

The Wisconsin Pediatric Cardiac Registry: A Mechanism for Exploring Etiologies of Congenital Heart Defects

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ABSTRACT

On January 1, 2000, the Wisconsin Pediatric Cardiac Registry began registering families of infants born with a congenital heart defect (CHD) in Wisconsin. Pediatric cardiologists across the state developed the Registry as a database and as a research study exploring potential etiologies of CHDs. Participating pediatric cardiologists identify the infants and refer families to the Registry. Families are asked to participate by completing a comprehensive questionnaire that inquires into exposures and illnesses experienced during the 6 months prior to the pregnancy and during the pregnancy itself. A subset of families, based on the infant's diagnosis (hypoplastic left heart syndrome, conotruncal abnormalities, and Ebstein's anomaly) participates in DNA testing. This article describes the development of the Registry, family referral and participation to date, genetic advances in the etiology of CHDs, and research initiatives utilizing the data provided by families for the WPCR.

INTRODUCTION

Congenital heart defects (CHD), while rare, constitute the most common birth defect encountered in Wisconsin. The prevalence of CHD in the literature ranges from 0.3% to 0.8%.¹ With Wisconsin's population now exceeding 5 million and a birth rate of 12/1000, an estimated 400-600 new cases of congenital heart defects are diagnosed annually, for an estimated prevalence of 0.5%-0.8%. In developed societies, CHDs are the leading cause of infant mortality and continue to contribute to childhood mortality and morbidity well into adult life.²

The exact cause of most cases of CHD is unknown. Approximately 5%-10% are associated with a chromosome abnormality, 3%-5% can be linked to defects in

single genes (Table 1), and about 2% are attributed to known environmental factors.¹ For the remaining 85%-90% of cases, gene-environment interaction theory—first described and investigated by Nora³—continues to be the subject of considerable interest and research. Past studies have attributed the development of certain heart defects to maternal diabetes, obesity, use of cocaine and marijuana, fever early in pregnancy, smoking, pesticides, exposure to paints, and maternal exposure to lithium and antiepileptic medications.^{1,4,5}

In recent years, studies of chick, zebrafish, and mouse embryos have significantly increased our knowledge of heart development by identifying pathways that control early cardiogenesis and by defining the stages of heart development.⁶ Since the heart is completely developed by the end of the first trimester of human pregnancy, the critical periods for teratogenic influences is now well defined⁷ and allows for correlation of reported environmental exposures with the development of certain defects.

THE WISCONSIN PEDIATRIC CARDIAC REGISTRY (WPCR)

The concept of a registry of children born in Wisconsin with a CHD began in the late 1990s when pediatric cardiologists noted a potentially higher than expected number of infants born with hypoplastic left heart syndrome (HLHS) in various parts of the state. The Baltimore Washington Infant Study (BWIS) (1981-1989),² the first regional population-based study to explore potential environmental etiologies of congenital heart defects, had demonstrated the utility of registries in defining epidemiological characteristics and trends, population differences, regional variations in incidence, patterns of specific disease, and etiologic hypotheses.

The Wisconsin Pediatric Cardiac Registry (WPCR), framed after the BWIS, was developed as an official record of infants born in Wisconsin with a CHD and a database of demographic and parental exposure and illness information. The primary aim of both the BWIS and the WPCR

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Table 1. Overview of CHD's Associated with Select Syndromes and Genetic Advances in Etiology

Gene	Locus	Syndrome	CHD
ZIC3	Xq26.2	Heterotaxy: ⁸	Situs abnormalities ⁸
TFAP-2b		Char syndrome ⁹	PDA
TBX5	12q24.1	Holt Oram ¹⁰	ASD-primarily VSD Atrioventricular septal defect
Multiple	22q11 deletion ¹¹	DiGeorge Velocraniofacial Conotruncal facial	Tetralogy of Fallot truncus arteriosus interrupted arch type B ASD, VSD, isolated vascular ring-less common right-sided cardiac defects
JAG1	10q12	Alagille ¹²	AVSD VSD ASD
DSCAM	21q22.2-21q22.3	Down ¹³	AVSD VSD ASD
		Noonan ¹⁴	AVSD, pulmonary stenosis, coarctation of aorta, ASD, Tetralogy of Fallot
		Williams	Supravalvular aortic stenosis, pulmonary stenosis, septal defects
		Charge	PDA, ASD, VSD, Tetralogy of Fallot ASD, VSD, Tetralogy of Fallot, Ebstein's
NKTX2.5 tinman	5q34		

ASD=atrial septal defect; VSD=ventricular septal defect; PDA=patent ductus arteriosus; AVSD=atrioventricular septal defect.

Heterotaxy syndrome: autosomal recessive disorder with right sided heart and reversed position of abdominal disorders¹⁴

DiGeorge syndrome: characterized by defects of thymus, parathyroid glands, and heart¹⁴

Holt-Oram syndrome: autosomal dominant disease with upper extremity and congenital heart abnormalities¹⁵

Alagille syndrome: autosomal dominant disorder with facial dysmorphism, vertebral defects, and congenital heart defects¹⁵

Velocraniofacial syndrome: autosomal dominant disorder with specific facial characteristics, some mental retardation, cardiac defects, and cleft palate¹⁵

Noonan syndrome: genetically heterogeneous disorder with short stature, mental retardation (not all), specific facial features, and heart defects¹⁵

Williams syndrome: autosomal dominant disease with disorder of Vitamin D metabolism, teeth abnormalities, growth deficiencies, heart problems, and mental retardation¹⁵

Charge syndrome: associate with coloboma, heart disease, atresia of choanae, mental retardation, genital hypoplasia, ear abnormalities, deafness¹⁵

is to allow for the study of characteristics and exposures that may contribute to the development of CHDs. The WPCR began January 1, 2000, and continues to operate.

METHODS

Inclusion Criteria

Any infant with a structural congenital heart defect who is conceived in Wisconsin and born January 1, 2000 onward is eligible for inclusion in the WPCR. Diagnosis is made by clinical exam performed by a pediatric cardiologist, or by echocardiography, cardiac catheterization, surgical inspection, and occasionally, through autopsy.

Exclusion Criteria

Diagnostic exclusions include infants with an isolated patent foramen ovale or patent ductus arteriosus, electrical conduction disturbances of the heart without an associated structural abnormality, and acquired heart diseases, such as Kawasaki's, rheumatic fever, or endocarditis.

Referral Process

An explanation of the WPCR along with a printed brochure is provided to each family with an infant newly di-

agnosed with a CHD. If a family agrees to participate, the infant's and parents' names, current address, infant's date of birth, gender, race, cardiac and non-cardiac diagnoses are sent to the WPCR office for input into the central database. All information is encrypted and strict confidentiality is maintained. If a family declines to participate, they are removed from further contact.

Families participate by completing a self-administered 35-page questionnaire that inquires into maternal and paternal illnesses, drug and toxic exposures prior to and during this pregnancy, as well as family history of congenital and acquired diseases (Table 2). It can be completed in either print form or directly on-line, with a unique, computer-generated ID code that allows the family to access their questionnaire for 30 days. Those completing the print form are provided with a stamped, addressed return envelope and asked to complete and return the questionnaire within 30 days. The questionnaire takes approximately 45-60 minutes. Follow-up reminders are made by phone or, when possible, in person.

A subset of families—based on the infant's diagnosis of HLHS, Ebstein's anomaly, or conotruncal abnormalities—

are asked to participate in DNA sampling. DNA testing includes the infant and first-degree relatives and is accomplished through a blood sample, the preferred method, or buccal samples using a swab or mouth wash. Each family member who agrees to participate in DNA testing signs a separate consent form.

PRELIMINARY RESULTS

Since January 1, 2000, over 2600 families have been referred to the WPCR. Of these, 1950 have agreed to participate, providing 1200 questionnaires and 950 DNA samples. Less than 5% of families have declined for a variety of reasons: disinterest, confidentiality concerns, or lack of time. Two other groups of non-participants are those who do not respond to the introductory letter (6%) and those who agree to participate but do not return the questionnaire despite follow-up efforts (12%).

We estimate that approximately 75% of infants born with a CHD in Wisconsin are referred to the WPCR. Centers across the state that actively refer families include Children's Hospital of Wisconsin (CHW) in Milwaukee, Marshfield Clinic, Prevea Medical Clinic in Green Bay, Dean Medical Center in Madison, and Gundersen Clinic in LaCrosse. CHW houses the premier cardiovascular surgical department and interventional catheterization lab in the state, assuring ascertainment of infants with complex congenital heart defects. Table 3 provides a breakdown of referrals by diagnosis, compared to percentages reported in the literature.

Research

A number of pilot studies utilizing the data from the WPCR have been completed. Table 4 outlines preliminary results of these studies. DNA samples are suitable for cluster analysis and for specific gene localization studies.

Several ongoing studies are investigating the incidence of CHD in eastern Wisconsin, while another is utilizing subject DNA samples to examine a gene that may be implicated in certain defects. CHW Foundation provides the primary funding for the WPCR, with money for specific research projects obtained through various grant sources. DNA testing is funded by the General Clinical Research Center Grant M01-RR00058 from the National Institutes of Health.

CONCLUSIONS

Research into etiologies of congenital heart defects remains in its infancy. Few large-scale population studies have examined associations between exposures reported by parents and the development of specific congenital heart defects. Laboratory research and analysis of specific genes and gene pathways, along with data from the WPCR, pro-

Table 2. Data Categories and Variables Investigated for the WPCR

Infant Factors

Gender, race, birth number, date of birth, and expected DOB
Specific CHD diagnosis and when diagnosed, associated syndromes, and other diagnoses
If infant has died, cause of death

Birth Control

Problems with and treatment for menstrual periods, birth control, fertility treatment, including in vitro fertilization, ultrasound, amniocentesis, chorionic villus sampling

Socioeconomic Factors

Mother/father race, date of birth, place of birth, income, schooling, occupation, marital status, type of house, heat, and water source, use of fireplace, pets in home

Maternal Illness

Diabetes, asthma, thyroid disease, epilepsy, lupus, eating disorders, cancer, hypertension, obesity, bladder/kidney infections, emotional problems, vaginal infections, arthritis, headaches, upper and lower respiratory infections, fever greater than 101, exposure to AIDS/HIV, hepatitis, chicken pox, measles, mumps, nausea/vomiting, bleeding/spotting

Other Maternal Factors

Use of multivitamins, vegetarian, use of protein supplements, health food/supplements, use of any OTC/prescribed medications, height/weight and amount of weight gained during pregnancy, conception/birth addresses, and months pregnant when mom moved

Paternal Illness

Diabetes, eating disorder, cancer, asthma, allergies, epilepsy, thyroid disease, lupus

Maternal/Paternal Exposures

X-ray, nuclear scans, anesthesia, cigarettes (smoke and exposure), alcohol use, cocaine, hashish, marijuana, heroin, barbiturates, caffeine, active duty, carpentry, paint, varnish, turpentine, welding, dry cleaning solvents, mercury, paper/pulp products, nickel, jewelry making, art oils and acrylics, hair dyes/perms, plastics, extreme heat/cold, ionizing radiation, anesthetic gases, fertilizers, pool cleaning chemicals, exposure to radiation, pesticides

Family History

CHD, acquired heart disease, other birth defects. Includes mother, father, full and half siblings, grandparents, aunts, uncles, and first cousins.

vide an exciting future for the study of potential etiologies and prevention strategies of CHD.

One goal of the Registry is to increase ascertainment of infants across the state. Alternatively, we welcome referrals from primary care physicians, with a copy of the echocardiograph report. The WPCR can be reached by phone (414.266.2325 or 877.809.9727) or e-mail: wpcr@mcw.edu.

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Table 3. Primary Diagnosis of Select Cases of CHD in WPCR, Compared to Literature^{16,17}

CHD Diagnosis	% in WPCR	% Cited in Literature
Coarctation of aorta	4.3	5-10
Secundum ASD	11	5-10
Bicuspid AV valve*	3.8	0.4-2.25
AV stenosis	1	2-6
Atrioventricular Septal Defects	6.2	2
With Down syndrome	3.6	
Without Down syndrome	2.6	
Hypoplastic left heart syndrome	3	1
Total anomalous pulmonary veins	1	1-3
Pulmonary valve stenosis*	11	5-12
Double outlet right ventricle	1	<1-1
Ebstein's anomaly	0.7	<1
D-transposition of great arteries	3.5	5
Tetralogy of Fallot	3.5	9-10
VSD's	39	15-28
Muscular*	25	30
Membranous	14	70
Shone's syndrome	0.6	
Pulmonary atresia with VSD	1.3	
Pulmonary atresia without VSD	1	<1

* Most likely unreported

Table 4. Preliminary Results from WPCR Research Studies

Comparison of descriptive characteristics and reported exposures in atrioventricular septal defects in infants with and without Down syndrome (DS), variables of significance:

DS, N=67	Non-DS, N=43
Maternal and paternal age >35	
Maternal:	Paternal:
Nausea/vomiting during pregnancy	Smoking
Medications used to treat nausea/vomiting (no one medication was significant overall)	Use of art oils and acrylics
Paternal exposure to:	
Lead	
Ionizing radiation	
Chemicals to kill weeds	
60% females	56% male
44% diagnosed prenatally	64% diagnosed prenatally
3% twinning	16% twinning

Analysis of seasonal distribution and gender variations in WPCR population, grouped into 5 diagnostic categories:

Total population:

- Total number of cases were increased in 2004 for quarters 1 and 3, but no significant variations noted across the 5 years
- 52.3% female, 47.7% male
- Septal defects were more common in females; more males had left ventricular outflow tract obstructions (LVOTO)

Comparison of incidence of CHD in upper and lower Fox River areas with Milwaukee County, using ARC-GIS software (Redlands, Calif):

80.3% of incidence cases in WPCR database mapped successfully. Incidence of CHD in tri-county area along Fox River: Brown County 0.665%, Outagamie County 0.384%, Winnebago County 0.394%. Milwaukee County had the highest incidence with 0.905%. This may reflect referral patterns as the WPCR is housed at the Medical College of Wisconsin and Children's Hospital of Wisconsin, both located in Milwaukee County.

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