The History of Congenital Hyperinsulinism

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Hypoglycemia

- Glucose was first measured in blood in 1880's
- First reported in children in 1910 by Cobliner from Germany
- First English Paper was by Mann and Magath in 1924
- In 1937 the first well documented account of the signs and symptoms of hypoglycemia in infancy was reported by Hartman and Jaudon in J Pediatr. 1937 11:1
- The breakthrough of the importance of hypoglycemia came in 1954 by McQuarrie

McQuarrie 1954

- “Apparently many practicing paediatricians are almost totally unaware of the existence of the entity of severe persistent hypoglycemia of unknown cause which occurs spontaneously in otherwise healthy infants.”
- “hypoglycemia usually went unrecognized until permanent brain damage was apparent”

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Neonatal Hypoglycemia

- Also in 1954 Komrower and Farquhar described the changes in glucose levels in infants immediately after birth
- Farquhar went on to describe the infant of a diabetic mother and specifically the intrauterine overgrowth that was later attributed to insulin
- 30% babies have glucose <50mg/dl (2.8mmol/L) within 12 hours of birth and this is normal in the majority

Hypoglycemia and brain damage

- Cornblath first described hypoglycemia in infants born to mothers with toxemia who went on to develop brain damage in 1959. This might have been the first description of **Perinatal Stress Hyperinsulinism**
- Brown and Wallace in 1963 showed that prolonged neonatal hypoglycemia may lead to survival with mental deficiency and cerebral palsy
- 2013 Brain damage occurs in up to 20-40% of patients with Hyperinsulinism

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Insulin

- 1869 Langerhans (a German medical student) discovered that there were cells in the pancreas that did not secrete digestive juices and whose function was unknown
- 1889 Minkowski (another German) discovered that if you removed the pancreas from a dog it got diabetes

Insulin “cures” diabetes

- 1921 Banting and Best discovered an abstract of the pancreas that when injected in a diabetic would lower the blood sugar
- Working in a laboratory funded by Prof John Macleod they injected the first insulin into a boy called Leonard Thompson in 1922 and cured his diabetes

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- By 1923 Eli Lilly started large scale production of Insulin and made enough to treat most of the diabetics of North America.
- 1923 Banting and MacLeod got the Nobel prize for discovering insulin

Insulin and hypoglycemia

- 1927 Wilder reported a pancreatic cancer in a patient with symptoms of hypoglycemia.
- William Mayo operated and found multiple tumors. His team extracted a substance from the tumor and injected it into a rabbit and it caused hypoglycemia
- 1929 the first person was cured of insulinoma by surgery

Insulin and hypoglycemia

- 1955 Cochrane in GOSH London reported leucine sensitive hypoglycemia in 3 family members and one additional case.
- First accurate measures of Insulin by Berson and Yalow in 1963 and they showed insulin was elevated in children with leucine sensitive hypoglycemia.

- 1970 Baker and Yacovak described nesidioblastosis in infants with idiopathic Hypoglycemia of infancy
- 1974 Haymond and Pagliaria say Idiopathic hypoglycemia of infancy is really hyperinsulinism
- 1975 Stanley and Baker show how to diagnose and treat HI

Hyperinsulinism treatment

- Prior to 1966
  - Steroids
  - Growth hormone
  - Zinc glucagon
  - Long acting Epinephrine
  - Low leucine diet

Diazoxide

- 1964 Drash and Wolff noted that the side effect of hyperglycemia caused by the blood pressure medication Diazoxide could be used to treat idiopathic hypoglycemia of infancy.
- 1966 Lester Baker et al reported 8 children treated with diazoxide and found that 6 of the 8 responded very well.

Octreotide

- Somatostatin infusions were first used in the early 70's to treat insulinomas in adults.
- First described use in 1977 in a 2 month old baby post pancreatectomy in Boston Childrens's hospital by Hirsch et al
- Lead to the use of somatostatin analogues in adult insulinoma by 1985 and then in infancy by the late 80's early 90's (Thornton and Glazer)

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Future therapies

- Long acting Octreotide
- GLP1 antagonist
- Other somatostatin analogues

History of pathology

- In the 70's nesidioblastosis shown in pancreas of babies with hyperinsulinism (Baker and Yacovak)
- In the early 80's several different groups show that nesidioblastosis is an normal finding and not the cause of hyperinsulinism (Jaffe, Gossens and Rahier)

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Pathology to Surgery

- 1984 Rahier described the basic structural lesion of the pancreas and went on later to describe focal and diffuse pathologies which lead to the development of a new surgical strategy pioneered by Nihoul-Fekete in Paris.
- Focal HI could be cured by partial removal of the pancreas.

History of localization

- So how do you find the focal lesion
  - 1989 Brunelle from Paris described Trans-hepatic portal venous sampling
  - 2003 Stanley in Philadelphia described Pancreatic arterial stimulation with venous sampling
  - 2005/6 Ribero and Otonkoski report 18FDOPA Pet as an improved and less invasive method to differentiate focal from diffuse

History of localization

- Now between all the major centers >500 patients have been reported and it is becoming standard of care
- Multidisciplinary team still required to manage patients with expertise in PET, surgery, pathology and medical management.

History of genetics

- 1991 Thornton et al in Philadelphia suggested that HI was an Autosomal Recessive condition and in 1994 suggested it was also Autosomal Dominant
- 1994 Glaser reported gene for HI was on chromosome 11p14-15
- 1995 Bryan et al discovered the SUR1 gene at this location and Thomas described the first HI mutation in SUR 1 and subsequently in 96 in KIR6.2

History of genetics

- 1996 Weinzimmer in CHOP and Zammarchi described Hyperinsulinism Hyperammonemia (HIHA)syndrome subsequently discovered by Stanley in 1998 to be caused by mutations in GDH (now known as Glud-1)
- 1998 Glaser et al described GK HI

History of genetics

- 1997/98 the genetic basis for focal disease was determined by de Lonlay, Verkarre in Paris and Ryan in Dublin
  - Loss of maternal chromosome 11 and a mutation in the fathers ABCC8or KCN11 gene
- Subsequently mutations in HADH, SLC16A1, HNF4a, HNF1a, UCP2

What have we learned

- The speed of advances in HI has accelerated in the last 25 years
- Development of multidisciplinary centers with expertise is essential
- Despite all we know, still 20-40% babies suffer brain damage and this needs to be a major focus of our efforts
- Collaboration and sharing of data is crucial
- Early identification and rapid treatment is vital to improved outcome

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