After 30 years, Rett syndrome remains an enigma

Back in the mid-1960s, pediatrician Andreas Rett noticed that several retarded girls in his practice made peculiar, continuous "hand-washing" motions. He eventually identified an unusual constellation of symptoms in these patients, and located 31 girls or women with similar symptoms.

Three decades later, the condition named after Dr. Rett—Rett syndrome—has been diagnosed in thousands of individuals, almost all of them girls. But the causes of the disorder remain a mystery, and effective treatments are elusive.

Children with Rett syndrome often receive an initial diagnosis of autism, because during an early stage of the disease many children become aloof and lose eye contact. The two disorders, however, have strikingly different prognoses, and apparently different causes. While children with autism tend to gain skills over time, or at least remain fairly stable, children with Rett syndrome—while they generally appear less "autistic" over time—decline physically and usually develop marked motor disability and severe mental retardation.

The most striking symptom of Rett syndrome is an almost constant "hand-washing," hand-wringing, or clapping movement during waking hours. Additional symptoms include hyperventilation or breath-holding; air swallowing resulting in bloating (sometimes to the degree that the girls appear to be pregnant); tooth-grinding; bizarre night-time laughing spells; screaming spells; small, cold, blue feet; scoliosis; unusual responses to pain; and, after autistic symptoms disappear, intense eye contact.

Once thought to be quite rare, Rett syndrome is now believed to occur in more than one in 10,000 girls. A 1995 study in Estonia, by T. Talvik and fellow researchers, reported that one in 15,000 girls exhibits all of the symptoms of classical Rett's.

In a recent article, Swedish researcher B. Hagberg has outlined the current diagnostic criteria for both classical Rett syndrome and variants of the disorder. According to Hagberg, one of the world's leading experts on Rett syndrome, symptoms of classic Rett's include:

1. Initial normal development in infancy (prenatal and birth period as well as first six months or longer).

2. Decelerated growth in head circumference somewhere between three months and four years of age.

3. Loss of purposeful use of the hands between 9 months and 2-1/2 years of age.

4. Psychomotor regression during the same time period, including loss of speech or babbling, social withdrawal, and signs of mental retardation.

5. Somewhere between ages 1 and 3, development of constant hand-wringing, clapping, or other abnormal hand movements.

6. Gait and postural abnormalities, developing at two to four years of age.

Girls with Rett syndrome, Hagberg says, generally go through four stages: a stagnation period, generally beginning before the age of two, at which physical and mental symptoms first appear; a stage of rapid regression, somewhere between the ages of 1 and 4; a "pseudostationary" period, which may last years or even decades, during which symptoms stabilize and some autistic behaviors disappear; and a stage of late motor deterioration, during which even patients who were ambulatory generally lose their ability to walk.

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Now that awareness of Rett syndrome is growing, Hagberg says, doctors are reporting both milder and more severe variants of the disorder. Girls with mild Rett's, he says, tend to have fewer motor problems, and a number have partially retained their ability to speak. At the other end of the spectrum are girls who are abnormal from birth, or experience rapid deterioration shortly afterward. In addition, he notes, about 5 to 10% of girls with Rett syndrome have infantile seizures.

Tests offer few answers

While EEGs show changes in the brains of girls with Rett syndrome, Hagberg notes that CT and MRI scans are unrevealing. "More sophisticated qualitative neuroimaging analyses, volumetric and planimetric," he says, "have revealed significant brain hypoplasias affecting gray matter areas." SPECT exams reveal abnormal patterns in most, but not all, girls with Rett syndrome.

Margaret Bauman and colleagues, who recently performed post mortem studies on the brains of three girls with Rett syndrome, report finding significant abnormalities that "appear to be consistent with a curtailment of development." Bauman et al. say that "reduced neuronal cell size and increased cell-packing density were present throughout the cortical and subcortical regions of the brain in all cases without evidence of active degeneration." They note that these abnormalities "appear to be more diffuse than previously thought, and probably account for the widespread symptomatology characteristic of this disorder." The researchers say that in each case, the degree of abnormality seen in the brain was more closely correlated with the severity of symptoms at time of death than with age or duration of symptoms.

As for laboratory tests, Hagberg says, "so far the large majority of these tests have been negative and the remainder confusing and disappointing for practical use," except to rule out other disorders.

Doctors have been equally disappointed by the failure to identify Rett syndrome's genetic roots. "The genetic basis for Rett syndrome is indisputable," Hagberg says; "the mode of transmission, however, is obscure." The search for abnormalities on the X chromosome (the most likely candidate, since the disorder affects only girls), has been fruitless, and recent preliminary findings of a defect on chromosome 11 believed to be related to the disorder were not replicated in later research.

The evidence to date, Hagberg says, implicates one of two factors in Rett syndrome: either the normal "programmed death" of certain brain cells in early development has gone awry, or the girls lack a specific brain growth factor.

Treatment: little success

Treatments for Rett syndrome remain as elusive as understanding about its causes. Some researchers have reported that the drug bromocriptine has some beneficial effects, but other drugs do not appear to improve the behavior or functioning of girls with the syndrome. And a new report indicates that behavior modification, which often produces dramatic improvements in children with autism, is of little or no help in cases of Rett syndrome.

Tristram Smith, Morten Klevstrand and O. Ivar Lovaas recently reported the discouraging results of intensive behavior modification programs for three girls who ranged in age from 31 to 37 months when their programs began. All of the girls had initially been diagnosed as having autism. Two were treated at the UCLA Young Autism Project, and the third in Norway at a replication site for the UCLA program.

Although the Young Autism Project has a noteworthy record of success in treating autism through behavior modification, the researchers report that their subjects with Rett's made little or no progress—and showed marked deterioration in many areas—despite treatment. In addition, they note that the few improvements seen in their subjects, such as a decrease in tantrums and increased affection, are also often seen in untreated girls.

"Subjects had poor outcomes even though they participated in a scientifically validated, closely supervised program of behavioral treatment, with thousands of hours of individualized instruction provided per subject," Smith et al. say. "Thus, despite its efficacy with other pervasive developmental disorders, behavioral treatment does not seem promising as an intervention for Rett's disorder."

The researchers noted one finding not mentioned in most reports on Rett's: "all subjects in the present study underwent periods of near-total unresponsiveness to sensory and social stimuli." While attention deficits are common in developmentally dis-

continued on page 7