LETTERS TO THE EDITOR

Do Cypher Gene Mutations Cause Left Ventricular Noncompaction With Subclinical Myopathy?

In their article, Vatta et al. (1) showed that dilative cardiomyopathy (DCM) is associated with cypher (Z-band alternatively-spliced PDZ-motif-protein) gene mutations in exons 4, 6, and 10 in 6% of the cases. Additionally, mutant cypher-gene-transfected myoblasts developed cytoskeletal disarray (1). Their findings raise the following concerns: It is not mentioned which clinical and echocardiographic criteria for DCM were applied. Were patients with DCM due to coronary heart disease also included, or did all patients have normal coronary angiograms? It remains unclear according to which criteria left ventricular hypertrabeculation/noncompaction (LVHT/NC) was diagnosed (2,3). It is not indicated whether patients with DCM were consecutively or selectively included and how many centers recruited the patients during which period. Did relatives of all 100 patients or only those of cypher-gene mutation carriers undergo clinical cardiological and neurologic examination, creatine-kinase determination, and genetic studies? How was cardiac affection defined? It is unclear why patient II:1 (family 065) was classified as cardiologically normal, although, according to their Table 3, no echocardiographic examinations were performed. Furthermore, the description of a “mildly dilated left ventricle” in patient III:1 does not match Table 3, indicating that echocardiography was not carried out at all in this patient. Concerning the authors’ speculations that mutations in the skeletal muscle cypher-isoform may go along with fatigue and exercise intolerance, it would be interesting to know whether any of the mutation carriers complained about symptoms suggestive of a neuromuscular disorder. How do the authors explain that cypher knock-out mice develop severe myopathy, whereas humans with cypher-mutations were neurologically normal? Normal clinical neurologic examination and normal creatine kinase, however, do not rule out myopathy. It is not clear whether the skeletal muscle cypher-isoform is regularly expressed in the skeletal muscle. Did any of the patients undergo muscle biopsy? It appears as if the 200 control subjects had not undergone clinical cardiological or neurologic investigations. Did any of these probands have DCM or LVHT/NC? It remains unclear how mutations in exon 4 were exclusively associated with LVHT/NC although the inclusion criterion was DCM. Did the authors find muscle carriers without clinical affection? It is not mentioned how many of the patients with cypher mutations also had LVHT/NC. Concerning their Table 3, the title is misleading because not all patients had cypher-mutations. It also is not explained from which measurements the standard deviation was calculated. Were patients repeatedly investigated or does it derive from a non-described control group? Figure 1B erroneously shows a 352M instead of a I352M mutation. The authors do not mention that LVHT/NC may be also associated with mutations in the DMPK, DMD, AMPD1, and mitochondrial gene(s) (4–6). Overall, the study lacks proper characterization of the phenotype and control group. Criteria for cardiac affection are ambiguous. Although the study nicely shows cypher-mutations to be associated with LVHT/NC, the prevalence of this association remains uncertain. To further clarify the pathogenetic background of LVHT/NC, we suggest that patients with LVHT/NC should undergo thorough investigation of the skeletal muscle in the light of previous findings, according to which LVHT/NC is associated with myopathies in up to four-fifths of these patients (3).

Josef Finsterer, MD, PhD
Postfach 20
1180 Wien, Austria
E-mail: duarte@aonmail.at

Claudia Stöllberger, MD

doi:10.1016/j.jacc.2004.06.007

REFERENCES


REPLY

We would like to thank Drs. Finsterer and Stollberger for their comments. Our study (1) was performed on patients with left ventricular (LV) dysfunction associated with classic dilated cardiomyopathy (DCM) or left ventricular noncompaction (LVNC). All patients had standard echocardiographic evaluations and/or cardiac magnetic resonance imaging with selected cases having cardiac catheterization and angiography. Because the vast majority of patients evaluated either had classic autosomal-dominant inheritance and/or were of a young age, coronary angiography was not indicated in many of these subjects. In addition, no patient had evidence of regional wall abnormalities on echocardiogra-