The Prevalence of Turner Syndrome in Girls Presenting with Coarctation of the Aorta

Sze Choong Wong, MBBS, MRCPCH[1,2], Trent Burgess, BSc (Hons)[3], Michael Cheung, MD[4,5,6], and Margaret Zacharin, FRACP[1,2,6]

Objective To determine the prevalence of Turner syndrome in girls presenting with coarctation of the aorta (CoA).
Study design A total of 132 girls with known structural CoA was identified. Those girls who had no previous karyotype analysis performed were asked to participate in a research study in which a banded karyotype with 50-cell count was performed.
Results Of 132 girls with CoA, 55 (41.7%) had karyotype analysis within 6 months of cardiac diagnosis. Three girls underwent karyotyping later because of clinical concerns. Of the 74 girls with CoA who had not had a karyotype, 38 (51.4%) consented to the study. Results were available for 37 girls. All were 46,XX. Five patients with Turner syndrome were identified in the 95 girls with CoA who had karyotype analysis (4 from early karyotype and 1 diagnosed later), which translated into a minimum prevalence of 5.3% of Turner syndrome in this group of girls with CoA. In addition, one infant with a 20-cell 46,XX karyotype had features of Turner syndrome.
Conclusion Our study demonstrated for the first time in a large cohort that 5.3% of girls presenting with CoA are found to have Turner syndrome when karyotyping is performed. Given the spectrum of preventable and treatable health problems after the diagnosis of Turner syndrome, we believe that all girls with CoA should have a karyotype analysis, ideally with at least 50-cell count, at the time of diagnosis of CoA. *(J Pediatr 2014;164:259-63)*.

Turner syndrome results from loss of or abnormality in the second X chromosome in a phenotypic female subject. Approximately 40% of girls with Turner syndrome have a 45,X karyotype, which is usually but not universally associated with characteristic and well-described dysmorphism, compared with those who have a mosaic karyotype, in whom dysmorphism may be minimal.[1,2] Girls with Turner syndrome often remain undiagnosed until other health problems occur that subsequently alert health professionals to the diagnosis.

Cardiac abnormalities are present in approximately 50% of girls with Turner syndrome.[3] Bicuspid aortic valve (BAV) is the most common cardiac malformation (appearing in approximately 30% of patients),[4] but coarctation of the aorta (CoA) also is frequently seen (in approximately 12%).[3-5] The incidence of aortic dissection in Turner syndrome is approximately 6 times greater than in the general population,[6] with the greatest risk in early adulthood and during pregnancy.[7] Risk factors for aortic dissection include BAV and underlying congenital heart disease, particularly CoA and hypertension.[7] CoA may present in a patient during early infancy as cardiovascular collapse and require emergency surgery, but it may present during childhood as the result of the discovery of hypertension or limb claudication.

Approximately 30% of girls with Turner syndrome are diagnosed in childhood and 19%-22% are diagnosed in adolescence.[8,9] Significant short stature is usually present in those children diagnosed in childhood (mean height SDS −2.0),[9] although milder degrees of height deficit can occur in girls with tall parents. Besides short stature and growth failure, which are not life-threatening, a spectrum of health, physical, educational, psychosocial, and emotional problems can occur in girls with Turner syndrome. As a result of late diagnosis, these problems may not be addressed adequately.

Expert consensus guidelines published within the last 10 years have recommended that karyotype analysis should be performed in all girls with short stature, delayed puberty, webbed neck, lymphedema, and CoA.[8-10] However, karyotype screening of all girls who have CoA for possible Turner syndrome has not been reported. Although the prevalence of CoA in girls with Turner syndrome is known, the prevalence of Turner syndrome in girls whose initial presentation is with CoA is unclear. Early diagnosis of Turner syndrome would confer benefit in terms of ability to intervene to improve outcomes of the complex problems associated with that condition.

Methods

Using a combination of 2 electronic databases housed in our department of cardiology (for cardiac admission, cardiology outpatient, and cardiac imaging

BAV	Bicuspid aortic valve
CoA	Coarctation of the aorta

From the [1]Department of Endocrinology, The Royal Children's Hospital; [2]Center for Hormone Research, Murdoch Childrens Research Institute; [3]Victorian Clinical Genetics Services Pathology, [4]Department of Cardiology, The Royal Children's Hospital; [5]Heart Research Group, Murdoch Children's Research Institute; and [6]Department of Pediatrics, University of Melbourne, Melbourne, Australia

The Murdoch Childrens Research Institute is supported by the Victorian Government's Operational Infrastructure Support Program. The Heart Research Group is supported by The Royal Children's Hospital Foundation (RCH 1000). The authors declare no conflicts of interest.

Portions of this study were presented as a poster at the European Society of Paediatric Endocrinology meeting (Glasgow, United Kingdom, September 25-28, 2011) and the Joint Australasian Paediatric Endocrine Group/Endocrine Society of Australia meeting (Perth, Australia, August 28-31, 2011).

 http://dx.doi.org/10.1016/j.jpeds.2013.09.031

activity), we identified girls with a diagnosis code that included CoA. Patients were identified from a search performed in September 2010. Patients included in the databases from 1990 to 2010 were part of the initial audit. However, age of diagnosis of CoA was before 1990 in some cases because these patients were either attending cardiology clinic or had cardiac investigations between 1990 and 2010 but CoA had been diagnosed earlier than 1990. Karyotype results were identified through the records of the Victorian Clinical Genetics Laboratory and also through The Royal Children's Hospital electronic investigation reporting database.

After the clinical audit, girls with CoA who had not had a karyotype analysis performed were invited to participate in a research study involving a single blood test for karyotyping. The clinical audit and research studies were approved by the Human Research Ethics Committee of The Royal Children's Hospital.

Contact was made by letter of invitation to participate, follow-up telephone call, with a further search for up to date contact details from the registered general practitioner on the hospital system and the online telephone directory. Written informed consent was acquired from all participating patients ≥18 years and from the parents of those subjects <18 years of age.

Karyotyping was analyzed centrally at the Victorian Clinical Genetics Laboratory by the use of a banded technique in which 50 cells are examined, which permits the exclusion of low-level mosaicism at a level of 6% with 95% confidence limits.[11,12]

Results

A total of 140 girls were identified with a diagnosis code that included CoA (**Figure**). Eight patients were excluded: 2 patients with coarctation due to Takayasu arteritis, 3 with complex congenital heart disease (coarctation suspected on initial imaging but subsequently ruled out), and 3 girls in whom CoA was diagnosed after the diagnosis of Turner syndrome, including one who was diagnosed from karyotyping at amniocentesis and confirmed postnatally. A total of 132 girls were identified in the clinical audit. Median age of the patients at the time of the audit was 8 years (range, 1-35). Thirty of the 132 (22.7%) were >18 years.

Fifty of the 132 girls (37.9%) had CoA in association with other congenital cardiac abnormalities. These included BAV (n = 27); BAV and ventricular septal defect (n = 6); isolated ventricular septal defect (n = 5), aortic stenosis (n = 2); aortic stenosis and other abnormalities of valvular structure (n = 10).

Fifty-five of the 132 girls (41.7%) had a postnatal karyotype performed clinically within 6 months of diagnosis of CoA, or "early" karyotype analysis. A request for a karyotype analysis close to the time of diagnosis of CoA was seen to be included by the attending physicians in more recent years. None of the 8 patients with CoA were diagnosed between 1975 and 1984, but 16 of 50 (32%) diagnosed from 1985 to 1999 and 39/74 (53%) diagnosed after 2000 had karyotype analysis.

Of those 55 patients who had karyotyping performed at the time of diagnosis of CoA, 4 (7.3%) had the Turner syndrome karyotype: 45,X/46,XX (n = 1), 45,X/46,XY (n = 2) and 45,X/46,XY/47,XYY (n = 1). Of the 4 girls with Turner syndrome and coarctation who had early karyotype analysis performed, 3 (75%) had Y chromosome material and underwent gonadectomy in infancy or early childhood. One of these 3 girls (**Table**; patient 2) presented at birth with clitoromegaly with normal external female genitalia and Müllerian structures. The gonads were found to contain dysgenetic testicular tissue. She had short stature, which was responsive to growth hormone therapy, and also had dysplastic nails. Three of the 4 patients who had "early" karyotyping had documented evidence of relatively low birth weight and/or lymphedema and neck abnormalities.

Of the other 51 girls with an identified CoA with early karyotype analysis and who did not have a Turner syndrome karyotype, one girl presented with cardiovascular collapse at birth. Her cardiac defect was CoA in association with BAV, multiple valvular, and septal defects. She died on day 24 from cardiac-related complications. This patient was born at 39 weeks' gestation with a birth weight of 2.7 kg. Mild dysmorphic features were noted: webbed neck, low hair line, and cubitus valgus. The karyotype was 46,XX in this infant, but only 20 cells were examined. This patient also was born before 1990. In addition to her severe cardiac condition, the presenting phenotype may have not been considered to warrant analysis with investigation of greater number of cell count or investigation of karyotype from a different tissue (eg, skin biopsy) to exclude low level mosacism, although Turner syndrome is a likely diagnosis. Six other patients of the 51 patients had an associated diagnosis: 22q11.2 microdeletion (n = 2), trisomy 21 (n = 1), Kabuki syndrome (n = 1), Goldenhar syndrome (n = 1), and Wolf-Hirshorm syndrome (n = 1).

Three of the 77 girls (3.9%) who did not have an "early" karyotyping performed at time of diagnosis of CoA had a "late" karyotyping performed because of clinical concerns. Two girls had normal female karyotype of 46,XX. One girl had Turner syndrome diagnosed (45,X/46,XX) at the age of 2.5 years (**Table**; patient 5). A karyotype and antigliadin and antiendomysial antibodies were requested resulting from concerns about the patient's ongoing diarrhea. Her height was on the 25th percentile (midparental height 50th percentile). At diagnosis of Turner syndrome, she has had 2 perforated tympanic membranes. There were no obvious clinical signs of Turner syndrome other than bilateral mildly upturned fourth fingernails.

Seventy four girls were eligible for the research study for late karyotype analysis. Twenty-four of the 74 (32.4%) eligible patients could not be traced, including 2 who had died in the neonatal period. Eleven of these 24 (45.8%) were adults (>18 years). Nine of the 24 (37.5%) had an address outside the state of Victoria and therefore were not undergoing regular follow-up in our hospital. One patient had an overseas address.

Twelve of the 74 (16.2%) eligible patients declined to take part in the study. The reasons documented were normal