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Pathological changes in anabolic androgenic steroid users

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ABSTRACT

Several classes of recreational and prescription drugs have additional effects on the heart and vasculature, which may significantly contribute to morbidity and mortality in chronic users. The study presented herein focuses on pathological changes involving the heart possibly due to anabolic androgenic steroid use. The role these hormones may play in their occurrence of sudden cardiac death is also investigated. 98 medico-legal cases including 6 anabolic androgenic steroid users were retrospectively reviewed. Autopsies, histology, immunohistochemistry, biochemistry and toxicology were performed in all cases. Pathological changes consisted of various degrees of interstitial and perivascular fibrosis as well as fibroadipous metaplasia and perineural fibrosis within the myocardium of the left ventricle. Within the limits of the small number of investigated cases, our results appear to confirm former observations on this topic and suggest anabolic androgenic steroid's potential causative role in the pathogenesis of sudden cardiac deaths in chronic users.

1. Introduction

Several classes of recreational and prescription drugs acting primarily on the central nervous system have additional effects on the heart and vasculature which may significantly contribute to morbidity and mortality. Use or abuse of illicit drugs such as cocaine and amphetamines is associated with an increased risk of cardiovascular complications including arrhythmias, myocardial infarction and cerebrovascular accident.[1]

In addition to recreational and prescription psychotropic drugs, numerous other substances acting primarily on other systems may also produce adverse effects on the heart and vessels, thus being potentially responsible for sudden deaths in chronic users. Both left ventricular hypertrophy and myocardial infarction with and without significant atherosclerotic coronary artery disease have been described in association with anabolic androgenic steroid abuse.[2–5] Exhaustive microscopic investigations of the myocardium, along with toxicology and biochemical investigations, are therefore mandatory in the evaluation of sudden unexpected deaths related to anabolic androgenic steroid use or abuse.

The study presented herein focuses on pathological changes involving the heart that may be due to anabolic androgenic steroid use and their possible role in the occurrence of sudden cardiac death.

2. Materials and methods

2.1. Study design and study populations

The study was designed as a retrospective study involving two centres. All cases collected for the study underwent medico-legal autopsies as requested by local inquiring authorities. Six anabolic androgenic steroid users (all males, mean age 39 years) were identified. All cases had been admitted to the mortuary due to sudden, unwitnessed deaths. Personal data and medical records, when available, were collected from families, clinical patient databases, general practitioners, and local health services. Electrocardiograms and/or echocardiograms performed during medical check-ups were not systematically available. Death and medico-legal autopsy intervals ranged between 24 and 48 h. The causes of death were not clearly identified based on macroscopic or microscopic findings. Moreover, toxicology and biochemistry failed

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to provide evidence suggesting death following drug intoxication or metabolic disturbances. The cause of death in these cases was considered cardiac arrhythmia based on the results of all post-mortem investigations and the exclusion of other obvious causes of death.

One control group (sudden death group) consisted of 46 forensic autopsy cases (42 males and 4 females, mean age 40 years). All cases included in this group originated from forensic practice and were admitted to the mortuary following sudden, unexpected death.

A second control group (suicide group) consisted of 46 forensic autopsy cases (42 males and 4 females, mean age 44 years). All cases included in this group originated from forensic practice and were admitted to the mortuary following hangings or gunshot wounds to the head.

All control subjects were void of any drug treatment at the time of death and had never assumed anabolic androgenic steroids. As in the anabolic androgenic steroid users group, personal data and medical records were collected from families, clinical patient databases, general practitioners, and local health services. Death and medico-legal autopsy intervals ranged between 20 and 46 h.

In the sudden death group, a cardiac cause of death could be identified in 21 out of 46 cases based on macroscopic and microscopic findings as well as negative toxicology and biochemistry. In the remaining 25 cases, the cause of death was not identified based on autopsy and histology results. Toxicological and biochemical investigation did not provide evidence suggesting drug intoxication or death due to metabolic disturbances. Cardiac arrhythmia was therefore judged the most likely cause of death based on all post-mortem investigation findings.

2.2. Postmortem investigations

Medico-legal autopsies, histology, toxicology and postmortem biochemical investigations were performed in all cases. Immunohistochemistry (antibodies against fibronectin and c5b9 in the myocardium) was also performed in anabolic androgenic steroid users. The immunohistochemical markers whose expression was investigated in this study were chosen because they are known to react in cases of early myocardial ischemia. Medical records and clinical histories as well as police reports pertaining to each case were consistently reviewed before conclusions were made. Conventional autopsies were performed within 48 h after death and were carried out jointly by two forensic pathologists (at least one board-certified) as in accordance with both local standards and international guidelines for medico-legal autopsies. The guidelines for autopsy investigation developed by the Association for European Cardiovascular Pathology were also adopted.

Peripheral blood from the femoral veins, cardiac blood, vitreous humor, urine, cerebrospinal and pericardial fluids as well as gastric contents, hair and samples of certain tissues (liver, brain and skeletal muscle) were recovered for toxicological and biochemical analyses. Toxicology consisted of ethanol determination in blood as well as general screening for common drugs and illegal substances by liquid chromatography coupled to tandem mass spectrometry. Anabolic androgenic steroid screening was performed in urine samples by gas chromatography-mass spectrometry. Testosterone abuse was assessed by urinary testosterone to epitestosterone ratio.

Biochemical investigations systematically included determination of blood acetone and beta-hydroxybutyrate, vitreous glucose, postmortem serum mast cell tryptase, postmortem serum inflammation (C-reactive protein, interleukin 6) and infection (procalcitonin) markers, postmortem serum troponin T, postmortem serum cholesterol, triglycerides and apoliproptein B as well as renal and hepatic function markers.

Conventional histology included haematoxylin-eosin (HE) stain of brain, heart, lung, liver and kidney samples. Representative samples of the myocardium and coronary arteries were obtained during autopsy for each case. Histology stains for the myocardium and coronary arteries included the following colorations: HE, Mallory-Azan, Masson trichrome Goldner with light green and Verhoeff van Gieson. Immunohistochemical reactions using antibodies against fibronectin and C5b-9 of both cardiac ventricles were also performed in all anabolic androgenic steroid users.

3. Results

Circumstantial elements (personal data collected from relatives and friends, house searches carried out by the authorities) confirmed chronic anabolic androgenic steroid use in all the cases.

External examinations and autopsies showed prominent muscular masses. Asymmetrical left ventricular hypertrophy and cavity dilatation were not observed. The pericardium, valvular apparatus and endocardium were normal. The coronaries arteries arose from normally located patent ostia possessing normal anatomical disposition and did not show evidence of significant luminal narrowing. In one case (weight 90 kg, height 178 cm, body mass index 28.4), the heart weighed 490 g (0.54% of body weight) with wall thicknesses of 20 mm for the left ventricle, 16 mm for the interventricular septum and 5 mm for the right ventricle. Acute myocardial infarction was not observed in any of these subjects. Autopsy and histology revealed various degrees of testicular atrophy in all cases.

The main myocardial and coronary artery histological findings (Table 1) consisted of interstitial and perivascular fibrosis, perineural fibrosis within the left ventricle (Fig. 1), fibroadipous metaplasia within the left ventricle, contraction band necrosis, myocardial cell segmentation and intercalated disc widening. Bundles of contracted myocytes alternating with bundles of distended myocardium were also noted. Most coronary arteries were normal or revealed only slight intima thickening in their subepicardial portion. Occasionally, the coronaries were characterized by scattered fatty streaks as well as intima and media thickening.

Immunohistochemistry failed to reveal diffuse myocyte or necrosis involving groups of myocytes. Occasional single myocyte necrosis within the left ventricle was observed. Postmortem biochemical investigations did not show significant increases in troponin T levels in any of these cases. Postmortem serum cholesterol, triglyceride and apolipoprotein B levels were increased in 3 out of 6 cases. Hepatic function markers were at normal levels in 5 out of 6 cases, though hepatic steatosis was histologically observed in 4 out of 6 cases.

Ethanol was detected in blood in one out of six cases. Toxicology performed in blood and urine failed to reveal other recreational or prescription drugs. Anabolic androgenic steroid screening was performed in urine samples and revealed high levels of nandrolone in three cases and high levels of testosterone in three cases (in one case, the urinary ratio of testosterone to epitestosterone was 21). Hair analysis confirmed the presence of nandrolone and testosterone, unveiling no other recreational or prescription drug intake during the months preceding the death.

In the control groups, autopsies and histology revealed occasional left ventricular hypertrophy and cavity dilatation, interstitial and perivascular fibrosis, contraction band necrosis and atherosclerotic changes varying from rare fatty streaks and wall thickening to significant luminal narrowing and diffuse interstitial fibrosis. Perineural fibrosis within the left ventricle was not observed. In the sudden death group, a cardiac cause of death could be identified in 21 out of 46 cases.