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Letter to the Editor

To clarify the cause of SIDS, not only a molecular, but also a biochemical, morphological, pathoanatomical, and toxicological autopsy is required

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Letter to the Editor

We were interested to read the article by Son *et al*. on a retrospective study on the prevalence of mutations in the cardiac RYR2 receptor gene in 249 patients with sudden infant death syndrome (SIDS), 45 with SIDS-A and 204 with SIDS-B [1]. Two of the included patients were found to have an RYR2 mutation [1]. It was concluded that post-mortem genetic analysis should be performed in SIDS cases [1]. The study is appealing, but some points should be discussed.

Firstly, it remains unproven whether ventricular arrhythmias due to the described RYR2 mutations were actually responsible for SIDS in the two children reported [1]. Was there any evidence of arrhythmias, syncope or presyncope in these two patients prior to SIDS? Was an ECG ever recorded in these two patients that indicated cardiac arrhythmias? Has echocardiography revealed cardiomyopathy with or without heart failure?

The second point is that a panel examination is not sufficient to identify genetic causes of SIDS. To clarify whether mutations in any of the genes associated with cardiac arrhythmias or cardiomyopathies are ultimately responsible for SIDS, it would have been imperative to perform whole-exome sequencing (WES) or even whole-genome sequencing (WGS).

Third, SIDS may be due not only to cardiac causes, but also to many other mechanisms that have been proposed to explain sudden infant death syndrome. These include Takotsubo syndrome (TTS), neurogenic pulmonary edema or sudden unexpected death in epilepsy (SUDEP). Before SIDS can be attributed to ventricular arrhythmias due to RYR2 mutations, all risk factors for SIDS must be excluded in all included patients. Risk factors for SIDS include not only maternal alcoholism, male gender, prematurity, maternal smoking or sleeping positions, but also late or no prenatal care, low birth weight, family history of SIDS, bed sharing, mothers under 20, hyperthermia, smoking and pregnancy, infections, sleeping on a soft surface, recent illness, immunizations, living in poor conditions, loose blankets, pillows or other items, multigravida, breastfeeding, ethnicity, temperature, brain defects and cribs [2]. Since the study was obviously conducted during the pandemic, SARS-CoV-2 infection or vaccination must also be excluded as a cause of SIDS.

The fourth point is that RYR2 mutations have been blamed for ventricular arrhythmias triggered by physical or strenuous activity [1]. However, if ventricular arrhythmias due to RYT2 mutations are truly responsible for SIDS, they should not occur during sleep or, when awake, at rest. This is an argument against RYR2 variants being responsible for SIDS in a large proportion of patients.

The fifth point is that central nervous system (CNS) disorders potentially responsible for SIDS were not systematically excluded in the study cohort [1]. Possible CNS causes of SIDS include cerebrovascular disease, encephalitis/meningitis, epilepsy, intoxication, neoplastic or immunologic diseases. Therefore, an autopsy of the brain must always be performed in SIDS patients.

In summary, this interesting study has limitations that put the results and their interpretation into perspective. Removing these limitations could strengthen the conclusions and reinforce the message of the study. All outstanding questions need to be clarified before readers can uncritically accept the conclusions of the study. To clarify the cause of SIDS, not only a molecular but also a biochemical, morphological, pathoanatomical and toxicological autopsy is required.

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