Rett's linked to opioids, but cause still a mystery

While researchers speculate that high levels of opiate-like brain chemicals may cause some autistic symptoms (see cover), Italian researchers (Andrea Genazzani et al.) say *low* levels of these same substances may be linked to Rett syndrome.

Rett syndrome, a degenerative disorder commonly believed to affect only girls, causes autistic-like symptoms, loss of normal hand use (replaced by a chronic hand-washing or hand-wringing motion), seizures, loss of mobility, scoliosis, and loss of speech. Other symptoms, according to an article by noted Rett researcher Bengt Hagberg, include tooth-grinding, episodes of both hyperventilation and breath-holding, extreme bloating, reduced sensitivity to pain, sleeplessness and strange periods of laughter during the night, growth retardation (many girls with Rett's wear the same shoe size for years), and jerky or shaky trunk movements.

Endorphins very low

Levels of B-endorphin were extremely low in the cerebrospinal fluid of nine girls with Rett syndrome—only 20.8 fmol/ml, compared to 69.1 for a control group—according to a study by Genazzani and colleagues. B-endorphin is one of several opiate-like substances which modulate pain and appear to help regulate emotions and behavior.

The researchers note that:

—Decreased levels of B-endorphins could be linked to the progressive deterioration seen in girls with Rett syndrome. A similar decrease is seen, they note, in people with degenerative dementias.

—Levels of two other substances (B-LPH and ACTH) were normal. However, in girls with seizures, the ratio of B-EP to ACTH was significantly higher than in other girls. This same finding has been reported in one type of infantile spasms, and, the researchers say, "further supports the hypothesis of an imbalance between ACTH peptides and opioids" as a contributor to seizures with no other known cause.

—The reduced levels of B-endorphin, coupled with normal levels of the other two substances, "is similar to patterns found in Parkinsonian patients," the researchers note. This similarity to Parkinson's was also noted by Huda Zoghbi et al.—see ARRI Vol. 3, No. 2—who found unusual levels of several transmitter chemicals in girls with Rett syndrome.

Are growth substances or viruses involved?

Hagberg, one of the first researchers to become deeply involved in the study of Rett syndrome, notes that despite many tests, surprisingly few structural or chemical abnormalities have been detected in the brains of girls with Rett syndrome.

Because of the early brain growth slowing, retarded foot growth, and overall slow growth of girl's with Rett's, Hagberg theorizes that growth regulators might be involved in Rett syndrome. While tests show that levels of traditional growth hormones are normal, Hagberg speculates that other growth regulators such as epidermal growth factor (EGF), nerve growth factor (NGF), or brain-derived neurotropic factor (BDNF) might play a role in Rett's.

It is also possible, Hagberg says, that Rett syndrome is caused by a virus. For instance, he speculates, a viral infection could lead to the release of an abnormal "messenger" protein that could interfere with normal nerve cell transmissions. He notes, however, that these and other theories are "wild speculations in a stage of complete causal mystery."

One of the few solid leads researchers have is data from twin studies, which offer strong evidence that genes are involved in Rett syndrome. In eight identical twin sets identified so far, both twins are affected; in each of two non-identical twin-girl sets, one twin is affected and the other is not.

Unusual cases seen

Hagberg also notes that researchers are seeing more atypical cases of Rett syndrome. The most common atypical forms are:

—cases in which there is no normal development. (Most girls with Rett's appear to develop normally for at least six months.)

—at least one case in which initial symptoms appeared, but the deterioration common to Rett syndrome did not occur.

—two cases with early, intense seizures—a symptom that usually does not develop until later stages in Rett syndrome.

Hagberg also has seen "forme fruste" cases of Rett's, in which the girls have mild and incomplete symptoms, and the course of the disorder is slower than normal. In other cases, infantile seizures occur even before the onset of symptoms of Rett's.

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"Reduced cerebrospinal fluid B-endorphin levels in Rett syndrome," Andrea R. Genazzani, Michele Zappella, Antonio Nalin, Youssef Hayek, and Fabio Facchinetti; *Child's Nervous System*, No. 5, 1989, pp. 111-113. Address: Andrea R. Genazzani, Department of Obstetrics and Gynecology, University of Modena, Via del Pozzo 71, I-41100 Modena, Italy.

—and—

"Rett syndrome: clinical peculiarities, diagnostic approach, and possible cause," Bengt A. Hagberg; *Pediatric Neurology*, Vol. 5, , No. 2, 1989, pp. 75-83. Address: Bengt A. Hagberg, Department of Pediatrics II, Children's Clinics, East Hospital, S-416 85 Goteborg, Sweden.