Causality between myopathic hypotonia-cystinuria syndrome (HCS) and noncompaction (LVHT) is not compelling

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Letter to the Editor

We read with interest the article by Kılıç et al. about 2 siblings from consanguineous parents with hypotonia-cystinuria syndrome (HCS) due to a homozygous deletion of exons 4–10 in the *SLC3A1* gene and of exons 4–14 of the *PREPL* gene of whom one child presented with dilated cardiomyopathy and left-ventricular hypertrabeculation (LVHT) / noncompaction (Kılıç et al. 2018). We have the following comments and concerns.

Though LVHT is frequently associated with chromosomal defects (Finsterer 2009), a causal relation has never been proven. Thus, it is conceivable that LVHT and HCS were not causally related. An argument for the absence of a causal relation between genetic defects and LVHT is that LVHT can be acquired, not being present at birth. Acquired LVHT is rare but has been reported in several neuromuscular disorders, in pregnant females, and in professional athletes (Finsterer and Stöllberger 2014). Further arguments against causality between LVHT and HCS are that LVHT may disappear, for instance after pregnancy, and that familial occurrence is rare. Additionally, cardiac involvement in HCS has not been reported previously, why it cannot be excluded that the simultaneous occurrence of LVHT and HCS in case 1 is coincidental. A further argument for the assumption that LVHT was independent of HCS is that only one of the two siblings had LVHT.

Arguments in favour of a causal relation, on the other hand, are that, though rare, LVHT may occur familiarly (Finsterer and Stöllberger 2016), and since the apex, where LVHT occurs most frequently, is not always easy to visualise, and many cardiologists are still not familiar with LVHT, LVHT can be easily overlooked. Thus, it is conceivable that HCS cases from the literature were either not investigated cardiologically at all or LVHT was missed in all these other cases. To find out if LVHT in the index case was familial it would be eligible to know if also the parents were echocardiographically investigated and if LVHT was detected in either of them. Family members of index cases with LVHT need to be prospectively screened for LVHT since it is most commonly asymptomatic and may remain asymptomatic during the entire life.

Since HCS may manifest with myopathy, it would be of value to know which muscle groups were particularly involved in the two presented cases and if hypotonia was attributable to involvement of the skeletal muscle or due to cerebral involvement.

Overall, causality between HCS and LVHT remains unproven and the cause of hypotonia remains speculative.

Author contribution JF: design, literature search, discussion, first draft, CS: literature search, discussion, critical comments.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

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