The nervy trial must go on

James Bashford

The true value of health is best appreciated in disease. How can a healthy person imagine what it feels like to be slowly starved of life's key ingredients, such as the ability to walk and talk, or the capacity to greet and eat? For the 5,000 people in the UK living with motor neuron disease (and thousands more globally), this is their stark reality. For everyone else, even our most heartfelt sympathies seem guiltily hollow.

Inexorably, the finely tuned network of nerves that has grown and flourished in health abandons you. Impulses that once had the ability to travel at spine-tingling speeds of 100 metres per second are forced to slam on the brakes. Muscles fall victim to a relentless and terrible siege. Before long the nerves supplying the breathing muscles become affected too, leading to the terrifying statistic that a half of patients die within four years of symptom onset.

When asked what causes this onslaught, the scientific community remains stumped. Like echoless bats in search for food, scientists flap frantically in the dark for a cure. In the mid-1990s, the drug riluzole offered a tantalising glimpse of a therapeutic bounty awaiting discovery. Two decades of clinical trials, an Ice Bucket Challenge, and hundreds of failed drugs later, we remain perched on a crest of false hope.

Or so it may seem, until one considers the huge discoveries that *have* come to light during this time. We know over twenty of the causative genes as well as the abnormal protein that accumulates inside the neurons of 95% of patients. Increasingly, researchers are diversifying their methods of discovery. One such approach is to find sensitive disease biomarkers, which are able to track the disease trajectory closely. We're looking for an accurate and reproducible monitoring tool, which can reduce the duration and cost of expensive drug trials.

During my PhD, I aim to tap into the telephone wires that silently communicate our actions from brain to muscle, thereby eavesdropping on motor neuron health. In motor neuron disease, unhealthy neurons bombard muscles with unwanted messages. Termed 'fasciculations', they are seen as ripples beneath the skin surface, heralding the onset of muscle weakness. The insertion of fine needles deep into the muscle remains the gold standard analytical method, but this approach points to a primitive past in much need of modernisation.

Instead, we employ painless skin sensors to decipher these signals, each one typically lasting less than one hundredth of a second. We have devised an automated computer tool to assess the number, size, shape and pattern of these signals. By correlating these findings with established markers of disease progression, we aim to devise a superior tracking tool.

Our pilot study of eight patients provided some promising insight, but a pleasing warm-up needed a good main act. We are now half way through our core study of 24 patients, tracking their disease trajectory every two months for one year. With an enriched vocabulary, we hope to make sense of the declining neuronal function over time. What do fasciculations tell us about the health of motor neurons? Can we find signatures of disease, which may allow us to diagnose patients at an earlier stage? This will be especially important as new therapies emerge and there's a need to treat patients as early as possible before significant neuronal loss has occurred. Can we predict the course of an individual's disease, allowing patients and healthcare providers to plan the future more effectively?

Throughout this project, we have teamed up with expert bioengineers to optimise our data collection. Each 30-minute recording is made up of 64 channels arranged in an 8x8 grid, covering a surface area surpassing 40 square centimetres. This provides excellent coverage and spatial resolution, enhancing our pick-up rate of fasciculations. In one case we detected over 10,000 fasciculations from one muscle in 30 minutes. By analysing the sizes and pattern of the signals, we have shown that fasciculations in motor neuron disease behave very differently to those that occur in a control group with benign fasciculation syndrome. We continue to refine the analysis in the development of meaningful diagnostic, prognostic and disease-monitoring biomarkers.

Our next major step is to scale up the quantity and frequency of data collection by introducing a portable, inexpensive device that can be setup and used by patients in their own homes. By recording muscles daily, weekly and monthly, we hope to fill many of the gaps in our knowledge.

Motor neuron disease is a crime against humanity. Despite our best efforts, the guilty offender goes on unchecked. However, our investigative powers are becoming increasingly honed, promoting fresh academic resolve. A committed research community and an expanding network of patients and relatives are poised in the wings, ready to assume the roles of judge, jury and executioner.