Recurrence of Atrial Septal Defect in Three Generations

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Beginning with a patient presenting with an atrial septal defect (ASD) of the secundum type, the genealogy was identified in four affected individuals who belonged to three successive generations of the same family. The defects were visually confirmed in all individuals and were found to be anatomically similar. No other congenital malformations were present in these individuals. The genealogy was identified in 1972, when ASD recurred in two generations, and it was concluded that the mechanism of transmission was autosomal recessive.

The fifth individual, identified 21 years later, and having an anomaly identical to that of the others, was the child of a couple who had no consanguinity and whose mother was a member of the previously studied genealogy.

Considering the absence of phenotype in the parents and the rarity of the ASD gene in the general population, the occurrence of the uniparental disomy for this family nucleus, and the same autosomal recessive mechanism of transmission by this affected individual is possible.

This study reports the familial occurrence of ASD by genetic mechanisms of transmission, emphasizing the necessity for genetic-clinical studies in members of the familial nucleus in order to detect new carriers, who usually are asymptomatic, thereby allowing for early and adequate treatment of individuals who may be affected.

The incidence of congenital heart diseases varies depending on the use of different diagnostic methods by different authors. From 1946 to 1953, 6053 children, including stillborns and newborns weighing >500g, were seen at the Presbyterian Medical Center in New York. Fifty cases of congenital heart disease were present, which represents an overall incidence of 8.3 per 1000, varying from 7.7% in stillborns and those who died in the first month to 6 in 1000 among those living more than a month.

The distribution of congenital heart diseases varies among different age groups; therefore, the prevalence is different from the incidence observed at birth. Campbell discussed this subject and compared his data about the preferential incidence in relation to sex, with that of MacMahon et al and Calgren, with the prevalence reported by Keith et al. For ASD, the incidence at birth is 1:1, and it reaches 2:1 in the adult age, which is the prevalence of the disease.

Congenital anomalies, including congenital heart diseases, may be the result of endogenous abnormalities, that is, genetic abnormalities that occur either in microscopic or chromosomal anomalies or in submicroscopic or genetic anomalies. On the contrary, exogenous abnormalities represented by external teratogens, such as radiation or even viral infection during embryogenesis, can cause identical anomalies (phenocopies and genocopies).

Few studies exist that demonstrate the familial recurrence of ASD. Courter et al, pioneers reporting the repetition of ASD without the association of other congenital heart abnormalities, included Lutembacher’s syndrome in their publication. Although it can not be proved that they were the first ones to do so, the lack of previous reports identifies this as a seminal contribution. Gänsslen et al studied 68 pedigree diagrams from various congenital heart diseases and described the existence of evidence of recessive transmission in some of them, particularly those with patent ductus arteriosus and ASD. Courter et al reported two sisters with the clinical diagnosis of ASD without the association of other congenital heart abnormalities, included Lutembacher’s syndrome. Carleton et al, based on the presentation of a single family, concluded that the mechanism of transmission was recessive; Howitt, also based on the presentation of a single genealogy, concluded that the type of transmission was dominant; Nora et al concluded that the mechanism was multifactorial; Zetterqvist et al agreed that the transmission was dominant based on three genealogies and Volti et al concluded the transmission was dominant.
In his PhD thesis, Ferreira performed a genetic-clinical study of the isolated ASD of the secundum type in 8 genealogies and, due to the series of patients and the methodology used, he concluded that transmission was autosomal recessive.

The present study reports the occurrence of a fifth carrier of an identical anomaly, detected in the third consecutive generation in the same genealogy.

In 1972, a genetic-clinical study of isolated ASD of the secundum type was conducted at UNIFESP (São Paulo, Brazil) and the present genealogy was selected from among the eight studied genealogies.

The affected individual (III-9) (fig. 1), presenting with an ASD with significant hemodynamic compromise, was admitted to surgery, and the defect and its characteristics were confirmed at surgery. Starting with this patient, 24 individuals from this pedigree diagram were examined. They underwent routine clinical examinations, including electrocardiogram (ECG) and chest X-ray. When there was a suspicion of a cardiac defect, the patient was required to undergo a hemodynamic study. Three other patients were then detected as having ASDs and underwent surgery, which demonstrated an identical defect.

In 1993, another patient with congenital heart disease was admitted to UNIFESP. After a clinical examination, ECG, chest X-ray and echocardiogram, the recurrence of ASD was demonstrated, which was confirmed by surgery to be of the same anatomical type found in the other patients in the same genealogy with the defect. Beginning from this patient, parents and siblings were studied using the same methodology, and further recurrences were excluded.

In medicine, in order to treat any disease adequately, its etiology must be determined and this is usually very difficult for any congenital defect. As reported by Gordon, who compared the mortality rate between deaths from diarrhea and congenital defects from 1910 to 1965, an inversion has occurred in the relative importance of these two conditions as causes of death.

When heart diseases are considered, because it is very difficult to elucidate the etiology of congenital heart diseases and because there has been a major improvement in primary and secondary prevention of acquired heart diseases, whose etiology is usually well defined, the genetic-clinical study of congenital heart diseases becomes even more relevant.

The main objection to the acceptance of a genetic hypothesis for congenital heart diseases was raised by studies among twins, which were performed in a way that can be criticized. In monozygotic twins, identical in their genetic constitution, a higher occurrence of heart diseases should be found when compared with dizygotic twins, who are just brothers or sisters of the same age. These studies, however, did not demonstrate this difference. Nora et al., however, in a review of the related literature, demonstrated that the results in twins support the genetic hypothesis for explaining congenital heart diseases. Eighty-eight monozygotic, 104 dizygotic and 78 twins in whom zygosis had not been previously established, were found. Thirty-six monozygotic and 41 dizygotic twins (a much smaller number than the one initially obtained) in whom the diagnoses of the zygosis and of the heart disease were accurate, were selected and some of their patients were included. Among these twins, concordance was much greater than that obtained by the previously cited authors, being 25% for monozygotic and 4.9% for dizygotic. With these results, genetic influence became evident, and the importance of the environment in determining congenital heart disease became incontestable.

Analyzing the observed recurrence in the present genealogy one can observe that only one horizontal line is present, which affected both females and males. Consanguinity was also present, thus suggesting an autosomal recessive mechanism. In the genetic-clinical study including the eight @ genealogies, the recurrence of defects of the atrial septum among brothers of patients with the defects was 11.5%, standard deviation 6.3%, when only patients who had a definite confirmation of the defect were included, and 16.7%, standard deviation 6.8%, when dead brothers with the possibility of having an ASD were also included. It is noteworthy that these results do not differ significantly from the expected proportions in recessive transmission, that is, three normal individuals for each affected person.

It must also be taken into consideration that this is the complement of a previous study, where six more genealogies were analyzed by the same methodology and, at that time, the above mentioned genetic mechanism was established.

The recurrence of ASD in five patients in a single genealogy calls attention to a genetic etiology, even to observers who are less familiar with genetics. This possibility becomes even more evident when the incidence of the defect in the general population (6:10000) is compared with the significant recurrence in the present genealogy. On the other hand, it should also be noted that the defect was identical in all affected persons, emphasizing once more the genetic etiology.

The importance of the genetic-clinical study of patients with congenital heart diseases, here exemplified by ASD, is demonstrated by the identification of new patients who are detected by a systematic approach. Patient III-7, for example,
References

20. Holman E, Gerbode F, Purdy A. Patent ductus: review of 75 cases with surgical