ELECTRO-CLINICAL PATTERN OF EPILEPSY IN A CHILD WITH ANKRD11 MUTATION ASSOCIATED WITH KBG SYNDROME: CASE REPORT OF DRUG-RESISTENT EPILEPSY

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INTRODUCTION

Epilepsy is a common neurological disorder affecting more than 70 million people around the world. It is the most common neurological disorder in the pediatric population, affecting 1% to 3% of children, and is defined as any disorder in which spontaneous recurrence of unprovoked seizures is the main symptom. A seizure is usually defined as a sudden alteration of behavior due to a temporary change in the electrical functioning of the brain, that continuously generates tiny electrical impulses in an orderly pattern. The etiology of epilepsy can be different, including structural, genetic, infectious, metabolic, and immune causes, but most often the cause is unknown, that is when it refers to the so-called idiopathic epilepsy, which occurs in 40% of people with epilepsy. Despite the recent introduction of new antiepileptic drugs (AEDs), about one-third of epilepsy patients have drug-resistant (refractory) epilepsy, affecting about 30% of children with epilepsy.

Refractory epilepsy, which is the most severe form of epilepsy, according to the International league against epilepsy (ILAE), is defined as failure to control seizures when using two or more appropriately chosen and tolerated antiepileptic drugs (as monotherapy or in combination) during an appropriate period. Severe and refractory epilepsies in children affect their cognitive function, leading to worsening of the prognosis, serious psychosocial consequences, difficulties in care and quality of life, anxiety in the family, as well as an increase in the risk of death, including unexpected death in epilepsy (SUDEP).

The expansion of genetic research and technologies in recent years and the advances in next-generation sequencing (NGS) have shown that a large proportion of unexplained epilepsies, especially idiopathic ones, have a genetic basis. Numerous epilepsy genes helped the understanding of mechanisms underlying epileptogenesis and guided the development of treatments.

ANKRD11 gene functions as a co-regulator in the developing brain. The role of the *ANKRD11* gene in neurodevelopment was suggested by subsequent reports of individuals with intellectual disability, facial dysmorphism, and ASD. In 1975, *Herrman et al.,* first described the KBG syndrome, a neurodevelopmental autosomal dominant disorder, caused by the haploinsufficiency of the *ANKRD11* at 16q24.3 locus due to heterozygous pathogenic variants or chromosomal imbalances/rearrangement such as point mutations, duplications or microdeletions involving this gene.

KBGS is characterized by global developmental delay (DD), intellectual disability (ID), learning difficulties, neurobehavioral problems, short stature, macrodontia, facial dysmorphism, skeletal anomalies, and multiple congenital anomalies, sometimes associated with seizures, delayed closing of fontanels and electroencephalo-

graphic (EEG) abnormalities. So far, there have been reported more than 200 cases of KBG syndrome.

The diagnosis of KBG syndrome is established, by the most commonly used criteria of *Skjei et al.* and *Low et al* . A diagnosis of epilepsy, a major criterion, according to *Skjei et al* ., and a minor criterion according to *Low et al* . has been reported in approximately 30% of patients in a systematic review of 140 patients with KBG syndrome. The onset of epilepsy is predominantly between infancy and mid-teens and seizure remission occurred in the majority after adolescence with good response to AEDs. Heterogeneous seizure types have been reported, with tonic–clonic seizures, absences, myoclonic seizures, and unclassified sleep-related seizures with motor symptoms being most common, but no specific epilepsy syndrome has been identified.

Detailed classification of the seizures, epilepsy type, or syndrome was only made in 26 patients from 12 studies. Only two patients had an epilepsy syndrome classification. No genotype–phenotype correlation studies have been performed for the presence and type of epilepsy in patients with KBG syndrome. Generalized epilepsy with febrile seizures plus (GEFS+) is reported in a de novo mutation of the *ANKRD11*gene, with a clinical phenotype compatible with KBG syndrome.

A systemic review of epilepsy and EEG anomalies in subjects with KBG syndrome is deficient. *Samanta* first described in a patient an intermittent bisynchronous temporo-occipital rhythmic delta activity and episodes of staring spells with no EEG changes suggesting that these findings may be specific to KBG syndrome. Here, we report a patient with a severe neurological phenotype of KBG syndrome associated with a novel heterozygous frame-shift de novo variant in the *ANKRD11* gene, to contribute to identifying a specific electroclinical pattern of KBG syndrome.

CASE REPORT

We report on a 16-year-old boy, referred to our department for afebrile unprovoked seizures. He was born at term by spontaneous vaginal delivery, of healthy unrelated parents, and with uneventful perinatal and postnatal clinical course. He did not experience febrile convulsions, traumatic brain injury, or central nervous system infections. Over time he was found to have a mild global learning difficulty that improved over time with occupational therapy. He was reported by the parents to be a very shy, quite timid, reticent, and solitary person. Also, stereotype and behavioral changes were noted. Emotional and social difficulties were reported by the family. During clinical assessment, craniofacial dysmorphic features of KBG syndrome were noted. Regarding the neurologic and behavioral aspects, the patient had mild intellectual disability, learning difficulties, and neurobehavioral problems such as attention deficit hyperactivity disorder (ADHD) since childhood. However, he was able to participate in normal school life without any help.

Targeted exome sequencing (TES) of 4800 clinically significant genes was performed and a pathogenic heterozygous variant, NM_001256183.2: c.4407dupG, frameshift, was identified in ANKRD11, c.4407dupG, (p. Arg1470GlufsTer84). As the parental genetic tests revealed that the parents did not have this frameshift, the variation was identified as a de novo variant. This variant was categorized as pathogenic by the American College of Medical Genetics and Genomics (ACMG) guideline (PVS1, PS1, PS2, and PM2) and has not been reported earlier. The variant is absent from control sequences (Genome Aggregation Database (gnomAD) and no alternative plausible variants or known mutations were identified as competing possibilities in this patient.

Seizure type	**EEG abnormalities**	**Age**	**AEDs**	**Seizure frequency**
GTCS	Multifocal discharges	8 yo	VPA	First seizure
GTCS + FS	Focal/ multifocal bursts	9 yo	VPA+ LTG (ex, ar) + ACZ	1-2 /month
Stabilization	No abnormalities	9-11 yo	VPA + ACZ	
GTCS One FS	Focal bursts	11 yo	VPA+ ACZ + LEV	1-2 /week

Seizure type	EEG abnormalities	Age	AEDs	Seizure frequency
GTCS	Focal /multifocal bursts	12 yo	VPA + ACZ + LEV	1/month
FS	Multifocal paroxysmal discharges	13-15 yo	VPA + ACZ + LEV LEV – ex	1/week
GTCS	Multifocal bursts	15 yo	OXC (ex,ar)+ TPM VPA – ex ACZ – ex	1/week
GTCS	Multifocal bursts	16 yo	TPM - ex + LTG	2-3/month
GTCS	Multifocal bursts	nowadays	LTG	2-3/year

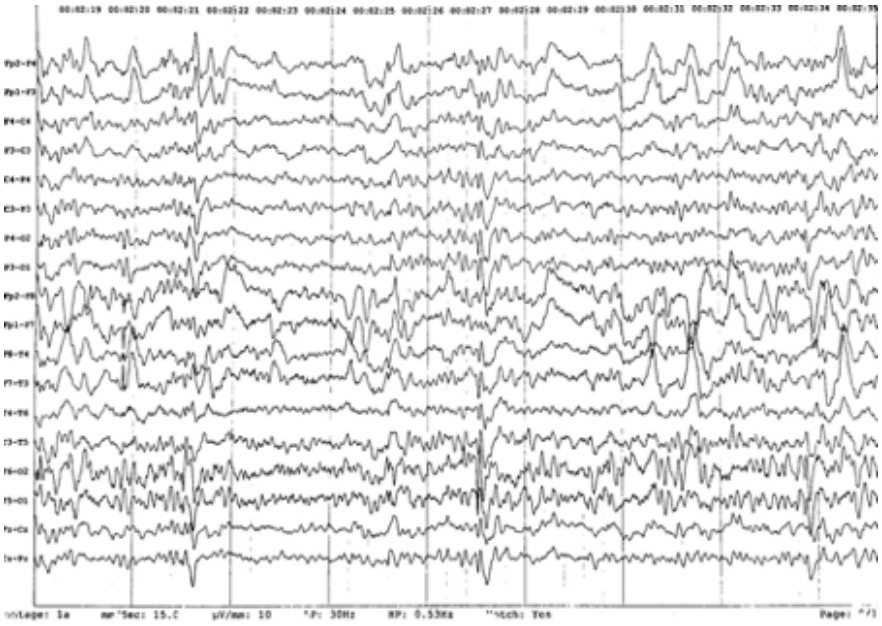
Table 1 : Electroclinical characteristics of epilepsy

Abbreviations: Generalized tonic-clonic seizures= GTCS, focal seizures= FS

Sodium valproate/valproic acid=VPA, Lamotrigine=LTG, Acetazolamide=ACZ, Topiramate=TPM, Levetiracetam=LEV, Oxcarbazepine= OXC

Allergic reaction=ar, years old=yo, excluded=ex

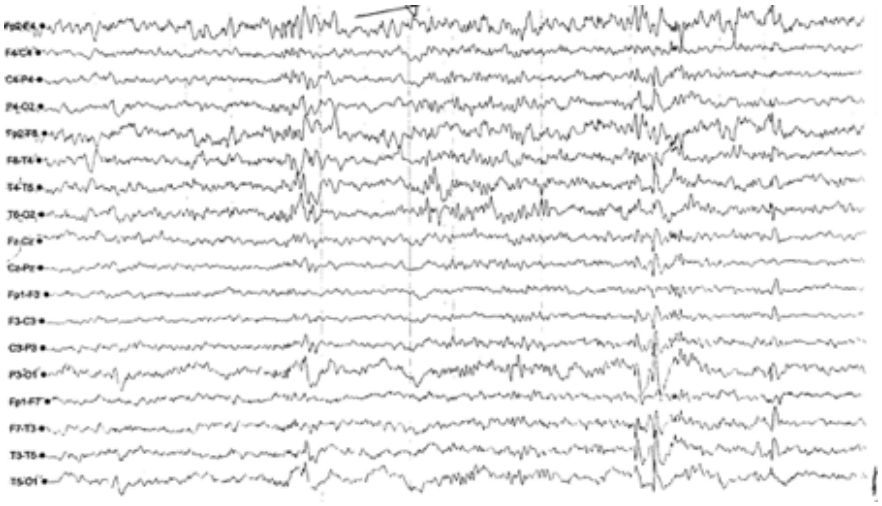
His first seizure was a generalized tonic-clonic seizure by description and occurred at the age of 8 years, when he was admitted in our clinic, department of neurology. The first wakefulness interictal EEG showed regular alpha activity, associated with occasional multifocal paroxysmal bursts of high voltage spike-wave complexes (*see* picture 1). Treatment with sodium valproate was started. Initially, there were 1-2 generalized tonic-clonic seizures per month on average, by the age of 9.



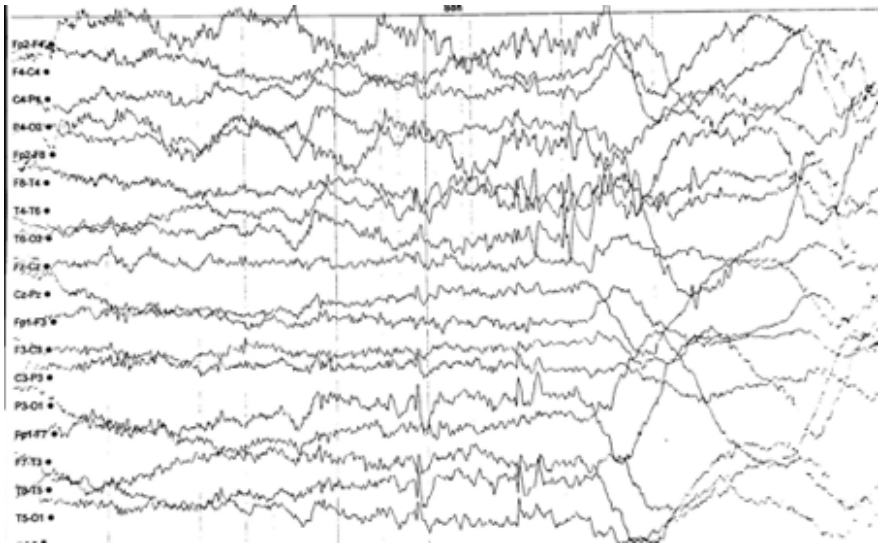
Picture 1. Wakefulness interictal EEG showing occasional multifocal paroxysmal bursts of high voltage spike-wave complexes.

Stabilization of seizures was not achieved, there were also focal seizures. Therefore, a second AED, lamotrigine, was added to the treatment. Regarding the allergic reaction due to lamotrigine, it was discontinued,

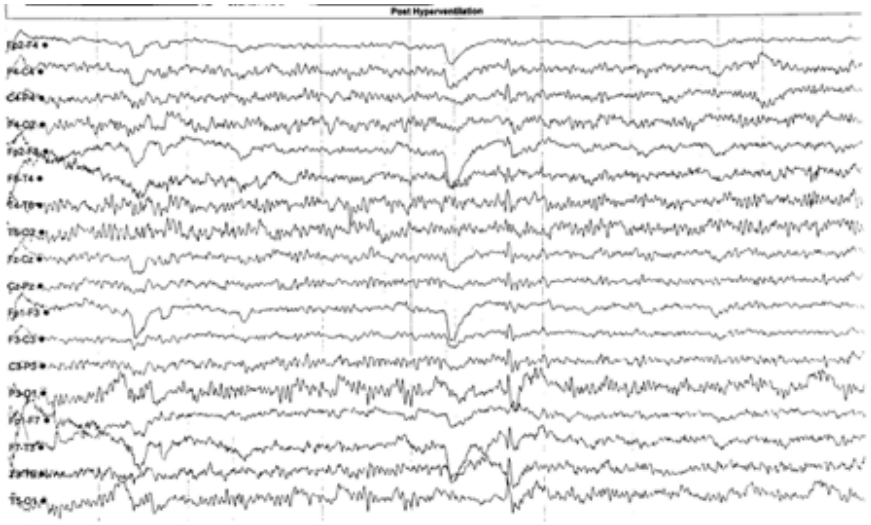
and the treatment included acetazolamide. During this period the EEG findings in wakefulness and post-hyperventilation, showed occasional multifocal mainly bitemporal bursts of spike-and-waves, while on sleep EEG revealed occasional multifocal left-sided frontotemporal and parietooccipital spike-and-waves bursts (*see* pictures 2, 3, 4).



Picture 2. Wakefulness EEG showing occasional focal bitemporal bursts of spike-and-waves.



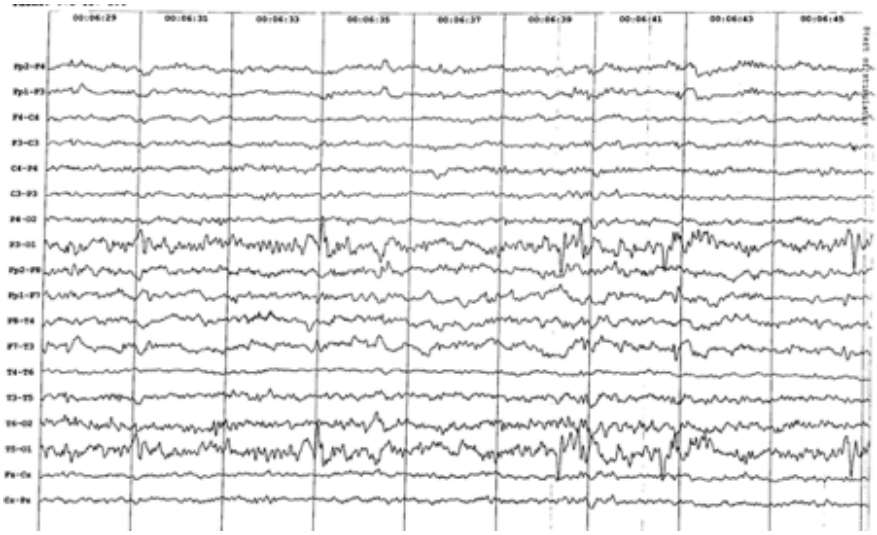
Picture 3. Sleep EEG showing occasional multifocal left-sided frontotemporal and parietooccipital spike-and-waves bursts.



Picture 4. Post-hyperventilation EEG showing occasional multifocal mainly bitemporal bursts of spike-and-waves.

A period of seizure freedom occurred from age 9 to 11 occurred after commencing acetazolamide. There was no history of absence seizures or myoclonic seizures, meanwhile, episodes of staring spells with no EEG changes were noted. The follow-up wakefulness EEG findings showed stabilization, meaning a regular brain activity of alpha rhythm with isolated right-sided spike-and-wave bursts.

Thereafter, followed a period of frequent twice-a-week generalized tonic-clonic seizures and one focal epileptic seizure. Levetiracetam was included in the antiepileptic treatment. Repeat wakefulness EEG findings showed focal bursts of left-sided parieto-occipital and temporal spike-wave discharges. (*see* picture 5). Epilepsy protocol magnetic resonance imaging of the brain was normal.

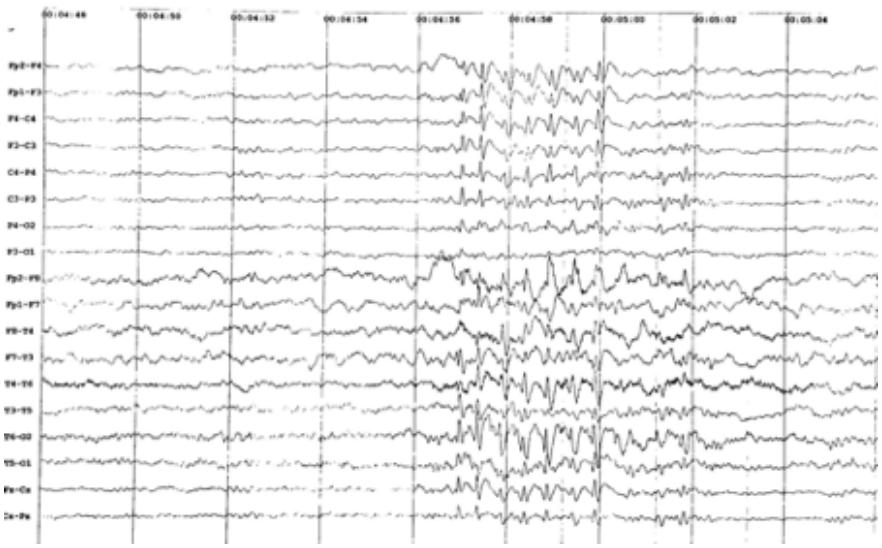


Picture 5. Wakefulness EEG findings showing focal bursts of left-sided parieto-occipital and temporal spike-wave discharges.

During a period of a year, the boy had one tonic-clonic generalized seizure per month, and no focal seizures

were noted. The wakefulness EEG findings revealed basic brain activity of regular alpha rhythm with intermittent photic stimulation and hyperventilation activation of focal bursts of frontal and temporal spike-and-waves.

A round two-year period of focal seizures followed, and the wakefulness EEG findings showed regular alpha activity with multifocal bilateral paroxysmal discharges of spike-and-wave 2 c/s, lasting 3-4 seconds (*see* picture 6).



Picture 6. Wakefulness EEG findings showing multifocal bilateral paroxysmal discharges of spike-and-wave 2 c/s, lasting 3-4 seconds.

The patient was not seizure-free for a long period of time. He had tonic-clonic generalized epileptic seizures once a week in the following years. In the epileptic treatment another AED, oxcarbazepine, was added. The EEG findings during this period showed focal bursts of right-sided spike-and-wave. After a short period of time, exactly a two-week period, oxcarbazepine was excluded, due to allergic reaction regarding the drug, and topiramate was added. Valproate was excluded from the treatment.

The period that followed was characterized by 2-3 tonic-clonic generalized epileptic seizures per month. Topiramate was excluded and lamotrigine was added. No allergic reaction was noted. For a short period of a few months, he was seizure-free. Now the patient is on treatment with lamotrigine, he is not seizure-free completely, but stabilized and has only a few seizures per year. The follow-up wakefulness EEG findings showed regular beta rhythm with right-sided multifocal bursts of spike-and-slow waves.

His seizures proved difficult to control from age 12 when generalized tonic-clonic seizures recurred reaching a frequency of up to 2-3 seizures per month, despite trials of lamotrigine, levetiracetam, and topiramate. A trial of topiramate in combination with lamotrigine led to a marked reduction in seizure frequency, reducing to three generalized tonic-clonic seizures in the year following treatment initiation.

DISCUTION AND CONCLUSION

Epilepsy and EEG abnormalities are frequently reported in KBG patients. Most often present with generalized or combined generalized and focal epilepsy with onset in childhood. Literature data are limited, incomplete, and inconclusive to identify a specific electroclinical pattern. Various seizure types have been reported in the literature, with tonic-clonic generalized seizures being the most frequent seizure types. Focal seizures are also rarely noted. Moreover, many cases of generalized and focal EEG abnormalities without clinically evident seizures have been reported. In most of the KBG syndrome patients with epilepsy,

seizures are drug-resistant. Moreover, epilepsy in patients with KBG syndrome is associated with poorer developmental outcomes.

We report a boy presenting with a drug-resistant, monogenic epilepsy syndrome, due to ANKRD11 pathogenic de novo variant found by TES associated with the KGB syndrome. This variant has never been reported so far in the literature. The reassessment of phenotypic features confirmed that he fulfilled the proposed diagnostic criteria for KBG syndrome.

We outline the electroclinical pattern of epilepsy in KBGs, types of the epileptic seizures and EEG features of this patient. He suffered from focal to tonic-clonic seizures, treated with various AEDs, making a drug-resistant epilepsy diagnosis. Even though our result cannot be conclusive, we hypothesize that the represented EEG pattern together with the epilepsy and seizure type, dysmorphic facial features, ID, and behavioral disorders, may help to characterize the phenotype of KBG syndrome. Future studies regarding these issues may outline the electroclinical pattern in a larger series of patients with KBG syndrome.

AUTHORS CONTRIBUTIONS

LAA had main contribution in literature search, writing and drafting the manuscript. All authors contributed in the diagnosing, treatment, and follow-up of the patient, edited the manuscript. All authors approved the final version.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to disclose.

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AVAILABILITY OF DATA

The data of the current case report are available from the corresponding author on reasonable request.

CONSENT

The case report protocol was performed in accordance with the Declaration of Helsinki.

INFORMED CONSENT

Written informed consent was obtained from the patient's parent to publish this report in accordance with the journal's patient consent policy.

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