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Primary or Secondary Complex-I Defect in Left Ventricular Hypertrabeculation /Noncompaction

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Short title: Genetics of noncompaction

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Letter to the Editor:

With interest we read the article by Dhar et al. about a newborn female with non-isolated left-ventricular hypertrabeculation / noncompaction (LVHT), noncompaction of the right ventricle, left ventricular wall thickening, pulmonary valve stenosis, and multiple septal defects who was followed up for $7y^1$. Cardiac abnormalities were attributed to the deletion 22q11 [1]. Additionally, complex-I deficiency without detection of an appropriate mutation was described.¹. We have the following comments and concerns.

We disagree with the notion that LVHT is a congenital disorder in each case. In some cases LVHT develops after birth, during adulthood, such as in patients with neuromuscular disorders (NMDs)², professional athletes³, and pregnant females (acquired LVHT)⁴.

We also disagree with the statement that LVHT is a genetic defect. Despite a frequent association with mutations in >30 genes and a number of chromosomal defects, it has never been proven that LVHT is a direct phenotypic feature of one of these genetic defects. Arguments against a causal relation between these genetic defects and LVHT are that in the light of the extensive genetic heterogeneity it is quite unlikely that these variable defects cause the same morphological abnormality, that LVHT most frequently does not segregate with these genetic defects, that a given genetic defect associated with LVHT in one family member may be associated with another cardiac abnormality in family members, and that LVHT can be acquired. Arguments in favour of a causal relation however, are that LVHT may occur familiarly, at least in some of the LVHT cases and that the frequency of LVHT can be high in genetic disorders such as Barth syndrome or mitochondrial disorders (MIDs). However, it has to be admitted that in most of the reported LVHT cases no systematic family screening for LVHT has been carried out. In certain cases LVHT occurs in more than a single family member. Were family members other than the index cases investigated for LVHT?

It is reported that pulmonary stenosis became less during follow up and that the multiple ventricular septal defects spontaneously regressed. Did also LVHT change over time, did the extension of LVHT change, did it regress as has been previously reported, did subendocardial fibrosis develop or late gadolinium enhancement (LGE) on cardiac MRI? Did the patient develop any of the known complications of LVHT, such as embolism, heart failure, or arrhythmias?

The authors found that the described patient had a complex-I defect on biochemical investigations¹. Which was the exact amount of activity measured on biochemical investigations? Which were the reference limits in the laboratory which carried out the investigation? Could the complex-I defect be secondary?

Did the authors consider a double trouble in the described patient? A chromosomal defect plus a mutation in one of the nuclear genes encoding subunits of complex-I or assembly factors of respiratory chain complexes?

Were other family members investigated for a mitochondrial disorder? Did any of the other family members present with clinical features of a mitochondrial defect? Was complex-I deficiency also found in the parents of the child? Did the child present with phenotypic features other than cardiac attributable to a complex-I defect?

Overall, this interesting case merits further work-up with regard to cardiac and neurological involvement in other family members and investigations for mutations in genes known to cause complex-I defects.

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