Pediatric Neurology 50 (2014) 1–3

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Historical Vignette

The American History of Rett Syndrome

Alan Percy MD *

Civitan International Research Center, University of Alabama at Birmingham, Birmingham, Alabama

Introduction

Rett syndrome was first recognized more than 50 years ago in Europe. Andreas Rett, a neurodevelopmental pediatrician in Vienna, Austria, who first described Rett syndrome, is credited for his attempts to raise awareness of physicians in Europe as to their understanding of this unique neurodevelopmental disorder.[1] Unfortunately, most of Rett's papers were written in German and not widely circulated. At about the same time, Bengt Hagberg, a Swedish child neurologist, was also noting girls with similar features. At a meeting of European child neurologists in the late 1970s, Bengt raised this clinical issue and was informed of Andy Rett's publications in Vienna regarding girls with similar hand stereotypies as well as a recent publication of Andy's in the *Handbook of Clinical Neurology* that described Rett syndrome but associated it with hyperammonemia.[2] Nevertheless, Bengt, together with colleagues from France and Portugal, moved forward in planning the publication of what became the first widely read English language publication of Rett syndrome. Then, he discovered that the hyperammonemia described by Andy had turned out to be a spurious finding. Indeed, the two were recognizing exactly the same disorder. Subsequently, he met Andy in Toronto in 1981 and learned of the experiences in Vienna first hand. Bengt and colleagues then decided that this disorder should be known by the eponym Rett syndrome. Their article, published in the *Annals of Neurology* in 1983, spurred the worldwide search that raised this diagnosis to prominence as the leading cause of significant cognitive disability among females.[3]

Rett syndrome in America

At that time, only three American physicians had knowledge of this disorder. Vanja Holm, a neurodevelopmental pediatrician from Seattle, had visited Sweden and learned about Rett syndrome from Bengt. Mary Coleman, a child neurologist from Washington, DC, had attended a medical meeting in Paris and learned of the disorder there. Upon returning to the United States in 1983, Mary informed three mothers searching for answers that she was certain that she now had a diagnosis for their daughters. Later that year, Alan Percy, a child neurologist at the Baylor College of Medicine and the Texas Children's Hospital in Houston was contacted by Ina Desmond, a pediatrician and head of the Meyer Child Development Center at Texas Children's Hospital. Ina had received a letter from a local pediatrician, Merlene McAlevy, with a copy of the *Annals of Neurology* article and a request to review a record of a child seen previously at the Meyer Center. Alan Percy, the child neurology consultant for the Meyer Center, visited with this family and confirmed that she had the same features as those described by Bengt and his coauthors. Thereafter, he arranged for this girl to be admitted to the Clinical Research Center at Texas Children's Hospital and invited other child neurologists and trainees. As a result, several other children were identified from throughout Texas, including one child whom Percy had evaluated for neurodevelopmental delay 1 or 2 years earlier. This child had been seen, coincidentally, by Huda Zoghbi during a genetics rotation while in her training; she informed Percy that this girl should be reevaluated. Although that child had received another quite specific and different diagnosis based on a peripheral nerve biopsy, both girls shared the same clinical features.

Research development in Rett syndrome

The Baylor Rett Syndrome Clinic was then established within the Blue Bird Clinic by Percy, who recruited two critically important coworkers: Daniel Glaze and Rebecca Schulz. The initial clinical studies were also facilitated by Joe Jankovic and Vic Riccardi, two members of the Baylor College of Medicine faculty. At the same time, Huda Zoghbi was continuing her training in molecular genetics at Baylor and,

Support is provided by grants from the International Rett Syndrome Foundation and from the National Institutes of Health, including the Intellectual and Developmental Disabilities Research Center (P30HD38985) and the Angelman, Rett, Prader-Willi syndrome consortium (U54HD61222) a part of the National Institutes of Health Rare Disease Clinical Research Network (RDCRN), supported through collaboration between the National Institutes of Health Office of Rare Diseases Research at the National Center for Advancing Translational Science, and the Eunice Kennedy Shriver Child Health and Human Development Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

* Communications should be addressed to: Dr. Percy; 1720 2nd Avenue South; CIRC 320E; Birmingham, AL 35294-0021.

E-mail address: apercy@uab.edu.

0887-8994/$ - see front matter
http://dx.doi.org/10.1016/j.pediatrneurol.2013.08.018

through the Rett Syndrome Clinic, was able to seek answers to the possibility of a genetic basis as the cause of Rett syndrome. With continuing support and encouragement from Percy, she pursued a program of critical research that ultimately led to defining the cause of Rett syndrome as the result of mutations in the gene, *MECP2*, or *methyl-CpG-binding protein 2*.[4] This has led to a redefinition of diagnostic criteria for Rett syndrome[5] and the knowledge that more than 95% of individuals with the classic features of this disorder will have a mutation in *MECP2*.[6] In addition, the early beginnings of natural history studies were evolving including a study of growth patterns and the analyses of biogenic amine metabolites in cerebrospinal fluid as a potential marker of the movement disorder encompassed in the stereotypic hand (orofacial and feet to a much lesser extent) movements.[7]

The limited experience with Rett syndrome in the United States and the extreme interest in possible therapies expressed by the parents of the first child seen in Houston led Percy to contact Bengt, whom he had met as a medical student nearly 20 years previously. Bengt referred Percy directly to Andy Rett, who then invited him to attend the second Viennese conference on Rett syndrome that was held in October 1984. At that meeting, which included interested physicians and researchers from Europe and Japan, two other American colleagues attended, Vanja Holm and Hugo Moser, a child neurologist from Johns Hopkins School of Medicine and the Kennedy-Krieger Institute. This international meeting sparked an immediate surge of clinical and research activity in this country that has continued unabated to this day. Even more, *MECP2* mutations and a related genetic anomaly associated with duplication of *MECP2* have been linked to a variety of other clinical conditions that are greatly expanding the role of this important gene in the basic neurobiology of humans. The discovery of mutations in *MECP2* led to a dramatic increase in basic neuroscience research. Since that time, concerted patient- and laboratory-oriented research in Rett syndrome has progressed at an ever-increasing pace, such that clinical trials and translational research in animal models are now evident throughout the world.

During the early years of the enlarging recognition of Rett syndrome in this country, Kathy Hunter, Gail Smith, and Jane Brubaker began to organize the parents of those with Rett syndrome and established the International Rett Syndrome Association. 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-Krieger Institute with the strong support and encouragement of Hugo. Additionally, Steny Hoyer, a member of Congress, began to advocate for Rett syndrome within the National Institutes of Health. The resulting support emanating through the National Institute of Child Health and Human Development resulted in program project grants being awarded to Alan Percy at Baylor and to Hugo at Kennedy-Krieger Institute. Following these initial steps, the increase in awareness of Rett syndrome among parents, physicians, and other health care providers increased at a similarly dramatic pace such that we are now engaged in a large-scale natural history study in the United States under the leadership of the National Institutes of Health Office of Rare Diseases Research and funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NCT00299312). Now, at the University of Alabama at Birmingham, we are leading this effort to understand the ramifications of mutations or duplications in this gene, along with many researchers throughout the country and around the world. We are presently completing the 10th year of the Rett Syndrome Natural History Study funded as mentioned previously and with additional support from the International Rett Syndrome Foundation, the Southeastern Rett Syndrome Alliance, and many interested families and friends. Through this grant, we are probing the clinical and research aspects of Rett syndrome with sites here at University of Alabama at Birmingham; Baylor College of Medicine with Daniel Glaze, Kathleen Motil, and Jeffrey Neul; Children's Hospital Boston (Harvard) with Walter Kaufmann and Daniel Tarquinio; and the Greenwood Genetic Center with Steve Skinner. The University of Alabama at Birmingham team consists, in addition, of a comprehensive group of clinical and basic research investigators including Jane Lane, Suzanne Geerts, Jerry Childers, Lucas Pozzo-Miller, Chris Chapleau, Vishnu Cuddapah, and Michelle Olsen and the larger medical community, all engaged in providing the optimal guidance for girls and women with Rett syndrome.

The Kennedy-Krieger Institute Rett syndrome clinic, now under the leadership of Sakkubai Naidu, and a clinic at the University of California—San Diego under the direction of Richard Haas have been operating for more than 25 years. More recently, other clinics devoted to Rett syndrome have emerged in Oakland, Los Angeles, St. Paul, New York City, and Denver. These clinics provide a rich network for the incorporation of comprehensive clinical trials that are starting and will be developing with increasing breadth and depth in coming years.

Conclusion

Remarkable progress has been made during these past 3 decades, particularly since the discovery of the association of Rett syndrome with *MECP2* mutations and the increasing pace of basic science investigations. We fully expect to accelerate this pace of understanding and discovery as clinical trials are already being conducted and others are planned. Without doubt, the girls and women encountered today with Rett syndrome are progressing well and are, overall, in better general, neurological, and behavioral health than those encountered earlier simply because of the concerted efforts of this broadly based consortium engaged in clinical and basic research, but equally importantly because of the efforts of parents, family, and friends throughout the country and around the world.

This brief history is dedicated to the memory of Mary and Roger Brumback for their many years of support for all disorders of the developing nervous system including Rett syndrome.

References

1. Rett A. [On a unusual brain atrophy syndrome in hyperammonemia in childhood]. *Wien Med Wochenschr*. 1966;116:723-726.
2. Rett A. Cerebral atrophy associated with hyperammonemia. In: Vinkin PJ, Bruyn GW, eds. *Handbook of Clinical Neurology*. Amsterdam: North Holland Publishing Company; 1977:305-329.

3. Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol*. 1983;14: 471-479.
4. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet*. 1999;23:185-188.
5. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010;68:944-950.
6. Percy AK, Neul JL, Glaze DG, et al. Rett syndrome diagnostic criteria: lessons from the Natural History Study. *Ann Neurol*. 2010;68:951-955.
7. Zoghbi HY, Percy AK, Glaze DG, Butler IJ, Riccardi VM. Reduction of biogenic amine levels in the Rett syndrome. *N Engl J Med*. 1985;313: 921-924.