Autism, Fragile X connection investigated

Recent studies indicate that there is a strong association between autism and Fragile X (or Martin-Bell) Syndrome, a constriction on the long arm of the X chromosome.

In one study, Gene S. Fisch and fellow researchers at the Institute for Basic Research in New York examined 144 autistic males and found that 18 (12.5%) had Fragile X Syndrome. In a second study, the same researchers noted that of a total of 614 autistic males tested in ll surveys, 47 (7.7%) tested positive for Fragile X.

"We think that any genetic disorder that is a cause of the condition in 7.7% of autistic males is of major importance in autism and should be screened for routinely," the researchers concluded. "This is especially true because the mothers of such autistic Fragile X males are most likely carriers and therefore at risk of having sons with developmental or learning disorders in future pregnancies."

One study of men with Fragile X found that nearly all had autistic traits.

While a recent South Carolina study (Wright et al.) found only one case of Fragile X in a group of 40 autistic children, a Swedish investigation (Wahlstrom et al.) found 16% of 101 autistic children to have Fragile X Syndrome. Canadian researchers (McGillivray et al.) found that three of 33 autistic males had Fragile X Syndrome; because two of the three subjects also had suffered from birth complications, the researchers speculate that a combination of Fragile X and other prenatal or perinatal factors may lead to autism. Other investigations also indicate that Fragile X is not a simple X-linked recessive disorder such as hemophilia, but rather may involve additional factors such as a "modifier gene" or abnormalities in the fetal environment.

A study of 50 males with Fragile X by Hagerman et al. found that virtually all had autistic traits such as odd hand mannerisms, language delays, and current or past lack of social responsiveness. While no members of the study group fit the classical Kanner syndrome according to the Rimland E-2 questionnaire, 16% fulfilled all of the American Psychiatric Association's criteria for infantile autism and an additional 30% fulfilled criteria for autism in a residual state.

Males with Fragile X tend to have physical anomalies including large or prominent ears, high arched palates, long faces, hyperextensible fingers, enlarged testicles, poor muscle tone, female-like body fat distribution, large feet, and mitral valve prolapse (a heart abnormality). Approximately 30 percent of females with Fragile X are mentally impaired, and a recent study found two Fragile X women who were autistic. One evaluation of four generations of a family in which Fragile X occurred found that all three female "carriers" had symptoms of severe depression, manic depressive disorder or other psychiatric illness (Reiss et al.).

In addition to its apparent role in causing autism, Fragile X has been linked to non-autistic mental retardation and in fact may be the second leading genetic cause of retardation following Down's Syndrome.

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Folic acid for Fragile X: treatment results mixed

In testing for Fragile X, researchers have found that the abnormality is evident only when cells are cultured in a laboratory medium deficient in folic acid, a B vitamin. This has led to speculation that Fragile X may be linked to a folic acid deficiency, and that administering folic acid to individuals with Fragile X might help alleviate their symptoms. Recently, studies at the University of Colorado, the New York Institute for Basic Research in Developmental Disabilities, and the Institut de Progenese in Paris have tested this theory.

Age may be a factor

Ted Brown et al. in New York tested five males, ranging in age from eight to 26. Subjects were given 250 mg. of folic acid per day for three months, followed by a placebo for three months and then folic acid for another three months. The researchers concluded that "based on IQ tests, behavior ratings, the Autistic Descriptors Checklist, and parental ratings, there was little evidence to suggest any positive effects seen during the administration of high-dose folic acid." They did note, however, that the short duration of the study, and the fact that many of their subjects were past early childhood (when folic acid treatment could possibly be more effective), may have influenced their results.

The Colorado researchers (Hagerman et al.) tested 25 males ranging in age from one to 31. Folic acid (10 mg. per day) and placebos were each administered for six months. While language and behavior did not improve significantly for the group as a whole during folic acid treatment, subjects who had not yet reached puberty did demonstrate a marked improvement in intellectual performance. Also, caretakers and parents noted that the younger children had longer attention spans, were less hyperactive, had fewer violent outbursts and showed decreases in unusual hand mannerisms.

The researchers believe their study "adds further support for the use of folic acid in males with the Fragile X syndrome."

They add that vitamin B6 levels should be monitored in patients receiving folic acid therapy, and that perhaps B6 should be given in conjunction with folic acid, as B6 appears to be used at an increased rate when folic acid is given in large doses.

According to the French study (Lejeune et al.), a majority of 42 people with Fragile X Syndrome improved when treated with folic acid. (Subjects in this study received dosages of .5 mg. per kilogram per day, equivalent to about 11 mg. per day for a 50-pound person.) The researchers found that most subjects had fewer behavior problems during folic acid treatment, and that IQ scores increased at least slightly.

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"High Dose Folic Acid Treatment of Fragile X Males," W. Ted Brown, Ira Cohen, Gene Fisch, Enid Wolf-Schein, Valerie Jenkins, Mazhar Malik and Edmund Jenkins; *American Journal of Medical Genetics*, 1986, 23:263-271. Address: W. Ted Brown, New York State Institute for Basic Research in Dev. Disabilities, Dept. of Human Genetics, 1050 Forest Hill Rd., Staten Island, New York 10314.

—and—

"Oral Folic Acid Versus Placebo in the Treatment of Males with the Fragile X Syndrome," Randi J. Hagerman, Alfred W. Jackson, Andrew Levitas, Marcia Braden, Pamela McBogg, Melinda Kemper, Loris McGavran, Rebecca Berry, Irwin Matus and Paul J. Hagerman; *American Journal of Medical Genetics*, 1986, 23:241-262. Address: Randi J. Hagerman, M.D., Child Dev. Unit, The Children's Hospital, 1056 East 19th Ave., Denver, Colorado 80218.

—and—

"Essai de Medication Par L'Acide Folique Dans le Syndrome de L'X Fragile" (with English abstract), J. Lejeune, Marie-Odile Rethore, Marie-Christine de Blois, and A. Ravel; *Annales de Genetique*, Vol. 27, No. 4, 1984, pp. 230-232. Address: Pr. J. Lejeune, Chaire de Genetique fondamentale, Institut de Progenese, 45 rue des Saints-Peres, 75270 Paris cedex 06.