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Historical Commentary

Rett Syndrome Turns 50: Themes From a Chronicle: Medical Perspectives and the Human Face of Rett Syndrome

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ABSTRACT

BACKGROUND: Fifty years ago Andreas Rett first described in great detail what came to be known as "Rett syndrome." Understanding girls and women with this syndrome and their families helped in many ways to revolutionize modern neurodevelopmental medicine. For some people the identification of the genetic underpinning of the syndrome and the ongoing biological research into this condition represented the peak of the scientific accomplishments in Rett syndrome. For others, it was developments in clinical research methodologies that were especially important. Above all, the patient- and family-oriented empathetic and collaborative approach to care by professionals collaborating with families has led to immense achievements, both scientific and humanistic. **AIM:** The aim of this narrative was to describe the medical and personal life story of a young woman with Rett syndrome and to offer a history that highlights developments in the unraveling of this condition from its initial recognition to our current understanding. **CONCLUSION:** We believe that much can be learned from the humanistic style of care provision combined with the best possible level of assisted autonomy and life enjoyment of the young woman with Rett syndrome. In addition, the approach to collaborative research by dedicated and often charitable leaders in the field can teach us many important lessons about the ethics of clinical and health services research.

Keywords: Rett syndrome, life story, history of neurology, MECP2, humanism

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Introduction

The history of the recognition, description, and clarification of *Rett syndrome* (labeled as RTT, Mendelian Inheritance in Man 312750) provides an interesting illustration of developments in contemporary medicine. It reflects many aspects in the progress of our thinking over the past 50 years about an evolving chronic and complex neurodevelopmental encephalopathy. The story of RTT parallels and perhaps illuminates many of the advances in our understanding of biological processes relating to brain development and epigenetic phenomena; the value of tracking and charting the lifelong trajectory of people with evolving chronic conditions; the importance of patient-/parent-reported outcomes and their active engagement; family-centered and multidisciplinary care; contemporary health concepts such as "quality of life" and "disability"; societal health perceptions, rights, and advocacy; and the integration of clinical and laboratory research.

Our starting premise is that no patient with a specific diagnosis is like another. Each personal lived experience teaches us lessons beyond what textbooks and most research articles describe. While many contemporary clinician scientists (and journal editors) tend to downplay the significance of a detailed longitudinal clinical neurological description, or a person's life story, there are others (notable examples include MacDonald Critchley and Oliver Sacks) who illustrated that there is tremendous value in an in-depth description of historical developments in neurology and the societal and especially the personal impact of neurological conditions.

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The 50-year anniversary of the initial description of RTT stimulated us to report the life history of a young woman with RTT, based on years of personal observation and repeated meetings with her and her family, as well as discussions with her family during their period of bereavement. Both parents consented to have their daughter's history published in this essay, whose purpose, like that of the authors, is to offer *personal reflections* on the lessons we believe we have learned from the experience of RTT over these past 50 years.

Jillian's story

Jillian was born in 1984 and lived her 30 years at home with her parents. Like most girls with RTT, she initially appeared to her family to be developmentally "normal." By age 14 months, she was walking, had typical symmetric hand dexterity, single-word vocabulary, and age-appropriate social behavior. At 16 months a neurological examination prompted by parental concerns about atypical (extrapyramidal) movements documented head titubation, intention tremor of both upper limbs that had been present since late infancy and mild midline ataxia while sitting. For a time, she lost the ability to walk and fell when she took two steps. Her head circumference was just above the 30th percentile, and the rest of her neurological examination was normal. Curiously, at age of two years, she was noted to walk again without falling and had started to run. Although there was no obvious ataxia, she could not sustain a sitting position and required support. She still demonstrated normal hand dexterity and was reported to have a vocabulary of 20 single words. The head titubation and tremor were still present. At 30 months, her atypical extrapyramidal movements became continuous, there was marked ataxia at rest, and no speech was heard. At 33 months the Vineland Adaptive Behavior Scales showed scores below average in all domains. She was described as very active and distractible and did not engage in any play activity.

Jillian had numerous, sometimes unpleasant, investigations; but when her parents declined the recommendation to perform a brain biopsy on their three-year-old daughter, they were told by their neurologist that nothing else could be performed in terms of either diagnosis or management—a comment perhaps typical for that era but certainly unfortunate. When Jillian was five years old, a neighbor showed her parents an article about RTT that they had just read in a Scottish newspaper. The family and their family practitioner felt that they recognized a probable diagnosis and asked their latest neurologist whether Jillian's presentation matched RTT. (This anecdote reflects a familiar occurrence wherein parents attempt to lead the clinician to the correct diagnosis.[1])

Some months later the family traveled to the international RTT meeting in Washington DC where they met Drs. A. Rett and P. MacLeod (a Canadian geneticist) who both confirmed that Jillian's symptoms were compatible with RTT. The parents felt gratitude and great relief to finally have a medical diagnosis. When the detection of an *MECP2* nonsense, p.Arg294stop, mutation (which tends to be associated with a milder neurological presentation[2]) became available, the expected laboratory findings came as a welcome confirmation. From the initial diagnosis onward the family felt that they could devote their energy to keeping their daughter happy and advocating for similarly affected girls.[1] They proceeded to organize the first meeting of the Ontario Rett Syndrome Association in their home community, supported by the Ontario "Biker Rights" Organization.

Over the years, Jillian developed and demonstrated the typical biomedical impairment stages of RTT. By age three years, she had developed the characteristic wringing hand movements; she also started pulling at her hair and developed episodic hyper- and hypoventilation. Itchiness began early in life and resulted in the parents being accused of child abuse due to the scratches on her body. She developed drug-resistant epilepsy at age six years and had as many as 100 seizures per day, partly in clusters happening most often on awakening and many episodes of status epilepticus that did not respond to a variety of anti-seizure medications.

At age 12 years, Jillian presented with decreased food intake and significant weight loss. There was a prior history of gastroesophageal reflux and prominent drooling. A feeding tube and later a gastrostomy tube were inserted at age 13 years, followed a few years later by a gastro-jejunostomy tube. Bowel discomfort and constipation were already present in middle childhood. By then, she had also had Achilles tendon lengthening, was wearing ankle-foot orthoses, and was walking with assistance on a broad-based gait. At age 17 years, she developed a progressive scoliosis measuring about 50° that interfered with her seating position. A spinal brace brought her scoliosis down to 30°. Convincing the parents that controlling the seizures with the ketogenic diet would improve Jillian's quality of life took a long time and much discussion, but once implemented at age 21 years, the almost complete seizure control turned out to be a blessing for Jillian and her family. She communicated with facial expressions, voice, pointing with her eyes, and a few hand symbols. She also had screaming spells and could appropriately articulate, "I am mad." In fact, she had a characteristic arm movement to indicate to people that they were dismissed.

Many medical crises occurred over the years, including pancreatitis (presumably related to valproic acid), cardiomyopathy leading to heart failure, macrocytosis, thrombocytopenia, recurrent infections, vomiting, and status epilepticus, necessitating numerous visits to the emergency department. Electrocardiograms were performed six-monthly and showed that her QT interval durations ranged from 257 to 492 ms. QT intervals in females greater than 470 ms are considered prolonged and greater than 500 ms as highly abnormal. Jillian died from subacute cardiac causes related either to a prolonged QT syndrome or to another fatal arrhythmia. She had common cold-like symptoms the week earlier. On the day of her passing, she looked "tired and pale" but in no distress. Jillian was taken to her family doctor who thought she might benefit from intravenous antibiotics and asked the family to bring her to the community hospital. She died in the hospital approximately two hours later. To her parents, "It was like she just fell off to sleep." Her parents were not prepared for her early death but appreciated being able to be next to her bed in her final minutes of life.

Jillian's parents and her companion nurse took turns in telling G.M.R. her story and in doing so provided insights for

him about the "person" who Jillian was. Jillian's ability to communicate by body language enabled her to express her enjoyment of being among people, attending birthday parties, and visiting shopping malls, the movie theater, and supermarkets. Her facial expression revealed her love and empathy for babies: she would cry whenever they cried. She valued watching animals at home or through the house windows: there were dogs, cats, birds, and fish at home and butterflies outside. The sensation of touching the animals' fur or touching bread dough gave her gratification. She had a great sense of humor and laughter and liked to scare her older brother with sudden yells. Her bed was her sanctuary for "time out." She grew up to show many of the behaviors and interests typical of teenagers and later of young women. She loved wearing fancy dresses and to have her hair done at the hairdresser. She loved any kind of loud music. She preferred watching her TV shows via a mirror. According to her nurse, Jillian had a critical eye for young men, watching them at the coffee shop, and enjoyed visiting the local firefighters at the nearby station. She also had an admirer—a secret companion whom she met regularly at the park with the help of her nurse; together, they kept the relationship secret from her parents. Only at the funeral, when the young man in a suit, in a wheel chair, brought dozens of roses, did the parents acknowledge this relationship where Jillian had discovered love.

Personal reflections (the bulleted personal reflections not otherwise specified are the authors' thoughts)

> *It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.*
>
> William Osler

> "Dave and I, as well as all of Jillian's caregivers and friends, have always said that JILLIAN was given to us to teach us unconditional love as well as patience, living with disabilities and RETT SYNDROME. Oh, and how could I forget seizures!! She also taught us that a smile or giggle far outweighed any disability and Jillian smiled a lot. My hope is that anyone reading Jillian's story remembers that our girls can have a very fulfilling quality of life and they have so much to give. Therefore, please use Jillian's name. We loved her and were so proud she was our girl." Carol (Jillian's mother, January 2016).

- This story demonstrates how, even in the presence of severe "impairment" (at the level of "body structure and function"), a loving environment can enhance the expression of a person's "personal factors," quality of life, "participation," and "activities" and decrease "disability" (as these several terms are conceptualized by the World Health Organization's International Classification of Functioning, Disability and Health).[3-5]
- The story illustrates the unpredictable and very imprecise correlation between the level of the biomedical impairments and the subjective quality of life of the person—a concept coined *the disability paradox* by Albrecht and Devlieger.[6]
- In a broader sense, this story helps us recognize and acknowledge that "impairment and disability will, in varying degrees, always be with us, and that health care in all societies will always have to address the consequences of adaptation to existing and new social and environmental influences. Moreover, even with optimal biological and social breakthroughs the major concern of families and health care providers will continue to be the imperative to provide life-long care and a fulfilled life, even when 'cure' is not possible."[7]
- The story also reflects parental relief once a definite clinical and genetic diagnosis is made, and everyone can start to focus their attention both on management and seeking connections with other affected families and engage in the different activities of advocacy.[1]
- Intriguingly the clinical evolution of RTT follows John Hughlings Jackson's 1875 dictum for neurological deterioration: "For in disease the most voluntary or most special movements, faculties, etc., suffer first and most, that is in an order the exact opposite of evolution. Therefore, I call it the principle of Dissolution."[8]

History of RTT

On September 10, 1966, Dr. Andreas Rett (1924 to 1997), a Viennese pediatrician interested in patients with neurodevelopmental conditions, published an article in the Viennese Weekly Medical Journal (Wiener Medizinische Wochenschrift) titled "Peculiar childhood syndrome with brain atrophy associated with hyperammonemia"[9] and published a book on the syndrome in the same year.[10] This article eventually earned him immortality with the eponym of RTT.

According to Andreas Rett the story began one afternoon, presumably in the early 1960s, when in his clinic waiting room were two girls followed for their seizures, each sitting on her mother's lap. He noticed that both mothers were holding the arms of their daughters, gently restraining them. What caught his eye was that, as the mothers simultaneously released the grip on their daughters' arms both girls began to make the same unusual but rather stereotyped hand (washing) movements. He asked the mothers to hold and release their daughters' arms repeatedly, which consistently resulted in the same movements. Rett decided to look into the situation further and recognized that these girls had strikingly similar clinical and developmental histories. After discussing these observations with his nurse Martha, Rett was able to identify an additional six girls with the same clinical and developmental features. He arranged for all these girls to attend the clinic together and to sit next to each other, where they engaged in repetitive hand-washing movements without looking at each other. Rett consulted his Viennese friends Professors Birkmayer and Neumayer, and together, they concluded that he was observing a previously unrecognized syndrome.[12] In his original 1966 publications, Rett described the findings of 22 girls that he believed represented this new entity.[9,10]

There is no more difficult art to acquire than the art of observation…

William Osler

- Serendipity is a necessary but not sufficient element in a development like the story of RTT, or the development of penicillin—one must also recognize its potential value and then confirm or replicate the initial observation ("It is a prime example of discovery coming to the prepared mind").[11]
- There is no substitute for meticulous description of clinical observations including single case reports to expand the knowledge and understand the evolving natural history of specific populations with conditions such as RTT, even if one is unable to connect all the dots.

In the original article, and later in a chapter in the English language (1977) reporting 21 patients, Rett accurately described the phenotypic features of the syndrome.[9,13] He explained that "dramatic vomiting" led him to identify a constant fivefold increased ammonia level in serum and cerebrospinal fluid in all of his patients.[13] Years later, Naidu et al.[14] found only minimally elevated serum ammonia in just four of 70 affected girls, whereas Hagberg found hyperammonemia in only one of his 22 patients.[15] In 1982, Rett acknowledged that by then, he had recognized that only four of 54 patients had consistent hyperammonemia.[16] It was later postulated that the hyperammonemia resulted from improper assessment methodology and storage of the specimens.[17]

I learned an important lesson: Never take the obvious for granted.[18]

V.S. Ramachandran

- One cannot but question the reliability of Rett's claim of the all-inclusive biochemical accompaniment of his otherwise meticulously described clinical syndrome.
- One implication of this finding is that the original "classical" cases may not reflect the average patient or what becomes the "typical" range of the phenotypes.

In 1966, when Rett presented a film on these patients to the Viennese medical society, a neurologist dismissively commented that the patients represented the known entity of the apallic syndrome (persistent vegetative state in today's terminology; p. 121).[12] Rett remained bitter about the lack of acceptance of this work in Austria. In his semi-autobiographical book in 1990, Rett noted that the significance of the syndrome had been accepted and confirmed worldwide except in his homeland and that nothing had changed, even when the debate about the existence of "RTT" returned to Austria via the United States in the 1980s.[12] Indeed the issue became unequivocally resolved in Austria much later than in the rest of the world. (Martha Feucht, pediatric epileptologist in Vienna, personal communication at the International Epilepsy Congress in Paris 2005.)

- Filming has been the best way to document and present condition-specific movements. Rett's films are available nowadays at the Department of History of Medicine, University of Vienna. Interestingly, at the same period and on the other side of the Atlantic, Oliver Sacks was filming his successful documentation on the "awakening" effects of L-DOPA.
- Trust your own observations but interpret them with caution.
- Treat others' opinions with openness, respect and humility—whether you think they are correct or wrong.

Rett made his observations in the early 1960s. Independently, in 1960 the renowned Swedish clinician and researcher Bengt Hagberg (1923 to 2015) recognized a 3 and 1/2–year-old girl with phenotypic manifestations identical to those described by Rett. After identifying similar girls during the 1960s, he named the disease "Morbus Vesslan" after the nickname of the first patient. By 1980, he had documented 16 such girls and presented his findings in Manchester to the Council Group of the European Federation of Child Neurology Societies.[19] It appeared that Karin Dias from Lisbon had already observed four girls with this phenotype, and subsequently Jean Aicardi in Paris retrieved data on 11 individuals from his practice. Hagberg, Dias, Aicardi, and Ramos (who worked with Aicardi at the time) had in 1981 already begun writing the article of their 35 cases that appeared in the 1983 Annals of Neurology.[16] However, it was a chance meeting of Hagberg and Rett in Toronto in 1981, when Hagberg was giving a lecture on aspects of mental retardation at a meeting and mentioned the work of Rett. Rett, who was in the audience, then met Hagberg, and the result was the decision by Hagberg to term this disorder RTT (instead of his original plan to name it "Morbus Vesslan") in recognition of Rett's groundbreaking work. Independently in 1978, Ishikawa et al.[20] in Japan had described three affected girls.

- The behavior of Drs. Hagberg, Dias, Aicardi, and Ramos in recognizing Rett's original contributions reflected humility, humanism, generosity, integrity, and team collaboration.

In an initial attempt to understand the condition, Dr. Rett undertook investigations on several of his patients; some of which were invasive (including lumbar puncture, pneumoencephalography, and liver and brain biopsies). Rett also used experimental treatments with approximately 20 different drugs without any success.[21] Indeed, all experimental therapies tried so far have failed. However, many studies focused on gaining evidence on how to improve the health and functioning of females with RTT. These various treatments provided symptomatic relief, primarily in improving seizures, sleep, behavior, nutrition, and scoliosis treatment.[22-26]

- Ronnie Mac Keith (1967), a pioneering developmental pediatrician contemporary of Rett in the United Kingdom, reminded us that "patients are not uninterested vehicles of interesting diseases". Any decision for invasive or painful investigation or experimental treatment needs to follow the strictest ethical considerations and protocols.[27]

The first international RTT symposium, chaired by A. Rett, Y. Fukuyama, and B. Hagberg took place in Vienna in

1984.[28] In addition, in 1984 in the U.S., Kathy Hunter, Gail Smith, and Jane Brubaker began to organize the parents of those with RTT and established the International Rett Syndrome Association.[29] In 1985 the first of what have become annual meetings of this critically important patient support organization for care and research was held at the Kennedy Institute in Baltimore with the strong support and encouragement of Dr. Hugo Moser. Around this time, Steny Hoyer, a member of the United States Congress, began to advocate for RTT within the U.S. National Institutes of Health. The support emanating through the National Institute of Child Health and Human Development resulted in program project grants.[30]

> "Nothing about us without us" provides an opportunity to focus on the active involvement and participation of persons with disabilities in the planning of strategies and policies that affect their lives *(United Nation international day of disabled persons 2004)*.[31]

- As illustrated by Jillian's parents, the role of families and their advocacy organizations has become an integral force to improve the plight of their impaired children at many levels: from provision of information and the importance of natural environments like children's homes to advocating for clinical services and research, to organizing family-focused conferences and workshops, and organize research fundraising opportunities. Examples include the early publications for parents and health professional by Lindberg et al.[32] and Hunter.[33,34]
- It was the foresight and openness of Dr. Moser to invite any potential RTT researcher in the world to the first RTT meeting in North America. Dr. Moser undoubtedly knew that there would be enough research "material" for everybody and that international research collaboration would likely get better funding and lead to better research than individual efforts alone.
- The RTT advocacy groups' achievements became a benchmark for other associations to follow.

TABLE.
Milestones and Progress in Rett Syndrome

Dimension	Milestone
Advocacy	International Rett Syndrome Association[29] Guidance book: understanding rett syndrome[32] Book: The Rett syndrome book[33,34]
Describing and charting natural history	Developing a staging system[44,45] Developing diagnostic criteria[46-49] Genetic and phenotypic correlation[2,52,53] Identifying affected male patients[38,39] Natural history data on developmental trajectories[63] Paucity of abnormal movements and other subtle signs that precede the regression period[50,64,65] Sleep–wake disturbance trajectories[66,67] Characterization of irregular breathing patterns[68] Mild improvement following regression[69] Cardiac arrhythmias and prolonged QT a potential cause for death[70,71] Describing myocardial dysfunction[72]
Population-based studies	Creation of national registries and international databases[51,56-60,73] Prevalence 1 of 15,000-22,800 girls[54-56] Incidence: 1 of 9000 female births[74] Scoliosis incidence and progression[75] Life span and longevity[61,62] Epilepsy: prevalence—68%; of whom uncontrolled 33%; onset 4.7 yr[76] Longitudinal population to study lifelong trajectories and aging[77] Person (parent)-reported outcomes studies[78,79]
Biological basis for the syndrome	Fragile site at X p22 identified[80] Discovery of the protein methyl-CpG binding protein 2 (*MECP2*)[81] Genetic and physical mapping of *MECP2* to X chromosome[82] Identifying gene mutation of the *MECP2* gene as the cause of RTT pathogenesis[35] Animal models mimicking RTT with *MECP2* null mutant mice model[83] Disrupted central CO2 chemosensitivity in RTT mouse model[84] Reversal of neurological defects in a mouse model of Rett syndrome[85] Better understanding *MECP2* mechanisms, with more gene functions being activated than repressed[86] *CDKL5* is able to phosphorylate itself and to mediate *MeCP2* phosphorylation. Both are thought to belong to the same molecular pathway[41]
Novel therapeutic approaches	Examples include[37]: • normalizing *MECP2* expression • reactivating the *MECP2* copy on the inactive X chromosome • *MECP2* gene replacement or editing • targeting more distal pathways to alleviate certain symptoms

While Hagberg et al.[16] suggested a dominant mutation on one X chromosome, the long search for the mutation underlying RTT pathogenesis culminated only in 1999 when Amir et al.[35] identifying the gene mutation of the methyl-CpG binding protein 2 (*MECP2*). Developing synapses and synaptic plasticity appears to be a special target of the disorder by disrupting the balance between glutamate excitatory synapses and GABAergic inhibitory synapses.[36] These discoveries assisted enormously with diagnosis and understanding the variations of the condition and have served as a platform for a massive suite of biological research that has potential to develop new treatments that target the synaptic abnormality.[37] Children of both sexes with phenotypic variants of RTT have been described with *MECP2*, *CDKL5*, and *FOXG1* genes mutations.[38-43]

You can't connect the dots looking forward; you can only connect them looking backwards.

Steve Jobs

Reflections on clinical research milestones

- Diagnostic criteria as well as classification, staging and categorization systems initiated by Hagberg and last revised in 2010, have helped enormously to clarify the uniqueness of this evolving encephalopathy and emphasizing the concept that RTT is a clinical diagnosis independent of molecular findings (Table).[44-49]
- Classification systems give order to groups of disconnected facts. They help differentiate between classical and "atypical" presentations and inform on intra-condition variability when a novel condition is described. The ability to recognize core group and outliers is precisely what is needed when one considers comparing information across studies, especially when there is lack of clarity about the pathognomonic/diagnostic features of a condition like RTT.[50,51]
- Classification systems provide a systematic approach to improve our understanding of conditions, generate ideas, improve the provision of rational management, and refine our ability to prognosticate for individual patients. On the research front classification systems help developing hypothesis and models. On the other hand, one needs to guard against being too rigid about classification systems as this attitude can truncate the real phenotypic spectrum by excluding those on the atypical margins.
- Genetic–phenotypic correlation can also be viewed as a form of classification for prognostication using large international registries for data collection.[2,52,53]

Reflection on the epidemiologic research

- In addition to obtaining traditional epidemiologic data on prevalence, incidence, and survival rates that Hagberg started publishing in 1985,[54,55] there came the observation that most affected girls who received appropriate medical care grow to become adults. With that reality came the realization of the need for detailed population-based longitudinal data collection. National registries began to appear in many countries and followed by international collaborations. The International Rett Syndrome Association North American database compiled information on 1928 individuals with either RTT or other diagnoses associated with *MECP2* mutations in the United States and Canada.[56] Leonard[51] and Moore et al.[57] described the creation of the Australian Rett syndrome registry that was initially developed with both retrospective and prospective data in an attempt to include every affected girl in Australia and has now probably achieved a close to complete set of longitudinal data.[58] In 2001 the International Rett Syndrome Association funded the formation of a Web-based database to collect and display the genetic data of individuals with RTT from around the world. In 2002 the InterRett database was funded by the same international association to collect a large number of affected individuals to allow phenotypic–genotypic correlations and other research projects.[59] In 2003 the National Institutes of Health in the United States funded a multicenter RTT Natural History Study consortium. The RTT Natural History Study was created to characterize the clinical spectrum and longitudinal natural history of RTT in preparation to initiate anticipated clinical trials.[60]
- The gradually expanding life span of females with RTT over the past 50 years can be viewed as an indication of the compelling need for improved management of care for these women. Of the original cohort of Rett the probability of survival to age 25 years was 21%, whereas in the North American database, more than 70% survived to the age of 45 years. Death due to extreme frailty has become rare, with most of the deaths nowadays related to respiratory disorders and epilepsy.[61,62]

Conclusions

The history of RTT illustrates how a combination of (1) professional and personal humanism, (2) empathy for patients, (3) traditional and innovative research methodologies, (4) biological breakthroughs, and (5) clinical and scientific collaborations within and among professionals and with parent groups have together led to achievements that the early scientists in the field—those who paved the way in such an incredible way—could hardly even have dreamed about at the time. These are important lessons for those of us who work at the boundaries of our fields, where the guideposts and guidelines for understanding and management of a condition need to be created and continually tempered and refined as we move forward into uncharted territory.

The authors are very grateful to Mr. and Mrs. Harrod for agreeing to share their daughter's story—and their own. Their love and affection for Jillian were always evident; in now allowing her story to be told this way they are being consistent with their own values of wanting people to see the person and not the disease. The authors are all better informed through their generosity. The authors also thank Drs. Helen Leonard and Jenny Downs for their critical review of the article and their constructive recommendations.

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