LETTERS TO THE EDITOR

Genetic Testing Is Not Required for Diagnosing Left Ventricular Hypertrabeculation / Non-Compaction

TO THE EDITOR:

COMMENTARY

With interest we read the article by Floria et al. about challenges and controversies concerning the etiology, diagnosis, and treatment of left ventricular hypertrabeculation / non-compaction (LVHT) (1). We have the following comments and concerns.

Concerning the taxonomy, there is no difference between noncompaction, noncompaction cardiomyopathy, left ventricular noncompaction, and LVHT. All these terms describe the same entity.

Concerning the first description of LVHT, there is no consensus on this point. Definitively however, Grant et al. did not provide the first description of LVHT. He described a condition in which intertrabecular recesses communicated with the pericardial blood supply (2). Engberding et al. were the first to describe LVHT on echocardiography. Biventricular hypertrabeculation was first mentioned by Westwood et al. in 1975 and by Feldt et al. in 1969 (2). Probably, LVHT had been described for the first time in 1932 at autopsy of a newborn with aortic atresia and a coronary-ventricular fistula (3).

There is no causal relation between LVHT and any of the multiple mutated genes having been reported in association with LVHT. For none of the mutations so far reported a causal relation with LVHT had been ever established.

Not only mutations in the taffazin, α-DTNA, ZASP, LMNA, α-cardiac actin, or NKX2.5 genes have been reported but also in the dystrophin, DMPK, TPM1, RYR1, ITGA7, MYH7B, MYH7, LAMP2, GAA, BGEI, MADD, SDH, COL7A1, MMACHC, PMP22, FXN, β-globin, PLEC1, and GLA genes (4).

In familial cases of LVHT not only an autosomal dominant or X-linked trait of inheritance had been reported, but also autosomal recessive traits and maternal traits of inheritance (5,6).

Differentiation between metabolic and genetic disease associated with LVHT is misleading since metabolic disease is most frequently genetic. LVHT may be associated with genetic or non-genetic disease but may also occur in the absence of any concomitant non-cardiac or additional cardiac disorder.

ZASP mutations associated with LVHT have not only been described in a family and three sporadic cases (7) but also in other patients carrying a cypher/ZASP/LDB3 mutation (6).

We do not agree with the statement that cardiac MRI is the method of choice to detect LVHT. The best method to detect LVHT is still under debate but most frequently applied is echocardiography, which is widely available and most easily applicable. Both methods produce false positive and false negative results. To assess which of the two methods is more favorable cannot be solved as long as there is no golden standard for diagnosing LVHT, which is needed to compare both methods.

For diagnostic and prognostic purposes it makes sense to distinguish between isolated and non-isolated LVHT since the prognosis of
non-isolated LVHT is worse than that of isolated LVHT.

Overall, this review could profit from some clarifications concerning definition, genetic background, and diagnosis of LVHT. The more appropriate diagnostic criteria are applied, the more accurate will be the diagnosis and the more efficient the treatment. In LVHT patients not only the heart but other tissues require focused attention, particularly if there is a concomitant neuromuscular disorder.

**Keywords:** non-compaction, unclassified cardiomyopathy, myopathy, neuropathy, cardiac involvement, diagnostic criteria, mutation, genetics

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The European Society of Cardiology in the 2008 Classification of the cardiomyopathies (3) uses the term “left ventricular non-compaction” while worldwide specialists publishing in the American Journal of Cardiology (4,5) use the term of “non-compaction cardiomyopathy” (NCC) to define the same pathology. In our paper, we used simultaneously both terms, NCC being more prevalent in our work as this nomenclature is widely used and known by specialists in our country.

According to Practical Cardiovascular Pathology by Allen Burke and Fabio Tavora, in left ventricular non-compaction three morphologic patterns have been described: spongy myocardium, polypoid trabeculations, and anastomosing trabeculae (6). In other words, the term spongy myocardium is just a gross finding that was first identified by Grant (7) in 1926 as stated in our article without thorough knowledge on the underlying disease in its clinical and genetically determination. Under these circumstances, we never mentioned that Grant et al. did not provide the first description of left ventricular hypertrabeculation because he was the first that only identified „the spongy myocardium“. Udeoli et al. state that left ventricular non-compaction was described for the first time in 1932 but fail to provide a reference in order to sustain their affirmation (8). You said „probably, left ventricular hypertrabeculation...
had been described for the first time in 1932”. Obviously this aspect is controversial.

Thank you very much for the complementary comments related to the gene mutations reported as to be in association with left ventricular hypertrabeculation. Klaasen et al (9) and Probst et al. (10) stated that left ventricular non-compaction is triggered by sarcomere genes mutations. In one of your article (11) you conclude “most frequently, LVHT is associated with mutations in genes causing muscle or cardiac disease or with chromosomal disorders” thus sustaining a possible causal relation.

Echocardiographic pitfalls in diagnosing left ventricular non-compaction have been widely described, including your paper (12). Compared to echocardiography, MRI is reproducible and not prone to subjective interpretation. Several physicians can review MRI images at any time if doubts exist. We did not affirm that „cardiac MRI is the method of choice to detect left ventricular hypertrabeculation”. We noted that suspected NCC (by echocardiography) must be completed by MRI because „it is difficult to know which echocardiographic criteria are “best” for making a valid diagnosis of NCC (there are a lots: California (13), Zurich (14), Vienna (15) or Milwaukee (16)) and because „universally accepted definition of NCC is still lacking both on echocardiography and on MRI”. In addition, differential diagnoses are challenging because there is no diagnostic “gold standard”.

We agree that a distinction between isolated and non-isolated left ventricular non-compaction has to be made, as the form associated with other disorders is characterized by a worse outcome.

Overall, your commentaries are for a real benefit in order to clarify some inconsistencies. Since we (the authors) are not specialists in genetics or in molecular biology, all the information regarding the pathophysiological background is strictly based on data contained in the literature cited. Moreover, your letter-to-the-editor (17) submitted in response to the article entitled “Familial Left Ventricular Non-compaction Associated with a Novel Mutation in the Alpha-cardiac Actin Gene” (18) was not yet published when our paper was in press, otherwise we would have used this information.

Our paper was entitled “Left Ventricular Non-Compaction - Challenges and Controversies”, (2) because there are still in debate the definition, the pathophysiology, the appropriate diagnostic criteria or the treatment of this entity. Obviously your commentaries are another proof of the fact that left ventricular non-compaction provoke more challenges and controversies.

No potential conflict of interest relevant to this letter was reported.

REFERENCES

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