

A Novel Cause of Toxic Encephalopathy in an Adolescent Boy

A 12-year-old boy presented to the emergency room with acute onset altered sensorium. His parents gave history of multiple episodes of non-bilious and non-projectile vomiting two hours after returning from school and having lunch. Following which he became drowsy, spoke in appropriately, had history suggestive of visual and auditory hallucinations, and bladder incontinence. There was no history of fever, seizures, weakness in any limb or cranial nerve palsies. There was no past history of altered sensorium or seizures and the child was not on any medications.

The child had a heart rate of 120 per minute, respiratory rate of 32 per minute, blood pressure of 100/60 mm Hg (50th to 90th centile), was febrile with a temperature of 101⁰F and was in a minimally conscious state (Glasgow coma scale 8). Both pupils were mid-dilated and were sluggishly reacting to light. The child had an involuntary pill rolling movement of his fingers which disappeared on sleeping. Rest of the motor examination was normal. There were no cerebellar signs, signs of meningeal irritation or signs of raised intracranial tension.

A provisional diagnosis of acute onset encephalopathy with mydriasis was kept with differential diagnosis of viral encephalitis, metabolic encephalopathies (including uremic and hepatic), intoxication, post-ictal state and snake envenomation. The child was managed empirically with intravenous fluids, injection ceftriaxone (1 g/kg/d) and acyclovir. On investigation, dextrose was 107 mg/dL, hemoglobin 10.5 g/dL, leukocyte count $6.7 \times 10^9/L$, platelet count $260 \times 10^9/L$, sodium 142 mEq/L, potassium 4.2 mEq/L and ionized calcium 4.5 mEq/L. Serum creatinine, bilirubin and alanine transaminase were within normal limits. Blood gas revealed a pH of 7.43, bicarbonate 23 mmol/L and lactate 1.3 mmol/L.

The child's vitals remained stable and with continued supportive care his sensorium improved to normal in the next 36 hours. Urine toxicology screen by qualitative radio immune assay (threshold for detection >50 ng/mL) showed presence of tetrahydrocannabinol (THC), thus supporting toxin ingestion (marijuana) as the cause of encephalopathy. After regaining his sensorium, the child revealed that he had consumed a chocolate-like sweet that had been given to him by a friend on the day of symptom onset.

Cannabis is consumed in different forms such as dried leaves (marijuana), resin (hashish), and concentrated resin extract (hashish oil). Hashish may be easily mistaken for a chocolate by a child, and this may be the reason why hashish is the most common (38%) documented oral ingestion [1]. THC is the main psychoactive ingredient that binds to brain cannabinoid receptors, producing dose- and time-dependent stimulant, hallucinogenic or sedative effects. Effects of cannabis starts from

30 minutes to 3 hours of ingestion and lasts up to 12 hours. With the increased bioavailability of cannabis concentrates and the smaller body mass in children, childhood cannabis ingestion results in high serum THC levels, even if small amounts are consumed [2].

Paediatric cannabis intoxication has a variable presentation, most commonly neurological (confusion, lethargy, coma or agitation) followed by ophthalmological (bilateral reactive mydriasis), cardiovascular (tachycardia, hyper- or hypotension) and respiratory depression needing mechanical ventilation [3]. These symptoms are nonspecific and mimic postictal state, encephalitis, metabolic causes and sympathomimetic agent poisonings which may lead to a delayed diagnosis and unnecessary diagnostic evaluation, particularly in a drowsy child. High index of clinical suspicion and early urine screening can prevent invasive and costly investigations like lumbar puncture and neuroimaging respectively, and may reduce the need for prolonged empirical treatment with intravenous antibiotics and antivirals. Its rare availability in most settings, lack of expertise in testing and high cost limits its widespread use. Initial urine screening is typically performed with enzyme multiplied immunoassay technique, which is then confirmed by gas chromatography-mass spectrometry [4,5]. Results of screening test are available in a few hours (reduced to minutes with point of care testing) whereas the confirmatory test requires a few days.

Examination of the pupils provides a valuable clue to the underlying disease, especially in cases of suspected toxin. Mydriatic pupils are seen in anticholinergic (atropine, antihistaminic, antipsychotic), sympathomimetic (cocaine, amphetamine, lysergic acid diethylamide, etc) toxidromes and cannabis ingestion, whereas miotic pupils are seen in cholinergic (organophosphate, carbamate) and opioid (morphine, heroin, codeine) toxidromes [6]. In this case of unexplained encephalopathy with reactive mydriatic pupils, we narrowed our differentials to the former category of intoxicants.

Clinical recognition of altered mental status by marijuana exposure can be challenging in children. However, increased awareness regarding childhood drug abuse, its clinical effects especially on pupils, as well as utilization of toxicology screen in those with high suspicion facilitates early diagnosis, limits extensive investigations and facilitates implementation of preventative measures, especially in a resource-constrained setting like ours.

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Introduction of Proton Beam Therapy in Intracranial Germ Cell Tumors in India

Intracranial germ cell tumors (ICGCT) represent rare tumors comprising 1-2% of brain tumors and <3% of all neoplasms in children [1]. Optimal management of ICGCT involves multimodal therapy including surgery, radiotherapy (RT) and systemic chemotherapy [2]. Proton beam therapy (PT) has unique features of delivering sharp fall-off of RT dose resulting in significant sparing of normal tissues compared to traditional photon therapy. We describe our initial experience in treatment of these tumors using image-guided intensity modulated proton therapy (IMPT) at our center, the first and only PT facility in South Asia.

An 18-year-old male presented with history of decreased appetite, weight loss, and generalized weakness for six months. Magnetic resonance imaging (MRI) of brain showed lesions in periventricular region and subsequent stereotactic biopsy was suggestive of intracranial germinoma with CD117 and Oct4 positivity. Cerebrospinal fluid (CSF) analysis revealed increased beta human chorionic gonadotrophin (β -HCG) and normal alpha fetoprotein (AFP) with no malignant cells. He received four cycles of etoposide and carboplatin according to ACNS0232 protocol [2], following which, his tumor markers normalized and he was subsequently treated with IMPT to a total dose of 40 GyE in 23 fractions (23.8GyE in 14 fractions craniospinal irradiation (CSI) and 16.2 GyE in 9 fractions boost to gross residual and pre chemotherapy volumes) [3]. He tolerated PT well and subsequent MRIs done 6 weeks, 6 months and 14 months post-PT did not show any residual disease. His tumor markers and endocrine values were within normal limits with his height relatively stable as he has already achieved his growth spurt. He has resumed his socio-academic activities and is on regular follow-up for the past 20 months.

A 16-year-old boy presented with sudden onset diplopia since five months. MRI showed well defined lobulated mass lesion measuring 2.4×2.1×3.1 cm in the region of third ventricle. Tumor marker analysis showed elevated serum β -HCG (1626 mIU/mL) and AFP (2.0 ng/mL). CSF analysis reported increased β -HCG measuring 3589 mIU/mL and AFP measuring 0.47 ng/mL. A diagnosis of NGGCT (choriocarcinoma) was made and he subsequently received four cycles of ifosfamide, cyclophosphamide and carboplatin (ICE), followed by IMPT to a total dose of 54 GyE in 30 fractions (CSI 30.6 GyE in 17 fractions followed by boost of 23.4 GyE in 13 fractions) [3].

Follow-up MRI post-PT after 2 month and 18 months showed interval decrease in residual disease. Post-PT tumor markers were normal and endocrine functions optimal, with the patient's height relatively stable. He has been on regular follow-up since past 20 months and has been continuing his normal socio-academic activities.

A 15-year-old female with amenorrhea, presented with increased thirst, micturition, weight loss, and blurring of vision towards left side over a period of two years. Visual perimetry showed bilateral temporal hemianopia. MRI brain with spine screening revealed a 2.1×2.3×2.3 cm suprasellar lesion compressing the optic chiasm. She underwent a right pterional craniotomy and gross total resection of lesion, reported as intracranial germinoma. Her tumor markers (serum and CSF) showed mild elevation of β -HCG (2.8 mIU/mL). She was on thyroid, cortisol and desmopressin supplements post-surgery because of decreased endocrine functions. Her neurocognitive evaluation before proton therapy showed her in the high average range. She received four cycles of three weekly etoposide and carboplatin followed by IMPT (**Fig. 1**) to a total dose of 40 GyE in 25 fractions (24 GyE in 15 fractions to whole ventricular volume and 16 GyE in 10 fractions to tumor bed) [4]. Post-PT tumor markers were within normal limits. Follow up MRI after one, six and twelve months did not show any residual disease. Post proton therapy, her endocrine function did not deteriorate and she was continued on hormone supplements. Subsequent ophthalmic evaluation showed no visual deficits. The patient has been on regular follow up for the past 15 months and has resumed her normal academic activities.

For all these patients, cases were discussed in multidisciplinary tumor boards. Patients, after customized immobilization, underwent a planning CT and MRI. Dedicated PT plans were generated for each case using Monte-Carlo optimization and 3-4 PT fields [3]. Treatments were delivered on a daily basis (5 fractions a week) after carefully laid out quality assurance checks as per institutional protocols. Significant reduction of the radiation dose to critical structures such as hippocampi and cochlea were observed.

RT is an integral part of treatment of ICGCT but can be associated with considerable late effects including neurocognitive disturbances and risk of secondary cancers, and chemotherapy alone is insufficient due to high rates of local and metastatic recurrence. Current standard of care is ventricular radiotherapy in case of localized and CSI in case of disseminated germinomas [4,5]. In comparison with conventional radiotherapy, PT due to its unique physical and biological