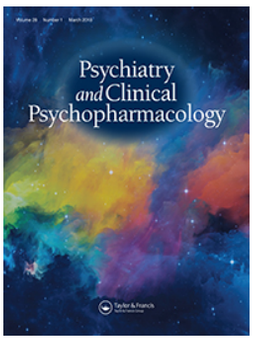

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Yasin Hasan Balcioglu, Simge Seren Kirlioglu & Pinar Cetinay Aydin (2018) Polysubstance use disorder as a probable self-medication in Isaacs' syndrome, Psychiatry and Clinical Psychopharmacology, 28:1, 116-118, DOI: 10.1080/24750573.2017.1389627

To link to this article: https://doi.org/10.1080/24750573.2017.1389627

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY, 2018
VOL. 28, NO. 1, 116–118
https://doi.org/10.1080/24750573.2017.1389627

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CASE REPORT

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Polysubstance use disorder as a probable self-medication in Isaacs' syndrome

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ABSTRACT

Isaacs' syndrome (IS) is an autoimmunological hyperexcitability syndrome of the peripheral motor nerves, manifesting with progressive muscle stiffness, involuntary continuous muscle twitching, muscle pain and cramping, sweating, and decreased reflexes. We report a 31-year-old man who was suffering from muscle twitches and stiffness in lower extremities and previously diagnosed with IS in his age of 16 through electrophysiological studies and the shown presence of autoantibodies against voltage-gated potassium channels. Without any adherence to the prescribed treatment, he had been using synthetic cannabinoids and opioids for 10 years. He admitted lessened complaints by using them. Current literature offered cannabinoid receptor agonists not only for symptomatic relief in IS, but also potential modulator effects on both potassium channels and autoimmunity. Opioids were also recognized with their analgesic and antispastic effects in the management of IS. This report aimed to discuss possible medicinal effects and therapeutic mechanisms of aforementioned psychoactive molecules on the symptomatology of IS.

ARTICLE HISTORY
Received 2 October 2017
Accepted 5 October 2017

KEYWORDS
Cannabinoids; Isaacs' syndrome; neuromyotonia; opioids; substance use disorder

Introduction

Isaacs' syndrome (IS) is an autoimmunological hyperexcitability syndrome of the peripheral motor nerves. The mean age of onset of the syndrome is in the mid-40s [1]. Progressive muscle stiffness, involuntary continuous muscle twitching, muscle pain and cramping, sweating, and decreased reflexes are the main clinical presentations of the disorder. Electrophysiological studies are the key diagnostic tools. These studies aid to demonstrate after-discharges in nerve conduction, fasciculation potentials, myokymia, and neuromyotonia (Figure 1). Recent literature offers autoimmunological mechanisms in the etiopathogenesis of IS. IS is also reported as a paraneoplastic syndrome, in which tumour antigens are suggested to trigger autoimmune response [2]. Autoantibodies against voltage-gated potassium channels (VGPCs) block the activity of the channels and lead to hyperexcitability and discharges consequently [1]. Continuous signalling of peripheral nerve fibres cause progressive muscle spasticity and severe pain. Initial treatment is suggested to be symptomatic rather than immune-mediated. Carbamazepine, phenytoin, and gabapentin are pointed out as appropriate treatment options to control the symptoms of neuromyotonia [2]. Without decent evidencing, psychotropics like dronabinol, antidepressants, and benzodiazepines are also offered in the treatment [3,4]. Nevertheless, precise therapeutic mechanisms of these drugs in the treatment have not been decently argued. We report a treatment-inadherent IS case with both synthetic cannabinoid and opioid use disorders, discussing possible therapeutic effects of those substances on the IS symptomatology.

Case

Index patient was a 31-year-old man, who was single, high school graduated, and unemployed. Preceding complaints were spontaneous, continuous, visible muscle twitching with undulations especially in lower limbs 15 years ago. He also complained of weakness in both lower limbs, which worsened on walking long distances or exertion. Severe calf pain, paresthaesia, stiffness, and fasciculations in his lower limbs with increased sweating had also been noted. Electromyography revealed continuous muscle fibre activities and myokymia, particularly in bilateral gastrocnemius. According to clinical findings and thorough examination, he had been diagnosed with IS at the age of 16 by the neurology outpatient department he was admitted to. The diagnosis was confirmed by the presence of serum VGPC autoantibodies. The treatment had been initiated with carbamazepine 400 mg/daily; however, he discontinued medication after a short notice. He started using psychoactive substances (primarily opioids) 10 years ago and added cannabis – including synthetic forms, ecstasy, and alcohol. He kept up substance use in spite of four attempts of

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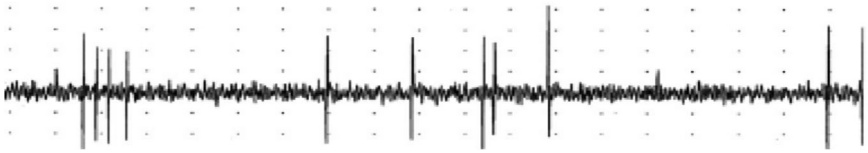

Figure 1. Electromyography showing fasciculation potentials.

addictology treatment. He referred us because of behavioural disturbance and polysubstance use intoxication, particularly with opioids and cannabinoids. He admitted regular use of synthetic cannabinoids every day for four years. He stated that his complaints of muscle pain and stiffness had been relieved while using opioids and cannabinoids over the past six years. He also told that he had been suffering from muscle stiffness, cramping, and pain when not using synthetic cannabinoids for two or three days. In his current psychiatric examination, he appeared his age and his self-care was normal. No psychotic nor affective symptom was determined. In the neurological examination, myokymia and stiffness were observed in his lower limbs. Motor examination revealed average muscle status with no wasting and sensory examination was normal. His plantar reflexes were flexor bilaterally. 35/100 of pain score was recorded according to the Visual Analog Scale administration. Spasticity was rated at 1/4 (slight increase in muscle tone) according to Modified Ashworth Scale. There was no abnormality in his hemogram and wide biochemical panel. We initiated the treatment with carbamazepine 200 mg/daily and potentiated to 400 mg in light of routine screening of blood carbamazepine levels. He was discharged with the improvement of his behavioural disturbance and impulsivity.

Discussion

Autoantibodies in IS reduce the number of VGPCs those control nerve excitability, and neurotransmitter releasing imbalance consequently occurs. Disrupted neural voltage potential and related imbalance of neurotransmitter release are held to account for spontaneous muscle fibre activities, spasticity, and pain [3]. Sodium channel blocking agents such as carbamazepine are assumed as good treatment options to compensate the reduction of functional potassium channels [1]. Therefore in our case, we preferred to use carbamazepine due to its beneficial effects on both impulsive behaviour and IS symptomatology. Cannabinoids are also regarded as novel therapeutic agents in IS. Clinical improvement was shown with the cannabinoid dronabinol in IS [3]. CB1 receptors are G-protein coupled receptors located at the presynaptic terminal and widely spread in both central and peripheral nervous system. CB1 receptor activation with cannabinoids is asserted to activate VGPCs and to inhibit voltage-gated calcium channels itself. Thereby, the main antispastic effect of cannabinoids seemed to be mediated through CB1. In neurological disorders such as multiple sclerosis, there is evidence of tonic control of spasticity and tremor by cannabinoids [5]. Beneficial effects of CB1 agonists are also demonstrated on spasticity-related pain. Activation of spinal CB1 receptors is suggested to modulate pain thresholds tonically via enhancing GABA neurotransmission [6]. Our patient had been using synthetic cannabinoids combined with opiods for four years and his muscle stiffness and pain had improved in this period. Studies regarding management of pain indicated that the combination of cannabinoids and analgesics such as opioids exerts synergistic nociceptive effects [7]. This synergistic mechanism was attributed to colocalization of opioid and CB1 receptors in the central nervous system that controls pain pathways and regulatory role of cannabinoids on endogenous opioid release. Cannabinoids have also been recognized with their immunomodulatory functions. CB2 receptors are primarily expressed in peripheral immune cells, and their activation with synthetic cannabinoids such as JWH-133 provided anti-inflammatory and analgesic effects in an animal model [8]. The clinical remission of our patient with substance use may be attributed to the immunomodulatory role of cannabinoids rather than symptomatic relief. This is concordant with the evidence of autoimmune pathogenesis in IS. This article aimed to promote awareness in clinical practice for possible subtle comorbidity of substance use disorders and neurological diseases with chronic pain and spasticity, in order to provide self-medication. Additionally, therapeutic mechanisms of psychoactive molecules in the management of IS need to be revealed with the comprehensive research.

Disclosure statement

No potential conflict of interest was reported by the authors.

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