Tattooing-induced inflammatory reactions, unusual trigger factor for stroke in a young man chronic user of tobacco and marijuana, with unknown neurovascular anatomical variants and patent foramen ovale – a "happy ending" case report

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Abstract

Introduction: Extensive tattooing co-occurring with other lifestyle risk factors (cannabis and tobacco smoking) represents unhealthy behavior trends in some groups of teenagers and young adults.

Case report: This case study synthetically presents a 2 years evolution of a 37-year-old man, with 20-year history of progressive and regular cannabis exposure and tobacco smoking. In January 2017 he suffered a severe paramedian thalamo-mesencephalic embolic stroke of undetermined source and coma, preceded by laborious tattooing maneuvers. Uncommon anatomical variants of cerebral circulation (a right-sided fetal type posterior cerebral artery and an inferred artery of Percheron) were detected. The rehabilitation program and abstinence from smoking tobacco and marijuana led to significant neurologic improvement, with no vascular recurrence until September 2018, when he suddenly suffered from a transient ischemic attack in the vertebrobasilar arterial territory. Recurrence of the cerebral ischemic event during a disciplined program of abstinence imposed clinical re-examination, blood analysis, peripheral venous Doppler, 24-hours ECG Holter. Finally transesophageal echocardiography has revealed the embolic source, and detected patent foramen ovale (PFO) with minimal shunt. He was informed that he should undergo PFO closure. His first option was for conservatory management, using a dual antiplatelet medication (75 mg clopidogrelum, 75 mg aspirin). In October 2019 his cardiac congenital malformation was successfully operated. Case closed.

Discussion: Stroke was triggered by extensive tattooing maneuvers that induced bleeding, local and systemic inflammatory reactions, in a young person predisposed to cerebral infarction. The complex physiopathological picture included a "puzzle" of harmful xenobiotics (contained in cannabis and tobacco smoke, respectively in tattooing ink), overlapping with the unknown pre-existing asymptomatic cardiac malformation, and neurovascular uncommon anatomic variant. Prevention of stroke in young adults is the primary treatment strategy, as Hippocratic Oath postulates: "*I will prevent disease whenever I can, for prevention is preferable to cure*". Healthcare professionals must educate people and promote prophylactic interventions against modifiable risk factors. Secondary prevention of recurrent strokes must be directed towards etiology, and mechanisms responsible for the incident, and a rigorous management of additional risk factors.

Key words: *tattooing; cannabis; tobacco; artery of Percheron; patent foramen ovale; stroke,*

Introduction

Nowadays, extensive tattooing and body piercing co-occurring with cannabis, alcohol, and tobacco smoking represent increasingly common forms of self-expression and behavioral trends in some groups of teenagers and young adults. Tattooing is a very common practice, and the number of people getting tattooed has substantially increased in recent years, encompassing 24% of the population in certain countries (1,2). The presence of bigger tattoos could be a rough indicator of possible emotional problems, depression, neuroticism, aggressive and violent behavior, drug abuse, risky sexual behaviors and promiscuity, increased risk for hepatitis B and/or C, even traffic offences (3,4).

Complications from decorative tattoos are relatively rare but can be unpredictable (1,2,5,6).

Risks may be increased with the current trend of home-based tattooing, especially in unhygienic settings or with inappropriate conservation of inks.[5,6] Marijuana is one of the most commonly used recreational drugs worldwide. Increasing evidence now links cannabis to the pathogenesis of cardio-cerebrovascular diseases in young adults, with a recorded 25.6% death rate associated with cannabis-related harm (7,8). In many EU countries, medical use of cannabinoids is authorised, but this should not become an argument for "unfettered and uncontrolled consumption" (9).

Romanian National Anti-Drug Agency estimated a 3.3% prevalence of regular cannabis use among young people aged between 15-34 years, with males comprising 4% and females, 2.7% (10).

Illicit cannabis ("weed, pot, grass, herb") is much more "powerful" than it was 40-50 years ago. Tetrahydrocannabinol (THC) levels have steadily increased from less than 1% in the mid-1970s, to 3% in 1980, 6% in 2002, approximately 8.5% in 2008 (11), and 12 % in 2012 (12). Many cardiovascular effects reported in recent papers are related to the increased content of THC (100–250 mg/joint, compared to 10 mg/joint in the 1960s (13).

Marijuana is an interactive cardiovascular negative factor in addition to alcohol, tobacco, and opioids, being associated with increased risk for stroke/transient ischemic attack (TIA), atrial fibrillation, myocardial infarction, and lower limbs arteritis (14-18). It is a precipitating factor for cerebral vasospasm and stroke, especially in chronically addicted young adults (16).

Case report

The patient and his next of kin have given written consents (in 2017 and 2018) to the inclusion of material pertaining to the case.

This case study synthetically presents the evolution of a 37-year-old man since January 2017 to today's days. He had a 20-year history of progressive and regular cannabis exposure and tobacco smoking (30-40 cigarettes daily). A timeline follow-back measure revealed that he had started smoking 1-2 "joints" weekly when he was 17 and then progressively increased the doses, becoming a "heavy" consumer (5-6 "joints" daily) over the past 4-5 years. He denied using alcohol or other street drugs. He had multiple, extensive and elaborate tattoos on his neck, arms, thorax and abdomen (fig.1) mainly in black ink, purchased online from American websites. The artist used to keep the ink in non-sterile receptacles.


Fig.1 Elaborate extensive tattoos; a large unfinished one is on the left flank.

In January 2017 he suffered a severe paramedian thalamic-mesencephalic embolic stroke of undetermined source and coma, preceded by laborious tattooing-maneuvers. He was diagnosed with uncommon anatomical variants of cerebral circulation: a right-sided fetal-type posterior cerebral artery (FPCA) and an inferred artery of Percheron (AOP) (19).

Neurological events were triggered by a "kaleidoscopic" association: laborious and painful tattooing maneuvers (lasting about 4½ hours) using unverified ink, application of a local gel with anti-inflammatory and anesthetic properties, smoking four "joints". A few hours later he complained of chills and subfebrility, dizziness, diplopia, slurred speech, disturbed balance, left third cranial nerve palsy (palpebral ptosis, divergent strabismus with unilateral mydriasis), right ataxic hemiparesis, and fluctuating consciousness. He dramatically deteriorated to coma (GCS 7/15) due to a paramedian thalamic and midbrain infarction. An evolutionary sequence of his medical history was presented in a previous article focused on anatomical, imagistic and pathophysiological aspects.

Sustained rehabilitation and abstinence from tobacco and cannabis led to favorable outcomes: modified Rankin score was 2 at four months after discharge, respectively 1, after twelve months. The patient was carefully followed-up, and had a favorable outcome with no vascular recurrence for 20 months. Imagery reflected the good clinical evolution (fig.2 and 3)
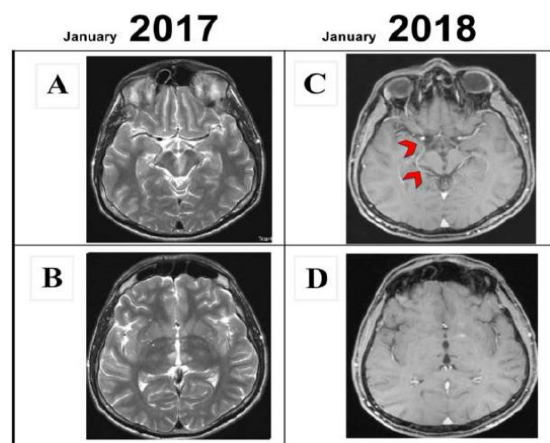
Fig. 2 MRI aspects recorded in January 2017 (**A**, **B**), and January 2018 (**C**, **D**).
(**A**, **B**): Axial T2-weighted brain images at mesencephalon and thalamus levels. Paramedian thalamic and rostral midbrain hyperintense aspects were suggestive for acute Percheron`s artery infarction.
(**C**, **D**): Axial T1-vibe sequences. Red arrows point the fetal-type posterior cerebral artery (FCPA). Multiple lacunae in the midbrain and paramedian thalamic nuclei are present.
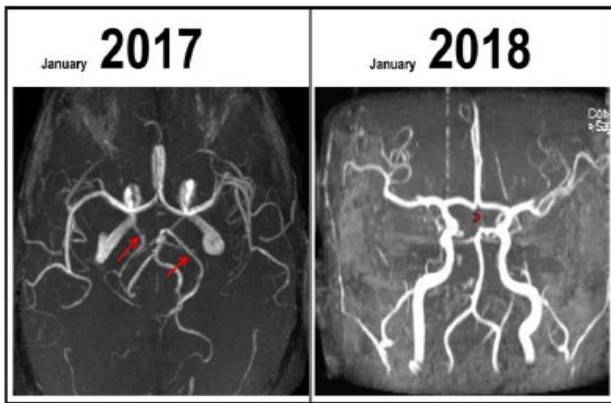
Fig. 3 Magnetic resonance angiography (MRA) recorded in January 2017. Posterior cerebral arteries are indicated by red arrows. Right fetal origin of the posterior cerebral artery (FPCA), arising directly from the internal carotid artery. Left thalamoperforating arterial group was not visualized, AOP was inferred. MRA control in January 2018 revealed permeabilization of one arteriole in the group of the left thalamoperforating arteries (arrow head).

In September 2018, during a disciplined abstinence program from tobacco and marijuana, he suddenly suffered from a transient ischemic attack (TIA) in the vertebrobasilar arterial territory (dizziness, nausea, axial ataxia), lasting about 15-20 minutes, possibly precipitated by morning hypoglycemia.

Clinical examination, peripheral venous Doppler, 24-hours ECG Holter monitoring did not reveal any embolic source. Repeated blood tests (white blood cells count, hemoglobin, electrolytes, cholesterol and triglycerides, liver and renal function) revealed normal results.

Repeated clotting tests were normal (antithrombin III was 98% (>80%), homocysteine was 8 mol (≤ 12), lupus anticoagulant was negative, antinuclear antibodies were 0.2 UM (<0.7), C ractive protein was 110% (70-130%).

Cerebral CT scan showed old lacunar images, and no additional abnormalities, no evidence of cerebral hemorrhage or encephalitis (fig.4).

Fig. 4 Axial CT scan performed in September 2018. Lacunar lesion in the midbrain.

Transesophageal echocardiography revealed a small patent foramen ovale (PFO, with no hemodynamically significant systolic shunt), which has not been disclosed in 2017 by transthoracic echography. No explanation for recurrent TIA other than PFO was found.

Confronted to a cryptogenic embolic ischemic stroke found to have PFO, with a risk of paradoxical embolism (RoPE score 6, with a 62% chance of PFO-related causality, and 8% risk of 2 year recurrence of stroke/TIA) (20), the subject was guided to interventional cardiology. He was informed that he should undergo PFO closure; the risks and complications after the interventional manoeuvre were explained.

His first option was for conservatory management, using a dual antiplatelet medication (75 mg clopidogrelum and 75 mg aspirin), to prevent recurrent stroke and/ or TIA.

In November 2018 he submitted an aesthetic ophthalmologic intervention, for the residual left-eye oculomotor paresis. Neurological examinations (pre- and postophthalmologic surgery) have revealed neither disturbed balance nor coordination, motor or sensory deficits.

In October 2019 he was convinced to submit a successful PFO closure intervention.

He has been abstinent from tobacco and cannabis since his first cerebral event (2017) and maintained good adherence to the rehabilitation program until nowadays.

Discussion

This paper is a pretext to analyze the challenging physiopathological circumstances of a cryptogenic stroke and coma, "triggered" by unedited factors (local and systemic inflammatory reactions, resulting from prolonged and extensive tattooing maneuvers), in contextual relationship with a complex "puzzle" of harmful xenobiotics (found in cannabis, tobacco and tattooing ink), in a young man, chronic cannabis abuser and heavy smoker, with a peculiar cardio-cerebrovascular background: association of Percheron`s artery (only 140 cases described since 1973) with a foetal variant of cerebral posterior artery (only 4 cases with this association type have been described in literature), and a pre-existing asymptomatic cardiac malformation (patent foramen ovale).

The presentation is useful for the young healthcare professionals (GPs, cardiologists, neurologists, toxicologists) who should educate people and

promote prophylactic interventions against modifiable risk factors for stroke in young adults, because prevention is the primary treatment strategy. Chronic intoxication with a "puzzle" of harmful xenobiotics may be incriminated in stroke pathogenesis, in predisposed individuals.

The initial diagnostic approach (19) had some important etiological weakness, because contrast transcranial Doppler ultrasound in the detection of right-to-left shunts, mobile cardiac telemetry and transesophageal echocardiography were not available. All were recommended as future investigations and mandatory for an analytical diagnostic procedure.

Recurrence of the cerebral ischemic event during a disciplined program of abstinence from tobacco and marijuana, without an apparent embolic source imposed investigations who revealed the cardiac congenital malformation, predisposing factor to paradoxical embolism.

The patient had neither atrial septal aneurysm, nor large PFO, cardiac or valvular pathology. No other peripheral sources of embolism were found, and TIA was less likely to have been caused by the common vascular risk factors.

The peculiarity of the case consists in the distinct pathophysiological context, associating a chronic unhealthy lifestyle with two asymptomatic predisposing conditions: the patent foramen ovale (PFO) and the unusual pre-existing neurovascular background (19).

Laborious tattooing maneuvers have generated multiple hypodermic trauma, bleeding, inflammation (rash), micro-clots (possibly source of paradoxical embolism), systemic inflammatory reaction (fever and chills), preceding the cerebral infarction.

Before tattooing he applied a local gel with anti-inflammatory and anesthetic properties. Each gram contains 5 mg piroxicam, 5 mg cyclobenzaprine hydrochloride (tricyclic analgesic with local anti-serotonin action), and 20 mg lidocaine. The producer's recommendations are 0.5-1 g of gel over an area 3-4 cm in diameter, corresponding to 7-12 cm^2. Anamnesis revealed an overdose of gel, applied on approximately 300 cm^2 of skin.

Tattoo ink can contain numerous potentially allergenic or carcinogenic ingredients, bacteria, viruses, and fungal species (21,22). It is a complex medium composed of solvents, pigments (azo dyes and metallic salts), resins, lubricants, surfactants, fluorescents, additives that confer color and fluidity, as well as hazardous chemicals, such as polycyclic aromatic hydrocarbons (43%), primary aromatic amines (14%), heavy metals (9%), preservatives (6%) and possible microbiological contamination (11%) (23). There are neither standards issued nor established methods for a quantitative determination of chemicals in tattoo and permanent make-up inks, that often have unknown or highly variable composition (24,25). Production of tattoo ink and pigments is unregulated in the USA (24), and no coloring agent has been officially approved by the FDA for injection under the skin (25). The safety of tattoo inks is somewhat higher in Europe, because of the improved quality control of pigment raw materials (22,23).

The most common complication of a decorative tattoo is a transient local acute inflammatory reaction, due to multiple needle punctures (26-29). Fujita et al (1988) demonstrated that Indian ink particles and latex beads were endocytosed by fibroblasts and macrophages in the dermis and subcutis (26). Deposition of exogenous pigments into the skin may induce immune-mediated reactions, hypersensitivity or allergy to tattoo pigments, may generate haptens in the skin (26-28), and even vasculitis (29). Repetitive traumatic punctures of the skin create conditions for bleeding, blood absorption of the ink, and implicit activates the coagulation cascade.

Vascular injury is associated with increased expression of adhesion molecules by the endothelial cells, recruitment of inflammatory cells, synthesis of proinflammatory cytokines (tumour necrosis factors, interleukins, lymphokines, monokines, interferons) and proteases, with negative repercussions on the endothelium, vascular smooth muscle cells and the extracellular matrix (30). Cytokines can influence the mitochondrial redox system, increasing the production of reactive oxygen species (31). Clinical and experimental evidence implies inflammation in the physiopathology of stroke. Systemic circulating inflammatory molecules and immune cells are capable of activating microglia, inducing cerebral neuroinflammatory response and contributing to ischaemic events (32-34). Positron emission tomography imaging has demonstrated activated microglia, involving a "primed" inflammatory environment in the brains of subjects associated with multiple risk factors(34).

Ink and topical analgesic substances (lidocaine, cyclobenzaprine and piroxicam) may have been interacting with the remaining phytocannabinoids in the tissues.

THC and its main active metabolite, 11-hydroxy-delta 9-THC, as well as other phytocannabinoids are highly lipophilic, cross the blood-brain barrier, and are stored in the liver, lung, spleen, and neutral fat cells, including in the hypodermis. Its half-life is approximately eight days and complete elimination of a single dose in humans can take up to one month (13,14,35).

In addition to 100 phytocannabinoids identified in the plant (14), street cannabis contains additives such as solvents, industrial etchants, pesticide derivatives, and chemical sugars intended to amplify the psychotropic effects. These substances may also have concomitant cardiac side effects (13).

Cannabis abusers in the general community are usually young people, and have a higher rate of non-fatal strokes or transient ischemic attacks compared with non-cannabis users (15,36). A heavy marijuana users' lifestyle is associated with consumption of tobacco (34%) and/or alcohol (11%) (17,36,37). The subject reported at least two behavioral risk factors: cannabis abuse and tobacco intoxication (defined by a daily cigarette consumption of more than 20 pieces, according to Fagerström nicotine dependence scale) (38).

Tobacco and cannabis combustion products represent well-documented cardio-cerebrovascular risk factors and can induce chronic cellular intoxication. One minute of marijuana secondhand smoke exposure (passive inhalation) substantially impairs vascular endothelial function, to a comparable extent as exposure to tobacco smoke inhalation, but recovery is considerably slower for marijuana (39).

One might assume that during the last two decades the subject was systematically exposed to over 4,000 toxic products of tobacco combustion, including at least 70 known carcinogens such as hydrogen cyanide, tar, formaldehyde, acetaldehyde, lead, arsenic, ammonia, nitrosamines, benzene, other polycyclic aromatic hydrocarbons, nicotine, and carbon monoxide (40), resulting in a chronic cellular intoxication. Heavy marijuana consumption amplifies the vulnerability to ischemic stroke, by increasing oxidative stress and cerebral mitochondrial respiratory chain dysfunction (41).

Cryptogenic stroke accounts for 30% to 40% of ischemic stroke (42,43). A literature search found one case report of cardioembolic stroke in Percheron`s vascular territory in a young man with patent foramen ovale, who smoked cannabis on a daily basis and used ketamine on occasion (44).

The diagnostic workup is essential to determine the possible mechanisms involved in the pathogenesis of cryptogenic stroke: occult paroxysmal atrial fibrillation, PFO, aortic arch atherosclerosis, atrial cardiopathy. PFO was found in 40% of patients with cryptogenic stroke and may be associated with paradoxical emboli to the brain (45,46).

With the advent of transesophageal echocardiography and transcranial Doppler, PFO can be routinely detected in clinical practice (43,46). The reported case had a recurrent cryptogenic ischemic cerebral event (TIA) who was attributed to PFO, detected with transesophageal echocardiography. The patient had neither an atrial septal aneurysm, nor a large interatrial shunt (47), and the stroke was less likely to have been caused by the common vascular factors, cardiac or valvular pathology.

No explanation for the recurrent TIA other than PFO was found on repeated investigations. The diagnostic workup limitation has persisted, due to the absence of prolonged, repeated ECG monitoring, to detect occult atrial fibrillation (47,48).

Management of cryptogenic stroke in young adults with PFO remains subject to controversy. Therapeutic management for secondary stroke prevention in patients associating PFO and cryptogenic stroke include medical treatment with antiplatelet agents or anticoagulants, respectively surgical closure or percutaneous device (45-52).

A quite recent meta-analysis of PFO closure trials has suggested potential, but uncertain benefit of PFO closure over medical management (49). Other systematic reviews and meta-analysis regarding percutaneous closure versus medical therapy for stroke with PFO emphasized that rates of recurrent stroke were significantly lower with PFO closure than with medical therapy alone (47,48, 50-52). Closure reduced the incidences of stroke recurrence in patients with cryptogenic events, and the composite outcome of cerebral infarction, TIA, or all-cause death, but increased risks for atrial fibrillation or atrial flutter and pulmonary embolism compared with medical therapy (51,52). The rate of new-onset atrial fibrillation or flutter was higher in the PFO closure group patients (4.6% vs. 0.9 %) (47,51). The subject was informed that he should undergo PFO closure; the risks and complications after the interventional maneuver were explained. His first option was for conservatory management, using dual antiplatelet medication (clopidogrelum 75 mg and aspirin 75 mg).

Finally he was convinced to submit a successful PFO closure intervention (in October 2019).

The case reported is illustrative for the medical staff's obstinacy to reveal the cryptogenic underlying pathology, and also for the patient`s ambition, hard work and compliance.

The subject didn't know that for decades he had "*Damocles` sword*" above his head, and adopted a hazardous lifestyle, playing "*Russian roulette*" with his *destiny*.

After the neurologic event he changed to a totally different person. One must emphasize his discipline and consistency, with absolute abstinence from tobacco and cannabis smoking, essential factors for his favorable neurologic evolution and excellent outcome.

Prevention of stroke in young adults is the primary treatment strategy, as Hippocratic Oath postulates: "*I will prevent disease whenever I can, as prevention is preferable to cure*".

Healthcare professionals should educate people and promote prophylactic interventions against modifiable risk factors. The general practitioner occupies an essential position in the approach of prophylactic health education.

Secondary prevention of recurrent strokes must be directed towards stroke etiology, the mechanisms responsible for the incident, and the rigorous management of additional risk factors (42,53).

Systematically medical education is essential for both primary and secondary prevention.

List of Abbreviations
AOP, artery of Percheron
CT, computed tomography
ECG, electrocardiography
FPCA, fetal posterior cerebral artery
GCS, Glasgow coma scale
MRA, magnetic resonance angiography
MRI, magnetic resonance imaging
PCA, posterior cerebral artery
PFO, Patent foramen ovale
RoPE (score), risk of paradoxical embolism
THC, tetrahydrocannabinol
TIA, transient ischemic attack

Compliance with Ethical Standards The authors disclose any potential conflicts of interest.

Written informed consent has been obtained from the patient`s next of kin (wife 2017), then from the patient (2018), for the inclusion of material pertaining to the case. Institutional consent for publication was obtained from our Hospital Ethic Commission.

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