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KABUKI SYNDROME AND EPILEPSY

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ABSTRACT

Background: Kabuki syndrome is a rare disease. In 2018, a global consensus on diagnostic criteria for Kabuki syndrome (KS) was published, diagnosing KS both with and without molecular genetic confirmation. Neurological symptoms are a major clinical problem in more than 80% of cases. Seizures occur with a frequency of 10% to 40% in Kabuki syndrome. Various degrees of severity of epilepsy in KS have been reported. There are isolated cases of West syndrome in KS worldwide.
Objective: To investigate the frequency of epilepsy in KS and the features of West syndrome comorbid with KS, using evidence from reviews and describing the clinical presentation based on the history of a patient with molecularly positive KS.
Methods: The study design was a two-centre retrospective observational study. Study subjects were paediatric patients with genetically verified KS. We conducted our own observation of 4 patients with KS and detailed a clinical case of a male patient with West syndrome in KS.
Results: Epilepsy was found in 2 patients. Onset of epilepsy at 1.5 and 20 months of age. Both cases were characterised by a severe course of epilepsy. A rare form of epilepsy in KS, West syndrome, was described in patient M. Initial complaints included first seizures and delay in psychomotor development from 1.5 months of age. The clinical features of West syndrome, an electroencephalographic image, MRI of the brain, and the patient's seizure management were presented.
Conclusion: Epilepsy in KS is not an uncommon clinical symptom that exacerbates the underlying disease. KS in combination with West syndrome exacerbates neurological deficits and leads to a significant delay in psycholinguistic and psychomotor development against a background of low efficacy of medication and differential effects of hormones and ketogenic diet.

Keywords: Kabuki syndrome, epilepsy, west syndrome, KMT2D gene, ketogenic diet, antiepileptic drugs

Introduction

KS is a rare genetic disorder characterised by specific facial morphological changes, growth restriction, various malformations, and varying degrees of intellectual disability.[1] The syndrome was described independently by the Japanese scientists Nikawa and Kuroki in 1981.[2] The syndrome affects one in 32,000 newborns in Japan and one in 86,000 in western countries. According to 2018 data, there are about 1,000 known patients with this syndrome around the world.

In terms of mutation type, studies in neuroscience and genetics distinguish two types of KS: in the *KMT2D* and *KDM6A* genes.

KS type 1 mutation (KABUK1) (# OMIM 147920) is an autosomal dominant inherited KS associated with the *KMT2D* gene (also known as MLL2), which encodes lysine-specific methyltransferase 2D. The *KMT2D* gene is located on chromosome 12q13.12. The mutation leads to the first type of disease (KS1) with an autosomal dominant inheritance pattern. It is detected in 70% of patients.[3]

The second type of KS mutation (KABUK2) (# OMIM 300867) is an X-linked disorder caused by heterozygous pathogenic mutations in a gene encoding histone demethylase that interacts with *KMT2D*. The *KMT2D* gene is located on the X chromosome (Xp11.3). It represents approximately 5% of clinical pathology cases.[4]

The diagnosis of Kabuki syndrome is made based on clinical criteria. Five cardinal signs have been proposed for this disorder.[5]

Typical facial phenotype (100%) - long eye slits, long eyelashes, elongated palpebral fissures with inversion of the lateral third of the lower eyelid (ectropion), broad nasal bridge, flat nasal tip, large protruding ears, arched and broad eyebrows with the lateral third sparse or notched, low hair growth.

Table 1. Epilepsy in KS.

No	Age	Gender	Genetics	Diagnosis of epilepsy	Age at onset of epilepsy	Frequency of seizures	Type of seizures	History of AEDs
1	8.2	Female	mutation in the *KMT2D* gene	Focal epilepsy, structural and genetic	20 months	3-4 times a week	complex partial seizures/ status epilepticus	phenobarbital, valproic acid, frizium, lamotrigine, levetiracetam
2	3.5	Male	mutation in the *KMT2D* gene	epilepsy, West sendrome	1,5 months	once or twice per day	spasms	Vigabatrin, Levetiracetam, Valproic acid

In one case, West syndrome is a rare variant of epilepsy in KS.

Table 2. Genetic test result of patient M.

Gene	position	nucleotide	Amino Acid	GnomAD	zygosity
KMT2D	49433219	c.8228A>C	p.Q.-2743-P	0	heterozygous

The identified mutation is described in the academic literature, and is a characteristic feature of Kabuki syndrome. In genetic testing of the parents, the child's father, who was phenotypically and clinically healthy, had a similar mutation. Later, genome sequencing was conducted. No mutations were found in suspected disease-related genes

Skeletal anomalies (92%) - cranial pathology and microcephaly, high arched or gothic palate, cleft lip/palate, dental problems (large gaps between teeth, inadequate natural healthy teeth and malocclusion), growth restriction, short fingers (especially the fifth), sacrococcygeal pits (epithelial coccygeal passage), improved joint mobility, scoliosis.

Dermatoglyphic anomalies: persistence of foetal fingertip pads (93%).

Variations in degrees of mental delay (92%). IQ test takers average scores are between 60 and 80. Neurological symptoms are a major clinical problem in more than 80% of cases.

Postnatal growth deficiency (83%). The nervous system is characterized by mental delay, epilepsy, developmental delays, and hypotonia. Children with KS are more likely to have autistic disorder.

Epilepsy occurs in KS with a frequency of 10% to 40% 6. Epilepsy occurs in all age groups; girls are more prone to it. Various forms of epilepsy in patients with KS have been described in the literature. Different severities of epilepsy have been reported in KS.

In general, epilepsy in patients with KS responds well to drug treatment, but drug-resistant seizures occur, especially in West syndrome. When KS is comorbid with West syndrome, it exacerbates neurologic deficits and causes a significant delay in psycholinguistic and psychomotor development.

However, due to the rarity of KS and the descriptive compilation of previously collected evidence for epilepsy in the clinical picture, rare cases of severe forms of epilepsy should be included in this clinical picture.

Objective: to investigate the frequency of epilepsy in KS and the characteristics of West syndrome comorbid with KS using evidence from reviews and describing the clinical presentation based on the history of a patient with molecularly positive KS.

Methods

The study design was a two-centre retrospective, uncontrolled, open-label observational study. The study subjects were paediatric patients with genetically verified KS. The research topic was epilepsy in KS.

The research team consisted of researchers and physicians (neurologists and epileptologists).

We conducted our own observation of 4 patients with KS and described in detail a clinical case of a male patient with West syndrome in KS.

Literature review and article selection

The study was based on scientific articles on children with KS and a specific epileptic syndrome, West syndrome. A literature search was conducted in global and local databases. We searched the OMIM, PubMed, Scopus and e-library databases for relevant material. We looked at articles describing cases of epilepsy in KS. The primary analysis included 200 publications; abstracts were excluded from further analysis. We selected 12 publications for full review, some of which described clinical cases of West syndrome in Kabuki syndrome.

Clinical case

We conducted our research and investigated the symptoms of West syndrome in a patient with molecularly positive KS and a *KMT2D* gene mutation. We studied the characteristics of the dynamics of the epileptic syndrome and the cognitive and physical development of the child. We investigated the efficacy of drug therapy and treatment with the ketogenic diet.

Ethical Approvals

The Ethics Committee of Almazov National Medical Research Centre approved this project on 07.05.2020 under the number CEV2020-P4-20. Parents of the patient signed a consent form that allowed the publication of the content. The eyes must not be covered as this is one of the main signs of the disease. The patient's parents have consented to the publication of the photograph.

Results

In 2018, a global consensus on diagnostic criteria for KS2 was published, in which the authors emphasised the importance of diagnosing KS both with and without molecular genetic confirmation. Epilepsy can be attributed to a characteristic lesion of KS[2]. Epileptic seizures with KS occur in a wide age range from infancy to primary school age. The focal form of epilepsy predominates.

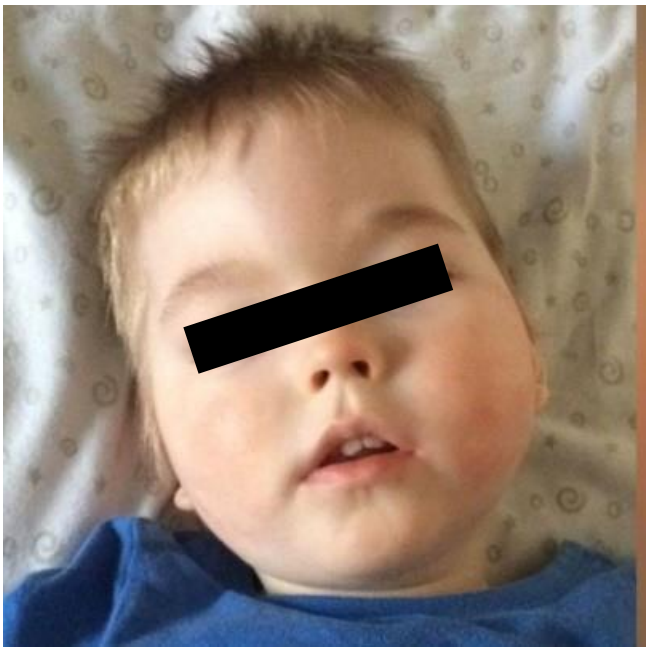

Figure 1. A patient with a mutation in the *KMT2D* gene

The descriptions of West syndrome in patients with KS are unique in scientific publications. A case of tonic seizures within West syndrome in patients with KS was described by A. Mitsudome et al. in 1997 in a six-month-old boy[6]. A. Ogawa studied epileptic seizures in nine patients with Kabuki syndrome. Generalised seizures were found in four cases and in two patients - complex partial seizures with a transition to secondary generalised seizures. One patient was diagnosed with West syndrome, representing 11.1 %, and one patient had atonic seizures[7]. Ito et al. presented an observation of West syndrome in a 6-month-old girl with Kabuki syndrome combined with mental delay and tonic infantile seizures that occurred at nine months of age[4]. At two years of age, mental delays continued to appear on examination.

Researcher's own observations

In response to the lack of information on the clinical manifestations and outcome of West syndrome treatment in patients with Kabuki syndrome, a described clinical observation is of interest.

Three girls and a boy aged 3, 4, 8.2 and 3.5 years, respectively, were included in the study. The mean age was 4.7 years. The ratio of boys to girls was 1: 3. The median age at epilepsy onset was 4.2 months. All patients met the diagnostic criteria for KS. 2 out of 4 children were diagnosed with epilepsy: a 3.5-year-old boy and an 8.2-year-old girl. In both cases, a severe course of epilepsy was observed (Table 1).

Clinical case

We present our clinical observation to illustrate the clinical dynamics and effective treatment of West syndrome in patients with KS2 (Figure 1).

Patient M. was observed at the Children's Consultative and Diagnostic Centre at the age of one and a half months. The first complaints were related to the first seizures and delays in psychomotor development.

Anamnesis morbi

In a 1,5-month-old baby boy, brief tensing and flexion episodes of the arms and legs (lasting about 3-4 seconds) occurred two to three times a day when he was asleep and

less frequently when he was awake. They were accompanied by a turning of the head and a turning of the eyes to the side and upward. The number of paroxysms was recorded each day.

Medical history

The boy was born to young parents who were pregnant for the second time, an abnormal pregnancy. This was an unrelated marriage. The first pregnancy ended in a miscarriage. From the 30th week of pregnancy, fetoplacental insufficiency, mild gestosis, oligohydramnios and gestational diabetes mellitus were detected. The delivery was the first. Labour was rapid and induced. The birth weight was 3130 g, the body length - 50 cm. The Apgar scores were 7 and 7 at 1 and 5 minutes. The baby boy was discharged on the fourth day of life. During the first months of the new-born baby, a pronounced developmental delay was determined: the infant did not fix the gaze, did not respond to others, had poor emotional development, apathy, did not roll over, did not react to toys.

Somatic status. The baby boy had Coombs-negative hemolytic anemia, biliary tract disorders (hepatomegaly, elevated alpha-fetoprotein, cyanocobalamin in the blood, alkaline phosphatase), dysgammaglobulinaemia, pyelectasis.

Phenotypically, the child had facial signs of KS: long palpebral fissures, ectopia elongated lower eyelids, arched eyebrows with sparseness of the lateral third, a wide nasal bridge with a flat tip, a high-arched palate, hypermobility of the joints, foetal finger pads, brachydactyly.

Neurological status

Marked delays in psychomotor development, convergent strabismus, left-side spasmodic torticollis, spastic tetraparesis with an emphasis in the left extremities, and deep tendon reflexes in the extremities (S> D), and Babinski's sign (+) were determined.

Medical examination

According to neurophysiological tests: a routine EEG, video EEG monitoring, the pattern of modified hypsarrhythmia with regional accent in the left temporal lobe was determined at 1.5 months of age (Figure 2). Ictal EEG patterns were not recorded.

Based on EEG data, age of onset and seizure semiology, the boy was diagnosed with West syndrome.

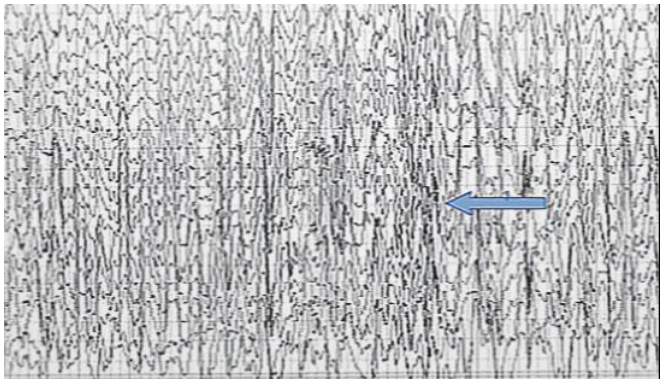

Figure 2. EEG of patient M. with type 1 Kabuki syndrome at the age of 1.5 months. A pattern of modified hypsarrhythmia with a regional accent in the left temporal lobe (blue arrow).

Taking into account the phenotypic characteristics, genetic testing was recommended. The patient was admitted as an inpatient. A complementary examination was performed in the hospital setting. MRI showed pathological changes in the brain (Figure 3).

Genetic testing excluded mitochondrial disorders. The epilepsy gene panel was negative.

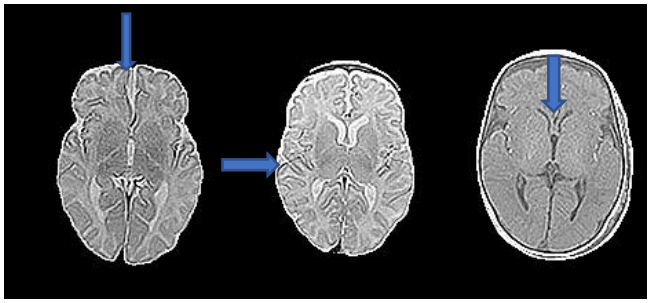

Figure 3. MRI of patient M. with type 1 Kabuki syndrome at the age of 1.5 months. Atrophic changes occurred in the frontal and temporal lobes of the brain and the terminal zones of myelination of the brainstem and the posterior part of the internal capsule, hypoplasia of the corpus callosum (blue arrow).

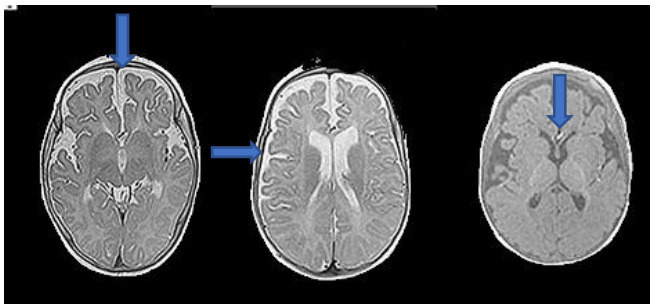

Figure 4. MRI of patient M. with type 1 Kabuki syndrome at the age of 9, 5 months. Atrophic changes of the brain. The dynamics showed an increase in atrophic changes in the frontal and temporal lobes in a substitution pattern (blue arrow).

Disease dynamics

A short course of hormone replacement therapy was administered as an inpatient and showed marked positive dynamics and a strong tendency to reduce the number of seizures. However, due to increased ALT and AST, hormone therapy had to be discontinued and seizures recurred with the same frequency.

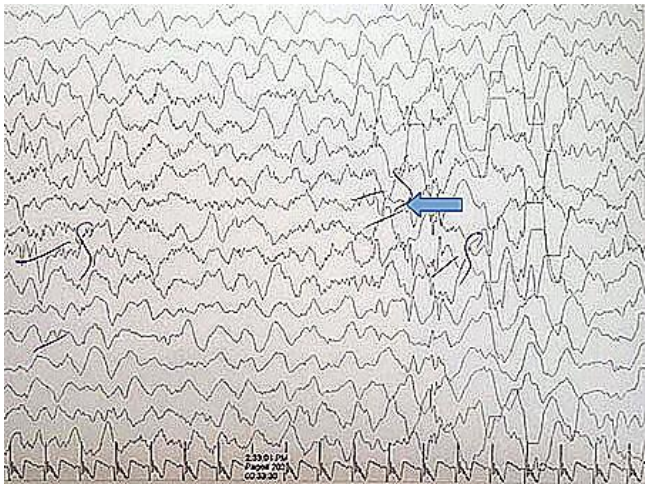

Figure 5. EEG of patient M. with type 1 Kabuki syndrome at the age of 10 months. Occasional slow waves and epileptiform activity in the left temp (blue arrow).

Antiepileptic treatment was chosen: Vigabatrin 600 mg / day, Levetiracetam 150 mg / day, Valproic acid 80 mg / day. Vigabatrin treatment initially helped to reduce the frequency of seizures. However, later on the seizures recurred daily with the same frequency. The seizures occurred once or twice a day. At the same time, there was a severe delay in motor and psycholinguistic development.

Disease dynamics

When M. was between 7 and 8 months old, he was examined as an inpatient: MRI (Figure 4), EEG (Figure 5).

Genetic testing was continued. As a result of exome sequencing, a mutation of the *KMT2D* gene was found within the chromosome (Table 2).

At eleven months, the first baby boy's emotional responses appeared: he hummed, smiled, and the "animation complex" was established. However, there was still a pronounced delay in motor and psycho-speech development, seizures occurred one to two times daily. Since the age of fourteen months, due to failure of AED treatment, the ketogenic diet was started. Against its background, a distinct decrease in seizure frequency was observed to one in three days, as well as an improvement in psychoemotional status and positive dynamics in motor development. Currently, at two and a half years of age, the boy's phenotype characteristics of Kabuki syndrome, a marked delay in psycho-speech and psychomotor development, convergent strabismus, spastic tetraparesis with an emphasis in the left extremities, retraction of the Achilles tendon, and Babinski's sign are still retained in neurological status.

Currently, the patient is receiving oxcarbazepine 240 mg once daily - 21.8 mg per kg, clonazepam 0.5 mg once daily - 0.45 mg per kg, and a ketogenic diet. This combination reduced the frequency of seizures to three paroxysms per month. The ketogenic diet made it possible to stop taking vigabatrin without any negative change in the number of paroxysmal episodes and contributed to the reduction of seizures. The boy began to recognise his parents, he cooed and his motor activity increased. However, his health condition remained serious.

The patient underwent genetic tests. The diagnosis was Kabuki syndrome-1 (molecular positive, *KMT2D* gene mutation)

As a result of a comprehensive investigation, the patient was diagnosed with KS (*KMT2D* gene mutation). Genetic focal drug-resistant epilepsy, a transformation of West syndrome. Severe spastic tetraparesis. Hypoplasia of the corpus callosum. Severe motor and psycholinguistic developmental delays. One of the symptoms is partial optic atrophy.

Discussion

Therefore, the study found that the incidence of epilepsy in KS was 50%, which is slightly higher than in the literature, but the validity of the study data is limited by the small sample of patients with rare disease.

It is interesting to note that this study is less quantitative than qualitative. There is limited data on West syndrome comorbid with KS, which highlights the importance of this clinical observation.

This rare genetic disorder in the population has been identified using advanced genetic research, exome sequencing. An interesting feature of this observation is that the patient's father is phenotypically and clinically healthy, despite having heterozygous germline mutations in the characteristic trait of KS on the X chromosome.[1]

Researchers have sporadically described similar cases.[4,8,9] According to our observation, the combination of KS with West syndrome resulted in a severe delay in psycholinguistic and motor development, which is not typical for KS under such poor conditions. KS in combination with West syndrome exacerbates neurological deficits and leads to the development of severe psychlinguistic delays together with motor developmental delays.

It should be noted that MRI does not show gross brain dysgenesis, which is often associated with this syndrome.

The features of hormone replacement therapy for West syndrome comorbid with KS in this case was an atypical response to hormone replacement therapy in the form of a marked positive dynamic - a clinically significant reduction in seizure frequency, along with elevated liver enzymes, which we believe is caused by the state of the immune system in KS. However, this response is not typical for KS; effective ACTH therapy of West syndrome comorbid with KS has been described.[9]

Therefore, West syndrome, together with KS, determines the severity of the disease, severe delay in psychomotor development, and mental delay, resulting from both West syndrome and Kabuki syndrome.

Conclusion

Epilepsy in KS is a common clinical symptom. KS comorbid with West syndrome exacerbates neurological deficits and results in severe delay in psycholinguistic and psychomotor development. The special characteristics of supportive therapy for West syndrome in combination with KS are the low efficacy of antiepileptic drugs and the pronounced effect of the ketogenic diet.

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Conflict of interest

The authors report that they do not have relevant conflicts of interest.

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