Harlequin Syndrome and Autonomic Seizures – A Rare Association

Sir,

Here we report a case of a twelve-year-old male child presented to the neurology clinic with a history of intermittent abnormal involuntary generalized body movements and flushing on one side of his body and face since infancy. He was born to non-consanguineous parents through full-term vaginal delivery, which was complicated by meconium aspiration and delayed cry. On the sixth day after birth, the patient's mother observed abnormal generalized clonic movements and flushing of the entire body during bathing, followed by episodes of drowsiness lasting 15–30 minutes. The frequency of these episodes gradually increased to 2–3 times per day and then decreased to once every 2–3 months. The episodes were triggered by fear, physical stress, straining during defecation, and high temperature. The patient reported experiencing abnormal sensations and fear before the episodes and sought immediate support from a family member. These episodes were characterized by intense body pain, followed by flushing, sweating, and raised temperature on the same side, whereas the opposite side remained dry and pale [Figure 1]. Flushing was associated with conjunctival injection, eyelid swelling, lacrimation, and nasal stuffiness on the same side [Figure 1]. The flushing was accompanied by abnormal clonic movements involving the entire body, lasting 2–3 minutes, and followed by a period of drowsiness lasting 10–20 minutes. The flushing could persist for 10–60 minutes, and the patient experienced thirst, severe generalized pain, fatigue, palpitations, and stool incontinence during these episodes. There was no history of any focal tonic-clonic limb movement involving the face or limbs, and there was no family history of similar complaints. The patient achieved normal growth and developmental milestones, and his IQ was within the normal range. General and neurological examinations revealed no remarkable findings. Routine hematological and metabolic panels were within normal limits. A 1.5 T MRI of the brain without contrast (T1, T2, and Flair sequences) showed no abnormalities [Figure 2]. Interictal EEG findings suggested right frontal spike and wave discharges with secondary generalization [Figure 3]. Video EEG did not capture any ictal episodes with corresponding EEG abnormalities. Bilateral carotid artery Doppler results were normal, and autonomic testing showed no signs of dysautonomia. Chest and neck CECT scans were normal. To rule out the possibility of paroxysmal extreme pain disorder, genetic testing (whole exome sequencing) was conducted, which yielded negative results for any significant mutations. Based on the clinical history of recurrent episodic hemi body autonomic flushing, generalized clonic movements, and abnormal interictal EEG findings, patient was diagnosed with focal to bilateral clonic seizure and harlequin phenomenon as a cutaneous autonomic manifestation during seizures. Anticonvulsant therapy was initiated with carbamazepine 100 mg twice daily, resulting in the cessation of these events.

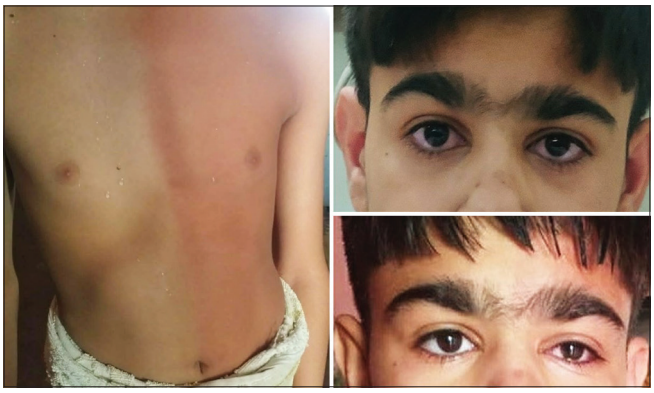

Figure 1: Flushing of left half of body and face. Conjunctival injection, tearing along with ptosis of left eye

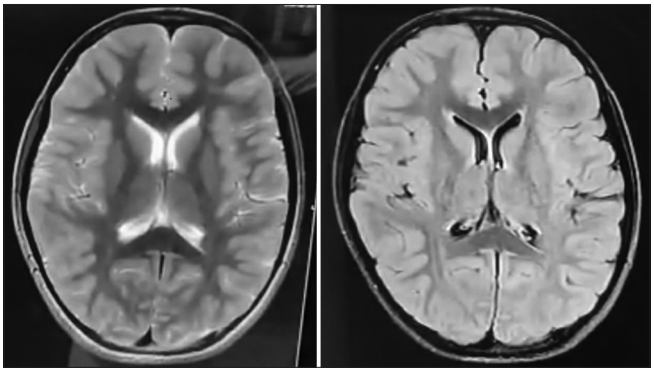

Figure 2: Normal MRI brain

Asymmetric facial flushing was initially reported and named "Harlequin Syndrome" by Lance *et al*.[1] They documented five adult patients who experienced sudden unilateral facial flushing when washing their faces with hot water or after vigorous exertion. The term "Harlequin" derives from the Italian word "Arlecchino," which refers to a famous character from Bergamo known for wearing masks and colorful clothing. Autonomic dysfunction has long been recognized as a phenomenon associated with epilepsy[2] and can manifest as early as the neonatal period, presenting as vasomotor activity accompanying neonatal seizures. In most cases, autonomic phenomena are part of a broader spectrum of symptoms, and the epileptic nature of the seizure is easily identifiable.

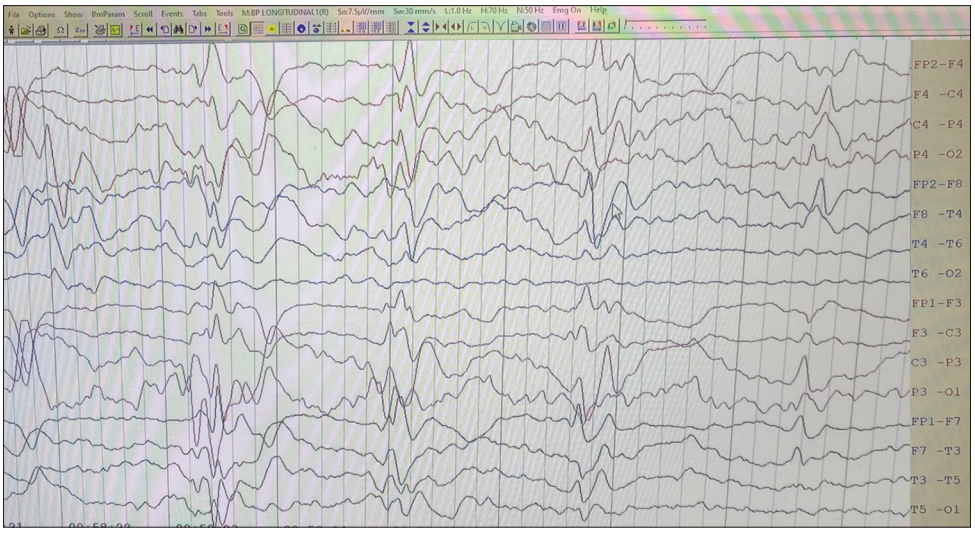

Figure 3: EEG (Bipolar Montage) showing right frontal spike and wave discharges

This is distinct from Harlequin color change (HCC), which is a benign and transient skin alteration primarily observed in the neonatal period.[3] Harlequin syndrome has been associated with Horner's syndrome (ptosis, miosis, and facial anhidrosis) and is considered part of a range of autonomic disorders involving both parasympathetic and sympathetic dysfunctions. These disorders include Holmes-Adie or Adie syndrome (characterized by tonic pupils and hyporeflexia)[4] and Ross syndrome (a combination of Harlequin syndrome, Adie syndrome, and more diffuse autonomic symptoms).[5,6]

In this report, we present an unusual form of focal to generalized clonic seizures that manifest as paroxysmal changes in skin color, known as Harlequin syndrome, affecting variably the right and left components of the autonomic nervous system. Despite several reports on autonomic manifestations in epilepsy, the underlying pathophysiological mechanisms remain poorly understood. The bilateral innervation of the vagus and sympathetic nerves in the thoracic and abdominal regions, along with the complexity of cutaneous autonomic innervation, make it unlikely for a unilateral irritative lesion to explain this phenomenon. However, it is well-known that both generalized seizures and complex partial seizures can produce autonomic symptoms.[7] The hypothalamus, known for its regulatory role in the autonomic nervous system, likely acts as a major relay center in temporal lobe seizures. The hypothalamus is closely interconnected with mesial temporal and limbic areas and can be activated by epileptic discharges.[7] The significance of the hypothalamus and limbic system in the pathogenesis of autonomic seizures has been demonstrated in both humans and animals.[8]

Upon reviewing the literature, we discovered a similar case of autonomic manifestations, including cutaneous changes resembling the harlequin color phenomenon.[9] The case involved an eight-month-old child with autonomic seizures, presenting as paroxysmal changes in skin color (resembling Harlequin-like syndrome) accompanied by bradycardia due to paroxysmal nodal rhythm. Similar to our case, treatment with carbamazepine was effective, as reported in other cases of this epilepsy variant.[7] Although Harlequin color change has been more frequently reported, cases of Harlequin syndrome are rare. Even rarer is its manifestation as part of an autonomic seizure. To the best of our knowledge, this is the first reported case from India. This case report aims to highlight an extremely uncommon manifestation of a rare form of seizure.

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Conflicts of interest

There are no conflicts of interest.

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