Less invasive technology now standard for ASD closure
John W. Moore
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FOCUS ON SUBSPECIALTIES

Childhood Cancer Survivor Study explores long-term outcomes

by Roger L. Berkow, M.D., FAAP, and Leslie L. Robison, Ph.D.

More than 70% of children diagnosed with cancer are expected to become long-term survivors with current therapies. The Childhood Cancer Survivor Study (CCSS) was initiated in 1994 to address the needs of these individuals, many of whom have grown to adulthood and now face the likelihood of experiencing delayed effects from the treatment of their illness.

The CCSS is the largest and most extensively characterized cohort of childhood and adolescent cancer survivors in North America. It serves as a resource for the investigation of such issues as risk of second malignancies, endocrine and reproductive outcomes, cardiopulmonary complications and psychosocial effects among this unique and ever-growing population.

The CCSS cohort consists of five-year survivors of cancer or a similar illness diagnosed during childhood or adolescence (before age 21). Participants were diagnosed between 1970 and 1986 at one of 25 collaborating research centers in the United States and Canada. Individuals diagnosed with leukemia, central nervous system tumors (all histologies), Hodgkin’s disease, non-Hodgkin’s lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma and bone tumor are included in the cohort.

The National Cancer Institute has funded the CCSS since its inception, allowing the cohort to serve as a base for investigator-initiated research relating to long-term survivors of childhood cancer. The study is coordinated through the University of Minnesota, Department of Pediatrics and Comprehensive Cancer Center. Other core facilities include the Statistical Center, located at the Fred Hutchinson Cancer Research Center (Seattle), the Biopathology Center (Columbus Children's Hospital) and the Radiation Physics Center at MD Anderson Cancer Center (Houston).

More than 14,000 survivors and about 3,500 siblings of survivors actively participate in the CCSS. The siblings serve as the study’s comparison group. Participants provide information to study researchers about their health and health-related behaviors through comprehensive self-administered questionnaires distributed approximately every two years. They also are asked to give permission for the release of medical records of their diagnosis and treatment for their original illness.

Information on the characteristics of their cancer diagnosis was obtained from the treating institution for all eligible cases at the time of their inclusion in the cohort; for participants, detailed information regarding their cancer treatment, including chemotheraphy, radiation and surgery, was abstracted from medical records. In addition, the CCSS collects certain biologic specimens, including buccal cell DNA, peripheral blood samples for selected subgroups and tumor tissue from subsequent malignancies, which are used to study genetic factors of cancer treatment. Study updates and other health information are provided to participants in a newsletter published twice a year.


The methodology of the CCSS has been described in a paper published in Medical and Pediatric Oncology (Robison LL, et al. Med Pediatr Oncol. 2002;38:229-239). Additional information about the study (including a full listing of publications, copies of the newsletters and the study questionnaires) is available at www.cancer.mrn.edu/ccss.

Dr. Berkow chairs the AAP Section on Hematology/Oncology. Robison is associate director of the University of Minnesota Comprehensive Cancer Center.

Less invasive technology now standard for ASD closure

by John W. Moore, M.D., FAAP

Open-heart surgery using the technique of cardiopulmonary bypass has been the standard method for closure of atrial septal defect (ASD) since it was first performed in 1954. Although the first transcatheter device closure of an ASD was reported in 1976, development of less invasive technology capable of achieving results comparable to surgery took decades.

Finally, in December 2001, the U.S. Food and Drug Administration (FDA) unconditionally approved a device and technology for percutaneous closure of atrial septal defect. This device, the Amplatzer Septal Occluder (ASO), has rapidly become the standard method for ASD closure in the United States and abroad.

The American Heart Association estimates that about 40,000 people are born in the United States each year with heart defects. Up to 10% have ASD amenable to closure with the ASO. Early experience confirms that 4,000 to 5,000 Amplatzer closures of ASD are being performed in the United States annually. As a consequence, pediatric cardiac surgery programs have experienced a dramatic fall-off in referrals for ASD.

An FDA study of the ASO involved 442 patients and a surgical control group. Results showed that device closure of an ASD was just as effective as surgical closure and was safer, resulting in considerably fewer and less significant complications than did surgery. Additional data reported from international centers confirm these FDA study findings.

The benefits to patients and their families from this less invasive technology are considerable. Amplatzer closure may be performed with conscious sedation and rarely involves a blood transfusion. Surgery requires general anesthesia, cardiopulmonary bypass, and by design, exposes most patients to blood and/or blood products.

Amplatzer closure is performed through a relatively small femoral vein catheter. Surgery requires a thoracotomy and an open-heart operation. Amplatzer closure is a day procedure, and surgery requires a minimum of three to four days in the hospital. Amplatzer recovery time at home is one day, whereas surgical convalescence is up to several weeks. The reduced hospital and recovery times translate into substantial monetary savings for families and the health care system.

Unlike critical and complex heart defects discovered in the newborn nursery, ASDs most often are diagnosed by pediatricians in the office. Patients often are children or teenagers who present for routine examination and have abnormal heart murmurs. Their medical history may include recurrent respiratory problems, slow growth and/or mild exercise intolerance.

An electrocardiogram shows right axis deviation and incomplete right bundle branch block or mild right ventricular hypertrophy. A chest X-ray shows enlargement of the heart, particularly the right ventricle. Referral to a pediatric cardiologist confirms the diagnosis of atrial septal defect and most often will include a recommendation for closure using the Amplatzer Septal Occluder.

The ASO is manufactured by AGA Medical Corp. in Golden Valley, Minn. The occluder is a wire-mesh device with two disks and a central waist. It is made of Nitinol, a nickel and titanium alloy, with shape-memory characteristics. Shape-memory allows the device to be compressed into a small tube (sheath) for insertion with rapid reconstitution of its design shape once released from the sheath. The device has polyester membranes sewn into each disk and the central waist. Multiple sizes are available with waist sizes and the health care system.

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Angiogram before (left) and after Amplatzer Septal Occluder closure of an atrial septal defect in a patient.

Amplatzer Septal Occluder
produce no problem as long as the lead paint is intact will have to be re-examined; current HUD post-abatement lead standards, e.g., 40 μg/ft² for floor dust lead loading, may not be sufficiently protective to keep a child's lead level below 10 μg/dL. This finding should advance initiatives toward primary prevention through the screening and abatement of homes that contain lead hazards before children become exposed.

It is equally important to put these findings into the proper perspective. Child neurodevelopment can be harmed by a number of factors, including lead exposure, iron deficiency, and limited environmental stimulation, e.g., lack of educational toys, books, and peer contacts. Conversely, it is optimally child rearing that provides developmental stimulation, good nutrition and early peer contacts. Parents should keep these mitigating factors in mind as they continue to minimize their children's exposure to lead.

Pediatricians, who undoubtedly will face questions and requests for more frequent lead screening from parents, need to make plans on how best to incorporate these important new findings into their practice. Both the CDC and the AAP Committee on Environmental Health have begun to examine the issue of lead neurotoxicity at levels less than 10 μg/dL with a goal of providing guidance on screening, management, and prevention. Until such guidance becomes available, the most valuable actions pediatricians can provide are continued screening and regular discussions with parents on principles of prevention and methods of optimizing neurodevelopment.

Dr. Sharon chairs the AAP Committee on Environmental Health.

### ASD Continued from page 62

- **Mouth and Oral Structures—**Abnormalities are reported to affect speech function in some patients. Changes may include speech delay, altered speech, or delayed language development.
- **Neurological—**Abnormalities are reported in some patients. These may include ataxia, tremor, and/or dystonia.

### OVERDOSAGE:
The effects of overdosage greater than twice the recommended daily dosage in humans are unknown. Clinical experience with overdose is limited to patients with ADHD controlled with a lower dose of atomoxetine. Overdosage, as with fluoxetine, may produce the adverse effects noted above, but no special features of overdose have been identified. There is no specific antidote for overdose and symptomatic treatment is the usual approach. Mental status examinations should be performed, including observation and measurement of blood pressure and pulse rate, cardiac and respiratory rates, and temperature. Atropine, 0.4 to 1.0 mg intramuscularly, should be given with caution to unresponsive patients, since atomoxetine causes atropine-like activity. Atropine doses should not exceed 1.0 mg, since larger doses can cause convulsions or respiratory arrest. Activated charcoal has been used successfully to prevent the absorption of orally administered drug. Hemodialysis and peritoneal dialysis are not effective for removing atomoxetine.

### Black Box Warning

- **Risk of Suicide and自杀ide ideation.** The prescribing information contains a boxed warning indicating the risk of suicide and suicide ideation associated with atomoxetine and other selective serotonin reuptake inhibitors (SSRIs).

### Adverse Reactions

- **Gastrointestinal—**Diarrhea and constipation are the most frequently reported adverse events associated with atomoxetine use in children and adolescents. Diarrhea occurred in 10% of patients treated with atomoxetine, compared to 3% of placebo-treated patients. Constipation occurred in 7% of patients treated with atomoxetine, compared to 3% of placebo-treated patients. These events are usually mild to moderate in intensity, but may require discontinuation of therapy in some cases.

- **Cerebrovascular—**Events associated with acute cerebrovascular events have been reported in adults who have received atomoxetine. Some of these cases have been temporally related to discontinuation of atomoxetine. Cerebrovascular events may be life-threatening and, if recognized, should be managed by appropriate medical intervention.

- **Neurological—**Abnormalities are reported in some patients. These may include ataxia, tremor, and/or dystonia.

### Drug Interactions

- **CYP 2D6—**Atomoxetine is a potent inhibitor of CYP2D6. The CYP2D6 genotype is highly polymorphic and is associated with increased plasma concentrations of atomoxetine in certain patients. The CYP2D6 genotype is associated with the extent of bioconversion of atomoxetine to noratomoxetine. Patients with the CYP2D6*10 allele are considered to be poor metabolizers, while patients with the CYP2D6*10 allele are considered to be extensive metabolizers. Patients with the CYP2D6*10 allele are at increased risk of experiencing adverse events associated with atomoxetine use, including hypertension, agitation, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia). The CYP2D6*10 allele is associated with an increased risk of sleep disorders, including insomnia, nightmares, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia). The CYP2D6*10 allele is associated with an increased risk of sleep disorders, including insomnia, nightmares, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia).

- **Serotonin—**Serotonin is a neurotransmitter that is involved in the regulation of mood, appetite, and sleep. Inhibitors of serotonin reuptake, such as atomoxetine, can cause certain adverse effects, including agitation, insomnia, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia). The CYP2D6*10 allele is associated with an increased risk of sleep disorders, including insomnia, nightmares, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia).

- **GABA—**GABA is a neurotransmitter that is involved in the regulation of sleep and the control of motor activity. Inhibitors of GABA reuptake, such as atomoxetine, can cause certain adverse effects, including agitation, insomnia, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia). The CYP2D6*10 allele is associated with an increased risk of sleep disorders, including insomnia, nightmares, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia).

- **Noradrenaline—**Noradrenaline is a neurotransmitter that is involved in the regulation of mood and the control of motor activity. Inhibitors of noradrenaline reuptake, such as atomoxetine, can cause certain adverse effects, including agitation, insomnia, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia). The CYP2D6*10 allele is associated with an increased risk of sleep disorders, including insomnia, nightmares, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia).

- **Serotonin and Noradrenaline—**Serotonin and noradrenaline are neurotransmitters that are involved in the regulation of mood, appetite, and sleep. Inhibitors of serotonin reuptake, such as atomoxetine, can cause certain adverse effects, including agitation, insomnia, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia). The CYP2D6*10 allele is associated with an increased risk of sleep disorders, including insomnia, nightmares, and other adverse events (e.g., headache, nausea, vomiting, diarrhea, abdominal pain, and anorexia).
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