

## 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





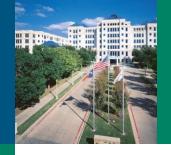


#### McQuarrie 1954

- "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"







## 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







#### 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







- 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)





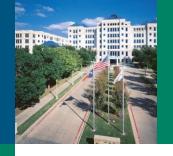


### **Future therapies**

- Long acting Octreotide
- GLP1 antagonist
- Other somatostatin analogues





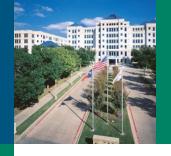


## History of pathology

- 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)







## 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.





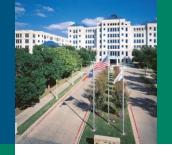


## History of localization

- So how do you find the focal lesion
  - 1989 Brunelle from Paris described Transhepatic 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





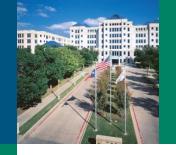


## History of localization

- 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.





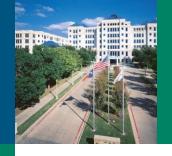


## History of genetics

- 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





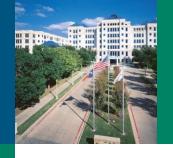


## History of genetics

- 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