Not So Rare But Rarely Diagnosed: From Demonic Possession to Anti-NMDA Receptor Encephalitis

In 1671, 16-year-old Elizabeth Knapp was possessed by the devil. Elizabeth served in the household of the Reverend Samuel Willard of Groton, Massachusetts, a prominent puritan Pastor, who meticulously recorded her sufferings across a four-month period. The following passage, by Cotton Mather, a contemporary and colleague of Willard’s, based on the Reverend’s report, captures the symptoms and signs that were historically attributed to demonic procession, providing an almost clinical description of the episodes of her possession:

“…Her tongue would be for many hours together drawn like a semi-circle up to the roof of her mouth, so that no fingers applied to it could remove it. Six men were scarce able to hold her in some of her fits, but she would skip about the house yelling and howling and looking hideously…Her tongue being drawn out of her mouth to an extraordinary length, a daemon began manifestly to speak to her; for many words were distinctly uttered, wherein are the labial letters, without any motion of her lips at all; words also were uttered from her throat, sometimes when her mouth was wholly shut, and sometimes when her mouth was wide open, but no organs of speech were used therein. The chief things that the daemon spoke were horrid railings against the godly minister of the town; but sometimes, likewise, she belched out most nefandous [sic] blasphemies against the God of Heaven.” (Mather, pg 391)

The demon-possessed have fascinated and terrified populations wherever they have made an appearance. This fascination is reflected in the volume of historical accounts referencing the behaviors of the possessed, and the number of attempts at characterizing the signs of the devil which include Cotton Mather’s Magnalia Christi Americana, the Rituale Romanum or Roman Ritual, the Catholic church’s official guide to the rites and rituals that are performed by Catholic priests, or the Malleus Maleficarum from 1486 by Heinrich Kramer, a treatise, on the identification and prosecution of witches. Throughout the ages, convulsions, contortions of the body and face, including the tongue, super-human strength, catatonic periods, long periods of wakefulness or sleep, insensitivity to pain, speaking in tongues, and a predilection for self-injurious behaviours have all been offered as physical evidence of possession.

This fascination continues in contemporary times, as evidenced by the success of many horror films, including The Exorcist (1973)—a dramatized thriller loosely based on the 1940’s
documented account of a 13-year-old boy from St. Louis, Missouri, who was allegedly possessed by the devil—and media-based accounts of new cases. The modern day interpretation, however, comes with a plot twist befitting a media spectacle.

There is growing consensus in the medical community that many prior accounts of “demonic possession” may have represented original accounts of what is now broadly known as “autoimmune encephalitis”. This term unifies a broad number of autoimmune diseases, which all result in severe symptomatic brain inflammation owing to an antibody-mediated attack on central nervous system tissues that is sufficient to account for the clinical presentation. Perhaps the best understood medical surrogate for demonic possession is the recently characterized diagnosis of anti-NMDA receptor encephalitis (NMDARE). To the patient or their loved ones, it is a malady like no other, characterized by the rapid onset of symptoms so fierce and so encompassing, that the patient is often described “as if possessed”.

The first diagnosed case of NMDARE in Canada occurred in a 12-year-old girl seen at the Children’s Hospital of Eastern Ontario (Ottawa, Ontario) in 2008. Symptoms began insidiously with memory loss following a flu-like illness. The child would ask a question of her mother, and then following an explanation, would ask it again. Routine blood tests and neurological testing in the local emergency department were unrevealing; the symptoms were attributed to anxiety and the patient was discharged to the care of her general practitioner.

Within days of evaluation, however, the nature of the illness changed. The child started exhibiting delusional behavior—speaking about herself in the third person while being assessed by her general practitioner—and suffered a dramatic change in behavior. While stopped in traffic, en route to the hospital to be reassessed, the child calmly undid her seatbelt, leapt from the car and started pursuing a city bus—as if possessed. When not allowed to board, she became aggressive, kicking and yelling obscenities: “blasphemies against the God of Heaven”, and all others in the vicinity. An ambulance was called, and the girl admitted to hospital. Six weeks of psychiatric and neurological assessment yielded no diagnosis until a single test performed on cerebrospinal fluid returned positive. The discovery of circulating autoantibodies directed against the GluN1 receptor subunit of central nervous system NMDA receptors confirmed the diagnosis of NMDARE, providing a medical diagnosis for the ethereal transformation witnessed by family.

As this case illustrates, NMDARE most often begins innocuously with flu-like symptoms that may serve to increase the permeability of the blood-brain barrier, allowing antibodies in the blood to penetrate to the privileged central nervous system, setting the stage for the main event. Over the following days or weeks, the transformation is unmistakable. Psychiatric symptoms predominate, characterized by delusions; hallucinations; extreme agitation; confused thinking; disinhibited behaviours, such as hypersexuality or hyper-religiosity. During this phase of the illness, most patients require admission to hospital and implementation of chemical or physical restraints. A further decline is heralded by the appearance of neurological signs: seizures, memory loss, loss of coherent speech, loss of mobility, ocular deviations, catatonia, the absence of sleep, lasting for days, weeks or even months and involuntary movements.
The abnormal movements attributed to NMDAR encephalitis closely overlap with those previously attributed to demonic possession, with a focus on perioral and peri-lingual disturbances, which are often complicated by severe disturbances or disruptions in autonomic functions of breathing, heartbeat, and blood pressure. The most severely affected patients are often rendered unconscious—either as a consequence of disease or of sedative medications required to manage intractable seizures, movement disorders or autonomic fluctuations. Supportive measures including ventilation, cardiac pacing, and supplemental feeding may be required for weeks, months, or in the most severe cases, years.

Considering the spectrum of terrifying symptoms, it is understandable why in earlier times they may have been attributed to demonic possession. It is equally comprehensible why many contemporary patients are initially admitted under psychiatry, with diagnostic considerations spanning the pages of the Diagnostic Statistical Manual of Psychiatry. Only recently, has a diagnostic test become available. The syndrome of NMDAR encephalitis is owed to the end-effects of a circulating autoantibody. As with most autoimmune diseases, NMDARE is more commonly described in younger females (approximately 80% of cases), but has been identified in males and females, from infancy to 85 years. In many patients, the disease is frequently associated with a hidden secret: a “monster” within.

Tumours of the ovaries are described in 60% of women of childbearing age. In most cases, these tumours consist of primitive cells, with the potential to differentiate into any tissue in the body, including hair and teeth, or even brain tissues. The fantastic appearance of these tumours earned them the designation of “teratomas”, derived from the Greek, teraton, meaning ‘monster.’ Inclusion of brain tissue within disease-associated teratomas may be especially important to the development of NMDARE. In these patients, it appears as though antibodies are produced against tumour cells containing NMDA-receptors, which then cross-react with native brain tissue accounting for the clinical presentation of NMDARE. In patients with teratoma-associated ANMDARE, identification of the tumour using magnetic resonance imaging (MRI), computerized tomography (CT scan) or ultrasound (US), is critical for the outcome of the patient, with removal of the teratoma heralding recovery in most cases. Tragically however, this is not always the case. In the subset of patients with disease not associated with an underlying tumour, in whom the trigger for this illness has yet to be identified, poor outcomes and /or susceptibility to relapses may be more common. Six percent of patients diagnosed with ANMDARE die or are left with severe and permanent consequences of their illness.

Although antibodies against the NMDARE were first identified in 2007 by Dr. Josep Dalmau, a professor of neurology and oncology at the University of Pennsylvania, clinical cases compatible with a diagnosis of NMDARE abound in the medical literature. One of the best described cases was reported in 1999 by Canadian doctors involved in the treatment of a 24-year-old Chinese female patient at Toronto Western Hospital. In the article, the author’s report her presentation as a reversible paraneoplastic encephalomyelitis associated with a benign ovarian teratoma. A diagnosis of NMDARE was retrospectively confirmed in 2007. By 2011, the number of positively diagnosed cases in Canada had jumped to 22 (data courtesy Dr. J.
Dalmau). Since then, the number has tripled and quadrupled as more and more cases are now being recognized and treated. According to Drs. Day and Peery of The Anti-NMDA Receptor Encephalitis Foundation in Canada, the disease is no longer as rare as previously thought, but rather “a rare diagnosis.” (Day and Peery, pg. 90)

With a dire lack of awareness on the part of many physicians, patients are still being incorrectly diagnosed, opening up the possibility of unnecessary internment in psychiatric and/or acute-care facilities, and delaying access to necessary treatment. Since the first descriptions of this illness, university-affiliated hospitals across Canada (including hospitals affiliated with the Universities of Calgary, McMaster, Ottawa, Montreal, and Toronto), have amassed considerable expertise in the diagnosis and management of NMDARE. They are well-equipped to manage the wide-ranging and unpredictable symptoms and sequelae associated with this illness, contributing to a medical literature filled with stories of near-miraculous recovery in affected patients receiving an expedited diagnosis and aggressive treatment, with immune suppressing and/or modulating medications.

One such extraordinary recovery was documented by Susannah Cahalan, a journalist for the New York Post, in her award-winning article, *My Mysterious lost month of Madness*, (NY Post, 4 October 2009). Three years later, building on the foundations of her article, she wrote the best-selling book, *Brain on Fire: My Month of Madness* (Simon and Schuster, 2012). The book has served to raise the profile of NMDARE, providing much needed momentum for patients, families, clinicians and researchers who are battling NMDARE and related forms of autoimmune brain disease.

The film based on the memoir will premiere at the 2016 Toronto International Film Festival, September 8-18. In the social media circuit, innumerable support groups have arisen. *Facebook* support groups and pages dedicated to the topic have been established in 9 countries (and growing), and registered Foundations committed to advancing research, education and support in this disease are beginning to take shape. On this front, Canada is leading the way with the incorporation of The Anti-NMDA Receptor Encephalitis Foundation in 2012 ([www.antinmdafoundation.org](http://www.antinmdafoundation.org)) and its recognition as a tax-deductible charitable foundation by the Canadian Revenue Agency (CRA) in 2013.

The storied history that led to the discovery of NMDARE is filled with travelers once thought to be demonically possessed or bewitched, paying the ultimate price of misdiagnosis by being wrongly accused, convicted and sentenced to torture and death. With recent discoveries, hope for quicker diagnosis and therapies continues unabated. Those who have teetered on the edge of the abyss because of an incorrect diagnosis are being brought back and will continue to be brought back. Although there are remarkable reports of recoveries that happen relatively quickly, there is continuing need for greater awareness, expedited treatment, and support for those caught directly or indirectly in the path of this illness. There may never be a cure, but thanks to recent scientific advances, a disease once characterized as “demonic possession” has a new name, and those on the dark journey from illness to health have reason to hope and to fight on.
The author wishes to thank co-founders, of the Anti-NMDA Receptor Encephalitis Foundation, Inc, Dr. G. Day, Dr. W. Foster and Dr. H. Peery for their invaluable input and guidance in the writing of this article.

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