Dravet syndrome Presenting with Extrapyramidal Features, Ataxia and Basal Ganglia Hyperintensity on Brain Magnetic Resonance Imaging

Sir,

Ataxia and extrapyramidal involvement have been recognized as a characteristic of Dravet syndrome (DS), with gait disturbance nearing 90% in the age group 16–25 years.[1] The period of highest seizure frequency usually corresponds to the lowest cognitive ability and worst behavior profile in children with DS.[2] Cerebellar origin of the neuropsychological defects in DS is supported by the presence of cerebellar symptoms and signs in many of these children.[3]

An 8-year-old boy, born to a non-consanguineous couple, with no other family member affected, presented with recurrent febrile seizures. His birth history and attainment of expected milestones were unexceptional. From 6 months age, he had monthly febrile seizures. His development continued on a normal trajectory. He was initiated on continuous medication with sodium valproate at age 3 years as the frequency of seizures, though with fever, was deemed unacceptable. Breakthrough focal seizures, though accompanied by fever prompted a pediatrician to change medication to carbamazepine. Soon he was encephalopathic and had emesis. A quick change back to valproate solved the issue.

From age 5 to 8 years he remained seizure free and had age-appropriate motor and language development. On completion of a 3-year seizure freedom, valproate was tapered. Two weeks following cessation of valproate, he presented with 10 episodes of focal febrile seizures in a day. He was ataxic, drowsy, talked irrelevantly, was aggressive and speech was slurred. Magnetic resonance imaging (MRI) of the brain was unremarkable. Electroencephalogram (EEG) showed a normal background with normal sleep architecture and no epileptiform discharges. Cerebrospinal fluid (CSF) revealed no cells, normal viral panel, sugar and protein and absent N-Methyl-D- Aspartic acid receptor antibodies. Serum autoimmune antibody profile was negative. Reintroduction of valproate saw him return to premorbid state. At 8 year and 5 months, he presented with an afebrile focal seizure and had levetiracetam added. Around 8 year and 8 months, valproate was stopped because of raised liver enzymes. In 2 weeks' time, he presented with ataxia, emesis, atonic seizures, an expressionless face and drooling. EEG done at this visit showed suppression of activity over the right fronto-central region, with retained sleep architecture and no epileptiform transients. The diagnosis seemed elusive and cerebellar and extrapyramidal signs were seen with varying diurnal intensity. He continued to have pancerebellar signs, mask like face, bilateral cogwheeling, action and rest tremor, crouched gait, right mimic facial and problems with recent memory and word finding.

Blood tests revealed normal ceruloplasmin, ammonia, lactate, amino acid, and organic acid profile and no acanthocytes. No excess organic acid was detected on Gas Chromatography-Mass spectrometry of urine.

Six months after presentation and several admissions, most heralded by emesis, and repeated near normal EEG (showing only low amplitude over the right frontocentral region), he presented with frequent focal seizures, drowsiness, problems with mathematics and word retrieval, ataxia and extrapyramidal signs. MRI of brain revealed T2/Flair symmetric hyperintensity of both putamen and globus pallidus, iso-hyperintense on T1 weighted image and no diffusion restriction [Figure 1]. Recurrent focal seizures prompted introduction of carbamazepine and he proceeded to become encephalopathic and eventually had status from which he was rescued.

Selective amplification and sequencing of the entire mitochondrial genome (at Medgenome labs) to mean >80-100X coverage on illumina sequencing platform revealed no abnormality. Targeted gene sequencing on DNA extracted from blood showed a heterozygous pathogenic missense mutation in exon 28 of the *SCN1A* gene (chr2:g. 165991708A>G; Depth: 303×) that resulted in the amino acid substitution of threonine for methionine at codon 1856 (p. Met1856Thr; ENST00000303395.8).

Two months following extrication from the first status epilepticus and on carbamazepine, lacosamide, clobazam, phenobarbitone and phenytoin, he was admitted with worsening ataxia and extrapyramidal signs. Based on the *SCN1A* mutation, he was rapidly weaned off sodium channel drugs and he progressed to refractory, life threatening status epilepticus in spite of oral topiramate, intravenous midazolam drip, thiopentone, ketamine, and oral perampanel. He finally responded to loading dose of phenobarbitone and continued seizure free on topiramate, phenobarbitone and clobazam. At last follow up, 5-months following the last SE, he is seizure free but has mild cognitive disability (word finding difficulty, defective recent memory and learning issues) and a normal EEG.

We have reported a case of DS that manifested with not only seizures but with pancerebellar signs, extrapyramidal features, basal ganglia hyperintensity on MRI brain and evolution to life threatening SE on two occasions. His disease course also witnessed an encephalopathic state early in life when he was initiated on carbamazepine which should have spelt out the mutation even before it was done in the laboratory. He also experienced anicteric hepatitis on valproate that resolved on withdrawing valproate from the regime.

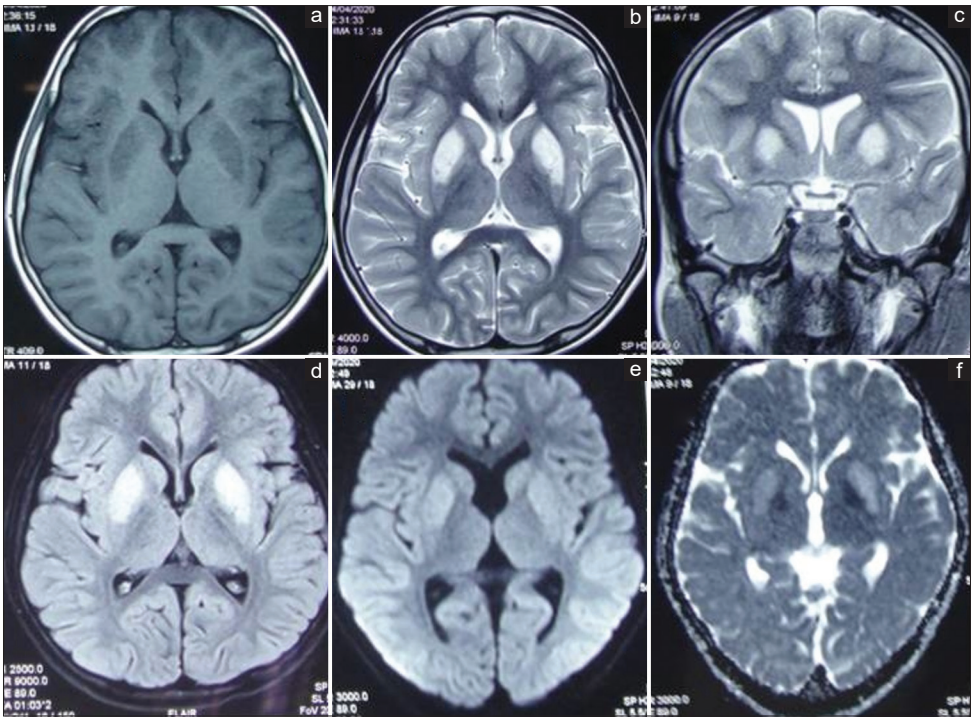

Figure 1: Brain magnetic resonance imaging revealed bilateral caudate nucleus and putamen iso-hyperintense on T1 weighted image (a), hyperintense caudate and putamen with putaminal swelling in T2 and Flair images (b, c and d) and no diffusion restriction (e and f)

Control of seizures and disappearance of ataxia and extrapyramidal features on withdrawal of sodium channel blocking drugs substantiates that the mutation observed on gene sequencing was indeed responsible for the disease manifestations in this child. Normal development before seizure onset, provocation of seizure by fever, emergence of ataxia, pyramidal signs and massive myoclonus are suggested by the International League Against Epilepsy as diagnostic features; the presence of three among them predicting 100% chance of *SCN1A* mutation.[4]

The sodium channel mutation in various sites explains epilepsy (cortical interneurones), ataxia (cerebellum), the crouching gait (the basal ganglia and motor neurons), and emesis (hypothalamus).[4]

Anicteric hepatitis that resolved on stopping valproate could be evidence for associated mitochondriopathy in DS.[5,6] Acute encephalopathy in DS has been attributed to inappropriate antiepileptic drug treatment and mitochondrial dysfunction.[6]

Reports of Parkinsonism, choreoathetosis, cognitive deterioration, and pyramidal signs have been variably reported as dependent on and independent of the seizure frequency in DS.[2,7]

Though there are rare reports of basal ganglia and hippocampal atrophy, there are no signatory neuroradiological signs of the syndrome. A perusal of available literature revealed only one Chinese report of a patient with basal ganglia hyperintensity and DS.[8] The basal ganglia hyperintensity observed in our patient, is notable as a rarity in DS. Structural changes like basal ganglia hyperintensity in our child can lead to a structural substrate that could possibly result in a more devastating epileptic encephalopathy.

The 6-month delay to clinch the diagnosis in this patient after initial presentation is not the recommended scenario. The case profile with frequent febrile seizures in a child with normal development and later appearance of ataxia and pyramidal/extrapyramidal signs should prompt the epileptologist to have a high index of suspicion of an *SCN1A* gene mutation, tailor drugs and avoid antiepileptic drugs acting on sodium channels. The two life-threatening SE in this patient could have been avoided. We advocate an early genetic testing in patients with generalized epilepsy with febrile seizure plus.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's relative has given consent for clinical information other than photograph to be reported in the journal. The patient and relatives 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.

Ethical consideration

Ethics clearance was not sought for genetic testing as it was done for diagnostic purpose to aid treating the child.

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Conflicts of interest

There are no conflicts of interest.

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