Central Nervous System Vasculitis Due to Substance Abuse

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KEYWORDS

• Substance abuse • Stroke • Vasculitis • Central nervous system

KEY POINTS

- Illicit drug abuse is a common differential diagnosis of acquired central nervous system vasculitis.
- There are only a handful of histopathologically confirmed cases in the literature from among the many potential classes of abused drugs traditionally implicated in this disease.
- Hemorrhagic and non-hemorrhagic stroke often preceded by vasospasm are common outcomes in confirmed cases.
- This article considers the major classes of illicit drugs in those with and without human immunodeficiency virus type-1 infection and acquired immune deficiency syndrome.

INTRODUCTION

Drug abuse is a rare cause of histopathologically verified central nervous system (CNS) vasculitis. With only a handful of confirmed patients in the literature, and rare association with progressive neurologic deficits, there is generally little justification for invasive laboratory investigation, especially given the availability of highly accurate vascular neuroimaging techniques. Management rests on avoidance of further exposure and minimizing the secondary neurotoxic effects of the abused substances and polypharmacy use. This article reviews the epidemiology, background, neuropharmacology, and histopathology of verified cases, and proposed etiopathogenic mechanisms that cause CNS vasculitis.

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CLASSIFICATION AND NOSOLOGY

The most widely used classification and nosology for the vasculitides is the 2012 Revised International Chapel Hill Consensus Conference Nomenclature.[1]

BLOOD BRAIN BARRIER

The past decade has witnessed extraordinary progress in our understanding of the blood brain barrier (BBB),[2] and progress in its understanding will likely afford new insights into our understanding of cerebral vasculitis and the impact of substance abuse on the nervous system. The neurovascular unit (NVU) of the BBB is composed of capillary endothelial cells, pericytes, smooth muscle cells, astrocytes, neuronal terminals, and white blood cells (in the extended NVU). Each of the components expresses a wide variety of receptors, ion channels, and transporters and resides in proximity to one another allowing for the dynamic modulation of blood flow, metabolism, and electrophysiologic regulation.[3] Many of the influx and efflux mechanisms of the BBB are present early in the developing brain, encoded by genes at much higher levels than in the adult.[4] The disruption of tight and adherens junctions, enzymatic degradation of the capillary basement membrane, or both, leads to disruption of tight junctions, altered expression and function of membrane transporters or enzymes, increased passage of inflammatory cells across the BBB from the blood to CNS, and dysfunction of astrocytes and other components. This leads to aberrant angiogenesis and neuroinflammation with concomitant vasogenic edema, accumulation of toxic substances in the brain interstitial fluid, oxidative stress, and impaired ion and water homeostasis.

AMPHETAMINES

The earliest reports of misuse of amphetamine sulfate were in late 1930 when it was used by students to avoid sleep during examination periods.[5] This was followed by reports of death by those who ingested the drug repeatedly as a stimulant for the same purpose,[6] in a suicide attempt that resulted in a fatal intracerebral hemorrhage,[7] or accidentally, when dexamphetamine and phenelzine were fatally ingested together decades later.[8] During the Second World War, amphetamine and methamphetamine were used clinically and illicitly but its abuse soared in San Francisco after 1962, wherein it was illegally produced and distributed.[9]

Amphetamine, methamphetamine, and their derivatives comprise a large spectrum of agents[10] available in powder, capsule, tablet, and injectable fluid form that can be swallowed, snorted or taken intranasally, smoked, or injected with highly variable purity and dosage equivalence. Their potent effects, which include elevation of blood pressure, pulse rate, and increased level of alertness, sometimes in association with insomnia, excitability, panic attacks, and aggressive behavior, also can be associated with seizure and stroke. Their effects distribute throughout the brain. Ecstasy refers to the different hallucinogenic amphetamine derivatives that contain 3,4-methylenedioxymethamphetamine and 3,4-methylenedioxyethylamphetamine as the main components[11] that alter brain serotonin concentrations, and postsynaptic 5-HT_2 receptors that play a role in the regulation of brain microvessels. The CNS toxic effects are mitigated through blocking of the reuptake of dopamine (DA) and stimulation of the release of DA and norepinephrine, as well as possible involvement on the serotonergic and endogenous opiate system. There can be DA receptor desensitization with marked reduction of DA transporters and drug levels, as well as other dopaminergic axonal markers. The neurotoxic effects of methamphetamine are believed to be mediated by multiple additional mechanisms including the generation of free radicals, nitric

oxide, excitotoxicity, mitochondrial dysfunction, apoptosis, and the induction of immediate early inflammatory genes and transcription factors. Methamphetamine is the most potent amphetamine and the most commonly abused. All forms of amphetamine administration increase the risk of stroke that may be ischemic, hemorrhagic and intraparenchymal,[12] which may be up to fourfold that of nonusers,[13] surpassing the rate of hemorrhagic stroke caused by cocaine use with odds ratios respectively of 4.95 versus 2.33.[14] Still, amphetamines and methamphetamine are the second commonest cause of all strokes after cocaine, occurring largely in persons younger than 45 years.

Cerebral vasculitis due to amphetamine, methamphetamine, and related agents is exceedingly rare with only 3 histopathologically studied patients in the literature.[15,16] This is surprising given the number of substances that could cause this disorder if there was a true association. Amphetamine-related multiorgan arteritis including the CNS was demonstrated by Citron and colleagues[16] in a highly publicized report of 14 Los Angeles multidrug abusers. The drug closest to a common denominator was methamphetamine used intravenously by all but 2 patients and exclusively by 1. Acute vessel lesions of fibrinoid necrosis of the media and intima with infiltration by polymorphonuclear cells, eosinophils, lymphocytes, and histiocytes was followed by vascular elastic and vascular smooth muscle destruction resulting in lesions considered typical for polyarteritis nodosa. Two patients, one abbreviated D.G. and the other E.V., who injected methamphetamine via intravenous injection had arterial lesions in cerebral and cerebellar (D.G.) and brainstem pontine vessels (D.G. and E.V.); however, detailed histopathologic descriptions were not provided. Their report was followed by correspondence by Gocke and Christian[17] who contended that exposure to the Australia antigen of hepatitis B antigen was likely in their cohort[16] conceivably associated with circulating immune complexes and complement activation as had recently been described.[18,19] The investigators[20] responded that no more than 30% of sera from drug abuse patients ultimately tested positive for the Australia antigen. Those with antigen-positive sera who had used drugs others than methamphetamine had no evidence of angiitis when studied angiographically. Baden[21] wrote that he had not observed a causal relation between drug abuse and necrotizing arteritis at the Office of Chief Medical Examiner of New York City for the past one-half century among thousands of autopsied drug abusers. Further, 14 cases claimed documentation for angiitis was presented in only 4 patients but no substantiation for the diagnosis was given in the remainder except that 5 were asymptomatic, and 5 had a variety of nonspecific systemic signs and symptoms. Citron and Peters[20] responded that evidence of aneurysms so noted in 13 patients, was in their opinion ample evidence of arteritis.

Almost 2 decades later, cerebral vasculitis was demonstrated in a dubious report[15] of a 3 week postpartum woman who took her first over-the-counter Dexatrim diet pill in many months containing phenylpropanolamine, without a history of amphetamine abuse. This was followed 90 minutes later by sudden headache, nausea, vomiting, and detection of subarachnoid blood on computed tomography neuroimaging and a frontal lobe hematoma. Bilateral carotid angiography demonstrated diffuse segmental narrowing and dilatation of small, medium, and large vessels and branches of the anterior and posterior circulation. Evacuation and histopathologic analysis of the hematoma was performed showing necrotizing vasculitis of small arteries and veins with infiltration of polymorphonuclear leukocytes particularly prominent in the intima with fragmentation of the elastic lamina and areas of vessel occlusion. It was unclear whether the findings were related to primary or drug-related CNS vasculitis. However, treatment with cyclophosphamide for 6 months was associated with almost complete resolution of cerebral angiographic abnormalities.

After the report of Citron and colleagues,[16] Rumbaugh and colleagues[22] described the cerebral vascular changes due to methamphetamine abuse in 5 rhesus monkeys given amphetamine in dose ranges used by human addicts. Two of the 5 monkeys developed generalized arterial spasm during a 2-week period following intravenous injection. Three of 5 animals demonstrated decreased caliber of named cerebral artery branches and flow of the contrast agent with normalization 1 day later, whereas 2 others showed marked general decrease in small branches and large named vessels that improved in one animal and progressed in another. Histopathologic changes at postmortem examination included microaneurysmal enlargement of arteriolar segments, mononuclear perivascular cuffing of small arterioles, parenchymal necrosis, petechial hemorrhages, and swelling of brain tissue, with most of the hemorrhagic lesions centered on small-size arteriolar and capillary vessels. Although reminiscent of the clinical and histopathologic findings of Citron and colleagues,[16] necrotizing arteritis and transmural inflammation were lacking. Five years later, Rumbaugh and coworkers[23] subjected monkeys to short-duration (2 weeks; 5 animals), medium-duration (1 month; 3 monkeys), and long duration (1 year; 3 monkeys) of thrice weekly (1.5 mg/kg body weight) intravenous amphetamine and related agents including methamphetamine, secobarbital, methylphenidate, and placebo, with performance of cerebral angiography and documentation of the resulting histopathology. Their studies showed relatively severe vascular injury and brain damage from intravenous methamphetamine that included occlusions and slow blood flow in small cerebral vessels, respectively, in 2 each of the 5 monkeys in the long-term administered drug, and in 3 each of those given drug for intermediate and short durations, with some animals and controls unaffected. There was less injury caused by secobarbital and methylphenidate. Further, the possibility of vascular spasm due to subarachnoid blood was excluded by lack of blood at postmortem examination in the subarachnoid space in any of the animals.

Cocaine

Cocaine is derived from the leaves of the *Erythroxylum coca* plant and found primarily in the eastern mountains of Peru, Ecuador, and Bolivia. It is abused as cocaine hydrochloride, a water-soluble white salt in crystal, granular, and white powder that can be sniffed and "snorted" intranasally or injected parenterally. The "free-base" alkaloid form, known as "crack," derives its name from the cracking sound that occurs after dissolution of the hydrochloride salt in water, heated, and mixed with ammonia without or without baking soda. This chemical reaction converts cocaine hydrochloride to a volatile form of the drug, almost pure cocaine. Street cocaine or the noncrack form is highly variable in purity, and often cut with various agents. When smoked as free-base, it is absorbed into the pulmonary circulation and transmitted to the brain in less than 10 seconds. After appearance in the bloodstream, cocaine is rapidly hydrolyzed to benzoylecgonine, which can be accurately tested in the urine; however, levels may persist for up to 27 to 36 hours depending on the route of administration and host cholinesterase activity. In recent years, with increasing availability and purity, and a drop in the price of cocaine from the early 1970s of $85 per gram, new cohorts from all socioeconomic backgrounds and age groups have been attracted to this highly addictive drug, and use has continued to expand on a year-by-year basis.

Cocaine is a highly potent CNS stimulant that rapidly crosses the BBB due to its highly lipophilic properties and is widely distributed through the brain with its major metabolites binding at receptors with varying affinities at presynaptic sites stimulating the release of DA from synaptic vesicles and blocking DA reuptake resulting in enhanced dopaminergic neurotransmission, in addition to its local anesthetic

properties. The investigation of single nucleotide polymorphisms that encode amino acid substitutions in opioid receptors and ligands implicated in drug addiction, particularly those of the mu opioid receptor (MUP-r) gene system (*OPRM1)* that releases DA from neural synapse when activated, and those of the kappa receptor (KUP-r) that instead lower extracellular dopamine levels, have contributed understanding to the variability in drug addiction among susceptible individuals.[24]

Only 10 histologically verified patients with cerebral vasculitis, including 6 men and 4 women, age 21 to 39 (mean age 28 years), occurred in the absence of other possible known causes including concomitant infection by human immunodeficiency virus type 1 infection and known causative coinfections[25–39]. In all but 1 patient,[30] who had a long-standing cocaine habit with abuse sometime in the 6 months before admission, onset of neurologic symptoms immediately followed cocaine use that was intranasal cocaine in 6 patients,[28–32] intravenous in 2,[26,27] smoked in 1,[26] and acquired via unknown modality in 1.[26] Cerebral vasculitis was associated with cerebral hemorrhage in 3 patients[29,30] and ischemia in the 7 patients[25–28,31,32] who typically presented with abrupt onset of headache and focal hemiparesis so noted in 6 patients,[25,26,29,30] confusion or agitation,[27,28,30–32] and grand mal seizures,[28] that progressed to stupor, coma, and death in 3 patients.[25,26,28] Lumbar cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis of 10 to 65 cells/cm^3 with elevation of the protein content from 185 to 630 mg/dL,[27,32] and was completely normal in 2 other patients.[26,30] Cerebral angiography performed in 7 patients showed an avascular mass in the patient with a putaminal hemorrhage,[29] abnormal large named vessel occlusions or segmental narrowing in 3 patients,[25,26,30] poor filling and irregularities in vessel appearance in 2,[31,32] and normal in 1 patient.[27]

The pathology of cerebral vasculitis was established by brain and meningeal biopsy in 7 patients,[26–32] at postmortem examination in 2 patients,[25,28] and by both in 1 patient.[26] The underlying pathology of cerebral vasculitis was non-necrotizing with transmural mononuclear cell inflammation affecting small arteries and veins in 3 patients[26,28,29] or veins alone in 3 patients,[30–32] and perivascular cuffing of small arteries and veins in another.[27] In 2 patients there was necrosis of small cerebral vessels associated with polymorphonuclear cell inflammation of small arteries and veins[30] or large named vessels.[25] Among 3 patients so studied at postmortem examination, non-necrotizing small vessel vasculitis was noted in the brains of 2 patients without evidence of systemic involvement,[27,28] whereas necrotizing large vessel vasculitis was found in both the brain and systemic organs.[25] Treatment consisting of corticosteroid was administered to 7 patients, 5 of whom improved [26,27,30,32] and 2 who died with refractory seizures despite anticonvulsant medication[33] or as a consequence of infection, coma, and decerebration.[25] There was no mention of treatment or outcome in 3 patients, [28,29,31] including 2 patients who succumbed to coma, hypoxic-ischemic decerebration, and death.[28,29]

Although cocaine-associated cerebral vasculitis has not been rigorously studied, several independent lines of experimental evidence suggest possible etiopathogenic mechanisms in susceptible individuals. The first was the observed effects of cocaine in the induction of adhesion molecules and endothelial leukocyte migration across cerebral blood vessel endothelia walls, particularly under inflammatory conditions, which may disturb the function of the BBB. Cocaine increased the expression of the endothelial adhesion molecules intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule-1, and endothelial leukocyte adhesion molecule-1 on brain microvascular endothelial cells (BMVEC) with a peak effect on ICAM-1 expression between 6 and 18 hours after treatment in human BMVEC cultures and increased monocyte migration in an in vitro BBB model[40–43]

constructed with BMVEC and astrocytes.[44] These effects of cocaine, exerted through a cascade of augmented expression of inflammatory cytokines and endothelial adhesion molecules, may contribute to the known cerebrovascular complications of cocaine abuse.

The second is the effect of cocaine on endothelial cell permeability and apoptosis as well as the induction of chemokines and cytokines. The immunomodulatory effects of cocaine on brain microvascular endothelial cells and its proinflammatory effects on induction of proinflammatory cytokines and chemokines was investigated using a human BBB model that included human immunodeficiency virus type-1 (HIV-1) neuroinvasion.[45] Cocaine increased the in vitro permeability of endothelial cells of the BBB model and induced apoptosis of mouse thymocytes in cultures of BMVEC and monocytes using an enzyme-linked immunosorbent assay of generated accompanied by upregulation of macrophage inflammatory protein (MIP)-1, MIP-1α, inducible protein-10, and IL-8 and TNF-α expression.

A third line of investigation has been the observed synergy of cocaine in facilitating pathogenic retroviral neuroinvasion, which may confer an independent risk factor for cerebral vasculitis. Both in vitro and in vivo studies have provided valuable tools in exploring the role of cocaine in mediating HIV-associated neuropathogenesis. The importance of drug abuse in conjunction with HIV-1 has been underscored by the ability of cocaine to induce retroviral replication in mononuclear cells[46] and enhance gp120-induced neurotoxicity.[47]

Opioids

Opioids or narcotic drugs have pharmacologic properties similar to those of morphine that include the derivatives hydrocodone, oxycodone, hydromorphone, codeine, fentanyl, meperidine, methadone, and opium. The source of opioids is the exudate of seed from the poppy plant, heroin is derived from acetylation of morphine. Heroin is administered intravenously, intranasally, and subcutaneously. A higher bioavailability of heroin is present after heating on foil for inhalation compared with smoking after heating. Intravenous injection leads to extreme euphoria that peaks at 10 minutes followed by profound sedation and analgesia that lasts for up to 1 hour. Opiate overdose produces the triad of coma, respiratory depression, and miosis. The medical complications of long-term heroin exposure include endocarditis, pulmonary complications of embolism, pneumonia, and granulomatosis or fibrosis; and nephropathy, immunodepression, infection at the site of injection due to cellulitis, thrombophlebitis, and bacteremia, and hepatitis due to needle sharing.[48] It binds to endogenous opiate mu_1 receptors, which are responsible for most of the analgesic effects, and for the actions of the CNS and cardiovascular system leading to bradycardia, hypotension, and respiratory depression. Agonist actions at mu_2 receptors are responsible for respiratory depression, delayed gastrointestinal motility, miosis, and physical dependence. Agonist actions at kappa receptors lead to separate analgesia. Circulating serum morphine is transformed into morphine-3-glucuronide or morphine-6-glucuronide by the liver and the kidney. Most fatal and nonfatal overdoses occur when heroin is administered intravenously.

This author could not identify any pathologically confirmed cases of heroin-induced cerebral vasculitis reported in the literature, nor was cerebral vasculitis suggested as a likely occurrence in heroin abuse,[49] heroin addiction,[48,50] or acute overdose.[51] Moreover, detailed neuropathologic studies carried out on 134 victims of acute heroin intoxication, including 18 who survived for periods of hours or days,[52] who respectively demonstrated cerebral edema in conjunction with vascular congestion, capillary engorgement, and perivascular bleeding attributed to toxic primary respiratory failure;

and ischemic nerve cell damage resembling systemic hypoxia, showed no evidence of cerebral vasculitis, except 1 focus of lymphocytic perivascular inflammation. The brains of 10 intravenous drug abusers who died from heroin overdoses, including one due to gunshot injury,[53] likewise show no evidence of cerebral vasculitis at postmortem examination, except to a few perivascular mononuclear cells associated with pigment deposition.

The postulated mechanisms of opioid-related neuronal and CNS vascular injury include increased oxidative stress, induction of inflammatory cytokines, and increased permeability of the BBB especially in intravenous drug abuse. Ramage and colleagues[54] described increased deposition of hyperphosphorylated tau in entorhinal cortex and subiculum of the hippocampus, AT8-positive neurofibrillary tangles in entorhinal cortex, and increase in β-amyloid precursor protein (βAPP) in both the hippocampus and brainstem of drug abusers compared with controls. Several postulated causative mechanisms included repeated head injury, hypoxic-ischemic injury associated with opioid-induced respiratory depression, microglial-associated cytokine release, and drug-associated neurotoxicity.

HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNE DEFICIENCY SYNDROME

Recognition of the propensity for cerebral vascular inflammation in association with human immunodeficiency virus type 1 infection (HIV-1)/acquired immune deficiency syndrome (AIDS) and drug abuse has provided new insights into the mechanisms of cerebral vasculitis. Early in the HIV/AIDs epidemic, it was clear that a significant proportion of infected persons engaged in intravenous drug user (IVDU). Their associated risk behavior exposed them to infection through sharing of contaminated needles, thereby increasing the risk of spread of HIV and other bloodborne infections.[55] Among 50 patients with AIDS and neurologic complication, 6 HIV-1 infected patients described by Snider and colleagues[56] were IVDUs; the others being male homosexuals and recently arrived Haitian refugees. The 2 postulated periods in the neurobiology of HIV-1 when autoimmune disease manifestations can occur that appear to be significant for the development of cerebral vasculitis are shortly after seroconversion and before the spread of productive infection[53,57] and after initiation of highly active antiretroviral therapy (HAART) in association with the immune reconstitution syndrome (IRIS).[58] The impact of IVDU in the development of cerebral vasculitis and other autoimmune sequel is not well understood; however, there is an extensive literature suggesting an independent contribution of IVDU to immune suppression, breakdown of the BBB, microglial activation, and neuronal injury,[59–65] and an additive or synergistic reinforcement of HIV-related brain damage by intravenous drug use.[66]

The timing of early HIV invasion has been difficult to ascertain based on the presence of one or more well-recognized clinicopathological HIV/AIDS syndromes. including HIV encephalitis,[67] HIV-associated dementia, and AIDS-dementia complex, all of which are indicative of symptomatic infection. HIV encephalitis is initially associated with myelin pallor and gliosis of the centrum semiovale found in more than 90% of brains from patients dying with AIDS.[68] With increasing severity of symptomatic disease, multiple glial nodules with the multinucleated cells characteristic of HIV encephalitis occur throughout the white matter, basal ganglia, cerebral and cerebellar cortex, brainstem, and spinal cord. HIV has been demonstrated in monocytes and multinucleated giant cells by electron microscopy, immunocytochemical techniques, and in situ hybridization. Vasculitides in the context of HIV infection was reviewed by Guillevin.[69]

Six patients with non-necrotizing cerebral vasculitis were described in a postmortem series of presymptomatic HIV-seropositive drug abusers by Gray and

colleagues,[53] and an analogous patient was described by Yankner and coworkers[70] with rapidly fatal necrotizing granulomatous angiitis of the brain without evidence of acquired immune deficiency, circulating human T-lymphotropic virus type III (HTLV-III) or HIV-1 antibodies. Seven other patients were described by Bell and colleagues[57] with lymphocytic infiltration of the walls of leptomeningeal and subarachnoid veins, without specific reference of cerebral vasculitis. Gray and colleagues[53] studied 2 cohorts of 11 patients, one HIV-seropositive and non-AIDS, and the other HIV-seronegative heroin abusers, 10 patients of each died from heroin overdose and another of a fatal gunshot wound. Neuropathological studies showed varying degrees of vascular inflammation including "true vasculitis" exemplified by dense vascular inflammation extending through the vessel wall, associated with leptomeningitis in 6 of the 11 HIV-seropositive AIDS-negative patients. However, there was no mention as to whether inflammatory process involved arteries and vein or the vessel caliber. Vascular inflammation was comparatively mild or absent and restricted to a few perivascular mononucleated cells associated with pigment deposition, without transmural vascular inflammation or meningitis in the HIV-seronegative cohort. HIV immunocytochemistry was negative in both cohorts, and multinucleated giant cells, considered the hallmark of productive HIV infection in the brain and an essential neuropathologic feature of HIV encephalitis, were not seen. One year later, Bell and coworkers[57] described the neuropathologic findings of 23 IVDUs from the Edinburgh HIV Autopsy Cohort who died suddenly after seroconversion but while still in the presymptomatic stage of HIV infection in comparison with 10 HIV-negative IVDUs, 12 non-IVDU controls, and 9 patients with full-blown AIDS, who also died suddenly. Seven of the presymptomatic HIV-positive patients showed infiltration of T-cells in the walls of veins in association with low-grade lymphocytic meningitis; 7 others demonstrated isolated lymphocytic meningitis, and 1 patient had focal perivascular lymphocytic cuffing and macrophage collections throughout the central white matter tissue of the brain and in basal ganglia. Neither conspicuous perivascular lymphocytic infiltration nor lymphocytic meningitis was noted in HIV-negative IVDU controls, those with no drug association, or others with full-blown AIDS. Neuropathological examination in presymptomatic HIV-seropositive patients failed to reveal characteristic lesions of HIV encephalitis and none of the subjects showed immunocytochemical evidence of p24 antigen in brain tissue. Nearly a decade later, Bell and colleagues[60] reiterated that in more than 50% of pre-AIDS cases so studied, the brain was characterized by a low-grade lymphocytic meningoencephalitis in which T-cell infiltration is present in leptomeninges and the perivascular compartment, with a very occasional HIV-p24 positive lymphocyte in the lymphocytic infiltrate, but no in brain parenchyma. According to the same investigators,[60] there was conversely no clear evidence of vasculitis in IVDUs with HIV encephalitis in the Edinburgh HIV Autopsy Cohort.[33] Yankner and colleagues[70] reported the clinicopathologic findings of a homosexual man with rapidly fatal cerebral granulomatous angiitis of the brain associated with isolation of HTLV-III in CSF and brain tissue. Mononuclear cellular infiltrates were present at postmortem examination in the walls of affected large named arteries without involvement of small arteries and veins, and with rare microglial nodules and multinucleated giant cells.

The early CNS changes of HIV infection have also been investigated among patients with hemophilia examined after sudden death from intracranial hemorrhage and liver cirrhosis and in experimental animal models of simian immunodeficiency virus (SIV) syndrome and feline immunodeficiency virus infection.[34] There were comparable neuropathologic changes of gliosis, occasional microglial nodules, perivascular mononuclear infiltrates, and occasional leptomeningeal meningitis in all 3, characteristically without multinucleated giant cells or evidence of HIV in the brain.[33,34,70] HIV-

infected cells were mainly perivascular, and expressed macrophage markers in the SIV model[33] suggesting transit of virus across the BBB as the main source of entry into the CNS. Moreover, the comparatively less pronounced vascular inflammation than that described in early HIV infection associated with drug abuse, suggests that IVDU contributes to vascular inflammation.

Literature of Patients with Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome–Associated Immune Reconstitution Syndrome

The introduction of HAART has changes the incidence, course, and prognosis of the neurologic complications of HIV infection concomitant with almost undetectable viral load in plasma and a rise in circulating T-lymphocytes.[35] One pathologically confirmed patient with cerebral vasculitis and IRIS was described by van der Ven and colleagues.[36] This HIV-seropositive homosexual man developed dysarthria and dysphagia after HAART with worsening and appearance of limb paresis after discontinuation of the medication. Treatment with corticosteroids preceded recommencement of HAART but there was worsening with discontinuation of corticosteroids. Biopsy of a hyperintense fronto-parietal lesion on T2-weighted MRI showed small vessel lymphocytic vasculitis, with microglial activation in the surrounding parenchyma. A severe demyelinating leukoencephalopathy in association with intense perivascular infiltration by HIV-gp41 immunoreactive monocytes/macrophages and lymphocytes was described by Langford and colleagues[37] in 7 postmortem patients. All were severely immunosuppressed and treated with HAART with presumed IRIS; however, high not low levels of HIV replication were noted and there was no consideration of cerebral vasculitis. Confirmatory neuropathology was not sought; however, Patel and coworkers[38] described an HIV-seropositive man who developed encephalitis 10 months after HAART in association with a lower thoracic dermatomal varicella zoster virus rash.

Levamisole

The anti-helminthic agent levamisole, first introduced for use in veterinary medicine, was later discovered to have potent immunomodulation properties, prompting its application in inflammatory and oncologic conditions, including rheumatoid arthritis, aphthous ulcers, and melanoma.[39] The US Food and Drug Administration approved levamisole as adjuvant therapy for the treatment of inflammatory conditions and cancer. In Asia, it has been used as an anti-helminthic and pesticide agent.

Levamisole was detected in cocaine bricks by the US Drug Enforcement Agency in 2003,[71] noting an increase from 44.1% of specimens in 2008 to 73.2% in 2009, signaling a rising public health problem. In 2011, Buchman and co-workers[72] reported a prevalence of 68% using a combination of immunoassay and gas chromatography–mass spectroscopy detection methodologies. Other drugs noted in positive urine specimens included the opioid analgesics methadone (45%), codeine (16%). heroin/6-monoacetylmorphine (6%), and morphine or oxycodone (5%). The importance of detecting levamisole in urine concomitantly with cocaine in affected cases is in being able to ascertain its separate contribution to the observed neurotoxicity in suspected cases.

Levamisole is 100-fold to 300-fold less potent than cocaine in blocking norepinephrine and dopamine uptake, and has a very low affinity for the serotonin transporter; and it does not trigger an appreciable substrate efflux. Nevertheless, the desired neuropharmacologic effects leads to its widespread contamination in cocaine production. It potentiates the euphoric effects of cocaine by inhibiting dopamine reuptake and forming amphetaminelike metabolites. Hofmaier and colleagues[73] studied the

allosteric effects of levamisole and cocaine at 30 μM, a concentration at which levamisole displayed already mild effects on norepinephrine transport but without an inhibitory action on cocaine. Levamisole metabolizes to aminorex, an amphetamine-like substance that exerts strong effects on dopamine, serotonin, and norepinephrine transporters in a manner that resembled amphetamine. They concluded that although the adulterant levamisole itself had only moderate effects on neurotransmission, its metabolite, aminorex, nonetheless exerted distinct psychostimulant effects and that after the cocaine effect "fades out," the levamisole/aminorex effects "kicks in."

Exposure to levamisole-adulterated cocaine is associated with a variety of well-described hematological, skin, renal, and pulmonary pathologies,[74] often in association with positive anti-neutrophil cytoplasmic antibody (ANCA) serology. Hematologic abnormalities include agranulocytosis and neutropenia, which occur in a dose-dependent fashion, and are not commonly associated with pure cocaine-linked side or a characteristic of drug-induced vasculitis. A distinguishing feature of levamisole-adulterated cocaine exposure is small vessel vasculitis, which involves the ear lobes and the skin overlying the zygomatic arch or lower extremities, often with purpuric plaques in a retiform pattern or central necrosis. Skin biopsy shows pathologic involvement of superficial and deep dermal vessels associated with numerous neutrophils and eosinophils that surround and invade the walls of dermal vessels with extravasation of red blood cells, leukocytoclastic debris (nuclear dust), and fibrinoid necrosis on hematoxylin and eosin–stained tissue sections. Such findings are similar to children with chronic levamisole treated for nephrotic syndrome, so noted in a minority of children who developed purpuric lesions of at least the ears and biopsies revealing cutaneous vasculitis.[75] Although organ involvement has not been characteristic of levamisole-adulterated cocaine-induced autoimmune disease, there is an established association with proteinuria or hematuria, acute renal injury, and focal necrotizing and crescentic pauci-immune glomerulonephritis in some cases, and increased titers to p-ANCA. As in other drug-induced vasculitides, pulmonary involvement can complete the triad of skin, kidney, and lung pathology in the form of diffuse alveolar hemorrhages, idiopathic pulmonary hypertension, or other clinicopathologic presentations.

It has taken 25 years to recognize the causal association of levamisole-associated multifocal inflammatory leukoencephalopathy (MIL) in cocaine users. In 1992, Hook and colleagues[76] described 3 patients, ages 45 to 74 years, who developed a cerebral demyelinating disease within 3 to 5 months of beginning adjuvant therapy with 5-fluorouracil (5-FU) and levamisole. Two patients presented with progressive encephalopathy and ataxia, and a third had unexplained loss of consciousness. Brain MRI revealed multiple gadolinium-enhanced white matter lesions, predominantly in a periventricular distribution. Cerebrospinal fluid obtained in 2 patients showed oligoclonal bands (2 patients) and pleocytosis (1 patient). Pathologic studies of brain biopsy specimens from 2 patients revealed cerebral demyelination and perivascular inflammation similar to multiple sclerosis. There was clear improvement after discontinuation of chemotherapy and administration of corticosteroids. The pathogenesis was unclear, and the investigators considered the etiologic basis to be 5-FU toxicity, although the role of levamisole was not excluded.

Three years later, Kimmel and colleagues[77] described a patient age 57 years, who developed progressive confusion and ataxia over a 3-week period, 5 weeks after adjuvant therapy with levamisole for malignant melanoma. Brain MRI showed multifocal enhancing white matter lesions. CSF showed pleocytosis with an increased immunoglobulin G index. The patient improved with a 3-month tapering course of corticosteroids. The cause of the leukoencephalopathy in previously described cases[76] of 5-FU and levamisole was assigned at least in part, to levamisole.

One year later, Luppi and colleagues[78] described 2 patients, age 54 and 60 years, treated with adjuvant 5-FU and levamisole for colon cancer who, after 10 weeks and 6 weeks, respectively from onset of treatment, noted confusion, aphasia, ataxia, and progressive obtundation leading to decerebration (case 1) and nasogastric feeding (case 2). Brain MRI in both showed widespread bilaterally symmetric periventricular and hemispheric white matter hyperintensities compatible with MIL. Treatment with parenteral corticosteroids (case 2) led to clinical improvement.

A decade later, Wu and coworkers[79] described a series of 31 patients with levamisole-induced MIL, including 7 from their institution and 24 from the medical literature, treated with a combination of levamisole and 5-FU adjuvant therapy (21 patients) or levamisole alone (10 patients) for malignant cancer, most commonly colon cancer.

Onset of gait ataxia in two-thirds of cases, was delayed in those treated with combination 5-FU and levamisole compared with levamisole alone (11.7 weeks vs 2.5 weeks). Brain MRI showed enhancing periventricular or supratentorial white matter lesions. CSF showed lymphocytic pleocytosis in 47% of cases. Treatment with corticosteroids and intravenous immunoglobulin led to improved clinical status in 29 (94%) cases.

In 2009, Xu and coworkers[80] described the clinical and neuroradiological findings in 16 patients, age 8 to 52 years, treated with levamisole for recurrent aphthous ulcers or ascaris infections noting weakness (75%), aphasia (50%), neurocognitive (50%), and facial palsy (44%) as the main presenting clinical features. Brain MRI showed typical plaque and round or oval demyelinating enhancing white matter lesions and hyperintense signal on T_2/fluid-attenuated inversion recovery (FLAIR) images. Brain biopsy in 1 case showed multifocal demyelinating lesions with lymphocytic perivascular cuffs. Treatment with corticosteroids and hyperbaric oxygen was associated with full recovery.

In 2012, Blanc and colleagues[81] described a 29-year-old woman and active crack cocaine abuser with AIDS who presented with fever, malaise, and back pain and an unremarkable neurologic examination. CSF showed acellular fluid with increased protein content and oligoclonal bands. A urine drug screen showed cocaine and opiates. Brain MRI showed lesions consistent with MIL. Sera later tested for both cocaine and levamisole by gas chromatography–mass spectroscopy were negative. The investigators speculated that levamisole contamination was responsible for MIL, citing that urine testing for levamisole would have been positive if performed at the time of cocaine detection.

In 2013, Yan and colleagues[82] described the clinical and neuroradiologic features of 15 patients, age 31 to 54 years, treated with levamisole for worm expulsion for 2 weeks to 2 months before onset of fever, headache, dizziness, neurocognitive disturbance, weakness, and visual impairment. Nine patients who underwent CSF examination showed only pleocytosis. Electroencephalography in all 15 showed high-amplitude slow waves. Brain MRI showed multiple hyperintense T_2/FLAIR bilateral centrum semiovale and periventricular lesions (all patients), and two-thirds showed lesions in basal ganglia; with lesser frequency in the frontal (26%), occipital (6%), and temporal lobes (6%), or brainstem or cerebellum (6%). Treatment with "hormone therapy" was effective in all patients.

In the same year, 2013, Gonzáález-Duarte and Williams[83] described a 40-year-old woman with chronic daily use of cocaine admitted for acute confusion, aphasia, and fever. CSF showed neutrophilic pleocytosis. Brain MRI showed hyperintense signal in left parietal lobe white matter on T_2/FLAIR images. She developed sudden visual changes and hemiparesis 10 days later, and a week after, a new episode of expressive aphasia each associated with respective right and left frontal white matter lesions reminiscent of MIL. Complete recovery occurred in 2 weeks and she remained stable

without further new episodes despite continued cocaine abuse. The investigators speculated a relationship to levamisole adulteration.

In 2015, Vosoughi and Schmidt[84] described MIL in 2 cocaine abusers, age 25 and 41 years, who presented respectively with unilateral progressing to bilateral sensorimotor deficits; and confusion with impaired balance. Serial brain MRI in the first patient showed increasing bilateral T_2/FLAIR enhancing white matter hyperintensities in periventricular white matter, pons and cerebellar peduncles, with similar presenting features in the second patient. Both patients improved with corticosteroids and plasma exchange. Urinary levamisole was not tested in either patient, although the investigators concluded that it was a likely cause of MIL in their cases.

Finally, Vitt and colleagues[85] described a case of MIL with positive urine testing for cocaine and levamisole in a cocaine abuser with a history of hepatitis C infection. This 63-year-old woman presented with 3 days of progressive confusion, fever, and headache. Over 2 days she developed spastic quadriparesis and stupor. Cocaine tested positive in the urine. Brain MRI revealed T2/FLAIR hyperintensities and incomplete ring-enhancement in periventricular subcortical white matter, many of which were ovoid shaped. CSF showed a lymphocytic pleocytosis and elevated protein content without oligoclonal bands. Gas chromatography–mass spectroscopy detected levamisole in the urine. High-dose intravenous methylprednisolone for 5 days followed by plasmapheresis was ineffective. The patient received intravenous cyclophosphamide with stabilization. Ten months later, the patient was minimally conscious with mutism and generalized spasticity.

The mechanisms underlying levamisole-adulterated cocaine-induced systemic pathology are not well understood, but a causal relation to ANCA-associated disease is suggested by the correlation of disease pathology, clinical relapse with detectable autoantibodies, sensitivity to immune modulatory and immunosuppressive therapy, and predictable levamisole-induced histopathology. Levamisole potentiates the production of interferon and interleukins; increases T-cell activation and proliferation, neutrophil mobility, adherence, and chemotaxis; and increases the formation of antibodies to antigens.[39] It acts as a hapten, triggering an immune response resulting in opsonization and leukocyte destruction. Levamisole may interact with neutrophil extracellular traps composed of a complex of DNA, histones, and neutrophil granules including myeloperoxidase, proteinase-3, and human neutrophil elastase. Neutrophil extracellular traps release in response to stress and provide a source of antigen that can activate the immune system.[74] There has not been a living patient or postmortem-studied case of MIL demonstrating vasculitis pathology in brain tissue.

SUMMARY

Drug abuse is a rare cause of histopathologically verified CNS vasculitis. Nonetheless, the complications of illicit substance use on the cerebral circulation can be highly lethal with secondary vasculopathy, hemorrhage, and aneurysm formation especially when the illicit substances are delivered parenterally. A likely diagnosis rests on the drug that is abused and the clinical and neuroradiologic findings of a presumptive case. Management rests on avoidance of further exposure and minimizing the secondary neurotoxic effects of the abused substances and polypharmacy use. HIV/AIDS has introduced new aspects of causation and patterns of drug use.

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