

Letter to the Editor

Diagnose SUDEP not exclusively upon autopsy reports

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With interest we read the article by Keller et al. about a forensic autopsy study of 167 patients with sudden unexpected death in epilepsy (SUDEP), in which electronic autopsy reports were electronically screened for appropriate search terms and selected for consensus decision about SUDEP as the cause of death (COD) according to the Nashef

criteria by two independent neurologists [1]. It was found that 108 patients had definite, 34 definite-plus, 22 possible, 1 probable, and 2 near-SUDEP and concluded that the frequency of SUDEP correlates negatively with age and that SUDEP may be underappreciated in elder adults [1]. The approach is appealing but has several limitations.

The first shortcoming is that several risk factors for SUDEP were not included in the algorithm for identifying SUDEP patients, which include adherence to anti-seizure drug (ASD) therapy, drug-drug interactions, seizure frequency, seizure type, and ASD serum levels [2]. Among the comorbidities, terms such as heart failure, arrhythmias, atrial fibrillation, QT-prolongation, pulmonary edema, or autonomic neuropathy were not considered.

A second limitation is that autopsies were not carried out with regard to the presence of acute heart failure or Takotsubo syndrome (TTS), also known as stress cardiomyopathy or broken-heart syndrome. TTS is suspected to play a pathophysiological role in SUDEP [3]. Though having been identified and documented as the cause of SUDEP in only a few cases [4]. TTS may be under diagnosed because alertness for TTS as the cause of SUDEP is still low and because autopsy has limited possibilities to confirm TTS as COD.

A third limitation is that troponin or pro-brain natriuretic peptide (pro-BNP) levels were not determined post mortem to assess if there was acute heart failure or TTS. Pro BNP remains stable after death and is applicable as a forensic biomarker for acute heart failure due to any type of cardiomyopathy, arrhythmia, myocarditis, or coronary heart disease [5]. The value of post mortem troponin is controversially discussed. On the one hand, there are studies confirming its value for the documentation of myocardial damage [6]. On the other hand, there are studies showing that post mortem troponin is neither specific nor useful for documenting myocardial damage as COD [7].

A fourth shortcoming is that autopsies did not specifically look for neurogenic pulmonary edema (NPE), also known as Takotsubo of the lungs [8]. NPE has been speculated to play a pathophysiologic role in the occurrence of SUDEP [8]. NPE may be triggered by seizures and may result in impaired oxygen uptake, leading to generalised hypoxia and eventually death.

A fifth shortcoming is that the brain was not included in autopsy. Since seizures may trigger cerebral vasoconstriction syndrome [9] and cerebral vasoconstriction syndrome may lead to ischemic stroke, [10] it should be excluded that SUDEP patients died from seizure-induced ischemic stroke.

Overall, this interesting study has limitations, which should be accomplished before drawing conclusions as those presented. The pathophysiology associated with SUDEP is more complex than anticipated why autopsy may not be the only means to confirm SUDEP. The retrospective evaluation of electronic autopsy reports may lead to underestimation of the SUDEP prevalence.

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REFERENCES

1. Keller AE, Ho J, Whitney R, Li SA, Williams AS, Pollanen MS, Donner EJ. Autopsy-reported cause of death in a population-based cohort of sudden unexpected death in epilepsy. *Epilepsia* 2021 Jan 5. doi: 10.1111/epi.16793.
2. May TW, Israel CW. Plötzlicher unerwarteter Tod bei Epilepsie (SUDEP): Epidemiologie, kardiale und andere Risikofaktoren [Sudden unexpected death in epilepsy (SUDEP): Epidemiology, cardiac and other risk factors]. *Herzschrittmacherther Elektrophysiol* 2019; 30: 274-286.
3. Stöllberger C, Wegner C, Finsterer J. Seizure-associated Takotsubo cardiomyopathy. *Epilepsia* 2011; 52: e160-7.

4. Finsterer J, Bersano A. Seizure-triggered Takotsubo syndrome rarely causes SUDEP. *Seizure* 2015; 31: 84-7.
5. Sabatasso S, Vaucher P, Augsburger M, Donzé N, Mangin P, Michaud K. Sensitivity and specificity of NT-proBNP to detect heart failure at post mortem examination. *Int J Legal Med* 2011; 125: 849-56.
6. Aissaoui A, Haj Salem N, Zaqout A, Boughattas M, Belhaj M, Mosrati MA, Chadly A. Intérêt du dosage post-mortem des troponines I cardiaques dans l'identification des lésions myocardiques Cardiac troponin I and the post-mortem diagnosis of myocardial damage. *Ann Cardiol Angeiol (Paris)* 2013; 62: 248-52.
7. Rahimi R, Dahili ND, Anuar Zainun K, Mohd Kasim NA, Md Noor S. Post mortem troponin T analysis in sudden death: Is it useful? *Malays J Pathol.* 2018 Aug; 40 (2): 143-148.
8. Finsterer J. Neurological Perspectives of Neurogenic Pulmonary Edema. *Eur Neurol* 2019; 81: 94-102.
9. Hess R. Epilepsie und Kopfschmerzen Epilepsy and headaches (author's transl). *EEG EMG Z Elektroenzephalogr Elektromyogr Verwandte Geb* 1977; 8: 125-36.
10. Caria F, Zedde M, Gamba M, Bersano A, Rasura M, Adami A, Piantadosi C, Quartuccio L, Azzini C, Melis M, Luisa Delodovici M, Dallochio C, Gandolfo C, Cerrato P, Motto C, Melis F, Chiti A, Gentile M, Bignamini V, Morotti A, Maria Lotti E, Toriello A, Costa P, Silvestrelli G, Zini A, De Giuli V, Poli L, Paciaroni M, Lodigiani C, Marcheselli S, Sanguigni S, Del Sette M, Monaco S, Lochner P, Zanferrari C, Anticoli S, Padovani A, Pezzini A; Italian Project on Stroke at Young Age (IPSY) Investigators. The clinical spectrum of reversible cerebral vasoconstriction syndrome: The Italian Project on Stroke at Young Age (IPSY). *Cephalalgia* 2019; 39: 1267-1276.