

Presentation, clinical and genetic outcomes in a series of infants with Congenital Hyperinsulinism

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Background

Congenital hyperinsulinism (CHI) is a rare condition but a significant cause of recurrent hypoglycaemia in infancy and childhood. It's incidence is estimated to be 1 in 40,000-50,000 in the general population¹. It is characterized by the dysregulated secretion of insulin from pancreatic β -cells. Prompt recognition and appropriate management is important to avoid long-term neurological sequelae². To date mutations in eight different genes, that regulate insulin secretion, have been described in association with CHI³.

Most patients respond to medical therapy but for those requiring surgery it is important to differentiate focal and diffuse disease. Focal disease may be treated with limited pancreatectomy rather than 95% pancreatectomy, resulting in fewer long-term complications. Invasive techniques were required to differentiate these forms of CHI prior to the use of 18F-Fluorodopa positron emission tomography (18F-L -dopa PET)⁴.

Aim

To describe the presentation, clinical and genetic outcomes in a series of infants with CHI.

Materials and Methods

Retrospective case series of thirty-five patients diagnosed with CHI between 1992 and 2014 at The Children's University Hospital, Temple Street. Patients with transient hyperinsulinism were excluded. All statistical analyses were performed using PASW statistical package (version 18).

Results

Presentation:

Twenty of the thirty-five patients were male. Median age at presentation was day 2 (range: day 1-21 months) with nineteen patients (54%) presenting in the first 48 hours of life. Seizure was the most common presentation occurring in thirteen patients (37%).

Diagnosis:

Mean glucose requirements to maintain euglycaemia were 14.5 mg/kg/min (range: 7.5-23 mg/kg/min).

Management:

First line treatment with diazoxide was commenced in all patients of whom 22 (63%) responded. Of those that did not respond to diazoxide, three were stabilized on octreotide and ten required surgery.

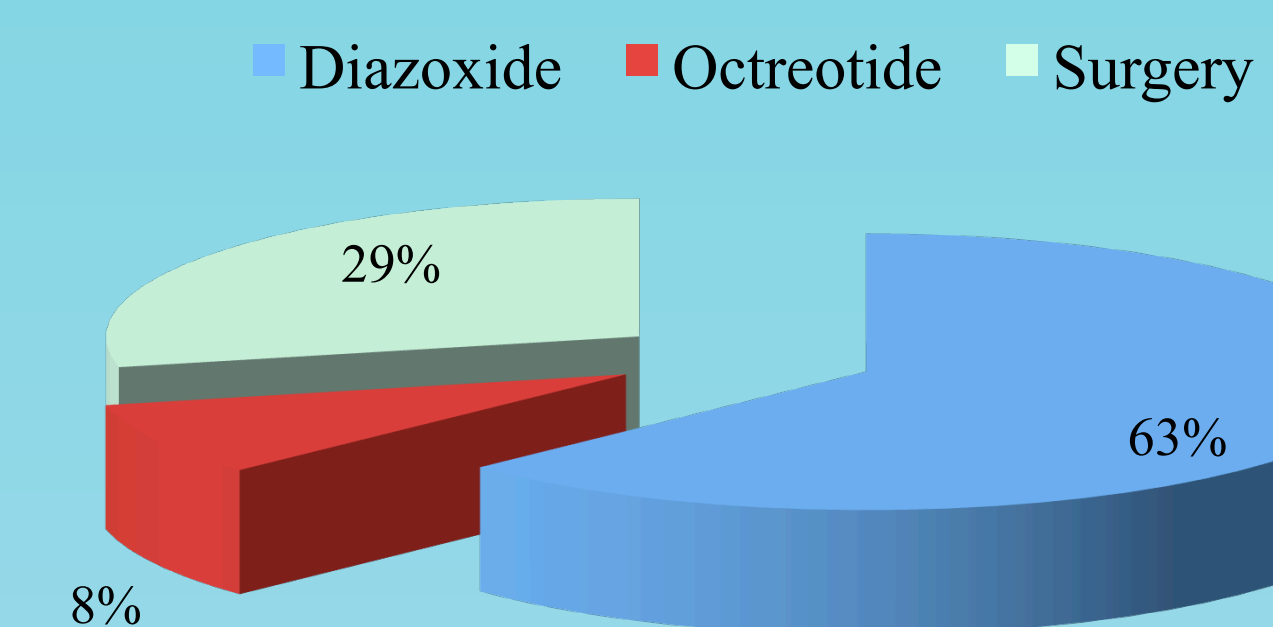
Genetic diagnosis:

Genetic testing was performed on thirty-one patients (89%). A genetic diagnosis was possible in eighteen patients (58%); thirteen had a mutation(s) in the ABCC8 gene, three had mutations in the HNF4A gene, one mutation in the KCNJ11 gene and one had a novel mutation in the HADH gene.

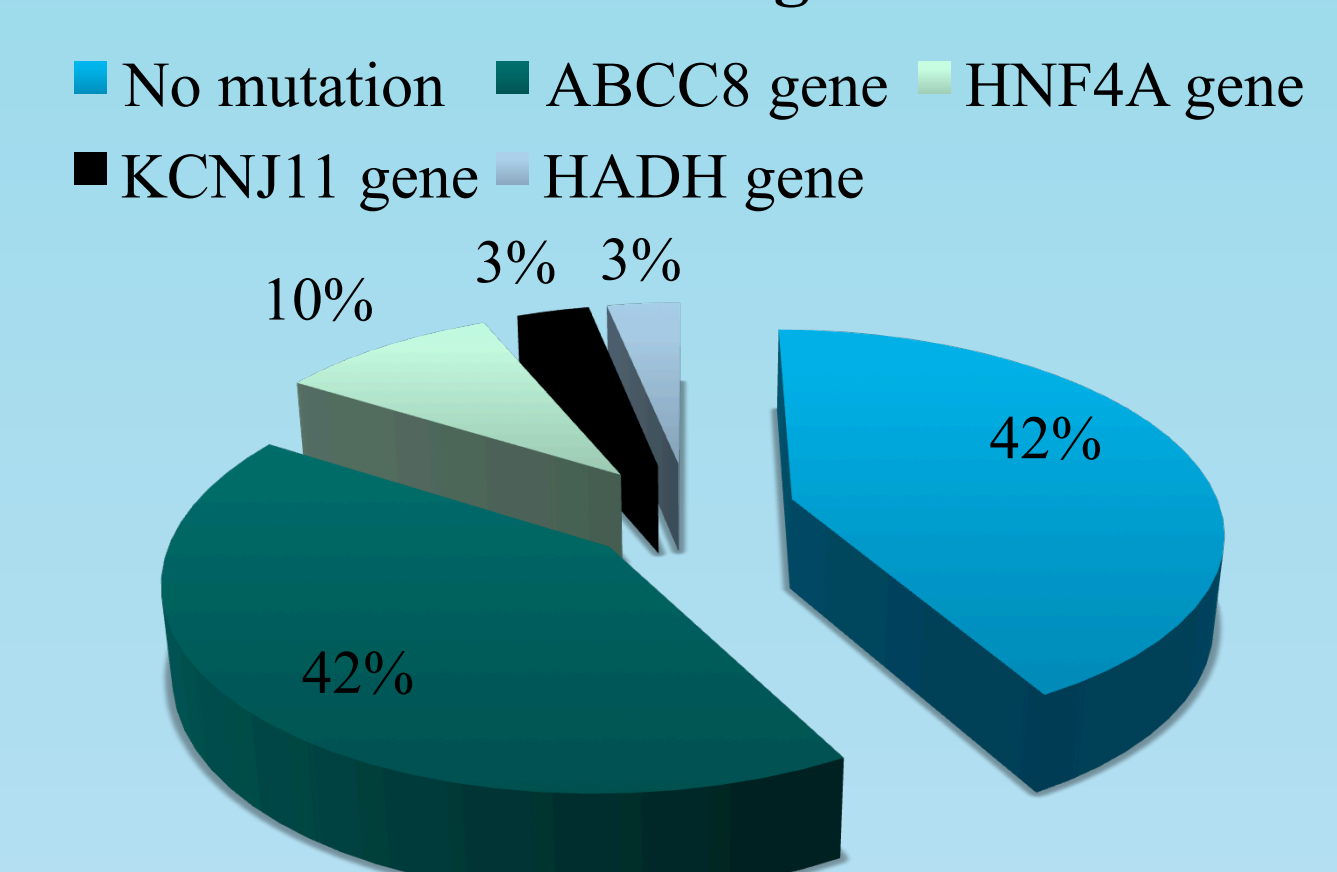
Development Outcome:

Twenty seven patients (77%) had a normal neurological outcome. Of the remaining eight patients, four have severe developmental delay, one of whom died of respiratory complications, one has moderate impairment and the remaining three patients have mild dyspraxia and speech delay. Oral aversion occurred in 14/35 (40%) of children but resolved by age 3 years in 11 of 14 (78%).

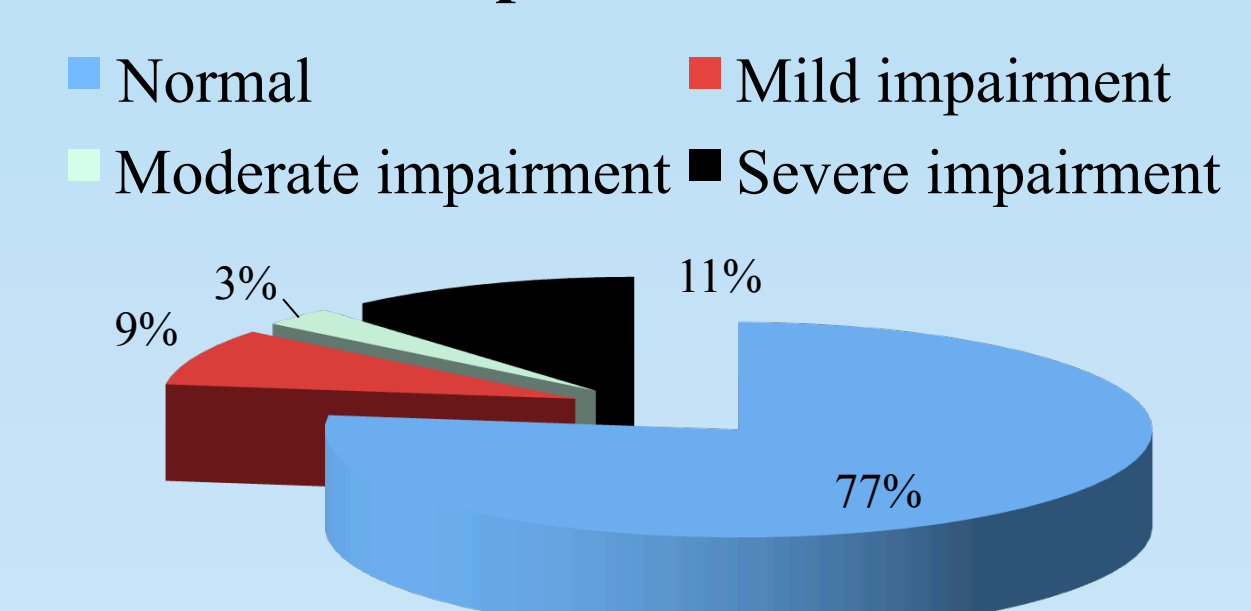
Response to medication



Genetic diagnosis



Developmental Outcome



Discussion

No clinical parameter significantly predicted developmental outcome. Advances in both molecular genetics and 18F-L -dopa PET scanning have revolutionised management of children diagnosed with CHI but early recognition and prompt appropriate treatment for hypoglycaemia are critical to reducing morbidity and mortality.

References

1. Ismail D, Werther G. Persistent Hyperinsulinaemic Hypoglycaemia of Infancy: 15 Years' Experience at the Royal Children's Hospital (RCH), Melbourne. *J Pediatr Endocrinol Metab.* 2005 Nov;18 (11):1103-09.
2. Menni F, de Lonlay P, Sevin C, Peigne C, Barbier V, Nihoul-Fekete C, Saudubray JM, Robert JJ. I. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinaemic hypoglycaemia. *Pediatrics* 2001;107:476-479.
3. James C, Kapoor RR, Ismail D, Hussian K. The genetic basis of congenital hyperinsulinism. *J Med Genet*; 46:289-299.
4. Hardy OT, Hernandez-Pampaloni M, Saffer JR, Suchi M, Ruchelli E, Zhuang H, Ganguly A, Freifelder R, Adzick NS, Alavi A, Stanley CA. Diagnosis and localization of focal congenital hyperinsulinism by 18F-Fluorodopa PET scan. *J Pediatr.* 2007 Feb; 150(2): 140-5