CsA, if not solely responsible, may, in the setting of another unknown underlying acquired or inherent condition, have stimulated these changes. In previous studies, estimates of the incidence of retinal microvasculopathy were biased by ascertainment of only symptomatic cases.[2] The true incidence may be higher. In a prospective study, Bernauer et al[4] discovered that 46% of transplant patients with ischemic fundi were asymptomatic. Therefore it may be beneficial to include ophthalmologists in the management of patients taking CsA, particularly those patients taking CsA to prevent transplant rejection. Because in previous studies[1–4,6,8] as well as in our case study the onset of symptoms after starting CsA therapy ranged from 31 to 332 days, routine ophthalmologic evaluations of patients using CsA should be considered, especially during the first year of therapy.

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CENTRAL SEROUS CHORIORETINOPATHY IN A PATIENT USING METHYLENEDIOXYMETHAMPHETAMINE (MDMA) OR "ECSTASY"

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In recent years, converging lines of experimental and clinical evidence have clearly identified steroids as a risk factor for acute manifestations of central serous chorioretinopathy (CSC).[1–7] The systemic use of steroids by virtually any route of administration[2,3,6,7] or systemic disorders associated with a state of hypercorticalism, such as Cushing syndrome,[4] have been implicated in the development of exudative macular detachments in patients with CSC. Drugs that stimulate an adrenergic effect or a catecholamine response are also thought to be potential risk factors for CSC, but this association has not been clearly established.[3,5] This report describes a patient who had primary, and subsequently recurrent, acute exudative manifestations of CSC after using the illicit drug methylenedioxymethamphetamine (MDMA), commonly referred to as ecstasy, a popular party or club drug with psychomimetic and adrenergic effects.[8]

Case Report

A 38-year-old man who was in perfect health and had no remarkable medical or ocular history experienced a visual disturbance in his right eye 3 days after the use of MDMA. The exact formulation and dose of the drug were unknown. His examination at that time showed a visual acuity of 20/40 in his right eye and 20/20 in his left eye. He also had metamorphopsia and a relative central scotoma on Amsler grid testing. A large neurosensory macular detachment was noted on slit-lamp examination with the Goldmann contact lens. No lipid or blood was seen. The macula in the left eye was unremarkable, except for two minor, punctate, atrophic pigment epithelial changes. After several weeks, visual acuity returned to 20/20 in the right eye, and there was a corresponding complete resolution of the neurosensory retinal detachment. Approximately 10 months later, he used the same drug again, and he experienced a decrease in vision of his right eye similar to what had been noted earlier. A recurrent neurosensory macular detachment was seen in the same eye, but this time, the detachment was smaller. The visual acuity was reduced to 20/25. The detachment again spontaneously resolved. This patient had not used MDMA at any other time except before the two episodes of acute macular detachment.

Discussion

Central serous chorioretinopathy is a well-known, complex clinical disorder whose pathogenesis is still poorly understood.[2,3,5,6] An array of risk factors, including refractive state, systemic blood pressure, gen-

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der, age, and corticosteroids (exogenous or endogenous), have been identified in the past.[2,3,5] The relationship between the use of exogenous corticosteroids and the pathogenesis of CSC have been reviewed by Gass and Little.[6] Although the precise mechanism for the relationship is unknown, a steroid-induced effect on the choroidal circulation is presumed to be responsible for the exudative changes. In a recent article by Carvalho and Yannuzzi,[7] steroids were implicated in the development of acute manifestations of CSC in more than 50% of patients in a prospective, consecutive series. The steroid use was by several routes of systemic administration, including oral, intramuscular, intraarticular, and inhalation. In this report, the authors suggested that other drugs that indirectly stimulate the adrenal cortex, inducing a catecholamine response, could also predispose patients to acute manifestations of CSC.

Accordingly, stimulation of the adrenergic system may also be implicated in acute manifestations of CSC, but evidence supporting this possible association, although attractive, is not conclusive. The possible mechanisms by which increased corticosteroid and catecholamine levels may contribute to the pathogenesis of CSC have been reviewed recently by Haimovici et al.[3] The basis of this concept involves the release of catecholamines and an increase in the sensitivity of adrenergic receptors by corticosteroids. The supporting evidence includes an experimental model of CSC that was induced by intravenous injections with epinephrine and norepinephrine in primates.[9] There is also a primate model for CSC using intravenous epinephrine and intramuscular corticosteroids.[10] Also, urinary epinephrine and norepinephrine levels are increased in patients with active CSC compared with control patients.[11] Clinical evidence supporting a link between hypercorticalism and adrenergic stimulation can be found in the known abnormal behavioral pattern, specifically a Type A personality, seen in patients with CSC.[5] These patients have an increased secretion of cortisol and adrenergic agents, such as epinephrine and norepinephrine.[5] Also, combined corticosteroids and β-adrenergic nasal inhalants have been reported to be a risk factor for CSC.[3] Furthermore, systemic hypertension is a known risk factor for CSC.[2] Increased catecholamine levels are common to systemic hypertension and to CSC.[2,11,12] There is also an increased vasoconstrictive sensitivity to corticosteroids in systemic hypertension.[13] Corticosteroids increase catecholamine-mediated vasoconstriction in the peripheral vasculature and in the choroid.[13,14] Although still unproven, vasoconstriction and associated perfusion abnormalities in the choroid have been hypothesized to be causative factors in the pathogenesis of CSC.[2,5] Corticosteroids are also known to induce transcription of α-adrenergic[15] and β-adrenergic[16] receptor genes, and they may potentiate the effects of adrenergic stimulation on certain target tissues, such as the retinal pigment epithelium.[17,18] Accordingly, a potential synergistic state exists between corticosteroids and catecholamine metabolism as a potential causative factor for the development of acute manifestations of CSC. Essentially, corticosteroids may increase catecholamine release and make critical tissues, such as the inner choroid and the retinal pigment epithelium, more susceptible to adrenergic effects.

Although an absolute causal relationship between the use of MDMA and the development of CSC in our patient is uncertain, there is a pharmacologic basis for the development of acute manifestations of CSC from the use of this agent. In MDMA, the pharmacologic component theoretically predisposing to CSC is likely to be methamphetamine, which is a combined α- and β-adrenergic agent.[8] It is known to stimulate peripheral and central α- and β-adrenergic receptors. A causal relationship is particularly possible because the patient experienced symptoms only on the two occasions when he used the drug. Discontinuation of the drug was also associated with spontaneous resolution of the macular manifestations, further implicating the use of the drug with the disorder.

The origin of this drug dates back to the early 1960s when MDMA was first synthesized by the pharmaceutical company, Merck, with no particular purpose in mind. The drug remained dormant until the 1970s, when it was studied by psychotherapists who claimed that it enhanced communication in therapy, essentially as a psychomimetic or psychedelic agent. By the 1980s, however, MDMA emerged as an illicit, so-called party or club drug used in discotheques by young adults. In recent years, this drug has become increasingly popular, and its users have extended into the teenage population. As a drug that is not approved for any medical purpose, its formulation is not regulated or controlled, and its use and distribution continue to be illegal. Research at the animal level to date has established that MDMA shares the properties of the psychedelic drug lysergic acid diethylamide and the adrenergic stimulant amphetamine. Structurally, it is similar to the hallucinogen mescaline and the adrenergic agent methamphetamine. Typically, it is used orally in a capsular, tablet form, and its effects last for 3 to 6 hours, depending on the dose. Persistent cognitive abnormalities, such as confusion, depression, insomnia, anxiety, and paranoia, are known to be side effects of the drug, even several weeks after its use. What is most disturbing about MDMA is that it is

extremely dangerous with regard to cardiovascular and neurologic effects, with potentially long-lasting adverse complications affecting the brain to alter memory function and motor skills.

The adrenergic changes relate to the cardiovascular side effects. Because it is a stimulant, MDMA increases the heart rate, blood pressure, and body temperature, and it may have serious side effects, including dehydration, persistent hypertension, and heart or kidney failure. It is known to increase the release of epinephrine,[19] accounting for these systemic cardiovascular changes. Plasma levels of steroids have also been found to be higher in patients using MDMA.[20] Thus, there is an adrenergic and a corticosteroid stimulation with MDMA that may be a factor in the development of CSC in our patient.

Neurologically, MDMA acts primarily as a serotonergic (5-HT) drug, a major neurotransmitter in the brain, synthesized from tryptophan through the intermediate 5-hydroxetryptophan.[8] MDMA actually affects 5-HT in the way that amphetamines affect dopamine, by inhibiting the uptake and causing the release of the molecule. This mechanism of action is similar to the way that selective serotonin reuptake inhibitors work. Serotonin effects are also thought to be responsible for the psychologic and physiologic effects of the drug, including mood, sleep, depression, and obsessive compulsions.[8] Its neurotoxicity can have permanent damage to neurons that release serotonin, impairing an individual's memory and cognitive performance.

This case report suggests that MDMA may also have ocular effects that are most likely mediated through its adrenergic and corticosteroid stimulation, which in turn may predispose patients to acute manifestations of CSC. In patients with steroids as a contributing causative effect of their acute CSC manifestations, discontinuation of the drug is usually associated with resolution of the neurosensory detachment.[7] The same outcome seemed to be evident in this case. Although additional research is obviously needed to confirm this singular observation, the relationship between the use of MDMA and the acute manifestations of CSC is rational, if not compelling. Accordingly, clinicians should be aware of this potential association so that they can counsel their patients, particularly those who have other risk factors for CSC or who are actually known to have had the condition itself. Therefore, patients who have acute manifestations of CSC should be carefully asked about drug use so that they can be advised to discontinue any drug that might have a systemic, adrenergic stimulating effect before any other form of treatment is considered.

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