Hyperinsulinemic Hypoglycemia in a Patient with Costello Syndrome: An Etiology to Consider in Hypoglycemia

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Keywords

Costello syndrome · Diazoxide · Hyperinsulinism · Hypoglycemia · RASopathy

Abstract

Several endocrine disorders have been defined in patients with Costello syndrome (CS). In this report, we describe a patient with CS accompanied by a clinical picture of hyperinsulinemic hypoglycemia responsive to diazoxide treatment. A 41-day-old female patient with a birth weight of 3,600 g was referred for atypical facial features and swallowing dysfunction. She had a weight of 4,000 g (−0.8 SDS), a length of 50 cm (−2.4 SDS), and a head circumference of 38 cm (0.2 SDS). The clinical findings were suggestive of a genetic syndrome, mainly a RASopathy or Beckwith-Wiedemann syndrome. Whole exome sequencing revealed a de novo heterozygous missense variant in the *HRAS* (NM_001130442) gene in exon 2: c.35G>C; p.(Gly12Ala), establishing the molecular diagnosis of CS. The patient developed symptomatic hypoglycemia (jitteriness and sweating) at the age of 13 months. The patient's serum glucose was 38 mg/dL with simultaneous serum insulin and C-peptide levels, 2.8 μIU/mL and 1.8 ng/mL,

respectively. Hyperinsulinism was suspected, and an exaggerated glucose response was detected in a glucagon test. Blood glucose monitoring indicated episodes of fasting hypoglycemia and postprandial hyperglycemia. Diazoxide of 10 mg/kg/day was initiated in 3 doses for hyperinsulinemic hypoglycemia, which resolved without new episodes of postprandial hyperglycemia. The patient deceased at the age of 17 months due to cardiorespiratory failure in the course of severe pneumonia complicated with pulmonary hypertension and hypertrophic cardiomyopathy. Several genetic syndromes including CS are associated with endocrinologic manifestations including abnormal glucose homeostasis. Although the frequency and underlying mechanisms leading to hyperinsulinemic hypoglycemia are yet unknown, hypoglycemia in CS responds well to diazoxide.

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Introduction

Costello syndrome (CS) is a rare multiple anomaly syndrome with a prevalence of ~1/300,000 live births and is one of the RASopathies due to germ-line variants in

RAS/Mitogen-Activated Protein Kinase (MAPK) pathway components and regulators [Abe et al., 2012; Rauen, 2013; Tidyman and Rauen, 2016]. CS is caused by heterozygous activating de novo germline variants in *HRAS* (OMIM, 190020) encoding the Harvey rat sarcoma viral oncogene homologue (HRAS), which is one of the most commonly studied RAS proteins. CS affects almost all organ systems with a wide phenotypic spectrum and is associated with characteristics such as prenatal overgrowth, poor postnatal growth, global developmental delay, coarse facial appearance, loose skin of hands and feet with characteristic hand position, joint laxity, deep palmar and plantar creases, and perinasal papillomas [Gripp and Lin, 2012]. Additional features include severe feeding difficulty, cardiac abnormalities (congenital heart defects, arrhythmias, and cardiomyopathy), and a predisposition to various types of cancer, with embryonal rhabdomyosarcoma being the most common [Gripp et al., 2002; Hennekam, 2003]. Several endocrine disorders, including growth hormone deficiency, adrenal failure, glucose intolerance, parathyroid adenoma, hyperprolactinemia, and hypoglycemia have been defined in patients with CS so far [Yetkin et al., 1998; Szalai et al., 1999; Cakir et al., 2004]. In the present report, we describe a CS patient with a clinical picture of hyperinsulinemic hypoglycemia who was responsive to diazoxide treatment.

Clinical Report

The patient was the second child of a nonconsanguineous healthy couple (maternal age 26, paternal age 35) who was born by vaginal delivery at 36 weeks of gestation (Apgar scores of 6 and 8 at 1 and 5 min, respectively) with a birth weight of 3,600 g (2.1 SDS). The pregnancy was complicated by polyhydramnios requiring repetitive (4 times) amniocentesis. Prenatal karyotype analysis was 46,XX. There was no history of diabetes mellitus in the family, and a 50 g oral glucose tolerance test was normal. At birth, the patient had respiratory distress and hypotonia requiring neonatal intensive care unit admission. She had episodes of hypoglycemia which responded to increased glucose infusion rates. The girl was discharged on postnatal day 27 with swallowing dysfunction requiring nasogastric tube feeding. She was first referred to our center when she was 41 days old for atypical facial features and swallowing dysfunction. She had a body weight of 4,000 g (−0.8 SDS), a body length of 50 cm (−2.4 SDS), and a head circumference of 38 cm (0.2 SDS). Relative macrocephaly, coarse facial appearance, high forehead, epicanthic folds, depressed nasal root, bulbous nose, macroglossia, thick lips, and short neck were noticed. The

Fig. 1. Clinical photo of the patient.

skin of her hands was thick and she had deep palmar creases. Upslanted palpebral fissures, low set ears, glabellar cutaneous hemangioma, and a posterior ear lobe crease were also noted (Fig. 1).

The facial features of the patient were suggestive of genetic syndromes including RASopathies, Beckwith-Wiedemann syndrome (BWS), or lysosomal storage disorders. The patient had global developmental delay (head control at 9 months, no babbling at 10 months) and required nasogastric tube feeding since birth. She had organoaxial malrotation and gastroesophageal reflux which required Nissen fundoplication and gastrostomy procedures when she was 7 months old. While echocardiography revealed pulmonary valve stenosis and biventricular hypertrophy, Holter rhythm monitorization detected multifocal atrial tachycardia, and antiarrhythmic treatment was initiated. Cranial magnetic resonance imaging displayed a diffuse thin corpus callosum. She had increased levels of serum alpha-fetoprotein (AFP) levels (28 ng/mL; normal range 0–9 ng/mL). No solid diagnosis could be established solely based on clinical grounds; therefore, whole exome sequencing (WES) was performed which revealed a previously reported *HRAS* variant, establishing the molecular diagnosis of CS.

The patient developed symptomatic hypoglycemia (jitteriness and sweating) and was evaluated at the endocrinology department at the age of 13 months. Her serum glucose level was 38 mg/dL, and the concurrently measured insulin level was as high as 2.8 μ IU/mL and C-peptide level was 1.8 ng/mL. The serum cortisol response was appropriate, serum growth hormone (GH) level at hypo-

glycemia was a little bit below the normal level of 10 ng/mL. Serum ammonia, lactate, pyruvate levels and serum amino acids, carnitine, and acylcarnitines levels were all normal (Table 1). Hyperinsulinism was suspected because the levels of insulin and C-peptide were elevated when measured while the patient was hypoglycemic. An exaggerated glucose response was also observed in the glucagon test, supporting the diagnosis of hyperinsulinism. Blood glucose monitoring indicated episodes of fasting hypoglycemia and postprandial hyperglycemia. Diazoxide of 10 mg/kg/day was initiated in 3 doses for hyperinsulinemic hypoglycemia, which was resolved with no new episodes of postprandial hyperglycemia occurring.

Since the patient had corpus callosum hypoplasia, the anterior pituitary hormones were evaluated as well (Table 2). Thyroid function tests, cortisol, and prolactin levels were all normal. Both IGF-1 and IGFBP-3 levels were below -3 SDS. Growth hormone level at hypoglycemia was 8.72 ng/mL, and peak GH level at glucagon stimulation test was 9.07 ng/mL. Peak GH levels of the patient were considered normal for this age. Total GH deficiency (GHD) was not considered, and follow-up was planned to reveal the growth velocity in terms of possible partial mild GHD. In terms of other possible hormonal disorders that may accompany CS, serum calcium, phosphorous, alkaline phosphatase, and parathormone levels were checked and were all within normal ranges. The patient deceased at the age of 17 months because of cardiorespiratory failure during a severe pneumonia probably complicated with pulmonary hypertension and hypertrophic cardiomyopathy.

Materials and Methods

After informed consent was taken from the family, a genomic DNA sample from peripheral whole blood using the standard procedure was extracted. WES was performed as described previously [Taskiran et al., 2017]. Identified variants of presumed pathogenic relevance were validated on the original DNA sample using conventional Sanger sequencing on an automated capillary sequence (Applied Biosystems 3500xL Genetic Analyzer).

Results

A de novo heterozygous, previously reported missense variant of *HRAS* (NM_001130442) in exon 2: c.35G>C; p.(Gly12Ala) was identified after removal of variants with high allele frequency (>1% in the ExAC data). Genetic counseling was provided to the family accordingly.

Table 1. Critical blood evaluations during hypoglycemia

Glucose: 38 mg/dL (normal range: 70–100 mg/dL)
Insulin: 2.8 µIU/mL (normal range: 1.9–23 µIU/mL)
C-peptide: 1.8 ng/mL (normal range: 0.9–7.1 ng/mL)
ACTH: 26.7 pg/mL (normal range: 0–46 pg/mL)
Cortisol: 26 µg/dL (normal range: 6.7–22.6 µg/dL)
Growth hormone: 8.72 ng/mL (normal range: >10 ng/mL)
Lactate: 13.69 mg/dL (normal range: 4.5–19.8 mg/dL)
Ammonia: 123 µg/dL (normal range: 20–120 µg/dL)
Pyruvate: 1.62 mg/dL (normal range: 0.3–0.9 mg/dL)
Urine ketone: negative
Tandem mass spectrometry: normal
Plasma and urine amino acid profiles: normal
Urine organic acid analysis: normal
Glucagon test: Glu (0 min): 44 mg/dL Glu (15 min): 126 mg/dL Glu (30 min): 156 mg/dL

Table 2. Evaluation of anterior pituitary hormones

Free T4: 9.10 pmol/L (normal range: 7.86–14.41 pmol/L)
TSH: 1.607 µIU/L (normal range: 0.38–5.33 µIU/L)
ACTH: 26.7 pg/mL (normal range: 0–46 pg/mL)
Cortisol: 26 µg/dL (normal range: 6.7–22.6 µg/dL)
PRL: 16.36 ng/mL (normal range: 5.18–26.53 ng/mL)
IGF-1: 4.66 ng/mL (< -3 SDS)
IGFBP-3: 1,082.93 ng/mL (< -3 SDS)
Peak GH level at glucagon stimulation test: 9.07 ng/mL

Discussion

Costello syndrome is a multisystem disease with a broad phenotypic spectrum ranging from a milder phenotype to severe forms that lead to early lethal complications. While older children with CS can be diagnosed more reliably, it can be challenging to diagnose patients at younger ages based solely on clinical findings. The present patient had dysmorphic facial features, loose and soft skin, and deep palmar creases suggestive of CS; nevertheless, some other differentials were considered as well. In infants and young children, BWS, cardio-facio-cutaneous syndrome, Noonan syndrome, Simpson-Golabi-Behmel syndrome, Williams syndrome, and lysosomal storage disorders may be considered in the differential diagnosis of CS. The presence of various organ malformations and the absence of severe feeding difficulty and growth failure in these syndromes usually allow them to be differentiated from CS. Other clinical findings suggesting CS in the present patient's history and physical examination included polyhydramnios, preterm delivery, macrosomic birth, relative macro-

Table 3. The clinical findings in individuals with Costello syndrome^a and in the present case

Organ system affected	Specific findings suggestive of Costello syndrome	Specific findings in the current patient
Prenatal and perinatal history	On prenatal ultrasound: increased nuchal thickness, polyhydramnios, characteristic ulnar deviation of the wrists, short humeri and femurs Fetal tachycardia Preterm delivery Macrocephaly	Polyhydramnios Preterm delivery Prenatal overgrowth Relative macrocephaly
Postnatal growth	Severe postnatal feeding difficulties Failure to thrive Short stature	Severe postnatal feeding difficulties Failure to thrive Short stature
Craniofacial appearance	Coarse facial features, full cheeks, full lips, wide mouth Prominent epicanthal folds Dolichocilia (long eye lashes) Wide nasal bridge, short full nose Fleshy ear lobes Curly or sparse fine hair Deep, hoarse voice	Coarse facial features, full cheeks, full lips, wide mouth Prominent epicanthal folds Wide nasal bridge, short full nose Fleshy ear lobes Sparse fine hair Deep, hoarse voice
Skin	Loose, soft skin Palmoplantar keratoderma Deep palmar and plantar creases Papillomas Acanthosis nigricans Diffuse hyperpigmentation	Loose, soft skin Deep palmar and plantar creases
Musculoskeletal system	Distinctive hand position with ulnar deviation of the wrists Vertical talus Hip dysplasia Tight hell cords Shoulder and elbow contractures Scoliosis Osteopenia Weakness	Shoulder and elbow contractures Weakness
Cardiovascular system	Hypertrophic cardiomyopathy (idiopathic subaortic stenosis, asymmetric septal hypertrophy, biventricular hypertrophy) Congenital heart defects (usually non-progressive valvular pulmonary stenosis, may be accompanied by subvalvular and supra-ventricular pulmonary stenosis, and double-chambered right ventricle, atrial septal defect, ventricular septal defect, mitral valve abnormalities, aortic thickening or stenosis, bicuspid aortic valve, coarctation of the aorta, patent ductus arteriosus, and aortic root dilation) Arrhythmias (chaotic atrial rhythm/multifocal atrial tachycardia, ectopic atrial tachycardia) Hypertension	Biventricular hypertrophic cardiomyopathy Valvular pulmonary stenosis Multifocal atrial tachycardia
Neurological system	Absolute or relative macrocephaly Ventricular dilatation Chiari 1 malformation Syringomyelia Tethered cord Seizures	Relative macrocephaly

Table 3 (continued)

Organ system affected	Specific findings suggestive of Costello syndrome	Specific findings in the current patient
Neurocognitive/psychological functions	Intellectual disability Speech and language impairment Delayed or deficient fine- and gross-motor skills Impaired adaptive functioning	Developmental delay Intellectual disability Speech impairment Delayed or deficient fine- and gross-motor skills Impaired adaptive functioning
Oncological	Benign tumors Embryonal rhabdomyosarcoma Bladder carcinoma Neuroblastoma	
Gastroenterological	Feeding and swallowing difficulties Pyloric stenosis Gastroesophageal reflux Constipation	Feeding and swallowing difficulties Gastroesophageal reflux
Endocrinological	Short stature Growth hormone deficiency Hypoglycemia Delayed or precocious puberty	Short stature Hypoglycemia (hyperinsulinemic hypoglycemia)
Respiratory	Structural upper and lower airway anomalies Frequent infections Central and obstructive apnea Cardiopulmonary disease	Structural upper and lower airway anomalies (respiratory distress) Frequent infections
Genitourinary	Cryptorchidism or labial anomalies Kidney malformation Vesicoureteral reflux Inguinal hernia Transitional cell carcinoma of the bladder	
Ophthalmological	Amblyopia Ptosis Refractive error Strabismus Optic nerve hypoplasia Cortical visual impairment	
Dental	Delayed tooth eruption Malocclusion Cross bite	Delayed tooth eruption

^avan Eeghen et al. [1999]; Lin et al. [2002, 2009]; Gripp [2005]; White et al. [2005]; Quezada and Gripp [2007]; Lin et al. [2009]; Gripp et al. [2019]

cephaly, severe postnatal feeding and swallowing difficulties, respiratory distress in the neonatal period, global developmental delay, and typical cardiac anomalies such as valvular pulmonary stenosis, hypertrophic cardiomyopathy and multifocal atrial tachycardia, of which the latter 2 may lead to death in the first 2 years of life. The present patient was lost because of pulmonary hy-

pertension and cardiorespiratory failure developed as complications during severe pneumonia, and the underlying hypertrophic cardiomyopathy might have contributed to the patient's mortality. The clinical findings of the patient and other CS patients are shown in Table 3.

An important endocrinological finding observed in the present patient was the rarely seen hyperinsulinemic

hypoglycemia. Hyperinsulinemic hypoglycemia has previously been described in some of the pre- and post-natal overgrowth syndromes which are also considered in the differential diagnosis of CS including BWS, Simpson-Golabi-Behmel syndrome, and Sotos syndrome. The most common overgrowth syndrome associated with hyperinsulinemic hypoglycemia is BWS, a somatic overgrowth and cancer predisposition syndrome with a complex genetic basis. While the association between BWS [Munns and Atch, 2001; Hussain et al., 2005] and hyperinsulinemic hypoglycemia is well documented, the underlying molecular mechanisms leading to hyperinsulinemic hypoglycemia in most of the other genetic conditions, including trisomy 13 [Tamame et al., 2004], congenital disorders of glycosylation (especially CDG Ia and Ib) [Böhles et al., 2001; de Lonlay et al., 2001], Sotos syndrome, Timothy syndrome, and Kabuki syndrome, are still unclear.

The literature contains various case reports covering the endocrinological problems that accompany CS. Nevertheless, very few cases of CS with hyperinsulinemic hypoglycemia have been reported since its first association in 2005 [Alexander et al., 2005]. Neonatal hypoglycemia is also more specific for CS than for other RASopathies. The ratio of neonates and infants with CS exhibiting hypoglycemia is reported to be 44% [Gripp and Lin, 2012; Myers et al., 2014]. The glucose metabolism disorders observed in CS may take the form of hypoglycemia or postprandial hyperglycemia, although these 2 conditions may also occur concurrently, as was observed in the present case. To date, the underlying reason for these glucose metabolism disorders observed in CS has yet to be elucidated. While there have been studies claiming an association between hypoglycemia and GHD or cortisol deficiency, others claim that hyperinsulinism causes hypoglycemia in a manner similar to what was observed in the present case [Yetkin et al., 1998; Legault et al., 2001; Delrue et al., 2002; Stein et al., 2004; Alexander et al., 2005]. In addition to the hypoglycemia observed during fasting, postprandial hyperglycemia was, similar to the present case, also defined in cases with CS. Di Rocco et al. [1993] suggested that the postprandial hyperglycemia observed in these cases may be a result of insulin resistance [Di Rocco et al., 1993]. Szalai et al. [1999] reported a case with decreased glucose tolerance accompanied by acanthosis nigricans. The present patient exhibited biochemical findings typical for hyperinsulinemic hypoglycemia, and there was also a measurable serum insulin level in the presence of nonketotic hypoglycemia. Growth hormone and corti-

sol levels were appropriate in response to hypoglycemia. The serum levels of ammonia, lactate, and pyruvate were all normal. The carnitine/acylcarnitine profiles, urine organic acids, urinary and plasma amino acid profiles were normal as well. As observed in other CS patients with hyperinsulinemic hypoglycemia, the present patient also responded well to diazoxide treatment, which led to the resolution of the hypoglycemia. Following diazoxide treatment, no reoccurrence was noted of the postprandial hyperglycemias observed prior to treatment.

An evaluation of the patient with regard to other endocrinological problems commonly reported with CS revealed normal thyroid function, normal prolactin levels, and no goiter. Furthermore, when the patient was evaluated with regard to parathyroid adenomas that were reported in similar cases, calcium, phosphorous, alkaline phosphatase, and parathormone values were all found to be normal. The patient exhibited no cortisol deficiency or total GHD. Concerning the peak GH response observed in the GH stimulation tests, there are no defined normal values for the patient's age group. While some consider 7 ng/mL and above as normal for this age group, others consider 10 ng/mL to be normal, independent of age [Ranke, 2011; Wagner et al., 2014; Guzzetti et al., 2016]. Although the present patient was identified as having low IGF-1 and IGFBP3 values, which is in agreement with a clinical picture of GHD, we did not consider starting GH treatment on the grounds that the hypoglycemia resolved completely with diazoxide treatment and that the peak GH response of the patient was very close to normal values. With respect to GHD, we planned to monitor the growth velocity of the patient. While there are publications in the literature reporting that GH treatment in patients supposed to have total GHD resolved their hypoglycemia, other publications report that GH treatment in cases presumed to have partial GHD only resulted in a limited response [Okamoto et al., 1994; Yetkin et al., 1998; Legault et al., 2001; Gregersen and Viljoen, 2004; Stein et al., 2004].

Gene-targeted testing using either a single-gene testing for *HRAS* or a multi-gene panel for RASopathies is recommended in the molecular diagnosis of CS, especially in patients with distinctive clinical findings. However, this may not always be the case as it was in the present patient. Since CS has a broad spectrum of clinical findings and some other genetic syndromes with overlapping features are considered in the differential diagnosis, comprehensive genomic testing (such as exome sequencing and genome sequencing) may be required.

Table 4. Genotype–phenotype correlations in Costello syndrome [Lo et al., 2008; Gripp et al., 2019]

<i>HRAS</i> mutation	Clinical phenotype
p.Gly12Ser	Classic features of CS
p.Gly12Cys, p.Gly12 Asp, p.Gly12Glu	Severe neonatal phenotype Severe cardiomyopathy Pleural and pericardial effusion Lung abnormalities
p.Gly12Ala	Severe neonatal phenotype Higher rate of malignancy
p.Gly12Val	Severe cardiomyopathy Tachycardia Respiratory distress Early death
p.Gly13Cys	Milder phenotype Lower risk for malignant tumors or papillomata Taller stature Absence of ulnar wrist deviation
p.Thr58Ile, p.Lys117Arg, p.Ala146Val, p.Ala146Pro	Milder phenotype Facial features are less coarse
p.Gly60Asp	Milder phenotype Reported with maternal transmission
p.Gly60Val	Only one case reported Died in infancy
p.Glu63Lys	Classic features of CS Congenital myopathy
p.Glu63_Asp69dup	Milder phenotype Milder intellectual disability Fewer feeding problems Lower tumor risk
p.Ala146Thr	Milder phenotype Minor skin and joint involvement Milder growth restriction Microcephaly Sparse, thin hair
p.Gly37dup	Very sparse hair Facial features are less coarse
p.Gly13Asp	Milder phenotype Fewer malignancy

The present patient exhibited swallowing dysfunction, facial dysmorphism, global developmental delay, and some minor anomalies, findings shared by several other genetic conditions, including Noonan syndrome, cardio-facio-cutaneous syndrome, BWS, and lysosomal storage disorders. Therefore, a solid diagnosis based solely on clinical grounds could not be established and WES was performed for the exact diagnosis.

CS typically arises de novo from the paternal germline as a result of heterozygous activating variants in *HRAS* located at 11p15.5 [Sol-Church et al., 2006; Gianoulitou et al., 2013]. Advanced paternal age is present in most of the cases with *HRAS* variants [Aoki et al., 2005; Estep et al., 2006; Sol-Church et al., 2006; Gianoulitou et al., 2013]. The present case also had advanced paternal age. Sometimes somatic mosaicism can

be observed in individuals with a milder phenotype involving a limited number of organ systems [Gripp et al., 2006b, 2017; Sol-Church et al., 2009]. Despite the limited available data due to the rarity of CS, some genotype-phenotype correlations have previously been reported. More than 95% of *HRAS* variants that cause CS involve the amino acid glycine at the 12th or 13th position in *HRAS* [Sol-Church and Gripp, 2009]. About 80% of variants cause a p.Gly12Ser missense change, resulting in the classical phenotype. In the present case, WES revealed a previously reported pathogenic missense variant (p.Gly12Ala) in *HRAS* which involves the alteration of a conserved nucleotide [Aoki et al., 2005; Niihori et al., 2011; Robbins et al., 2016]. This variant not only represents the second most common mutation reported in CS [Aoki et al., 2005; Gripp et al., 2006a; Kerr et al., 2006] but also has been associated with a higher risk of malignancy with a more severe phenotype. With this clinical report we also have shown that hyperinsulinism may be another clinical feature of CS. Other *HRAS* variants known to be related to hyperinsulinism in the literature are p.Gly12Glu, and p.Gln22Lys. Rare variants in CS may also be associated with hyperinsulinemic hypoglycemia compared to the commonly encountered p.Gly12Ser variant. The other already known genotype-phenotype correlations in CS are given in Table 4.

Dickson et al. [2004] identified for the first time a case of CS with pancreatic hyperplasia [Dickson et al., 2004]. A year later, Alexander et al. [2005] reported 2 cases in which hyperinsulinemic hypoglycemia was the underlying reason for the hypoglycemia seen during fasting with CS. Severe neonatal hypoglycemia accompanying congenital hyperinsulinism was identified in an individual with an *HRAS* p.Gly12Glu mutation, and the autopsy of this case revealed hypertrophy and hyperplasia in the Langerhans cells [Kerr et al., 2006]. In 2015, Sheffield et al. also reported hyperinsulinemic hypoglycemia in a rare case with a p.Gln22Lys mutation in *HRAS* [Sheffield et al., 2015]. This patient eventually developed and died of medical treatment-resistant pulmonary hypertension and hypertrophic cardiomyopathy. Post-mortem examinations identified a pancreatic nodule that was similar to the focal lesions seen in congenital hyperinsulinism. Studies of this nodule, however, revealed no underlying molecular changes (no mutation in *KCNJ11* or *ABCC8* which are located at 11p15.1 close to *HRAS* at 11p15.5) that might have led to hyperinsulinism. In addition, it has been shown that epigenetic alterations in the *IGF2* and *H19* loci that are seen in BWS are not present but that there is a loss of *CDKN1C* ex-

pression in the nodule; the reason for this could not be explained. In 2016, Gripp et al. performed studies on the lesion of this case who has both CS and the pancreatic nodule, and demonstrated that, similar to the paternal uniparental disomy (pUPD) of 11p15.5 seen in cases with BWS, the patient in question had UPD [Gripp et al., 2016]. According to Gripp et al. [2016], demonstrating the loss of heterozygosity in the pancreatic lesion of a case with CS not only explains the neonatal hypoglycemia observed in these cases but also suggests that a combination of heterozygosity loss and pUPD may be the mechanism that leads to disorders of cell growth and tumor formation. This mechanism would explain both hyperinsulinism and the tumor and papillomata formation observed in CS. In isolated sporadic malignancies, somatic variants in *KRAS* and *HRAS* have been reported at varying frequencies. The risk of malignancy in CS is considerably higher when compared to other RASopathies that develop as a result of *KRAS* variants, such as Noonan syndrome. This difference might be related to the different effect and function of *HRAS* compared to *KRAS*. That said, it may also be attributable to the colocalization of *IGF2* in this region and the contribution of the combined effect of pUPD on both the *HRAS* and *IGF2* genes to its oncogenic potential within 11p15.5. Kerr et al. [2003] also showed the loss of heterozygosity at 11p15.5 in rhabdomyosarcoma and suggested that loss of the wild-type allele could be the second hit in tumor development in patients with CS [Kerr et al., 2003]. This theory is furthermore supported by several authors who showed the monoallelic expression and the loss of the wild-type allele in CS-associated tumors [Aoki et al., 2005; Estep et al., 2006].

In conclusion, several developmental genetic syndromes including CS are associated with endocrinologic manifestations. Hyperinsulinemic hypoglycemia, one of the endocrinologic manifestations of abnormal glucose homeostasis, should be kept in mind in CS patients. Although the frequency and the underlying mechanisms leading to hyperinsulinemic hypoglycemia in CS is yet unknown, hypoglycemia responds well to diazoxide treatment.

Statement of Ethics

Informed consent was obtained from the parents, and investigations were conducted in line with the principles detailed by the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received.

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Authors Contributions

All authors read and approved the manuscript.

D.V. participated in the design of the study, performed clinical investigations, and wrote the manuscript. C.K. and E.T. performed the molecular investigations. P.O.S.-K. and A.A. participated in the design of the study, contributed to performing clinical investigations and writing the manuscript. G.E.U. participated in the design of the study and contributed to the clinical investigations. K.B. and M.A. coordinated the molecular investigations and the coordination of the study.

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