Case Report

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Medically Refractory Epilepsy Comorbid with Psychogenic Non-Epileptic Seizures and Intellectual Disability in a Patient with Balanced t(14;X) Translocation

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Abstract

We present the case of a women in her 30's with treatment-resistant epilepsy (TRE), psychogenic non-epileptic seizures, intellectual disability, psychosis, and a maternally inherited balanced t(14;X)(q32.3;p11.2) translocation. Despite multiple antiepileptic drugs, vagus nerve stimulation, and deep brain stimulation (DBS) of the anterior thalamic nuclei, she continues to experience daily seizures. DBS implantation led to partial seizure reduction but was complicated by worsening behavioral disturbances, consistent with reported psychiatric side effects and the phenomenon of forced normalization. This case highlights the complex interplay between epilepsy, psychiatric comorbidities, and neurostimulation, as well as the potential genetic underpinnings of TRE. The association of balanced X-autosome translocations with intellectual disability and epilepsy suggests pathogenic disruption of neurodevelopmental genes influencing inhibitory signalling. Awareness of psychiatric risks in DBS recipients and consideration of genetic etiologies are essential for optimizing management strategies in refractory epilepsy.

Keywords: treatment-resistant epilepsy; psychogenic non-epileptic seizures; deep brain stimulation; anterior thalamic nucleus; forced normalization; psychiatric comorbidity; balanced X-autosome translocation; intellectual disability; epilepsy genetics; inhibitory signaling

Background

Epilepsy is one of the most common neurological disorders worldwide, affecting over 50 million individuals, with approximately 30% of cases consisting of treatment-resistant epilepsy (TRE). Patients with TRE face disproportionate burdens due to the medically intractable nature of the epilepsy, including frequent seizures, medication toxicity, cognitive decline, and psychiatric comorbidities that together lead to significant disability and reduced quality of life. In recent years, neuromodulatory therapies such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS) of the anterior thalamic nuclei (ANT) have provided additional treatment avenues for individuals where pharmacotherapy fails to adequately manage symptoms. While DBS has demonstrated efficacy in reducing seizure frequency, its effects on behavior and mood remain a concern given the connectivity of the thalamus with limbic and prefrontal circuits.

Epilepsy also has strong genetic underpinnings, particularly in early-onset, intractable forms. Balanced X-autosome translocations, such as t(14;X) in this case, have been implicated in intellectual disability, neurodevelopmental delay, and epilepsy syndromes. Although these rearrangements do not necessarily produce overt chromosomal imbalances, pathogenicity can arise through gene disruption at breakpoints or altered epigenetic regulation.

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Case Presentation

This case report presents a 37-year-old female with a lifelong history of epilepsy, psychogenic non-epileptic seizures (PNES), intellectual disability (ID), psychosis, and a maternally inherited balanced [t(14;X) (q32.3; p11.2)] translocation. The patient was seen at a follow-up appointment for a recent hospitalization after she reportedly bumped her head on the bed at her group home. The group home staff additionally reports her continuing to have seizures although no generalized tonic-clonic seizures were observed.

Her history of epilepsy began at 6 years of age after experiencing a grand-mal seizure. Through her childhood and into early adolescence, her epilepsy worsened, and her seizures grew in intensity and frequency. In an attempt to treat her epilepsy, she was placed on multiple antiepileptic drugs to no avail and eventually had a vagus nerve stimulation (VNS) device implanted at 12 years of age. Despite polytherapy with an array of antiepileptic drugs and the VNS device, she continued to experience daily seizures and by the time she began high school, she required a wheelchair for mobility due to her atonic seizures. By adulthood, her epilepsy had progressed to multiple seizures per day with accompanying psychosis, with each episode lasting 30 to 60 minutes.

At 34 years of age, she had a deep brain stimulation (DBS) device implanted, targeting the bilateral anterior nuclei of the thalamus. However, while she initially tolerated the DBS implantation procedure well, increasing the stimulation current from 3.0 mA to 3.5 mA resulted in behavioral deterioration, prompting reprogramming to the original lower stimulation parameters. Yet, after returning to the reduced stimulation settings, the patient continues to exhibit behavioral abnormalities, particularly increased aggressive behaviors. Although her behavioral deterioration seems to be attributed to the DBS implantation, she has a history of anxiety disorders that may have predisposed her to the adverse neuropsychiatric side effects.

The patient's epilepsy is currently managed by the DBS and VNS devices, as well as five antiepileptic drugs (Clonazepam 0.5 mg BID, Cannabidiol 6.8 mg BID, Phenobarbital 97.2 mg BID, Lacosamide 200 mg BID and 50 mg QHS, and Zonisamide 300mg BID). Despite the extensive range of therapies implemented to manage the patient's epilepsy, seizures continue to be observed daily, although no grand mal seizures have been reported recently.

A PET scan prior to DBS implantation showed subtle hypometabolism in the left parietal cortex, as well as hypermetabolism of the left thalamus relative to the right. This asymmetry in thalamic and cerebral metabolism is suspected to be due to seizure activity around the time of FDG injection. A MEG scan prior to DBS implantation identified interictal dipoles in the right frontal and left frontoparietal regions, with ictal dipoles in the left inferior frontal region and fronto-parietal operculum.

Long-term video EEG monitoring showed interictal background slowing with bifrontal generalized spike-wave complexes and left parietal sharp waves. Multiple ictal patterns were recorded, with variable corresponding clinical effects. Generalized spike and wave patterns corresponded with behavioral arrest. Paroxysmal fast activity followed by rhythmic slowing with sharp waves in the left central parietal region and left central rhythmic theta-delta activity did not result in any clinical signs. The patient seemed to exhibit paroxysmal events, such as body shaking and holding legs up without any epileptiform activity detected on EEG, consistent with the patient's diagnosis for PNES.

Discussion

DBS of the bilateral anterior nuclei of the thalamus (ANT) has emerged as an effective device therapy used in patients where pharmacotherapy fails to adequately manage seizures. However, given the connections between the anterior thalamus with limbic and prefrontal circuits, ANT-DBS has been demonstrated to have potential side effects on behavior and mood. It is well recognized that epilepsy and psychiatric disorders are bidirectionally associated, with up to one-third of people with epilepsy experiencing a lifetime psychiatric illness (Mula et al., 2021).

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The introduction of neurostimulation further increases the risk of serious symptoms, particularly in patients with pre-existing neuropsychiatric disorders. Clinical trials have documented notable psychiatric side effects in a subset of DBS patients. In the SANTE trial of ANT-DBS, 14-15% of patients reported new or worsened depression during the blinded stimulation phase, compared to only ~2% in the sham group (Imbach et al., 2023). Over long-term follow-up, the prevalence of depressive mood symptoms rose to 37% of patients (Salanova et al., 2015), and about 12% reported suicidal ideation, although most of those who reported suicidal ideation had prior histories of depression. Anxiety symptoms and psychotic symptoms have additionally been observed in some patients during chronic stimulation.

Fortunately, these psychiatric effects are usually reversible with adjustments to stimulation parameters, such as reducing stimulation current or duty cycle duration. For example, one report stated that two DBS recipients with prior histories of depression developed acute depressive episodes immediately after certain programming settings, and two others with no prior history of psychosis gradually developed paranoid anxiety (Järvenpää et al., 2018); in all cases, changing the DBS settings led to resolution of the psychiatric symptoms. This reversibility suggests that DBS itself, likely the intensity and/or location of stimulation, may contribute to the psychiatric irregularities.

In the context of our patient, the worsening behavioral disturbances after DBS despite a partial reduction in seizures is consistent with these reported phenomena. It is possible that her history of psychosis and intellectual disability may have predisposed her to such complications. It is noteworthy that improving seizure control can sometimes unmask or exacerbate psychiatric symptoms, a phenomenon known as forced normalization: the emergence of psychosis or behavioral disorder when epileptic activity is suppressed in a previously uncontrolled patient. This has been described with various therapies including pharmacological treatments, VNS, and DBS. It is thought to reflect neurochemical shifts when ictal control is suddenly established. One case report describes a man with mental retardation and medically intractable epilepsy who became delusional after his seizures abruptly ceased post-VNS implantation (Loganathan et al., 2015).

In our patient, a similar mechanism could explain why reducing her seizure burden via DBS coincided with heightened psychotic and behavioral issues, in addition to the inherent risks of neuropsychiatric side effects as a result of thalamic stimulation. Awareness of this possibility is critical in determining adequate treatment plans and calls for close psychiatric monitoring of DBS patients and a careful titration of stimulation to maintain a delicate balance that controls seizures without inducing intolerable mood or behavioral changes.

Treatment-resistant epilepsy (TRE) in pediatric patients is increasingly understood as a manifestation of underlying genetic and neurodevelopmental disorders, especially when conventional imaging fails to reveal a focal structural lesion. Literature has linked early-onset, intractable epilepsy to chromosomal abnormalities, single-gene mutations, and disorders of neuronal development, particularly those affecting GABAergic interneurons and the excitatory/inhibitory (E/I) balance in the maturing brain.

Balanced chromosomal translocations involving the X chromosome and autosomes, particularly the t(14;X), have been associated with intellectual disability, developmental delay, and various epilepsy syndromes. Although such reciprocally balanced translocations do not result in any gross loss or duplication of genetic material, their pathogenicity could arise from gene disruption at breakpoints or aberrant gene regulation due to altered chromatin structure or skewed X-inactivation. Disruptions involving FGF13 and PHF8, two X-linked genes critical for neurodevelopment, have been implicated in prior t(14;X) cases with phenotypes including generalized epilepsy with febrile seizures plus (GEFS+) and intellectual disability. Notably, FGF13 plays a role in neuronal excitability and the function of voltage-gated sodium channels, while PHF8 is a histone demethylase involved in X-linked mental retardation and cleft lip/palate (Loenarz et al., 2010).

A particularly relevant study (Puranam et al., 2015) described a family with a t(X;14)(q27;q21) translocation disrupting FGF13, in which affected males exhibited febrile seizures in childhood progressing to refractory temporal lobe epilepsy in adolescence and adulthood. Animal models of

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Fgf13 haploinsufficiency showed decreased inhibitory synaptic input and heightened neuronal excitability, supporting the theory that deficits in GABAergic signaling underlie the clinical phenotype (Puranam et al., 2015). This mechanism aligns with the broader hypothesis that impaired interneuron development or migration during critical periods of brain maturation can lead to a lasting E/I imbalance, predisposing individuals to seizures that become increasingly resistant to treatment over time.

Although the precise impact of a 14;X translocation varies with the genes affected, the clinical trajectory observed in many of these cases, including early febrile seizures followed by medically refractory focal epilepsy, supports a model in which subtle widespread disruption of inhibitory networks contributes to epileptogenesis. This hypothesized mechanism provides strong implications for diagnosis and management, as traditional neuroimaging and EEG findings may underestimate the extent of diffuse network dysfunction. In such cases, genome sequencing can be instrumental in identifying causal mutations and informing prognosis, potential targeted therapies, or eligibility for clinical trials.

Given these findings, it is reasonable to hypothesize that the epilepsy observed in the present case may stem from a similar genetic disruption affecting early inhibitory circuit formation. While confirmatory genomic data is not yet available for this patient, the clinical features and resistance to therapy are consistent with previously described translocation-linked developmental epilepsies.

Learning Points/Take Home Messages 3-5 Bullet Points

In summary, this case highlights several key points. Deep brain stimulation (DBS) of the anterior thalamus can reduce seizure frequency in medically refractory epilepsy but is associated with risks of psychiatric and behavioral complications, particularly in patients with pre-existing psychiatric or neurodevelopmental disorders, making close psychiatric monitoring and careful programming essential. Clinicians should also be aware of the phenomenon of forced normalization, in which improved seizure control may unmask or exacerbate psychiatric symptoms, complicating management. In addition, balanced chromosomal translocations such as t(14;X) may disrupt critical neurodevelopmental genes, contributing to intellectual disability, psychiatric comorbidity, and pharmacoresistant epilepsy. Finally, in patients with early-onset treatment-resistant epilepsy without clear structural lesions, genetic testing should be pursued, as it can help identify underlying mechanisms of the epilepsy, inform prognosis, and guide consideration of emerging targeted therapies or clinical trial enrollment.

Informed Consent Statement: Written informed consent was obtained from the patient and her legal guardian for publication of this case report and any clinical information for educational purposes. All identifying details have been anonymized to ensure patient privacy and confidentiality in accordance with ethical standards.

References

1. Imbach L, Kaufmann E, Schulze-Bonhage A. Comparison of the effectiveness of anterior thalamic stimulation in a European registry and a phase III study. Clin Epileptol. 2023;36:150-6.
2. Järvenpää S, Peltola J, Rainesalo S, Leinonen E, Lehtimäki K, Järventausta K. Reversible psychiatric adverse effects related to deep brain stimulation of the anterior thalamus in patients with refractory epilepsy. Epilepsy Behav. 2018;88:373-9.

 doi:10.20944/preprints202601.1049.v1

3. Loenarz C, Ge W, Coleman ML, Rose NR, Cooper CD, Klose RJ, et al. PHF8, a gene associated with cleft lip/palate and mental retardation, encodes for an Nepsilon-dimethyl lysine demethylase. Hum Mol Genet. 2010;19:217-22.
4. Loganathan MA, Enja M, Lippmann S. Forced normalization: epilepsy and psychosis interaction. Innov Clin Neurosci. 2015;12:38-41.
5. Mula M, Kanner AM, Jetté N, Sander JW. Psychiatric comorbidities in people with epilepsy. Neurol Clin Pract. 2021;11:e112-e20.
6. Puranam RS, He XP, Yao L, Le T, Jang W, Rehder CW, et al. Disruption of Fgf13 causes synaptic excitatory-inhibitory imbalance and genetic epilepsy and febrile seizures plus. J Neurosci. 2015;35:8866-81.
7. Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015;84:1017-25.