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Prevalence and Outcome of Congenital Heart Disease in Patients With Neural Tube Defect

Gülendam Koçak, MD, Çağatay Önal, MD, Ayhan Koçak, MD, Cemşit Karakurt, MD, Özkan Ateş, MD, Süleyman R. Çaylı, MD, and Saim Yoloğlu, PhD

A prospective clinical study was designed to establish the risk factors, the prevalence, and the progress of congenital heart defects in children with neural tube defects. Study included 90 children with a mean age of 13.5 ± 30.4 months. There were 53 (59%) patients with spina bifida occulta and 37 (41%) patients with spina bifida aperta. The overall prevalence of congenital heart disease was 27.8% (40.5% in spina bifida aperta and 18.9% in spina bifida occulta; $P = .024$). There was no statistically significant difference for maternal age, usage of periconceptional folate, and maternal diabetes between the patient and control groups. The authors conclude that congenital heart defects are more common than reported in neural tube defects, and screening echocardiograms are warranted. This should be kept in mind especially in patients requiring minor or major surgical procedures. Furthermore, routine obstetric examination and therefore the use of periconceptional folic acid during pregnancy is still lacking in our country.

Keywords: neural tube defect; congenital heart defect

Neural tube defects are the second most common birth defects, after congenital heart disease.[1] Although genetic and environmental factors are involved in the pathogenesis, the majority of defects are categorized as multifactorial inheritance.[2-6] Associated malformations are common, and congenital heart defects have been reported in patients with neural tube defects.[7] The association of neural tube defects with congenital heart defects varies considerably according to the study method and selected population, being much higher in autopsy series, in which the most severe forms are represented.[8] Although knowledge of a coexistent congenital heart defect in neural tube defects is crucial, there is only 1 retrospective study addressing this topic in patients with meningomyelocele.[7] We designed a prospective study to describe the prevalence and types of congenital heart defects associated with neural tube defects, the maternal risk factors, and follow-up of the patients with cardiac anomaly. To the best of our knowledge, this is the first prospective study in which echocardiography was systematically performed in a large number of patients with neural tube defects.

Material and Methods

This study was carried out between September 2000 and May 2007. The neural tube defect families were recruited through the Neurosurgery Clinic of the Inonu University, Turgut Ozal Medical Centre. All children with neural tube defect were included in the study, and the only exclusion criterion was suspicion of known chromosomal abnormalities. After physical examination, type of defect, age, sex, and associated abnormalities were recorded.

A specialist in neurosurgery coded the kind of neural tube defect as spina bifida occulta and spina bifida aperta.[9] All patients were examined by a pediatric cardiologist, and all had standard echocardiographic evaluation with 2-dimensional and color Doppler echocardiography using 3.5- and 5-MHz transducers (Toshiba SSA Powervision 6000, Toshiba Medical Systems Corporation, Tokyo, Japan). Patent foramen ovale was not considered as congenital heart disease, and patent ductus arteriosus was not considered abnormal in the newborn period. According to the main structural cardiac anomaly, heart defects were classified into major categories. Definitions were based on the International

From the Department of Pediatric Cardiology (GK, CK), Department of Neurosurgery (CO, AK, OA, SRC), and Department of Biostatistics (SY), Inonu University, Turgut Ozal Medical Center, Malatya, Turkey.

Address correspondence to: Gülendam Koçak, MD, Inonu University Faculty of Medicine, Turgut Ozal Medical Center, Department of Pediatric Cardiology, Malatya 44069, Turkey; e-mail: gul_endam@yahoo.com.

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Classification for Disease codes. Periodic follow-up was done in patients who had heart defect.

The control group consisted of normal children admitted to the social pediatrics clinic of the University Hospital. All mothers of patients and control children completed an interview with questions on maternal health, use of medications, and history about their index pregnancy. The use of periconceptional folate supplements was considered adequate if started before conception until 8 weeks thereafter. Women who started to use folate supplements after this period were categorized as nonusers.

The study complies with the Declaration of Helsinki, the study protocol was reviewed and approved by the local medical ethics committee, and written consent was obtained from parents prior to commencement.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 11.0 program (SPSS Inc, Chicago, Illinois). Normality for continuous variables in groups was determined by the Shapiro Wilk test. Continuous variables showed normal distribution ($P > .05$). So, continuous variables were tested using the unpaired *t* test. Continuous variables expressed as mean ± standard deviation. Categorical variables were tested using either Pearson chi-square or Fisher exact chi-square test, where appropriate. Values of $P < .05$ were considered to be statistically significant.

Results

There were 96 patients with neural tube defect, and 6 of them were suspected clinically as having a chromosomal anomaly and were excluded. Genetic and chromosomal studies could not be performed, but the phenotype suggested the chromosomal conditions that are commonly associated with the neural tube defect.

The study was performed on 90 neural tube defect–affected children. Mean age was 13.5 ± 30.4 months (range = 1 day to 10 years). Of these patients, 77 were younger than 1 year of age and, among these, 56 were in the newborn period. There were 45 female children (50%) and 45 male children (50%). Except congenital heart defect, none had major associated anomalies or facial dysmorphism.

The control group consisted of 151 apparently normal children (74 male and 77 female children) with a mean age of 12.7 ± 26.2 months (range = 3 days and 7 years). The male-female ratio was not different between the patient and control groups ($P > .05$).

Neural Tube Defect

The frequency of each type of defect is presented in Table 1. There were 53 (59%) patients in the spina bifida occulta group and 37 (41%) patients in the spina bifida aperta group. Meningomyelocele and meningocele were the 2 most frequent defects (each being 40%). Of the 37 patients with spina bifida aperta, 1 patient had a severe myeloschisis in the thoracolumbosacral region with complete flask paraplegia and had no improvement after surgical repair. The remaining 36 patients had meningomyeloceles with varying degrees of motor weakness. Of these, 16 patients had a total loss of motor movement (44%). None revealed a significant improvement after surgery. Twenty patients with mild to moderate weakness had at least preserved their preoperative status, and some patients showed improvement after the rehabilitation programs (56%). All the open neural tube defects were localized mainly on the lumbosacral region. Larger defects expanded to the lower thoracal area. No intraoperative or anesthesiological complications were encountered due to the congenital heart disease during surgery.

Table 1. Frequency of Different Types of Neural Tube Defects

Type of Neural Tube Defect	n	%
Spina bifida occulta	53	59
Meningocele	36	40
Tethered cord	8	9
Encephalocele	9	10
Spina bifida aperta	37	41
Meningomyelocele	36	40
Myeloschisis	1	1

Spina bifida occulta was more frequent in male children, whereas spina bifida aperta was more frequent in female children. A total of 39% of patients in the spina bifida occulta group and 65% of patients in the spina bifida aperta group were female ($P = .018$).

Congenital Heart Defect

Congenital heart defect was detected in 25 out of 90 patients (27.8%; Table 2). Of these, 10 were in the spina bifida occulta group and 15 in the spina bifida aperta group. The prevalence of congenital heart defect was more frequent in the spina bifida aperta group than the spina bifida occulta group (40.5% vs 18.9%, respectively; $P = .024$). Cardiac examination was abnormal in 10 of the 25 patients with heart defects (sensitivity = 40%). Of the patients with heart defects, girls were more frequently affected, but it was not statistically significant (16 of 25 vs 9 of 25; $P = .099$). Follow-up examinations were completed in 17 of 25 patients with congenital heart disease. An ostium secundum type atrial septal defect was present in 17 patients. Size of the defect was small in 11, moderate in 4, and large in 2 patients. It was isolated in 15 patients and combined with other defects in 2 patients, 1 patient with ventricular septal defect, and the other patient with double-outlet right ventricle. Follow-up examination revealed that 8 of the isolated defects closed

Table 2. Data of 25 Patients With Congenital Heart Defect

Patient No.	Sex	Age[a] (mo)	NTD	CHD
10	M	12	Meningomyelocele	TGA, VSD, PS
12	F	6	Meningomyelocele	PS
16	M	8	Meningocele	ASD
19	F	1	Meningomyelocele	ASD
22	F	120	Encephalocele	ASD
23	M	1	Meningocele	ASD
32	F	72	Tethered cord	MVP
39	F	4	Meningomyelocele	PDA
42	F	8	Meningomyelocele	ASD
45	F	84	Myeloschisis	PDA
50	M	1	Meningocele	ASD
52	F	1	Meningocele	ASD
56	F	1	Meningomyelocele	ASD
63	F	7	Meningomyelocele	BAV, AS
64	F	1	Meningomyelocele	ASD, VSD
66	M	5	Meningocele	PDA
69	F	1	Meningomyelocele	ASD
70	F	1	Meningomyelocele	ASD
71	M	1	Meningocele	ASD
77	F	1	Meningomyelocele	ASD
78	F	1	Meningomyelocele	ASD
79	M	1	Meningocele	ASD
81	F	1	Meningomyelocele	VSD
82	M	1	Meningomyelocele	DORV, ASD, VSD
87	M	1	Meningocele	ASD

NOTE: M = male; F = female; NTD = neural tube defect; CHD = congenital heart defect; TGA = transposition of great arteries; VSD = ventricular septal defect; PS = pulmonary stenosis; ASD = atrial septal defect; MVP = mitral valve prolapse; PDA = patent ductus arteriosus; BAV = bicuspid aortic valve; AS = aortic stenosis; DORV = double-outlet right ventricle.
a. 1 means the newborn period.

spontaneously before the age of 1 year. Three patients with atrial septal defect are on follow-up, and 1 patient with a large atrial septal defect underwent surgery at the age of 10 years. Follow-up could not be completed in the remaining 3 patients. Patent ductus arteriosus was present in 3 patients; in 1 patient, it closed spontaneously before the age of 1 year, 1 patient with a small patent ductus arteriosus is still on follow-up, and the follow-up for the last patient could not be completed. One patient with a small muscular ventricular septal defect is still on follow-up. One patient had a perimembranous ventricular septal defect combined with an atrial-septal defect; these defects were small and closed spontaneously before the age of 1 year. There was 1 patient with bicuspid aortic valve with mild valvular stenosis, 1 patient with mild pulmonary valvular stenosis, and 1 patient with mitral valve prolapse. Two patients had cyanotic congenital heart diseases; 1 had transposition of great arteries with ventricular septal defect and pulmonary stenosis; another patient had double-outlet right ventricle with atrial and ventricular septal defects. These 2 patients with conotruncal defects were operated on in infancy. One infant with meningocele had dilated cardiomyopathy on echocardiographic examination. Two patients with chronic renal failure had left ventricular hypertrophy and pericardial effusion on echocardiographic examination.

Maternal age of infants with neural tube defect and the control group did not differ, 27.32 ± 5.79 (range = 17-44) and 27.94 ± 5.92 (range = 17-42) years, respectively ($P = .312$). Adequate use of folate was observed in 2 of 90 (2.2%) mothers in the patient group and 7 of 151 (4.6%) mothers in the control group. There was no statistically significant difference in using periconceptional folate between the patient and control groups ($P = .49$). The consumption rate of folate was 2.7% in the spina bifida aperta group, which was not different from the control group ($P > .05$). No mother in either group used antiepileptic drugs during pregnancy. History of maternal diabetes was present in 2 of 90 mothers in the patient group and 3 of 151 mothers in the control group (2.2% and 1.9%, respectively; $P = .617$). Most of the mothers in the patient group did not get routine obstetric examination during their pregnancy (78%). None of the patients with congenital heart defect had prenatal diagnosis of their cardiac anomaly.

Discussion

Cardiac anomalies are the most common type of congenital anomalies with a birth incidence of 1/100. They are seen as isolated defects or associated with other congenital anomalies.[10-14] Prevalence of congenital heart defect was found to be 9.5% in oral clefts,[10] 23% in gastrointestinal malformations,[11] 8% in urinary system malformations,[12] 11% to 15% in diaphragmatic hernia,[13] and 2.7% in undescended testes.[14] Neural tube defects with a birth incidence of approximately 1/1000 are also associated with a number of other central nervous system and nonneural malformations.[15] It is traditionally believed that approximately 5% of children with neural tube defects have an associated congenital heart defect. However, in a retrospective study, it was shown that 37% of 105 newborns with meningomyelocele had congenital heart defects on echocardiographic examination, and secundum atrial septal defects with ventricular septal defect were the most common defects.[7] Only 1 patient had tetralogy of Fallot, which can be classified as a conotruncal heart defect. This was a retrospective study including newborn patients; therefore, it is not apparent whether the defects disappeared spontaneously or not. It is obvious that there can be a wide variability among clinical studies dealing with prevalence studies of congenital heart diseases, depending on the age of the patient population, because some congenital heart defects may undergo spontaneous closure and disappear later on. In a recent prospective study, 78.6% of 1072 neonates had atrial septal openings with a mean diameter of 3.35 ± 1.12 mm.[16] A total of 96% of these defects closed in approximately 3.6 months. In the present study, the prevalence of congenital heart

defects in patients with neural tube defect was found to be 27.8%. In follow-up, in 69% of patients who could be followed up, atrial septal defects and in 50% of patients, ventricular septal defects and patent ductus arteriosus, closed spontaneously before the age of 12 months. However, even excluding defects that closed before 12 months, the prevalence of congenital heart defects among patients with neural tube defect is still higher than that in the general population (17.7% vs ~1%).[17] Similar to Ritter's report,[7] secundum atrial septal defect was the most common cardiac anomaly observed in our study. Conotruncal abnormalities, which are known to be specific in neural tube defects, were present in 2 patients. Our study revealed that congenital heart defects were more prevalent in the spina bifida aperta group than in the spina bifida occulta group. The explanation for this may be the fact that the spina bifida aperta is a more extensive pathology, which may be a simultaneous manifestation of ongoing multisystem malformations.

It is generally accepted that the heart develops mainly from neural crest cells, arising from the dorsal part of the neural tube, and mesoderm. Neural crest cells contribute to the aorticopulmonary septum and smooth muscle cells in the great vessels. However, it has been recently reported that there is an additional cell population originating from the ventral part of the neural tube, migrating into the developing heart, and differentiating into cardiac myocytes.[18] These cells are called the ventrally emigrating neural tube (VENT) cells. In an experimental study, VENT cells were detected in the wall of both ventricles and atria, interventricular, and interatrial septum.[18] They were also found in the aorticopulmonary septum, aorta, pulmonary arteries, and brachiocephalic arteries. In the same study, extirpation of VENT cells resulted in ventricular and atrial septal defects, persistent truncus arteriosus, and vessel stenosis. As a result, conotruncal heart components originated from at least 2 different parts of the neural tube, and conotruncal anomalies may result from failure of contribution by any of these sources, neural crest cells or VENT cells. The developmental origin of septation defects, as atrial and ventricular septal defects, may be a result of disruption of early embryonic events relating to VENT cells.

The presence of cardiac neural crest cells is necessary for normal differentiation and function of the myocardium during early heart development. It is known that in the absence of cardiac neural crest, the myocardium is composed of disorganized myofibrils.[19] However, it is shown that the walls of the ventricles and atria are thinner than expected in VENT cells extirpated animals.[18] These data may explain the pathogenesis in our patient with idiopathic dilated cardiomyopathy associated with neural tube defect.

Etiology of neural tube defect is unknown. Most of the nonsyndromic defects are believed to be multifactorial in origin, and this makes it difficult to identify the underlying causes. Epidemiological studies have primarily focused on maternal factors including environmental exposures within the first trimester of pregnancy. Increased risk for neural tube defects is definitively associated with maternal diabetes, maternal obesity, and maternal use of anticonvulsant drugs.[2,3,5,6] Our study revealed that there was no difference for maternal diabetes between the study and control group, and no mother received anticonvulsant drugs. Most of the mothers did not know their prepregnancy weight. Because of this reason, we could not get accurate data on maternal obesity as a risk factor.

Established risk factors for neural tube defects are dietary, with several randomized clinical trials demonstrating a protective effect of folic acid supplementation.[20,21] It is known that folic acid supplementation also reduces the risk of congenital heart defects.[22] Our study revealed that there was no difference for periconceptional folic acid supplementation between the study and control group. The explanation for this unexpected data can be the fact that folic acid supplementation is in a very low level in our overall study population; consequently, we cannot see the protective effect of folic acid.

Most studies investigating birth defects include maternal age as a potential confounder. Young and advanced maternal ages are reported to be associated with different types of birth defects.[23] In our study, there was no difference in maternal age between the study and control groups. This could be explained by the association between maternal age and chromosomal defects, which we did not include in the study.

Conclusions

In this study, the prevalence of congenital heart defects diagnosed by echocardiography was 27.8% in patients with neural tube defects. Most of them were simple and without hemodynamic compromise, although there were 2 patients with serious cyanotic heart diseases. Because the clinical examination especially in the newborn period is insensitive for detecting heart defects, screening echocardiograms are warranted. This information has important implications especially for minor and major surgical procedures. Another important point is that routine obstetric examination and therefore use of periconceptional folic acid during pregnancy is still lacking in our country.

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