CASE REPORT

'Legal high' associated Wallenberg syndrome

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alokjarora@hotmail.com**SUMMARY**

'Legal highs' are substances of synthetic or natural origin having psychotropic properties. 'Legal highs' are often new and, in many cases, the actual chemical ingredients in a branded product can be changed without notifications and the risks are unpredictable. Acute recreational drug toxicity is a common reason for presentation to both hospital and prehospital medical services. It appears that, generally, the pattern of toxicity associated with 'legal highs' is broadly similar to that seen with classical stimulant recreational drugs such as cocaine, MDMA (3,4-methylenedioxymethylamphetamine) and amphetamine. Lack of clear literature pertaining to their chemical properties, pharmacology and toxicology makes an evaluation of their effects difficult. We describe a unique case in which consumption of such a substance led to hospital admission and a diagnosis of 'lateral medullary stroke' or 'Wallenberg syndrome'. We believe that this is the first described case of a 'legal high' intake linked to a posterior circulation stroke.

BACKGROUND

'Legal highs' are substances made from assorted herbs, herbal extracts and 'research chemicals' and are now controlled under the Misuse of Drugs Act. They are considered illegal to be sold, supplied or advertised for 'human consumption'. To get round this sellers refer to them as research chemicals, plant food, bath crystals or pond cleaner and sell them via internet marketing and in pubs.

Legal highs can carry serious health risks, the chemicals they contain have in most cases never been used in drugs for human consumption before, and little research has been done on the short-term or long-term effects of use. Most surveys of recreational drug use focus on classical drugs such as cocaine and ecstasy, and there is limited information on how commonly emerging novel psychoactive substances are used.

The UK Home Office website has also identified 'legal highs' as a problem area and has a public advert as well.¹

More than 40 deaths were linked to a group of now-banned legal highs in 2010, eight times as many as the previous year.²

Emergency department and hospital staff are often not aware of these agents when they first become available and so they may be misrepresented in the medical notes.

Healthcare professionals may contact the National Poisons Information Service (NPIS) for support in managing patients with acute recreational drug toxicity and the database is not equipped to deal with such enquiries.

The experience of 'Guy's and St Thomas' NHS Foundation Trust Clinical Toxicology Service is that up to 50% of patients with acute recreational drug toxicity are coded wrongly and discharged directly from the emergency department. Therefore, for a number of different reasons, the dataset significantly underestimates the true burden of acute toxicity associated with the use of 'legal highs'.

Toxicological screening of blood and/or urine samples in patients presenting to hospital with acute recreational drug toxicity is not routinely undertaken as these patients are managed on a clinical basis and the results of comprehensive toxicological screening will not be available in a time-frame to be able to influence management decisions and when it is undertaken it fails to detect them due to lack of reference compounds.

With Parliament's approval, the government has brought a range of so-called 'legal highs' under the control of the Misuse of Drugs Act 1971, with effect from 23 December 2009. It aims to address the health risks associated with the use of these substances, which are considered dangerous or otherwise harmful.

The Advisory Council on the Misuse of Drugs (ACMD) makes recommendations to the government on the control of dangerous or otherwise harmful drugs, including classification and scheduling under the Misuse of Drugs Act 1971 and its regulations. It considers any substance which is being or appears to be misused and of which is having or appears to be capable of having harmful effects sufficient to cause a social problem.

Under the ACMD advice the home secretary banned mephedrone in 2010 via a generic legislation encompassing a wide range of cathinone derivatives, a world-first for the cathinones. By proposing this chemically complex legislation, the government expect that the drug laws will be more robust and more difficult for chemists to develop new substances to flout the law.

In 2009, the ACMD investigated 'legal highs'; following the council's advice, synthetic cannabinoids and γ -butyrolactone and benzylpiperazine were banned by the government. New synthetic cannabinoids (such as those contained in 'Black Mamba' and 'Annihilation'), O-desmethylnaloxone, methoxetamine (sold as 'Mexxy') were the latest to be banned in February 2013.

We are seeing an increasing number of cases of misuse of these substances (usually unknown description and contents) in the hospital's 'acute take' and there is very little clinical literature available to help us deal with the associated complications. People who take 'legal highs' are taking serious risks with their lives because often they do not know what they

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are taking and the drugs may contain harmful substances.

The case described suggests an association between 'herbal haze' inhalation to the development of a posterior circulation stroke which has not been described in the medical literature before, it also highlights the diagnostic dilemmas faced in 'legal highs' toxicities.

There is an urgent need to disseminate this information in the medical circles about a 'clear and present danger' and for once Toxbase cannot help!

CASE PRESENTATION

A 56-year-old male commercial driver self-attended accident and emergency (A&E) after inhaling an unknown quantity of a legal high 'herbal haze' few hours before. He presented to A&E as he felt unwell and the symptoms did not improve during the day.

He complained of a right-sided headache with double vision, dizziness, nausea, vomiting and paraesthesia in both hands that started immediately after inhalation of 'herbal haze'. He described the headache as 'brain freeze' and also noted that the right side of the face felt like 'cold water'.

The observations were normal apart from blood pressure which was 158/83; glucose was 7.9 mmol/dl. A quick neurological examination in A&E was noted to be grossly normal but no comment was made on gait and cerebellar functions.

He admitted to occasional cannabis use in the past but denied any intravenous drug use. His medical history was not significant other than very occasional migraine and he was not on any regular medications. He admitted to consuming 2–4 units of alcohol per week, smoked tobacco in past and his body mass index was 25.

Initial laboratory investigations (full blood count, kidney, liver function and inflammatory markers) were normal. The ECG noted sinus rhythm and the cholesterol was 5 mmol. The initial working diagnosis in A&E was 'migraine and vasospasm-related problem' as 'herbal haze' was not a medicine as such and no Toxbase information was available.

Due to persistence of double vision, dizziness and paraesthesia he was admitted to acute medical unit and a CT of the head was requested. The CT of the head could not explain his clinical findings and he was started on 300 mg aspirin and stroke team's opinion was requested due to his balance problems.

The stroke team reviewed the patient on Medical Admission's Unit 4 days postadmission and it was noted that there were clear and relevant neurological signs.

The patient had:

- ▶ Mild expressive dysphasia but no pharyngeal weakness.
- ▶ Right ptosis and right miosis consistent with Horner's syndrome.
- ▶ Rotatory nystagmus was noted bilaterally.
- ▶ The patient said right side of the tongue does not contribute to taste.
- ▶ He had right facial numbness and decreased pin prick on the left lower limb.
- ▶ His deep tendon reflexes were brisk on left side with an indeterminate planter response.
- ▶ There were subtle cerebellar signs, he could not sit unaided and had a tendency to fall on the right.

This presentation of 'acute headache and vertigo' with crossed sensory and long tract signs with autonomic, cerebellar features was suggestive of a lesion in the right medulla and led to a diagnosis of 'Lateral medullary (Wallenberg) syndrome' most likely triggered by 'vasospasm' due to the legal high substance.

INVESTIGATIONS

MRI/magnetic resonance angiogram (MRA) showed a right medullary infarct and small right inferior cerebellar infarct. There was occlusion of the visualised right vertebral artery in its intracranial portion and just below the skull base (figures 1A,B). This was the only reported abnormality on the angiogram.

Carotid Doppler scanning prior to the MRI/MRA showed unobstructed carotids and high resistance in right vertebral artery indicating distal obstruction consistent with the MRA findings.

The 'bubble echocardiogram' study did not show any patent foramen ovale. The vasculitis and thrombophilia screen were done to exclude other potential causes of stroke.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis was a pure cerebellar stroke.

Figure 1 (A) Magnetic resonance angiogram shows completely blocked right vertebral artery (arrow) with its branches. (B) MRI shows right medullary infarct (arrow).

TREATMENT

The patient was continued on high-dose aspirin and a statin was added. Vascular surgeons were unable to offer intervention to such a deep, thin calibre vessel with difficult anatomy.

OUTCOME AND FOLLOW-UP

The patient needed extensive rehabilitation and occupational therapy input due to persistence of diplopia and disabling ataxia. He also lost his drivers licence and job, by the time this article was written he was still being followed up in stroke clinic.

DISCUSSION

The ACMD in UK defines 'legal highs' (novel psychoactive substances) as: 'psychoactive drugs which are not prohibited by the United Nations Single Convention on Narcotic Drugs or by the Misuse of Drugs Act 1971, and which people in the UK are seeking for intoxicant use'.

Novel psychoactive substances report (2011)² say that the issue of 'legal highs' is not recent, but has become prominent due to a range of complex factors, including: chemical technologies, market availability, internet supply, trends in substance misuse, price and others. A recent British crime survey² of young people suggested that 20–40% have tried 'legal highs'.

This is the first case report that we know of where consumption of a 'legal high' substance (herbal haze) has been linked with a brain stem stroke. There is one PubMed indexed article in Spanish³ which links cannabis consumption to Wallenberg syndrome but there are numerous others with various 'legal high' associated medical complications, most recent being mephedrone.

'Lateral medullary or Wallenberg syndrome' results from occlusion of intracranial part of vertebral or its major branch posterior inferior cerebellar artery but can be due to basilar, superior and middle cerebellar artery occlusion (box 1).

The patient in the case discussed above is a middle-aged man but physically active, who smoked in past and had high normal cholesterol. Risk of vascular events was perhaps slightly higher than the general population, but his carotids showed no significant disease and the rest of the vascular tree on MRA had no other occlusions.

A clear temporal relationship between the inhalation of 'herbal haze' and the full spectrum symptom onset is indicative that inhalation of the illicit material caused/precipitated the stroke; the postulated mechanism could be the intense

Figure 2 Image of a commercially available and easily bought "herbal haze" via internet.⁴

vasospasm due to sympathetic stimulation associated with the use of these substances.

Unfortunately there was no 'herbal haze' left for us to perform a chemical constituent analysis and check for potential adulterants/contaminants, but it is postulated that it could be similar to 'Spice' (a herbal material adulterated with a synthetic cannabinoid).

Searching the internet marketing sites⁴ ('Head Shops' sell them as research chemicals, plant food, bath crystals or pond cleaner) and specific commercial sites revealed that 'herbal haze' (figure 2) comes in 3 g sachets and is one of the emerging psycho actives/novel psycho substances. The UK Home Office website has also identified 'legal highs' as a problem area and has a 'Talk to Frank' advert.^{1 5}

'Herbal haze' is advertised as one of the lifestyle accessories similar in composition to synthetic legal marijuana/cannabinoids. Ingredients include seeds of *Althaea officinalis* (marsh mallow), *Verbascum thapsus* (mullein) and *Turnera diffusa* (damiana leaf) but it is not uncommon to find various psychotropic contaminants in such preparations.

By looking in standard reference texts on herbal medicines it is possible to gain some insight into the likely actions of these herbs.⁶

Althaea preparations are thought to provide a protective layer over mucous membranes to reduce local irritation and promote healing. It is unlikely therefore that these would have any effects centrally or on the cardiovascular system. Mullein is thought to have antiviral, antibacterial and possible antitumour effects and has been used mainly for these effects. It is noted, however, that it has been used as a sedative or narcotic suggesting central activity.

Damiana preparations are promoted as centrally acting stimulants and aphrodisiacs which does suggest that it may affect the cardiovascular and/or central nervous systems. It is also possible that it possesses antiaromatase activity.⁷

This case also points out the diagnostic difficulties in acute 'legal high' toxicity. The patient went through the following diagnostic possibilities before reaching the correct one after a delayed stroke team referral.

- ▶ 'Migraine and vasospasm-related problem'.
- ▶ 'Adverse reaction to smoked substance'.
- ▶ 'Behavioural/intentional'.

Box 1 Symptoms of lateral medullary syndrome

- ▶ Vertigo, nausea and diplopia
- ▶ Crossed sensory findings, face and body are considered *pathognomonic*
- ▶ Ipsilateral headache, facial or eye pain
- ▶ Ipsilateral facial hemianaesthesia
- ▶ Contralateral body anaesthesia
- ▶ Ataxia, opposite cerebellar signs, hiccups
- ▶ Horner's syndrome, nystagmus
- ▶ Motor, tongue and dorsal column spared as fibres are medial
- ▶ Ipsilateral palatal and vocal cord weakness

► 'Demyelinating causes'.

This very importantly highlights the deficiency in practising knowledge and clinical literature to deal with such presentations.

Based on the spectrum of their actions on the cognitive processes, mood and behaviour 'legal highs' can be classified into three basic categories: amphetamine-like and ecstasy-like psycho-stimulants, hallucinogens and synthetic cannabinoids (spice).⁸

ACMD has classified 'legal highs' into four broad categories as²:

1. Products with names which give no indication of what they contain.
2. Named and specific substances which are designed to be similar chemically and/or pharmacologically to known specific controlled drugs.
3. Substances related to medicines.
4. Herbal and fungal materials or their extracts.

CONCLUSION

The advent of novel psychoactive substances has changed the face of the drug scene remarkably and with rapidity. The range of substances now available, their lack of consistency and the potential harms users are exposed to are now complex and multifaceted.

The risks of complications following consumption of such over-the-counter unknown psychotropics remain high, particularly when combined with alcohol, including the risk of death.

'Legal highs' from the phenylethylamine, cocaine, tryptamine and phencyclidine classes are increasingly being marketed and, in the majority of cases, little is cited in the literature on their true chemical identity, pharmacology or toxicology.⁹

Most of these substances affect the central nervous system and present with seizures, confusion, hallucinations, anxiety, phobias, weakness, dizziness and somnolence with the circulatory system (hypertension, tachycardia, chest pain) and dilated pupils.¹⁰ There have been reports of cases of dependence which require detoxification and psycho-social treatment.

Because legal highs are often new and, in many cases, the actual chemical ingredients in a branded product can be changed without notifications, the risks are unpredictable like a brain stem stroke in the case described above.

The ACMD provides key recommendations in their report on legislation, public health, education and research. The key legislative measures are primarily concerned with tightening the enforcement of existing legislation and moving the responsibility for the supply of novel psychoactive substances to the vendors, such that the burden of proof falls on them.

The ACMD believes it is for vendors to prove that such substances are neither analogues of current medicines nor products harmful to consumers in their intended form. The ACMD also makes key recommendations around public awareness from local to international initiatives and the possibility of new legislation similar to the Analogue Act (1986) used in the USA and similar laws in other countries, in conjunction with generic definitions of chemical scope.

As for clinicians here is an urgent need for wider dissemination of information regarding 'legal high' toxicities as PubMed/

Toxbase are poorly equipped to deal with any emergency information sought and to classify such patients correctly with 'acute recreational drug toxicity' to generate a proper local database.

Learning points

- 'Legal highs' are drugs which mimic, or are claimed to mimic, the effects of illegal drugs. There is a common, but mistaken, perception that because such drugs are not legally controlled or banned they are safe.
- This is potentially the first case of a posterior circulation stroke reported with the use of a 'legal high' substance.
- Thorough neurological examination should be undertaken for all patients with 'legal high' to pick up subtle signs. MRI would be the investigation of choice if there is any clinical suspicion.
- The paucity of information on the pharmacology and toxicology of most 'legal highs' makes it hard to understand their possible dangers, or even to know what substances are contained in the products.
- 'Legal highs' are gaining in popularity and the rapidity with which these new substances have emerged appears to be increasing. It is difficult to gauge with any certainty what will be the next 'big thing' that will capture the attention of the experimenter or regular recreational drug user.

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