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Gregory S. Day
Washington University School of Medicine in St. Louis

David F. Tang-Wai
University of Toronto

Michel C.F. Shamy
University of Ottawa

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A Case Study in the History of Neurology

Gregory S. Day, MD, MSc, FRCP(C)¹,
David F. Tang-Wai, MDCM, FRCP(C)²,
and Michel C. F. Shamy, MD, MA, FRCP(C)³

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Abstract

We review the case of a young man who developed a constellation of symptoms and signs—bizarre behavior, seizures, abnormal movements, and autonomic instability—that evaded diagnosis at the time of presentation. We use this case to explore the way medical knowledge changes over time. Despite the dramatic advances in our understanding of neurological diseases in recent decades, physicians tend to approach diseases and diagnoses as if they were immutable. Our case reinforces how the diagnosis and treatment of disease are determined by an ever-changing historical context driven by the rapid expansion of medical knowledge. We discuss the implications of this realization and present strategies for navigating the boundaries of knowledge, both in practice and in principle.

Keywords

NMDA receptor encephalitis, diagnosis, history of medicine, medical knowledge

Ignorance was just as dynamic as knowledge, and it grew in the same proportion. Still, each generation of physicians imagined that ignorance was the special provenance of their elders.

Abraham Verghese, *Cutting for Stone*

Introduction

Physicians tend to define diseases with straightforward, declarative statements like “Multiple sclerosis is a recurrent demyelinating disease of the white matter of the CNS, which usually becomes progressive.”^{1(p3)} These pronouncements imply that our knowledge is stable and accurate: that multiple sclerosis is a particular *thing* and has always been so. If physicians in past eras thought of diseases differently, they did so due to their own ignorance. Yet, a long-range view of medical practice suggests just how much our thinking changes across time.² The way a physician names and understands diseases reflects the knowledge and values of that physician’s era and place. That knowledge and those values evolve over time; with them, so too do our diagnoses. We present a brief case that provides an opportunity to explore the way that physicians understand and interpret the world and that illustrates how the diagnostic process is shaped by our place in history.

A Case

A 19-year-old right-handed Canadian-born Chinese male complained of new frontal headache,odynophagia, and pyrexia. He had previously enjoyed excellent health, with no past medical or psychiatric issues and no history of substance abuse. One week later, he became physically aggressive resulting in his dismissal from work. Over the ensuing 3 weeks, he developed progressive lethargy with periods of reduced responsiveness. He was admitted to a psychiatric team for evaluation and management of “bizarre behavior.” Four days later, he experienced a right-sided focal seizure and was transferred to our tertiary care hospital for neurological assessment.

¹ Department of Neurology, Charles F Knight Alzheimer Disease Research Center, Washington University School of Medicine, Washington University in St Louis, St Louis, MO, USA

² Department of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada

³ Department of Medicine (Neurology), University of Ottawa, Ottawa, Ontario, Canada

Corresponding Author:

Michel C. F. Shamy, The Ottawa Hospital—Civic Campus, 1053 Carling Avenue, Room C2182a, Ottawa, Ontario, Canada K1Y 4E9, Canada.
Email: mshamy@toh.on.ca

Upon arrival, he was diaphoretic, febrile (38.0°C), hypertensive (150/63 mm Hg), and tachycardic (110-120 bpm). His level of consciousness fluctuated with decreased verbal output. Examination of the cranial nerves and motor systems was normal. Involuntary repetitive chewing movements of the tongue and lips were observed. Extensive blood and spinal fluid tests, including all infectious and autoimmune panels, were normal. Routine awake electroencephalogram demonstrated only left temporal slowing (3-5 Hz). A brain magnetic resonance imaging demonstrated scattered nonenhancing T2/Fluid Attenuated Inversion Recovery (FLAIR) hyperintense lesions within the left corona radiata.

Within days of transfer, he developed autonomic instability with persistent tachycardia and episodes of hypotension, necessitating transfer to the intensive care unit. His level of consciousness continued to fluctuate and he had seizure-like paroxysms resistant to multiple anticonvulsant medications. Empiric treatment with pulse methylprednisolone was administered and followed with a prednisone taper. Over the course of 4 weeks, his autonomic instability stabilized and the level of consciousness improved. He remained disoriented to place and time but was able to participate in physiotherapy and was eventually discharged to inpatient rehabilitation.

Case Analysis

Many readers will recognize features that are familiar for the diagnosis of anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis: a limbic encephalitis with rapidly progressive encephalopathy, seizure-like episodes, orofacial dyskinesias, and autonomic instability in association with IgG-type autoantibodies against the GluN1 subunit of central nervous system (CNS) NMDARs.³⁻⁵ However, our patient was never tested for autoantibodies against NMDAR. In fact, the diagnosis was never considered because *NMDAR encephalitis did not exist at that time*.

Our patient was assessed and managed during the summer of 2006—6 months before the first series of 12 women was published³ and 18 months before the first case in a man was documented.⁶ While we cannot be certain that our patient would be diagnosed with NMDAR encephalitis today, we believe that his case emphasizes the important impact that historical context exerts on the diagnostic process and on the conceptualization of disease.

The Historical Understanding of Disease and Diagnosis

Physicians tend to think about diseases as if they possess inalienable properties that are stable across time and space. In this way, we tend to imbue diseases with the properties of *natural kinds*.⁷ A natural kind is a thing that exists in nature and is beyond human influence; the classic example is gold whose properties (density, boiling point, etc.) are determined by its unalterable atomic structure and are therefore constant across time and space. While the biological element of a

disease is essential to its nature, modern scholarship has convincingly argued that biology alone is insufficient to understand disease.⁸

Diseases are manifested by patients and diagnosed by doctors using a process that is influenced by historical and geographical context. Physicians from different eras looking at the same patient may understand the patient's symptoms differently. Epilepsy serves as a classical example of this phenomenon, with seizures variably interpreted as a mark of divine intervention, demonic possession, familial neuroses or genetic predisposition.⁹ This variability reflects our tendency to interpret diseases in a manner that integrates the knowledge and values of the society in which we live.¹⁰ Therefore, diseases are better understood as *social constructs* rather than natural kinds. Put simply, diseases are *ideas*, not *things*.

As ideas, diseases build upon earlier foundational ideas. In 1934, Polish physician Ludwik Fleck wrote a landmark history of syphilis, demonstrating how that disease had been understood differently throughout history.¹¹ For Fleck, the understanding of any disease in a given era is built upon acceptance of certain "scientific facts" or unquestioned truths. In one's historical moment, it is impossible to separate the concept of a disease from the foundational "facts" upon which it is based. Similarly, our contemporary understanding of NMDAR encephalitis is dependent upon foundational concepts like autoimmunity, neuronal receptors, neuroanatomical localization, and electrophysiology. Without these concepts, it would be impossible to conceive of "NMDAR encephalitis" as we do today, or to attribute a seemingly disparate group of symptoms and signs to antibody-mediated dysfunction of CNS receptors.

This reality highlights one of the flaws with historical studies that attempt to levy retrospective diagnoses.¹² While it is popular to diagnose historical figures with modern diseases,¹³⁻¹⁵ doing so requires applying diagnoses (and hence terminologies and concepts) from one era to patient descriptions encoded in another. Retrospective diagnosis therefore tells us little about how patients in those eras experienced their illness: our concepts would have no meaning for them, just as theirs have little meaning for us. Moreover, retrospective diagnosis does not promote a better understanding of disease in our time, in that it contributes to the faulty notion that diseases are natural kinds, and that physicians in past eras were ever so ignorant about the truths of disease that are now accepted as "fact."

Evolution of NMDAR Encephalitis

Recognition of the historical dependence of our diagnostic constructs does not invalidate the notion that science progresses. On the contrary, our increasingly sophisticated understanding of NMDAR encephalitis illustrates how rapidly our conceptualization of a disease can advance. The serendipitous description of 4 young women with "paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian

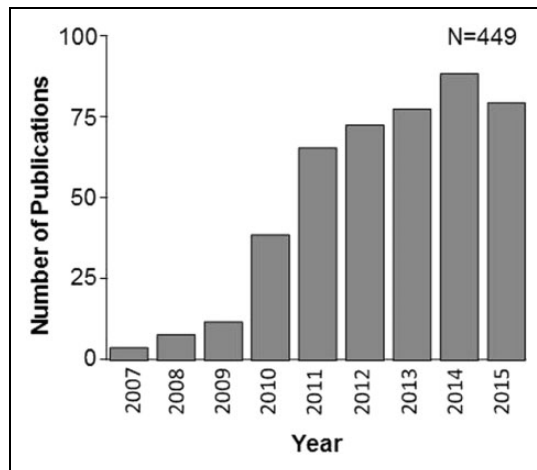


Figure 1. Bibliometric analysis summarizing the number of academic publications concerning NMDAR encephalitis from diagnostic inception to 2015. Articles featuring NMDAR encephalitis were identified through a Web of Science search using the key word phrase “NMDA receptor encephalitis.” Articles were further screened to select English-language manuscripts focusing on the diagnosis, pathophysiology, or management of NMDAR encephalitis. Summary totals include original investigations, case reports, review articles, and letters to the editors divided by the year of publication. NMDAR indicates N-methyl-D-aspartate receptor.

teratoma,”¹⁶ by a single group in 2005, facilitated the isolation of the etiologic agent (ie, NMDAR autoantibodies) in 2007.³ The description of a causal autoantibody provided not only a novel understanding of disease pathogenesis but also a name for this “new” disease, and a scaffold upon which to integrate the knowledge of NMDAR encephalitis.

To date, well-over 1000 cases of NMDAR encephalitis have been detailed within an expanding medical literature comprising over 400 manuscripts (Figure 1). These publications have greatly broadened the clinical experience with NMDAR encephalitis, yielding an increasingly refined picture of common symptoms (eg, acute psychiatric symptoms, memory deficits), signs (eg, seizures, decreased level of consciousness, movement disorders,^{17,18} central hypoventilation), and disease-associated characteristics (eg, ovarian teratoma,^{5,19} changes on electroencephalogram,²⁰ neuroimaging findings,²¹ immunoglobulin composition²²). At the same time, increasing experience with the diagnosis has heralded a marked expansion in the disease spectrum.²³ Whereas NMDAR encephalitis was initially thought to affect only women of childbearing age with an associated ovarian teratoma,^{3,16} the disease is now recognized in males (accounting for approximately 20% of cases)^{4,6,24} and all age-groups (from <1- to 84-year-olds^{25,26}). Predominantly behavioral presentations with minimal neurological sequelae are increasingly recognized.²⁷ Just as we would now look back at the initial 2005 reports as incomplete if not outright inaccurate, future physicians will likely consider our present day conceptualizations of NMDAR encephalitis naive. This realization should foster humility within us as

we learn to appreciate the limits of both our diagnostic expertise and of the efficacy of our treatments.

Conclusions

We present a young man with a cluster of symptoms and signs that were unique and perplexing at the time of presentation. In the contemporary context, our patient would have been investigated for, and likely diagnosed with, NMDAR encephalitis. As the diagnostic concept of NMDAR encephalitis did not yet exist, no such diagnosis was made in our patient, exemplifying how diagnostic concepts are dependent upon a foundation anchored in time and place. The way we understand and diagnose disease does, and will continue to, change.

Our analysis suggests 3 relevant lessons. First, case reports and case series remain essential to the advancement of modern medical science. The characterization of NMDAR encephalitis was catalyzed by the publication of a small case series. Yet, the culture of medicine has devalued case reports for producing “biased” evidence.²⁸ However, a historical perspective on medical knowledge reminds us that all knowledge—even that generated by “objective” experiments like clinical trials—are biased, because all knowledge arises within a historical context. Detailed case reports are a highly impactful way for physicians and scientists to explore unexpected or unexplained phenomena and to probe the boundaries of our knowledge. Case reports also offer the best opportunity to communicate the story of a patient suffering from an illness, rather than the antiseptic list of symptoms and signs that typify well-powered evidence-based studies. It is this story that appeals to physicians across the world and endures the passage of time; likewise, it is this story that we should encourage trainees and seasoned clinicians to tell. Therefore, we encourage journals to publish case reports, and academic institutions to value them on par with randomized trials.

Second, physicians should be willing to accept that diagnoses and concepts will change. In his influential book, *The Structure of Scientific Revolutions*, historian and physicist Thomas Kuhn proposed that progress in science occurs through “revolution,” when new ideas overthrow accepted “facts” by better explaining observations or predicting results.²⁹ In medicine, we might add that revolution occurs when new concepts reframe how we think about diseases and lead to better outcomes for patients. However, physicians are notoriously resistant to changes in their concepts and practices. We suggest that increased exposure to the history of medicine—from medical school to continuing medical education—provides an opportunity for physicians to assess the origins of our ideas and to reassess the foundations upon which our modern understanding of disease are constructed.

Finally, recognition of the humble beginnings and tenuous boundaries that circumscribe our knowledge should lead physicians away from the need for certainty and toward a renewed focus on the patient experience. Modern guidelines and treatment algorithms will inevitably be modified and replaced, but

caring for individual patients will remain central to the practice of medicine. When our available diagnostic concepts fail to encapsulate the patient experience, we should be willing to reconsider, reassign, or redefine frameworks; to incorporate new information whenever possible; and to confront emergent questions. We become better doctors when we adapt this process to provide the best care for today's patients. We become the *best* doctors when we use the lessons from yesterday to improve diagnosis today and treatment tomorrow.

Declaration of Conflicting Interests

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