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Co-occurrence of Beckwith-Wiedemann Syndrome and Familial Long QT Syndrome Type I: A Case Report

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ABSTRACT

Long QT syndrome type I is an autosomal dominant disorder caused by a heterozygous loss-of-function mutation in the KCNQ1 gene, located on chromosome 11p15. This chromosomal region is subject to genomic imprinting and is also implicated in Beckwith-Wiedemann syndrome. This report describes a female patient with inherited long QT syndrome type I, present in her mother and sister, concurrently with Beckwith-Wiedemann syndrome due to hypomethylation in the imprinting control region 2 (IC2). Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) identified hypomethylation at the KvDMR/IC2 locus, while Sanger sequencing confirmed a pathogenic variant in the KCNQ1 gene. Not all individuals harboring both IC2 hypomethylation and a pathogenic KCNQ1 variant exhibit features of both syndromes, and the mechanisms behind this variability remain unclear. Timely diagnosis, coordinated multidisciplinary care, and appropriate therapeutic management are essential for optimal outcomes and optimal growth.

Keywords: Beckwith-Wiedemann syndrome, Long QT syndrome type I, KCNQ1, IC2 hypomethylation

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Introduction

Long QT syndrome (LQTS) is an autosomal dominant cardiac disorder with an estimated prevalence of 1 in 2,500 live births in the general population [1]. Among the 16 identified subtypes, LQTS type I—also known as Romano-Ward syndrome (MIM #192500)—accounts for approximately 38% of all cases. Around 10% of affected individuals carry two pathogenic variants, often presenting with a more severe phenotype. LQTS type I results from a heterozygous loss-of-function mutation in the KCNQ1 gene, which encodes a potassium channel and is located on chromosome 11p15 [2]. On electrocardiography, LQTS1 is characterized by a prolonged QT interval and may lead to torsades de pointes, a form of polymorphic ventricular tachycardia that is more commonly observed in types one and two than in other subtypes. Physical exertion, particularly swimming, or emotional stress may precipitate ventricular arrhythmias, syncope, or sudden cardiac death. Even though not all mutation carriers exhibit clinical symptoms, LQTS remains a notable cause of death, especially among the young. Management involves beta-blocker therapy alongside appropriate lifestyle modifications [3].

Beckwith-Wiedemann syndrome (BWS; MIM #130650) is a congenital overgrowth disorder with an incidence of approximately 1 in 12,000 live births [4]. It is clinically characterized by features such as macrosomia, macroglossia, and neonatal hypoglycemia, along with an elevated risk for developing embryonal tumors,

including Wilms tumor, hepatoblastoma, neuroblastoma, adrenocortical carcinoma, and rhabdomyosarcoma [5–7]. Diagnosis is guided by the updated BWS consensus scoring system **(Table 1)** [8–10], in which cardinal features are assigned 2 points each and suggestive features 1 point. A cumulative score of 4 points confirms a clinical diagnosis, while a score of 2 points indicates the need for molecular testing.

Table 1. Beckwith-Wiedemann syndrome (BWS) diagnostic scoring criteria

Primary (cardinal) features	Secondary (suggestive) features
Enlarged tongue (macroglossia)	Birth weight more than 2 standard deviations above the mean
Excess insulin production (hyperinsulinism)	Facial nevus simplex (salmon patch)
Abdominal wall defect (omphalocele)	Polyhydramnios and/or an abnormally large placenta
Asymmetrical body growth (lateralized overgrowth/hemihypertrophy)	Preauricular ear pits and/or folds
Bilateral/multifocal Wilms tumors or nephroblastomatosis	Temporary episodes of low blood sugar (transient hypoglycemia)
Histological findings such as adrenal cortex cell enlargement, mesenchymal placental dysplasia, or diffuse pancreatic cell proliferation	Embryonal tumors, including hepatoblastoma, isolated Wilms tumor, neuroblastoma, pheochromocytoma, rhabdomyosarcoma, or adrenocortical carcinoma
–	Enlarged kidneys (nephromegaly) and/or liver (hepatomegaly)
–	Umbilical hernia or separation of abdominal muscles (diastasis recti)

Beckwith-Wiedemann syndrome is genetically diverse, arising from a range of alterations affecting growth-regulating genes located on chromosome 11p15. This chromosomal region is under the influence of genomic imprinting and includes two distinct, independently regulated domains: Imprinting Center 1 (IC1), which is typically methylated on the paternal allele, and Imprinting Center 2 (IC2), which is methylated on the maternal allele [11]. In the majority of cases, aberrations in the methylation patterns at one or both of these imprinting centers are observed [12]. Additionally, paternal uniparental disomy (pUPD) accounts for roughly 20% of cases. Approximately 10–15% of patients may exhibit a classic clinical presentation of BWS despite the absence of detectable molecular abnormalities.

All individuals with a confirmed BWS diagnosis should undergo tumor surveillance. Recommended screening includes complete abdominal ultrasound and measurement of alpha-fetoprotein (AFP) levels every three months until the age of 4 years, followed by renal ultrasound every 3 months from ages 4 to 7 years [13].

This report describes a female patient with inherited long QT syndrome type I, present in her mother and sister, concurrently with Beckwith-Wiedemann syndrome due to hypomethylation at the imprinting control region 2 (IC2).

Materials and Methods

This report details the case of a female patient presenting with the rare coexistence of Beckwith-Wiedemann syndrome (BWS) and familial Long QT Syndrome type I (LQTS1), under observation at the Regional Center for Medical Genetics in Bihor since 2022. The clinical diagnosis of BWS was confirmed through molecular analysis conducted at the Bambino Gesù Pediatric Hospital in Rome. Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) revealed hypomethylation at the IC2 locus, consistent with BWS. Further genetic testing at the same institution identified a pathogenic variant in the KCNQ1 gene, inherited maternally: NM_000218.3 KCNQ1:c.604G>A, p.Asp202Asn.

Results and Discussion

The patient is the second-born child in the family **(Figure 1)**. She was delivered at 37 weeks of gestation following an in vitro fertilization (IVF) pregnancy complicated by third-trimester preeclampsia. At birth, her anthropometric measurements were above the 90th percentile, with a weight of 4220 grams and a length of 53 cm. Cutaneous findings included hemangiomatosis. Laboratory investigations revealed significantly elevated alpha-fetoprotein (AFP) levels and severe neonatal hypoglycemia.

The family history is notable for a confirmed diagnosis of LQTS1 in both the patient's mother and older sister. Additionally, the patient's father had a spontaneously resolved atrial septal defect (ASD).

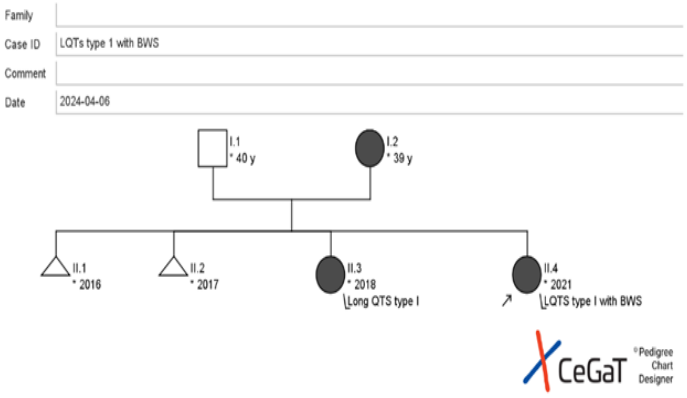

Figure 1. Family tree-index case II.4

Cardiac assessment

The patient underwent a comprehensive cardiac evaluation, including Holter monitoring, which revealed a sinus rhythm with a heart rate of 145 beats per minute. The QT interval was prolonged, exceeding age-appropriate reference values. No arrhythmias or abnormal pauses were detected during the recording. Echocardiographic imaging identified a small atrial septal defect (3 mm, ostium secundum type), accompanied by a left-to-right shunt.

Abdominal findings

Ultrasonography of the abdomen demonstrated an enlarged liver and a duplicated renal pelvis (bifid bassinet) on the right side. There was no indication of dilation within the urinary drainage system.

Genetic and epigenetic testing

To confirm the clinical suspicion of Beckwith-Wiedemann syndrome, a methylation-specific MLPA test was performed using the ME030-B2 BWS/RSS kit (SALSA MS-MLPA), designed for the detection of epigenetic changes associated with BWS and Silver-Russell syndrome. The analysis revealed hypomethylation at the KvDMR (IC2) region, supporting the diagnosis.

Additionally, Sanger sequencing identified a pathogenic KCNQ1 gene variant—NM_000218.3: c.604G>A (p.Asp202Asn)—which had already been documented in the patient's mother and sister. This variant is classified as pathogenic (class 5) according to ACMG guidelines. Both the methylation and sequencing tests were performed at the Bambino Gesù Pediatric Hospital in Rome.

Case management

This patient has been under the care of the Regional Center for Medical Genetics in Bihor since the age of 13 months. She is now 2 years and 5 months old and has undergone consistent monitoring through clinical assessments, laboratory tests, and imaging studies.

In terms of managing long QT syndrome type I, the patient is receiving beta-blocker therapy with Nadolol, which is periodically titrated under the guidance of pediatric cardiology specialists. Patient and family education plays a crucial role in managing the condition. Since certain commonly prescribed medications, including some antibiotics, have the potential to exacerbate arrhythmias, the family has been provided with a detailed list of drugs that must be avoided [14]. Additionally, they were advised to maintain a diet rich in potassium, particularly during periods of increased risk, such as hot weather or episodes of dehydration.

Ongoing follow-up is conducted every three months, under international surveillance protocols. Each visit includes a physical examination, serum alpha-fetoprotein (AFP) testing, and abdominopelvic ultrasound imaging [15, 16].

Throughout the follow-up period, both clinical presentation and paraclinical findings have shown progressive improvement **(Table 2)**.

Table 2. Progression of clinical and paraclinical parameters

Parameter	At birth	13 months	2 years, 5 months
Alpha-fetoprotein	92 ng/ml (NV < 7 ng/ml)	24.61 ng/ml	12.79 ng/ml
Weight	4220 g (> 90th percentile)	15.6 kg (> 97th percentile)	16.5 kg (90th-95th percentile)

Significant progress has been observed in the patient's weight over time. Upon initial registration at our center at 13 months of age, her weight was above the 97th percentile. Currently, her weight has stabilized between the 90th and 95th percentiles **(Table 1, Figure 2)**.

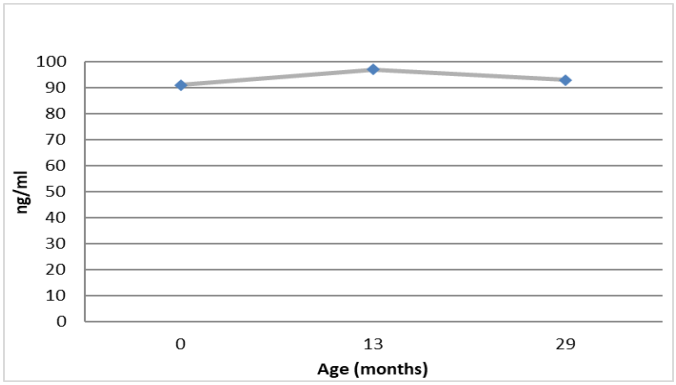

Figure 2. Evolution of weight

Alpha-fetoprotein (AFP) levels have decreased from 92 ng/ml at birth to 12.79 ng/ml at the current follow-up **(Table 1, Figure 3)**. Although still elevated above the normal range (less than 7 ng/ml), the declining trend of AFP levels indicates a positive prognosis.

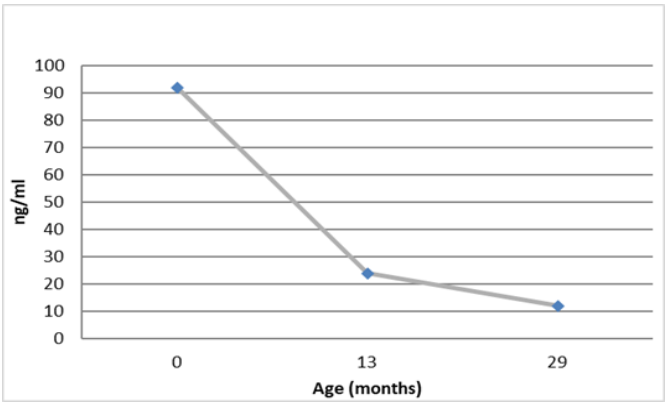

Figure 3. Evolution of alpha-fetoprotein

There have been no significant changes in the ultrasound findings. The patient would continue to have abdominal ultrasounds as part of preventive monitoring until she reaches 4 years old. After that, she will undergo renal ultrasounds until she turns 7 years old.

A positive outcome has been observed regarding the hemangiomas, which have undergone rapid and complete resorption as a side effect of the prescribed beta-blocker treatment (Nadolol).

This case represents a rare co-occurrence of two genetic conditions that are not commonly seen together in the medical literature. To date, that is the first reported case of such a combination in Romania.

Autosomal genes are expressed from both parental alleles, whereas imprinted genes are expressed from one allele only, either from the mother's or father's side. These imprinted genes are regulated by specialized regions, termed imprinting centers, that influence the gene's expression through epigenetic modifications such as methylation. The KCNQ1 gene, located on chromosome 11, is situated within a region that is subject to such genetic imprinting. In this patient, hypomethylation of imprinting center 2 (IC2) on the maternal allele has been detected, which affects the KCNQ1 gene located in this region [17]. This gene spans 400 kb and consists of 16 exons [18]. It encodes a protein involved in the function of voltage-gated potassium channels. Normally, the KCNQ1 gene is

only expressed from the maternal allele, except in the heart, where both alleles are active [19]. The antisense gene KCNQ10T1, located between exons ten and eleven of KCNQ1, is expressed exclusively from the paternal allele. It is important to note that not every individual who inherits the pathogenic mutation in the KCNQ1 gene along with IC2 hypomethylation will exhibit both genetic disorders, and the exact reasons for this discrepancy are not yet fully understood. The precise role of KCNQ1 in the development of Beckwith-Wiedemann syndrome (BWS) is still a subject of ongoing research. In this case, the patient's mother was diagnosed with LQTS1 during the birth of her 1st child. She did not experience any symptoms of LQTS1 until the development of preeclampsia in the later stages of pregnancy and never displayed any features of BWS.

The first documented case of the simultaneous occurrence of BWS and LQTS1 involved a family in which three children affected by BWS were also found to carry the condition due to a deletion in the ICR2 region, which silenced the maternal CDKN1C gene, leading to the development of BWS [20]. A similar deletion was observed in another family, where maternal inheritance resulted in BWS due to the decreased expression of CDKN1C [21]. Another case, described by Gurrieri *et al.* [22], involved a 20-year-old woman who experienced a cardiac arrest related to LQTS1 and exhibited a mild form of BWS. In this case, a microdeletion in the IC2 region, including the maternal KCNQ10T1 gene and part of the KCNQ1 allele, was identified. The deletion inactivated the maternal allele, while the paternal allele remained unaffected. Screening of the patient's first-degree relatives led to the identification of mild LQTS1 in her mother. Another instance of a maternally inherited ICR2 deletion, involving both CDKN1C and additional genes, clarified that the BWS phenotype resulted from the absence of the maternal CDKN1C transcript [23].

In 1993, Bonduelle proposed that fetal death might be a manifestation of Ward-Romano syndrome in some families [1]. For the first two miscarriages in this family, we cannot rule out this possibility, as no preimplantation genetic diagnosis was conducted. We recommend that individuals with long QT syndrome caused by mutations in the KCNQ1 gene (LQTS1) undergo a comprehensive clinical genetic evaluation to determine the appropriate genetic testing for both the affected individuals and their extended families. Further genotype-phenotype correlation studies are essential to gain a better understanding of the relationship between these syndromes.

Genetic counseling

The recurrence risk for LQTS type I in subsequent pregnancies for this couple, as well as for the proband's offspring, is 50%. However, the recurrence risk for Beckwith-Wiedemann syndrome (BWS) cannot be clearly defined, as not all individuals with hypomethylation of IC2 will show signs of BWS.

Conclusion

The combination of these two syndromes is rarely reported in the literature. More research is needed to clarify the mechanisms behind this association in certain cases. Early detection is crucial for optimizing the patient's development and prognosis, and regular monitoring is essential. The involvement of a multidisciplinary team plays a vital role in managing the case.

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Ethics Statement: None

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