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Editorial

A polygenic risk score after corrective surgery for transposition of the great arteries: Can genetics add value to clinical predictors of outcome?

1. Introduction

Transposition of the great arteries (TGA) is a devastating congenital cardiac defect where the pulmonary artery (pumping deoxygenated blood) and the aorta (oxygenated blood) are reversed (Fig. 1). TGA affects approximately 3 per 10,000 live births [1]. In a normal developing heart, the straight embryonic heart tube loops to the right to initial cardiac septation to form left and right ventricles as well as left and right atria. Cardiac looping is an important step in cardiac morphogenesis to ensure the formation of separate but connected left-right chambers to pump oxygenated and deoxygenated blood, respectively.

TGA occurs when the outflow tracts of the pulmonary artery and the aorta fail to loop. Subsequently, the aorta arises from the right ventricle (RV) and the pulmonary artery arises from the left ventricle (LV) resulting in ventriculoarterial discordance, causing deoxygenated blood to be pumped into the systemic circuit via aorta. Consequently, newborns with TGA typically present with cyanosis during the first month of their life. All infants with TGA will require open heart surgery as the disease is postnatal lethal. There are two main surgeries: 1) atrial switch procedure (Senning/Mustard procedure) and 2) arterial switch procedure (more commonly practiced today). The atrial switch procedure creates an atrioventricular discordance to counteract the ventriculoarterial discordance and reestablish the systemic circulation of the great arteries. However, the venous tunnels surgically created to reroute the systemic and pulmonary venous returns, leaves the patients with a systemic RV which, because of abnormal loading conditions, over time tends to decompensate. The atrial switch procedure is currently superseded by arterial switch procedure where the transposed great arteries are surgically removed and reconnected to their morphological position. The atrial switch procedure has been shown to effectively prolong the patient life to reproductive ages, but the post-surgery management of these patients remains challenging and requires a team of specialized pediatric cardiologists.

Currently, most patients operated by atrial switch have reached adult age, lead active lives, but need ongoing expert care in an adult congenial cardiac center.

2. TGA etiopathogenesis and outcome: the role of genetics

To date, the cause of TGA has been mainly ascribed to maternal teratogenic factors such as maternal infections, obesity, hypertension and diabetes mellitus [2]. Although TGA has been found to be sporadically associated with 22q11.2 deletion, 3p14.3 and heterotaxy syndromes (conditions in which the internal organs are abnormally arranged in the chest and abdomen), the genetic causes of majority of TGA cases remain largely unknown [3–6]. The findings of rare genetic variants and sporadic familial recurrence cases suggest that TGA could be a polygenic disease. Furthermore, the genetic and environmental factors involved in the extremely heterogeneous clinical course after corrective surgery remain largely unknown.

In the current issue of *International Journal of Cardiology,* Woudstra et al. combined clinical and genetic scores to construct a risk stratification model to predict the outcome of adult patients after atrial switch operation for TGA) [1]. For the analysis they use a composite endpoint of symptomatic ventricular arrhythmia, heart failure hospitalization, ventricular assist device implantation, heart transplantation, or mortality. The authors perform a genome-wide association study (GWAS) in TGA patients who underwent atrial switch surgery starting from the late '60s and have reached adulthood. The purpose is to determine the effects of common single nucleotide polymorphisms (SNPs) on event-free survival and to determine if genetic factors may add value to the clinical risk model of poor outcome prediction. The authors build a risk score by combining the polygenic and the clinical scores and show that the new model improves patients risk stratification over clinical factors alone.

The current challenges of polygenic diseases are that: 1) the expression of the disease is affected by a large number of genetic variants which implicates the need to perform either exome (protein coding genes) or whole genome sequencing to identify these genetic variants, 2) although a large number of disease-associated variants have been identified, the individual contribution of each "disease-associated" variant is negligible. Because of these challenges, it is an arduous process to utilize GWA summary statistics to calculate additive genetic risk scores for a specific disease based on the sum of all associated SNPs in a genome. A clear limitation of this study is the small sample size (n = 133) which is known to affect the strength of the GWA findings. However, TGA is a relatively rare disease and the number of TGA patients operated by the atrial switch surgical technique that reached adulthood is small. Another limitation is the lack of genetic diversity of the study, which by design includes a population of mainly North-European subjects. Hence, it is expected that the polygenic risk score calculated from European DNA sequences could not be applied to predict outcome in patients from other races.

Despite its limitations, this study is a first step to elucidate the genetic underpinnings of systemic right ventricular failure in TGA operated patients. The findings support the hypothesis that including genetic variants in risk assessment may be beneficial and suggest that the combined genetic-clinical risk stratification model could lead to actionable and cost-effective prevention care for TGA patients after the

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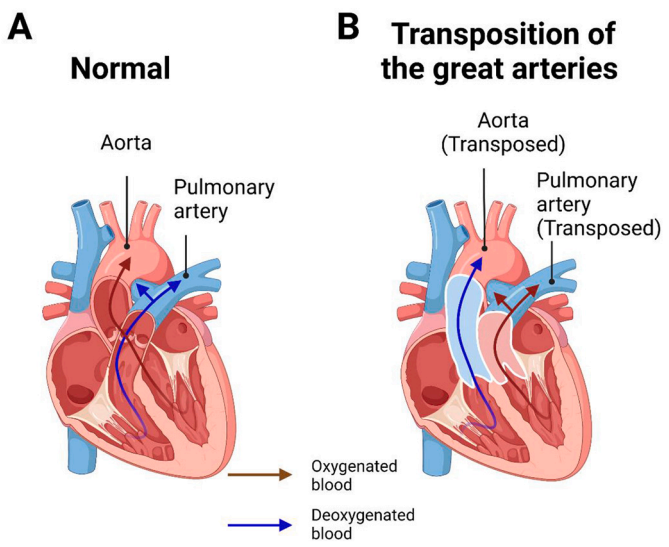

Fig. 1. Dextro-Transposition of the Great Arteries (dTGA). A) Morphology of a healthy heart. The oxygenated blood from the lungs reaches the left atria via the pulmonary veins and gets to the left ventricle which pumps it into the aorta from where it will be transported to the whole body through the systemic circulation. The deoxygenated blood reaches the right atria via the superior and inferior vena cava; from the right aria deoxygenated blood gets to the right ventricle which pumps it into the pulmonary artery which will direct it to the lung through the pulmonary circulation. B) Morphology of a heart with dTGA. The oxygenated blood reaches the left atrium and then the left ventricle, but instead of entering the systemic circulation, it is pumped back to the lung via the pulmonary artery which originates from the left ventricle; On the other hand, the deoxygenated blood which returns to the right atrium and the right ventricle is pumped back to the systemic circulation via the aorta which originates from the right ventricle.

corrective surgery. Hence, the study is a call for further worldwide collaborative research to validate the promising value of genetics in risk prediction in adults with congenital heart diseases.

In summary, the risk score model proposed in this paper should be used with high cautious due to the small sample size and the lack of genetic diversity in the studied population. Clinicians or genetic counseling specialists should be watchful when communicating with patients regarding implementation of the risk scores. The patient should be made aware that being at hight risk does not necessarily mean that he will develop a complication; while having a low score does not mean that he will surely remain complication- free. The key point of using the proposed polygenic risk score is to enhance the awareness of the clinicians toward the TGA patients at higher risk who needs closer follow-ups and individualized therapeutic and lifestyle adjustments.

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Declaration of Competing Interest

No conflict of interest.

References

[1] O.I. Woudstra, D. Skoric-Milosavljevic, B.J.M. Mulder, F.J. Meijboom, M.C. Post, M. R.M. Jongbloed, A.P.J. van Dijk, J.P. van Melle, T.C. Konings, A.V. Postma, C. R. Bezzina, B.J. Bouma, M.W.T. Tanck, Common genetic variants improve risk stratification after the atrial switch operation for transposition of the great arteries, Int. J. Cardiol. (2022 Sep 13), https://doi.org/10.1016/j.ijcard.2022.09.021. S0167-5273(22)01331-6, Epub ahead of print. PMID: 36108765.

[2] X. Liu, W. Chen, W. Li, J.R. Priest, Y. Fu, K. Pang, B. Ma, B. Han, X. Liu, S. Hu, Z. Zhou, Exome-based case-control analysis highlights the pathogenic role of ciliary genes in transposition of the great arteries, Circ. Res. 126 (2020) 811–821.

[3] M.C. Digilio, B. Casey, A. Toscano, R. Calabro, G. Pacileo, M. Marasini, E. Banaudi, A. Giannotti, B. Dallapiccola, B. Marino, Complete transposition of the great arteries: patterns of congenital heart disease in familial precurrence, Circulation. 104 (2001) 2809–2814.

[4] A. De Luca, A. Sarkozy, F. Consoli, R. Ferese, V. Guida, M.L. Dentici, R. Mingarelli, E. Bellacchio, G. Tuo, G. Limongelli, M.C. Digilio, B. Marino, B. Dallapiccola, Familial transposition of the great arteries caused by multiple mutations in laterality genes, Heart. 96 (2010) 673–677.

[5] D. Skoric-Milosavljevic, R. Tadros, F.M. Bosada, F. Tessadori, J.H. van Weerd, O. I. Woudstra, Tjong FVY, N. Lahrouchi, F. Bajolle, H.J. Cordell, A.J. Agopian, G. M. Blue, D. Barge-Schaapveld, M. Gewillig, C. Preuss, E.M. Lodder, P. Barnett, A. Ilgun, L. Beekman, K. van Duijvenboden, R. Bokenkamp, M. Muller-Nurasyid, Group KO-S, H.W. Vliegen, T.C. Konings, J.P. van Melle, A.P.J. van Dijk, R.R.J. van Kimmenade, J.W. Roos Hesselink, G.T. Sieswerda, F. Meijboom, H. Abdul-Khaliq, F. Berger, S. Dittrich, M.P. Hitz, J. Moosmann, F.T. Riede, S. Schubert, P. Galan, M. Lathrop, H.M. Munter, A. Al-Chalabi, C.E. Shaw, P.J. Shaw, K.E. Morrison, J. H. Veldink, L.H. van den Berg, S. Evans, M.A. Nobrega, I. Aneas, M. Radivojkov Blagojevic, T. Meitinger, E. Oechslin, T. Mondal, L. Bergin, J.F. Smythe, L. Altamirano Diaz, J. Lougheed, B.J. Bouma, M.A. Chaix, J. Kline, A.S. Bassett, G. Andelfinger, R.L.F. van der Palen, P. Bouvagnet, S.B. Clur, J. Breckpot, W. S. Kerstjens-Frederikse, D.S. Winlaw, Bauer UMM, S. Mital, E. Goldmuntz, B. Keavney, D. Bonnet, B.J. Mulder, Tanck MWT, J. Bakkers, V.M. Christoffels, C. J. Boogerd, A.V. Postma, C.R. Bezzina, Common genetic variants contribute to risk of transposition of the great arteries, Circ. Res. 130 (2022) 166–180.

[6] M. Unolt, C. Putotto, L.M. Silvestri, D. Marino, A. Scarabotti, M. Valerio, A. Caiaro, P. Versacci, B. Marino, Transposition of great arteries: new insights into the pathogenesis, Front. Pediatr. 1 (2013) 11.

Raffaella Lombardi[a,b], Suet Nee Chen[a,*]

[a] *University of Colorado Cardiovascular Institute, University of Colorado-Anschutz Medical Campus, USA*

[b] *Department of Advanced Biomedical Sciences "Federico II" University of Naples, Naples, Italy*

[*] Corresponding author at: 12700 E. 19th Ave, Aurora, CO 80045, USA.
E-mail addresses: raffaella.lombardi@unina.it (R. Lombardi), Suet.Chen@cuanschutz.edu (S.N. Chen).