NEUROLOGICAL CONSEQUENCES OF ABUSIVE USE OF ANABOLIC-ANDROGENIC STEROIDS

CONSEQUÊNCIAS NEUROLOGICAS DO USO ABUSIVO DE ESTEROIDES ANDROGÊNICOS ANABOLIZANTES

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ABSTRACT

The abuse of anabolic-androgenic steroids (AASs) is associated with high morbidity and mortality rates. The highest incidence of this malpractice documented in males (prevalence rate about 6.4%), a third of which develop adverse reactions. Accordingly, the objective was to review published studies about the neurological complications triggered by the indiscriminate use of AASs, with focus on the pathogenesis of lesions in the nervous system (NS). As a result, it was observed that at NS, these stimulants actuate through a complex signaling systems that include the neuroendocrine alteration of the hypothalamic-pituitary-gonadal axis, modification of neurotransmitters and their receptors, as well as the induction of neuronal death by apoptosis in several pathways. These organic neurological alterations can lead to a clinical symptomatology with neurological, mood and sleep disorders. Consequently, varying adverse effects were observed analogous to the class of AAS utilized, how it was administered and time of use. Even though to date, only a few classes were submitted for scientific analyses, on dosages, mode of administration and specific exposure times. Furthermore, the illegal use and production of these drugs does not propitiate their appropriate application, quality control and purity. It was concluded that the abuse of AAS has inimically severe and complex effects, including serious neurotoxic issues.

KEYWORDS: Anabolic steroids; hormones; neurology; psychiatry; adverse effects.

1. INTRODUCTION

Steroids comprise a large group of fat-soluble substances derived from cholesterol molecules. Their basic structure comprises seventeen carbon atoms, arranged in four rings connected to each other[1]. They are widely distributed in living organisms (e.g. sex hormones and vitamin D). The gonads and the adrenal cortex naturally synthesize steroid sex hormones by actualizing several anabolic and androgenic functions (metabolic control and the development of sexual characteristics) in the body. These hormones can also be produced synthetically for medical-therapeutic purposes[1, 2, 3].

Anabolic steroids, also known as anabolic-androgenic steroids (AASs), are synthetic drugs that have a chemical structure analogous to steroids produced by the body [3]. These steroidal androgens mimic the effects of testosterone by altering functions related to metabolic control and the development of sexual characteristics [2, 3]. Legally, AASs are employed for specific medical conditions, such as hypogonadism. Illegitimately, they are primarily used to improve aesthetics, increase muscle mass increase performance and endurance, and reduce recovery time between workouts. However, many users can underestimate the health risks associated with the abusive use of these medications[2, 4].

Currently, exploitation of anabolic steroids is a worldwide problem and involves millions of individuals, mostly young men[4, 5]. The primary objectives of these individuals are stimulation of muscular hypertrophy and enhancement of athletic performance, ensuring greater resistance, physical strength, allied with improved self-confidence and body fat reduction[1, 4]. It is estimated that 43% of cases of hypogonadism in young men are related to previous abuse of AASs [6]. Moreover, the misuse of AASs is globally documented among 18.4% of recreational athletes and 6.4% of men[7].

Data from current literature show that anabolic steroid abuse is associated with increased morbidity and mortality[9,10], given that a third of AASs consumers develop disadvantageous effects from abusive use [11,12]. In the medical and scientific community, the deliberation on the side effects from AASs is still inadequate[10]. Accordingly, further studies are essential to specify their instability and whether the collateral developments are linked to a particular mode of use. Thereby, preventive and control measures could be established, to regulate such inimical reactions, as well as seek adequate measures to limit the perversion of these substances[10,11].

Due to the relevance of the theme, the present study sought to review, analyze and compile the

published data on the main adverse effects and neurological complications triggered by the indiscriminate use of AASs with focus on the etiopathogenesis of central nervous system lesions.

2. MATERIAL AND METHODS

Search strategies and article selection

To perform this study, PubMed, Scopus and SciELO databases were searched for articles, published up to April 2019. The search strategy was based on three components: (i) anabolic-androgenic steroids, (ii) neurotoxicity and neurological complications and (iii) common adverse effects. The search filters were developed in concordance with the thesaurus platform - MeSH terms (Medical Subject Headings). The following descriptors and Boolean operators were utilized "Anabolic Agents AND Neurotoxicity Syndromes", "Testosterone Congeners AND Neurotoxicity Syndromes", and "Anabolic Agents AND Adverse effects". Neither language nor chronologic restrictions were applied when searching for the articles. The initial screening was carried out considering the title and abstract of all articles found. Contrasting the authors, title, year and journal of publication eliminated duplicated studies. After this first selection, all potentially relevant studies were downloaded in their entirety to have their eligibility assessed.

Exclusion and Inclusion Criteria

The exclusion of studies relied solely on the following well-defined criteria: (i) studies concerning AASs not associated with adverse effects, (ii) studies relating to AASs that didn't include data of common clinical/neurological aspects, (iii) adverse effects by drugs abuse with no relation to AASs; iv) studies from secondary or incomplete texts (i.e. editorials, remarks/comments, letters to the editor, dissertations, theses, book chapters, publications in event annals and articles unavailable in full-text). The reference lists of the relevant articles were selected for potentially admissible documents. The inclusion criteria focused on articles which dealt with individuals who engage or partook in the use of AASs and suffer from the adverse effects correlated to the common clinical/neurological aspects. Moreover, this criteria was specifically defined to contemplate the proposed objective, granting a greater in-depth analysis of the use of anabolic steroids and the probable damage to the nervous system or alterations to general clinical standards.

Data extraction

Qualitative data was obtained from all of the included articles. The extraction of the data was classified as follows: (i) Therapeutic indications; (ii) Chemical composition; (iii) Effects - therapeutic and general adverse effects; and (iv) Neurological effects: general neurological signs and symptoms; Etiopathogenesis of neurological disorders; AASs and morphological changes; AAS and the death of neurons.

3. LITERATURE REVIEW

Therapeutic indications

Clinical indication for therapeutic intervention with AASs is associated with situations of hypogonadism, to promote the increase of gonadocorticoids and gonadal steroids, and as a result, stimulate the development and maintenance of the body's sexual characteristics. They are also indicated in cases of delayed puberty and growth stimulation, neonatal micropenis, deficiency of protein metabolism, partial androgen deficiency in elderly men and the treatment of androgen deficiency subsidiary to chronic diseases[2,3,4,5]. In addition, the adoption of these stimulants in AIDS-related cachectic patients or associated chronic diseases (cancer, chronic renal failure, and chronic obstructive pulmonary disease) has substantiated the studies on the manipulation of body weight[3,4,5,6,7,8]. Thusly, the pharmaceutical dispensing of these drugs should only be executed under medical supervision[9,12].

Currently, AASs are widely used to promote muscular hypertrophy and greater athletic performance, which guarantees greater resistance, physical strength, tiredness relief and muscular fatigue, allied with increased self-confidence and body fat reduction[11,12,13]. These effects are triggered by increased muscle mass, increased hemoglobin and hematocrit concentration, nitrogen retention, increased calcium deposition, and increased fat combustion[3]. Due to many physical and predominantly aesthetic improvements, there has been an increase in the application of AASs in the last five decades worldwide[14,15].

Chemical composition

The name anabolic-androgenic steroids is attributable to its chemical structure, which is analogous to the hormones produced by the organism. These synthetic compounds have several active principles, among them: testosterone & some of its esters, methyltestosterone, oxandrolone, fluoxymesterone, nandrolone decanoate and oxymetholone[1,3,4].

The AASs have in their structure chemical variations classified as 17-α-Alkylation, 17-β-esters and 1-methyl steroid, which exhibit distinct peculiarities, but with similar objectives. The most used variations are divided into two pharmaceutical forms: oral (17-α-nickel) and injectable (17-β-esters). The injectable type (administered intramuscularly) is less harmful when compared to the oral formulations. Another advantage they present is lipid solubility, which minimizes contamination by bacteria and slows its circulation in the bloodstream, thus prolonging its action[4,17]. Most oral AASs have hepatic metabolism and are alkylated at the 17th carbon atom, with extensive first-pass metabolism in the liver, making them highly hepatotoxic[10]. The principal injectable forms, generally accepted by users, on the market are

Stanozolol, Nandrolone; composite of four synthetics: propionate, phenylpropionate, and testosterone isocaproate and decanoate. Additionally, they include drugs exclusively implemented in veterinary medicine, mainly in horses (e.g. testosterone cypionate & boldenone undecylenate). The oral varieties commonly appropriated by users are oxandrolone and metandienone[4,16,17,18] (Figure 1).

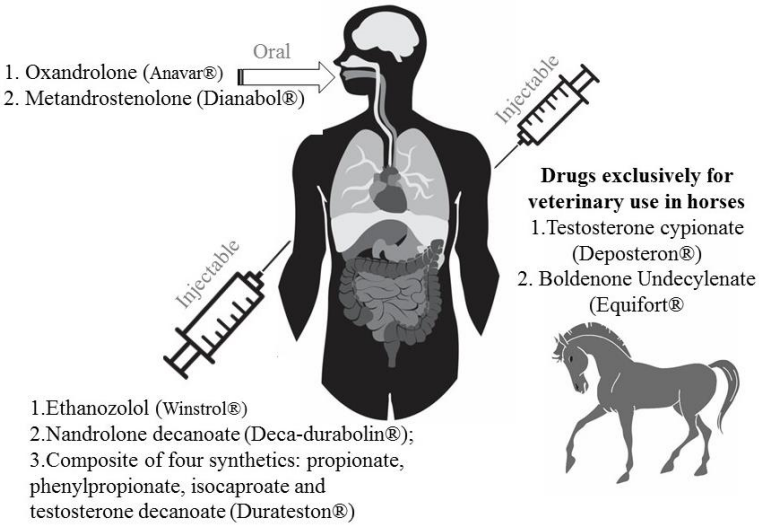

Figure 1: Most used anabolic-androgenic steroids divided according to the route of administration, active principle and trade name[4,16,17,18] * In parenthesis: commercial name.

Effects

Therapeutic effects

At therapeutic doses, the androgenic effects of AASs are usually acknowledged as those, which generate masculinization in the organism, being the development of internal & external genitalia, thickening of vocal cords, and an increase in libido, terminal hair growth, secretion from the sebaceous glands. Whereas the anabolic effects are manifested as manipulations of the skeletal muscle and bone, hemoglobin and hematocrit concentrations, retention of nitrogen and bone deposition of calcium with body fat reduction[4,18,19]

General adverse effects

The adverse effects are induced from the application of AASs in high dosages, in most cases without prescription; these doses are said to be 10-100 times greater than the usual effective concentration (EC). Furthermore, the fact that specific pharmacological receptors of the drug are saturated with doses well below the aforementioned should be highlighted[8].

The two major reasons for the exploitation of these stimulants are (i) efficiency and performance enhancement of competitive and recreational athletes, and (ii) solely aesthetic purposes. Both reasons are physiologically linked to the anabolic actions of these substances, which can stimulate nitrogen fixation, with positive nitrogen balance, stimulus to erythropoiesis, increased protein synthesis in several tissues, muscle development in the body[1,3,4,22]. Wherefore, users perceive it as seemingly advantageous the continuous exploitation of the AASs[1,3,7]. In the United States, it is estimated that 67% of elite athletes use these drugs[20], whereas in Brazil, the prevalence is around 11.1%[21].

Although complete dissociation of the side effects have not yet been achieved, some AASs have shown a significant increase in anabolic activity with reduction of androgen effects[1,4], which favors the heightened consumption of the drug for those seeking rapid gains. The anti-catabolic effects of these compounds occurs mainly through inhibition of bone resorption and reduction of protein degradation[1,19].

Most users are aware of the adverse effects from misuse (e.g. mood fluctuations, gynecomastia, decreased libido and suppression of spermatogenesis, besides reduction in HDL cholesterol, and increases in hematocrit and liver toxicity) which they egocentrically choose to ignore, classifying them as mild or transient[10, 11]. In women, there are plausible changes in the menstrual cycle, thickening of the voice, and growth of facial hair. In adolescents, growth may be interrupted prematurely and permanently[1,4,5]. Effects such as testicular tissue atrophy, hepatic & prostate tumors, cirrhosis, endocrine system disturbances, and lipid metabolism alterations[4,5,8,18] are commonly documented over continuous usage, at high doses. Withdrawal of androgens after chronic use may induce prolonged and sometimes irreversible hypogonadism; with frequently reported hepatotoxic & nephrotoxic effects and musculoskeletal system issues[4,5,6,7].

Recent studies have confirmed that long-term supra-physiological exposure to AASs produces cardiovascular toxicity, leading to acute myocardial infarction, caused by significant reductions in diastolic measurements and hypertrophy of the heart muscle in addition to atherosclerotic disease[4,5,6,8].

Neurological effects

General neurological signs and symptoms

The effects of AASs in the Central Nervous System (CNS) have a wide spectrum of signs and symptoms, depending on the variety consumed, dose and duration of use. They can range from the neuroendocrine inhibition of the hypothalamic pituitary gonadal axis (causing hormonal disorders), cardiovascular and hemodynamic changes, and even behavioral disorders such as mood and sleep disorders[23, 26].

Emerging evidence suggests that long-term abusive exposure to anabolic steroids can cause neurotoxicity. The neurological alterations triggered by neurotoxicity can lead to the establishment of distinct clinical symptomatology such as mood & sleep disorders (expressed as depression and insomnia), increased irritability, and aggression.

The depression is usually interpreted as a withdrawal symptom[2,3,4]. In addition, there is also an increased possibility of dementia after prolonged high dosage application[4,5].

The administration of these pharmaceuticals, in abusive doses, is also associated with anxiety, hypomania or mania[27,28]. These changes reflect the remarkable psychopathological comorbidity between drug dependence and disorders that induce neurotrophic changes in the neural circuits[29].

Etiopathogenesis of neurological disorders

The anabolic steroids trigger pharmacological effects in the CNS in two distinct ways: directly, with modulation in their intracellular receptors; and indirectly, by influencing the binding site located at the neurotransmitter receptor or causing the release of neuropeptides [30, 31]. These actions can affect the expression of neurotransmitter receptors namely gamma-Aminobutyric acid (GABA), serotonin (5-HT), glutamate (GLU) and dopamine (DA), which, among others, are abundantly expressed in areas of the brain associated with varying physical and psychological comportments[32,33,34,35] **(**Figure 2).

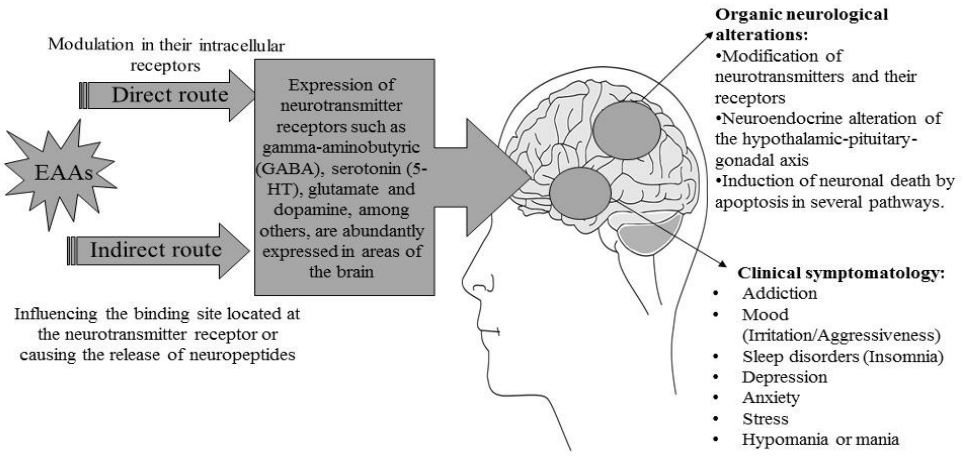

Figure 2: Etiopathogenesis of neurological disorders by pharmacological actions in the Central Nervous System triggered by anabolic-androgenic steroids (AASs) (32, 33, 34, 35).

Moreover, the interaction between the polymorphic region of the 5-HT receptor expression and neuroticism has been identified in athletes predisposed to anxiety, depression and aggressiveness, and the dose-dependent effect[36]. The regions of the brain involved in this expression are the hypothalamus, basal gland, amygdala and hippocampus, which seemingly have a greater effect on the steroidogenic enzymes and the receptors involved in their synthesis and metabolism[37,38]. Studies have shown that anabolic activity provokes drastic neurological modifications by reducing the amount of proteins that are employed as 5-HT (modulator of several physiological processes) receptors; this justifies the onset of withdrawal symptoms (e.g. depression), especially after the discontinuation in intake of AASs, considering the possible evolution to suicidal tendencies[5,15,39].

In addition to 5-HT, anabolic steroids also interfere with the signaling of DA (neurotransmitter responsible for motor and behavioral synapses in the CNS). Differently to the commonly abused drugs, they do not trigger amplified euphoric impulses, nor do they present immediate intoxication, since they do not immediately alter the DA levels in the organism. However, they do activate the reward system (drug dependency), signaled by DA, and consequent, abstinence withdrawal syndrome[5,11,40]. AASs exert different effects on distinct DA receptors. Specifically, they can decrease the density of the D1 receptors in the striatum and that of both of the D1 and D2 receptors in nucleus accumbens (NAc/NAcc). In contrast, they increase the density of the D2 receptors in the putamen[32]. Studies of Nandrolone administration have shown that the drug reduces DA activity, in addition to decreasing the levels of its metabolites[41]. This is worrying since NAc is part of the mesocorticolimbic dopamine system and is involved in important physiological events such as cognition, decision-making, motivation and reward[32].

In a study evaluating age variability amongst AASs abusers and consumers (athletes and habitual users), it was suggested that anxiety disorders were more prevalent among those who were also engaged in excessive consumption of alcohol, compared to non-AAS users[42]. Therefore, researchers have proposed that the abuse of AASs in adolescence can alter the body's androgen levels, which can negatively influence their psychological comportment[43].

Emotional and behavioral burnouts have been conceptualized as sudden and exaggerated provocations from the application of the stimulants[43,44]. In addition, users suffer from an inability to adapt to situations, generating frustration and impulsivity[45].

Piacentino *et al.* (2015)[45] argued that the relationship between the use of the pharmaceuticals and the observed psychopathologies should not be considered as simple and isolated events. Citing the importance of the analysis of the complex circuitry regulated by the neuroendocrine mechanism encompassing different regions of the CNS and the hypothalamic-pituitary-adrenal axis (HPA axis)[45]. Another aggravating factor corroborating this analysis is the fact that most AASs bind to the androgenic and estrogenic receptors, found abundantly in the CNS, with high local aromatase activity, generating strogenic metabolites[46]. This metabolites, to activating secondary messengers, are able to interact with both the estrogen receptor

alpha (ERα) and the estrogen receptor beta (ERβ), and/or the progesterone receptors, without being metabolically converted into estrogen[26,47]. Thus, these stimulants can expand their effects to systemic levels and reinforce the exponential increase of adverse effects.

The signaling initiated by anabolic steroids in the CNS include classical genomic and non-genomic actions. After combining with the androgenic intracellular receptors, the steroids induce oxidative stress and impair mitochondrial activity, when in high doses. These drugs also affect GABAergic transmission (in the forebrain)[26,48,] which intensifies aggressiveness and irritability[46,49].

Utilizing *in vivo* testing, the exploitation and chronic use of anabolic steroids were shown to reduce levels of the neurotrophic factor in the hippocampal and prefrontal cortex regions; also demonstrating a reduction in the glucocorticoid receptor (GR/GCR) expression in the hippocampus and an increase in diurnal basal levels of corticosterone[50]. In human subjects, around 500 AAS users, nearly half had insomnia, and the others experienced varying sleep disturbances such as increased non-REM sleep phase 4 and REM sleep latency[51,52]. Additionally, patients under chronic anabolic use also presented reduction in total sleep time with reduced efficacy, together with reductions in the non-REM phases and increases in the N253 stages. This develops from increase neuronal excitability derived from actuation of these steroids on the CNS[51,52,53].

Psychological and psychiatric manifestations were other topics extensively described in the literature. Mood changes (euphoria, increased self-esteem, emotional lability, impulsivity); modifications in comportment such as cognitive skills, aggression and violence[21]; antisocial behavior; and manic episodes, delirium, paranoia, and schizophrenic outbreaks were observed in several cases[54]. These symptoms require further examination to elucidate the relationship between dosage and period of exposure to AASs.

AASs and morphological changes

Regarding the CNS anatomy, these stimulants alter the morphology of neurons and the glial cells in the region of the NAc shell. These neuroanatomical changes are a likely cause of the cognitive effects produced by the drugs. Male subjects who administer anabolic steroids have exhibited a smaller volume of gray matter in their cortex and putamen compared to those who do not[55]. Prolonged exposure to the drug probably has the greatest impact on the structural characteristics of the brain, especially in individuals who develop dependence.

In the evaluation of the cellular alterations, *in vivo* was incorporated to assess the structural alterations in the particular regions of the brain that were briefly exposed to the anabolic steroid Nandrolone decanoate. Recent research concluded that no significant changes were noted in the cellular framework, particularly in Purkinje fibers of the cerebellum[56]; the neurons responsible for the afferent modulation of afferent sensory information reaching the cerebellar cortex[57,58]. In contrast, another similar study, but which adopted the testosterone cypionate as its focal point, demonstrated a decrease in Purkinje cells in female animals and a noticeable increase in the aggressiveness of treated animals compared to the control group[59]. Furthermore, similar investigations using alternating dosages and periods of administration of Boldenone and Stanozolol also revealed variations in the levels of reactive oxygen species (ROS) in the cerebral cortex and hippocampus[57], responsible for the cellular neurotoxicity of these regions.

Using a magnetic resonance imaging (MRI), structural and functional analyses were executed on weightlifters using AASs. These subjects exhibited increased amygdala volume and reduced functional MRI coupling in the resting state of the amygdala. It was suggested that prolonged use of such might negatively modulate functional and structural brain networks related to the amygdala[58]. This data emphasized the need for further investigation in this area to substantiate the involvement of anabolic steroids in cerebellar lesions, considering the importance of this region for the organisms' cognitive and motor capabilities.

AAS and the death of neurons

Cases of dementia in chronic users of AAS have been associated with induction of neuronal death (4, 5). The neuronal apoptosis was observed in assorted extensions, through several mechanisms, and solely varying according to the class of AAS used[2].

High concentrations of anabolic steroids can alter intracellular calcium-dependent transmission, affecting inositol trisphosphate (IP_3) receptors, leading to the apoptosis[60]. Apoptosis is also caused by the over-stimulation of GLU receptors associated with increased calcium influx through ion channels linked to these receptors[13,26]. Also N-Methyl-D-aspartate (NMDA), a GLU receptor agonist, can trigger extrinsic apoptosis via signaling of extracellular stress. There is a suggestion that AASs increase neuronal susceptibility to apoptotic stimuli[14], corroborating the results of the *in vitro* studies in which the apoptotic repercussions were only observed in dopaminergic neurons cultured through the oxidative stress induced by these stimulants[2].

By amplifying the apoptotic events induced by anabolic steroids, the involvement of the beta-Amyloid 42 peptide (Aβ42), may contribute to the onset and/or progression of neurodegenerative diseases (Alzheimer's disease)[15]. It was also shown

that trenbolone acetate increases Aβ42 production and induces apoptosis in primary hippocampal neurons[22].

4. CONCLUSION

Despite the seemingly detrimental effects derived from the misuse of anabolic steroids, there is still a scarcity in the implementation effective strategies to prevent this reoccurrence. It is difficult to deliberate upon the specific risks involved from the abuse of these pharmaceuticals in general terms by virtue of several determinants, namely their contrasting classes, mode & duration of administration and the particular characteristics of each user.

There is a consensus that based on their chemical properties many types of AASs are not equally harmful. According to the distinct class, some provide gynecomastia while others are more androgenic. Regarding the mode of administration, most oral androgens have hepatic metabolism and manifest high hepatotoxicity, whereas the injectable may result in hematoma and infection. Chronic exposure causes a cumulative increase of the severity of these effects.

Another factor to consider is the probable infringements derived from the clandestine utilization and production of most steroids. These illicit practices usually lack adequate quality control procedures, meaning an increased likelihood of contamination and/or altering the chemical composition of the specific classes of the AASs; done through additives (growth hormone {GH}, aromatase inhibitors {AIs} & insulin) that can enhance or diminish the quality of the product. Moreover, the combined administration of several classes of anabolic steroids is also another exploited method.

The abuse of AAS has inimically severe and complex effects, including serious neurotoxic issues. Morphological changes in the nervous tissue and the death of neurons were already reported in several studies. This morphological alterations along with physiological alterations, triggers, by several pathways, clinical symptomatology in the nervous system.

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