Paradoxical Worsening Of Seizure Activity With Pregabalin In An Adult With Isodicentric 15 (IDIC-15) Syndrome Involving Duplications Of The GABRB3, GABRA5 And GABRG3 Genes

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CASE REPORT Open Access

Paradoxical worsening of seizure activity with pregabalin in an adult with isodicentric 15 (IDIC-15) syndrome involving duplications of the GABRB3, GABRA5 and GABRG3 genes

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Abstract

Background: Isodicentric 15 syndrome (IDIC-15) is due to partial duplications of chromosome 15 that may includes the q11–13 region that includes genes encoding the α5 (GABRA5) and β3 - γ3 (GABRB3) receptor subunits. The disease causes intellectual and physical developmental delay, seizures, intellectual disability and behavioral disorders that may be related to abnormal GABA receptor function and morphology. Seizures are often severe and may be refractory to treatment. There are however no specific guidelines for the treatment of the seizures and it is unknown whether drugs that affect the GABAergic system have a different effect in IDIC-15 seizures.

Case presentation: We report the case of an adult individual with IDIC-15 whose complex-partial seizures worsened dramatically after the introduction of pregabalin, with increased seizure frequency, frequent generalization, and appearance of new seizure pattern. Her cognitive function and verbal skills also worsened during treatment with pregabalin. Her seizures and cognitive skills quickly improved after pregabalin was discontinued and treatment with lacosamide started.

Conclusion: As her genetic testing confirmed that her region of duplication included GABA receptor encoding genes, it is plausible that the worsening of seizures were due to induction of an abnormal GABAergic response to pregabalin.This case may help define proper therapeutic strategies for the treatment of IDIC-15 associated seizures.

Keywords: IDIC-15, GABA receptors, Pregabalin, Seizures, Lacosamide

Case presentation

The subject of this report is a 53-year-old woman with IDIC-15

- Physical and intellectual developmental delay
- Psychomotor slowing
- Moderately severe intellectual disability
- No autistic behavior
- Mild sleep disorder
- History of Paradoxical agitation and confusion with BZDP
- Seizures first manifested at age 24

Case presentation

Diagnosed in 2001; Cytogenetic analysis evidenced a **large supernumerary IDIC (15)** in all the cells analyzed.

Duplicated Region: 15q11.1 - 13.1

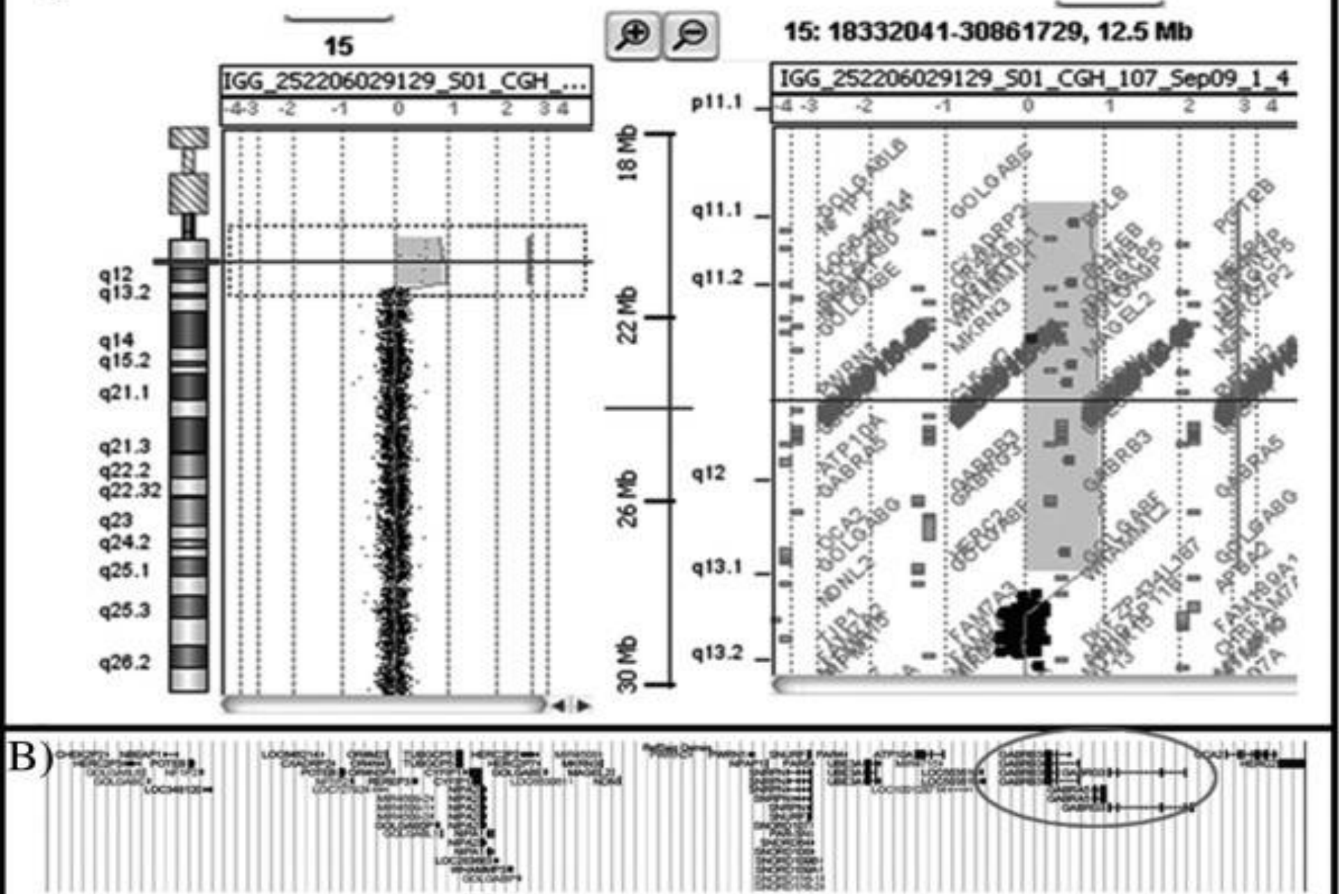
Duplication 8.433 Mb, between oligomers A_16_P02992133 (20,102,541 bp, first duplicated) and A_16_P02998642 (28,535,051 bp, last duplicated)

Gaba-receptor encoding genes

GABRB3 (gamma-aminobutyric acid A receptor, beta 3, MIM 137192),

GABRA5 (Homo sapiens gamma-aminobutyric acid A receptor, alpha MIM 137142)

GABRG3 (gamma-aminobutyric acid A receptor, gamma 3 MIM 600233)



Array CGH graphical overview of chromosome 15 duplication. The **15q11.1q13.1 duplicated region** extends between probes A_16_P02992133 (20,102,541 bp, first deleted) and A_16_P02998642 (28,535,051 bp, last deleted). B) Gene content of the duplicated region. Genes **GABRB3, GABRG3, andGABRA5** are circled

Case presentation – Seizures 1

- Her seizure disorder first appeared at age 24 when she developed complex partial seizures with staring and blanking-out episodes accompanied by stereotypical head turning or raising of the arms, without loss of muscle tone or falls that typically lasted a few seconds.
- At age 24 she also had an isolated generalized tonic-clonic seizure and was started on carbamazepine.
- Over the years, the complex partial seizures episodes became more frequent and when she was 34 years of age, Lamotrigine was added.
- As the frequency of the complex partial seizures increased, both drugs were kept at a dosing level to sustain serum medication levels at the higher limits of the norm.
- At age 46 oxcarbazepine was initiated and carbamazepine stopped. Stable seizure pattern (3-4 per week).

Case presentation – Seizures 2

At age 50 she had a fall and sustained severe head trauma that caused a large left parietal subdural hematoma and a small frontal contusion.

After emergent surgical evacuation of the hematoma her seizures worsened with complex-partial episodes that occurred daily and up to 2-3 times per day, with more prominent stereotypical hand and arm movements.

The daily doses of oxcarbazepine and lamotrigine were increased until she developed clear signs of drug toxicity with ataxia and imbalance and occasional nausea and vomiting, but with minimal improvement

Case presentation – Seizures 3

A year after the trauma, seizure frequency had decreased but still not at baseline (5-6 / week).

A 3rd drug was deemed necessary and **Pregabalin** was added with doses that were slowly increased to **150 mg/day** in three divided doses.

Soon after she experienced worsening of her seizures:

. Her complex partial crisis became even more frequent and severe (up to 5-6- per day).

-More prominent motor automatisms Longer (up to 15 - 20 sec.)

- followed by several minutes of obtundation and aphasic garbled speech.

A new seizure pattern also developed,

with **atonic seizures** characterized by sudden arrest and falls with altered level of consciousness and atonia.

The dose of **Pregabalin** was then increased to the maximum tolerated dose of **300 mg daily** in three divided doses, and her seizures became even more severe.

Within days:

four episodes of **generalized tonic-clonic seizures** that lasted up to five minutes and were followed by prolonged post-ictal confusion, while continuing to experience frequent complex-partial seizures and atonic seizures.

Case presentation

She had also become **cognitively more impaired**, losing verbal capacity and often appearing obtunded and had become **incontinent** of urine and feces while remaining **ataxic**.

Suspecting that the worsening of seizure and cognition were related to the addition of Pregabalin, the drug was tapered and eventually discontinued

Seizures improved after discontinuing Pregabalin, with no more GTC seizures and reduced frequency and severity of complex partial seizures

Lacosamide was then introduced and increased to a dose of 100 mg twice daily. Within two weeks of the drug change she experienced a dramatic improvement that has lasted now for 2 and ½ years, with 2 to 3 episodes of complex partial seizures per month, milder, limited stereotypies.

Oxcarbazepine and Lamotrigine dosing were decreased with improvement of ataxia.

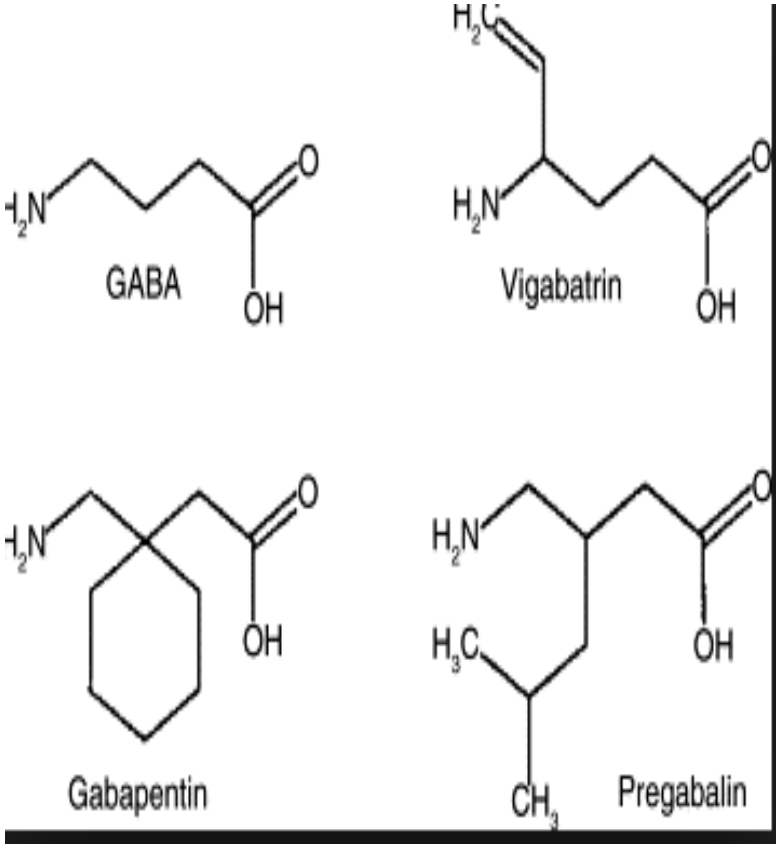
Improved cognition (almost to levels prior to SDH) regaining her prior level of motor performance and continence

Discussion

Pregabalin is a GABA analog, structurally derived from GABA

- Its anti-epileptic effect is mostly mediated by the high-affinity binding to the α2δsubunit of the voltage dependent calcium channel .

- In human motor cortex pregabalin produces a physiological effect similar to that of GABAergic drugs and the drug affects the GABA transporter GAT-1, increasing neuronal GABA uptake



Discussion

Was this real drug-induced exacerbation?

- Temporal pattern: started with medications introduction, worsening with dose increase, and improvement with withdrawal support drug-induced mechanism
- Unlikely related to prior trauma, natural evolution or history.

Increased of seizure activity and modification of seizures patterns reported with other GABAergic drugs (vigabatrin and tiagabine) and non-GABAergic (levetiracetam).

Gabapentin has been reported to induce life- threatening myoclonic status in a patient with benign adult familial myoclonic epilepsy.

Conclusions

INDIVIDUAL OR SYNDROMIC ?

- Is it possible that at least some individuals with IDIC-15 may not tolerate pregabalin and possibly other GABA analogs or Gabaergic drugs?
- Is prior response to benzodiazepine a predictor of poor or paradoxical response to GABAergic antiepleptics?
- Are some refractory IDIC-15 seizures related to medications?

- Lacosamide, and presumably other ionic pump inhibitors may instead be safer and more effective in subjects with IDIC-15.

QUESTION:

Should we plan PET - SPECT Imaging Studies?

Selective GABA radioligands are available, small study can define pattern of distribution of these receptors in the brain, changes in receptor binding physiology. This may have immediate practical implications

This could help during various physiologic activities or resulting from pathologic conditions can be visualized.

DATABASE AND CLINICS NETWORK TO DEFINE PRACTICE PARAMETERS?

Define best practice for diagnosis and treatment of seizures, sleep, behavior, rehabilitation, GI problems, etc.

Define possible treatment risks (GABAergic drugs?)

Time to update medical literature - review article (A. Battaglia, Orphanet J Rare Dis. 2008 Nov 19;3:30. doi 10.1186/1750-1172-3-30.2008)

Alert cards for children and families?

IDIC-15 Aging and Seizures

- Seizures may appear in adulthood (age 24) and evolve with age

- No intellectual or motor decline into advanced middle age, now 55 yo (unlike Down and other syndromes)

- Normal brain morphology at MRI (no atrophy)