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Physical Activity and Epilepsy

Proven and Predicted Benefits

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Abstract

Epilepsy is a common disease found in 2% of the population, affecting people from all ages. Unfortunately, persons with epilepsy have previously been discouraged from participation in physical activity and sports for fear of inducing seizures or increasing seizure frequency. Despite a shift in medical recommendations toward encouraging rather than restricting participation, the stigma remains and persons with epilepsy continue to be less active than the general population. For this purpose, clinical and experimental studies have analysed the effect of physical exercise on epilepsy. Although there are rare cases of exercise-induced seizures, studies have shown that physical activity can decrease seizure frequency, as well as lead to improved cardiovascular and psychological health in people with epilepsy. The majority of physical activities or sports are safe for people with epilepsy to participate in with special attention to adequate seizure control, close monitoring of medications, and preparation of family or trainers. The evidence shows that patients with good seizure control can participate in both contact and non-contact sports without harmfully affecting seizure frequency. This article reviews the risks and benefits of physical activity in people with epilepsy, discusses sports in which persons with epilepsy may participate, and describes the positive effect of physical exercise in experimental models of epilepsy.

1. Epilepsy: General Aspects

Epilepsy is one of the most common serious neurological conditions. Approximately 50 million people worldwide have epilepsy.[1] In the US each year, about 100 000 new cases of epilepsy are diagnosed.[2,3] In the UK, between 1 in 140 and 1 in 200 people (at least 300 000 people) are currently being treated for epilepsy.[4] Epidemiological studies suggest that between 70–80% of people developing epilepsy will go into remission, while the remaining patients continue to have seizures and are refractory to treatment with the currently available therapies.[5,6] The most common risk factors for epilepsy are cerebrovascular diseases, brain tumours, alcohol, traumatic head injuries, malformations of cortical development, genetic inheritance and infections of the CNS.[7] In resource-poor countries, endemic infections, such as malaria and neurocysticercosis seem to be major risk factors.[8]

The epilepsies are characterized by spontaneous recurrent seizures, caused by focal or generalized paroxysmal changes in neurological functions triggered by abnormal electrical activity in the cortex.[9] As it involves hyperexcitable neurons, a basic assumption links the pathogenesis of epilepsy and the generation of synchronized neuronal activity with an imbalance between inhibitory (GABA-mediated) and excitatory (glutamate-mediated) neurotransmission, in favour of the latter.[10] Seizures and epilepsy are usually divided into two groups: partial and generalized. Partial or focal seizures have clinical or EEG evidence of local onset, and may spread to other parts of the brain during a seizure. Generalized seizures begin simultaneously in both cerebral hemispheres.

Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy, probably affecting at least 20% of all patients with epilepsy[11] and is the most common form of drug-refractory epilepsy.[12] Atrophy of mesial temporal structures is well known to be associated with TLE and hippocampal sclerosis, which is the most frequent histological abnormality in this form of epilepsy.[13]

This article reviews the risks and benefits of physical activity in people with epilepsy, discusses sports in which persons with epilepsy may participate, and describes the positive effects of physical exercise in experimental models of epilepsy.

Articles identified for this review were obtained from the PubMed database (English language, all ages, no search period limitation) using the search terms 'epilepsy', 'exercise', 'physical activity', 'seizure physical training', 'human' and 'animal model of epilepsy'.

2. Epilepsy and Exercise: Human Studies

Although the favourable effect of physical fitness on general health is unquestionable, patients with epilepsy are often excluded from participation in physical activity. This is surprising because for many high-risk patients, such as those with coronary heart disease and diabetes mellitus, physical exercise has proved quite beneficial. This reluctance of both patients and physicians is due in part to fear of injuries and in part to fear that exercise will cause seizures.[14] Although the question of a positive or a negative impact of physical exercise on seizure frequency remains unsolved, patients with epilepsy should have the same benefits as others from the positive impacts on maximal aerobic and work capacity, bodyweight and self-esteem.[15] In these lines, it has been observed that people with epilepsy experience a considerable lack of physical fitness that might have an impact on their general health and quality of life. Patients with epilepsy present significant deficits in aerobic endurance, muscle strength endurance and physical flexibility.[16] For example, Nakken et al.[15] found considerably lower maximum oxygen uptake ($\dot{V}O_{2max}$) in patients with epilepsy than in the healthy population. These findings are also observed in children with epilepsy. An elegant study conducted by Wong and Wirrell[17] demonstrated that teens with epilepsy were less physically active than their sibling controls.

The attitude towards restriction and protection of the epileptic patient has, however, changed dramatically in the last decades and general recommendations have been recently reviewed. In 1968, the American Medical Association Committee on Medical Aspects of Sports advised that people with epilepsy not controlled by medication should avoid not only collision sports, but also non-contact sports.[18,19] In 1974, the Committee revised its decision, describing that people with epilepsy with rational seizure control should be allowed to play any sport except activities in which chronic head trauma may occur.[20] In 1983, the American Academy of Pediatrics allowed for further individual consideration and said, "epilepsy *per se* should not exclude a child from hockey, football, basketball and wrestling."[21] The International League against epilepsy recommended in 1997 that the only prohibited sports for athletes with epilepsy are skydiving and scuba diving.[22] In order to give patients with epilepsy satisfactory advice about sports, it is essential to understand the factor in sport that could affect the epileptic disorder. Many circumstances during physical activities or sports are presumed and have not been investigated. Likewise, it is rather difficult to indicate the specific effects that epilepsy will have on sports participation and to draw general conclusions.

Various studies have been designed to study the relationship between epilepsy and exercise comparing physical and social activities among patients with epilepsy based on questionnaires and/or clinical studies.[23,24] They also assess physical fitness by using standardized tests of physical endurance[16,24] and physical training programmes.[15] With few exceptions, regular physical exercise is beneficial to the individual with epilepsy. For example, a study conducted by Nakken et al.[15] reported that 4 weeks of a physical training programme at an intensity of 60% of $\dot{V}O_{2max}$ for 45 minutes a day, did not change the average frequency of seizures.[15] Another study evaluating physical exercise in women with intractable epilepsy demonstrated that aerobic physical training decreased the number of seizures during the exercise period.[25]

The degree of participation in physical activity among epileptic patients appears to be low.[23,26,27] In a study of epileptic patients in Norway, only 23% participated in organized physical activity.[14] Despite the fact that several epidemiological studies have been performed on this subject, these patient samples may not be directly applicable to developing countries. A study conducted by Arida et al.,[28] analysed the degree of participation in physical activities among Brazilian patients with epilepsy. Although only 15% of patients were qualified as active, that is, exercised regularly, more than half of the patients participated in physical activities once or twice per week or on the weekends. While the main concern with regard to physical exercise by persons with epilepsy has been exercise-induced seizures, other factors such as lack of training facilities, problems with transportation, low motivation, reduced energy due to medication, fear of qualified instructors who know how to handle such problems were noted as important explanatory factors.[14] A comparison of leisure time habits of people with epilepsy with to those of the general population has shown a great number of inactive persons with epilepsy.[15,16] In contrast to previous observations, a subsequent study conducted by Nakken[27] showed that the exercise pattern of people with epilepsy was similar to that of the average population. It seems that they are now being informed about the beneficial effect of physical activity.

2.1 Risks of Sports Participation

Studies have addressed the magnitude of risk for the person with epilepsy in certain activities. The general opinion is that these risks are determined by the occurrence of a seizure while the patient is participating in sport. The risk from injury due to a sudden fall without warning has been addressed in a few studies. Aisenson[29] found that over a period of 16 years, children with epilepsy had no higher rate of injury during daily activities than children who had never had a seizure. However, there is a potential hazard of falling during a seizure, so several sports must be avoided by patients who have regular seizures.

Studies have also looked into the risk of injury in water sports because of the known increased risk of drowning due to seizures. Pearn et al.[30] found that 4 of 140 immersion accidents were caused by seizures over a 5-year period in Hawaii. They reported that no children died and that the accident rate was similar to that in the general population. Conversely, Kemp and Sibert[31] identified four children who drowned in the UK in just a 1-year period. Ryan and Dowling[32] reported that 25 of 482 drowning deaths during a 10-year period in Alberta were due to seizures. It is generally recommended that water sports may be permitted with appropriate precautions. A review of these studies would suggest that this risk could be further reduced when performed with direct supervision.

Concerning contact sports, in general, there is no evidence that repetitive minor head trauma will worsen the frequency and/or severity of epilepsy. In fact, contact sports, especially football, are common activities for children and adolescent boys, so their prohibition can have critical consequences.[33] Some contact sports have been contraindicated to epileptic patients. Although boxing has been a sport to be avoided among epileptic patients, a study has shown no severe abnormalities on EEG or neuroimaging in 47 Swedish amateur boxers when compared with soccer and field athletes.[34] In these lines, there is epidemiological evidence that head injury causes epilepsy, but the association is only significant for severe head injury.[35] Therefore, the decision for a person with epilepsy to participate in sports is concerned whether the benefit outweighs the risk. The risk-benefit analysis for a person with epilepsy is highly dependent on the athletic activity considered, the type of seizure that might occur as well as the likelihood that a seizure will occur during the sport. Examples of some sporting activities with their restrictions to the epileptic individual are outlined in table I.

Seizures induced or exacerbated by exercise are relatively uncommon in patients with epilepsy. One study already mentioned[27] found that only 2% of patients with epilepsy had exercise-induced seizures (defined as seizures in >50% of training sessions). Most of the evidence suggesting that exercise exacerbates seizures is anecdotal. For example, Ogunyemi et al.[37] reported three cases of exercise-induced seizures. Similarly, Korczyn[38] published five case reports of exercise-induced seizures, one of whom was a long-distance runner who had a seizure during one of his runs. It has also been hypothesized that some types of seizures are more susceptible to activation during physical activity. For example, there are reports of seizures induced by exercise associated with idiopathic generalized epilepsy, symptomatic frontal lobe epilepsy[39-41] as well as temporal lobe epilepsy.[42] In summary, most of the previously reported cases show a history of additional seizures independent of exercise.

Table I. Recommendations on specific sporting activities for persons with regular epilepsy[36]

Activities to be avoided
Scuba diving
Parachuting
High-altitude climbing
Gliding
Hand-gliding
Aviation
Motor-racing
Boxing
Activities requiring precautions or supervision
Water-skiing
Swimming
Canoeing
(Wind) surfing
Sailing
Activities requiring knowledge of seizure type and sports
Cycle racing
Skating
Horse-riding
Gymnastics

2.2 Epilepsy and Exercise Physiology

Most experiments on brain electrical activity have shown that abnormal discharges disappear in most patients during physical activity, but return at rest.[43,44] It has also been observed that fewer seizures occur during both mental and physical activity compared with periods of rest.[45] The increased vigilance and attention involved in exercise could explain the reduction in the number of seizures.[44] Another hypothesis relates the β-endorphins released during exercise with inhibition of epileptic discharges.[46]

Although exercise has been shown to reduce epileptic activity on the EEG and the number of seizures, there are numerous factors that could cause seizures during sports and exercise, and any links at this point are largely speculative. It appears that these factors occur as the result of a disturbed balance of physiological parameters. Fatigue is one such issue. In sports, general fatigue and local muscular fatigue must be distinguished. The stress of competition has been commented on. Physical and especially psychic stress is generally accepted as factors that precipitate seizures.[47] In competitive sports, this stress could induce seizures in stress-sensitive patients.[45,48] Hypoxia, hyperhydration and hypoglycaemia are other possible considerations. Hypoxia does not occur during normal sporting activities, although it may occur in climbing or alpine skiing at high altitude (2000 m).[48,49] Hyperhydration can result from a great ingestion of water or from an extreme loss of sodium and is a well known factor in provoking seizures. Hyperhydration can occur during swimming or prolonged physical exercise such as marathon running and triathlon. Overingestion of isotonic or hypotonic liquids may lead to hyponatraemia.[50-52] Hypoglycaemia can occur during long-distance running, cycling or swimming, especially when regular liquid and food intake is reduced.[53] Hyperthermia is also known to trigger seizures. Prolonged exercise (marathon, triathlon) at high temperatures and under humid conditions puts people at risk.[54,55] One factor that is raised frequently, but inappropriately, is that of hyperventilation. Following this reasoning, as hyperventilation in the laboratory may provoke epileptiform discharges on EEG and even epileptic seizures, especially absence type, some have erroneously believed that increased ventilation during exercise may cause seizures.[56] However, increased ventilation during physical training is a compensatory homeostatic mechanism; the respiratory alkalosis of induced hyperventilation does not occur.[57] In these lines, seizures during exercise may be related to acute metabolic and respiratory changes. How efficient the respiratory control systems are in untrained subjects is not known, but untrained persons lose homeostatic balance more easily than trained persons.

3. Epilepsy and Exercise: Animal Studies

3.1 Animal Models of Epilepsy

Epidemiological data have shown that the most frequent type of seizures in humans are complex partial seizures with or without generalization, which occur in about 40–50% of all patients with epilepsy.[58,59] The majority (70–80%) of complex partial seizures originate in the temporal lobes, particularly in hippocampus and amygdala, and the term 'TLE' is used in this regard.[60] Animal models constitute one of our most valuable tools to better understand the pathophysiology of TLE.

Between many animal models of TLE, this article focuses on two specific models of epileptogenesis that were used to understand the mechanisms by which physical exercise interfere in epilepsy: the Kindling model and the Pilocarpine model (for a review see Goodman[61]).

3.2 Effect of Physical Exercise in Experimental Models of Epilepsy

Experimental studies have also demonstrated a positive effect of physical exercise in animals with epilepsy.[62-66] The first study relating the effect of physical exercise on epilepsy used the kindling model. Kindling can be induced by repeated administration of a subconvulsive stimulus administered through a bipolar electrode implanted into a limbic structure such as the amygdala, hippocampus, entorhinal cortex or other brain areas. Over a period of several stimulation days, the animal displays both behavioural and electrographic seizures that spread to become secondarily generalized. In rats stimulated in the amygdala, the initial stimulus often elicits focal paroxysmal activity (i.e. so-called 'after discharges') without apparent clinical seizure activity. Subsequent stimulations induce the progressive development of seizures, generally evolving through the following stages:[67]

1. immobility, facial clonus, eye closure, twitching of the vibrissae;
2. head-nodding;
3. unilateral forelimb clonus;

4. rearing;
5. rearing and falling accompanied by secondary generalized clonic seizure.

In this study, it was verified the effect of acute and chronic physical exercise on amygdala kindling development.[62] To assess the acute effect of exercise on kindling evolution, animals were submitted to a daily bout of aerobic exercise that consisted of 40 minutes running on the treadmill at 20 m/min. One minute post-exercise, animals were kindling stimulated. To the chronic effect of exercise, animals were submitted to an aerobic exercise programme (45 sessions of 40 minutes running on a treadmill at 20 m/min, 7 days/week). After this period of training, they were submitted to 40 minutes running at the same speed and kindling stimulated 1 minute post-exercise.

The number of stimulations required to reach stage 5 was statistically higher for the chronic exercise group when compared with the acute exercise group and control group. The number of stimulations required to reach stage 5 in the acute exercise group was higher but not statistically different from the control group. Thus, the acute and chronic exercise groups spent a longer time and a shorter afterdischarge (AD) duration during stage 1 than the control group.

Some factors could probably be contributing to this effect. Several lines of evidence show that brain neurotransmission is influenced by exercise. For example, an increase in noradrenaline levels in whole brain has been reported.[68,69] It is well known that among catecholamines, noradrenaline has a tonic inhibitory effect on kindling development, but not on kindling state.[70] Bortolotto and Cavalheiro[71] observed that the depletion of noradrenaline induced by DSP4 facilitated the propagation of epileptiform activity and the rate of hippocampal kindling. Although most of these studies relate the brain noradrenergic system with kindling development, Welsh and Gold,[72] showed that a single intraperitoneal injection of epinephrine, administered 30 minutes or 24 hours prior to the first trial, retarded the development of seizures, suggesting that endogenous peripheral catecholamines may play an important role in regulating epileptogenesis. Evidence in favour of changes in synthesis and metabolism of catecholamines during exercise and the inhibitory involvement of this neurotransmitter system in the amygdala kindling support the hypothesis that the effect of chronic exercise on brain catecholamines can contribute to retard the kindling development.

It was also observed that the time spent in stage 1 was longer and that the AD duration during this stage was shorter in the exercise animals. As a general rule, the rate of kindling seems to be related to the length of the initial AD: the longer the initial AD, the more rapidly kindling appears.[73] Thus, the assessment of different stages is important, since the catecholamine effect is primarily observed during the development of kindling and it does not act after stage 5 seizures are established.[70] Taken together, these findings suggest that physical exercise inhibits amygdala kindling development in rats.

A subsequent study, using the pilocarpine model of epilepsy, evaluated the effect of a physical aerobic programme on seizure frequency.[63] The pilocarpine model of epilepsy reproduces the main features of human TLE in rats and mice. The pilocarpine model is probably the most commonly studied chemical-inductive models for TLE. After the first spontaneous recurrent seizure, animals were submitted to an aerobic exercise programme of 45 sessions on a treadmill, 7 days per week at the intensity of 60% $\dot{V}O_{2max}$. A reduced frequency of seizures in trained animals with epilepsy was observed. The main concern with regard to physical exercise by people with epilepsy has been exercise-induced seizures. Seizures occur during physical exercise, but apparently infrequently.[38] In this study, only two animals presented three seizures each during 3600 hours of exercise and two animals presented one seizure, 1 minute post-exercise.

Further investigations were performed to better clarify the factors that may interfere with this process. Using local cerebral metabolic rates for glucose (LCMRglu), a study evaluated whether physical training modifies the functional activity in rats with epilepsy.[64] LCMRglu was measured by the quantitative [14C]2-deoxyglucose (2DG) method.

To determine changes in cerebral functional activity in trained animals with epilepsy, rats with epilepsy were studied during the interictal phase of the pilocarpina model of epilepsy. The purpose for studying the brain metabolism during the interictal phase was that all the animals present seizures at rest and not during exercise.[63] The hypothesis that animals with epilepsy submitted to a physical training would exhibit a marked metabolic alteration in the interictal phase was, however, not confirmed. An increase in interictal LCMRglu in inferior colliculus and auditory cortex in trained rats with epilepsy was observed when compared with rats with epilepsy. Although no substantial LCMRglu changes were observed after physical training, exercise did reverse the low metabolic rates in several structures of animals with epilepsy.[64] Vissing et al.[74] reported a higher local cerebral glucose utilization in the auditory and visual cortex during exercise, suggesting that these changes are not related directly to the exercise *per se*, but to a higher mental alertness in exercise than in resting rats. Since physical activity does need a certain level of alertness, the increased attention and vigilance observed during physical activity could reduce the number of seizures.[44] Although these changes were observed at rest, the increased metabolic rate in these structures could explain a lower seizure number in trained rats with epilepsy in the present and previous work.[63]

A recent study investigated the effect of aerobic exercise on *'in vitro'* hippocampal electrophysiological parameters observed in rats submitted to the pilocarpine model of epilepsy.[65] Electrophysiological changes were monitored by extracellular field potentials recorded from the CA1 area. Trained rats with epilepsy exhibited a reduction in population spikes when compared with untrained rats. These results indicate that physical training reduces CA1 hyperresponsiveness and can modify synaptic plasticity in rats submitted to the pilocarpine model of limbic epilepsy.

Based on the above observations, an investigation was performed to study the occurrence of structural changes in hippocampal formation of trained rats with epilepsy by means of an immunohistochemical approach. Markers of the GABAergic system, such as calcium-binding proteins; parvalbumin and calbindin have been extensively used in different models of epilepsy to visualize morphological changes occurring in the brain.[75,76] They represent effective and sensitive markers of hippocampal cells[77] and in particular, of a population of inhibitory interneurons.[78] Along these lines, animals with epilepsy were submitted to voluntary or forced exercise, trained acutely or chronically utilizing parvalbumin as a marker of morphological changes. Both voluntary and forced exercise lead to prominent changes in the staining of parvalbumin in the dentate gyrus from control rats and rats with epilepsy. In particular, the acute physical exercise promoted a marked increase in the number of PV-positive cells and staining intensity of PV fibres in the hilus.[66]

In these animal models of temporal lobe epilepsy it seems that physical activity in general cannot be considered a seizure-inducing factor. Thus, the mechanisms by which physical training is able to induce such changes are not completely understood and deserve further investigations.

4. Conclusions

Generalizations about persons with epilepsy can never be made. Every patient is unique concerning the type, frequency, severity and impact of his or her seizures. A good insight into the patients' history regarding accidents caused by seizure, periods of freedom from seizures, and drug compliance is required. Therefore, before giving advice about the most suitable type of sport, the physician should know the patient's medical history, have a good insight into the different types of sport and be able to judge the role and function of sport to the particular patient. Experimental studies in animal models of epilepsy have also confirmed the positive effects of exercise in human studies. Beyond the discussion about the influence of physical activity on seizure frequency, knowing that physical activity has beneficial physical and psychological effects on patients with epilepsy, it appears justifiable that physicians should encourage most patients with epilepsy to participate in regular physical exercise to enhance their physical fitness, self-esteem and social integration.

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