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Atrioventricular Nodal Reentrant Tachycardia Triggered by Edible Marijuana: A Case Report and Review of the Literature

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Abstract Marijuana (Cannabis) is the most commonly produced and illicit drug used worldwide with an estimated 182.5 million users globally, constituting 3.8% of the world population. There is a rising trend in the reporting of cardiovascular complications related to cannabis use. Marijuana is composed of more than 460 chemicals with delta-9- tetrahydrocannabinol (THC) being the psychotropic ingredient. It acts via CB1 and CB2 G-protein coupled cannabinoid receptors. Various cardiac manifestations, associated with marijuana use, such as bradyarrhythmia, tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia and fibrillation, asystole have been reported so far. To the best of our knowledge, there is a single case report of atrioventricular nodal reentrant tachycardia (AVNRT) triggered by smoking marijuana. Our case report is unique and probably the only one reported, in which AVNRT is triggered by edible marijuana, which was consumed in the form of marijuana burger. As compared to inhaled marijuana, marijuana ingestion has a delayed onset ranging from half an hour to three hours, with its effect lasting up to 12 hours. The effects of marijuana on the cardiovascular system are extremely worrisome owing to the legalization of marijuana for medicinal and recreational use across many states in the USA. Our case emphasizes the importance of keeping marijuana as one of the possible causes of AVNRT, not explained by any other cause. Physicians should keep in mind while elucidating history from the patient, all the possible routes of marijuana consumption and detailed and repetitive questionnaire should be put to the patient in order to reach a conclusive diagnosis.

Keywords: *cannabis, edible marijuana, atrioventricular nodal reentrant tachycardia*

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1. Introduction

Marijuana is the most commonly produced and illicit drug used worldwide with an estimated 182.5 million users globally, constituting 3.8% of the world population [1]. As per the latest information, in the United States, 33 states along with the District of Columbia, Guam, Puerto Rico and U.S. Virgin have allowed comprehensive medical marijuana/cannabis programs [2]. Marijuana is composed of more than 460 chemicals with delta-9- tetrahydrocannabinol (THC) being the psychotropic ingredient [3,4,5]. Delta-9-THC exerts neurological, antiemetic and cardiovascular effects in humans but less data is available on the effect of marijuana on the cardiovascular system [6]. It mediates its functions via CB1, CB2 and an endothelial receptor, distinct from the Cannabinoid receptors, which are present in the heart and vessels [7]. Marijuana causes various electrophysical manifestations such as tachycardia, bradyarrhythmia, atrial flutter and fibrillation [8,9,10,11], ventricular tachycardia, asystole and fibrillation [12,13,14]. To the best of our knowledge in the literature, only one case has been reported of atrioventricular nodal reentrant tachycardia (AVNRT) triggered by smoking marijuana [1]). Our case is unique as in this case AVNRT is triggered by the edible form of marijuana, that is otherwise unexplainable.

2. Case Report

A 55 years old male with a past medical history of hypertension, hyperlipidemia presented to the Emergency department (ED) with palpitations for one day. The palpitations were associated with pressure-like chest pain, which was non-radiating, not pleuritic, not related to the change of position. There was no history of nausea, vomiting, loss of consciousness, cough, shortness of breath or dizziness. His family history was nonsignificant. He was allergic to peanuts and shellfish derived products. He denied any smoking, alcohol consumption or illicit drug/substance use. His examination was unremarkable except for tachycardia. At the admission, his BP was 120/64 mm of Hg , pulse rate- 194 beats per minute (bpm), and he was afebrile. Electrocardiography (EKG) revealed AV nodal re-enterant tachycardia (AVNRT) (Figure 1). He was given up to 12 mg of adenosine with failed conversion to sinus rhythm. After 18 mg of Cardizem, the rhythm was converted into sinus rhythm (Figure 2). His blood work showed no abnormalities. Troponin I was elevated at 0.167 (0-0.034 ng/ml). Urine toxicology screen was positive for marijuana use and negative for other illicit drugs. The patient was advised admission in view of Non-ST elevation myocardial infarction (NSTEMI) in the setting of AVNRT. Diagnostic Cardiac Catheterization which showed no evidence of obstructive coronary artery disease with normal left ventricular function. Urine toxicology screen was positive for marijuana,. He was discharged after 3 days on aspirin, atorvastatin, metoprolol, nifedipine, and lisinopril. He was counselled not to use marijuana.

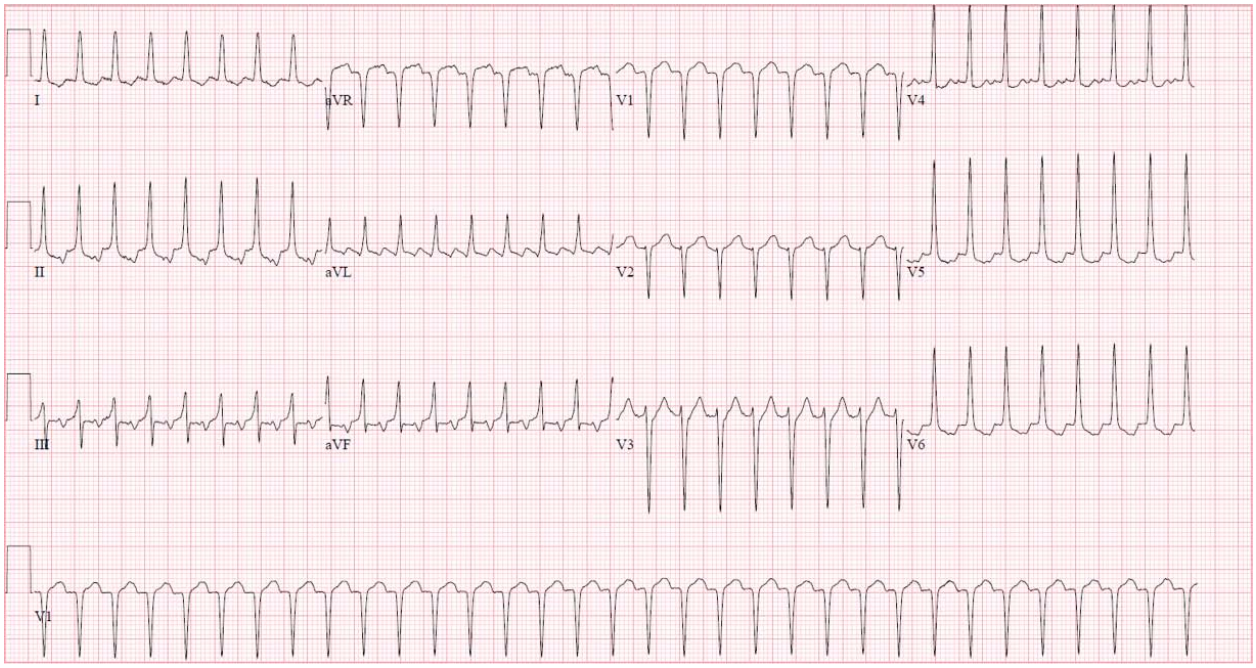

Figure 1. ECG showing AVNRT at the time of presentation

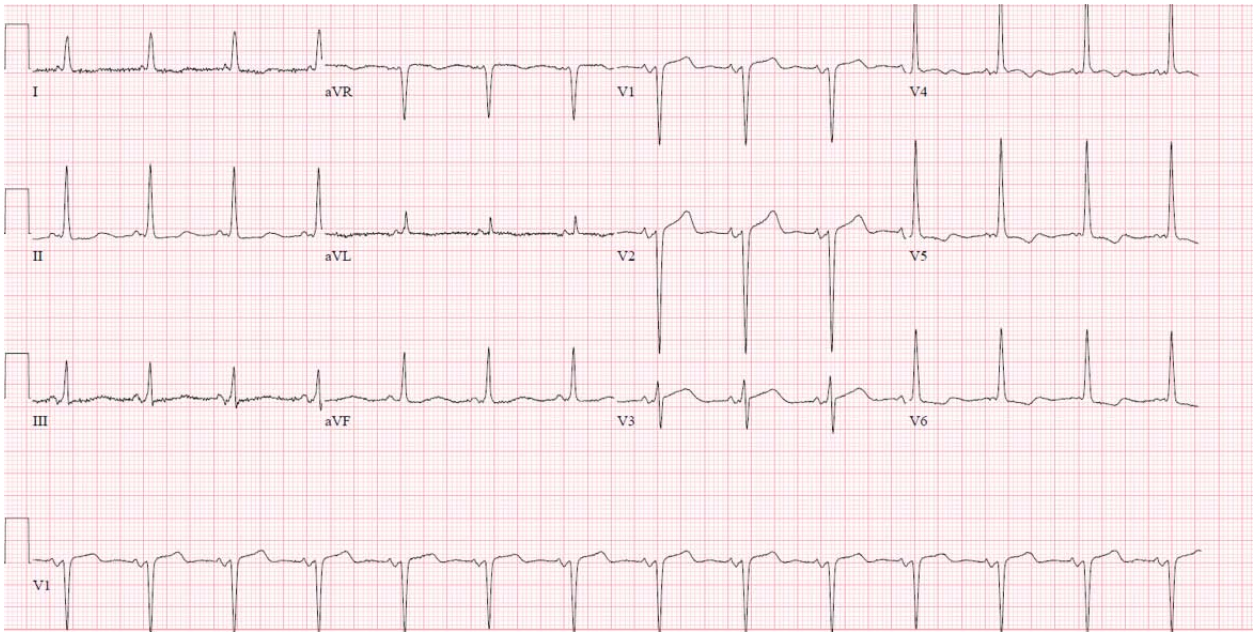

Figure 2. ECG showing return of normal sinus rhythm after cardiazem injection

3. Discussion

AVNRT is one of the types of paroxysmal supraventricular tachycardia occurring as a result of a re-entry circuit within or adjacent to the AV node [16,17]. A difference in conduction velocity and refractory period of the pathways is the basis of the origin of a re-entry circuit. A fast conduction pathway is characterized by fast conduction and a slow refractory period, whereas slow conduction pathways have slow conduction coupled with rapid refractory period [16,18]. Atrial impulses reach AV node via two distinct pathways- one located in the anterior part of the triangle of Koch (fast pathway), and the other in the posterior part of the triangle of Koch (slow pathway) [15]. Normally in a healthy individual, conduction occurs through the fast pathway but in a susceptible individual, a premature atrial beat comes across a refractory fast pathway. There is anterograde conduction via the slow pathway. On reaching the common endpoint, there is a retrograde conduction via the fast pathway back to the atrium leading to a typical AVNRT [15,19,20]. Based on the ECG findings, the re-entrant circuits can be categorized as (a) Slow-fast AVNRT, characterized by Pseudo-S wave in leads II, III, and AVF ; Pseudo-R in lead V1 (b) Fast-slow AVNRT with P waves between QRS and T wave; QRS-P-T complexes (c) Slow-slow AVNRT with late P waves after QRS, appearing as atrial tachycardia. 90% of AVNRT is Slow-fast AVNRT [16].

There has been an increase in the reporting of various cardiovascular events after the consumption of marijuana along with its serious consequences [21]. One of the prominent effects of marijuana smoking is tachycardia, with 20-100% increase in the heart rate, due to reflex tachycardia caused by marijuana -induced vasodilation [9,22,23]. Delta-9-THC, the active component of Cannabis sativa, acts via cannabinoid receptors, namely CB1 which is expressed in liver, muscle, brain, fat cells, heart, peripheral and autonomic nervous system; and CB2 present in spleen, immune cells and peripheral tissues [24,25]. The primary target of delta-9-THC is CB1 receptors mediating the majority of cardiovascular effects through activation of the sympathetic nervous system [9]. A scoping study conducted by Kariyanna et al. enlists the marijuana use with cardiac arrhythmias reported last year [26]. The result of the study concluded that 81% of the patients were young males with a mean age of 28±10.6 years. The most common arrhythmias reported were atrial fibrillation (26%) and ventricular fibrillation (22%) [26]. An observational study was also conducted by Desai et al. to measure the temporal trends of the frequency of arrhythmia in hospitalized marijuana users in the US [27].

The possible mechanisms involved in the pathophysiology of AVNRT by marijuana are not well understood due to the rarity of its incidence and proper study trials. The postulated theories could be a difference in the regional sympathetic and parasympathetic neuronal distributions in the heart with prominent vagal influence in the SA node and sympathetic nerves in the atrium [15,28]. Marijuana has a dose-dependent effect on the autonomic nervous system with lower doses stimulating the sympathetic nerves and higher doses affecting the parasympathetic system [15]. Some studies also state the direct effect on autonomic activity or Purkinje fibers [29,30]. As stated earlier, the fast pathway and the slow pathway are the key factors in the origin of the re-entry circuit. Vagal tone increases the refractory period of the fast pathway but does not have the same effect on the slow pathway and retrograde fast pathway. This leads to the development of AVNRT at the peak of the parasympathetic tone [15,31]. Marijuana induced parasympathetic activation leads to inhibition of the fast pathway, and a generation of premature atrial complex which is conducted via the slow pathway in an anterograde manner with subsequent retrograde conduction, thus triggering AVNRT [15].

Marijuana toxicity depends on many factors such as the type of exposure, acute or chronic use, route of administration, quantity, quality of marijuana preparations which specifically differ depending on the time and place of supply [32,33]. Many factors interplay in underestimating the incidence of cardiovascular effects caused by marijuana. Patients failed to report, physicians failed to inquire, delay in ordering the test, delay in relating the reason for hospitalization, failed to know the origin and composition of marijuana [32]. Approximately 16-26% of the patients, who are using medical marijuana, also consume its edible products [34,35,36]. There is a significant overlap between the two groups of marijuana users which are self-medication users and recreational users [37,38]. It is an issue of concern, especially in the states where marijuana use has been legalized, the rising trend of use of edible marijuana [39,40].

Edible marijuana, are the food products with cannabis extract, which are available as baked goods, candies, gummies, chocolate, lozenges and beverages [39]. About 29.8% of marijuana users, reported consuming it in the form of edible or beverages, as per nationally representative study of adults in the US [41]. Cone et al conducted a study on the subjects, with a history of marijuana use, in the form of marijuana -infused brownies and measured the behavioral and physiological effects [42]. The result displayed that participants experienced peak responses approximately within 3 hours of ingestion and disappearing within 24 hours [41,43]. One of the advantages of this route is the long duration of action [44]. The route of administration affects the pharmacokinetics of any drug. 5-20% is the bioavailability of the orally ingested marijuana and new users experiencing the psychotropic effects with 5-20 mg of ingested THC [45]. Edibles enter the gastrointestinal tract from where delta-9-THC, the active ingredient of marijuana, enters the bloodstream and then reaches the liver to undergo first-pass metabolism. Liver enzymes (the cytochrome P450), converts delta-9-THC into 11-hydroxy tetrahydrocannabinol (11-OH-THC) which is a potent metabolite that can readily cross the blood-brain barrier [46]. 11-OH-THC is more potent [47] and can be found in the blood in higher quantities when marijuana is ingested than when it is inhaled [48], hence causing stronger and long-lasting effects as compared to smoked marijuana [49]. Due to the lack of consistency and delayed intoxication, users of edible marijuana tend to consume a higher amount leading to more adverse reactions [39]. A study conducted at the University of Colorado, between 2012-2016, estimated that about 9% of the marijuana-linked visits to the ER were involving edibles

and 8% of them had cardiovascular complaints [50]. Though edibles constituted only 0.32% of sales in 2014-2016 they were leading to more ER visits each year as compared to smoked marijuana [51]. Recently marijuana laden products have reached the market resembling commercially available products like gummies, candies, lollipops, burgers, energy drinks aiming to attract younger people [9,52,53]. Recently a 70 year-old man suffered from non-ST segment elevation myocardial infarction (NSTEMI) after consuming a marijuana lollipop as reported by a Canadian Journal [54]. There is a growing number of psychoactive synthetic cannabinoids, known as 'designer drugs' entering the market, acting as CB1 agonists with 10-200 times the potency of THC. They are often mixed with herbs, oily solutions, brownies and sold with the names of black Mamba, Bombay blue, fake weed, K2, spice to name a few [55]. One of the journals reported symptomatic patients, aged 20-75 years, unknowingly ingesting brownies laced with synthetic CB1 agonists like AM-2201 [56].

The lack of standardization in the manufacturing and labeling of the formulations on the packet, showing the correct amount of delta-9-THC and marijuana, has lead to catastrophic consequences [39]. Researchers encounterd that only 13 out of the 75 edible marijuana products had accurate labels of the correct dosage of delta-9-THC in the product [57]. The 2016 report from the WHO on The Health and Social Effects of Nonmedical Marijuana stated that marijuana use is associated with adverse cardiovascular effects and there has been an increase in the content of delta-9-THC from 2-3% to 20% resulting in the rise of cannabinoid-receptor mediated harmful cardiovascular events [58]. More clinical studies are needed to highlight a causal association between marijuana use and arrhythmias. Acute marijuana intoxication is a clinical diagnosis. Urine tests, used for detection of THC in urine, reflects chronic usage of marijuana [59]. Mass spectral gas chromatography, though not easily available in the emergency department, is the most suitable method to determine the time of consumption [42,60]. The range for detection of THC in urine by immunoassay is 20-100 ng/ml; 50ng/ml has been determined as positive level by the Substance Abuse and Mental Health Services Administration (SAMHSA) Standards [61].

Well-conducted controlled studies are the needed to alert the physicians of the potentially lethal and harmful effects of unregulated use of marijuana and its effects on the cardiovascular system. Edible products should have standardized product formulations, adequate processing quality control and appropriate packet labeling. Awareness among the users about the correct dosage and toxicities of marijuana should be provided with education.

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