Transient, neonatal hyperinsulinemic hypoglycemia may be monogenic, not only secondary to perinatal stress

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Objective

To examine genetic variants and perinatal stress factors as determinants for transient, neonatal hyperinsulinaemic hypoglycaemia (HH), in a cohort excluding hypoglycaemia explained by maternal diabetes.

Background

Congenital hyperinsulinism may be transient, as known for maternal diabetes and perinatal stress.

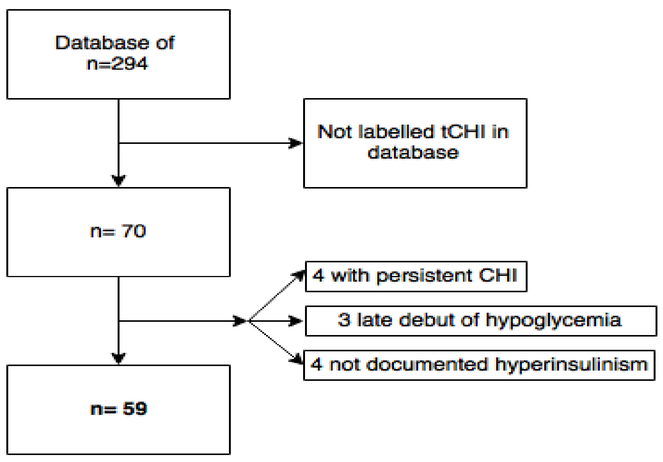
Cohort studies elucidating genetic mutations have not been performed.

Methods

- Retrospective file-review for hospitalized infants at Odense University Hospital with a diagnosis of hyperinsulinaemic hypoglycaemia.
- Exclusion criteria:
  - 1) maternal diabetes or gestational diabetes without a suspicion of monogenic diabetes
  - 2) maternal medication known to cause neonatal, transient HH
  - 3) late debut of hypoglycaemia beyond one year of age
  - 4) lack of spontaneous clinical remission at six months after onset.
- Spontaneous clinical remission defined as no pancreatic surgery; no history of hypoglycaemia symptoms; repeated fasting blood glucose above 3.2 mmol/L without medical treatment; and no relapse at one-year follow up.
- Data were extracted for the diagnosis of hyperinsulinaemic hypoglycaemia, a transient course (defined as clinical remission of hypoglycaemia before six months of age), risk factors, genotype, glucose status, neurological outcome at follow up, and family investigations.

Results

Table 1: Patient inclusion flow chart



Conclusion

Conclusions

- Neurological complications were frequent
- Perinatal stress and CHI-mutations were equally prevalent in tCHI
- Genetic testing in tCHI is encouraged

Results

- Perinatal stress 14/59 (24%)
- Mutations in 11/59 (19%) Table 1
  - higher birth weigth Table 2
- Neurological complications at follow up: n=9 (15%)
  - Perinatal stress, n=2, mutation, n=1
- Family
  - two patients (*HNF1A)* had known MODY 3 family members
  - One mother diagnosed with diabetes (*HNF1A)*
  - one mother diagnosed with recurrent hypoglycaemia (*KCNJ11*)

Table 1: Found mutations in tCHI-patients

Pt. ID:	Sex	Gene	Mutation type	cDNA NM	Amino acid NP	Inheritance
P1	F	*KCNJ11*	missense	c.617G>A	p.Arg206His	maternal
P21	F	*KCNJ11*	missense	c.530G>A	p.Arg177Lys	maternal
P29	F	*HNF1A*	stop codon	c.526C>T	p.Gln176X	Maternal
P36	M	*ABCC8*	Missense	c.4141G>A	p.Gly1382Ser	paternal
P43	M	*ABCC8*	Missense	c.689A>G	p.Tyr230Cys	paternal
P45	F	*HNF1A*	stop codon	c.526C>T	p.Gln176X	maternal
P55	F	*HNF1A*	Missense	c.476G>A	p.Arg159Gln	paternal
P58	M	*ABCC8*	missense	c.1252T>C	p.Cys418Arg	paternal
P59	F	*KCNJ11*	missense	c.868G>A	p.Val290Met	maternal

+ 2 patients with genetically verified Beckwith Widemann Syndrome

Table 2: Comparison of clinical data in patients with and without mutations

	Patients with mutation (female=8,male=3)	**Patients without mutation** (female=15, male=33)	**p-value**
Birth weight, mean (SD)	4272.9 g (768.2)	3113.5 (919.4)	0.0116
Gestational age	268 days (13.3)	264 days (28.3)	N.S.
Risk factors, n (%) – severe asphyxia – IUGR	2 (18.2%) – 2 severe asphyxia – 0	12 (25%) – 4 severe asphyxia – 7 IUGR – 1 both	N.S.
Neurological sequelae n (%)	1 (9.1%) - cerebral palsy and epilepsy	8 (16.7%) patients: – 3 cerebral palsy – 3 mental retardation – 1 epilepsy – 1 microcephaly	N.S.
Lowest blood glucose Median (range)	1.2 mmol/l (0.9-1.9)	0.7 mmol/l (0-2.0)	N.S.
Max. glucose infusion rate median (range)	9.1 mg/kg/min (6-17)	10.8 mg/kg/min (2.8-40)	N.S.
Max. diazoxide dose median (range)	15.7 mg/kg/day (4.8-18)	10 mg/kg/day (2.4-20)	N.S.
Duration of diazoxide, days median (range)	10 days (6-30)	9 days (3-94)	
Medical response	Yes; n=7 (64%) No; n=3 (27%)	Y; n=30 (63%) N; n=4 (8%)	N.S.
Age at debut, median (range)	Day 1 (1-3)	Day 1 (1-11)	N.S.
Time to remission (days) median (range)	23.5 days (3-30)	16 days (3 to 110)	N.S.
Relapse at follow up, n (%)	1 (9.1%)	5 (10.4%)	N.S.

Disclosure statement:
The authors have nothing to disclose.

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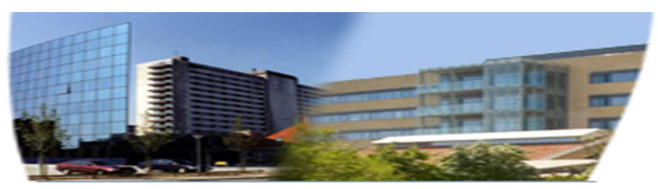

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