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Leber's Hereditary Optic Neuropathy associated with cocaine, ecstasy and telithromycin consumption

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Sirs: Leber's hereditary optic neuropathy (LHON) is a matrilinear disorder characterised by acute to subacute bilateral optic neuropathy, mostly affecting young males at variable age of onset. More than 90% of patients harbour one of the three pathogenic mitochondrial DNA (mtDNA) mutations: 3,460, 11,778, and 14,484, all in genes encoding subunits of respiratory chain complex I. In most patients visual loss is severe and permanent, though spontaneous recovery of central vision may occur, particularly in patients with the 14,484 mutation.

Expressivity is 100% and penetrance variable, suggesting that secondary etiological factors are involved [1].

We recently examined a 17-year-old boy (Figure 1: V-2), who experienced acute, bilateral, asymmetrical, painless visual loss after two consecutive treatments with telithromycin (800 mg/die for five days, each time) and simultaneous abuse of cocaine and ecstasy.

Visual acuity was 20/100 in the right eye and 20/200 in the left eye, colour vision (Ishihara) 2/15 bilaterally without afferent pupil defect (APD). Fundoscopy showed optic discs with shaded margins and teleangectasic vessels. Goldmann's visual field showed bilateral cecocentral scotoma.

Two first cousins of the patient's grandmother (III-6/7) suffered transient visual loss for a few months at age 20 years (Figure 1). Molecular genetic testing of mtDNA, performed by RFLP and sequencing analysis, revealed a T>C homoplasmic mutation at nucleotide position 14,484 in blood mtDNA of proband, mother and grandmother.

LHON mutations cause chronic overproduction of reactive oxygen species (ROS) due to dysfunction of complex I [2]. Recently, the hypothesis that increased ROS production and subsequent induced apoptosis of retinal ganglion cells (RGC) may be implicated in the pathogenesis of LHON has gained support [3,4]. The incomplete penetrance of LHON suggests that other genetic determinants [5], or exogenous etiological factors (diet, toxins, drugs) may influence clinical presentation [2,6,7].

Toxicity by cocaine and its *N*-oxidative metabolites has been demonstrated in many organs including the central nervous system [8]. Cocaine leads to cell death, by ROS generation and subsequent oxidative damage on mitochondria, inducing both apoptosis and necrosis [9]. *In vitro* exposure of neonatal rat cardiomyocytes to cocaine resulted in slight leakage of lactate dehydrogenase and significant inhibition of glutamate/malate-mediated respiration of isolated mitochondria, suggesting inhibition of complex I. *N*-oxidative metabolites of cocaine are known to deplete the ATP pools in isolated mouse liver mitochondria [10]. Acute cocaine administration to rats revealed the significant downregulation of several mitochondrial genes in the cingulate cortex, resulting in reduced mitochondrial function and increased ROS production [11].

Ecstasy (including 3,4-Methylenedioxy-*N*-Methylamphetamine [MDMA]) consumption may attenuate many cell functions. Treatment with amphetamine derivatives may stimulate ROS production and oxidative damage [12]. MDMA promotes disruption of mitochondrial membrane potential through ROS and activates caspase cascade, leading to apoptosis [13]. Administration of MDMA may also increase extracellular glutamate concentration [14], which may mimic impaired activity of the EAAT1 glutamate transporter, recently linked to mtDNA mutations of LHON [15]. The resulting exocytotoxic damage to RGC contributes to their degeneration.

Recently, severe hepatotoxicity of telithromycin has been reported [16], and post-marketing surveil-

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