New-onset Seizures Due to Heroin Addiction

Sir,

Tobacco, alcohol, cannabis, solvent abuse and opioids are the most common substances abused by adolescents in India.[1] At least 1.8%% of all adolescent boys aged 10 to18 years were found to be using opioids repeatedly in a recently completed large, nationwide household survey on prevalence and pattern of substance abuse in India.[2] In this survey, heroin was found to be the most commonly used opioid in India with a 1.14% prevalence.[2] Opioid withdrawal symptoms usually occur after 2-6 days of abstinence if attempted by the dependent person. The time of occurrence depends on the half-life or opioid consumed. Opioid withdrawal symptoms are usually uncomfortable to the patient, but are rarely life-threatening, and these include severe muscle cramps, profuse diarrhea, abdominal cramps, rhinorrhoea, lacrimation, fever, yawning, piloerection, hypertension, pupillary dilatation, tachycardia, and temperature dysregulation.[3] Although opioids have both convulsants and anticonvulsants properties, seizures are not considered one of the predominant opioid withdrawal symptoms, except in newborns born to opioid-dependent mothers. Neonatal abstinence syndrome due to opioid withdrawal may lead to generalized or even myoclonic seizures. Similarly, 12.5% of opioid users were found to have seizures in a study conducted in Chandigarh, India. But most of those users had dextropropoxyphene and poppy husk, and a minor proportion of them used heroin.[4,5] However, seizures after heroin withdrawal after the neonatal period is extremely rare and only a few anecdotal case reports and case series are available in this regard.[6-8] Here, we report a case of new-onset multiple generalized tonic-clonic seizures in an adolescent boy after withdrawal from heroin. To the best of our knowledge, this is the first reported case in the adolescent age group. Written informed consent was taken from the child and his guardian.

A 16-year-old previously healthy boy presented with 6 episodes of generalized tonic-clonic seizures within the past 2 days. These seizures were characterized by frothing from the mouth, tongue bites, urinary, and fecal incontinence and postictal drowsiness, apart from tonic-clonic movements. In between seizure episodes, he used to regain sensorium. But he was agitated, restless and had excessive sweating. He also had a loss of orientation to time and place, visual hallucinations, psychosis, aggressiveness, and irrelevant talking. There was no focal deficit, tonal abnormalities, gait instability or dysarthria. There was no history of fever, head trauma or any other associated symptoms. On further eliciting the history, the boy was found to be taking heroin by inhalational route for the last three months and was in a deaddiction center for two days, where he was started on oral methadone for two days when he developed these seizures. The child had a history of heroin use four days before the onset of the first seizure. The heroin he used was of street quality bought from a local vendor, from whom he used to buy regularly along with one of his peers from the neighborhood. All 6 seizures occurred within 2 days and the first seizure occurred after one day of stay at the de-addiction center. There was no history of other drug prescriptions like Tramadol, Buprenorphine, Dextropropoxyphene, Naloxone or Naltrexone. There was no history of co-morbid alcohol or benzodiazepine dependence and also the child did not have a history of cannabis or inhalant addiction. There was no family history of seizures or substance abuse. At presentation, the child was agitated, anxious with insomnia for the previous two days, having hypersalivation, repetitive yawning, goose bumps, and nausea. Neurological and other systemic examination, as well as hematological, biochemical parameters, blood sugar, liver and renal function tests, C-reactive protein, chest X-ray, electrocardiogram, human immunodeficiency serology, hepatitis B, and hepatitis C were normal. Magnetic resonance imaging of the brain was normal. A urine drug screen was positive for 6-acetylmorphine, a heroin metabolite. An electroencephalogram at presentation with activation maneuvers like hyperventilation and photic

Table 1: Comparison of demographic, clinical and laboratory features of various published cases of seizures after heroin withdrawal

Variables	Total number of published cases with seizures after heroin withdrawal (n-11)	Index patient
Age (in years)	20 to 38	16
Sex	Male (11/11)	Male
Country of origin	India (10/11), Sri Lanka (1)	India
Duration of Heroin abuse	2-6 years in Indian patients, 15 years in patient from Sri Lanka	Eight months
Time interval between abstinence and seizures	2-6 days	3 days
Primary mode of consumption	Inhalation/Intravenous	Inhalation
Variety of Heroin used	Street variety in all (? contaminated with adulterants)	Street variety (? contaminated with adulterants)
Other psychoactive substance use	Benzodiazepine (1) Alcohol (0)	None
Seizure semiology	Generalized tonic-clonic	Generalized tonic-clonic
Number of seizures	1 to 10 episodes	4 episodes
Antiepileptic drug used	Valproate and Benzodiazepine	Valproate and Benzodiazepine
Duration of antiepileptic drug	Few days to few weeks	Four days
Presence of associated delirium	6/11	Yes
Drugs used for opioid dependence	Dextropropoxyphene, Methadone, Clonidine, Haloperidol, Buprenorphine	Haloperidol, Methadone
Urine drug screen result	Radioimmunoassay positive in 7/11 (urinary opioid level 0-2000 ng/dl)	6-acetylmorphine (qualitative test)
Neuroimaging (CT/MRI)	Normal (11/11)	Normal
EEG	Normal (10/11), Diffuse cortical dysfunction (1)	Mild diffuse slowing without any epileptiform activity
Seizure recurrence in follow-up	No (11/11)	No (3 months follow up)
Any neurological sequelae in follow-up	No (11/11)	No

stimulation did not yield any epileptiform abnormalities and only showed mild diffuse slowing, consistent with delirium and encephalopathic status of the child. A diagnosis of heroin-induced withdrawal seizures was concluded.

He was started on valproate, along with clonazepam, haloperidol, and methadone for withdrawal symptoms. A repeat electroencephalogram after one week was completely normal. His symptoms resolved within 2 weeks and antiepileptic drugs were tapered after 4 weeks. At a 3-months follow-up, he was maintaining abstinence without any seizure recurrence.

Although he had received methadone in the de-addiction facility and methadone can prolong QTc interval, which can lead to transient arrhythmias like *torsades de pointes* and loss of consciousness followed by seizure, heroin withdrawal still seems to be the most reasonable explanation for recurrent seizure episodes in the index case. In rare cases, methadone may lead to ventricular fibrillation and death too. However, the case that is presented does not fit this as there were multiple seizure episodes and clinical features of delirium as well suggesting a bigger problem than the transient decrease in cerebral blood flow.

Published literature has only a few cases of seizures after heroin withdrawal[6-8] [Table 1]. A systematic search in MEDLINE, SCOPUS, Google Scholar and ScienceDirect was performed with MESH terms "Heroin", "Opioid", "Withdrawal" "Substance abuse" and "Seizure" alone or in combination, which yielded 34 articles. However, after excluding cases of neonatal withdrawal due to maternal opioid dependence, review articles, and duplicate entries, only 3 articles describing 11 adult patients (2 case series and a single case report) with new-onset seizures following heroin withdrawal were found. All these patients were between 20 and 38 years and seizures occurred between 2 to 6 days after abstinence.[6-8] All patients had generalized tonic-clonic seizures. Neuroimaging and electroencephalogram were normal in all the patients. All of them responded favorably to transient monotherapy (antiepileptic drug). Benzodiazepines, haloperidol, and clonidine were used to deal with withdrawal symptoms in these patients, apart from buprenorphine, methadone, and dextropropoxyphene, which were used as opioid analogues. All cases refused other psychoactive substance abuse, apart from only one case with coexisting benzodiazepine abuse. The opioid consumed by all the patients was of the street variety and the possibility of contamination with adulterants can't be ruled out completely. Route of consumption was inhalation of vapors generated from opium

heated on an aluminum foil predominantly or intravenous administration in a few.[6]

Chronic opioid use causes homeostatic adaptations throughout the neuronal and glio-neuronal network of the brain and leads to selectively depressed or enhanced electrical activity at various sites.[7] Changes in the excitability of one neural network are well known to produce a change in the excitability of other neurons and synapses throughout the brain due to various interconnections.[7] Although the exact site and mechanism of this neuroadaptation after opioid dependence is not exactly known, previous research has revealed some potential mechanism of action behind epileptogenesis after opioid withdrawal. The most promising postulate among them is increased activation of noradrenaline containing neurons in the locus ceruleus caused by excitatory amino acid output.[7] Continued opiate use also modifies the activity of medium spiny neurons in nucleus accumbens, which are primary targets of dopaminergic neurons. The output neurons of nucleus accumbens contain GABA and other opioid peptides and they project to the ventral pallidum and ventral tegmental area.[7,9] Heroin-induced spongiform leukoencephalopathy, rhabdomyolysis, mononeuropathy, and cerebral cortical infarction are other rare complications of intravenous heroin abuse.[6]

Although the occurrence of seizures remains a remote possibility in patients with opioid withdrawal, still few recent clinical reports including the index case try to aware the clinicians to maintain reasonable suspicion for this life-threatening complication in opioid-dependent subjects. Timely management leads to control of these seizures in all cases, without any neurological sequelae. Antiepileptic drugs are only required transiently in most of the opioid withdrawal seizures, without any long-term seizure occurrence.

Finally, the importance of performing serum and urine drug screens in adolescents with new-onset seizures can't be undermined. American Epilepsy Society and Neurocritical Care Society guidelines recommend for urine drug screen routinely in children with prolonged seizures or multiple seizures occurring at short intervals.[10,11] In India, although previously substance abuse or withdrawal were considered a remote etiology for new-onset seizures in adolescents and drug screen used to be performed only in cases with a strong suspicion of addiction, currently with the increasing prevalence of substance abuse like heroin and cocaine in adolescents, it is worthwhile to perform drug screen in all unexplained seizure cases, especially in those with associated delirium.[12]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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