Internal and Emergency Medicine (2019) 14:1209–1211
https://doi.org/10.1007/s11739-019-02139-8

IM - COMMENTARY

Left ventricular non-compaction in patients with β-thalassemia: structural remodeling or cardiomyopathy?

George Lazaros[1] · Georgia Vogiatzi[1] · Emilia Lazarou[1] · Charalambos Vlachopoulos[1] · Dimitris Tousoulis[1]

Received: 19 June 2019 / Accepted: 25 June 2019 / Published online: 3 July 2019

In the era of the modern imaging techniques, cardiac magnetic resonance (CMR) has become the key component to confirm or rule out left ventricular non-compaction cardiomyopathy (LVNC), as echocardiography cannot always allow proper visualization of the apex and apical segments [1]. Although initially described and recognized as a rare entity in the general population, after the first report of LVNC in identical twins with β-thalassemia major [2], more and more studies aimed to explore the prevalence and evolution of LVNC in this setting.

In this issue of *Internal and Emergency Medicine*, Bonamini and co-authors [3] add certain interesting findings to the growing literature on the prevalence and the disease progression of the LVNC in patients with β-thalassemia. In this elegant study, in a 7-year period, 560 patients with thalassemia major or intermedia underwent assessment of left ventricle structure, dimensions, and systolic function with CMR, as this diagnostic tool is utilized to this population to evaluate heart iron load and cardiac function. For the assessment of the presence of LVNC, the modified Petersen and the Jacquier methods were applied and the cases which fulfilled the following three criteria were considered positive: (i) diastolic $M_{\text{non-compacted}}/M_{\text{total percentage}} > 25\%$, (ii) diastolic $M_{\text{non-compacted}}/\text{BSA} > 15$ g/m^2 and (iii) diastolic non-compacted/compacted myocardium ratio of > 2.5 in at least one of the segments, excluding the apical. According to the above-mentioned criteria, a diagnosis of LVNC was determined in 44 patients (7.9%).

Interestingly, intracardiac thrombi were not detected with CMR in none of the 560 patients. Moreover, no relationship was found between splenectomy, iron chelation therapy and hematological parameters (serum ferritin and total hemoglobin) with the presence of LVNC, while T2*, time for the evaluation of cardiac and liver siderosis, similarly did not depict any significant difference between β-thalassemia patients with and without LVNC. It should be also emphasized that no adverse events occurred in patients with thalassemia and LVNC during follow-up. In line with this observation, no further dilatation of the left ventricle or significant differences of its systolic function or LVNC mass changes were detected by CMR overtime.

The main finding of the present study consists of the high prevalence of LVNC in β-thalassemia patients, which was 7.9%. This rate is pretty higher as compared with previous reports from echocardiographic studies in the general adult population where the relevant prevalence was between 0.014 and 1.3% [4]. However, a prevalence as high as 13.2% has been reported previously with CMR studies this time, although as it was mentioned by the authors themselves an overestimation could have accounted for this finding [5]. Concerning the methodology applied in the work of Bonamini and co-authors, the study population underwent CMR assessment in the context of a regular control program in a population of patients with β-thalassemia. Nevertheless, some patients may have been selected for measurement based on pre-existing cardiac risk factors. If such factors are potentially linked to LVNC occurrence, this may offer a plausible explanation for the high prevalence of LVNC depicted in this study.

One of the major strengths of this observational study consists of the high number of thalassemia patients included, namely 560, which is the highest recorded for this disorder. It should be also mentioned that the stringent CMR methodology adopted enhances its accuracy. Visual analysis and measurements of CMR parameters were performed by experienced operators. For instance, a more restrictive modification of the original criterion or the ratio of non-compacted to compacted myocardium during the diastole from 2.3 to 2.5 was used [1]. In addition, the criterion of diastolic $M_{\text{non-compacted}}/\text{BSA} > 15$ g/m^2, which was proposed

✉ George Lazaros
glaz35@hotmail.com

[1] First Cardiology Department, Athens Medical School, Hippokration General Hospital, National and Kapodistrian University of Athens, Vas. Sofias 114, 11528 Athens, Greece

by Grothoff was proved to be the most accurate marker for differentiation of LVNC from the LV structural remodeling in β-thalassemia patients [6].

The pathophysiological pathway which increases the incidence on LVNC in β-thalassemia has not been completely elucidated so far. Chronic oxidative damage due to ineffective erythropoiesis and inflammatory stress which triggers myocardial remodeling as well as nutritional disorders (such as carnitine, selenium, and thiamine deficiencies) have been encountered as possible underlying mechanisms [5]. However, the exact chronological relationship between the occurrence of LVNC and the evaluated risk factors cannot be determined. The possible series of events leading to LVNC in β-thalassemia patients are summarized in Fig. 1.

Another important observation of the present study is that despite the lower ejection fraction and the increased indexed LV end-systolic volume detected in β-thalassemia patients with LVNC at baseline, no major changes were observed during the 5.1 years of follow-up based on repeated CMR studies. This holds also true for the amount of the left ventricular non-compacted mass (which is a reliable and accurate marker for the LNVC diagnosis [7]), that remained unchanged as well. From a clinical perspective, we wish to stress once more that it is of paramount importance to understand whether LVNC in β-thalassemia parallels with typical LVNC cardiomyopathy on a clinical and prognostic basis or whether it is a benign condition observed for reasons to be determined in a subgroup of β-thalassemia patients.

In the present study, the authors did not document any impact of LVNC on cardiac mortality or clinical events and concluded that LVNC does not affect overall prognosis. However, it has not been specified which clinical events have been assessed during the observation period and most important, the prognostic impact of this condition beyond this study observation period is not known. This is a crucial issue for an entity like β-thalassemia where the life expectancy has been substantially increased and where cardiac disease remains a primary cause of morbidity and most important, mortality. A thorough cardiological workup may provide important clues on the prognostic relevance of LVNC in β-thalassemic patients. In this line, electrocardiographic ambulatory monitoring, signal-averaged electrocardiography, and QT interval measurement among others could provide valuable information on the arrhythmogenic potential of β-thalassemia patients with LVNC as compared to those without. Toward the same goal, a detailed echocardiographic evaluation ideally with adoption of the new techniques may be useful to unveil the clinical significance of this finding [8].

In conclusion, according to this prospective observational study results, with the adoption of strict CMR criteria, the prevalence of LVNC in patients with major and intermedia β-thalassemia was relatively high, namely ~ 8%. Although functional and structural changes were most commonly detected in the subgroup of LVNC patients, such changes do not seem to worsen overtime, at least in the medium term. Important questions to be answered in the future concern the pathogenesis of LVNC in the context of β-thalassemia syndromes. Should it be elucidated, it could contribute to the adoption of preventive measures and individualized

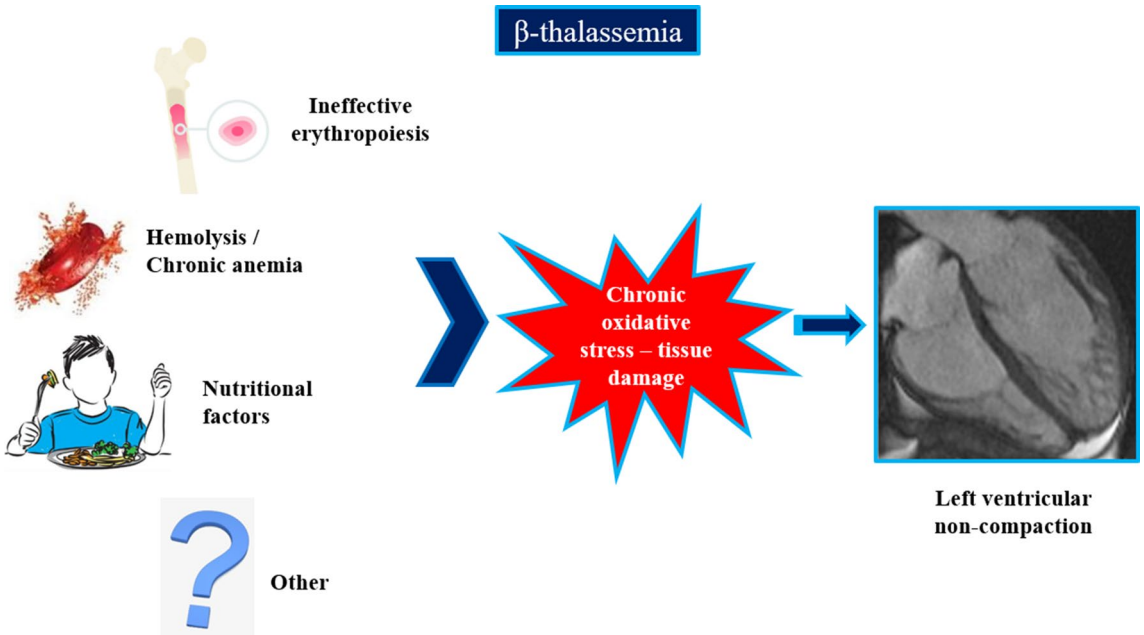

Fig. 1 Possible pathophysiological pathways involved in left ventricular non-compaction in β-thalassemia

treatments aiming at the stabilization or even regression of LVNC. Regarding outcome, the quite reassuring results stemming from this study should be confirmed in properly designed prospective studies with pre-specified clinical outcomes in the long term.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement on human and animal rights All procedures performed in this study were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

References

1. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, Watkins H, Neubauer S (2005) Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 46:101–105
2. Luckie M, Irwin B, Nair S, Greenwood J, Khattar R (2009) Left ventricular non-compaction in identical twins with thalassaemia and cardiac iron overload. Eur J Echocardiogr 10:509–512
3. Bonamini R, Imazio M, Faletti R, Gatti M, Xhyheri B, Limone M, Longo F, Piga A (2019) Prevalence and prognostic impact of left ventricular non-compaction in patients with thalassemia. Int Emerg Med. https://doi.org/10.1007/s11739-019-02114-3
4. Ritter M, Oechslin E, Sütsch G, Attenhofer C, Schneider J, Jenni R (1997) Isolated noncompaction of the myocardium in adults. Mayo Clin Proc 72:26–31
5. Piga A, Longo F, Musallam KM, Veltri A, Ferroni F, Chiribiri A, Bonamini R (2012) Left ventricular noncompaction in patients with β-thalassemia: uncovering a previously unrecognized abnormality. Am J Hematol 87:1079–1083
6. Grothoff M, Pachowsky M, Hoffmann J, Posch M, Klaassen S, Lehmkuhl L, Gutberlet M (2012) Value of cardiovascular MR in diagnosing left ventricular non-compaction cardiomyopathy and in discriminating between other cardiomyopathies. Eur Radiol 22:2699–2709
7. Chiodi E, Nardozza M, Gamberini MR, Pepe A, Lombardi M, Benea G, Mele D (2017) Left ventricle remodeling in patients with β-thalassemia major. An emerging differential diagnosis with left ventricle noncompaction disease. Clin Imaging 45:58–64
8. Di Odoardo LAF, Giuditta M, Cassinerio E, Roghi A, Pedrotti P, Vicenzi M, Sciumbata VM, Cappellini Pierini A (2017) Myocardial deformation in iron overload cardiomyopathy: speckle tracking imaging in a beta-thalassemia major population. Intern Emerg Med 12:799–809