Heterogeneity in Phenotype of Usher-Congenital Hyperinsulinism Syndrome

Hearing loss, retinitis pigmentosa, and hyperinsulinemic hypoglycemia ranging from severe to mild with conversion to diabetes

Angham N. Al Mutair, MD[1,2]
Klaus Brusgaard, MSC, PHD[5]
Bassam Bin-Abbas, MD[3]
Khalid Hussain, MD, PHD[4]
Naila Felimban, MD[1]
Adnan Al Shaikh, MD[1]
Henrik T. Christesen, MD, PHD[6]

OBJECTIVE—To evaluate the phenotype of 15 children with congenital hyperinsulinism (CHI) and profound hearing loss, known as Homozygous 11p15-p14 Deletion syndrome (MIM #606528).

RESEARCH DESIGN AND METHODS—Prospective clinical follow-up and genetic analysis by direct sequencing, multiplex ligation-dependent probe amplification, and microsatellite markers.

RESULTS—Genetic testing identified the previous described homozygous deletion in 11p15, *USH1C*:c.(90+592)_*ABCC8*:c.(2694–528)del. Fourteen patients had severe CHI demanding near-total pancreatectomy. In one patient with mild, transient neonatal hypoglycemia and nonautoimmune diabetes at age 11 years, no additional mutations were found in *HNF1A*, *HNF4A*, *GCK*, *INS*, and *INSR*. Retinitis pigmentosa was found in two patients aged 9 and 13 years. No patients had enteropathy or renal tubular defects. Neuromotor development ranged from normal to severe delay with epilepsy.

CONCLUSIONS—The phenotype of Homozygous 11p15-p14 Deletion syndrome, or Usher-CHI syndrome, includes any severity of neonatal-onset CHI and severe, sensorineural hearing loss. Retinitis pigmentosa and nonautoimmune diabetes may occur in adolescence.

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Congenital hyperinsulinism (CHI, MIM #256450) is a heterogeneous disease with hyperinsulinemic hypoglycemia, most frequently caused by mutations in *ABCC8* (1,2). Usher syndrome 1C (USH1C, MIM #296904) is caused by mutations in *USH1C* (3), a gene situated next to *ABCC8* on chromosome 11p15.1. A very rare, homozygous contiguous gene deletion, including *USHIC* and *ABCC8*, has been described in three patients, characterized by severe CHI, deafness, vestibular hypofunction, severe enteropathy, and renal tubular dysfunction (MIM #606528) (4,5).

We report on 15 new patients from eight consanguineous families with the same homozygous deletion, but with clinical heterogeneity and with manifestations from β-cells, inner ear, and retina only.

From the [1]Department of Pediatrics, Endocrinology Division, King Abdulaziz Medical City-Riyadh, Riyadh, Saudi Arabia; the [2]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; the [3]Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; the [4]London Centre for Paediatric Endocrinology and Metabolism, Great Ormond Street Hospital for Children NHS Trust and The Institute of Child Health, London, U.K.; the [5]Department of Clinical Genetics, Odense University Hospital, Odense, Denmark; and the [6]H.C. Andersen Children's Hospital, Odense University Hospital, Odense, Denmark.
Corresponding author: Henrik T. Christesen, henrik.christesen@ouh.regionsyddanmark.dk.
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RESEARCH DESIGN AND METHODS

—Among children with CHI in Riyadh and London, we identified 15 patients with severe congenital hearing loss. *USH1C*, *ABCC8*, and *KCNJ11* were analyzed by sequencing and multiplex ligation-dependent probe amplification (MLPA) (for details, see Supplementary Figs. 1–4). Patient 3 was analyzed through two separate blood samples with additional sequencing of the nonsyndromic diabetes-related genes *HNF1A*, *HNF4A*, *GCK*, *INS*, and *INSR*. DNA microsatellite markers were used for haplotype analysis. Informed consent was obtained.

RESULTS

—Fifteen patients from eight apparently unrelated, consanguineous families in Saudi Arabia and Kuwait were identified with deafness and CHI. Of these, 14 had severe CHI with need of subtotal pancreatectomy (Table 1). One patient (patient 3) had mild hypoglycemia only, which was diagnosed at 3 months of age. By 11 years, his HbA_{1c} level gradually increased to 8.5% (reference 4.4–6.4%), fasting blood glucose increased to 15 mmol/L, and postprandial hyperglycemia increased to 13 mmol/L. Serum insulin was low, 49 mU/L (reference 72–150 mU/L), blood glucose was 12.6 mmol/L, and 2-h oral glucose tolerance test (OGTT) glucose was 16 mmol/L. Autoantibodies were negative, and BMI was 21.6 kg/m^2. No syndromic features were found and the mother had normal hearing, giving no clues for inheritance of syndromic diabetes mutations. The patient responded to metformin treatment.

Profound hearing loss with absent brain stem auditory-evoked response was diagnosed in all patients, with the exception of one who died early (Table 1). It is noteworthy that the atypical patient 3 also had severe hearing loss and developed retinitis pigmentosa at age 13 years. One other patient had retinal changes with absent visual-evoked response at 9.5 years. No patients had clinical evidence of vestibular dysfunction, prolonged

Table 1—*Patient data*

Family	A	A	A	A	A	B	B	B	C	C	D	E	F	G	H
Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Current age (years, months)	11, 10	0, 19	16, 10	4, 4	3, 1	6, 7	6, 8	Died at 28 days	6, 8	Died at 2 years	9, 6	1, 5	4, 11	3, 2	0, 10
Proband (+)				+		+				+	+	+	+	+	+
Clinical data															
Sex	Boy	Girl	Boy	Girl	Girl	Girl	Girl	Girl	Boy	Boy	Girl	Girl	Girl	Boy	Boy
Gestation	Term	Term	Term	Term	Term	Term	Term	Term	Term	Term	Term	Term	36 Weeks	Term	Term
Birth weight (kg)	3.3	3.07	2.5	3.5	3.0	3.1	3.6	3.2	4.0	3.8	4.0	5.5	2.5	3.2	3.4
SD score	−0.82	−1.08	−2.73	−0.05	−1.25	−1.01	+0.18	−0.77	+0.85	+0.37	+1.14	+4.72	−0.78	−1.06	−0.58
Age of first known episode of hypoglycemia	Day 1	Day 1	3 Months	Day 1	Day 1	Day 4	Day 1	Day 2	Day 2	Day 1	Day 1	Day 1	Day 3	Day 1	Day 1
Presenting sign	Seizures	Seizures	Irritability, apnea	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures	Irritability, poor feeding	None
Severe hearing loss	+	+	+	+	+	+	+	N/A	+	+	+	+	+	+	+
Brain stem auditory-evoked response	Absent	Absent	Absent	Absent	Absent	Absent	Absent	N/A	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Vision	N	N	RT	N	N	N	N	N	N	N	Blind	N	N	N	N
Visual-evoked response	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Absent	N/A	N/A	Affected	N/A
Gastrointestinal involvement	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Renal tube defect	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Growth (actual percentile)															
Weight	50%	25%	75%	50%	50%	25%	50%	25%	50%	75%	10%	50%	25%	50%	50%
Height	50%	10%	50%	10%	50%	25%	10%	25%	10%	25%	10%	50%	50%	25%	50%
Development															
Motor	MD	N	N	SD	N	N	N	N	MD	SD	MD	N	MD	MD	N
Cognitive	MD	N	N	SD	N	N	N	N	MD	SD	MD	N	MD	N	N
Epilepsy	+	—	+	+	—	—	—	—	+	+	+	—	+	—	—

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Table 1—*Continued*

Family	A	A	A	A	A	B	B	B	C	C	D	E	F	G	H
Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Electroencephalography	Rolandic (8 years)	N/A	Rolandic (11 years)	Slow background, bilateral discharge	N/A	N/A	N/A	N/A	Slow background	Slow background	Slow background, left hemisphere epileptic discharge	N/A	Focal epileptic discharge during sleep	N	N
Spontaneous progression to diabetes	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—
Biochemical and genetic data															
Insulin level at hypoglycemia (pmol/L)*	237	205	14	92	66	130	80	273	122	N/A	228	41	38	282	144
Intravenous glucose requirement (mg/kg/min)	29	25	6	6	18	20	26	28	11	N/A	12	20	20	17	19
Other hormonal and metabolic evaluation	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ABCC8-USH1C homozygous deletion	+	+	+	N/A	+	+	+	N/A	N/A	N/A	N/A	+	+	+	+
Last follow-up HbA_{1c} (ref. 4.4–6.4%)	8.5%	5.4%	6.8%	5.3%	N/A	5.0%	5.6%	N/A	4.8%	N/A	4.7%	9.0%	N/A	N/A	N/A
Treatment															
Maximal dose															
Diazoxide (mg/kg/day)	25	25	0	20	25	20	25	20	20	20	20	20	20	20	20
Octreotide (μg/kg/day)	50	50	0	30	44	50	50	40	30	30	30	40	40	35	35
Glucagon (μg/kg/h)	Bolus	Bolus	—	—	10	Bolus	—	Bolus	—	—	—	Bolus	Bolus	—	—
Nifedipine (mg/kg/day)	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Near-total pancreatectomy	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+

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Table 1—*Continued*

Family	A	A	A	A	A	B	B	B	C	C	C	D	E	F	G	H
Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Postoperative complications																
Malabsorption	—	—	N/A	—	—	—	—	—	—	—	—	—	—	—	—
Hypoglycemia	+	+	N/A	—	—	—	+	+	—	—	—	+	+	+	—
Progression to diabetes	+	—	N/A	—	—	—	—	—	—	—	—	—	—	—	—
Cochlear implant	—	+	—	—	—	+	+	—	—	—	—	+	—	+	—

+, yes; —, no; MD, mildly delayed; SD, severely delayed; N, normal; RT, retinitis pigmentosa; N/A, not available or not applicable. *To convert insulin value from pmol/L to mU/L, divide by 6.00.

diarrhea, vomiting, signs of renal tubular defects, or amino or organic acid in the urine.

None of the parents or other siblings had a history of hypoglycemia, diabetes, hearing loss, dizziness, vision anomalies, or signs of enteropathy or nephropathy. Parents had normal HbA_{1c} (5.2–6.0%), fasting blood glucose (4.8–6.7 mmol/L), and 2-h OGTT glucose (4.1–9.3 mmol/L), except one with 2-h OGTT glucose (12.5 mmol/L), which was explained by severe obesity (BMI 31 kg/m^2).

In all 10 patients with available DNA, sequence analysis revealed a 122.815-base pair deletion of *USH1C* exon 3–28 and *ABCC8* exon 1–22, *USH1C*:c.(90+592)_*ABCC8*: c.(2694–528)del. MLPA analyses confirmed the heterozygous state of the parents and the homozygous state of the offspring. In the atypical patient 3, the homozygous deletion was verified in two separate blood samples. No mutations were found in antagonizing, nonsyndromic diabetic genes. Microsatellite analysis in 12 parents showed a common ancestral haplotype. The mutation was calculated to be introduced in all the families approximately 3.9 generations previously for the parental generation.

CONCLUSIONS—We added 15 new patients to the only three patients already described with Usher-CHI syndrome and made a much longer follow-up until 16 years of age. Our data alter the phenotype description of the syndrome, not only in terms of a variable degree of hyperinsulinism with possibility of conversion to diabetes in the second decade but also in the Usher-related manifestations.

The deletion in *USH1C-ABCC8* was exactly the same in all the investigated patients as in the two previously reported families (4,5) and calculated to be introduced in all six families studied approximately 3.9 generations before. Using an average generation time of 21.28 years in Saudi Arabia (6), this corresponds to a mutation age of 85 years.

In 14 patients, the hyperinsulinemic hypoglycemia was severe with early neonatal onset and did not respond to medical treatment, which is in line with the previous reports (4,5) and three other patients described with *ABCC8* macrodeletions (7,8). In contrast, one patient had very mild hypoglycemia only with conversion to diabetes in puberty, without any clue of mosaicism, type 1 diabetes, type 2 diabetes, or additional diabetes gene mutations. A homozygous *ABCC8* deletion is expected to result in a completely nonfunctional β-cell K_{ATP} channel (9,10) as in mice SUR1 knockout (11,12). However, SUR1$^{-/-}$ and Kir6.2$^{-/-}$ mice have mild, transient neonatal hyperinsulinism only, with rapid reversion to glucose intolerance and loss of insulin secretion in adulthood because of a lack of first-phase and an attenuated second-phase insulin secretion in response to glucose (11–13). Species differences include an attenuated β-cell–amplifying pathway in mice, suggesting that the amplifying pathway *1*) has an important role in producing severe and persistent hyperinsulinism in the patient with typical Usher-CHI syndrome and *2*) may be attenuated in the atypical mild patient.

The large *USH1C* homozygous deletion resulted in profound, congenital sensorineural deafness in all investigated patients, identical to the effect of reported *USH1C* point mutations (3,14). Progressive retinitis pigmentosa is seen in *USH1C* patients with onset of nyctalopia (night blindness) from 7 to 15 years (15). Retinitis pigmentosa was diagnosed in two of our patients only because of young age. In *USH1C*, vestibular dysfunction may only be detected as absence of nystagmus on caloric stimulation (15) and was not detected in our patients, in contrast to the previous study (5). The three previously reported patients with Usher-CHI syndrome also had severe enteropathy and renal tubular defects (4,5). Such manifestations were not seen in our patients and have not been reported in others with USH1 or CHI only, neither in *USH1C* knock-in or knockout mice nor in SUR1 knockout mice. It is suggested that the gut and renal manifestations in the previous reports were not the result of the homozygous deletion.

In conclusion, the phenotype of Usher-CHI syndrome is characterized by Usher 1 manifestations and a heterogeneous CHI pattern ranging from severe, persistent CHI to mild and transient hyperinsulinism with conversion to diabetes in the second decade.

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A.N.A.M. collected and analyzed data and wrote the manuscript. K.B. performed genetic analyses and reviewed the RESEARCH DESIGN AND METHODS section. B.B.-A., N.F., and A.A.S.

collected and analyzed data. K.H. collected and analyzed data and reviewed the manuscript. H.T.C. wrote the manuscript. H.T.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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