● Editorial

RELATIVE CERTAINTY AS OPPOSED TO UNCERTAINTY IN THE DIAGNOSIS OF ISOMERISM

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Abstract

The situation in which the bodily organs are "jumbled up", frequently described in terms of visceral heterotaxy, was first brought to prominence by Ivemark, who emphasised the situation in terms of anatomy and development of the spleen. Putschar and Mannion then indicated that "between the normal situs, which is asymmetrical, and the situs inversus, which is the asymmetrical mirror-image of normality, a symmetrical situs sometimes exists, and this is the essence of bodily isomerism".

In the setting of the congenitally malformed heart, however, the isomeric features are found uniformly only in the atrial appendages. To date, these such subtle features have largely been recognised at autopsy, but if specifically sought for, they should be identified by the echocardiographer, even when working in the prenatal setting.

The positive diagnosis of cardiac isomerism, therefore, depends on the recognition of isomeric atrial appendages. There is no evidence of isomerism at ventricular or arterial level. The relationship of the great vessels as they traverse the diaphragm, nonetheless, has been shown to be helpful in pointing to the need for more specific examination of the atrial appendages. When analysed on this basis, there can only be left or right isomerism, although the isomeric features are not always found uniformly throughout the bodily organs. Should there be disharmony between the systems, the specific findings should be described for each system, thus removing any suggestion of ambiguity.

The distinction between left and right isomerism is crucial for counselling, not only for immediate decisions regarding the progress of the pregnancy in question, but for future potential pregnancies. Distinguishing between pregnancies developing with right and left isomerism could also provide the key for determining the genes responsible for the production of laterality.

Key words: *visceral heterotaxy, asplenia, polysplenia, sequential segmental analysis, morphological method*

INTRODUCTION

It is a truism that the chances of obtaining a correct answer to any question are significantly improved when the question itself is correctly posed. This is certainly the case when we consider the ongoing debate as how best to recognise and segregate the lesions still described in many centers in terms of "visceral heterotaxy". These syndromes were first brought to prominence by Ivemark, who chose to emphasise the anatomy and development of the spleen[1]. Although concentrating on splenic structure, nonetheless, Ivemark did point to the presence of visceral symmetry within the overall bodily arrangement. In a sadly neglected contribution, Putschar and Mannion[2] then indicated that "between the normal situs, which is asymmetrical, and the situs inversus, which is the asymmetrical mirror-image of normality, a symmetrical situs sometimes exists, exhibiting symmetrical rightness or leftness on both sides." It is the presence of the features of rightness or leftness on both sides of the body that is the essence of bodily isomerism. It is unfortunate, therefore, that this key statement from Putschar and Mannion[2] has not achieved greater priority. It is particularly significant to the concept of segmental analysis. This method for analysis and description of congenitally malformed hearts depends initially on the accurate assessment of atrial arrangement. The architect of the initial segmental approach,[3] however, promulgated the

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notion that one of the arrangements was neither the usual, nor its mirror-imaged variant, but rather was one of ambiguity, or uncertainty. This was followed by a suggestion that isomeric features did not exist in the cardiac malformations known to be associated with visceral heterotaxy[4]. These assertions, however, were based on the mistaken assumption that it was the entirety of the atrial chambers that were isomeric in these syndromes. As had been shown, when assessed according to the extent of the pectinate muscles relative to the atrioventricular junctions, it is only the atrial appendages that are truly isomeric in hearts obtained from patients with "splenic syndromes"[5]. As yet, of course, it has still to be established whether such subtle features can be recognised echocardiographically, particular in the setting of prenatal cardiology. There are, nonetheless, sufficient clues that now permit the prenatal cardiologist to segregate so-called heterotaxy into the subsets of right and left isomerism. In this review, we draw attention to these clues, and the philosophy which underscores their usage.

HOW DO WE RECOGNISE ISOMERISM IN THE AUTOPSY ROOM?

The so-called splenic syndromes are nowadays considered to represent "heterotaxy"[6]. "Heterotaxy", however, is far from an optimal word for their description. When used in literal fashion, it would account for any departure from the expected norm. It could be argued, therefore, that all congenital malformations represent examples of heterotaxy. The essence of the conditions included within the syndromes is an overall arrangement of the bodily organs that is neither harmoniously usual, nor uniformly mirror-imaged. In most instances, the liver is midline, and the remaining abdominal organs are jumbled-up (Figure 1).

As was emphasised by Ivemark[1], the spleen is typically absent in such settings, or else can be multiple (Figure 2).

It is a mistake, nonetheless, to think that the abnormal arrangement of the bodily organs are themselves uniform in all patients with these derangements. On the contrary, the features of isomerism are frequently subtle, involving only those structures which themselves are either normally morphologically right, or morphologically left. The features, furthermore, are not always harmonious throughout the different systems of organs. It is possible, nonetheless, to recognise two basic patterns. The isomeric features are seen most obviously in the arrangement of the lungs, and best in the pattern of the bronchial tree. In the usual arrangement, often called "situs solitus", the morphologically right bronchus, which is right-sided, is significantly shorter than its morphologically left partner, and is eparterial as opposed to being hyparterial. These

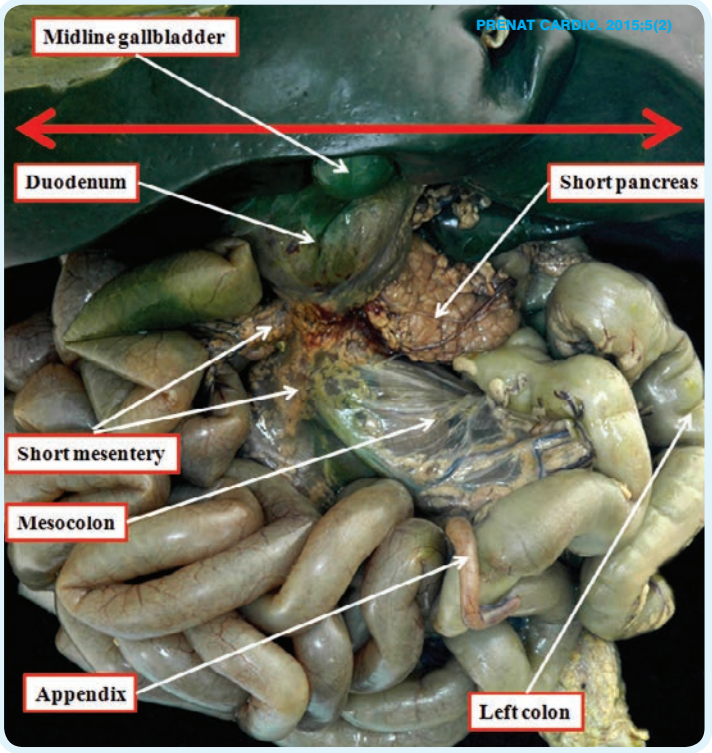

Figure 1. The image shows the abdominal contents from an autopsy performed on a fetus that might be diagnosed as having "heterotaxy". The liver is midline, as is the gall bladder, and the gut is malrotated, the appendix being on the same side as the left-sided colon. The mesentery is short, as is the pancreas, which is roughly in the midline.

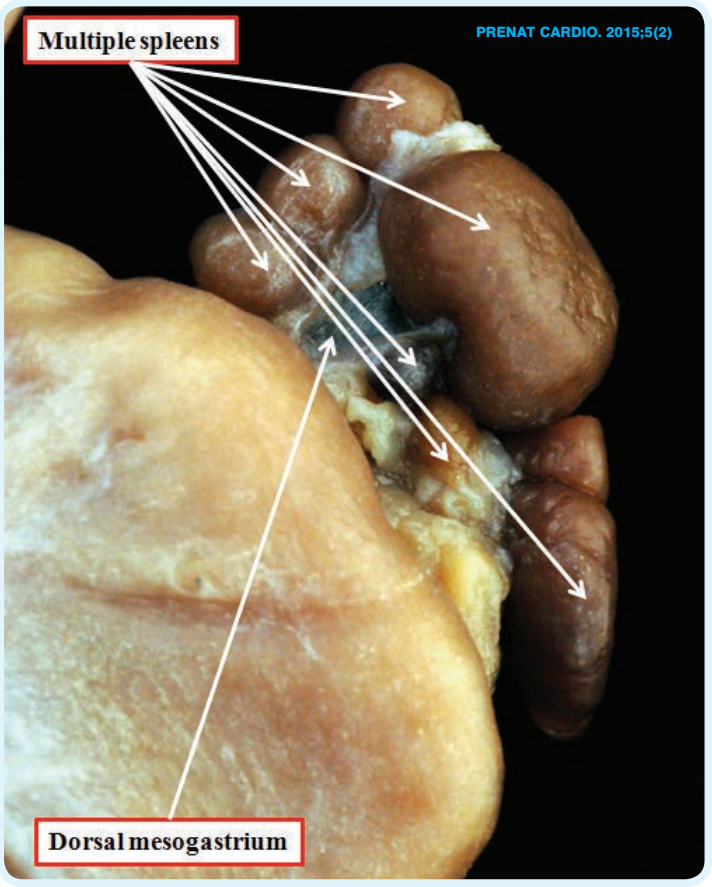

Figure 2. The image shows the feature of multiple spleens. The splenic tissue is found on both sides of the dorsal mesogastrium.

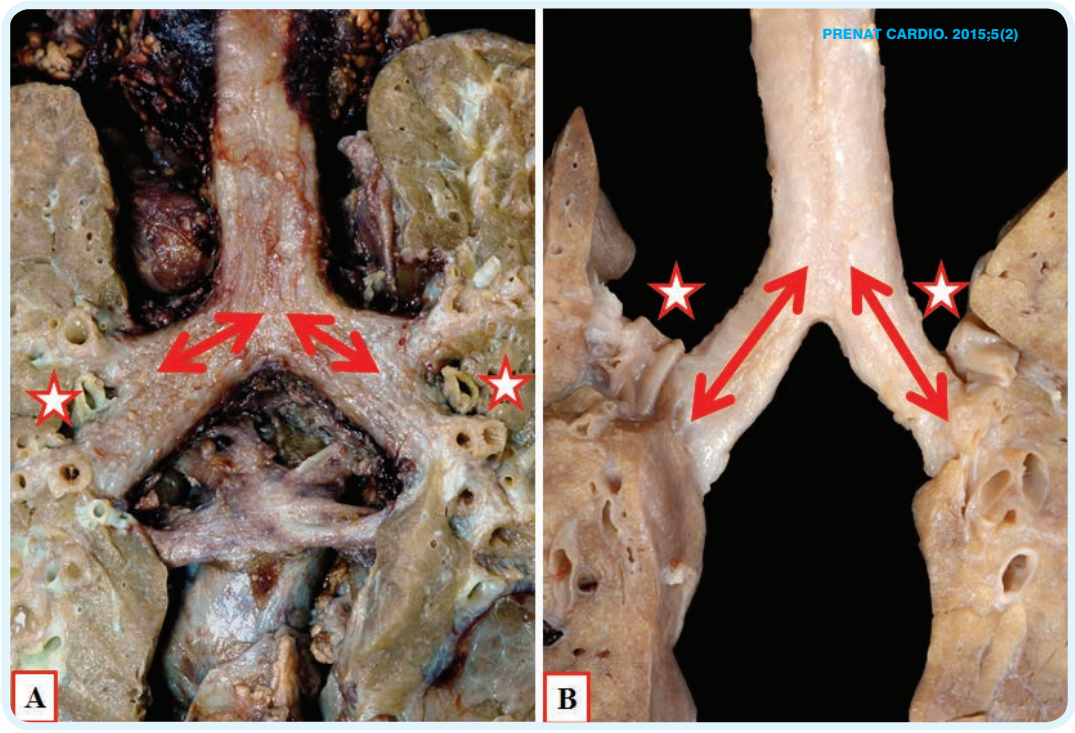

Figure 3. The images show the dissected bronchial trees from two fetuses with so-called "heterotaxy". Panel A shows bilaterally short bronchuses (red double headed arrows). Both give off their first branch cranially relative to the pulmonary artery supplying the lower lobes of the lungs (white stars with red borders). It is this feature that makes them eparterial. The bronchial tree shown in panel A is from the fetus shown in Figure 1, and is indicative of right isomerism. Panel B shows bilaterally long bronchuses, which are hyparterial, with the first branch arising below the arteries feeding the lower lobes. The bronchial tree shown in Panel B came from the fetus illustrated in Figure 2, and is indicative of left isomerism.

features are then mirror-imaged in the much rarer variant, still typically described as "situs inversus". In the isomeric variants, both of the bronchuses are either, short and eparterial (Figure 3A), or long and hyparterial (Figure 3B).

On the basis of bronchial arrangement, therefore, it is an easy matter for the fetal pathologist to make the distinction between right and left isomerism. It is equally easy for the fetal pathologist to describe precisely arrangement of the abdominal organs, including the spleen, rather than opting for labels such as "solitus", "inversus", or "ambiguus", the more so since the arrangements rarely fit neatly into these presumed patterns. Note should be taken in this regard, however, that in fetuses seen prior to midterm, the liver is always large and relatively symmetrical. The fact that the appendix can be left-sided in the otherwise normal situation is also pertinent to such descriptions.

WHAT IS THE EVIDENCE FOR CARDIAC ISOMERISM?

The pathologist, using the feature of bronchial morphology, can now distinguish with relative certainty the subsets of right and left isomerism. It had long been established that clinicians could also achieve such discrimination.[7] The question still remains, however, as to whether isomeric features are also to be found within the heart, and if so, which components are involved? All devolves on how rightness as opposed to leftness is to be distinguished within the heart. Van Praagh and his colleagues[8] provided the key to resolving this debate when they introduced the concept of the so-called "morphological method". This concept emerged from a criticism of a definition proposed for the allegedly "univentricular heart"[9]. In the criticized work, the European collaborators had sought to disqualify chambers from ventricular status simply because they lack an inlet component. Van Praagh and his colleagues[8] rightly pointed to the flaw in such logic, arguing instead that components within the heart should be defined according to their own intrinsic morphology, and not on the basis of features which were themselves variable. The stance taken by Van Praagh and associates[8] was unequivocally correct. It is just as applicable to the definition of isomerism within the heart as to the nature of ventricles.

Uemura and associates[5], therefore, when assessing the morphology of the atrial chambers, concentrated on their most constant feature, namely the appendage (Figure 4).

They noted that in hearts from patients known to have heterotaxy, when judged on the extent of the pectinate muscles relative to the atrioventricular junctions, it was possible uniformly to distinguish isomeric left (Figure 4A) as opposed to isomeric right (Figure 4B) appendages. They also emphasised that it is only the atrial appendages that show evidence of isomerism. This reflects the fact that, during development, the appendages are able to respond in lateralised fashion to the genes responsible for producing laterality within the developing fetus. It is now well established that, when using genetically modified mice, knocking out the genes *Cited-1* or *Pitx-2* produces right isomerism, specifically isomerism of the right atrial appendages,[10] while knocking out the gene *Lefty-1* produces left isomerism.[11] The venoatrial connections, in contrast, show marked variability, although certain features are suggestive of either right or left isomerism. Interruption of the inferior caval vein, for example, is much commoner in the setting of left isomerism. Totally anomalous pulmonary venous connections are always present in right isomerism, even when the pulmonary veins return to the heart[5].

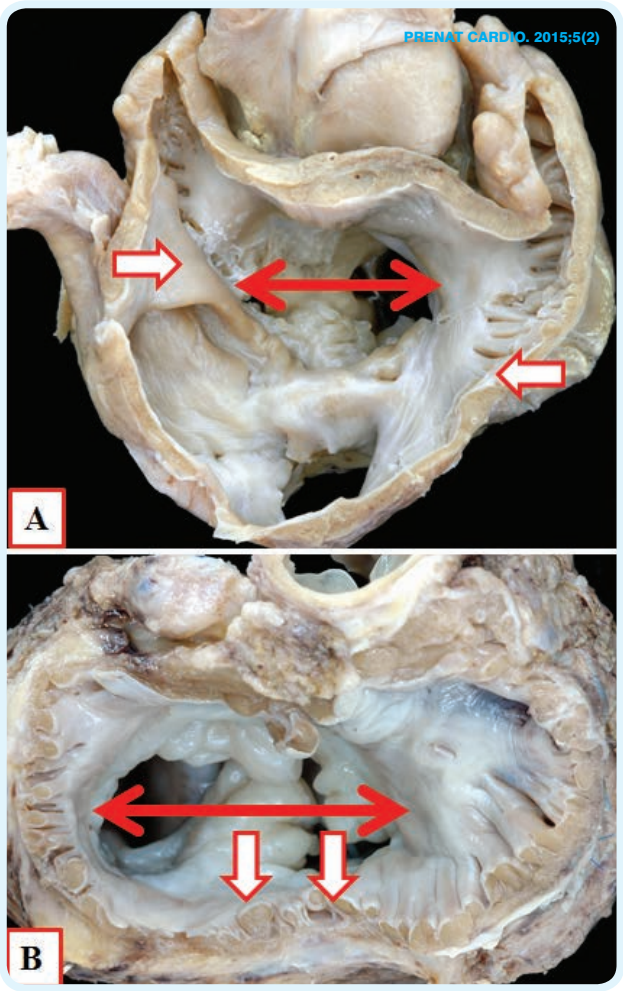

Figure 4. The images show how, when assessed on the basis of the extent of the pectinate muscles relative to the atrioventricular junctions (white arrows with red borders), isomeric left appendages (panel A) can be distinguished from isomeric right appendages. Note that both hearts are from patients with common atrioventricular junctions (double headed red arrows), and are viewed from their atrial aspects.

The coronary sinus, however, is uniformly absent in those with isomeric right appendages. The ventricular chambers and arterial structures, in contrast, respond in comparable fashion to the genes responsible for producing laterality. Hence, there is no evidence of isomerism at ventricular or arterial level. The positive diagnosis of cardiac isomerism, therefore, depends on the recognition of isomeric atrial appendages. We have already shown how this can be achieved by the fetal pathologist (Figure 4). The question remains as to whether the same distinction can be expected from the prenatal cardiologist?

HOW SHOULD THE PRENATAL CARDIOLOGIST SEGREGATE SO-CALLED "HETEROTAXY"?

The experience now reported from the Evelina Hospital in London[12] shows that it is entirely feasible to expect the prenatal cardiologist not only to recognise the presence of so-called "heterotaxy", but also to distinguish its isomeric subsets. In an excellent handbook, Sharland[12] has summarised the overall echocardiographic findings produced by their unit, one of the first to be involved in prenatal diagnosis of congenital cardiac malformations, from 1980 through 2010. Over this period, they encountered 111 pregnancies in which the diagnosis was made of right isomerism, and 173 instances of left isomerism. This accounted for 6.6% of their overall experience. As yet, they have not indicated whether it is possible, with certainty, to identify the morphology of the atrial appendages. The observed features, nonetheless, were sufficient for them to discriminate between left and right isomerism. Sharland[12] rightly places emphasis on the feature of the relationship of the great vessels as they traverse the diaphragm. In the setting of right isomerism, the inferior caval vein lies to the same side of the spine as the aorta, with the venous channel in anterior position. When the inferior caval vein is interrupted, a feature usually but not always associated with left isomerism, then the venous channel, represented by the azygos system, is usually on the same side as the aorta, but is always posteriorly located. When this information is collated with the constellations of intracardiac malformations, the experience reported from the Evelina Hospital shows that the prenatal cardiologist should, with a high degree of certainty, be able to distinguish right from left isomerism[12]. Initial analysis of our images obtained in Lodz suggests that it should also now be feasible to distinguish, in selected cases, the morphology of the atrial appendages (Figure 5).

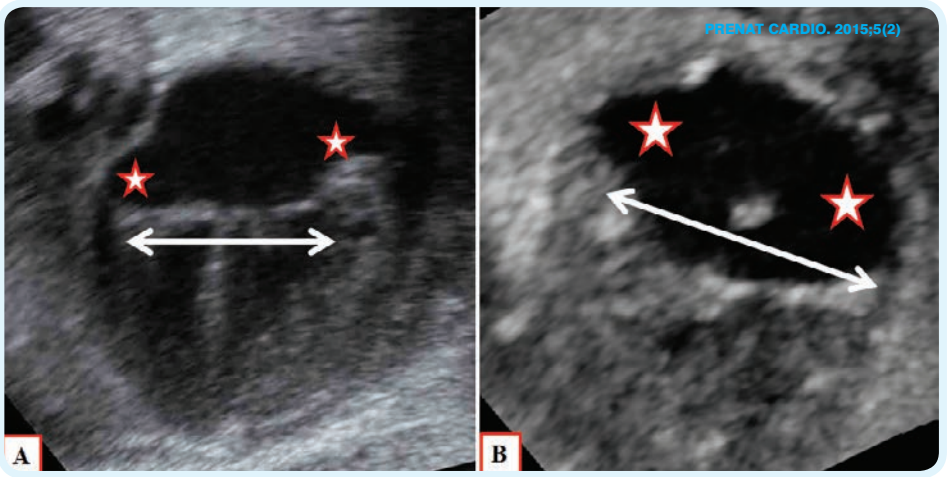

Figure 5. The images are from selected fetal scans taken during assessment of pregnancies for cardiac malformations at the University of Lodz. The four-chamber images shown in Panel A, from a fetus with a common atrioventricular junction and separate valvar orifices for the right and left ventricles (double headed white arrow) is suggestive for the presence bilaterally of morphologically left appendages (white stars with red borders). In contrast, the image shown in Panel B, again from a fetus with common atrioventricular junction, is suggestive of bilaterally morphologically right appendages. The arrangement of the great vessels at T10 were supportive of the diagnoses of left as opposed to right isomerism.

This distinction, of course, is then crucial for counselling, not only for immediate decisions regarding the progress of the pregnancy in question, but for future potential pregnancies. Distinguishing between pregnancies developing with right and left isomerism could also provide the key for determining the genes responsible for the production of laterality. The time has come, therefore, to jettison descriptions of bodily arrangement that are suggestive of uncertainty, such as "situs ambiguus"[3]. The evidence is now overwhelming that, when judged according to the extent of the pectinate muscles relative to the atrioventricular junctions, patients with so-called heterotaxy, including fetuses, have appendages bilaterally of either right or left morphology. It is only the appendages, however, that are truly isomeric. It was a mistake, therefore, to suggest that patients with heterotaxy exhibited "atrial isomerism"[12]. It was this misuse of words that prompted the suggestion that patients with left atrial isomerism would have eight pulmonary veins[4]. This was never, of course, the suggestion of those promoting the concept of isomerism[12]. The criticism, nonetheless, is justified, but is readily defused by describing isomerism of the atrial appendages[5]. It follows, of course, that it is also necessary to provide precise descriptions of the variable venoatrial connections, along with the other cardiac features, such as ventricular morphology and ventriculo-arterial connections. It is equally necessary to provide precise descriptions of the arrangement of all the thoracic and abdominal organs, since these can also be variable in the setting of isomeric atrial appendages. It is such precise descriptions that will remove any suggestions of uncertainty, but only when commencing from the starting point of left as opposed to right isomerism.

Conflict of interest: The authors declare no conflict of interest

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