Rett Syndrome progressive, affects only girls

Rett Syndrome, a severe neurological disorder which produces many "autistic" symptoms, may occur in as many as one in 15,000 births.

The syndrome affects only girls, who appear normal until between seven and eighteen months, then begin to lose previously acquired language skills, social behaviors and motor abilities. A constant "hand-washing" or hand-wringing motion is a characteristic of the disorder.

Children with Rett Syndrome exhibit autistic-like symptoms such as withdrawal, hyperactivity, abnormal sleep patterns and self-stimulating behaviors in the early stages of the disorder, but many of these symptoms improve with age. However, deterioration of higher brain functions in these children leads to severe retardation, and about two-thirds of children with Rett Syndrome develop epilepsy. Most lose their ability to speak in early childhood, and do not regain language.

Symptoms of Rett Syndrome also include microcephaly (abnormally small head circumference), abnormal gait, seizures, hyperpnea (forced breathing), shakiness of the limbs and torso, tooth-grinding, extreme difficulty in chewing, inexhaustible appetite combined with weight loss and reduction of muscle mass, and facial grimaces. In adolescence, girls with Rett Syndrome frequently develop spasticity, curvature of the spine, and poor circulation in the legs, and many become wheelchair-bound. Precocious puberty appears to be common.

May be X mutation

Because Rett Syndrome affects only girls, there is speculation that the disorder is caused by a dominant mutation on an X chromosome, lethal to males. However, studies have not found that there are fewer male children in families with Rett Syndrome children or more miscarriages among these children's mothers. According to Michel Philippart of UCLA, "the involvement of the X chromosome seems obvious since no boy is affected but [there is] a puzzling apparent lack of inheritance for an assumed genetic trait."

However, Philippart and fellow researchers note that they know of two half-sisters, two sisters and one set of twins with Rett Syndrome, and that a maternal cousin of one of their Rett Syndrome patients also has the disorder. German researchers recently reported identifying another set of identical twins both having Rett Syndrome (Tariverdian et al.).

Wolfgang Killian of Austria suggests that each case of Rett's may be a new mutation, rather than an inherited defect, but acknowledges that this would not explain the instances of sisters with Rett Syndrome. He speculates that the cause may be a "two-step" mutation, in which a first (harmless) mutation occurs in the mother and a second (harmful) mutation occurs in the fertilized egg; this would be lethal to males and cause the syndrome in females. The German researchers note, however, that new mutations are often related to increased age of parents (as in Down Syndrome), and that the ages of parents of Rett Syndrome patients are not higher than average.

Vanja A. Holm of the University of Washington suggests that "environmental factors should be kept open (as) this striking disorder appears to have a history dating back only 20-some years." Philippart says a slow virus might play a role in the disorder, but notes that this alone would not explain why boys are not affected.

An International Rett Syndrome Association has been established to aid parents and professionals in dealing with this disorder. The Association's address is 8511 Rose Marie Drive, Fort Washington, Maryland 20744; the phone number is (301)248-7031.

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A list of the seven references cited in this article is available from the ARRI. Please send a self-addressed, stamped envelope to ARRI, 4182 Adams Avenue, San Diego, CA 92116, and specify that you are requesting references for the article on Rett Syndrome.

Rett treatment holds promise

Italian researchers Michele Zappella and Andrea Genazzani recently treated seven Rett Syndrome patients with Bromocriptine, a drug which improves the functioning of the dopamine system in the brain.

They report that within two weeks, all of the patients became more relaxed, aware, social and affectionate. "Hand-washing" decreased in four girls, and the motor skills of three improved; all of the children slept better, and one girl spoke for the first time.

The researchers tried Bromocriptine following tests that showed that girls with Rett Syndrome may have abnormally low levels of naturally-occurring opium-like brain chemicals called endorphins. Because the brain's dopamine system helps regulate endorphin levels, Zappella and Genazzani believe low levels of these chemicals may be caused by a defect in the dopamine system. While Rett Syndrome resembles autism, several studies have shown that autistic children seem to have *higher* than normal levels of these opium-like substances in their brains. (See related story on page 1.)

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"Girls with Rett Syndrome Treated with Bromocriptine," Michele Zappella and Andrea Genazzani; *Wiener klinische Wochenschrift*, 1986. Address: Michele Zappella, Regional Hospital, USL 30, Siena, Italy.

—and—

"Plasma Endorphins in Rett Syndrome: Preliminary Data," Fabio Facchinetti, Felice Petraglia, Antonio Nalin, Andrea R. Genazzani, Michele Zappella, and Sergio Bernasconi; *American Journal of Medical Genetics*, 24:331-338, 1986. Address: Fabio Facchinetti, University of Modena, via del Pozzo 71, 41100 Modena, Italy.

Opioids linked to autism (continued)

other two boys dropped significantly. The researchers' findings support the theory that by blocking pain, high opioid levels encourage self-destructive behavior.

Some studies have shown that opioid-blocking drugs also reduce self-injurious behavior in individuals who are not autistic. Curt Sandman et al. recently administered naloxone (a drug related to naltrexone) to a 21-year-old non- retarded, non-autistic woman with self-injurious behaviors. He reports that the girl did not injure herself during the treatment period, and that treatment resulted in decreased anxiety, improved cognitive ability, and normalization of brain wave responses to stimulation.

While these findings are encouraging, researchers emphasize that their studies are preliminary and that much more testing will be required to establish whether or not naltrexone is safe and effective.

Panksepp and colleague Tony Sahley believe that high opioid levels could lead to cognitive defects and could also cause the immature physical development occasionally seen in autistic children. They cite a study by Sandman and Kastin showing that prenatal exposure of rats to high levels of opioids leads to profound physical and cognitive impairment, as well as delayed development.

A study conducted at Tel Aviv University by R. Weizman et al. appears to contradict the opioid theory because the ten autistic subjects in the study actually had reduced, rather than elevated, blood levels of opioids. However, Panksepp believes that the "calming and stress-relieving effects" of high opioid levels in the brain might actually lead to a reduction of these levels in other parts of the body.

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A list of the nine references cited in this article is available from the ARRI. Please send a self-addressed, stamped envelope to ARRI, 4182 Adams Avenue, San Diego, CA 92116, and specify that you are requesting references for the article on opioid-blocking drugs.