Cerebral intraparenchymatous and ventricular hemorrage after cocaine consumption: a case report.

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ABSTRACT

Introduction: *Cocaine is one of the most widely consumed psychoactive substances worldwide. It is highly addictive and can produce serious systemic and neurological symptoms due to sporadic or habitual use or withdrawal. Acute exposure to this substance triggers immediate psychiatric manifestations such as changes in affect or behavior: feelings of irritability, hyperactivity, anxiety, restlessness, euphoria or psychosis; this symptomatology contrasts with induction in certain cases of depression, isolation or sadness with the chronification of its consumption. In addition to the various sensory-perceptual effects described, the substance can cause serious neurological and/or cardiovascular damage, such as heart rhythm disorders, malignant arrhythmias, hypertensive emergencies, coronary syndromes and cerebrovascular diseases.* ***Methods:*** *We present the case of a patient who was admitted to the Hospital Universitario del Valle, in the city of Santiago de Cali, department of Valle del Cauca, in Colombia, for a neurological condition that suggested a central origin. This patient had no cardiovascular risk factors, but had a history of Guillain Barré syndrome and cocaine use since adolescence.* ***Results:*** *The aforementioned patient underwent multiple studies, highlighting the imaging studies (CT, MRI and MRA of the brain) and the invasive strategy of cerebral angiography, in which it was possible to document that the patient's neurological manifestations were due to severe hemorrhagic cerebrovascular disease secondary to cocaine consumption.* ***Conclusions:*** *Always inquire in patients with intraparenchymal bleeds the consumption of psychoactives, especially cocaine, for its injurious effects on the cerebral vasculature.*

Key words: *cocaine, brain, cerebral hemorrhage, cardiovascular diseases.*

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INTRODUCTION

Cocaine is an alkaloid extracted from Erythroxylum coca, a plant endemic to South America, Mexico and Indonesia. Historically used in the celebration of religious rituals by pre-Columbian tribes; during the Spanish colonization, it was considered an energizer for indigenous slaves[1]. In 1855, Friedrich Gaedcke achieved the first isolation[2]; in 1959 Albert Niemann characterized the substance and the active principle of coca leaves[3]. In 1868, the Peruvian physician Tomas Moreno published his study on coca, describing the effects as physical and mental stimulation, less fatigue and the reversibility of the effects by co-ingestion of alcohol.[4]

By 2006, some 6 million Americans had abused cocaine in any form: "lines", bazuco or "crack"(1). Recently, its manufacture rose 56% between 2013-2016; reaching its peak in the records of the United Nations Office on Drugs and Crime (UNODC, 2018). In 2016, they totaled 18.2 million regular cocaine users globally; accounting for a 7% increase in total users versus those reported in 2015.[5]

The most commonly used form is powdered hydrochloride; some users also consume the so-called "bazuco", the most impure form[1] which is snorted, insufflated or injected intravenously. Completely metabolized by enzymatic hydrolysis; involving plasma and hepatic esterases. Its metabolites, benzoylecgonine and ecgonine methyl ester, appear immediately after the alkaloid is degraded; their oxidation maximizes toxicity.[6]

Its acute or chronic use generates physiological responses that cause pathological effects in most systems[6]. We present the case of a patient with no serious comorbidities who suffered a hemorrhagic stroke as a complication of cocaine use.

Case presentation

50-year-old male, born in Cali, who was admitted to the emergency room of our institution on February 6, 2020, due to symptoms of 3 days of evolution, consisting of asthenia, adynamia, hyporexia and nausea, associated with alterations of consciousness such as confusion, disorientation and abnormalities in the content of his thoughts.

Pathological history: Guillain-Barre syndrome 2 years earlier, complete recovery, without functional sequelae. Additionally, he was a drug addict since adolescence with marijuana, bazuco and cocaine; having been consuming cocaine hydrochloride during the 5 days pre-hospitalization.

On examination: Normal vital signs (blood pressure: 100/60 mm Hg); regular general conditions.

Neurological examination

Consciousness: Alert, confused, oriented in person, not in time-space. Cranial nerves: No evident involvement. Motor system: Right hemiparesis (muscle strength 4/5). Meningeal signs: Absent. Gait: paretic, motor involvement of the right extremities. Symmetrical reflexes in the extremities. Mental examination: confused, disoriented, uncooperative, hypoprosexic, dysphoric, perseverative, with ideoverbal poverty, partially obeyed simple verbal orders; alterations in judgment and recent or working memory.

Simple cranial tomography at admission showed cerebral and intraventricular bleeding, involving the third ventricle and left lateral ventricle, without hydrocephalus **(see figure 1).**

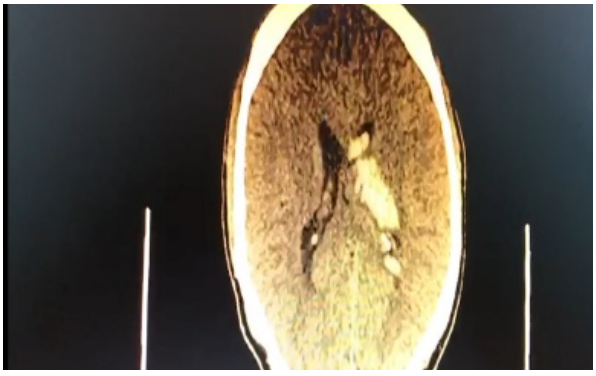


Figure 1.

The admission blood biochemistry is shown in **Table 1**.

Table 1. Initial laboratories.

Parameter	*Result*
Lactic acid	**1.5 mg/dl**
Glucose	**93 mg/dl**
BUN	**14.8 mg/dl**
Chlorine	**99 mEq/L**
Potassium	**4.7 mEq/L**
Sodium	**138 mEq/L**
Creatinine	**0.99 mg/dl**
C reactive protein	**<5 mg/dl**
Leukocytes	**7920/mm3**
Neutrophils	**73.4%**
Lymphocytes	**19.2%**
Hemoglobin	**14.8 g/dl**
Hematocrit	**45.8%**
Platelets	**272.000/mm3**
PT	**10.3 seconds**
INR	**0.95**
PTT	**25.5 seconds.**

1. The Toxicological profile was not included here.

Toxicological profile positive for cocaine and opioid metabolites **(see figure 2)**.

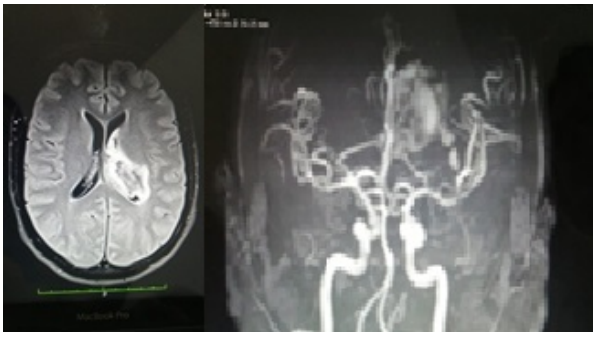
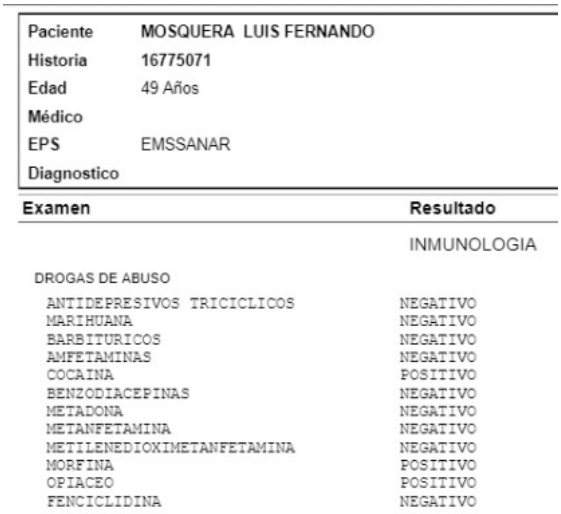


Figure 2.

During his hospital stay, he presented psychomotor agitation and generalized tonic-clonic seizures; resolved with valproic acid. Additionally, his right hemiparesis worsened.

Magnetic resonance imaging of the brain showed a left gangliobasal hemorrhage with secondary intraventricular drainage. However, both cerebral arterio-venous vasculature angioresonance and cerebral arterial angiography via endovascular route were normal **(see figure 3)**.



Paciente	MOSQUERA LUIS FERNANDO
Historia	16775071
Edad	49 Años
Médico	
EPS	EMSSANAR
Diagnostico	

Examen	Resultado
	INMUNOLOGIA
DROGAS DE ABUSO	
ANTIDEPRESIVOS TRICICLICOS	NEGATIVO
MARIHUANA	NEGATIVO
BARBITURICOS	NEGATIVO
AMFETAMINAS	NEGATIVO
COCAINA	POSITIVO
BENZODIACEPINAS	NEGATIVO
METADONA	NEGATIVO
METANFETAMINA	NEGATIVO
METILENEDIOXIMETANFETAMINA	NEGATIVO
MORFINA	POSITIVO
OPIACEO	POSITIVO
FENCICLIDINA	NEGATIVO

Figure 3.

With these results, it was concluded that the bleeding was a cerebrovascular complication of cocaine hydrochloride consumption.

With the established in-hospital treatment, the patient was stabilized and discharged with multidisciplinary therapy with the participation of Clinical Neurology, Psychiatry, Physiatry, Physical Rehabilitation and Physiotherapy.

DISCUSSION

Cocaine is an alkaloid extracted from the leaves of the Erythroxylum coca plant, endemic to Latin America, Indonesia and the West Indies[1]. Its use dates back to pre-Columbian times, as an anesthetic for trepanations in communities of ancient American civilizations, and mummies found in Peru corroborate this fact[1]; later, during the time of the conquest, the Spanish legalized it when they discovered its energizing properties, evident in the native Indians, who showed greater vigor and less fatigue after the consumption of coca leaf during their work in the silver mines.[1]

Cocaine hydrochloride is currently the most

widely used narcotic drug in the West, and is also the leading cause of emergency hospitalizations and drug-related deaths in the USA.[1,6]

The latest figures on drug use in Colombia date from 2013: the departments with the highest cocaine consumption are Antioquia (1.63%) and Atlántico (1.14%), higher than the national average (0.7%).[7]

Of its 4 varieties, cocaine hydrochloride stands out; a whitish powder that, due to its solubility in water and easy absorption, can be inhaled, ingested or dissolved in water for intravenous injection; it is obtained after dissolving coca leaves in solvents such as kerosene, alkaline bases or sulfuric acid; This produces a pasty substance, the "coca paste", with 40-80% of the alkaloid; it is then treated with hydrochloric acid, obtaining hydrochloride salt, whose cocaine content is around 50-100 mg per line inhaled; it cannot be smoked because of its high melting point and its instability at high temperatures.[1,6,8]

Coca base is the one that is usually insufflated; it is prepared by dissolving the hydrochloride in water and ammonia; this mixture is dissolved in ether or alcohol; finally it is evaporated for the final extraction of the base[1,6,8]. Crack, an infrequent solid variant, is the most potent and addictive; produced by mixing the hydrochloride with sodium bicarbonate; it is then heated to solidify it, turning it into a hard mass upon drying, constituting crack, non-flammable and so called because of the sound emitted when insufflated or smoked.[1]

The most impure form is "bazuco", very common in Latin America: a crude extract of coca leaf adulterated with substances such as water, talc, flour, sand, sulfuric acid, etc., which increase its toxicity[6,8]. Other alkaloids such as quinine, strychnine, and local anesthetics are also associated.[1]

Once cocaine enters the circulation, plasma, intestinal and hepatic esterases (hepatic carboxylesterase) hydrolyze the ester groups of cocaine generating inactive metabolites, such as benzoylecgonine (BE) and methylecgonine ester (MME). BE appears in plasma usually after 15-30 minutes after intravenous, intranasal or smoked administration; it reaches peak concentrations after 1 to 4 hours[6,9]; it may have a longer plasma life, depending on the amount and time of consumption by the user. BE is the most monitored metabolite in urine to detect its use in occasional or regular users; it accounts for 45% of the metabolites eliminated after consumption; it can be identified in urine up to 2 days after ingesting 20 mg or up to 14 days after consuming a large amount.[9]

At cutaneous level it usually exerts a local anesthetic effect by blocking sodium channels[6]. It alters synaptic transmission by inhibiting presynaptic reuptake of norepinephrine and dopamine, with consequent accumulation of these neurotransmitters at postganglionic level. It has sympathomimetic action increasing the release of epinephrine in the adrenal medulla; thus contributing to generate vasoconstriction, hypertension, hyperglycemia, hyperthermia and mydriasis.[6]

At the Cardiovascular level, there is blockade of sodium channels predisposing to arrhythmogenicity; also, direct myocardial toxicity, inducing band necrosis, tissue disorganization and dilated cardiomyopathy; its sympathomimetic action (by inhibition of catecholamine reuptake) causes positive inotropism, vasoconstriction, increased blood pressure and arrhythmias (sinus, tachycardia and ventricular fibrillation with Brugada patterns); It can also generate alterations in electrical conduction (branch block of the His bundle and the atrioventricular node), accelerate atherosclerosis and induce intravascular thrombus formation with consequent acute coronary syndromes; in certain cases it can be associated with other complications such as infectious endocarditis, due to the reuse of syringes for intravenous administration of psychoactive drugs.[6]

At the pulmonary level, the effects on its vasculature due to alpha and beta-adrenergic overstimulation

and increased levels of endothelin-1 generate pulmonary hypertension; patients present pulmonary edema due to cardiovascular compromise, alveolar rupture due to increased intra-alveolar pressure and a higher incidence of emphysema due to exposure to by-products of the combustion of the smoked substance ("crack lung"); Acute Pulmonary Syndrome is also observed after inhaling coca base or crack, consisting of sustained inflammatory lesion, associated with fever, hypoxemia, hemoptysis, respiratory failure and diffuse alveolar infiltrates.[6]

There may be alveolar hemorrhage with eosinophilic inflammatory infiltrate and IgE deposits, which in the long term cause obliterative bronchiolitis and organizing pneumonia.[6]

There may also be hepatotoxicity attributable to the oxidative effect of cocaine metabolites (norcocaine and nitrosonium nitroxide) through the cytochrome P450 pathway[10]. There is disruption of cellular respiration at mitochondrial level due to toxicity of the mentioned metabolites, fatty infiltration in non-necrotic areas of the hepatic parenchyma (predominantly centrolobulillar) and ischemic lesions due to hypoperfusion secondary to vasoconstriction.[6]

In the gastrointestinal tract, mesenteric ischemia occurs mainly mediated by vasoconstriction and hypoperfusion, which causes perforations of hollow viscera and usually occurs in "body packer" traffickers by rupture in the digestive tract of one or more capsules filled with the alkaloid; It would also increase the incidence of gastric ulcers and retroperitoneal fibrosis.[6]

At the renal level, it is associated with nephrotic syndrome and acute glomerulonephritis, due to degradation of the extracellular matrix and syndromes due to anti-GBM autoantibodies. Amyloidosis, interstitial nephritis, renal infarcts due to renovascular disease and acute thrombosis of renal arteries and veins have been described.[6]

In pregnant women, the utero-placental axis and the fetus also suffer: it crosses the placenta reaching high concentrations in the fetal organs; generating cardiac toxicity, with myocardiocyte apoptosis, ischemic damage and dilated cardiomyopathy, structural congenital malformations and arrhythmogenic disorders; also, serious neurological alterations by altering the cerebral cytoarchitecture, the neurotrophic function of monoamine neurotransmitters and the genetic expression of apoptotic transcription factors; cortical infarcts, anomalies in cerebral cortical development (pachygyria or schizencephaly) and the formation of interhemispheric, subependymal and periventricular cysts may occur[6]. The vasoconstrictor effect decreases the placental flow of oxygen and nutrients to the fetus, which, in addition to malformations, may cause intrauterine growth retardation.[6]

It can generate neurophysiological, cerebrovascular and/or psychiatric manifestations. It reduces cerebral irrigation through vasospasm due to endothelial dysfunction, oxidative stress and smooth muscle hypersensitivity due to increased intracellular calcium concentration[6]. Among the most common neurological complications caused by cocaine is Intraparenchymal Cerebral Hemorrhage, initially described in 1977, caused by vasculitic phenomena induced by direct endothelial damage or by elevations in blood pressure due to sympathomimetic stimulus in acute consumption; plus failures in cerebral autoregulation with arterial vasodilatation and ischemia-reperfusion lesions.[6]

In a report of 45 cases by Tapia et al. 62% of the patients with hemorrhages were men; the average age was 33.6 years; mortality rate: 31%; the most frequent locations of these hemorrhagic processes: lobar (57%), putaminal (18%), massive hemispheric (9%), thalamic and intraventricular (7% each) and the remaining 2% in the caudate nucleus. 15% of the cases had a history of underlying vascular or neoplastic lesions in the central nervous system[11]. Some case reports report ischemic vascular accidents in the spinal cord, due to the mechanisms previously described.[12]

Another adverse effect is epileptogenesis due to synaptic accumulation of excitatory neurotransmitters with generation of convulsive activity. Likewise, there may be a non-competitive inhibitory effect on gamma-amino butyric acid currents in neuronal membranes. Reverse tolerance" phenomena of N-methyl-D-aspartate receptors may occur, since cocaine stimulates it repeatedly below the convulsive threshold[6]. It is toxic in dopaminergic cells, increasing the intraneuronal expression of α-synuclein, which generates neurodegenerative processes that predispose, mainly, to Parkinson's disease.[6]

At the psychiatric level, monoamine reuptake blockade also occurs in the ventral tegmental area, the accumbens and caudate nuclei, the dorsal-ventral prefrontal cortex and the insula. Exaggerated euphoria, hyperactivity and impulsivity are observed. Its repetitive use depletes dopaminergic reserves, causing anxiety crises and craving, and the syndrome known as "wash-out", consisting of a sensation of anhedonia, lethargy and hypokinesia[1,5,6]. Potentially fatal hyperthermia has also been described, caused by alteration of the hypothalamic thermoregulatory centers due to local vasoconstriction and hypoperfusion.[6]

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