Flouting the rules

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There should be a rule in medicine: cardiologists shouldn't have heart attacks, oncologists shouldn't get cancer, lupus should spare rheumatologists. Why? Because they know too much. They can see what's coming. They know the complications. They know the drug side effects.

Following this rule, neurologists should never develop ALS.

Unfortunately, there is no such rule.

Other rules also apply. ALS only affects nice people. The disease has a peculiar predilection to attack nice people and spare mean people. And ALS loves the ironic twist.

Another rule: when you hear hoofbeats, think horses, not zebras. This maxim reminds physicians that common things are common. A patient with fever and a cough probably has a viral upper respiratory infection, not anthrax. The aphorism is all well and good, except when the horse is an inexorably progressive and inevitably fatal disease—when the horse is ALS. Then you have to be absolutely certain this thing that appears to be a horse is not a zebra in disguise.

We know that certain diseases can mimic the clinical picture of ALS. Some of these mimickers are treatable. The evaluation of an ALS patient includes a search for conditions known to mimic it, but all of them are rare and the search is usually futile.

A new mimicker appeared on the scene in the late 1980's, a condition called multifocal motor neuropathy (MMN). Researchers from Johns Hopkins University described two patients with a disorder involving the motor fibers of multiple peripheral nerves in the upper extremities, sparing sensory fibers.[1] Both patients had presented with painless, progressive, asymmetric upper extremity weakness, and both were initially diagnosed as having ALS. But their nerve conduction studies showed striking abnormalities not typical of ALS.

Temporal dispersion refers to the normal tendency of things moving at different velocities to spread out over distance. Runners of differing footspeed will separate further from each other the longer the race. The same phenomenon normally occurs with a compound muscle action potential (CMAP) because not all motor nerve fibers conduct at the same velocity. Conduction block refers to the failure of a nerve potential to transmit, analogous to a runner spraining an ankle and never finishing the race. Both temporal dispersion and conduction block affect the amplitude of the CMAP, and distinguishing between the two may prove difficult.

The patients in the Hopkins paper describing MMN had conduction block in the involved nerves on nerve conduction studies. Conduction block never occurs in ALS. These patients also had high titers of antibodies to GM1ganglioside.

Crucially, the Hopkins MMN patients responded to treatment with cyclophosphamide. So, the Hopkins researchers had reported patients initially thought to have ALS who had conduction block on nerve conduction studies and antibodies to GM1 ganglioside, and who responded to treatment with cyclophosphamide.

In the late 1980s and 1990s, papers appeared with titles such as: *Chronic multifocal demyelinating neuropathy simulating motor neuron disease, Multifocal motor neuropathy mimicking motor neuron disease* and *Motor neuropathies mimicking amyotrophic lateral sclerosis/motor neuron disease*.[2-4] In a large Irish study, the most common ALS mimic was MMN.[5]

Neurologists around the world became obsessed with not missing MMN in patients who appeared to have ALS.

The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) convened a panel to develop consensus criteria for distinguishing between temporal dispersion and true conduction block. The head of the panel and lead author of the paper that followed was Dr. Richard K. Olney, the Director of the ALS Treatment and Research Center at UCSF.[6] Rick was a stellar physician and researcher and an esteemed colleague, highly regarded yet unpretentious and always amiable. He was universally recognized as a very nice guy.

The conduction block paper was published in 1999. In 2003, Rick noticed problems with his right leg. His doctors at first thought he had a lumbar disk herniation and he underwent surgery, but the weakness progressed and Rick soon knew he had ALS.

Rick was cared for in his own ALS center by physicians he had trained. Even as his personal illness progressed, he continued to study it.[7] He enrolled as the first patient in a clinical trial he had designed before his diagnosis. Rick Olney died in 2012, at age sixty-four. The AANEM honored his memory by creating the Richard K. Olney Lecture, given annually at its association meeting.

Rick survived eight years. Another ALS researcher, Dr. Lisa Krivickas of Harvard, wasn't as lucky. Lisa and I were colleagues on the Board of Directors of the American Board of Electrodiagnostic Medicine. From the time Lisa told us in a board meeting that she had ALS until she was gone was only a little over two years. She was forty-five. The disease had taken her mother when Lisa was young.

In 2017, Dr. Rahul Desikan, a prominent researcher in the field of neurodegenerative diseases, including ALS, at UCSF, found he had ALS. He died in July 2019 of a rapidly progressive form of the disease. He was forty-one.

It almost seems as if the disease is an evil, sentient entity intent on tracking down and eliminating the specific people trying to find a cure for it. It appears to have license to flagrantly flout the rules.

References

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