Is transposition a defect of laterality?

In the investigation published in the current issue of the Journal, the team from Saudi Arabia have explored the troubled area of the potential association between transposition and defects of laterality. They have succeeded in bringing a degree of sanity to this topic. In order to appreciate the full significance of their analysis, we should remember that both of these issues were the source of significant previous controversies amongst those who investigate and treat patients with congenitally malformed hearts. For many years, the essential feature of transposition was considered to be the presence of the aortic root in anterior position,[1] rather than it its "normal" location, which of course is posterior and rightward relative to the pulmonary root in those with usual arrangement of their organs. It was the landmark study of Van Praagh and his colleagues that showed that the arterial trunks could rarely arise from morphologically inappropriate ventricles even when the aortic root was positioned posteriorly and rightward, and with its leaflets in fibrous continuity with those of the mitral valve in the roof of an accompanying ventricular septal defect.[2] Since this recognition, it has become accepted that discordant ventriculo-arterial connections are the phenotypic feature of transposition.[3]

What then of defects of laterality? It has always been recognised that the parietal components of the body are themselves mirror-images of each other in the same individual. This is not the case for the organs. There is, nonetheless, a usual arrangement for the bodily organs. Any arrangement in which the organs are found other than in this usual pattern, therefore, is a disorder of lateralisation. In the least common variant, all the organs remain lateralised, but in mirror-imaged fashion relative to the usual situation. Often called "situs inversus" this arrangement is one of overall mirror-imagery as opposed to "upside-downess". Much more frequently, although still rare when set against the arrangements found in the overall cohort of patients with congenitally malformed hearts, the thoracic organs are mirror-imaged in the same individual. The mirror-imaged, or isomeric, structures can show the morphology of either the normal right-sided or left-sided thoracic organs. For the lungs, such isomerism involves both the patterns of pulmonary lobation and bronchial branching. For the heart, it is only the atrial appendages that are truly isomeric. Such isomerism is not, however found in the abdominal organs.[4] In the setting of thoracic isomerism, the abdominal organs show the features of heterotaxy, in other words a pattern that is other than normal. As the group from Saudi Arabia emphasise, the isomeric and mirror-imaged variants are all examples of heterotaxy, although pediatric cardiologists have tended to exclude mirror-imagery from this grouping. The detailed investigation now published by the group from Saudi Arabia demonstrates the advantages of grouping together all three patterns of variation from normal.

Should we, therefore, consider transposition, or discordant ventriculo-arterial connections, as another of the defects of lateralisation? The excellent analysis of the cohort of patients from Saudi Arabia shows the answer to this question to be a resounding "no". The essence of deficient cardiac lateralisation is either mirror-imaged atrial arrangement or isomerism of the atrial appendages.[4] Having assessed their cohort of patients with various forms of discordant ventriculo-arterial connections, it is a very small proportion that show the morphological features of such cardiac heterotaxy. We had reached comparable conclusions having analysed the detailed cardiac database maintained at Birmingham Children's Hospital. Of 727 patients listed in the database who have undergone the arterial switch procedure, all bar four were noted to have usual atrial arrangement. The outstanding patients all had mirror-imaged atrial appendages. This is not to deny that patients with isomeric atrial appendages can have discordant ventriculo-arterial connections. There are 178 patients coded thus far in the Birmingham database as having isomeric atrial appendages. Of those, 92 have discordant ventriculo-arterial connections, with 65 having right isomerism and 27 with left isomerism. Many of these patients, nonetheless, also have left-handed ventricular topology. Such patients are "close-cousins" of those with congenitally corrected transposition. The essence of congenitally corrected transposition is discordance of the atrioventricular as well as the ventriculo-arterial connections. Discordant atrioventricular connections cannot exist in the setting of isomeric atrial appendages. Irrespective of the type of isomerism and the topology of the ventricular mass, half the ventricular mass will be concordantly connected across the atrioventricular junctions, while the other half will be discordantly connected. This produces an atrioventricular connection that is biventricular but mixed.[5] Thus, in agreement with the conclusions of the group from Saudi Arabia, the analysis of the Birmingham database shows that deficient lateralisation is not the basic problem in the

setting of congenitally corrected transposition. Instead, it is a problem with ventricular looping.

Those who cite problems of lateralisation as underscoring the finding of discordant ventriculo-arterial connections are seeking to establish the genetic cues that might underscore the pathogenetic mechanisms.[6] If they are to establish these processes in the clinical setting, the findings from the group working in Saudi Arabia, along with our findings from Birmingham, show that attention paid exclusively to those patients diagnosed with transposition is unlikely to yield significant information. Very few of these patients exhibit problems with lateralisation. Those that do show mirror-imagery rather than isomerism. The same goes for those having congenitally corrected transposition. The yield regarding problems of lateralisation will be much greater if geneticists, and those seeking to unlock the keys to pathogenesis, focus on patients known to have isomeric atrial appendages, but in combination with discordant ventriculo-arterial connections. Such a combination is frequent in patients with right isomerism, and is also to be found in those with left isomerism. The discordant ventriculo-arterial connections themselves, nonetheless, can be found in the settings of both right-handed and left-handed topology. Only when comparisons are made of the genetic backgrounds of those with comparable combinations of cardiac lesions will it prove possible to make meaningful analyses of available genetic information. In this regard, lumping together patients with right and left isomerism as representing "heterotaxy" is akin to mixing apples with oranges. And, when considering the influence of disorders of lateralisation, mirror-imagery is just as much a departure from the usual situation as is isomerism. The group from Saudi Arabia have now demonstrated the accuracy with which all of these features can be illustrated in the clinical setting. Their excellent analysis established unequivocally that transposition is not a problem of laterality. It represents disordered development of the ventricular outflow tracts.

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