

BACKGROUND

Hyperinsulinaemic hypoglycaemia (HI) is a biochemical profile reflecting hyperinsulinaemic, hypoketotic, hypofattyacidaemic hypoglycaemia with increased glucose requirements [1, 2]. HI is the most common cause of persistent hypoglycaemia in the neonatal period after the first few hours of life. In severe cases hypoglycaemia is devastating. It may be difficult to control even in a hospital setting and may be associated with early brain damage [1, 2]. Published overseas data suggests an incidence of about 1/40,000 births [3, 4],

HI includes a continuous spectrum of conditions with differing genetic aetiology. Clinical features range in severity from subtle signs such as 'floppiness', 'jitters,' 'twitchiness' and poor feeding, through to overt signs such as seizures. While mild disease may be controlled by frequent feeding, severe disease may require medication (diazoxide) and severe unremitting hypoglycaemia may only be relieved by surgical removal of the pancreas (up to near-total resection) [5]. Pancreatic histology from surgical cases is usually abnormal. Disease may be focal on a background of normal pancreatic tissue or diffusely abnormal tissue may be located throughout the pancreas. It has been suggested that different histological types may require varying degrees of surgical resection, although currently this is unclear. [5].

HI is a well known cause of neurological damage [2, 6-8], thus it is essential that HI is rapidly diagnosed and controlled. Patients who respond well to medical treatment do not need pancreatic resection, however patients who are either non-responsive or unreliably responsive to medical intervention are at risk of brain damage. In the latter group, the decision to undertake pancreatic resection is very difficult because the risk of diabetes must be balanced against the risk of brain damage. Early definitive molecular diagnosis is an important goal because this may help us predict which patients do not respond to medication and require surgery. This is important because early surgery is associated with a reduced risk of diabetes [8].

The incidence of HI in Australia is unknown. European and middle eastern data suggests that the incidence of HI varies from 1/2,500 in consanguineous populations to 1/50,000 births [3, 4]. Our collaboration has identified over 70 children from Australia and New Zealand since 1977, estimated as around 1/70,000 births. However these children were identified retrospectively and this is likely to be an under-estimate of the true incidence.

STUDY OBJECTIVES

In this study we seek to document the epidemiology of HI in Australian children and to record known risk factors. With the assistance of reporting clinicians, we will also attempt to recruit notified cases to a longitudinal follow-up study. This will allow collection of prospective data about response to treatment and to identify factors associated with good or poor outcomes. This information will contribute to efforts to improve the detection and outcome of HI in affected children.

CASE DEFINITION

Please report all children under 10 years of age seen in the previous month with newly diagnosed hyperinsulinaemic hypoglycaemia. That is:

- Low blood sugar (<2.6 mmol/L) with low blood fats and low ketones
- **AND** inappropriately high insulin level
- **AND** persistent or recurrent hypoglycaemic episodes and/or glucose infusion for more than 10 days

FOLLOW-UP OF REPORTED CASES

A brief questionnaire requesting further details will be forwarded to clinicians who report a case of HI to the APSU. Reporting clinicians will also be invited to send a study information sheet to families of affected children to inform them how to contact study investigators should they wish to participate in the longitudinal study of HI in Australian children.

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REFERENCES

1. Hussain K and Aynsley-Green A. Hyperinsulinaemic hypoglycaemia in preterm neonates. *Arch Dis Child Fetal Neonatal Ed.* 2004;89:F65-F67.
2. Aynsley-Green A, Hussain K, Hall J, et al. Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed.* 2000;82(2):F98-F107.
3. Daneman D and Ehrlich RM. The enigma of persistent hyperinsulinemic hypoglycemia of infancy. *J Pediatr.* 1993;123(4):573-5.
4. Otonkoski T, Ammala C, Huopio H, et al. A point mutation inactivating the sulfonylurea receptor causes the severe form of persistent hyperinsulinemic hypoglycemia of infancy in Finland. *Diabetes.* 1999;48(2):408-15.
5. Lovvorn HN, 3rd, Nance ML, Ferry RJ, Jr., et al. Congenital hyperinsulinism and the surgeon: lessons learned over 35 years. *J Pediatr Surg.* 1999;34(5):786-92; discussion 792-3.
6. Meissner T, Brune W, and Mayatepek E. Persistent hyperinsulinaemic hypoglycaemia of infancy: therapy, clinical outcome and mutational analysis. *Eur J Pediatr.* 1997;156(10):754-7.
7. Menni F, de Lonlay P, Sevin C, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics.* 2001;107(3):476-9.
8. Jack MM, Greer RM, Thomsett MJ, et al. The outcome in Australian children with hyperinsulinism of infancy: early extensive surgery in severe cases lowers risk of diabetes. *Clin Endocrinol (Oxf).* 2003;58(3):355-64.