

**Editorial Commentary****Energy drinks and sudden death: If it swims like a duck ...**

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Medicine is fascinating because it is much more than just science. It intermingles with the art of healing, and its progress not infrequently springs from a mix of intuition, common sense, and daring. We might have never heard of the cardio-auditory syndrome, better known as the Jervell and Lange-Nielsen syndrome, if Professor Anton Jervell and his associate, Fred Lange-Nielsen, had not decided to report the bizarre story of their first family in 1957.<sup>1</sup> Indeed, as their article was published, Levine and Woodworth in Boston rushed to send to the *New England Journal of Medicine* their own similar case stressing that they had observed their patient for several years but had hesitated before reporting it because they feared that “these extraordinary features might be regarded just as coincidental.”<sup>2</sup> In other words, they were afraid of making statements or of drawing conclusions on facts that might have been in association just by chance alone.

The phenomenon is far from new, and medical literature abounds in examples of spurious associations, frequently the consequence of subgroup analyses conducted with enthusiasm and accepted without blinking. Some have had negative consequences, whereas some were funny.<sup>3</sup> A notorious example is the one that occurred in the ISIS-2 trial (Second International Study of Infarct Survival). The trial showed the overwhelming benefit of aspirin over placebo, but a subgroup analysis by astrological star signs identified 2 (Gemini and Libra) for which aspirin had an adverse effect!<sup>3</sup> Clearly, common sense is required before accepting, as real, results that may have occurred by chance. However, one should not forget the lesson of the Jervell and Lange-Nielsen syndrome that was brought to light by Jervell’s decision to publish his observation despite its being so odd.

This issue of the *Journal* includes an article important for various reasons but that deserves special credit for having overcome the frequently encountered hesitation, especially by respected medical scientists, to sticking their neck out on something for which critics might say “it’s just an association

by chance,” as illustrated before. Martinez and colleagues,<sup>4</sup> from Mike Ackerman’s group at Mayo Clinic, describe their experience regarding sudden cardiac arrest (SCA) occurring in proximity to consumption of energy drinks in patients with underlying genetic heart diseases. They reviewed the medical records of 144 SCA survivors and found that 7 (5%; 6 female patients; mean age,  $29 \pm 8$  years) experienced an unexplained SCA associated temporally with energy drink consumption. Of these, 2 had long QT syndrome (LQTS), 2 had catecholaminergic polymorphic ventricular tachycardia (CPVT), and the remaining 3 were diagnosed with idiopathic ventricular fibrillation. Their conclusion is that 5% of SCA survivors experienced the event in proximity to consuming an energy drink. They recognize the need of larger cohort studies but consider it correct to sound an early warning on this potential risk.

Martinez and colleagues, independently of their actual data, place the issue of energy drinks in a broader context and note that how, during the last several years, there has been a major increase in their consumption, with significant revenues (\$58 billion at the end of 2022) and with Red Bull and Monster leading the industry in sales. They also wisely call attention to the fact that as energy drinks are classified as dietary supplements rather than medications, monitoring by the US Food and Drug Administration is not required. They are aware that the issue of potential arrhythmic risk associated with energy drinks is not novel and that several reports, mostly anecdotal, and a few studies of their effect on cardiovascular parameters have been published. However, the fact remains that theirs is the first study specifically designed to explore the potential association between energy drinks and SCA.

Already 20 years ago, one of us (P.J.S.) was involved in a medicolegal case outside Europe in relationship to an episode of SCA with catastrophic brain damage in a 26-year-old woman with LQTS that followed 8 days of drinking the energy drink Ripped Fuel. In our large LQTS cohort, we are aware of 2 cases of SCA, 1 lethal, that occurred during

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physical and emotional stress in close temporal relation with intake of energy drinks. Anecdotal cases of life-threatening arrhythmias or of emergency department admissions in conjunction with intake of energy drinks have been reported.<sup>5,6</sup> One study, by Semsarian's group,<sup>7</sup> assessed the cardiovascular responses to energy drinks in 24 patients with LQTS. Importantly, 3 (12.5%) had an increase in their QTc  $\geq 50$  ms, a biologically relevant and clinically dangerous QTc increase, especially in patients who by definition have abnormally long QT intervals. In a somewhat similar study, Chorin and coworkers<sup>8</sup> investigated the effect of drinking grapefruit juice on QTc in healthy volunteers and in LQTS patients; they found that grapefruit juice prolongs the QT interval in general and more so in LQTS patients, which suggests that certain food may also become dangerous for LQTS patients. We have already reviewed some of these studies and called attention to potentially significant risks for patients with LQTS or with reduced cardiac electrical stability.<sup>9</sup>

An important and specific contribution by Martinez and colleagues lies in not having hesitated before warning patients with channelopathies, such as LQTS and CPVT, to avoid, if possible, these drinks. This is not only important but also interesting because, at least for the last 10–15 years, our group has been regularly recommending to our young channelopathies patients, and especially teenagers, to avoid energy drinks. We, as well as the Mayo Clinic group, are perfectly aware that there is no clear and definitive evidence that energy drinks indeed cause life-threatening arrhythmias and that more data are necessary, but we would be remiss if we were not sounding the alarm. At one point, clinical experience, solid understanding of pathophysiology, and common sense should join and speak up. It is well known that sympathetic activation can be arrhythmogenic and that this effect is largely mediated by norepinephrine and epinephrine release. Emotional stress acts in the same way, and so do caffeine and taurine. The use of energy drinks at the time of physical or psychological stress acts synergistically to increase the probability of life-threatening arrhythmias, especially in the presence of LQTS or CPVT. For the general population, the actual risk could be low; but for patients with channelopathies and with ischemic heart disease, it could be high, and often these patients are still asymptomatic and without a diagnosis.<sup>6</sup> Yes, admittedly, we have no final proof that the association is causal, but old common sense often can be of help: "If it looks like a duck, if it swims like a duck, and quacks like a duck, then it probably is a duck."

More data are necessary, and everyone can help. One of the best ways to deal with rare diseases or uncommon events

is to create a registry. We did it in 1979 with Art Moss for LQTS and in 2015, with Lia Crotti and Mike Ackerman, for calmodulin mutations. We will do it now for this serious issue: anyone who has direct knowledge of SCA occurring in temporal proximity with the consumption of energy drinks is invited to contact either one of us or Mike Ackerman at Mayo Clinic as we had already decided in the past to create such a registry.

For the time being, we will continue to alert our patients with channelopathies to avoid energy drinks as much as possible because safety comes first. At the same time, the US Food and Drug Administration should look seriously into this matter and specifically into the biologic effects of the substances included in the so-called dietary supplements. Safety first.

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