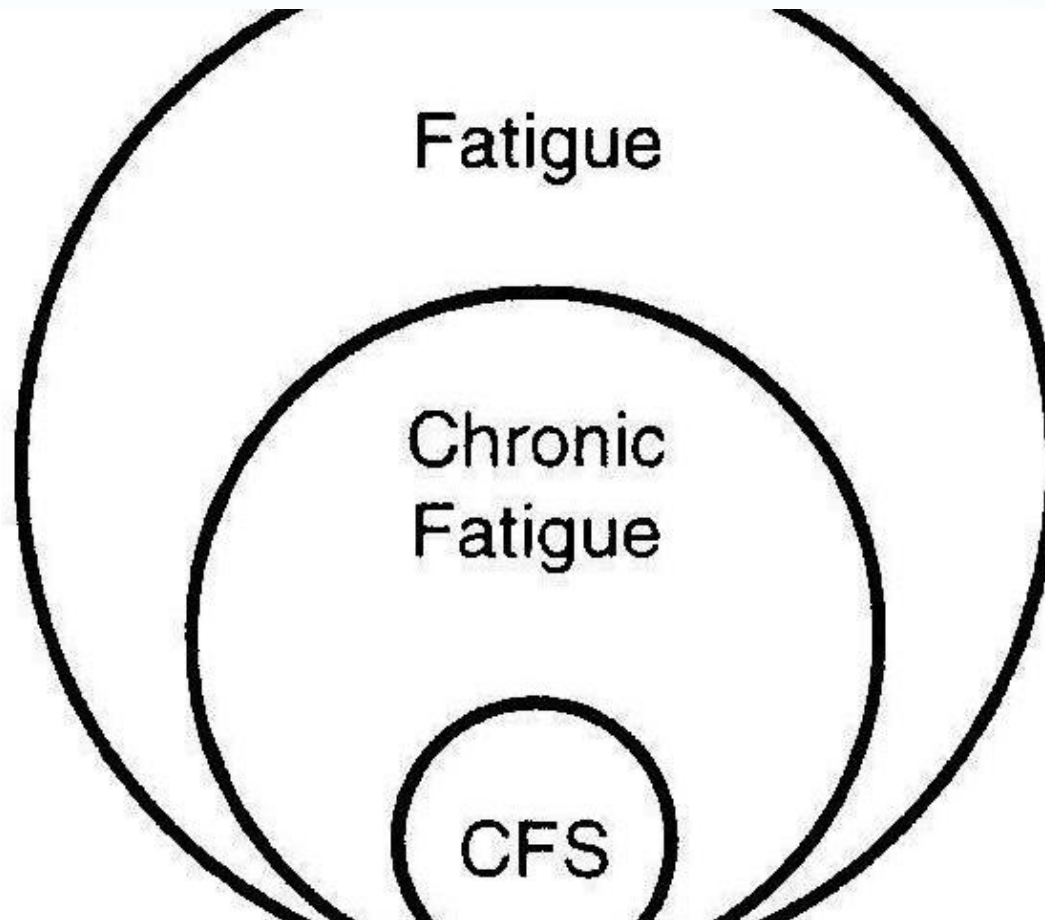
Publications

- MEA purple booklet
- MEA Management Report – download from MEA website: www.meassociation.org.uk
- NICE guideline (2007) – available on-line and due for revision in 2013
- CMO Report on ME/CFS (2002) – available on-line at DoH website
- APPG on ME: Inquiry into NHS Service Provision
- Fluctuating Conditions Group Report (2011)
- ‘Living with ME’ (Vermilion paperback)

Hot Topics in 40 minutes

- (Epidemiology of chronic fatigue and ME/CFS)
- (What is ME/CFS?)
- (What should we call it? ME, CFS, ME/CFS, PVFS)
- (How should we define it? Research and Clinical)
- 1 Research: is the cause? >> Research and MRC
- 2 Management: clinical assessment, making a diagnosis of ME/CFS and treatments
- 3 DWP Benefits

Epidemiology of chronic fatigue



Epidemiology

- Chronic fatigue – up to 10% of adult population
- ME/CFS as a clinical entity = 2 to 5/1000
- Up to 250,000 people in UK
- Age 20 to 40 at onset
- Children and adolescents >> commonest cause of long term school absence
- All social classes – not ‘yuppie flu’
- Female:male 70:30

What is ME/CFS?

Core symptoms:

- Fit young adults >> viral illness++ >> do not recover >>
- Exercise induced muscle fatigue
- Post-exertional malaise
- Pain (75%) musculoskeletal, arthralgic (not inflammatory), neuropathic
- Cognitive dysfunction affecting short term memory, concentration, attention span, information processing
- ANS: Orthostatic intolerance, postural hypotension, POTS
- Sleep disturbance: hypersomnia >> unrefreshing sleep
- >> SUBSTANTIAL (50%>) reduction in activity levels

Secondary symptoms

- Alcohol intolerance
- Balance/dysequilibrium
- Sore throats and tender glands
- Sensory disturbances: paraesthesiae, numbness
- Thermoregulation upset - ?hypothalamic
- (Depression)
- Symptoms fluctuate – ‘good days and bad days’ - and change over time

Nomenclature: What should we call it?

- ME: myalgic encephalomyelitis (1955 Lancet editorial) >> myalgic encephalopathy
- PVFS: post-viral fatigue syndrome
- CFS: chronic fatigue syndrome – ME renamed and redefined in 1980s
- ME/CFS >> messy compromise >>

Covering a wide spectrum of chronic fatigue clinical presentations and causations – similar to placing all types of arthritis under chronic joint pain syndrome and saying they all have the same cause and treatment

How do we define it – symptom based definitions

Clinical and Research for ME CFS and ME/CFS

ME: Ramsay, London criteria

CFS: Fukuda >> Oxford >> NICE >> broader

ME/CFS: Canadian

International consensus criteria

>> Different groups of patients being selected for research studies and clinical trials

>> MRC Expert Group: Need for sub-grouping

RESEARCH: What causes ME/CFS?

- Predisposing

Genetic predisposition

- Precipitating

Viral infections++ and other immune system stressors, including vaccinations – hepatitis B+ >> abnormal host response

Gradual onset in up to 25%

- XMRV.....False hope and flawed science

XMRV.....



THE CENTER FOR
INFECTION AND IMMUNITY



The multicenter study on
CFS/ME and XMRV/pMLV

Perpetuating and Maintaining

- Persisting infection +/- -
- Central nervous system +++: central fatigue, hypothalamic dysfunction, autonomic dysfunction and neuroinflammation
- Muscle: +/- mitoc dysfunction > peripheral fatigue
- Immune system dysfunction: ++ low level activation
- Neuroendocrine: ++ downregulation of HPA
- Symptoms: ++ pain, sleep etc
- (Psychosocial model: abnormal illness beliefs and behaviour)

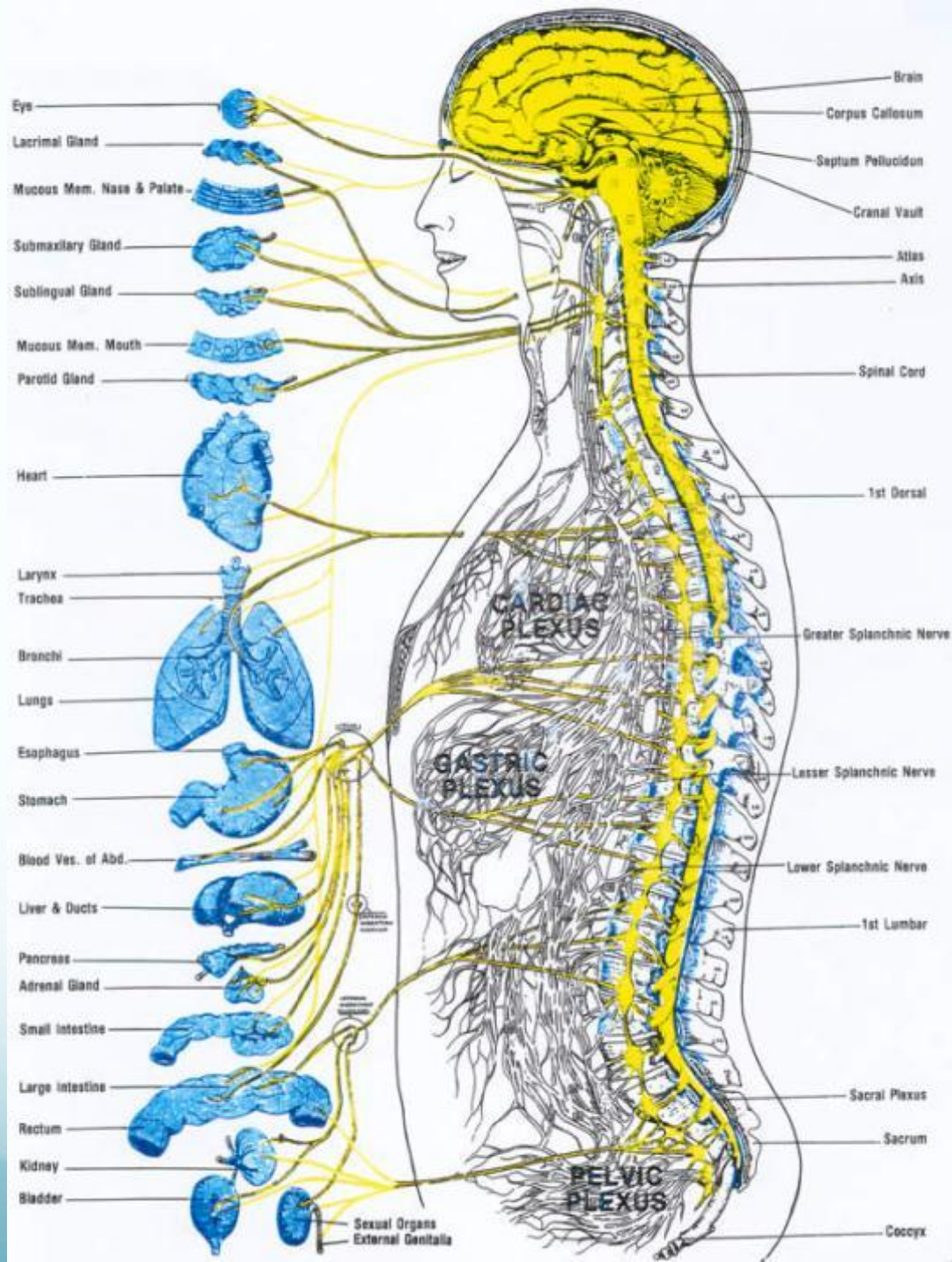
MRC Expert Group

- Established in 2009 in response to criticism of failure to fund biomedical research
- Chaired by Prof Stephen Holgate
- Produced a list of biomedical research priorities
- Secured £1.5 million ring fenced funding
- Dec 2011 >> 5 grants awarded
- October 2012 >> UK Research Collaborative
- Website:
<http://www.mrc.ac.uk/Ourresearch/ResearchInitiatives/CFSME/index.htm>

MRC Research Priorities

- Autonomic dysfunction
- Cognitive symptoms
- Fatigue – central and peripheral, including mitochondrial function and energy metabolism
- Immune dysregulation: NK cells, cytokines
- Neuroinflammation
- Pain
- Sleep
- Developing interventions: cytokine inhibition and treatment of symptoms
- Access to blood and tissues for research

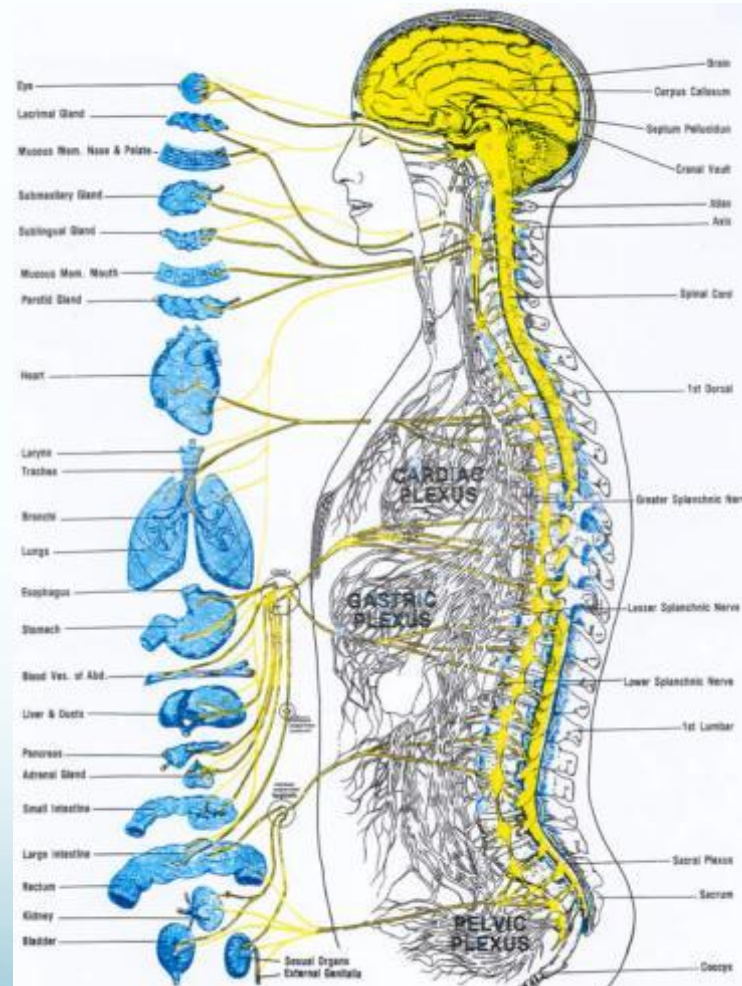
Autonomic nervous system



Autonomic nervous system

- Professor Julia Newton, University of Newcastle
- ‘Upstream’ >> ANS control centres in the brain
- ‘Downstream’>> ANS control of cardiac and vascular responses that may be involved in orthostatic intolerance and hypotension
- Plus >> role of cerebral hypoperfusion in cognitive dysfunction
- ME/CFS with ANS dysfunction and those without and sedentary controls

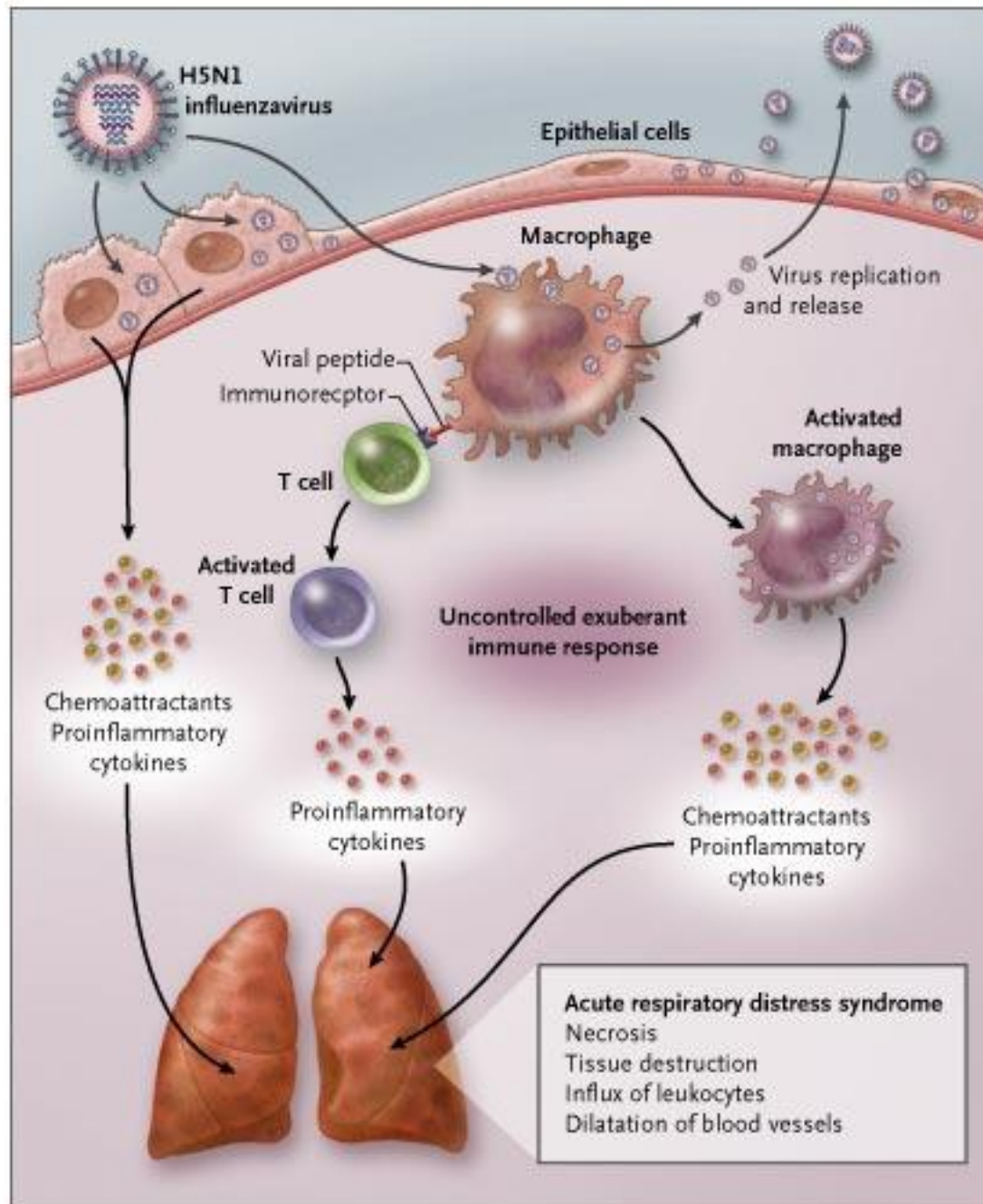
Autonomic nervous system



Gene expression biomarker?

- Dr Wan Ng, University of Newcastle
- Sjogren's Syndrome biobank: 550 samples
- Clinical and pathological overlap with ME/CFS
- Whole blood gene expression for markers of immune system dysregulation in relation to fatigue
- >> Biomarker for fatigue?
- Repeat in ME/CFS group

cytokines



Immune system activation

Pro-inflammatory cytokines?

- Dr Carmine Paiante, King's College Hospital
- 100 patients with hepatitis C infection treated with interferon alpha – an immune system activator – which often leads to fatigue and flu like symptoms
- Follow course of potential biomarkers pre during and post treatment – cytokine and HPA profiles – in those who do/do not develop an ME/CFS like illness
- Role of drugs that dampen down immune system activation: Etanercept >> Norwegian trial

Muscle: mitochondria



Muscle Mitochondria

- Professor Anne McArdle et al, University of Liverpool
- Building on previous muscle research >> fatigue not due to deconditioning
- Mitochondria damage >>
- Chronic activation of NFkB >> low grade inflammatory response
- Muscle can become a source of pro-inflammatory cytokines
- Possible therapeutic interventions using inflammatory mediators

Sleep Studies and treatment

- Professor David Nutt et al, Imperial College
- Relationship between disturbed sleep and fatigue
- Slow wave sleep disturbance = deep restorative sleep
- Role of sodium oxybate in enhancing slow wave sleep. CFS vs Placebo
- Expensive drug with potential to cause side effects+
- Sodium oxybate improves function in fibromyalgia syndrome: a randomized, double blind, placebo-controlled, multicentre trial. Russell IJ et al. Arthritis Rheum 2009, 60, 299 - 309
- Belgian trial: University Hospital Ghent (Mariman A et al) due to start in June

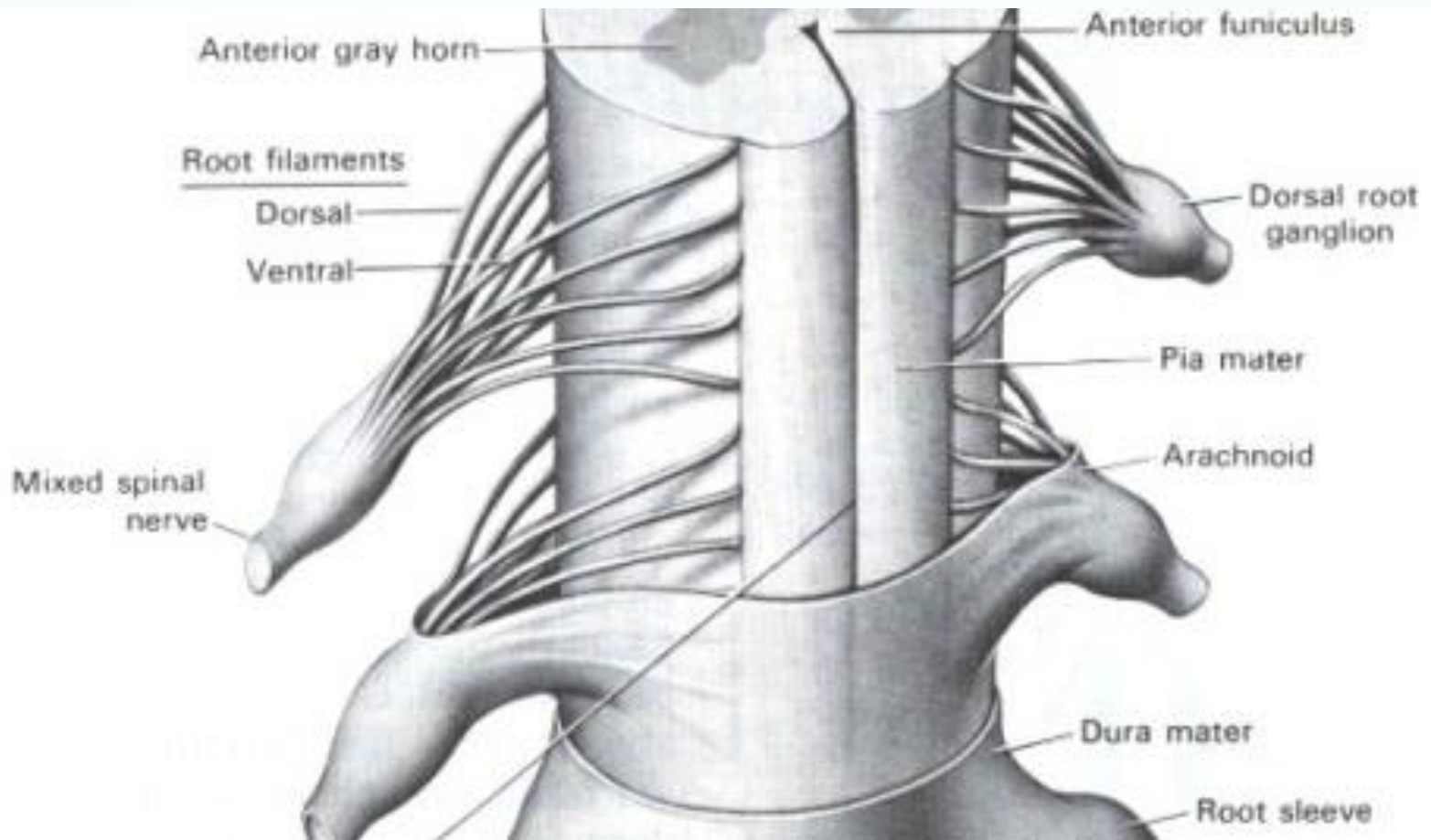
MEA Biobank and Post mortems

- MEA Biobank at Royal Free Hospital, UCL
- Update on the MEA website:
www.meassociation.org.uk
- Post-mortem studies >>
- Dorsal root ganglionitis – dorsal root ganglion are bundles of neurons on the sensory nerve roots that pass to the spinal cord. DRG has also been found in Sjogren's syndrome with a sensory neuropathy

Neuropathology of post-infectious chronic fatigue syndrome. Journal of the Neurological Sciences 2009 (S60-S61)

Cader S., O'Donovan D.G., Shepherd C., Chaudhuri A.

Dorsal root ganglionitis



MANAGEMENT

- Timescale for diagnosis and management:
- First three months of post viral fatigue >> PVFS, which is often self resolving but can >> ME/CFS
- NICE and CMO WG: Working diagnosis of ME/CFS if symptoms persist beyond 3 to 4 months and no other explanation found
- Primary care
- Referral to hospital based services >> CMO report >>postcode lottery

Differential diagnosis of chronic fatigue/TATT

- Haematological
- Infective
- Neurological
- Muscular
- Psychiatric
- Rheumatological
- >> p18 purple booklet

How do we diagnose ME/CFS/PVFS?

- History +++ Needs more than 10 minutes!
- Examination: 'Hard' neuro signs >> refer
- Routine investigations to exclude other causes of ME/CFS-like symptoms >>p16
- Additional investigations where clinical judgement deems appropriate >>p17

Misdiagnosis

Self-diagnosis

Routine investigations

- ESR + C reactive protein
- FBC +/- serum ferritin in adolescents
- Biochemistry: urea, electrolytes, + calcium
- Random blood glucose
- Liver function tests >> ?PBC, ?hepatitis C ?NAFLD – raised transaminases, link to Gilbert's syndrome
- Creatinine
- Creatine kinase – ?hypothyroid myopathy
- TFTs
- Screen for coeliac disease - tissue transglutaminase antibody >> arthralgia, fatigue, IBS, mouth ulcers
- Morning cortisol
- Urinalysis for protein, blood and glucose

In some circumstances....

- MCV macrocytosis >> folate or B12 deficiency? Coeliac disease?
- Pursue abnormal LFTs: primary biliary cirrhosis (anti mitochondrial antibodies); Gilbert's syndrome, NAFLD
- Raised calcium: ? sarcoidosis
- Joint pain+ Autoantibody screen for ? SLE (anti nuclear antibodies, anti DNA antibodies, complement)
- Infectious diseases: hep C (blood transfusion), Lyme; HIV, Q fever (contact with sheep), toxoplasmosis
- Dry eyes and dry mouth > ? Sjogren's syndrome (Schirmer's test for dry eyes)

Low cortisol and suggestion of Addison's (hypotension; low sodium; raised potassium) >> synacthen test

- Autonomic function tests >> tilt table test for POTS
- Muscle biopsy or MRS?
- Serum 25-hydroxyvitamin D (25-OHD) if at risk: restrictive diet; lack of sunlight; severe condition

How do we manage patients with ME/CFS

- Correct diagnosis
- Specialist referral +/-
- Activity management >> time and expertise
- Role of CBT?
- Symptomatic relief
- Drugs aimed at underlying disease process
- Help with education, employment
- DWP benefits: ESA
- Information and support

Activity management: GET vs Pacing



Activity Management: Balancing rest and activity

- Depends on stage, severity and fluctuation of symptoms
- Graded exercise therapy

Clinical trial evidence +ve, including PACE trial

Patient evidence –ve

MEA Management Report: N = 906

22% improved; 22% no change; 56% worse

- Pacing

Clinical trial evidence –ve/not there

Patient evidence +++

N = 2137: 72% improved; 24% no change; 4% worse

Cognitive behaviour therapy

- Covers abnormal illness beliefs/behaviours >> Practical coping strategies
- RCT evidence +ve
- PATIENT EVIDENCE (N =998):
- 26% improved
- 55% no benefit
- 19% worse

Symptomatic relief

- Pain – overlap with fibromyalgia in some

OTC painkillers >> low dose sedating tricyclic – amitriptyline >> gabapentin >> opiates?

- Sleep

Short acting hypnotics; sedating tricyclics; melatonin?

Sleep hygiene advice

- ANS dysfunction
- (IBS)
- (Depression)
- (Psychosocial distress >>CBT)

Can we treat the underlying disease process? Not yet!

- Antiviral medication: valganciclovir?
- Immunotherapy: cytokine inhibition/Etanercept?
- Neuroendocrine: cortisone? thyroxine NO!
- Central fatigue: modafinil?

Recent clinical trials:

- Ampligen
- Rituximab

Rituximab

RESEARCH ARTICLE

OPEN  ACCESS

Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study

Article


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Rituximab

- Anti-CD20 antibody >> B cell depletion
- Used to treat lymphoma
- Significant response in 3 lymphoma cases with ME/CFS
- MOA? removal autoantibodies or reactivated infection
- Norwegian RCT 30 placebo/30treated >> significant benefits
- Expensive
- Potential to cause serious++ side effects
- Further Norwegian trial underway but not yet replicated

DWP



Benefits: ESA and WCA

- Major problems for fluctuating conditions
- ‘Snapshot’ questions >> reliably, repeatedly, safely and in a timely manner
- Professor Harrington’s FCG: Arthritis, HIV/AIDS, IBS – Crohns and UC, ME/CFS, Parkinsons
- FCG Report available on-line
- FCG >> reworded WCA descriptors to make them multidimensional to cover both frequency and severity
- FCG >> New descriptor covering fatigue and pain
- Recommendations about to be tested by the DWP in a EBR....

ESA – the claimants journey

- ESA50 Form
- Initial screening
- Atos medical assessment
- >> Support Group
- >> Work related activity group >> WI
- >> Claim fails
- >> Going to appeal

Atos medical assessment: tips!

- Providing additional medical evidence
- Asking for a recording
- Taking a companion
- Obtaining a copy of your report from DWP
- Making a complaint if you are not happy with the way you were assessed
- If you have to appeal turn up in person
- Tribunal service video by Dr Jane Rayner – on the MEA website

ME Association

- Information: literature pdf order form on the MEA website
- Support: ME Connect information and support:

Tel: 0844 576 5326

- Campaigning: benefits, services
- Political: APPG on ME
- Website: www.meassociation.org.uk and Facebook page

Questions after the break...