The Heart in Selected Congenital Malformations

A Lesson in Pathogenetic Relationships*

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ABSTRACT

The application of new knowledge on the pathogenesis of congenital heart defects has increased our understanding of associated, non-cardiac malformations seen in certain syndromes.

Defects in the proliferation and migration of neural crest cells are thought to contribute to conotruncal defects. These are seen in association with conditions such as DiGeorge syndrome, CHARGE association, hemifacial microsomia, and Shprintzen syndrome. They also form part of the isotretinoin and thalidomide embryopathies. Their association with conotruncal defects suggests that abnormal migration of neural crest cells may play a role in the pathogenesis of these syndromes.

Recent advances in cardiac embryology have increased our understanding of the developmental mechanisms involved in the production of congenital heart defects. The application of this knowledge to the study of associated, non-cardiac malformations seen in certain syndromes has shed light on their pathogenesis.

Clark has proposed four mechanisms which may operate during early embryogenesis to produce congenital heart defects. These include (1) abnormal proliferation and migration of cells from branchial arch mesenchyme and neural crest, (2) changes in the proportion of right and left heart blood flow, (3) defects in programmed cell death, and (4) abnormal cellular matrix formation. Morphologically similar congenital heart lesions, such as ventricular septal defects (VSDs), may be produced by different developmental mechanisms (table I). Much research interest has centered on the role of the neural crest and its interactions with cardiac mesenchyme and this report shall concentrate on this interrelationship.

Kirby and Stewart, working with a chick embryo model, have shown that neural crest cells destined to become
part of the autonomic nervous system are located in the aortico-pulmonary septum. These authors subsequently demonstrated that removal of premigratory neural crest cells from the cranial region of the neural fold consistently produced cardiac defects. Of these, three defects predominated: high VSDs, a single outflow vessel originating from the right ventricle, and a single outflow vessel overriding the ventricular septum.

These malformations are similar to truncus arteriosus communis and double outlet right ventricle and were often seen in association with thymic hypoplasia. The cardiac defects were probably caused by absence of neural crest cells or their defective interaction with cardiac mesenchyme. They are known as conotruncal defects; in humans they include supracristal VSD, aortico-pulmonary window, double outlet right ventricle, tetralogy of Fallot, transposition of the great vessels, truncus arteriosus communis, interruption of the aortic arch type-B, and pulmonary atresia with VSD.

Recently, an analysis of 265 cases of interruption of the aortic arch (IAA) and coarctation of the aorta (CA) was reported by Van Mierop and Kutsche. In IAA-type A, the interruption is between the left subclavian artery and the ductus arteriosus; in IAA-type B, it lies between the left common carotid artery and the left subclavian artery. The pattern of associated congenital heart defects is different in the two groups. The IAA-B is associated with a supracristal ventricular septal defect, bicuspid aortic valve, aberrant subclavian artery, and DiGeorge syndrome (DiGs), while IAA-A and CA are associated with miscellaneous forms of congenital heart disease. The VSDs are almost universally present in IAA-B but are found in only about half of the patients with IAA-A and CA. What is even more important is the difference in the type of VSD. The IAA-B is associated with supracristal VSD; the infundibular septum nearly always crosses the defect, and there is encroachment on the left ventricular outflow tract producing subaortic stenosis. This defect was rarely found in the other group.

In a further analysis of 161 cases of DiGs, van Mierop and Kutsche noted that 156 had associated congenital heart defects, and that these were predominantly conotruncal. An IAA-B, persistent truncus arteriosus, and tetralogy of Fallot accounted for 60 percent of the cardiac lesions, occurring in 48, 37, and 10 of the 156 cases, respectively.

These relationships are probably best explained by defects in the development and migration of the neural crest. Neural crest cells make a large contribution to the development of the skeleton and soft tissues of the face and visceral arches. They contribute to the formation of the tongue, thymus, thyroid, and parathyroid glands and also form the walls of the large arteries derived from the branchial arches. Van Mierop and Kutsche suggested that IAA-B is one manifestation of a spectrum of branchial arch anomalies involving the neural crest, of which DiGs represents the most severe. Both IAA-A and CA have a different pathogenesis.

Hemifacial microsomia (HM), or Facio-Auriculo-Vertebral syndrome (FAVS), is a group of conditions com-
prising hemifacial microsomia, ear anomalies, and, frequently, findings in other organ systems. These may consist of epibulbar dermoids (Goldenhar syndrome), other ocular anomalies, renal, cardiac, and vertebral defects. Ardinger et al. analyzed the congenital heart defects in a series of patients with hemifacial microsomia and compared them with those of patients with Treacher Collins (TC) syndrome. In the HM group, there was a much higher incidence of heart defects, 46 percent as against nine percent in the TC group. The HM-associated anomalies were conotruncal in almost 42 percent, while in the TC group, not one of the cardiac defects was conotruncal.

The CHARGE association and Shprintzen syndrome are both associated with congenital cardiac defects. The former also includes a non-random association of choanal atresia, colobomata, ear anomalies, small stature, mental retardation and genital hypoplasia, while the latter includes clefts of the palate and slender fingers. Graham et al. recently reported that the heart defects seen in the CHARGE association were commonly conotruncal. Of 51 cases, 35 percent were conotruncal defects compared with an expected frequency of 16 to 22 percent. In the Shprintzen syndrome, the heart defects include tetralogy of Fallot, aberrant subclavian artery, and a double outlet right ventricle. The cardiac defects in both of these conditions are overwhelmingly conotruncal, which, as mentioned previously, are related to defective proliferation and migration of the neural crest. By implication, it is logical to assume that the non-cardiac malformations may well have the same pathogenesis.

The effects on the fetus of maternal ingestion of isotretinoin and thalidomide have been the subject of a recent review. Both syndromes are associated with heart defects. The isotretinoin embryopathy is also associated with ear anomalies, cleft palate, and skull defects, while thalidomide exposure is associated with severe limb defects. The heart lesions in the former include tetralogy of Fallot, transposition of the great vessels, and IAA-B, while in the latter, they include tetralogy of Fallot and double outlet right ventricle. The association with conotruncal defects seen in both of these patterns of malformation suggests that interference with the normal development and migration of neural crest cells plays a significant role in the pathogenesis of their non-cardiac defects.

These analyses of the developmental mechanisms involved in the production of cardiac defects suggests that they share a common pathogenesis with defects in other systems. Even though much of the research work may be preliminary and rather speculative, it is likely that its application will greatly contribute to our understanding of developmental defects in man.

References


