Take the chronic guessing out of chronic fatigue Dx

Belgian expert brings his biomarker test to Canadian docs

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Dr Ellie Stein is on a mission. The Calgary psychiatrist and chronic fatigue syndrome (CFS) sufferer is determined to drag "yuppie flu" out of the shadows – and she's enlisted one of the world's leading CFS experts to help her do it.

Belgian clinician and researcher Dr Kenny De Meirleir has treated over 13,000 CFS patients at his Brussels clinic and published over 500 peer-reviewed papers on the subject. But what caught Dr Stein's attention was his work that confirmed that RNase L — an important enzyme in the innate immune system's fight against viruses and other intracellular pathogens — is abnormally spliced and overactive in CFS patients. Based on this, Dr De Meirleir has developed a panel of four tests he says can help physicians not only diagnose CFS, but also determine the appropriate treatment plan. "Biological markers have now been identified, and tests can be conducted to support a diagnosis," says Dr Stein.

Dr De Meirleir's work is largely unknown in North America, so Dr Stein invited him to conduct a workshop for Calgary physicians in early April; sessions in Montreal and Quebec City were added as well. He was glad to accept. "This is a topic that a lot of big journals are trying to avoid because it's still controversial," says Dr De Meirleir. "You have to create awareness and take your science on the road."

Meet your marker

Researchers from Temple University in Philadelphia first identified an abnormal protein — a smaller version of the RNase L enzyme — in a subset of CSF patients in 1995. Five years later, Dr De Meirleir independently confirmed this group's findings, concluding that the appearance of the abnormal 37 kDa protein resulted from the cleavage of the normal 80 kDa enzyme. The resulting fragment was found to be three to six times more active than usual, destroying not only its natural target — viral RNA — but also cellular mRNA, preventing cells from producing the proteins needed to function normally and leading to widespread cell death.

"The 37 kDa RNase L is present in over 90% of CFS patients and less than 5% of healthy controls," explains Dr Stein. This makes it a great candidate for a biological marker. What's more, four independent research groups have confirmed that the fragment isn't found in patients with fibromyalgia or primary depression, the two conditions most often confused with CFS. With this and many years of research into CFS's underlying cellular mechanisms under his belt, Dr De Meirleir has developed a panel of tests for CFS. His Belgian lab has recently opened its first North American branch in Nevada, where the standard diagnostic tests — 37 kDa RNase L levels, RNase L function, and two others — can be sent and analysed for $1,000. "Even if the test doesn't turn out to be the be all and end all, it gives doctors something objective and that makes a huge difference," says Dr Stein. But she says the basis of the diagnosis should still lie in clinical judgement. "By and large," she says, "physicians still don't know nearly enough about the disease."

Diagnosis dilemma

Dr Stein is uniquely positioned to understand the challenge the disease presents to both patients and to their treating physicians. "I'm classically trained, so I understand that physicians don't like to diagnose something they can't see," says Dr Stein. "But as a patient, I know what it's like not to get any diagnosis at all."

"The key problem is that the symptoms are subjective," notes Dr Harvey Moldofsky, a psychiatrist and sleep specialist at University of Toronto who has an interest in CFS. Slow recovery after exercise or exertion is a CFS hallmark, but muscle weakness, pain, sleep disturbances, intestinal irregularities, neurocognitive difficulties and of course, fatigue, are also common.

In 2001, Health Canada commissioned an 11-member international expert panel — which included Dr De Meirleir — to develop CFS diagnosis and treatment guidelines. But despite the excellent reviews the resulting Canadian Consensus Document (CCD) received from international CFS experts, its publication in the obscure *Journal of Chronic Fatigue Syndrome* in 2003 went largely unnoticed. So two of the original authors pared the lengthy document down to 20 pages, available at www.mefmaction.net, which they hope will be more accessible to the busy physician.

Dr Moldofsky remains cautiously sceptical about the CCD. "I really don't know who's using [the document]," he says. "Physicians are very cautious about applying these labels, and rightly so." He says he relies on an earlier definition of CFS published by Fukuda et al in the *Annals of Internal Medicine* in 1994.

He's in good company: the Fukuda definition remains the most widely used in the world, which doesn't sit too well with Dr De Meirleir and Dr Stein. "The Fukuda criteria isn't scientifically based," he argues. "Thirty people in a room agreed on which symptoms should make it into the definition." Dr Moldofsky says you could say the same for the newer Consensus document. "The Canadian criteria are just based on the consensus of a committee, and there's a weakness in consensus," he says.

Dr Stein disagrees that the new criteria fell into this age-old trap. "The Canadian document takes into account 10 more years of research," she says. "And though it is consensus-based, every recommendation has a literature reference." She says the other big difference between the two criteria is that the people who contributed to the Fukuda definition were researchers who'd never actually seen a patient with CSF. "The 11 members of the Canadian panel have collectively treated 25,000 patients," she says. "This is the first true definition of CFS for clinicians." ♦