

REVIEW ARTICLE

Drug Abuse as an Emanating Risk for Stroke in Young Adults

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Abstract

Drug abuse is a substantial risk factor for stroke among patients under 45 years of age and ranks second among the most commonly identified potential risk factors. Drug abusers aged 15 to 44 years are 6.5 times more likely to have a stroke than non drug users. Stroke occurring in persons under 45 years of age accounts for only 4% of all strokes but causes an enormous toll in personal suffering, lost productivity, and health care costs.

Introduction

Cerebrovascular disorders, contribute to the morbidity and disability associated with illicit drug use.¹ These drugs can affect nervous system at any level extending from the cortex to the neuromuscular junction.² Drug addicts are at a greater risk of having multiple substance abuse, alcohol abuse problems and/or HIV infection, all of which are associated with their own blend of neurological syndromes which may coexist or develop subsequently. We shall be discussing stroke due to illicit drug abuse in this review as it is the most common neurological event associated with the prolonged morbidity and mortality.

Epidemiology

Substance use is influenced by factors which affect the demand, supply, and actual use of a particular set of substances.³ Earlier epidemiological studies did not recognize drug abuse as a cause of stroke and most evidence that illegal drugs are risk factors for stroke was anecdotal.

The first report of cocaine-associated stroke was in 1977 when intramuscular administration in a male user was followed 1 h later by aphasia and right sided hemiparesis.⁴ The case-control study in 1999 emerged as a strong study to prove that drug abuse is one of the risk factor (47%) for hemorrhagic and ischemic stroke in young population.⁵ In the recent study, a strong association with odds ratio of 6.4 is seen between acute cocaine use and early-onset ischaemic stroke.⁶

In the Baltimore- Washington Young Stroke Study, 12.1 % of young stroke victims had recent drug use and in 4.7 % it was considered the sole cause of stroke.⁷ The incidence of stroke are greater among men than women in the 35 to 44 year old age group.^{8,9}

In the western data, the most frequent recreational drug causing stroke is Cocaine (57%), followed by heroin, amphetamine, methylphenidate, and Phencyclidine.⁵ Cannabis,

heroin, and Indian-produced pharmaceutical drugs are the most frequently abused drugs in India.¹⁰ About 50 percent of boys have tried at least one of the substance of abuse nature by the time they reach the ninth grade.¹¹ In a study from India, illicit drug abuse was seen in 10% of patients with acute ischaemic stroke in young population.¹² In another study, besides other risk factors (regular tobacco user 38%, current smoking 34%, current alcoholism 42%, Illicit drug abuse was seen in 8% of acute hemorrhagic stroke in young subjects.¹³ A large population-based study of 1935 patients with stroke revealed that 14.4% of intracerebral haemorrhages and 14.4% of ischaemic stroke were associated with drug use.¹⁴ Some drugs are preferentially related to certain stroke subtypes. For example, heroin is most often associated with cerebral ischemia and has rarely been linked to subarachnoid hemorrhage or intracerebral hemorrhage. In a cross-sectional study of hospital discharges, amphetamine increased the risk of hemorrhagic stroke (4.95 times), whereas cocaine increased the risk of both hemorrhagic stroke (2.33 times) and ischemic stroke (2.03 times).¹⁴ The etiological attributable fraction of illicit drug use for stroke in the young may be even higher in some developing countries, particularly in those which are drug producers. For

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Table 1: Common drugs associated with stroke

Cannabis	Ecstasy
Opium	γ -hydroxybutyrate
Cocaine	Heroin
Ketamine	Ketamine
Amphetamines	LSD (Lysergic acid diethylamide)
Metamphetamine	

Table 2: Common street names of common drugs

Cannabis: Marijuana, Pot, Puff, Resin, Hash, Hashish, Dope, Ganja, Hemp, Weed, Whackybacky, Gunk, Smoke, Spliff

Cocaine: Coke, Charlie, Lady, Percy, Snow, Toot

Crack (alkaloidal cocaine): Base, Gravel, Pebbles, Rocks, Stones, Wash

Amphetamines: Speed, Base Ice, Crystal, Billy, Whiz, Dexies

Methamphetamine: Crystal Meths, Ice, Krank, Tina, Tweak

Ecstasy: E, X, XTC Brownies, Eckies, Hug drug, M & Ms, Sweeties

γ -hydroxybutyrate: GHB, GBH, Liquid Ecstasy, Midnight blue, Blue nitro

Heroin: H, Horse, Smack, Skag

Ketamine: Green, K, Special K, Supa K and Vitamin K

LSD: Acid, Lucy, Tabs

Poppers: Liquid Gold, Ram, Rock hard, Thrust and TNT

Magic mushrooms: Shrooms, Mushies, Happies, Sillies, Liberties

instance, in a series of stroke patients from Iran, 45.7 % were addicted to opium.¹⁵

Approximately 25% of these patients die during their initial hospitalization, and many of those who survive are left with permanent neurologic handicaps.¹⁶ Fifty-six (26%) patients with stroke died during the acute admission; 48 (86%) of these had hemorrhagic strokes (16 subarachnoid hemorrhage, 32 intracerebral haemorrhage).⁵ Amphetamine abuse is associated with increased risk of death after a hemorrhagic stroke.¹⁴ The Location of intracerebral hemorrhage may be lobar or basal ganglia in cocaine users.

Drugs associated with stroke are mentioned in Table 1. Addicts may use more than one drug, each of which they may describe by a variety of "street" names which are far from standard Table 2.

Table 3: Mechanisms of ischaemic infarct associated with drug abuse

Arterial vasoconstriction
Arteritis
Small-vessel disease
Infective endocarditis with septic embolization
Structural heart disease
Foreign body embolization

Pathophysiology of Drug Abuse Induced Stroke

The various mechanisms of Ischaemic infarct and haemorrhage due to drug abuse are shown in Tables 3 and 4 respectively. These drugs have pharmacologic effects on neurotransmitters and physiologic actions.¹⁷ Most of these compounds gain entry into the central nervous system and have a variety of effects on neurotransmitters including increase catecholamine release from central noradrenergic nerve terminals (amphetamines, OTC sympathomimetics), block reuptake of catecholamines into nerve terminals (cocaine, PCP), or increase plasma catecholamine levels (ethanol, cocaine, tripeleminamine and pentazocine) Elevated catecholamine levels may predispose to cardiac arrhythmias such as atrial fibrillation and ventricular dysrhythmias.

The temporal proximity of drug administration that is within hours suggests a direct association between drug abuse and stroke.⁵

Clinical Presentation

Patient can present from neonatal or perinatal to 63 years of age but 85–90% of strokes associated with use of illicit drugs occur in the third or fourth decade.

Symptoms may occur on the background of chronic abuse, overdose, "binge" use, reexposure after a prolonged abstinence, or even first exposure to the offending agent. Symptoms frequently occur during or within minutes to several hours (usually within 48 hours) after intravenous, intranasal, inhalational, oral, intramuscular,

Table 4: The mechanisms of intracranial hemorrhage associated with drug abuse

Hypertension
Unmasking pre-existing lesions
Arteritis/vasculopathy
Infective endocarditis
Reperfusion
Drug interactions

subcutaneous, or inadvertent intra-arterial administration of drugs.

Individual Drugs

Cocaine

Cocaine is extracted from an Erythroxyton Coca plant. It is consumed in two chemical forms cocaine hydrochloride and cocaine alkaloid¹⁸. Cocaine hydrochloride is a water-soluble crystal powder and absorbed through the nasal mucosa. Nasal insufflation of cocaine hydrochloride results in peak levels in about 50–60 min, as uptake is limited by the small available surface area, and associated vasoconstriction in the nasal mucosa.¹⁸

Cocaine alkaloid is produced by dissolving cocaine hydrochloride in water, ammonia, and ether to obtain "free base" or in water and baking soda to produce "crack." The name comes from the popping sound it makes when heated. The onset of symptoms is usually immediate or within 3 h of cocaine use, and 73% of patients with cocaine-induced stroke have no prior cardiovascular risk factor.¹⁹

Cocaine is associated with both ischaemic and haemorrhagic stroke depending on the type of cocaine used. Daras et al studied 54 patients over a 6 year period reported that ischaemic and haemorrhagic strokes occurred in roughly equal proportions with 25 infarcts and 29 haemorrhages.¹⁹ Eighty percent of strokes related to nasal insufflation of the hydrochloride form are haemorrhagic, as compared to alkaloidal "crack" results in equal numbers of ischaemic and haemorrhagic stroke.²⁰

The majority (50–80 %) of infarcts

involve the middle cerebral artery and may include hemispheric, subcortical, cerebellar, brain stem, retinal, and spinal infarcts. Haemorrhagic strokes can be intraparenchymal, intraventricular and subarachnoid.²¹

Amphetamines

An estimated 35 million people abused amphetamines worldwide, as compared with 15 million cocaine abusers.²² Amphetamine use increases the odds of stroke by almost four times that of nonusers and results in greater disability and mortality rates.¹⁴ The risk of Hemorrhagic stroke is twice as compared to cocaine. Up to 75% of patients with methamphetamine-related stroke have significantly elevated blood pressures.²³ Methamphetamine use is associated with a 3.7-fold increase in the odds of detecting cardiomyopathy which results in arrhythmias and thrombosis, leading directly to cardioembolic strokes.²⁴ Acute increase in systolic blood pressure during amphetamine use leads to spontaneous intracerebral haemorrhage. Amphetamine-related SAHs frequently report underlying aneurysms.

Ecstasy

Ecstasy are derivatives of amphetamine and most commonly used is 3,4-methylenedioxymethamphetamine. There are no epidemiological studies specifically studying the incidence of Ecstasy-related strokes. There are a small number of case studies of both ischemic and hemorrhagic strokes occurring within hours of ingestion of Ecstasy.²⁵

Opiates/Heroin

Heroin is a semi-synthetic derivative of opium. Opiates are 16 times less likely to cause hemorrhagic strokes and five times less likely to cause ischemic stroke than amphetamines.¹⁴ Most reported strokes associated with heroin use are ischemic and are most

often due to cardioembolism in the setting of infective endocarditis and embolism is foreign bodies that have been added to the heroin.²⁶

Phencyclidine (PCP)

A total of five cases of PCP-associated stroke are found in the literature and all of them are hemorrhagic. PCP's sympathomimetic hypertensive effect may be the provoking factor.²⁷ Spikes of severe hypertension can occur hours to days after use. PCP-related SAH has been reported and may result from weakening of arterial walls.

Lysergic Acid Diethylamide

Lysergic acid diethylamide, or LSD, is a potent hallucinogen. Only four cases of stroke related to LSD have been reported in the literature. All of the cases involved in ischaemic stroke were under the age of twenty five.²⁸

Marijuana/Cannabis

Marijuana is the most commonly used recreational drug in the United States, Cannabis use has been prevalent in India since a long time, and ancient Indian texts describe medicinal use of cannabis.²⁹ Evidence supporting marijuana's role in stroke is scarce, considering its widespread use. One study demonstrated an odds ratio for ischaemic stroke with marijuana use of 1.76 even when controlling for other risk factors.⁵ Twenty-one cases of imaging positive stroke related to marijuana use have been reported.

Organic Solvents

Organic solvents are chemicals used routinely in commercial industries. The exposure may be occupational, environmental or recreational by inhaling paints, glues, and other products. The effects are short lived often leading to repetitive use to maintain the effect. Chronic exposure produces

incoordination, double vision, ataxia, dysarthria, and nystagmus and paralysis. With increasing exposure, there is worsening disorientation, confusion, and respiratory depression that may lead to coma.³⁰

Athletic Performance Enhancing Drugs

They are pharmacologic agents used by athletes and nonathlete weightlifters to enhance performance. They may be anabolic effects (steroids, insulin, growth hormone), amphetamines, cocaine, erythropoietin or b2 agonists. Apart from other neurological effects, they can cause hypertension and stroke.³¹

Diagnosis

The clinician should keep a high index of suspicion for drug use or abuse, when confronted with a stroke patient, particularly one who is less than 50 years old and without stroke risk factors. This is especially true in large metropolitan and inner city regions. It should well be considered that the history may be unreliable. In fact, one study of cocaine use in an inner city walk-in clinic showed that 72% of men with positive urine toxicology screens denied illicit drug use in the 3 days before sampling.³² Therefore, one should repeatedly question the patient, family members, and friends for a history of drug use by all possible routes.

It is important for the clinician to be aware of the common features associated with illicit substance misuse as these can lead to a rapid clinical diagnosis. Look for associated physical stigmata of drug use, such as hypertension, cardiac arrhythmias, needle marks, other cutaneous signs, other organ system signs (nephropathy), signs of endocarditis³. All such patients should be evaluated with toxicologic screens of urine, blood, pill vials, and even gastric juice.

Various methods used are thin-layer chromatography, gas-liquid chromatography, high-pressure liquid chromatography, combined gas chromatography-mass spectroscopy, radioimmunoassay, and enzyme multiplied immunoassay.¹⁷ Confirmatory testing, typically using a second method, is recommended to reduce the chance of false positives. The duration of detectability is generally about four urinary half-lives, typically up to 2-3 days, except for severe PCP poisoning (2-4 weeks) or marijuana metabolite (1 month). These tests only confirm the presence of a substance in urine, indicating consumption of the drug during the previous 24 to 72 hours, but do not give any indication of blood levels or of the relationship of the drug to the clinical effects observed.³³ Patients presenting with stroke should be investigated with an appropriate neurodiagnostic evaluation, including CT scan, MRI scan, and selected investigations like cardiac enzymes, electrocardiogram, echocardiography, including contrast and transesophageal and Holter monitoring and non-invasive vascular tests (carotid and transcranial Doppler).¹⁷ Echocardiography is required for all those patients with fever and any type of stroke, to look for evidence of infective endocarditis, even in those who deny injecting intravenously. Transoesophageal echocardiography is done to look for evidence of a right-to-left shunt. Cerebral angiography help determining the stroke mechanism (extracranial or intracranial large-vessel lesions, such as stenosis, occlusion, or findings consistent with arteritis) if performed early after stroke onset.³⁴ For patients with intracerebral hemorrhage (especially lobar) and subarachnoid hemorrhage, cerebral angiography has a high yield for a saccular aneurysm, mycotic aneurysms, arteriovenous malformation.

Treatment

Once a stroke is recognized as drug-related, acute intervention is required for treatment of hypertension and enhance drug elimination by either urinary acidification (PCP), urinary alkalinisation (amphetamines), and gastric lavage (PCP).

Manage fever and increased intracranial pressure. Patients with ischemic stroke may be considered for intravenous thrombolytic therapy, however, data are scant on the safety of thrombolysis in this setting and its use should be carefully considered.³⁵ A retrospective study found no complications in patients with cocaine associated stroke treated with tissue plasminogen activator. Cocaine-positive and cocaine-negative treated patients had similar stroke severity and safety outcomes.¹

All ischemic stroke patients should be treated with appropriate secondary preventative antithrombotic therapy. Anticoagulants are reserved for clear indications and demonstration of abstinence from drug use. Patients with intracerebral hematomas and subarachnoid hemorrhage should additionally be treated with empiric or standard medical and surgical therapy, as appropriate.

Underlying structural lesions, such as aneurysms and arteriovenous malformations, can be treated with surgical or interventional neuroradiologic techniques, or both, as appropriate. Although unproved, patients with arteritis may benefit from drug discontinuation, empiric high-dose steroids followed by gradual taper, and interval angiography to document resolution.¹⁷ All patients who survive the event should be referred to drug-treatment programs and rehabilitation

Outcome

Kaku and Lowenstein showed

that mortality was higher in the patients whose strokes were linked to drug abuse than among the non-drug users.⁵ Similarly, Sloan et al. reported poor outcome associated with drug abuse in stroke patients.¹⁷ However, in the Baltimore-Washington Cooperative Young Stroke Study, there was no difference in mortality between drug users (13.7%) and non-drug users (10%), although drug users were more likely to be transferred to a rehabilitation facility (24% versus 17%) and were less likely to go home or to a self-care environment (58% versus 70%).³⁶ Of the well-documented intracerebral hemorrhages attributable to drug abuse the mortality has been approximately 25-35% with significant morbidity in survivors.³⁷

Conclusion

Substance abuse is a common and important risk factor for stroke in young adults. There is increase in consumption of illicit drug use and stroke among young adults who are aged 35 to 54 years. All patients aged <55 years who experience a stroke and in patients who lack other known vascular risk factors should be routinely screened for drug abuse especially in the younger age group. Patients in addition to acute treatment should also be counselled for rehabilitation and drug treatment groups.

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