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Is a History of Seizures an Important Risk Factor for Sudden Cardiac Death in Young Athletes?

Elizabeth D. Paratz, MBBS, PhD, FRACP[1,2,3*,]
Ingrid E. Scheffer, MBBS, PhD, FRACP[3,7]
Christopher Semsarian, MBBS, PhD, MPH, FRACP[4,5,6]

Address
[*,1]Baker Heart & Diabetes Institute, 75 Commercial Rd, Prahran VIC 3181, Australia
Email: elizabeth.paratz@baker.edu.au
[2]St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy VIC 3065, Victoria, Australia
[3]Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne, Parkville VIC 3004, Australia
[4]Agnes Ginges Centre for Molecular Cardiology, at Centenary Institute, The University of Sydney, Sydney, Australia
[5]Faculty of Medicine and Health, University of Sydney, Sydney, Australia
[6]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia
[7]Department of Medicine, University of Melbourne, Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia

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Abstract

Purpose of Review This review examines the significance of seizures in young athletes and the complex inter-relationship between seizures, epilepsy, and sudden cardiac death.
Recent Findings A history of seizures may reflect a diagnosis of epilepsy, which should be medically optimized for athletic participation. Epilepsy is associated with sudden unexplained cardiac death (sudden unexplained death in epilepsy, SUDEP), with multiple genetic links identified to define some patients as experiencing a "cardiocerebral channelopathy." It is also important to consider that a history of seizures may reflect a misdiagnosis of cardiac syncope, requiring careful cardiac evaluation and risk stratification.
Summary A history of seizures in a young athlete is important to characterize fully and investigate as required. The association of seizures with young sudden cardiac death is still under investigation.

Introduction

Sudden cardiac death (SCD) occurs in approximately 1 in 60,000 athletes [1]. Many professional sporting bodies conduct screening programs for elite athletes, undertaking a medical and family history, physical examination, and cardiac investigations in order to mitigate the risk of SCD in their athletes. As part of a cardiac history, symptoms such as chest pain, shortness of breath, and syncope are of high priority to identify. A history of seizures or epilepsy may appear less relevant for cardiac screening purposes; however, 15% of young athletes with sudden unexplained death have a past history of seizures and/or epilepsy [2]. Furthermore, a study of children and young adults with sudden cardiac arrest identified that 24% had a history of syncope or unexplained seizures, with an average of 2.6 seizure episodes over a period of 6 years prior to their life-threatening cardiac arrest [3]. Studies of athletes experiencing unexplained sudden cardiac arrest during exercise have reported a preceding history of syncope or seizure in 55% [4]. The relevance of seizure as a potential cardiac symptom is related to either (i) the possibility of underlying epilepsy with potential for a sudden death event, or (ii) misdiagnosed anoxic seizures indicating the presence of ventricular arrhythmias and an underlying channelopathy (Fig. 1). This review explores the significance of a history of seizures in young athletes, examines potential implications for SCD risk, and provides guidance for the treating practitioner.

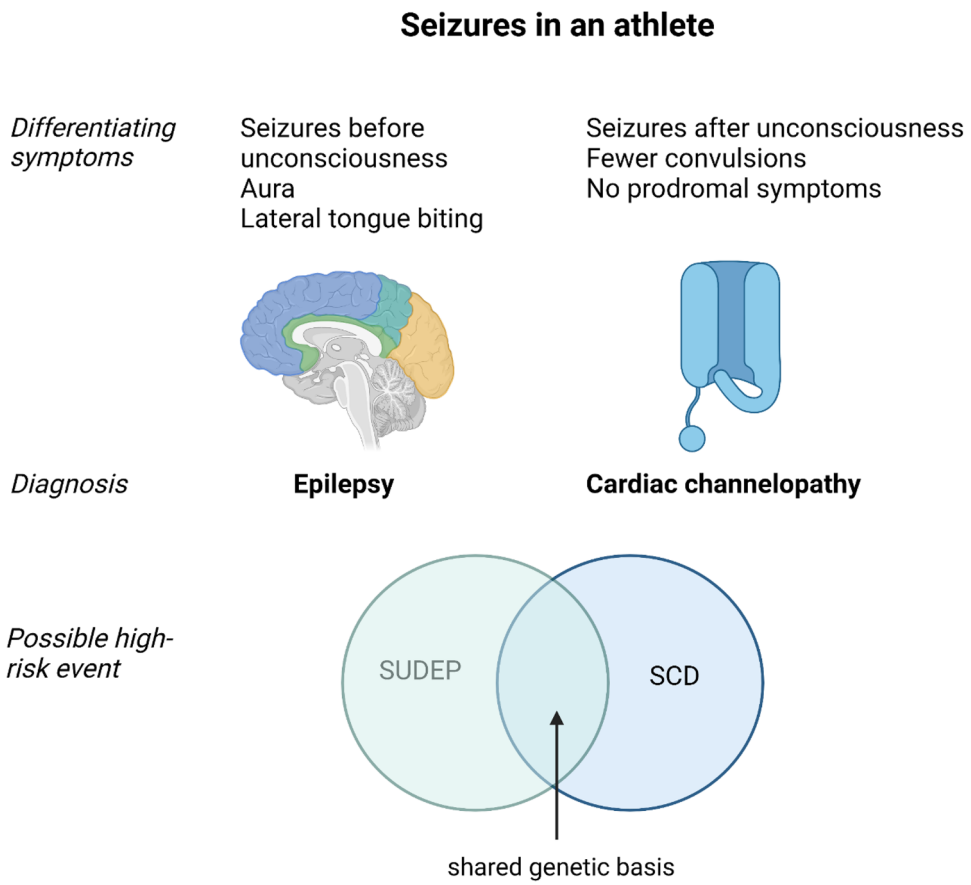

Fig. 1 Overview of important possibilities to consider when assessing a history of seizures in an athlete. SCD, sudden cardiac death; SUDEP, sudden unexplained death in epilepsy.

Athletes with epilepsy

Epilepsy, defined by a predisposition to unprovoked epileptic seizures, is common and affects approximately 1% of the world or 50 million people [5]. More broadly, it is estimated that up to 10% of people worldwide will have one seizure in their lifetime [6•]. With such high prevalence, there are inevitably a number of athletes with epilepsy, including high-profile Olympians Florence Griffith Joyner, Marion Clignet, and Davis Tarwater.

The participation of people with epilepsy in sporting activity was traditionally restricted, with official guidance from the American Medical Association in 1968, recommending broad-ranging exclusion of people with epilepsy from exercise [6•]. This recommendation was based upon the possibility that physiological changes in exercise (i.e., hyperventilation) might increase seizure frequency, as well concern for risk of injury if seizures occurred during exercise. Following such medical recommendations, it has unfortunately been demonstrated that people with epilepsy are less likely to participate in regular physical activity and are more likely to be overweight or obese than their age-matched peers [7].

More recent research has demonstrated that participation in exercise leads to improved physical and psychosocial well-being for people in epilepsy, as well as reductions in seizure activity [8–11]. The International League Against Epilepsy has now provided guidance recommending regular exercise and sporting activity participation to the highest levels in a range of scenarios [12]. Studies are underway into prescribing exercise as a form of anti-epileptic therapy, representing a comprehensive about-turn in the approach to exercise in epilepsy [6•, 13–16]. The inclusion of athletes with a history of seizures should therefore be expected to increase in future years, and an approach to informed risk assessment is essential.

Impact of epilepsy on the cardiovascular system

When seizures occur, a variety of cardiovascular physiological abnormalities have been documented [17, 18]. Peri-ictal cardiac rhythm abnormalities were first identified by Russell in 1906, who described a case series of patients with peri-ictal asystole, noting that "cardiac arrest does occur in some cases of epilepsy and… such arrest may be far commoner than is suspected [19]."

The reported prevalence of peri-ictal arrhythmias varies widely, reflective of different methods of ascertainment. A study of patients undergoing simultaneous EEG and ECG monitoring identified an arrhythmia rate of 18% [20], whereas a Russian study of 193 patients with drug-resistant epilepsy and implanted loop recorders reported that 74% of patients experienced arrhythmias [21•]. The most commonly reported peri-ictal arrhythmia is sinus tachycardia, but other peri-ictal transient cardiac abnormalities include sinus bradycardia, asystole, and hypertension [22]. Autonomic abnormalities

associated with epilepsy include excessive sympathetic activity, low parasympathetic activity, reduced heart rate variability, high vasomotor tone, and severe dysautonomia [23].

Rates of malignant arrhythmias appear low, with asystole occurring in 0.3–1.0% of patients with epilepsy [24, 25]. The mechanism of high-grade atrioventricular block or asystole in the peri-ictal state has been ascribed to initial stimulation of the limbic cortex activating parasympathetic outflow, with sympathetic activation followed by a profound vagal cardioinhibitory reflex [22]. Isbister et al. noted that "if the primary mechanism is centrally mediated cardiac inhibition, it is not surprising that the majority of seizure-induced brady-arrhythmias are self-resolving, paralleling neurogenic syncope [26]." Dynamic QTc prolongation has also been reported in the peri-ictal state [27], and prolonged QTc interval at baseline is more commonly observed in people with drug-resistant epilepsy on anti-epileptic therapy [17, 28]. Rates of torsades de pointes or ventricular arrhythmias have not, however, been reported at high rates in the peri-ictal setting [18].

In the longer term, the effect of repetitive seizures upon the heart and accompanying arrhythmias contributes to maladaptive changes [29]. People with temporal lobe epilepsy have increased left ventricle stiffness, left ventricle-filling pressures, and left greater atrial volumes compared to controls [30]. Patients with epilepsy have higher rates of myocardial fibrosis, accelerated atherosclerosis, systolic and diastolic dysfunction, and arrhythmias [31]. In more elite athletes, these changes may intersect with exercise-induced cardiovascular adaptations to exercise to either impair athletic performance or provide an enhanced substrate for arrhythmia.

Sudden Unexpected Death in Epilepsy (SUDEP)

Epilepsy is associated with a threefold elevation in the risk of sudden cardiac arrest [32]. Among people with epilepsy, the most common cause of premature mortality is sudden unexpected death in epilepsy, known as SUDEP [33, 34]. Sudden unexpected death, where no cause is found after investigation, occurs at 24 times the rate of the general population [17].

SUDEP is strictly defined according to the criteria established by Nashef et al. as "a sudden, unexpected, witnessed or unwitnessed, nontraumatic, and non-drowning death in people with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, and in whom post-mortem examination does not reveal a cause of death [35]." To account for case variations, a taxonomy of aligned conditions such as "SUDEP Plus" and "near-SUDEP" has been defined to provide clarity in case definitions [36] (Table 1). Identified risk factors for SUDEP include drug-resistant epilepsy, tonic–clonic seizures, high seizure frequency, nocturnal seizures, antiepileptic drug polytherapy, non-adherence to anti-epileptic therapy, young age of epilepsy onset, intellectual disability, and autonomic dysfunction [17, 37, 38•]. Proposed cardiac-specific risk factors for SUDEP include echocardiographic abnormalities indicating diastolic dysfunction [39, 40••].

Table 1. Definitions of sudden unexpected death in epilepsy (SUDEP)*

Definite SUDEP	Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration > 30 min or seizures without recovery in between) in which **post-mortem examination does not reveal a cause of death.**
Definite SUDEP Plus	Satisfying the definition of Definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the **death may have been due to the combined effect of both conditions**, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death.
Probable SUDEP/Probable SUDEP Plus	Same as Definite SUDEP but **without autopsy.** The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.
Possible SUDEP	A **competing cause of death** is present.
Near SUDEP/near SUDEP Plus	A patient with epilepsy **survives resuscitation** for more than 1 h after a cardiorespiratory arrest that has no structural cause identified after investigation.
Not SUDEP	A clear alternative cause of death is known.
Unclassified	Incomplete information available; not possible to classify.

*Derived from Nashef et al. [35]

The precise nature of SUDEP remains elusive. It is uncertain whether it may represent a subset of unexplained sudden cardiac death, happening to occur more commonly in people with epilepsy, or whether it is a unique entity. The pivotal study to date, the MORTEMUS study, identified that in SUDEP following a convulsive seizure, terminal apnea occurred prior to terminal asystole in all cases. There were no ventricular arrhythmias observed in the cohort of 29 patients [18]. These findings have lent weight to the hypothesis that SUDEP represents a distinct subset of sudden death, in which combined cardiorespiratory failure occurs rather than a primary cardiac arrhythmia.

Genetic basis of SUDEP

In the debate regarding the nature of SUDEP, there is also increasing evidence for the counter-argument that SUDEP represents a subset of SCD and is predominantly driven by the same mechanisms [41, 42••, 43]. A range of pathogenic genetic variants has been identified to date with concurrent effects on both the heart and brain, creating a substrate for "cardiocerebral channelopathies" [44] (Table 2).

Cardiac channelopathies such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome are conditions in which genetically mediated alterations in cardiac channel structure and function create a substrate for arrhythmias and SCD. A common presenting symptom of the cardiac channelopathies may be episodes of syncope

Table 2. The genetic basis of SUDEP and cardiocerebral channelopathies

Gene	Protein	Function	Effect on brain	Effect on heart
KCNQ1	Potassium channel Kv7.1	Ventricular repolarization	Epilepsy	Long QT syndrome
KCNQ2	Potassium channel Kv7.2	Potassium channel	Benign neonatal epilepsy; epileptic encephalopathy	Long QT syndrome
KCNH2	Potassium channel Kv11.1	Repolarization of cardiac action potential	Epilepsy	Long QT syndrome, short QT syndrome
KCNJ2	Potassium channel Kir2.1	Decreases intracellular potassium	Epilepsy, autism spectrum disorder	Long QT syndrome, short QT syndrome
KCNA1	Potassium channel Kv1.1	Potassium channel	Epilepsy, ataxia	Atrial fibrillation, AV block
SCN1A	Sodium channel Nav1.1	Sodium channel	Dravet syndrome	Increased risk of peri-ictal arrhythmia
SCN2A	Sodium channel Nav1.2	Sodium channel	Benign neonatal epilepsy; epileptic encephalopathy	Increased risk of arrhythmia
SCN5A	Sodium channel Nav1.5	Sodium channel – rapid depolarizing sodium current	Epilepsy	Long QT syndrome, Brugada syndrome
SCN8A	Sodium channel Nav1.6	Sodium channel	Epileptic encephalopathy, movement disorders	Ventricular arrhythmias
SCN10A	Sodium channel Nav1.8	Sodium channel	Epileptic encephalopathy	Long QT syndrome, Brugada syndrome
HCN1	Hyperpolarization-activated cationic channel HCN1	Depolarization of the sinus node	Epileptic encephalopathy	Sick sinus syndrome
HCN4	Hyperpolarization-activated cationic channel HCN4	Potassium channel: slow kinetics of activation and inactivation	Benign myoclonic epilepsy in infancy, generalized epilepsy	Sick sinus syndrome
CACNA1C	L-type calcium channel Cav 1.2 alpha 1	Increases intracellular calcium	Epileptic encephalopathy, Timothy syndrome	Long QT syndrome, short QT syndrome, Brugada syndrome, idiopathic VF
CACNA2D1	L-type calcium channel Cav 1.2 alpha 2-delta 1	Decreases intracellular calcium	Epilepsy	Brugada syndrome, short QT syndrome
RYR2	Ryanodine receptor 2 (intracellular calcium channel)	Intracellular calcium-release channel	Epilepsy	Catecholaminergic polymorphic ventricular tachycardia

or seizure, and so it is important to be alert to the possibility of a coexistent or primary cardiac channelopathy in people with seizure presentations [45•]. This is particularly the case when therapy with anti-epileptic drugs targeting sodium channel blockade is intended, as such therapy may heighten the risk of malignant cardiac arrhythmia [22].

Specific epilepsy syndromes have an increased SUDEP risk. Dravet syndrome, the prototypic developmental and epileptic encephalopathy, in whom more than 90% have a pathogenic *SCN1A* variant [46], has a mortality rate of 17% by 20 years of age; more than half of the affected individuals die of SUDEP. Other sodium channel developmental and epileptic encephalopathies also carry an increased SUDEP risk [47].

Exome sequencing in 61 SUDEP patients identified a large number of pathogenic variants implicated in cardiac arrest. Variants known to cause LQTS, a cardiac channelopathy causing SCD, were identified in 7% of cases, with a further 15% of patients having candidate variants in genes believed to predispose to malignant cardiac arrhythmias [33]. The study concluded that "SUDEP in patients with LQTS mutations may be predictable and preventable" [33]. In mice, it has been shown that a point mutation in the most common LQTS gene (*KCNQ1*) results in an ion channelopathy co-expressed in heart and brain, manifesting as both cardiac arrhythmias and epileptic seizures, with subsequent sudden death captured on both cardiac and cerebral monitoring [48]. Likewise, in patients with genetically verified LQTS but no known history of epilepsy, 71% have abnormal EEG studies, compared to only 13% of control subjects [49].

With regard to the MORTEMUS study findings that death was associated with a centrally mediated alteration of both respiratory and cardiac function, researchers have suggested that people with epilepsy exhibit a higher genetic susceptibility to SCD and are, therefore, more vulnerable to death in the setting of post-ictal hypoxia [50]. Given the rate of cardiogenetic pathogenic variants in people with epilepsy and SUDEP, it is important to consider that many cardiac channelopathies are, in fact, more accurately described as "cardiocerebral channelopathies" [51, 52]. Implications of this research are not limited to reducing SUDEP risk in people with epilepsy by tailoring preventive neurological and cardiac therapy, but findings may also cascade to other family members with critical strategies to reduce the risk of sudden cardiac death in first-degree relatives [53].

"Cardiac" seizures indicating primary arrythmia

Although an increasing amount of research points to a significant overlap between epilepsy and an arrhythmogenic substrate for sudden cardiac death, it is also important to consider the possibility that reported seizures may represent misdiagnosed primary cardiac arrhythmias.

The mechanism by which convulsive movements occur in syncope or cardiac arrest is predominantly believed to be secondary cerebral hypoperfusion causing anoxic seizure activity. In severe cerebral hypoperfusion, electroencephalographic (EEG) monitoring demonstrates a characteristic

"slow-flat-slow EEG pattern" in which a generalized short-lasting period of delta waves is followed by flattening of the EEG followed by recurrent delta waves with restoration of cerebral perfusion and then resolution to a normal EEG. Myoclonic jerks, observed in approximately half of these patients, typically appear after the patient has fallen. They result from hypoxia in the telencephalon-inhibiting cortical activity, resulting in unopposed subcortical (brainstem) activity, with the brainstem reticular formation causing sudden contractions [54]. These jerks correlate strongly with the "slow" phase of the EEG and are usually asynchronous and unilateral. Following recovery of the hypoperfusion event, late myoclonic jerks may be seen as cerebral reperfusion is established. These may be associated with characteristic skin flushing as more general perfusion is established [25].

Cardiac syncope and even sudden cardiac arrest are, therefore, frequently misdiagnosed as seizures [45•], and differentiation can be challenging [51]. Video analysis of thirty-five episodes of sudden cardiac arrest during sporting events identified that 20% of cases were associated with seizure-like activity [55]. Likewise, a study by Drezner et al. of sudden cardiac arrest in student athletes identified seizure-like movements in 50% of the athletes at the time of their cardiac arrest [56].

Suggestive differentiators between a seizure and a primary arrhythmia may include the number of "jerks" observed (reported to be fewer in syncope than an epileptic seizure) and the timing of onset of convulsions, with convulsions before the onset of unconsciousness favoring a primary seizure event [57] (Fig. 1). An abrupt collapse without warning may also be more indicative of the onset of a ventricular arrhythmia [3]. Tongue biting is rare in arrhythmogenic syncope and predominantly involves the tip rather than the lateral tongue as a consequence of injury rather than tongue biting during convulsions. Urinary incontinence may occur, but fecal incontinence is extremely rare [57]. However, syncopal signs that may cause confusion with a seizure are head turning to one side, oral automatisms, snoring, gasping, sounds, and dystonic posturing—these all reflect predominant brainstem activity during the period of cortical suppression [57]. Pallor may be observed in both conditions as an indicator of generalized hypoperfusion [25].

Syncope that occurs during an athlete's exercise is an ominous sign suggestive of underlying malignant cardiac disease. In a study of 474 patients with a history of syncope, 33% of those with exercise-induced syncope were ultimately diagnosed with structural cardiac disease placing them at risk of SCD [58]. Video analysis or at least witness descriptions from team members or spectators may be more readily available in the setting of athletes experiencing syncope or seizures during exercise and may provide valuable clues to the challenge of differentiating between a seizure and a primary arrhythmia [59].

Practical implications for the cardiologist or sports physician

For cardiologists and sports physicians evaluating young athletes either as part of pre-participation screening or as a clinical cardiac evaluation, there are clear practice points to emphasize. A history of seizure in a young athlete is concerning

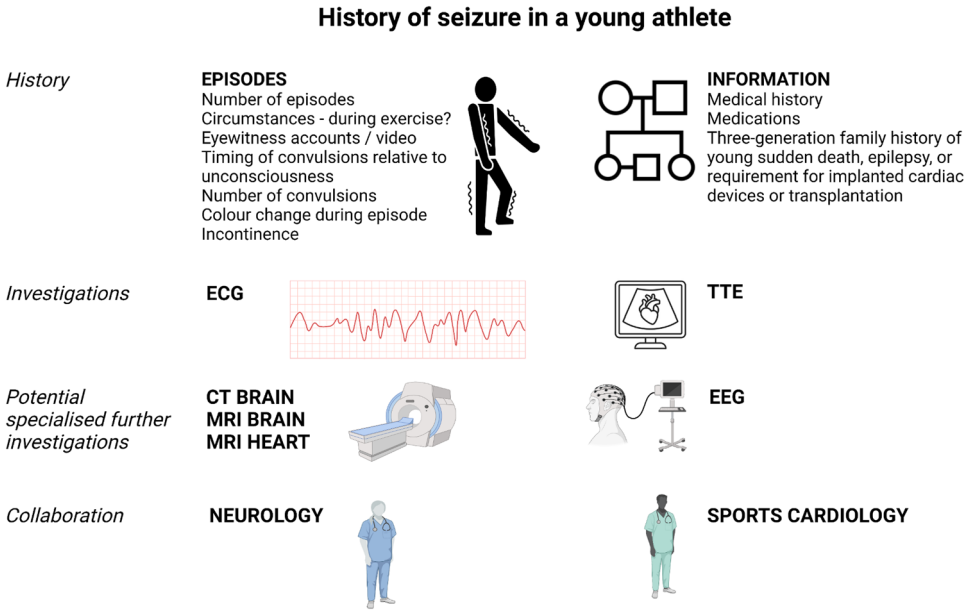

Fig. 2 A guideline for evaluation of a history of seizures in an athlete. CT, cardiac tomography; ECG, electrocardiogram; EEG, electroencephalogram; MRI, magnetic resonance imaging; TTE, transthoracic echocardiography.

and warrants further investigations (Fig. 2). High-risk differential diagnoses include epilepsy with risk of SUDEP or an undiagnosed cardiac channelopathy.

In taking a history, it is important to delineate all features of reported episodes. Episodes occurring during exercise are particularly concerning and warrant a comprehensive cardiac evaluation. Details regarding any prodromal symptoms, color changes, abnormal limb movements, tongue injuries, incontinence and post-episode confusion, drowsiness, and headache should be obtained. The exact timing of abnormal limb movements with respect to loss of consciousness should be clarified as precisely as possible [60]. Video or witness descriptions are critical and should be actively sought. With regard to the patient's broader medical history, a full medical and medication history should be obtained. A three-generation family pedigree is also valuable to ensure there is no family history of epilepsy, febrile seizures or sudden deaths, cardiac device implantation, or transplantation at under 50 years of age [3].

An electrocardiogram should be performed in all athletes with a history of syncope or seizures [61, 62]. It is reasonable to perform an exercise stress test and echocardiogram to ensure the athlete's heart is structurally and functionally normal. More advanced investigations such as cardiac MRI, EEG, and cerebral imaging (computed tomography or MRI) should be performed as required according to initial results and degree of concern. If a diagnosis of epilepsy is suspected, a neurologist should be part of the multidisciplinary evaluation team.

If a firm diagnosis of either epilepsy or a channelopathy is made, this is not necessarily a barrier to participation in sports. Participation in sports confers mental and physical benefits, and a blanket ruling on non-participation is unnecessary [63, 64]. Awareness of high-risk features of SUDEP and mitigation

of cardiac risk in channelopathies is the mainstay of treatment. Involvement of sports cardiology colleagues at this point is highly valuable to assist in providing informed evaluations and information to the patients and their families.

Conclusion

A history of seizures in a young athlete is a concerning symptom that requires further investigation. Both epilepsy and cardiac channelopathies causing sudden death appear to be intimately related, and the degree of their entanglement as a "cardiocerebral syndrome" is still being elucidated. Physicians should take a detailed history and appropriate clinical investigations and collaborate in a multidisciplinary manner to best support the athlete's comprehensive risk profiling and mitigate risk of sudden cardiac death while encouraging ongoing physical activity where safe.

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Compliance with Ethical Standards

Conflict of Interest

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This article does not contain any studies with human or animal subjects performed by any of the authors.

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