Discontinuation of Diazoxide therapy in children with Hyperinsulinaemic Hypoglycaemia with no identified genetic aetiology. A long-term follow-up study.

Mouza AlYahyaei [1,2], Pratik Shah [2,3], Maria Guemes [2,3], Clare Gilbert[2], Kate Morgan[2], Sian Ellard [4], Sarah Flanagan [4], Khalid Hussain [2,3]

[1] Department of Paediatric Endocrinology, Royal Hospital, Muscat.
[2] Department of Paediatric Endocrinology, Great Ormond Street Hospital for Children, London.
[3] Department of Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, Institute of Child Health, University College London, London.
[4] Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter EX2 5DW.

Great Ormond Street Hospital for Children NHS Foundation Trust

Background

Congenital hyperinsulinism (CHI) is a cause of severe persistent hypoglycaemia in children. Diazoxide is the first line medical therapy for CHI; however diazoxide is usually ineffective in CHI with K_{ATP} channel gene mutations. Patients with no mutations in the K_{ATP} channel genes do respond to therapy with diazoxide. There are no previous studies assessing how long diazoxide therapy is needed in those patients with no genetic aetiology identified for the CHI.

Aims

To describe the clinical, biochemical, genetic aspects and duration of therapy in a cohort of CHI patients who no longer required diazoxide

Methods

Retrospective review of diazoxide-responsive CHI patients admitted to Great Ormond Street Hospital. Data on gestation age, birth weight, maternal risks, age of diagnosis, biochemical and genetic studies on *ABCC8* and *KCNJ11* were obtained. Follow up data on glycaemic profile, fasting studies, dose of diazoxide and duration of therapy were recorded.

Patient No	Gender	Age of Presentation	Biochemistry profile at the time of diagnosis				Genetic mutation for *ABCC8/ KCNJ11*	Max dose of diazoxide	Years on medications	Age when Diazoxide was stopped	Biochemical results when off diazoxide					Neurological outcome
			Glucose mmo/L	Insulin mU/L	NEFA mmol/L	BOHB mmol/L					Hours of fast	Glucose mmol/L	Insulin mU/L	NEFA mmol/L	BOHB mmol/L	
1	F	16 days	0.7	35	0.82	0.33	Negative	20mg/kg/day	4years	4 years	16hrs	3.9	<2	0.89	0.08	Developmentally appropriate to age
2	M	6.5months	1.6	47	0.09	1.06	Negative	6.2mg/kg/day	14.6 years	15years	20hrs	4.7	<2	0.69	0.11	Subtle cognitive impairment
3	M	5months	2.3	10.4	<0.05	0.3	Negative	14 mg/kg/day	7.5yrs	8yrs	18hrs	3.6-8	2.4	1.34	0.11	Developmental delay mainly speech
4	F	23months	3.2	7.9	0.12	<0.05	Negative	9mg/kg/day	7yrs	9yrs	18hrs	3.7-6.3	<2	0.74	0.51	Initially delayed in speech, then catched up
5	M	9 days	1.7	3.5	0.3	<0.05	Negative	14mg/kg/day	7yrs	7yrs	18hrs	4.7-6.1	5	1.52	0.5	ADHD, Difficult in learning, IQ low average
6	M	18months	NA	NA	0.23	0.06	Negative	6mg/kg/day	8yrs	9.1yrs	16hrs	3.4-5.5	<2	0.31	<0.05	Developmentally appropriate to age
7	M	2wks	2.7	3.4	NA	NA	Negative	15mg/kg/day	7.8yrs	8yrs	18hrs	3.9-5.5	2.3	0.8	0.29	Developmentally appropriate to age
8	F	3months	1	32	NA	NA	Negative	18mg/kg/day	11yrs 8months	11yrs 11months	18hrs	4.6-6.2	7	0.37	0.11	Developmental delay with receptive and expressive language delay
9	M	10months	NA	NA	NA	NA	Negative	7mg/kg/day	5.3yrs	6.5yrs	18hrs	3.3-6.7	<2	1.11	0.33	Developmentally appropriate to age
10	M	18mnths	2.9	7.8	0.65	0.13	Negative	5mg/kg/day	2.9yrs	12.9yrs	14hrs	4.2-5.9	2.8	1.11	0.9	Slow and behind at school with poor concentration
11	M	5months	2.5	6	0.06	0.1	Negative	10mg/kg/day	3.5 years	4.0 years	18hrs	3.7-6.9	<2.0	0.7	0.8	Epilepsy, mild developmental delay
12	M	6months	2.7	5.8	0.07	<0.05	Negative	11.3mg/kg/day	4.5 years	5 years	19 hours	4.1-6.9	<2.0	1.1	0.35	Absence seizures, developmental delay

Results

Twelve diazoxide-responsive CHI patients with no known genetic aetiology were identified. Diagnosed between 9days and 23months old, three presented as neonates. Nine were male and all were born at term with median birth weight of 3.793kg (2.99-4.99kg). Three had pregnancy induced hypertension; none had gestational diabetes. All responded to diazoxide, with median maximum dose of 11.5mg/kg/day (5-20). All were negative for *ABCC8* and *KCNJ11* mutations. In all patients diazoxide was stopped at a median age of 8.5 years (4-15); the median duration of diazoxide therapy was 7.25years (2.9-14.6). Fasting studies done after stopping diazoxide showed resolution of CHI.

Conclusion

CHI children with no known genetic aetiology may be able to come off diazoxide at some stage during follow up. These children need regular assessments for continuing diazoxide therapy. The molecular mechanism(s) that lead to the gradual improvement in CHI over time are not known.

Authors have nothing to disclose

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Mouza Said AlYahyaei
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