

A Case of Dystonic Storm: Storm That Was Mastered

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Case Report

Keywords: Dystonic Storm, Intrathecal Baclofen Pump, Deep Brain Stimulation, to Globus Pallidus Interna and CACNA1E gene

Posted Date: June 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-587765/v1>

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Abstract

Background: Hyperkinetic movement disorder characterized by involuntary sustained or intermittent muscle contractions causing repetitive twisting movement, abnormal postures, or both is called dystonia. Its extreme severity is called 'Dystonic Storm', which is a life-threatening medical emergency. This is the only case that was managed with two surgical interventions, the Intrathecal Baclofen pump followed by Deep Brain Stimulation to Globus Pallidus Interna in addition to medical management

Case presentation: 16 years old boy, presented with insidious onset gradually progressive dystonia. Initially, he developed in lower limbs than in both upper limbs and the cervical region at the age of 08 years. His dystonia of the neck, arms, and trunk increased, walking became a problem, and even sitting became difficult over 24 hours. Dystonia movement continued even during sleep associated with dysautonomia. On investigation, his Creatine Phosphokinase was raised with 1324 IU/l. Bilirubin was normal but, liver enzymes were mildly raised. Urine for myoglobin was negative, MRI was normal.

He was managed as a case of dystonic storm injectable Vecuronium infusion and Midazolam infusion. However, even then dystonia continued. Since dystonia was refractory to supportive and specific medical management, two-step procedures were planned to control the refractory dystonic storm. The first step was an Intrathecal Baclofen Pump as bridge therapy and then Deep Brain Stimulation to Globus Pallidus Interna was done. As part of an etiological investigation, his Clinical exome sequencing showed the CACNA1E gene, autosomal dominant (heterozygous) missense mutation on chromosome 1. Pathogenic CACNA1E variants presented with variable Developmental and Epileptic Encephalopathies characterized by movement disorders including dystonia in 60% cases.

Conclusion: Status dystonicus is a rarest and life-threatening movement disorder emergency that requires both medical management (supportive and directive to precipitating factor and dystonia) and surgical intervention in a stepwise manner. Appropriate time of surgical intervention is key in management of dystonic storm.

Background

Hyperkinetic movement disorder characterized by involuntary sustained or intermittent muscle contractions causing repetitive twisting movement, abnormal postures, in its extreme severity, it is called 'dystonic storm', which is life threatening emergency^(1, 2). It is a movement disorder emergency with mortality of 10% even in treated patients⁽³⁾. We are describing a case of dystonic storm, which was refractory to all supportive and dystonia specific medication and managed with dual neurosurgical intervention with Intrathecal Baclofen Pump (ITB) and Deep Brain Stimulation (DBS) to Globus Pallidus Interna (GPI). It should be published in your journal because nowhere in the world medicine literature both neuromodulation was done in single patient. His clinical exome sequencing showed CACNA1E gene on Chromosome 1 autosomal dominant (heterozygous) missense mutation and missense mutation

Heterozygous Autosomal dominant gene KCNC3 on Chr19. This is also unique that two abnormal genes are present in a single patient with same syndrome.

Case Presentation

16 years boy presented with continues dystonic movements which was continues even in sleep. At the age of 8 years he developed insidious onset progressive dystonia in lower limbs. Later dystonia progressed in both upper limbs and cervical region. But, there was no oral or tongue dystonia. Gradually he had worsening of handwriting, independent walking became difficult and even sitting without back support was difficult.

He was born without any anti-natal complication and it was a full term normal home delivery. There was no jaundice at birth, seizure, myoclonic jerks, chorea, sensory symptoms, motor weakness, and family history of dystonia. He achieved the language and social milestones in time.

Wilson's disease was ruled out since his 24 hours urinary Copper and serum Ceruloplasmin levels was normal and Kayser–Fleischer (KF) Ring was absent. He was advised Tetrabenzine and Baclofen in optimal dosages.

He had rapidly worsening generalised dystonic movements over 24 hours which was not relived by previous oral medication. On examination his pulse was 102/min, respiratory rate was 26/min, blood pressure was 146/92 mm Hg and there was generalised sweating. Dystonic movements included bilateral upper and lower limb dystonia, torticollis, and truncal dystonia with dystonic tremor of the neck. There was no oral, buccal or lingual dystonia.

On investigation, his hemogram was normal. CPK was raised with 1324 IU/l. Bilirubin was normal but, liver enzymes were mildly raised (AST/AST: 128/246 IU/l). Urine for myoglobin was negative. Brian MRI was normal. As part of etiological investigation his clinical exome sequencing showed CACNA1E gene on Chromosome1 autosomal dominant (heterozygous) missense mutation. His additional Variant of Unknown Significance (VUS) Variant Findings (Secondary) also showed missense mutation Heterozygous Autosomal dominant gene KCNC3 on Chr19.

He was managed for more than 4 weeks with mechanical ventilator support and nutritional supplementation via nasogastric tube (1800 kcal with 60 gm proteins daily). Drugs were optimized with Tab Baclofen SR 20mg QID, Tab Tetrabenzine 25mg TDS, Vecuronium infusion and Midazolam infusion (at the rate of 50 mcg/kg/hours). Even then dystonia continued. Trihexyphenidyl 4 mg QID and Clonidine 200 mcg TDS were added. Dystonia reduced but developed drug induced hypotension. Reduction in dosage of Midazolam and Vecuronium would result increase in the dystonia. He developed ventilator associated pneumonia, which was managed with appropriate antibiotics. Since dystonia was refractory to supportive and specific medical management, dual neuromodulation was planned. First step was ITB pump placement as a bridge therapy. There was some improvement. Gradually dosages of Baclofen were increased to 800 mcg/day, which is the maximum recommended dosage. After 14 days

DBS to Gpi was done. Initially there was reduction of dystonia because of lesioning but dystonia recurred. Gradually DBS stimulation voltage was also increased at amplitude 2.7V, Pulse with 90, Rate 130 200 Hz.

Over 2 years Baclofen infusion was gradually reduced to 25 mcg/day. His dystonic movements reduced and he became independent for all activities with minimal support. However, minimal dystonic movements still remained in right leg and hand. Due to this he is still not able to write and walk fast even on even surface.

Discussion

Dystonic storm occurs in known patient of dystonia due to infection, withdrawal of IT Baclofen, initiation of D penicillamine and paradoxically DBS failure^(3,4,5). However one third of events are unprovoked. There was no identifiable triggering factor in our patient.

Dystonia which continue in sleep and associated with metabolic disturbance like fever, dehydration, abnormal electrolytes, CK more than 1000 IU/L, myoglobinuria or respiratory cardiovascular compromise, requiring organ support be treated as Status dystonicus⁽⁶⁾. Status dystonicus, proposed by Mangi and colleagues, are bulbar weakness compromising airway patency, progressive impairment of respiratory function causing respiratory failure, metabolic derangements, exhaustion and pain⁽⁴⁾. Our patient also developed respiratory difficulty, which required continued mechanical ventilatory support. He also had raised CK level and transaminitis. However, because of aggressive management he never developed myoglobinuria or any derangement in renal function. Duration of dystonia prior to storm is 6 years and mean age of presentation is 14 years and duration of storm is 4-6 weeks with gradual recovery⁽³⁾. Our patient also presented at similar age with similar duration of disease. However, he didn't improve even after more than 4 weeks of supportive optimum medical management. Any reduction of dosages of drug resulted in worsening of symptoms.

As per Fasano and colleagues, surgical intervention (DBS, Lesioning'or ITB) is required in 40.2% status dystonicus⁽³⁾. We also planned surgical dual neuromodulation by implantation of IBP followed by DBS to bilateral Gpi (Figure1). Patients with dystonic storm don't improve immediately with DBS, it takes 4-6 weeks and amplitude should be gradually increased^(7,8). ITB has limited role due to its complications, especially hypotension on higher dosages⁽⁹⁾. Primary dystonia responds well to ITB or DBS⁽¹⁰⁾.

His clinical exome sequencing showed Variant Undermine Significant (VUS) autosomal dominant CACNA1E gene. This VUS variant was categorized as pathogenic variant by carefully correlated with clinical symptoms. *CACNA1E* encodes Cav2.3, an R-type VGCC. Patients with pathogenic *CACNA1E* variants presented with variable Developmental and Epileptic Encephalopathies (DEE) characterized by refractory epilepsy (87%) with myoclonus or clonus, movement disorders including dystonia (60%), spastic quadriplegia (53%), congenital joint contractures (43%), macrocephaly (43%), and profound developmental impairments like poor or absent eye contact, nystagmus, cortical visual impairment and loss of head control (88%)⁽¹¹⁾. Helbig and colleagues, brain imaging in few

patients showed nonspecific white matter volume loss, atrophy of the corpus callosum, or cortical atrophy⁽¹¹⁾. Our patient presented with only movement disorder in the form of dystonias. However, his brain imaging was normal. Additional VUS Variant Findings (Secondary) showed missense mutation Heterozygous Autosomal dominant gene KCNC3. KCNC3, encoding the Kv3.3 voltage-gated potassium channel, as the gene mutated in SCA13⁽¹²⁾. This gene was considered de novo pathogenic and inherited as benign. This VUS variant cannot be categorized into Pathogenic or Benign and needs to be carefully correlated with clinical symptoms or parental studies (inherited or de novo). The pathogenicity level is based on American College of Medical Genetics and Genomics (ACMG) classification recommended a five-tier classification system⁽¹³⁾. The variant is called Pathogenic if it directly contributes to the development of disease and Uncertain significance if there is not enough information at that time to support a more definitive classification of that variant.

Conclusion

Status dystonicus is a rarest life-threatening movement disorder emergency seen in younger adolescent or paediatric patient. It is crucial for clinicians to be vigilant when any patient presents with worsening dystonia from the baseline. Adequate management should be supportive and directed to precipitating factors and dystonia that include calibration of sedation and dystonia specific medication. Surgical intervention in a stepwise manner and at appropriate time is the most important step in management of dystonic storm.

Abbreviations

American College of Medical Genetics and Genomics (ACMG) classification, Intrathecal Baclofen Pump (ITB), Deep Brain Stimulation (DBS), to Globus Pallidus Interna (GPI), Developmental and Epileptic Encephalopathies (DEE).

Declarations

Participant consent - The parent of the patient consented to participate and publish their clinical data and images.

Competing interests: The authors declare that they have no competing interests.

Funding: It is certified that author's team are not currently in receipt of any research funding.

Authors' contributions: All authors have read and approved the manuscript, and ensure that this is the case. RS was managing when patient was in ICU, SG and PD was managing as OPD case prior and follow up. MSS was neurosurgeon who has done the DBS and Baclofen Pump implantation.

Acknowledgements: Not applicable

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Figures

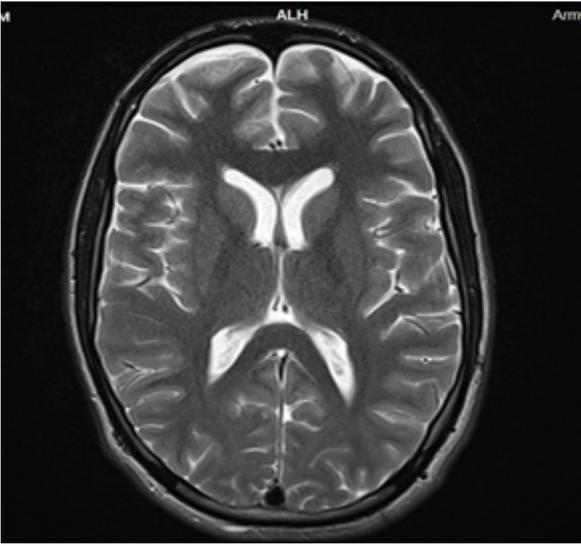


Figure 1

T2W Brain MRI image of patient ; Arrow showing Globus Pallidus Interna.