CASE REPORT

Lethal high: acute disseminated encephalomyelitis (ADEM) triggered by toxic effect of synthetic cannabinoid *black mamba*

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Accepted 9 April 2017

SUMMARY

A previously well 25-year-old man presented with agitation, double incontinence and left-sided incoordination. His symptoms started after smoking a synthetic cannabinoid (*black mamba*) 5 days earlier. Over 48 hours, he developed aphasia, generalised hypertonia, hyper-reflexia and dense left hemiparesis. This progressed to profuse diaphoresis, fever, tachycardia, hypertension and a possible seizure necessitating admission to the intensive care unit. CT head and cerebrospinal fluid analysis were unremarkable. MRI brain demonstrated asymmetric multifocal hyperintense lesions in white and grey matter, which raised suspicions of acute disseminated encephalomyelitis (ADEM). An electroencephalogram showed widespread brain wave slowing, indicating diffuse cerebral dysfunction. Cerebral angiogram was normal. Toxicology analysis of the substance confirmed a potent synthetic cannabinoid *NM2201*, technically legal at the time. The patient made a slow but significant recovery after a course of intravenous methylprednisolone, intravenous immunoglobulins and oral steroids, and was later transferred to a rehabilitation bed.

BACKGROUND

The so-called 'Legal Highs', or new psychoactive substances (NPS), are novel drugs formulated to mimic the desired effects of illicit drugs while exploiting loopholes in existing drug laws to remain legal to supply and possess. While some reports suggest prevalence of NPS use is declining,¹ there was a 56% increase in UK NPS-related hospital admissions between 2009 and 2012.²

Increasing evidence of adverse effects following consumption of NPSs and *black mamba* specifically is a cause for concern. Psychoactive effects include anxiety, agitation, hallucinations and delirium, with presentations of extreme agitation following *black mamba* use becoming more frequent. More significant adverse effects include seizures, hypokalaemia, rhabdomyolysis, acute kidney injury, myocardial infarction and persistent psychosis.³

To our knowledge there has been no report of acute disseminated encephalomyelitis (ADEM) secondary to *black mamba* usage previously. It is important to raise awareness of this devastating complication.

CASE PRESENTATION

A 25-year-old man presented acutely with agitation, double incontinence and rapidly increasing difficulty in coordinating movements and verbalising. He was previously fit and well, with a background

of well-controlled asthma, and had no history of mental health issues. There were no recent viral symptoms or illnesses. He had taken cocaine in the past but had never been an intravenous drug user.

Collateral history revealed the patient was a regular smoker of 'skunk' cannabis and had smoked *black mamba* in addition to cannabis 5 days prior to presentation. His symptoms of incoordination and 'not feeling right' started almost immediately after taking the *black mamba*. A green packet labelled *black mamba incense* was found in the patient's belongings and sent for toxicology analysis. The patient denied alcohol consumption and had no history of head trauma.

Clinical assessment on admission demonstrated a Glasgow Coma Score (GCS) of 14 with hyperactive agitation. Initial physical examination demonstrated left-sided incoordination. The patient was doubly incontinent. The patient's signs progressed over 48 hours to aphasia, generalised hypertonia, hyper-reflexia and left-sided hemiparesis with an up-going left plantar reflex. At no point was there evidence of any rash, meningism or signs of head injury.

The patient developed a transient acute kidney injury while in the medical assessment unit, which resolved with intravenous fluids. This was likely due to dehydration secondary to inadequate oral intake, possibly worsened by the initial acyclovir usage for presumed viral encephalitis (later discontinued). It is unclear whether the toxic substance may have played a part in this renal dysfunction.

Four days later, the patient's consciousness deteriorated to a GCS of 10 (E3 V1 M6). Examination revealed bilateral reactive pupils with spontaneous roaming eye movements with no visual tracking, hyperpyrexia (38.7°C), profuse diaphoresis, tachycardia, hypertension and agitation. He proceeded to have a possible 30 s tonic-clonic seizure without full resolution of consciousness. The patient was transferred to the intensive care unit (ICU) for close monitoring. During a 14-day ICU stay, the patient had recurrent episodes of autonomic hyperactivity (tachycardia, extreme hypertension, fever and profuse diaphoresis). These episodes continued following discharge to the neurology ward, but there were no further seizure-like episodes. The patient's consciousness deteriorated leading to anticipation that he would need long-term airway and secretion management but without needing

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To cite: Samra K, Boon IS, Packer G, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218431

Figure 1 (A) MRI head non-contrast showing widespread multifocal lesions, raising the suspicion of acute disseminated encephalomyelitis (ADEM). (B) MRI head with contrast performed 11 days after previous MRI showed large, confluent, multifocal and asymmetric lesions in the subcortical and periventricular white matter (also in grey matter). These T2-weighted/fluid attenuation inversion recovery (FLAIR) hyperintense lesions of different sizes demonstrated contrast enhancement, in keeping with ADEM.

respiratory support. A decision was therefore taken to electively intubate and proceed immediately to percutaneous tracheostomy to provide a long-term secure airway while minimising exposure to sedation and positive pressure ventilation.

INVESTIGATIONS

Full blood count, serum blood glucose, inflammatory markers, and renal and liver function tests on admission were unremarkable. CT of the head without contrast in the emergency department showed normal intracranial appearances. A septic screen including blood culture, urine culture and chest X-ray were negative. Autoimmune profile including antinuclear antibodies, antineutrophil cytoplasmic antibodies and complements (C3, C4) were normal.

Initial MRI of the brain showed widespread multifocal T2-weighted/fluid attenuation inversion recovery

(FLAIR) hyperintense lesions of different sizes, typical of ADEM (figure 1A). Contrast was initially not given because of the acute kidney injury. A repeat MRI brain on day 14 (after treatment, see below) showed persistent widespread multifocal lesions with patchy contrast enhancement in almost all lesions in both white and grey matter (figure 1B). Electroencephalography showed widespread excess delta waves (slow rhythms <4 Hz) indicating a degree of diffuse cerebral dysfunction (figure 2). MRI of whole spine was normal. A full-body CT was performed and excluded any occult abscess, or malignant source of sepsis. Cerebral angiogram revealed no evidence of cerebral vasculitis or vessel abnormalities.

Cerebrospinal fluid (CSF) was not suggestive of an infective or inflammatory process: four mononuclear cells and normal protein and glucose concentrations. CSF oligoclonal bands and autoimmune encephalitis antibodies were negative. Subsequent PCR analysis excluded varicella, Epstein-Barr virus, adenovirus, enterovirus, cytomegalovirus and herpes simplex virus 1 and 2. HIV and hepatitis A, B and C serologies were negative. Treponemal serology was negative using rapid plasma reagin and treponemal pallidum particle agglutination tests.

A single anaerobic culture grew *Streptococcus mitis* several days after hospital admission. Antibiotic therapy made no clinical difference and echocardiogram did not demonstrate infective endocarditis. The significance of this single blood culture is therefore doubtful, as several serial blood cultures (during feverish episodes) before and after this sample were negative.

The toxicology lab screened the green herbal substance found within the *black mamba* packet for compounds by ultra-performance liquid chromatography-time-of-flight-mass spectrometry (UPLC-TOF-MS). This is a qualitative test that can detect substances against a selection of thousands of known substances in their reference library, which is continually updated. UPLC-TOF-MS can detect classic drugs of abuse, such as THC (tetrahydrocannabinol), prescription and over-the-counter drugs, and novel substances or so-called legal highs, as in this case. Toxicology analysis of the sample confirmed the presence of

Figure 2 Electroencephalogram showed excess delta waves (slow waves <4 Hz) suggestive of gross cerebral dysfunction.

the highly potent synthetic cannabinoid NM2201. A urine drug screen was unremarkable, but was not tested specifically for cannabinoids.

DIFFERENTIAL DIAGNOSIS

The rapid onset agitation and focal neurology raised clinical suspicion of acute intracranial pathology, including cerebral infarction or haemorrhage. Fever, seizures and deteriorating consciousness prompted considerations of viral encephalitis, autoimmune limbic encephalitis, non-convulsive status epilepticus and cerebral vasculitis. An important differentiating feature between ADEM and viral encephalitis, for instance, is the acute and fulminant onset with viral encephalitis, and a more subacute pattern of onset with ADEM.⁴

Importantly, toxic leukoencephalopathy was considered and should be in the differential of any patient presenting with an acute neurobehavioural deficit following exposure to an agent that is known to be toxic to cerebral white matter.⁵ This disease has been described following exposure to heroin,⁶ cocaine⁷ and methylenedioxymethamphetamine (or ecstasy).⁸ A pertinent report of fatal toxic leukoencephalopathy following an overdose of a psychoactive designer drug, legal in the USA at the time, called 2C-E or Europa, was published by Sacks *et al.* This has since been banned.⁹ We are not aware of any such reports after *black mamba* exposure. While MRI changes in toxic leukoencephalopathy tend to be symmetrical, affect white matter and do not usually enhance with contrast,⁵ ADEM is often asymmetrical, with different-sized lesions, involving grey as well as white matter, and enhances with contrast, as in this patient. This is supported by the patient's prominent and persistent aphasia that would not be present if this was a leukoencephalopathy.

In the context of substance abuse, occult abscesses, infective endocarditis and retroviral infection were also considered, especially given the patient's persistent fever.

TREATMENT

On admission, the patient was administered broad-spectrum antibiotics, intravenous acyclovir and intravenous fluids on clinical suspicion of encephalitis and sepsis. Antibiotics and antivirals were discontinued when CSF analysis excluded infection. The patient initially received several small doses of diazepam to control his agitation.

In light of several features in this patient's presentation, including his radiological profile, he was diagnosed with ADEM and initially treated with a 5-day regime of intravenous methylprednisolone with minimal immediate clinical response. This was followed by a 5-day regime of intravenous immunoglobulin and tapering oral steroids, which proved to be effective.

During his ITU admission the patient received 5 days of piperacillin/tazobactam (following a single positive blood culture). Nonetheless, his centrally driven fever persisted. The autonomic storms of tachycardia, hypertension and fever in intensive care were managed with clonazepam and levetiracetam with good benefit. As aforementioned, concerns around the patient's reduced consciousness and difficulty clearing secretions resulted in a percutaneous tracheostomy to allow tracheal suctioning.

OUTCOME AND FOLLOW-UP

The patient had significantly improved by discharge and was able to move all four limbs, although with some persistent upper limb weakness. Autonomic storms subsided and he was able to eat and drink normally. He was transferred to a neurorehabilitation unit for ongoing physiotherapy and occupational therapies.

His repeat MRI scan done a few weeks later showed substantial radiological improvement. He was reviewed in outpatients, 11 months later, and he had no significant neurological deficits.

DISCUSSION

Synthetic cannabis

Black mamba (also commonly known as *Spice*) contains a highly potent endogenous cannabinoid-1 receptor agonist, up to 100 times as potent as delta-9-tetrahydrocannabinol—the active ingredient in cannabis. *Black mamba* is usually smoked or vaporised, although, as with most NSPs, is overtly marketed as incense in packaging marked 'not for human consumption' in order to circumvent the Medicines Act 1968.³ However, the Psychoactive Substances Act, which came into force in May 2016 (after this patient's admission), criminalises the production and supply of all psychoactive substances, including *black mamba*.¹⁰

In this case, the active compound in the *black mamba* sample was identified as NM2201 or naphthylindole-based synthetic cannabinoid (C₂₄H₂₂FNO₂), at the time a technically legal analogue of the illegal synthetic cannabinoid AM2201 (C₂₄H₂₂FNO). Notably, AM2201 became illegal in the UK in April 2012, and there are a few case reports of AM2201-related toxicity, including death from psychiatric complications.¹¹ A further report highlights two cases of a first generalised tonic-clonic seizure after smoking synthetic cannabis, with no prior neurological disease. In these patients the mechanism was unidentified, although one of the patients displayed MRI findings of FLAIR hyperintensity and postcontrast enhancement. Repeat MRI 13 days later showed resolution and both patients were conservatively managed.¹²

Acute disseminated encephalomyelitis

A multifocal postinfectious or postvaccinal inflammatory demyelinating disease of the central nervous system (CNS), ADEM was first recognised more than 100 years ago.¹³ ADEM is most typically a monophasic illness with frequent manifestations of fever, disturbance of consciousness, seizures and MRI brain evidence at onset of symptoms of an extensive lesion load of similar radiological age.^{13 14}

ADEM is seen more frequently in paediatric than in adult populations, but it remains a rare illness, with annual incidence for patients younger than 15 years reported to be 0.64/100 000.¹⁵ It has most commonly been reported following a diverse range of viral and bacterial infections and immunisations, although less than half of adult patients give a history to suggest prior infection.¹³ Moreover, despite its close association with infection, ADEM does not cover patients with acute viral encephalitis caused by direct CNS invasion,¹⁶ such as herpes encephalitis. Indeed, several pathological studies examining ADEM indicate the absence of infectious agents in the CNS.⁴

Diagnosis

In practice, ADEM is diagnosed from the clinical presentation and several ancillary investigations, in particular MRI of the brain. Recent diagnostic criteria have been proposed when all five of the following criteria have been met (box).

MRI of the brain is a crucial investigation and typically reveals large, confluent white matter lesions with homogeneous contrast enhancement, as opposed to smaller, sharply demarcated and heterogeneously enhancing lesions in multiple sclerosis that display a periventricular preponderance.¹⁶ As discussed earlier, unlike in toxic leukoencephalopathy, ADEM lesions tend to be

Box Diagnostic criteria for acute disseminated encephalomyelitis (ADEM)¹⁷

- ▶ A first multifocal, clinical CNS event of presumed inflammatory demyelinating cause
- ▶ Encephalopathy that cannot be explained by fever
- ▶ Abnormal brain MRI:
 - ▶ Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter
 - ▶ T1 hypointense lesions in the white matter in rare cases
 - ▶ Deep grey matter abnormalities (eg, thalamus or basal ganglia) can be present
- ▶ No new clinical or MRI findings after 3 months of symptom onset
- ▶ Reasonable exclusion of alternative causes. Clinicians must therefore consider several mimics, described above under 'differential diagnosis', before arriving at a diagnosis of ADEM.

Patient's perspective

"This has been the worst experience in my life. When I first initially took the drugs, I experienced vivid life-like dreams, auditory hallucinations, incontinence and developed profound weakness. All these remain in my memory as this is a significant life event for me. I am keen for my case to be written up to inform and increase awareness to the public of how dangerous the substance that was given to me is. I am extremely lucky to be alive as I recall during the initial stages of my admission, I was told that I would not have recovered from this."

Learning points

- ▶ New psychoactive substances such as synthetic cannabinoids affect individuals differently, and in this extreme case led to acute disseminated encephalomyelitis (ADEM) with associated autonomic dysfunction.
- ▶ Other neurological disorders such as viral and limbic encephalitis, cerebral abscess, vasculitis and non-convulsive status epilepticus must be excluded in the initial stages, especially in atypical presentations of ADEM.
- ▶ Radiological changes characteristic of ADEM are confluent white matter T2-weighted/FLAIR hyperintense lesions of varied sizes with homogeneous contrast enhancement, which may involve the grey matter.
- ▶ More research is needed around legal highs, with greater awareness of their dangers brought to the public eye, as well as to clinicians.

asymmetric, of varied size, contrast-enhancing and can involve grey matter.

Pathogenesis

The pathophysiology of ADEM has not yet been completely elucidated, although in postinfectious cases molecular mimicry has been implicated between virus and myelin antigens.¹³ The

characteristic pathological cerebral finding consists of inflammatory demyelination in a perivenous distribution.¹⁸

Management

There have been no randomised control trials investigating the treatment of ADEM, but there is good evidence to suggest early use of immunomodulatory treatments in the form of intravenous corticosteroids, immunoglobulins or plasma exchange.¹³ Supportive management is vital, with escalation to intensive care if required (as in our case). Adults are less likely to recover completely than paediatric patients (46% vs 60%–80%)¹⁹ and mortality is higher in adults than children, especially if the initial diagnosis is delayed (12% vs 1%).²⁰

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Competing interests None declared.

Patient consent Consent obtained from next of kin.

Provenance and peer review Not commissioned; externally peer reviewed.

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