

Neonatal hypoglycaemia: consider hyperinsulinism!

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ORIGINAL

Summary

Hyperinsulinism (HI) is the most common cause of severe and persistent hypoglycaemia in infancy, and can lead to irreversible brain damage or death if not promptly recognised and appropriately managed. This article provides an overview of HI, including signs, risk factors and the key steps required for initial treatment and management. A glucose measurement is a vital sign: prompt recognition and treatment of hypoglycaemia by midwives, neonatal nurses and paediatricians can prevent potentially life-changing brain injuries for babies and their families.

What is HI?

HI is the most common cause of severe and persistent hypoglycaemia in infancy. It is caused by excessive insulin secretion from the pancreas, resulting in hypoglycaemia and suppression of alternative fuels for the brain (fatty acids, ketone bodies). As the brain is continuously dependent on a normal circulating blood glucose (BG) level, HI babies are at significant risk of irreversible brain damage or even death. Approximately 50 per cent of HI babies experience neurodevelopmental abnormalities (Avatapalle et al 2013, Lord et al 2015). Therefore, prompt hypoglycaemia recognition and management is an emergency and paramount to avoid brain injury and death.

HI can be transient or persistent. Transient HI (also known as perinatal stress-induced HI, PSHI) is thought to be triggered by significant perinatal stressors and requires medical intervention but typically resolves within the first weeks or months of life (Hoe et al 2006). In persistent HI, the need for medical intervention to manage the condition persists into childhood and sometimes adulthood. The affected beta cells can be throughout the entire pancreas (diffuse HI) or located in just a small part of the pancreas (focal HI) (Rosenfeld et al 2019). At least 30 genes have been identified as causative for HI, some of which are associated with syndromes (Hewat et al 2022). A genetic cause can be identified in approximately 50 per cent of people with HI

(Hewat et al 2022). Despite the type or cause, all forms of HI — focal and diffuse; transient and persistent — are associated with risk of neurological damage and so HI should be considered a medical emergency that must be managed immediately. If left untreated, the severe hypoglycaemia resulting from HI can cause various degrees of neurodevelopmental disorders, seizures and, sadly, even death (Avatapalle et al 2013, Lord et al 2015, Thornton 2021).

HI is rare. Prevalence estimates are approximately one in 28,000 in European ancestry births and may be up to one in 2500 in populations with high rates of consanguinity (Lapidus et al 2024). Transient forms of HI are more common, with an estimated incidence between one in 1200 and one in 2000 (Gray et al 2018, Bailey et al 2021). In the UK, the minimal incidence of HI measured by genetic testing referral rates for hyperinsulinism persisting beyond six months of age is one in 28,389 live births (Yau et al 2020).

Although HI is a rare disease, its clinical burden can be substantial. Each patient's care is individual; however, it is estimated that the annual cost of the illness to the UK's NHS is approximately £3,408,398 (Eljamel et al 2018).

HI commonly presents in the neonatal period, and many babies with HI develop hypoglycaemia during the first days and weeks of life (Banerjee et al 2022). Midwives, bedside nurses, neonatologists and paediatricians therefore play a key role in early

recognition and the prompt initiation of life- and brain-saving management.

Signs of hyperinsulinism

Within the first few hours or days of life, many infants with HI usually start to show signs of hypoglycaemia. The signs of hypoglycaemia reflect the brain's responses to glucose deprivation. These signs can be missed, as they are often confused with some typical behaviours seen in newborns (Table 1).

Table 1. Common signs of hypoglycaemia

Common signs of hypoglycaemia include:

- Irritability
- Lethargy
- Jitteriness/tremors
- Tachycardia or bradycardia
- Abnormal breathing patterns/apnoea
- Hypothermia
- High-pitched cry
- Hypotonia
- Pale/pallor/cyanosis
- Sweating
- Abnormal feeding behaviour (not waking for feeds, not sucking effectively, appearing unsettled and demanding very frequent feeds, especially after a period of feeding well).

(Committee on Fetus and Newborn & Adamkin 2011)

More severe signs, such as seizures, can occur with a prolonged or extremely low blood glucose level. If the blood glucose level is not corrected, it can lead to loss of consciousness and potential brain injury.

Parents often describe concerns for their babies ‘not feeding well, being sleepy, jittery, cold, pale, floppy’ (Banerjee et al 2022). A simple blood glucose measurement is essential if there are any signs of hypoglycaemia (Shaikh et al 2023, De Leon et al 2024).

Risk factors


There are several factors that increase an infant's risk of severe hypoglycaemia, including being large for gestational age (LGA) or small for gestational age (SGA), having a family history of hypoglycaemia or diabetes (including gestational diabetes), and perinatal stressors such as labetalol use during pregnancy, premature delivery or traumatic delivery (Hoe et al 2006, Bailey et al 2021). Babies who have any risk factors for hypoglycaemia require glucose screening before discharge, even in the absence of any signs of hypoglycaemia, as not all babies with HI exhibit the typical signs of hypoglycaemia. However, it is important to know that not all babies with HI exhibit risk factors for hypoglycaemia and all babies showing signs of hypoglycaemia should receive blood glucose screening immediately. Data from the HI Global Registry shows that 30 per cent of babies with HI were discharged from the birthing facility without a blood glucose test (Congenital Hyperinsulinism International 2024), therefore putting them at critical risk of severe hypoglycaemia at home.

Treatment and management

Step 1: protect the brain

The critical aim of the clinical management of HI is to prevent hypoglycaemia-induced brain damage; therefore, it is essential to treat hypoglycaemia as

A healthy brain depends on normal blood glucose.



NEWBORN VITAL SIGNS

Temperature: **Normal**

Heartbeat: **Normal**

Breathing rate: **Normal**


Blood pressure: **Normal**

Oxygen saturation: **Normal**

Blood glucose: **LOW**

It's vital to check and manage blood glucose in newborns.

Prolonged hypoglycemia is one of the most common causes of preventable irreversible brain damage.



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soon as possible. The most crucial first treatment is the administration of intravenous glucose to restore the blood glucose level to the normal range as specified in endocrinology guidelines (Shaikh et al 2023, De Leon et al 2024), followed by the treatment plan to diagnose and treat HI, with the aim to prevent further hypoglycaemic episodes.

Step 2: diagnose HI

In normal physiology, when the blood glucose level is low, insulin secretion is suppressed. However, infants with HI have insulin present in the blood at the time of hypoglycaemia. To diagnose HI, blood samples are needed to prove the presence of insulin at the time of hypoglycaemia. This is also supported by the infant's need for increased glucose requirement (for example, > 8 mg/kg/minute in a newborn with HI, compared to a normal rate of 4–6 mg/kg/minute) (Bier et al 1977). Free fatty acids and ketones (beta-hydroxybutyrate, BOHB) should also be measured at the time of hypoglycaemia. Low/undetectable BOHB supports a diagnosis of HI, as the action of excess insulin suppresses their production and protective actions.

Step 3: management

Once HI is diagnosed, specific treatment should be initiated. There are recognised centres of excellence (COEs) worldwide (Congenital Hyperinsulinism International n.d.). The UK and international guidelines for the management of HI are available to offer guidance and reference when it is appropriate to consult with a COE (Shaikh et al 2023, De Leon et al 2024).

In cases of focal HI, a potential cure is possible with surgical excision of the focal lesion (Shaikh et al 2023, De Leon et al 2024). For infants with diffuse HI, medical therapy is the preferred option. Diazoxide is the only approved medication to treat HI (Chen et al 2021). In some cases, diazoxide is not effective in preventing hypoglycaemia. In such cases, the condition is often managed with continuous carbohydrates delivered through a feeding pump and a gastrostomy tube, and/or off-label use of medications such as somatostatin analogues (Shaikh et al 2023, De Leon et al 2024). Only in the most severe cases, which are considered medically unresponsive, is surgery considered for diffuse HI. Clinical trials for alternative treatments are in development.

Take-home message

The brain is dependent on a continuous supply of glucose and is vulnerable to damage when blood glucose levels are low. Infants with HI are at high risk of irreversible brain damage or even death.

By simply measuring capillary blood glucose levels by the bedside, you can promptly identify hypoglycaemia and have a big impact on the treatment journey.

Prompt action by midwives, neonatal nurses and bedside clinicians can prevent potentially life-changing brain injuries for babies and their families.

Bedside midwives, neonatal nurses and paediatricians are best placed to identify and to measure a blood glucose level in an infant who is causing any clinical concern. **A glucose measurement is a vital sign.**

Parent narrative

'If his blood glucose could have been checked after birth when I was concerned or at least when the midwife came to visit us at home, he may not have got to the point of cardiac arrest which led to the rest of his problems. I believe that all midwives should carry blood glucose kits and be able to measure glucose levels — what harm can it do?'

(Parent of a child with HI)

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For more information on this topic see MIC database Search Pack: PN44 Hypoglycaemia and glucose levels in the neonate.

References

- Avatapalle HB, Banerjee I, Shah S, Pryce M, Nicholson J, Rigby L, Caine L, Didi M, Skae M, Ehtisham S, Patel L, Padidela R, Cosgrove KE, Dunne MJ, Clayton PE (2013). Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism. *Frontiers in Endocrinology* 20 May 2013. <https://doi.org/10.3389/fendo.2013.00060> [Accessed 15 September 2025].
- Bailey MJ, Rout A, Harding JE, Alsweiler JM, Cutfield WS, McKinlay CJD (2021). Prolonged transitional neonatal hypoglycaemia: characterisation of a clinical syndrome. *Journal of Perinatology* 41(5):1149-57.
- Banerjee I, Raskin J, Arnoux JB, De Leon DD, Weinzimer SA, Hammer M, Kendall DM, Thornton PS (2022). Congenital hyperinsulinism in infancy and childhood: challenges, unmet needs and the perspective of patients and families. *Orphanet Journal of Rare Diseases* 17(1):61. <https://doi.org/10.1186/s13023-022-02214-y> [Accessed 15 September 2025].
- Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM (1977). Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* 26(11):1016-23. <https://doi.org/10.2337/diab.26.11.1016> [Accessed 15 September 2025].
- Chen X, Feng L, Yao H, Yang L, Qin Y (2021). Efficacy and safety of diazoxide for treating hyperinsulinemic hypoglycemia: a systematic review and meta-analysis. *PLoS One* 16(2):e0246463. <https://doi.org/10.1371/journal.pone.0246463> [Accessed 15 September 2025].
- Committee on Fetus and Newborn, Adamkin DH (2011). Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics* 127(3):575-9. <https://doi.org/10.1542/peds.2010-3851> [Accessed 15 September 2025].
- Congenital Hyperinsulinism International* (2024). [Unpublished] The HI Global Registry.
- Congenital Hyperinsulinism International (no date). The CHI Centers of Excellence (COE) Program. <https://congenitalhi.org/the-chi-centers-of-excellence-coe-program/> [Accessed 30 May 2025].
- De Leon DD, Arnoux JB, Banerjee I, Bergada I, Bhatti T, Conwell LS, Fu J, Flanagan SE, Gillis D, Meissner T, Mohnike K, Pasquini TLS, Shah P, Stanley CA, Vella A, Yorifuji T, Thornton PS (2024). International guidelines for the diagnosis and management of hyperinsulinism. *Hormone Research in Paediatrics* 97(3):279-98. <https://doi.org/10.1159/000531766> [Accessed 15 September 2025].
- Eljamel S, Griffiths A, Evans J, Banerjee I, Hussain K, Thompson R (2018). The burden of congenital hyperinsulinism in the United Kingdom: a cost of illness study. *Orphanet Journal of Rare Diseases* 13(1):123. <https://doi.org/10.1186/s13023-018-0867-6> [Accessed 15 September 2025].
- Gray KD, Dudash K, Escobar C, Freel C, Harrison T, McMillan C, Puia-Dumitrescu M, Cotten CM, Benjamin R, Clark RH, Benjamin DK Jr, Greenberg RG; Best Pharmaceuticals for Children Act-Pediatric Trials Network Steering Committee (2018). Prevalence and safety of diazoxide in the neonatal intensive care unit. *Journal of Perinatology* 38(11):1496-502. <https://doi.org/10.1038/s41372-018-0218-4> [Accessed 15 September 2025].
- Hewat TI, Johnson MB, Flanagan SE (2022). Congenital hyperinsulinism: current laboratory-based approaches to the genetic diagnosis of a heterogeneous disease. *Frontiers in Endocrinology* 7 July 2022. <https://doi.org/10.3389/fendo.2022.873254> [Accessed 15 September 2025].
- Hoe FM, Thornton PS, Wanner LA, Steinkrauss L, Simmons RA, Stanley CA (2006). Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. *Journal of Pediatrics* 148(2):207-12. <https://doi.org/10.1016/j.jpeds.2005.10.002> [Accessed 15 September 2025].
- Lapidus D, De León DD, Thornton PS, Hood D, Breit J, Raskin J, Pasquini TLS (2024). The birth prevalence of congenital hyperinsulinism: a narrative review of the epidemiology of a rare disease. *Hormone Research in Paediatrics* 98(5):566-73 <https://doi.org/10.1159/000539464> [Accessed 15 September 2025].
- Lord K, Radcliffe J, Gallagher PR, Adzick NS, Stanley CA, De León DD (2015). High risk of diabetes and neurobehavioral deficits in individuals with surgically treated hyperinsulinism. *Journal of Clinical Endocrinology & Metabolism* 100(11):4133-9. <https://doi.org/10.1210/jc.2015-2539> [Accessed 15 September 2025].
- Rosenfeld E, Ganguly A, De Leon DD (2019). Congenital hyperinsulinism disorders: genetic and clinical characteristics. *American Journal of Medical Genetics Seminars in Medical Genetics* 181(4):682-92. <https://doi.org/10.1002/ajmg.c.31737> [Accessed 15 September 2025].
- Shaikh MG, Lucas-Herald AK, Dastamani A, Salomon Estebanez M, Senniappan S, Abid N, Ahmad S, Alexander S, Avatapalle B, Awan N, Blair H, Boyle R, Chesover A, Cochrane B, Craigie R, Cunjamalay A, Dearman S, De Coppi P, Erlandson-Parry K, Flanagan SE, Gilbert C, Gilligan N, Hall C, Houghton J, Kapoor R, McDevitt H, Mohamed Z, Morgan K, Nicholson J, Nikiforovski A, O'Shea E, Shah P, Wilson K, Worth C, Worthington S, Banerjee I (2023). Standardised practices in the networked management of congenital hyperinsulinism: a UK national collaborative consensus. *Frontiers in Endocrinology* 30 October 2023. <https://doi.org/10.3389/fendo.2023.1231043> [Accessed 15 September 2025].
- Thornton PS (2021). Recent updates in the management of infants and children with hyperinsulinism. *Current Opinion in Pediatrics* 33(4):424-9. <https://doi.org/10.1097/MOP.0000000000001022> [Accessed 15 September 2025].
- Yau D, Laver TW, Dastamani A, Senniappan S, Houghton JAL, Shaikh G, Cheetham T, Mushtaq T, Kapoor RR, Randell T, Ellard S, Shah P, Banerjee I, Flanagan SE (2020). Using referral rates for genetic testing to determine the incidence of a rare disease: the minimal incidence of congenital hyperinsulinism in the UK is 1 in 28,389. *PLoS One* 15(2):e0228417. <https://doi.org/10.1371/journal.pone.0228417> [Accessed 15 September 2025].

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