Emergency Medicine: Open Access
ISSN: 2165-7548

O'Connor et al., Emergency Med 2013, 3:4
DOI: 10.4172/2165-7548.1000145

Case Report Open Access

Dangers of Cocaine Ingestion in MELAS Syndrome

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Abstract

The genetic metabolic disorder known as Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS) is characterised by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes and is also associated with epilepsy. Pathogenesis is driven by a chronic state of energy failure, but is poorly understood with at least two hypotheses. The angiopathy (ischaemic) hypothesis suggests the presence of abnormal mitochondria in vascular endothelial cells, while the cytopathy hypothesis is thought to involve neuronal hyperexcitability, resulting in prolonged epileptic seizure activity and vasogenic oedema. We present an acute case of recurrent seizures and severe lactic acidosis precipitated by cocaine use in a patient with MELAS syndrome. The triad of lactic acidosis, seizures, and stroke-like episodes focus on the diagnosis. The neurological complications are probably precipitated by oxidative stress.

Case Presentation

A 25 year old female was brought to the Emergency Department (ED) by her boyfriend after he found her poorly responsive with generalised tonic clonic acitvity at home. He gave a collateral history of her being unwell the previous evening with generalised malaise and headache. She had complained of lethargy and headache that morning. On his return from work mid-afternoon, he found her unresponsive and he witnessed a tonic-clonic seizure of approximately 5 minutes duration. He brought her by car, unconscious, to the ED for medical assessment.

On arrival to the resuscitation room, she had a further tonic- clonic seizure. Her GCS was 3/15, with equal and reactive pupils bilaterally. She tolerated an oropharyngeal airway and required assisted ventilation with 100% Oxygen, to support her inadequate ventilation. She had widespread expiratory wheeze on auscultation. She was in sinus tachycardia with a rate of 130 bpm and her blood pressure was 90/60 mmHg. Her bedside blood glucose was 7.3 mmol/L. She was afebrile. She was notably cachetic with a BMI of 17. Intravenous Lorazepam was administered for initial management of her ongoing seizure activity. She was subsequently intubated and ventilated and intravenous fluid resuscitation was commenced. Initial arterial blood gas (ABG) revealed a severe metabolic acidosis with pH 6.9, $PaCO_2$ 6.6 mmHg, PaO_2 8.4 mmHg, bicarbonate 9.2, base excess- 21.5 and lactate 16.3 mmol/L. Her sodium was 139 mmol/L, potassium 4.5 mmol/L and chloride 104 mmol/L. A bedside urine toxicology screen was positive for cocaine and cannabis. The remainder of her urinalysis and urinary HCG were negative.

A collateral history from her boyfriend revealed a history of regular illicit drug use of cocaine and cannibis, penicillin allergy and attendance at a specialist neurology service for a longstanding condition. Contact with her neurological service established a genetically confirmed diagnosis of MELAS syndrome. She was commenced on intravenous Chloramphenicol, Vancomycin and Acyclovir to cover for possible meningo-encephalitis and Levetiracetam for seizure management. An initial non-contrast cranial CT revealed bilateral basal ganglia calcification (a normal variant which was subsequently confirmed on MRI), there was no evidence of infarction, haemorrhage or mass. MRI (Figures 1) was subsequently performed. T2W and FLAIR imaging revealed a 2 cm focal area of increased signal enhancement within the medial left occipital lobe with evidence of restricted diffusion indicating an acute infarct. Gadolinium enhanced imaging revealed no abnormal enhancement thus excluding a tumour or abscess.

Her remaining blood results and CSF following lumbar puncture were unremarkable. She was subsequently transferred to intensive care

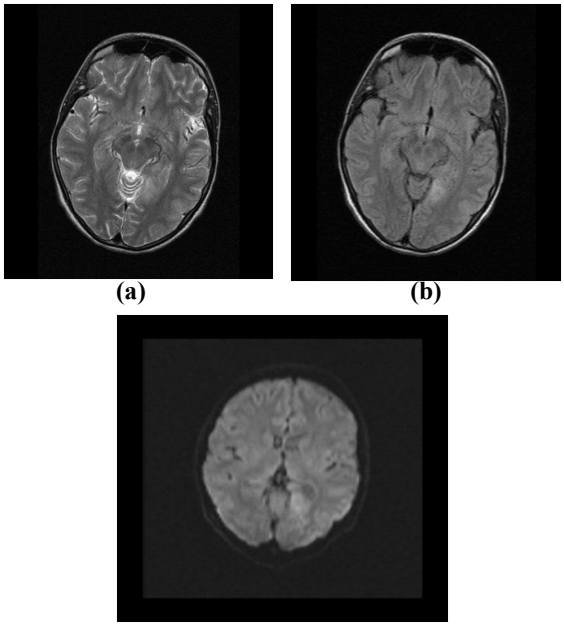

Figure 1: Axial T2W (a) and FLAIR (b) imaging of the brain revealed an area of increased signal intensity within the medial left occipital lobe (circled). Diffusion-weighted imaging (c) showed a corresponding area of abnormality at the same location. The findings were classical of acute infarction.

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Received May 23, 2013; **Accepted** July 16, 2013; **Published** July 18, 2013

Citation: O'Connor G, Doherty C, Meaney J, Mc Mahon G (2013) Dangers of Cocaine Ingestion in MELAS Syndrome. Emergency Med 3: 145. doi:10.4172/2165-7548.1000145

and underwent early haemodialysis to dialyse the excessive lactate, which had failed to respond to optimum resuscitation. An infusion of dextrose and saline was required to optimise her carbohydrate replacement. She was commenced on oral feeding and supplementation of L-carnitine, riboflavin, Vitamin E and coenzyme Q10 via a nasogastric tube. Her acidosis recovered well and stablised over a 12-24 hour period. Her sedation was weaned after 24 hours and she was following simple commands 48 hours after her ED presentation.

In terms of her neurological examination the patient was comatose on arrival but with pupillary, dolls eye and corneal responses present. There were mild hyporeflexia and down going toes. She recovered after treatment with a GCS of 15/15, mild proximal weakness (4 ± 5) in shoulder and limb girdles with persistent hyporeflexia without sensory findings. The EEG showed normal posterior dominant alpha rhythm with frequent runs of intermittent frontally predominant irregular delta activity. These findings were notes without clinical correlate. The findings were suggestive of a mild metabolic encephalopathic pattern. She made an uneventful recovery and was discharged home one week later with follow-up arranged with her neurologist.

Her background history was that she was attending a neurology service at another institution where she had initially been referred by her general practitioner with anorexia, generalised weakness, prominent fatigue, intermittent diplopia and muscle cramps. Her mother had died at a young age of complications of MELAS syndrome. The clinical features identified by her neurology specialist included small stature, very low BMI and lateral rectus muscle palsy. She had a muscle biopsy which was positive for red ragged fibres and subsequent genetic studies identified an m32342 A>G mutation with a high level of heteroplasmy.

Discussion

We present this case as a rare clinical entity, where treatment requires a consideration of possible underlying metabolic disorders in patients presenting with markedly elevated lactate levels that fail to respond to optimum intial resuscitaiton measures. Tailored treatment in this case which included early hemodialysis of the elevated lactate, contributed to early normalising of her metabolic status which had failed to respond to fluid resuscitation, normalisation of mean arterial blood pressure and ventilatory support. Furthermore this was enhanced by specific measures to support mitochondrial dysfunction. Cocaine ingestion is well known to cause serious complications including acute cerebral infarction. It is possible that she had an acute stroke due to cocaine alone, but the profound acidosis points to a metabolic contribution to this pathology secondary to her underlying MELAS syndrome, precipitated by cocaine ingestion.

MELAS syndrome is a genetic metabolic disorder characterised by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes and is also associated with epilepsy [1]. Pathogenic mutations of the mitochondrial DNA were first described only in 1988 by Holt et al. [2]. The overall incidence of mitochondrial disease is 12.5 per 100,000 Population [3]. However, the most common mutation associated with MELAS syndrome (3243A>G mutation), which is present in about 80% of cases, has an estimated absolute prevalence as high as 60 per 100,000 (0.06%) of a general population [3,4]. Inheritance is maternally linked as all mitochondrial DNA derive from the ovum, with one notable exception suggestive of partial paternal transmission [5]. The genetics are complex with mitotic segregation providing further random redistribution of mutant DNA and heteroplasmy, where both normal and mutant DNA are present in the same cells [6].

At a cellular level, pathogenesis is driven by a chronic state of energy failure, with an inability of dysfunctional mitochondria to generate sufficient energy via the oxidative phosphorylation pathway. Therefore, shunting of pyruvate to lactate occurs. Systemically this manifests as chronic lactic acidosis [3]. This syndrome results in multi-organ system pathology as energy-starved organs fail to meet physiologic demands. The threshold for disease is lower in tissues that are highly dependent on oxidative metabolism such as brain, heart, skeletal muscle, retina, renal tubules and endocrine glands [7]. This was seen in our patient with seizures, respiratory depression and severe metabolic acidosis. However, our patient had no electrocardiographic evidence of a conduction disorder, which can be seen in these cases [3]. Initial management of these patients should focus on standard resuscitation care including, anti-seizure and anti-microbial therapy. Impaired glucose homeostasis may also contribute, together with lactic acidosis, to brain injury in MELAS [8]. It is therefore important to maintain glucose levels in acute presentations, in conjunction with treating the lactic acidosis. Sodium valproate is contraindicated in patients with MELAS syndrome as there is evidence of direct damage to mitochondria with this drug, together with the potential for hepatotoxicity and it may also provoke seizures in these patients [9].

The triad of lactic acidosis, seizures, and stroke-like episodes remains central to the diagnosis and pathology [3]. The term stroke-like episodes was coined to stress the non-ischaemic pattern of these events. Affected areas therefore do not correspond to classical vascular distributions, but have an irregular distribution more consistent with metabolic or small-vessel disease [3]. The pathogenesis, however, is not fully understood. The angiopathy (ischaemic) hypothesis suggests the presence of abnormal mitochondria in vascular endothelial cells, while the cytopathy hypothesis is thought to involve neuronal hyperexcitability, resulting in prolonged epileptic seizure activity and vasogenic oedema [1]. Possibly the most important factor underpinning both is oxidative stress [1,10]. Our case report emphasises, for the first time in the literature, the effects of illicit drug use as a precipitant for oxidative stress in these patients. Radiological investigations are also important in these patients to rule out cocaine-related subarachnoid haemorrhage.

Therapeutic options for MELAS syndrome are currently limited [3,7]. The main goal is to improve ATP production and electron transfer and so includes coenzyme Q10 (an oxygen-radical scavenger) and L-carnitine (to restore secondarily lowered levels of free carnitine) [7]. L-arginine supplementation has been reported to reduce severity of the acute phase of stroke-like episodes [1,11,12]. Although there is a paucity of evidence to support the efficacy of these supplements, the risks are minimal [3,7].

The prognosis for patients with MELAS syndrome is poor, with a mean survival time from disease onset to be 6.5 years [8]. Progressive dementia and neurological deterioration are related to stroke-like episodes and recurrent seizures [13]. Patients with MELAS syndrome should, therefore, be educated regarding the dangers of illicit drug use as a precipitant for stroke-like episodes and seizures.

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