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, MD1,2
Klaus Brusgaard, MSC, PhD3
Bassam Bin-Abbas, MD3
Khalid Hussain, MD, PhD4
Naila Felimban, MD1
Adnan Al ShaiKH, MD3
Henrik T. Christesen, MD, PhD6

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+392)ABCC8:c.(2694+528)del. Fourteen patients had severe CHI demanding near-total pancreatectomy. In one patient with mild, transient neonatal hypoglycemia and non-autoimmune diabetes at age 11 years, no additional mutations were found in HNF1A, HNF4A, GCK, INS, and INSR. Retinitis pigmentation 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 pigmentation and non-autoimmune 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 USH1C 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 1Department of Pediatrics, Endocrinology Division, King Abdulaziz Medical City-Riyadh, Riyadh, Saudi Arabia; the 2College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; the 3Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; the 4London Centre for Paediatric Endocrinology and Metabolism, Great Ormond Street Hospital for Children NHS Trust and The Institute of Child Health, London, U.K.; the 5Department of Clinical Genetics, Odense University Hospital, Odense, Denmark; and the 6H.C. Andersen Children’s Hospital, Odense University Hospital, Odense, Denmark.

Corresponding author: Henrik T. Christesen, henrik.christesen@ouh.regionsyddanmark.dk.
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| Patient no. | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 |
|------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Family     | A  | A  | A  | A  | A  | B  | B  | B  | B  | C  | C  | D  | E  | F  | G  | H  |
| 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 (+) | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Sex        | Boy | Girl | Boy | Girl | Girl | Girl | Girl | Girl | Boy | Boy | Girl | Girl | Girl | Girl | Boy |
| Gestation  | Term | Term | Term | Term | Term | Term | Term | Term | Term | Term | Term | Term | Term | 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 | −0.38 |
| 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 1 | Day 1 | Day 1 |
| Presenting sign | Seizures | Seizures | Irritability, apnea | Seizures | Seizures | Seizures | Seizures | Seizures | Seizures | Seizures | Seizures | Seizures | Seizures | Seizures | 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 |
| Vision     | N  | N  | RT | N  | N  | N  | N  | NT | N  | Blind | N  | N  | N  |
| Visual-evoked response | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Absent | N/A | N/A | Affected |
| 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% | 25% | 50% | 50% |
| Motor      | MD  | N  | N  | SD | N  | N  | N  | N  | MD  | SD  | MD  | N  | MD  | MD  | MD  |
| Cognitive  | MD  | N  | N  | SD | N  | N  | N  | N  | MD  | SD  | MD  | N  | MD  | N  | N  |
| Epilepsy   | +   | −   | +   | +   | −   | −   | −   | −   | +   | +   | +   | +   | +   | +   | −   | −   |

Continued on p. 559
| 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 (EEG) | 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 |
| 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 |
| ABCG8-USH1C homozygous deletion | + | + | + | N/A | + | + | + | N/A | N/A | N/A | N/A | + | + | + | + |
| Last follow-up HbA1c (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 |
| Octreotide (mg/kg/day) | 50 | 50 | 0 | 30 | 44 | 50 | 50 | 40 | 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 | + | + | — | + | + | + | + | + | + | + | + | + | + | + | + |

Continued on p. 560
diabetes, hearing loss, dizziness, vision anomalies, or signs of enteropathy or nephropathy. Patients had normal HbA1c (5.2–6.8%), fasting blood glucose (4.8–6.7 mmol/L), and 2-h OGGT glucose (4.1–9.3 mmol/L), except one with 2-h OGGT glucose (12.5 mmol/L), which was explained by severe obesity (BMI 31 kg/m²).

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)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 

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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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