Biomedical Update:

Clomipramine: pros, cons reported

A new study suggests that the drug clomipramine (Anafranil) may be useful for some adults with autism and autistic-like disorders. However, like previous research, this study raises cautions about side effects, including seizures.

Edward Brodkin and colleagues administered clomipramine to 35 adults with autism, Asperger's syndrome, or pervasive developmental disorder (PDD). Participants' behavior was rated before the study began and after 4, 8, and 12 weeks of clomipramine treatment. The researchers report that "eighteen (55%) of the 33 patients who completed the trial were categorized as treatment responders," based on scores of 'much improved' or 'very much improved' on a behavioral rating scale.

Improvements included diminished repetitive thoughts and behavior, reduced aggression (including self-injury and property destruction), and some improvements in social relatedness. Several subjects, Brodkin et al. say, responded dramatically; "for example," they note, "a 40-year-old woman with Asperger's disorder went from long-term hospitalization to living with a roommate in a supported apartment [and] a 32-year-old nonverbal man [with PDD] began attending a sheltered workshop though previously he had been housebound." The researchers add that there appeared to be no relationship between subjects' IQ levels or the severity of their symptoms and their responsiveness to clomipramine.

The researchers also report, however, that 13 of their patients suffered significant adverse effects. One patient dropped out of the study due to agitation, and another because of abdominal cramping. Of the remaining subjects, three—two of whom had pre-existing seizure disorders—suffered seizures while on the drug. Other side effects included constipation, weight gain, and sedation. Unlike a previous study by Mark Lewis and colleagues, this study did not report any cardiac abnormalities in subjects.

In earlier studies of clomipramine, Lewis et al. reported that the drug reduced self-injurious behavior in six of eight retarded adults, while Laura Sanchez and colleagues concluded that the drug was of little value for children and caused "serious and common" side effects (see ARRI 10/4).

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"Clomipramine in adults with pervasive developmental disorders: a prospective open-label investigation," Edward S. Brodkin, Christopher J. McDougle, Susan T. Naylor, Donald J. Cohen, and Lawrence H. Price; *Journal of Child and Adolescent Psychopharmacology*, Vol. 7, No. 2, 1997, pp. 109-121. Address: Christopher J. McDougle, Connecticut Mental Health Center, 34 Park Street, Room 333B, New Haven, CT 06519.

Another genetic defect linked to autistic behavior, retardation

In the past few years, researchers have identified approximately 20 children with a deletion of the q37 area of chromosome 2. Recently, B. D. Friedman and colleagues reported on an additional seven children (plus one previously reported child) with this chromosomal abnormality, which appears to be linked to retardation and autistic behaviors.

Common characteristics of individuals with the 2q37 deletion include self-stimulatory or ritualistic behaviors, developmental delays, short stature, obesity, poor muscle tone, umbilical and inguinal hernias, hyperextensible joints, shortened hand and foot bones, cardiac abnormalities, eczema, and unusual facial features (including a "flattened" midface, minor ear anomalies, abnormal eye folds, a depressed nasal bridge, downturned mouth corners, rounded forehead bones, and a small jaw).

The researchers say a number of children with 2q37 resemble patients with Albright hereditary osteodystrophy (AHO), a disorder caused by an abnormal gene—not a deletion—at the same location. AHO causes retardation and short fingers and toes.

Friedman and colleagues are using sophisticated tests to study the possible link between 2q37 deletions and autism, and say that "further knowledge of genes in this region may provide insight into the pathogenesis of autistic behaviors."

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"Deletion of chromosomal region 2q37: clinical phenotype in eight cases," B. D. Friedman, J. L. Gorski, B. D. Hall, A. Brothman, J. C. Carey, and W. L. Flejter; conference poster, 1997. Address: B. D. Friedman, University of Utah, Salt Lake City, UT 84112.

Skin lesions suggest genetic influence

According to a new Israeli study, skin abnormalities seen in many autistic individuals may offer clues about the origins of the disorder.

While conducting routine dermatological examinations in psychiatric facilities, Avigdor Srebrnik and colleagues noticed that autistic individuals exhibited a number of skin abnormalities. This led them, Srebrnik et al. say, "to the speculation that there might be an inborn association between autism and certain cutaneous [skin] manifestations, and that autism may be a component of an inherited neurocutaneous disorder." Neurocutaneous disorders, which affect both the skin and the nervous system, occur when a genetic defect or other insult causes an abnormality of the early fetal cells from which both the skin and the nervous system develop.

To determine if skin abnormalities are more common in autism than in psychiatric disorders in general, Srebrnik and colleagues compared two groups of hospitalized patients: 74 autistic subjects, and 67 psychiatric patients with no history of autism or mental retardation. All patients were evaluated by a dermatologist unaware of the subjects' diagnoses.

The researchers report that autistic subjects were significantly more likely than other subjects to have seborrheic dermatitis, atypical nevi (moles and related skin blemishes), hyper- and hypo-pigmented skin lesions, and male pattern baldness. None of these conditions appeared to be linked to drugs the subjects were taking.

The researchers conclude that there is "a significant association of certain skin manifestations and autism," and that the possible genetic roots of this association should be investigated.

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"Cutaneous manifestations in an autistic population," Avigdor Srebrnik, Sarah Brenner, Agatha Holan, Daniel Stein, and Avner Elizur; *Journal of the European Academy of Dermatology and Venereology*, Vol. 9, 1997, pp. 118-122. Address: Avigdor Srebrnik, Department of Dermatology, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel.

L-dopa disappointing

Because autistic individuals show some evidence of abnormal metabolism of the brain chemical dopamine, Japanese researchers recently tried low dose levodopa therapy on autistic subjects. The drug levodopa is converted into dopamine by the body.

Of the 20 children given the drug in a double-blind, crossover study, four showed slight improvement. N. Sugiyama and colleagues report, however, that "administration of low dose levodopa to autistic children resulted in no clear clinical improvements."

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"Low-dose levodopa therapy of autistic disorder: evaluation of clinical effectiveness," N. Sugiyama, H. Sugie, Y. Igarashi, M. Ito, and T. Fukuda; *No To Hattatsu*, Vol. 30, No. 1, January 1998, pp. 51-55. Address: N. Sugiyama, Department of Pediatrics, Haibara General Hospital, Shizuoka, Japan.