Guildford ME/CFS Support Group
(& West Surrey)

Newsletter

March 2021

Future dates

Due to the Covid-19 Pandemic we are unable to offer monthly meetings until further notice. Contact us at Guildfordme@hotmail.co.uk if you would like to be added to our Whatsapp chat. We will require the mobile number to add.

NICE announce new publication date for the ME/CFS clinical guideline

Source: https://meassociation.org.uk/2021/03/nice-announce-new-publication-date-for-the-mecfs-clinical-guideline

Dear Stakeholder, because of the large number of comments received during consultation on the ME/CFS guideline, and the additional work needed to respond to them fully, the publication date has changed. The guideline will now publish on 18th August 2021.

Grief, loss and acceptance following a diagnosis of ME/CFS

By Hilary Adams, a Counsellor and one of our members
30th March 2021

Diagnosis

If the last year's pandemic has brought home our need for connection and community, it has also highlighted our mortality and the precarious nature of life in the most shocking and visible way. This may be easy enough to acknowledge from a place of confidently good health. How much harder it can be when life is suddenly turned upside down by illness and disability, and we are rudely ejected from a world of certainty and familiarity into a foreign land, a place that may feel hostile and unpredictable. We may feel very vulnerable and defenceless, anxious, angry or tearful and as if our personal world is crumbling around us. The diagnosis of any serious, chronic illness can be existentially shocking and destabilising.

Add to this the uncertainties and controversy surrounding ME/CFS and it is hardly surprising that we can feel lost and in need of a roadmap to guide us back to more familiar territory.

Other people's expectations?..

We live in a world where there is pressure to do, to progress, to achieve and this is still predominantly the case despite the current interest in 'wellness', meditation, mindfulness and self-care. As a therapist, I have often seen these potentially useful practices adopted as extra boxes to tick in a hectic day's schedule, rather than being part of a more permanent shift in mind-set. Societal messages around illness can also be unhelpful with talk of 'fighting the battle' and 'not giving in', and admiration expressed for the 'survivors', 'heroes' and the bravery they have displayed. What if we don't feel brave? What if we are too exhausted to 'fight' or the pain is too overwhelming?

And what about the feelings of shame and disappointment these messages may provoke, that it is somehow our fault? There is an added layer of challenge we face with ME/CFS, resulting from the widespread misrepresentation and misunderstanding of the condition both in the medical establishment and in the wider community. It can be hugely tempting, for example, to respond to those siren calls to exercise (surely it must be good for us?) just to prove that we have not given up, we are not 'just' depressed…until we learn to our cost that it is not the answer.

….or our own?

What of our self-concept, our plans, the future we may have had mapped out? We tend to take our freedoms for granted and assume that we have control over the pattern of our lives, but these characteristics of our daily existence can evaporate as ME/CFS rewrites the script. The sense of self cannot easily be separated from the body. We cannot be neatly compartmentalised - in sickness and in health we are the sum of our parts and our self-concept (which we may never have given much thought to) can be shattered by the onset of such a chronically disabling condition. Lacking the energy to participate, to contribute in the way we did, to be who we were, who then are we now?

So how might we tolerate and move through our grief and the losses we feel, to find that easier place of compassion and acceptance? Perhaps it depends to some extent on recognising and accepting that changed sense of self. Adapting to this new world into which we have been thrown is a very gradual process and it may begin, as when we are bereaved, with recognising and honouring what has been lost, before we are able to arrive at a place of acceptance and to reinvent ourselves and find new meaning in life.

Allowing our sadness – what may help?

Language is probably the first medium that comes to mind for expressing our thoughts and emotions, whether we use our own words or those of another.

We might write in a journal, either a cathartic stream of consciousness, or perhaps poetry – whatever helps, this is for your eyes only. We might read what others have written - poetry or prose, myth or metaphor, fiction or non-fiction – whatever speaks to us in our loss and helps us to connect with how we feel when we cannot articulate it for ourselves. Or we might choose to share how we are feeling with another – a friend, a family member or a counsellor – someone who is able to be alongside us as we fall apart, someone who doesn't try to put us back together or avoid the discomfort but who just says by their presence alone, "I'm with you, I see your sadness".

But there are languages other than words. Art or music can evoke a visceral response, again helping us to grasp what it is we are feeling so that we are able to allow and express it. Strong emotion is part of the experience of significant loss and the initial stages of the grieving process can, and often do, feel overwhelming - accepting the new reality takes time. Consider perhaps the qualities you would hope to demonstrate towards a newly bereaved friend – kindness, compassion, gentleness – and then ask why you wouldn't treat yourself similarly? Allow yourself time to grieve, keeping in mind that it can be easier to focus only on today or just this present moment – looking too far ahead can exacerbate the sense of being overwhelmed, of feeling out of control.

Recovering ourselves

What else might help when we are feeling overwhelmed, as if we are riding an emotional rollercoaster with no brakes? Focusing on the breath may alleviate the intensity of the moment, helping to ground us and recover stability. This may be as simple as noticing the inhale and the exhale, perhaps counting as you breathe. You may find 7-11 breathing particularly calming. A longer outbreath helps to slow the heart rate and reduce the production of adrenaline, so calming the system - in addition to which this requires a degree of concentration which helps to keep your cognitive faculties online rather than disappearing in the maelstrom of emotion. Some people like to find something rectangular to focus on (perhaps a window or a mirror) and follow the outline as they breathe.

As so many of us have found during the pandemic, developing a routine, however limited, and breaking the day into smaller, measurable parcels of time can help create some sense of control and autonomy, even though to a dispassionate observer apparently nothing has changed. Linked with this, focusing on what you can control, rather than what you cannot, will also help gently to change your perspective. At first this might seem pointless – who cares about your choice of breakfast or book if the career you worked so hard for seems lost? The process can be very slow, so try to pay attention to your self-talk, that conversation that rumbles along unbidden in your head. Is it kind and supportive, accepting of ups and downs, good days and bad days? Or is it essentially a bit of a bully, a doom-monger and a nag? Think again about how you would talk to and support a good friend - and remember that grief and feelings of loss are not predictable or static. They are dynamic, shifting, ebbing and flowing just as we may experience when we lose someone we love.

What is 'right'? What is 'wrong'? Does it matter….?

Many people are familiar with the five Stages of Grief as described by Elisabeth Kubler-Ross. This 'framework' for grief took hold in the public imagination, as if there was a need for a guide to show us how we 'should' grieve. But there is no 'should' about grief. It is seductive to believe that there is a clear pattern that we follow but Kubler-Ross herself didn't believe the stages followed any particular order, nor that there are only five. Her primary intention was only ever to start a conversation about grief and grieving, rather than being in any way linear or prescriptive. The experience of loss and grief is unique to every one of us – there is no right or wrong, and we may not experience the specific 'stages' Kubler-Ross described. Of course, it can be helpful to know that you are not alone in experiencing anything that is described in theories of grief – but it should not be limiting, nor should you feel that somehow you are getting it 'wrong' if your experience is different from someone else's.

What is more, we may move back and forth, thinking we are done with being angry for example, only to find that six months further down the line it resurfaces and once again we rage and rail against the lot we have been dealt. This sense of movement can also be experienced as we shift between times of strong emotion (when we grieve, perhaps cry and feel able to do little more than curl up under the duvet) and times when we are more able to engage with the outside world, to accept our changed reality and to try out new-found coping skills. Again, you are not alone if you oscillate back and forth in this way. We may find new meaning in life, new purpose or satisfaction in what we can do, but that doesn't mean that we won't still have times when we fall to pieces. Give yourself permission to experience whatever it is you are feeling. Emotions are neither right nor wrong (although undoubtedly some are more comfortable) – they just are.

A new story
As we remake our lives, a focus on what has meaning for us and also what gives us joy (however small) will help us write our new narrative. One example which holds true for me is the benefit of a connection with nature which I had never consciously acknowledged (although I believe it was always there). Many may identify with this, or with the pleasure to be found in music, in crafts, in podcasts and the rewards in being a good listener, supporting those newly diagnosed or a family member.. the story will be unique for you although there will be many themes which will be commonly experienced amongst us.

Professor Robert Neimeyer, a leading researcher and clinician working with grief and loss describes the search for a new life narrative in the following way:

"Restorative retelling, as opposed to merely ruminating about what has happened, involves a self-compassionate search for ways to revise the story of our changed lives, rather than simply repeating it. Rebuilding means paying close attention to what we feel and what these feelings say about what we need, and then taking…. steps to fulfil these needs in new ways.." (Therapy Today Vol. 30 Issue 7).

So as you practise self-compassion, pay attention to how you feel and what this tells you about what you need in your life. Experience of this condition can be intensely isolating, leading to the bleakest sense of loneliness, when connection with others is of fundamental importance for humankind to thrive – back where we started, the pandemic has made this plain. So remember that you are very much not alone and always, always reach out for that connection and support when you need it.

Post and long-Covid-19

Created by group member Cathy Gould

The British Medical Journal defines 'post-acute Covid-19' as symptoms extending beyond 3 weeks from the onset of the illness and 'chronic Covid-19' as extending beyond 12 weeks.

Approximately 10% of people remain unwell beyond 3 weeks and a smaller proportion for months. Many such patients recover spontaneously (if slowly) with holistic support, rest, symptomatic treatment and a gradual increase in activity, but for some the symptoms last a lot longer and it doesn't seem to be linked to how ill you became when you first contracted Covid-19.

Since many people were not tested at the beginning of the pandemic and false negative tests were common, the BMJ suggests that a positive test is not a prerequisite for diagnosis. post-Covid-19 patients can initially be divided into 3 groups:

1. post ventilated patients/those in intensive care;
2. those who have serious complications (e.g., major organs; blood clots; fatigue; and breathlessness); and
3. those with a non-specific clinical picture but continue to suffer from breathlessness, fatigue and a number of other symptoms.

It is those in group 3 who may be of interest to those of us with ME/CFS because it would seem that the symptoms of long-Covid can be very similar to our own and patients will require long term services from the NHS like ourselves.

Symptoms of long-Covid include: extreme fatigue; shortness of breath; chest pain or tightness; problems with memory or concentration ('brain fog'); insomnia; heart palpitations; dizziness; pins and needles; joint pain; anxiety and depression; tinnitus and ear aches; nausea; diarrhoea; abdominal pain and loss of appetite; raised temperature; cough; headaches; sore throat and changes to sense of smell and or taste; and rashes.

NICE guidelines
NICE - The National Institute for Clinical Excellence, has issued official guidance on best practise for recognising, investigating and rehabilitating patients with long-Covid. The guidelines make recommendations in a number of key areas including:

- assessing people with new on ongoing symptoms after acute Covid-19;
- investigations and referral;
- planning care;
- management including: self-management; supported self-management and rehabilitation;
- follow-up and monitoring;
- service organisation; and
- key recommendations for research on long-Covid to better understand the condition and refine appropriate treatment.

In October 2020, Sir Simon Stevens (Chief Executive of the NHS) announced a five-part package of measures to boost NHS support for those experiencing long-Covid Symptoms:

1. new guidance from NICE (shown above) on the clinical case definition of Long Covid;
2. www.yourCovidrecovery.nhs.uk NHS website resource to support recovery after Covid-19 that provides general information on all aspects on recovery including: physical; emotional and psychological wellbeing; and advice on recovery and information for families and carers;
   www.england.nhs.uk takes you to a document giving guidance on accessing and referring into a digital rehabilitation programme;
3. additional £10 million to be invested in setting up specialist post-Covid assessment services across England, to complement existing primary community and rehabilitation care. At the moment there are 68 post-Covid assessment services, including one at the Royal Surrey County Hospital in Guildford;
4. National Institute for Health Research to fund research on long-Covid to better understand the condition and refine appropriate treatment; and
5. an NHS long-Covid taskforce to include patients with long-Covid, medical researchers and specialists.

What is the support like for long-Covid patients at the present time?
According to 'Covid support Facebook groups', some are getting good care from their GP's and being referred to other specialists and rehabilitation clinics, whilst others are getting no help at all. Of course, Facebook is just a small source of information and we are in the early stages of long-Covid support services. We will have to wait to see if all long-Covid sufferers will get the care that they so desperately need.

Further reading:
patient.info/news-and-features/long-Covid-what-support-is-available?

https://meassociation.org.uk/2021/02/horizon-tv-interview-gives-a-hugely-encouraging-boost-to-people-with-me-cfs

www.cam.ac.uk/research/news/likelihood-of-severe-and-long-Covid-may-be-established-very-early-on-following-infection

www.vox.com/22298751/long-term-side-effects-covid-19-hauler-symptoms

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Long-Covid19 and ME/CFS – the brainstem & dysautonomia connection

Source: www.healthrising.org/blog/2021/02/22/long-Covid-chronic-fatigue-syndrome-brainstem-dysautonomia

Anyone who's been around the scientific literature on chronic fatigue syndrome (ME/CFS) knows that dysautonomia – a dysregulation of the autonomic nervous system – is common. Two different kinds of orthostatic intolerance – postural orthostatic tachycardia syndrome (POTS) and neurally mediated hypotension (NMH) have been found. Virtually everyone with ME/CFS has reduced blood flows to the brain, and low heart rate variability is ubiquitous as well.

If long-Covid is anything like ME/CFS, then dysautonomia is going to show up in the medical literature – and it's starting to. Recent long-Covid studies are starting to validate the dysautonomia link, and as they do that, they're validating the connection between long-Covid and ME/CFS.
Because they're coming from around the world, they also open the possibility – so long as ME/CFS and long-Covid are firmly linked – of creating a new global understanding of ME/CFS.

Small Fibre Neuropathy
A recent Indian/French study is a good example. I can't remember the last Indian or French study on ME/CFS, but this long-Covid study found evidence of small fibre neuropathy (SFN) in about 25% of long-Covid patients. Because the study measured just one possible facet of SFN (sudomotor dysfunction), it's possible that even more people had SFN. It stated, interestingly, that infections such as mumps, HIV, Hepatitis C, Epstein-Barr, and Coxsackie B often produce dysautonomia (who knew?). Interestingly, people who had been treated at home instead of the hospital (i.e. had a less severe illness) were more likely to show evidence of SFN.

The only real disappointment from the study was that it neglected to mention fibromyalgia (!).

Last month, in "Autonomic dysfunction in 'long Covid': rationale, physiology and management strategies", Hammersmith and Imperial College researchers in London raised the spectre of widespread dysautonomia – a subject one suspects many doctors have little knowledge of.

ME/CFS was not mentioned but postural orthostatic tachycardia syndrome (POTS), of course, were. The authors reviewed symptoms, tests and drug and other treatments that might be helpful and told doctors to be on the lookout.

> "We suggest that all physicians should be equipped to recognise such cases, appreciate the symptom burden and provide supportive management."

They also posited a cause that was right up POTS and ME/CFS's alley – an autoimmune-induced hurt to the autonomic nervous system. This idea will hopefully be fully explored in the long-Covid studies.

> "We posit that this condition may be related to a virus- or immune-mediated disruption of the autonomic nervous system resulting in orthostatic intolerance syndromes. ….we speculate that there is an underlying autoimmune component to the post-Covid syndromes that we report."

Next, in a letter to the editor, "Covid-19, fatigue, and dysautonomia", a Singapore researcher reported increased fatigue was found in 50% of recovered Covid-19 patients after 6 months – a fatigue that he believed was likely due to autonomic dysfunction and problems with the neuro-cardiac axis.

Brainstem

But why are these autonomic nervous system problems occurring? One answer might lie in the brainstem. The brainstem is the first recipient of all the sensory and "motor" signals from the spinal cord. It regulates very basic functions – like breathing, heart rate, blood pressure, digestion, alertness, sleep/wake – a lot of which has gone wrong in chronic fatigue syndrome (ME/CFS).

In "The vagal autonomic pathway of Covid-19 at the crossroad of Alzheimer's disease and aging: a review of knowledge", French researchers report that the SARS-CoV-2 coronavirus has a predilection for nestling itself within the vagus nerve. They propose that a failure of the vagus nerve to institute an anti-inflammatory response may lay behind the oft-noted cytokine storm that can accompany Covid-19. (Could an inhibited ant-inflammatory response also explain why people with more severe symptoms are more likely to come down with ME/CFS in the wake of an infection?)

From there, it moves into the dorsal vagal centre of the brainstem – an "integrative centre" which regulates both respiration and inflammation. Mice experiments indicate that past SARS viruses have a propensity to attach to the brainstem. Plus, the brainstem has high levels of the ACE2 receptor that the virus binds to.

When the virus gets to this part of the brainstem, they believe it begins affecting the "autonomic nervous centres" that regulate breathing and other cardiovascular factors. A recent paper, "Computing the effects of SARS-CoV-2 on respiration regulatory mechanisms in Covid-19", stated that "overwhelming evidence" linked acute respiratory failure in Covid-19 to viral entry into the brainstem. The virus produces a "neurogenic switch" which causes, among other things, hypoventilation – which has been found in abundance in ME/CFS.

Another potential consequence involves increased sympathetic ("fight or flight") and decreased parasympathetic ("rest and digest") tone – exactly what is found in ME/CFS and fibromyalgia (FM).

The brainstem popped up again this month in "Persistent brainstem dysfunction in long-Covid: a hypothesis", by Shin Jie Yong, a Malaysian researcher. Yong noted that most explanations for long-Covid involve some sort of tissue damage, persistence of the virus, and chronic, unresolved inflammation, but none of those, he thinks are correct. The problem, Yong proposes, is "persistent, low-grade brainstem dysfunction" driven by a virus which loves to inhabit the brainstem.

Autopsy results, Yong reports, have found evidence of inflammation and neurodegeneration in the brainstem area. SARS-CoV-2 genes and proteins were detected in 50% and 40% of the brainstem samples in other studies. Still others have found evidence of microglial activation (neuroinflammation) and small blood vessel bleeds.

Avindra Nath found numerous small blood vessel bleeds in the brainstems of the Covid patients he autopsied. Interestingly, most apparently initially had a mild illness presentation.

> www.healthrising.org/blog/2021/01/26/nath-leaky-brains-long-Covid-chronic-fatigue-and-fibromyalgia

Since the brainstem is an important source of serotonin, norepinephrine and dopamine producing neurons, it could produce a vast array of symptoms including fatigue, pain, headache, depression, anxiety, sleep and cognitive impairments.

Yong believes damage to the brainstem could also be responsible for the gastrointestinal symptoms (vomiting, diarrhoea, and abdominal pain) seen in long-Covid. The ventral tegmental area and substantia nigra also reside in the brainstem's midbrain, which supplies dopaminergic neurons to the higher brain regions.

Then comes the clincher. After noting that brainstem damage has been found in migraine, Yong writes:

> "Notably, long-Covid resembles and is closely associated with myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS)… Interestingly, brain imaging research has found that symptom severity of ME/CFS associates and correlates with brainstem dysfunction, particularly at the reticular activating system (RAS)."

As Yong noted, there are papers by Barnden in Australia that have been painstakingly showing that the brainstem is affected in ME/CFS. Jeff and Jen Brea's craniocervical stories demonstrate that a damaged brainstem can produce all the symptoms of ME/CFS. The French researchers believe this organ is at particularly high risk in a coronavirus infection.

> Has the "reptilian brain" gone haywire in ME/CFS? back to the brainstem we go

ACE2

ACE2 presents another intriguing possible connection between ME/CFS and the coronavirus. As was noted, the virus binds to the ACE2 receptor, and the ACE2 protein is densely found in the brainstem (and the amygdala).

The first thing that happens once the virus gets into the dorsal vagal nerve is that ACE2 levels drop, Ang II levels rise, the anti-inflammatory component of the renin-aldosterone-angiotensin (RAS) Ang (1-7), declines, and problems with baroreflex sensitivity occur.

Compare that to what appears to be happening in ME/CFS. The ACE2 inhibition found in ME/CFS also appears to result in high levels of Ang II and low levels of the anti-inflammatory Ang (1-7). The high Ang II levels in ME/CFS could be contributing to a host of problems including a ramped-up fight/flight system, narrowed blood vessels, inflammation, heart rate and blood pressure issues, and possibly reduced blood flows to the brain.

> The paradox in ME/CFS and POTS

Hypoventilation and ventilation problems during exertion, in particular, and shortness of breath have been found in ME/CFS. Low CO2 levels may be common. Time will tell if the many respiratory problems found in Covid-19 are cousins to those found in ME/CFS. Given what we know so far, it would be very interesting to see what happens when people with long-Covid are put on an exercise bike. Avindra Nath reportedly is going to do just that.

Conclusions

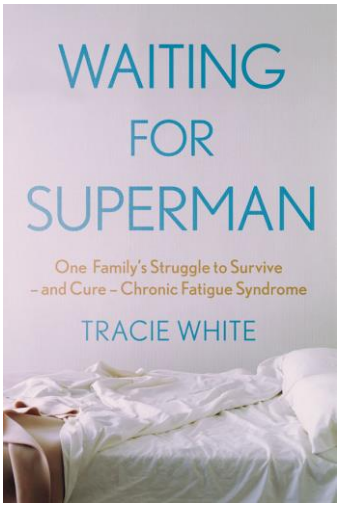
It's nice to see so many possible fruitful connections pop up between chronic fatigue syndrome and long Covid. It's good, as well, to see long-Covid researchers heading to the autonomic nervous system, the brainstem and the renin-angiotensin-aldosterone – three areas one suspects not many doctors and researchers are all that aware of.

It would also make sense that the brainstem might have been missed in ME/CFS and other diseases. VanElzakker has pointed out that most brain imaging studies don't produce a clear picture of the bottom of the brain. With the massive funding long-Covid is about to get, though, hopefully the brainstem and the autonomic nervous system will get their shot.

It would be shocking if the potential autoimmunity issue wasn't fully addressed as well. The presences of small fibre neuropathy adds another intriguing factor.

Are the stars lining up? Time will tell. Note that if these findings are validated in long-Covid studies, they all showed up first in ME/CFS and fibromyalgia.

Waiting for Superman: one family's struggle to survive and cure Chronic Fatigue Syndrome



Amazon UK Paperback £11.68

For the past six years, Whitney Dafoe has been confined to a bedroom in the back of his parents' home, unable to walk, eat or speak. His diagnosis? The mysterious disease ME/CFS which affects 20 million people around the world who largely suffer in silence because the condition is little known and much misunderstood.

Waiting for Superman follows Whitney's father, ground-breaking geneticist Ron Davis, as he uncovers new possibilities for treatments and potentially a cure. At its heart, this book is about more than just cutting-edge research or a race to find an answer - it's about the lengths to which a parent will go to save their child's life.

Publisher: Atlantic Books
ISBN: 9781911630616
Number of pages: 240

Reviews
A compelling story of the love of a father who as a scientist preserved through a maze of uncertainty to help his son. Anyone who has endured undiagnosed chronic illness or has been subjected to the blanket dismissal of the medical community will find refuge in this book. -- Dr Rana Awdish, author of 'In shock'

Both a gripping read and a heart-wrenching story, but far more, it's inspiring, showing how we, and those we love, can band together to withstand challenges, even those beyond our worst nightmares. -- Julie Rehmeyer, author of 'through the shadowlands'

A medical mystery with a heart. It's a poignant memoir of a scientist whose determination, ingenuity and love for his son drives him to the limits of science and medicine to unravel an enigmatic illness that has eluded doctors for decades. -- Steffanie Strathdee, author of 'the perfect predator'

The author's keen commitment to capturing Dafoe's illness and Davis's work makes for a story of heartbreak balanced with unexpected beauty. White succeeds in casting chronic fatigue syndrome in a new light in this inspirational account. — Publishers Weekly

A complex, well-related story of medical detective work. — Kirkus Reviews

Action for ME - Crisis, support and advocacy service

Source: www.actionforme.org.uk/get-support-now/help-and-support-for-you/crisis-support-and-advocacy-service

In April 2020, we launched our Crisis, Support and Advocacy Service for anyone living with or supporting someone with M.E./CFS of any age, anywhere in the UK.

Our team has experience and understanding of living with M.E. Our supportive “brain-fog busting” approach aims to help you break issues down so they feel less overwhelming, explore priorities, outline options available to you, and frame questions you want to ask professionals.

We can:

- share information and support around all aspects of living with M.E., for adults, parents and children and young people, including welfare benefits processes, rights and entitlements, social care, symptom management, accessing health services, liaising with your child's school and getting reasonable adjustments at work;
- offer emotional support via active, empathic listening, and connect you with other people with M.E., particularly during these challenging times;
- source practical assistance near to you, such as your local mutual aid group, parish council and/or community hub; we can also source local producers/food outlets who are making home deliveries; and
- for more in-depth support in complex cases, refer you to Action for M.E. advocacy for adults or family support and advocacy (for young people 18 and under, and their parents/carers).

Please call 0117 927 9551 (10am to 5pm Monday to Friday) or email us to speak with a member of the team.

Update Monday 22 March 2021: To ensure we can effectively support you as we train new staff, we are likely to close earlier than our usual 5pm between now and Easter. Normal service will resume in April. Thank you for your patience.

Please note that our team are not medically trained and are unable to offer specialist legal, employment or medical advice, or counselling, befriending or specialist mental health support, though we can signpost to specialist organisations that do.

Blood MicroRNA patterns linked to ME/CFS

Source: www.the-scientist.com/news-opinion/blood-microrna-patterns-linked-to-chronic-fatigue-syndrome-68213

By Katarina Zimmer 30th November 2020

A finding of distinct patterns of gene-regulating RNA snippets in the blood of ME/CFS patients in response to a stress test could pave the way for a diagnostic tool for the condition and help untangle its underlying mechanisms.

ME/CFS has long been neglected by physicians, researchers, and funding agencies, not least due to its mysterious causes. It’s often hard for patients to find doctors who can diagnose ME/CFS, a widespread condition characterised by debilitating post-exertion fatigue and other symptoms.

A new study appears to make headway toward solving those difficulties. A recent analysis from more than 40 ME/CFS patients reports that a disease-specific stress test leaves a distinct signature of 11 microRNAs in their blood that change in abundance compared with blood drawn before the test. Most of these microRNAs are involved in regulating immunity, supporting the idea that immune dysfunction plays a key role in the disease's pathology. The findings lay the groundwork for developing a molecular diagnostic test for the disease, the authors write in their study, which was published on November 12 in Scientific Reports.

Although the findings need to be replicated in larger cohorts, "I think there are many strengths here," remarks Mady Hornig, an immunologist at the Columbia University Mailman School of Public Health who wasn't involved in the research. "There's a lot here, in terms of the findings, that are really intriguing and important clues."

MicroRNAs are short nucleotide snippets that act inside cells to regulate gene expression and have garnered much research interest over the past decade as potential diagnostic tools for several conditions in which they're dysregulated. To Alain Moreau, who specialises in the molecular genetics of musculoskeletal diseases at the University of Montreal and the Sainte-Justine University Hospital, they were an attractive focus for exploring ME/CFS, in part because microRNAs also circulate in the blood, providing an easily accessible source of gene-regulatory information.

Previous studies have flagged distinctive circulating or cellular microRNAs in ME/CFS patients, but some had very small sample sizes or didn't compare patients with appropriate controls, making the data often hard to interpret, Moreau says. He and his colleagues wanted to overcome these issues, while also looking for microRNAs tied to specific symptoms in the condition, which he says he hoped would yield robust biomarkers.

The hallmark symptom of ME/CFS is post-exertional malaise (PEM), a worsening of fatigue and other symptoms following physical or mental exercise that can leave patients bedridden for weeks. The researchers sought to probe microRNAs associated with this symptom, but to spare patients a full-blown bout of PEM in the clinic, Moreau's team figured out that they could use a therapeutic massager—an inflatable arm cuff that exerts gentle pulsating compressions—to induce a milder form of PEM, as evidenced by headaches, muscle pain, and profound fatigue that patients reported in later questionnaires.

Starting with 11 severely affected, housebound ME/CFS patients, the team drew plasma samples before and 90 minutes after this challenge and screened for differences in levels of microRNAs. Computational analysis revealed 17 microRNAs whose levels had changed significantly after the test; their response also differed from that of eight age- and sex-matched healthy individuals who had been subjected to the massager but didn't report any PEM symptoms.

Repeating this analysis in a larger cohort of 32 ME/CFS patients and 17 matched controls, the team discovered the same response patterns for 11 microRNAs. In fact, a machine learning algorithm the researchers trained could correctly diagnose someone with ME/CFS based solely on the change in concentration of these microRNAs after the massage intervention. "We were unable to misdiagnose a [healthy] control as ME/CFS, or inversely, ME/CFS as a control," Moreau says.

The need for diagnostics and drugs for ME/CFS

There's an overwhelming need for definitive diagnostic tests for ME/CFS, says Frances Williams, a genomic epidemiologist at King's College London who wasn't involved in the research. Diagnosis is currently made by excluding other conditions, which is difficult, time-consuming, and a frustration for patients. The fact that Moreau's team could replicate their results in a larger cohort is encouraging, but she says she doubts that microRNAs will form a standalone test for ME/CFS, simply because of the genetic and epigenetic complexity of the disease. However, microRNAs "could be helpful in combination with other things," she says.

Hornig says the test has many strengths in terms of translating it for use in a clinical setting. For one, its focus on free-floating sequences in the blood makes it technologically simpler than a technique used in a previous study that requires extracting microRNAs from inside blood cells. She also praises the team's PEM-inducing stressor, which reflects the sensitivity of severely affected ME/CFS patients to their sensory environment, but is less taxing than physical exertion "and respectful of the patients' experience and fears," she says.

Moreau encourages other institutions to replicate the results. The findings will require validation in larger cohorts to ensure the test can diagnose patients with all subtypes of ME/CFS, different stages of the disease, and those from a variety of regions and ethnicities. Hornig adds it's also important to investigate differences with the results of other studies—for instance, previous work on cellular microRNAs in ME/CFS suggested disparities in how men and women responded to exercise, whereas Moreau's results found no sex-based differences. She's also curious about where the microRNAs come from, suspecting immune cells or muscle tissue as possible origins. "This opens a lot of questions."

Using a different algorithm, Moreau's team found that they could cluster the patients into four discrete groups based on the precise pattern of their microRNA responses to the PEM challenge. Interestingly, these groups happened to also share clinical features—one group, for instance, had markedly severe symptoms. To Moreau, this indicates that different mechanisms operate in different subsets of the disease, which could help explain why drug trials for ME/CFS patients have so far been largely inconclusive. But he says he hopes to use microRNA data soon to match patients with drugs they're more likely to respond to. His team suspects, for instance, that the immunomodulating drug rintatolimod, which activates Toll-like receptor 3, might not be effective in patients with high levels of microRNAs that impede the transcription of that receptor. "I [hope] the test will open the door to more . . . precision medicine in the field of ME/CFS," Moreau says.

To Williams, the major value of the study lies in an analysis Moreau's team conducted with the microRNA data that untangles the molecular pathways the 11 sequences are involved in.

This revealed that 7 out of the 11 microRNAs were involved in regulating immune functions, which "certainly fits with one arm of the research that suggests that immune activation is very important in leading to chronic fatigue," she says.

An additional network analysis flagged the key genes each microRNA is associated with and other diseases they've been linked to, which included viral infection, sleep disorders, and cognitive impairments. "Using a network approach, you can start to shed light on which cellular processes are important. And then if that ties in with what we know already about the cellular processes in ME/CFS, then that all begins to paint a bit of a picture."

The findings are relevant in light of the COVID-19 pandemic and the increasing numbers of "long-hauler" patients left with enduring fatigue symptoms, a phenomenon that has many experts concerned that the coronavirus could trigger ME/CFS in a subset of infected people. The pandemic "will bring a huge number of new [ME/CFS] patients, and some of them are relatively young. That will create some devastating impacts for themselves and their families," Moreau says. "That's why we need to hurry and hope that we will convince governments and funding agencies to [put more funding into the field]."

E. Nepotchatykh et al., "Profile of circulating microRNAs in myalgic encephalomyelitis and their relation to symptom severity, and disease pathophysiology," Sci Rep, doi:10.1038/s41598-020-76438-y, 2020.