Neonatal Diabetes Mellitus

Ibuola Olu'nifemi*, Elusiyan J. B. E.^
*Clinical II Student, OAU
^Consultant Paediatric Endocrinologist, Department of Paediatrics and Child Health, OAUTHC, Ile-Ife

DEFINITION, FORMS AND EPIDEMIOLOGY

Neonatal diabetes mellitus (NDM), a subset of monogenic diabetes mellitus, is a rare but possibly overwhelming metabolic disorder characterized by hyperglycaemia and low levels of insulin. Documented incidence is 1 in 300,000–400,000[1] live births, although values as high as 1:89,000[2] have been reported. Neonatal diabetes is insulin-requiring diabetes which is usually diagnosed in the first three months of life[3]. Based on clinical presentations, transient NDM (TNDM) and permanent NDM (PNDM) have been recognised as the two subgroups and they differ in the duration of insulin dependence early in the disease[1].

The characteristics of several identified causes of NDM are outlined below.

Table 1: Neonatal diabetes: characteristics of diabetes presenting in the first 6 months of life[3].

Gene/Clinical Syndrome Inheritance	PNDM/ TNDM	Age of diagnosis in weeks. Mean (range)	Pancreatic appearance	Other features
ZAC/HYMAI imprinting defect on 6q24	TNDM	0.5 (0-4)	Normal	Macroglossia (23%)
Kir6.2 (KCNJ11)	PNDM TNDM (10%)	6 (0-260)	Normal	Developmental delay (20%) Epilepsy (6%) DKA (30%)
SUR1 (ABCC8)	PNDM TNDM (78%)	6 (0-17)	Normal	Developmental delay
EIF2AK3 Wolcott-Rallison syndrome recessive	PNDM	13 (6-65)	Exocrine dysfunction (25%)	Epiphyseal dysplasia (90%), Osteopenia (50%) Acute liver failure (75%), Developmental delay (80%) Hypothyroidism (25%)
FOXP3 IPEX syndrome X linked	PNDM	6 (0-30)	Normal	Only boys affected Chronic diarrhoea with villous atrophy (95%) Pancreatic and thyroid autoantibodies (75%) Thyroiditis (20%), Eczema (50%), Anaemia (30%) Often die young
GCK (Glucokinase) Recessive	PNDM	—	Normal	Parents have fasting hyperglycaemia as heterozygotes
IPF-1 Recessive	PNDM	—	Absent	Parents may have early-onset diabetes as heterozygotes
HNF-1β dominant (60%)	TNDM	—	Atrophy	Renal developmental disorders
Spontaneous PTF-1A	PNDM	—	Absent	Severe neurological dysfunction and cerebellar hypoplasia

Adapted from Global IDF/ISPAD Guidelines for Diabetes in Children and Adolescence 2011
DKA-Diabetic Ketoacidosis, GCK-Glucokinase, HNF-1β - Hepatocyte nuclear factor 1 beta, IPF-1-Insulin Promoter Factor-1, PNDM-Permanent Neonatal Diabetes Mellitus, TNDM-Transient Neonatal Diabetes Mellitus

TYPES OF NDM

There are basically two types; Transient Neonatal Diabetes Mellitus (TNDM) and Permanent Neonatal Diabetes Mellitus (PNDM). The clinical presentations are the same but the only difference being that TNDM usually resolves by 3 months of age while PNDM persists for longer.

CLINICAL DESCRIPTION

Neonatal diabetes mellitus presents with hyperglycaemia, failure to thrive and, in some cases, dehydration and ketoacidosis within the first months of life. All forms of NDM are due to failure of the pancreas to release insulin in sufficient amounts to respond to high blood glucose levels thereby requiring exogenous insulin therapy[1]. NDM can be mistaken for the commoner Type 1 Diabetes Mellitus but this usually occur later and as found by Iafusco et al[4] in a study conducted in all infants developing diabetes before the age of one year that a clear difference was demonstrated between those infants developing diabetes before the age of 180 days and those after.

Babies with NDM, especially TNDM, are usually low birth weights secondary to intrauterine growth retardation (IUGR) which is usually present and is in concord with the role of insulin in fetal growth, especially during the last trimester of pregnancy[1].

A. Clinical description of TNDM

TNDM is a temporary developmental disorder of insulin production that usually resolves at a median of 12 weeks although as many as 50% of cases will eventually relapse3. TNDM represents 50% to 60% of cases of neonatal diabetes[5,6].

Patients could present with hyperglycaemia, failure to thrive, osmotic polyuria and, sometimes, dehydration. Insulin production is inadequate thus requiring exogenous insulin therapy. Tests are negative for anti-islet antibodies and for HLA class II haplotypes conferring susceptibility to type 1 diabetes[6]. Exocrine pancreatic insufficiency is present in only a few patients[7]. Most of the recurrences are consistent with non-autoimmune type 1 diabetes, although the mechanism remains unclear [5, 6, 8]. A permanent insulin requiring hyperglycaemia has been noticed leading to thoughts that TNDM is probably a permanent ß-cell defect with variable expression during growth and development. A major factor in the recurrence of diabetes is probably puberty, which is associated with significant insulin resistance[1].

Shield et al examined the indices of pancreatic ß-cell function, peripheral insulin sensitivity and the pancreatic response to intravenous glucose loading in children with a previous history of transient neonatal diabetes currently in remission repeated after a period of two years[9] and concluded that the majority of children with TNDM in remission have no evidence of ß-cell dysfunction or insulin resistance in the fasting state. Measures of insulin response to intravenous glucose loading are often normal but could be suggestive of future recurrence if profoundly abnormal[9].

B. Clinical description of PNDM

Permanent neonatal diabetes mellitus is the less common form of the condition. Here, diabetes develops in the neonatal period and does not go into remission1. There are no certain clinical features that can predict whether a neonate with diabetes but no other dysmorphic features will eventually have permanent or transient disease, although IUGR is less common[10,11].

MECHANISMS OF NDM

The clinical differences between transient and permanent neonatal diabetes is not always accounted for by a different molecular mechanism. The chromosome 6q anomalies have not so far been found to be associated with permanent neonatal diabetes although mutations in the SUR1 and Kir6.2 subunit have been found in association with both transient and permanent neonatal diabetes[12,13].

A. Molecular mechanisms of TNDM

TNDM is usually sporadic, but paternal transmission has been documented in about one-third of reported patients, some of whom had non-diabetic fathers[5]. It is associated with an abnormality of imprinting of the ZAC and HYMAI genes on chromosome 6q in the majority of patients11 including paternal uniparental disomy of chromosome 6, complete or incomplete[14], paternally inherited duplications of 6q24, and a methylation defect in this region[15]. These abnormalities strongly suggest that TNDM may result from over-expression of a paternally expressed gene located on chromosome 6q24. The two paternally expressed genes located in the region are therefore considered candidate genes for the disease: these are ZAC gene (LOT1, PLAGL-1) a gene encoding transcription factor that regulates both cell cycle arrest and apoptosis and the Pituitary

Adenylate Cyclase Activating Polypeptide Receptor 1 (PACAP1) being a potent insulin secretagogue, and the HYMAI gene, whose function is unknown[16].

B. Molecular mechanisms of PNDM

Heterozygous activating mutations in KCNJ11 encoding the Kir6.2 subunit of the pancreatic B-cell ATP-sensitive potassium channels (KATP) is the most common cause of PNDM. Mutations in the ABCC8 gene which encode the SUR1 subunit of the channel have also been identified. These channels couple cell metabolism to electrical activity by regulating trans-membrane movement of potassium. These channels are made up of an octameric complex with an equal number of both regulatory sulfonylurea receptors (SUR) and inwardly rectifying potassium channels (Kir)[1].

Other causes of PNDM include syndromic occurrences.

I. Pancreas agenesis and the Insulin Promoter Factor-1 (IPF1) gene: The first patient had pancreatic agenesis and marked endocrine and exocrine failure and was homozygous for a single nucleotide deletion within codon 63 of IPF-1 (Pro63fsdelC) [18]. The role of IPF-1 is in the control of exocrine and endocrine pancreatic development[19] and later, as a regulator of insulin and somatostatin gene expression. Cases of pancreas agenesis without IPF-1 mutation have also been described[15]. The heterozygous form causes Maturity Onset Diabetes of the Young (MODY) 4

II. Anomalies at the homozygous state in the Glucokinase gene : Glucokinase is a key regulator of glucose metabolism in islet cells, controlling the levels of insulin secretion. Reported cases include homozygosity for missense mutations within the glucokinase gene that rendered them completely deficient in glycolytic activity, while the heterozygous parents had mild to moderate glucose intolerance20.

III. IPEX syndrome and FOXP3 gene: This condition affects only males and present with a combination of exfoliative dermatitis, intractable diarrhea with villous atrophy, haemolytic anaemia, autoimmune thyroid disease and neonatal onset diabetes. Most children die in the first year of life due to overwhelming sepsis [3, 21]. The mutation in this condition lies in the FOXP3 gene that encodes a forkhead domain-containing protein[22] 'scurfin' which is essential for normal immune homeostasis.

IV. Wolcott-Rallison and EIF2AK3 gene: Wolcott-Rallison syndrome is an autosomal recessive disorder characterized by infancy onset (often within the neonatal period) diabetes associated with a spondyloepiphyseal dysplasia. There is also a syndrome of hepatomegaly, mental retardation, renal failure and early death[23]. In 2000, the condition was mapped to the locus 2p12[24] within which lays the gene EIF2AK3 that is highly expressed in islet cells and acts as a regulator of protein synthesis.

Other reported syndromes includes the cases of two boys with X-linked phosphoribosyl-ATP pyrophosphatase hyperactivity who became diabetic on day one of life has been described. Glucose intolerance persisted throughout life but improved as the children grew older. Both boys had other problems including mental retardation, ataxia and progressive axonal neuropathy[25].

Yorifuji et al. described a condition of neonatal diabetes associated with severe hypoplasia of the pancreas (only head and uncus present) and congenital cyanotic heart disease with apparent autosomal dominant inheritance. Not all the cases developed diabetes as a neonate, the timing is probably related to the size of remaining pancreatic tissue[26].

A syndrome was found to be linked to mutations in the PTF1A transcription factor, a major gene involved in pancreatic development and also expressed in the cerebellum which involved neonatal diabetes and cerebellar hypoplasia. Early mortality occurs from a combination of metabolic dysfunction, respiratory compromise and sepsis[27]

Mutations in Glis3 (another transcription factor) can explain syndromic neonatal diabetes, hypothyroidism, congenital glaucoma, kidney cysts and hepatic fibrosis[28].

DIAGNOSIS

Some accepted conclusions from current knowledge on neonatal diabetes mellitus includes that patients with TNDM are more likely to have intrauterine growth retardation and less likely to develop ketoacidosis, are younger at the age of diagnosis of diabetes and have lower initial insulin requirements than patients with PNDM. Also, very early onset diabetes mellitus seems to be unrelated to autoimmunity in most instances, recurrent diabetes is common in patients with "transient" neonatal diabetes mellitus and, consequently, prolong follow-up is imperative.

However, a considerable overlap occurs between the two groups, so that TNDM cannot be distinguished from PNDM based on clinical features and therefore, molecular analysis of chromosome 6 anomalies and the KCNJ11 and ABCC8 genes (encoding Kir6.2 and SUR1 respectively) provide a tool for identifying transient from permanent neonatal diabetes mellitus in the neonatal period1.

The uniparental disomy of the chromosome 6 can be shown by the analysis of polymorphic markers on chromosome 6; meiotic segregation of the chromosomes can be determined by comparing the allelic profiles of polymorphic markers close to 6q24 in the child and his parents.

A total uniparental disomy of the chromosome 6, a partial one or duplications can be found[29]. Methylation sensitive enzyme used with Polymerase Chain Reaction (PCR) can detect methylation defects[30].

The presence of a chromosome 6q anomaly suggests but is not pathognomonic of TNDM1.

TREATMENT

Insulin therapy and high caloric intake are the basis of the treatment.

Insulin therapy helps to obtain adequate growth in newborns and it is recommended that this is adjoined with a high caloric intake in these newborns. Management of insulin therapy in the newborn period is a difficult call as few data are available on the methods of insulin delivery in neonatal diabetes.

Mitamura R. et al recommended subcutaneous injection of ultralente insulin, rather than lente or isophane insulin, to avoid hypoglycaemia[31].

Polak et al also opined that multiple injections of regular insulin are sometimes difficult to manage and short acting insulins, both human and analogue, are best avoided except when using intravenous insulin infusions to initially stabilize the infant. In the UK, isophane insulin once daily has achieved reasonable control. The insulin analogue (insulin glargine) is a hopeful therapeutic candidate with its very steady pharmacokinetic profile[1].

The advances in the comprehension of the Kir6.2 and SUR1 subunits of the KATP channels has found a major clinical application for patients having permanent neonatal diabetes due to mutations of KCNJ11 or ABCC8. The transfer from insulin injections to oral sulfonylurea, particularly glibenclamide, therapy seems highly effective and safe for most patients[12,32]. Oral sulphonylurea therapy, unlike insulin alone, can improve both the glycaemic control and neurological status in some patients[33]. Transfer of the patients from insulin to sulfonylureas should be made within the legal rules of the country, as the use of sulfonylureas in children is not licensed in some countries because of the potential side effects[1].

When available, paediatric endocrinologists or specialized centers are the standard care givers.

GENETIC COUNSELLING

The chance of occurrence differs according to the form of the disease and to the particular molecular mechanisms involved.

Of the 6q anomalies, recurrence is theoretically absent in the case of uniparental disomy because none of the mother's allele is found in the proband and there is no transmission by the child. The recurrence risk in partial uniparental disomy is probably weak or close to zero, as the anomaly is post-zygotic. If partial duplication, there is a risk of disease recurrence in the family and parents have to be tested. Carriers of the duplication have a 50% risk of transmitting the defect.

Fathers will transmit both the disease and the genetic defect. Half of the children will have the disease with no sexual predilection. If the mother has the anomaly, her children will not have the disease but the male offspring will eventually pass on the disease but so far no familial case is known and the risk of transmission is unknown[1].

Most of the other mechanisms have a Mendelian inheritance. Recurrence risk is 25% in the autosomal recessive disorders (EIF2AK, Glis3, PTF1A, and PDX1 genes). IPEX syndrome is an X linked disorder.

Mutations in the KCNJ11 and ABCC8 genes are transmitted in the heterozygous state in a dominant way.

PROGNOSIS

Acutely, the prognosis is determined by the severity, early diagnosis and treatment of the disease and also the degree of dehydration and acidosis. The follow-up metabolic control or otherwise and associated conditions also play essential parts in prognosticating[1].

CONCLUSIONS

Neonatal diabetes is a rare condition but of great importance because of its associations with certain forms of the commoner Maturity Onset Disease of the Young (MODY) and type 2 diabetes, both of early onset and in young adults. Additionally, understanding neonatal diabetes will furnish information on normal pancreatic development and the basis of the pathology underlying pancreatic dysfunction[1]. The possibility of hyperglycaemia should therefore be an important reason for random blood glucose determination at admission for children.

Abbreviations

NDM- Neonatal Diabetes Mellitus
TNDM- Transient Neonatal Diabetes Mellitus
PNDM- Permanent Neonatal Diabetes Mellitus

REFERENCES

1. Polak M, Cavé H: Neonatal diabetes mellitus: a disease linked to multiple mechanisms Orphanet Journal of Rare Diseases 2007;2(12) doi:10.1186/1750-1172-2-12 (accessed 28 September 2013)
2. Grulich-Henn J. et al. Entities and frequency of neonatal diabetes: data from the diabetes documentation and quality management system. Diabet Med. 2010;27:709–12.
3. International Diabetes Foundation: Global IDF/ISPAD Guidelines for Diabetes in Children and Adolescence 2011
4. Iafusco D, Stazi MA, Cotichini R, Cotellessa M, Martinucci ME, MazzellaM, et al: Permanent diabetes mellitus in the first year of life. Diabetologia 2002;45(6):798-804.
5. von Muhlendahl KE, Herkenhoff H: Long-term course of neonatal diabetes. N Engl J Med 1995;333(11):704-708.
6. Shield JP, Gardner RJ, Wadsworth EJ, Whiteford ML, James RS, RobinsonDO, et al: Aetiopathology and genetic basis of neonatal diabetes. Arch Dis Child Fetal Neonatal Ed 1997;76(1):F39-42
7. Fosel S: Transient and permanent neonatal diabetes. Eur J Pediatr 1995;154(12):944-948
8. Shield JP, Baum JD: Transient neonatal diabetes and later onset diabetes: a case of inherited insulin resistance. Arch Dis Child 1995;72(1):56-57.
9. Shield JP, Temple IK, Sabin M, Mackay D, Robinson DO, Betts PR, et al: An assessment of pancreatic endocrine function and insulin sensitivity in patients with transient neonatal diabetes in remission. Arch Dis Child Fetal Neonatal Ed 2004;89(4):F341-3.
10. Metz C, Cave H, Bertrand AM, Deffert C, Gueguen-Giroux B, Czernichow P, Polak M: Neonatal diabetes mellitus: chromosomal analysis in transient and permanent cases. J Pediatr 2002;141(4):483-489.
11. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP: Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. Diabetes 2000;49(8):1359-1366.
12. Babenko AP, Polak M, Cave H, Busiah K, Czernichow P, Scharfmann R, et al: Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med 2006, 355(5):456-466.
13. Gloyn AL, Reimann F, Girard C, Edghill EL, Proks P, Pearson ER, et al: Relapsing diabetes can result from moderately activating mutations in KCNJ11. Hum Mol Genet 2005, 14(7):925-934
14. Das S, Lese CM, Song M, Jensen JL, Wells LA, Barnoski BL, et al: Partial Paternal Uniparental Disomy of Chromosome 6 in an Infant with Neonatal Diabetes, Macroglosssia, and Craniofacial Abnormalities. Am. J. Hum. Genet. 2000 671586-1591
15. Seick Barbarini D, Haslinger V, Schmidt K, Patch A-, Muller G, Simma B : Neonatal Diabetes Mellitus due to pancreas agenesis: a new case report and review of literature. Pediatric Diabetes 2009: 10: 487-491
16. Arima T, Drewell RA, Arney KL, Inoue J, Makita Y, Hata A, et al: A conserved imprinting control region1 at the HYMAI/ZAC domain is implicated in transient neonatal diabetes mellitus. Hum Mol Genet 2001, 10(14):1475-1483.
17. Chen R, Hussain K, Al-Ali M et al. Neonatal and late-onset diabetes mellitus caused by failure of pancreatic development: report of 4 more cases and a review of literature. Pediatrics 2008: 121: e1541 - e1547.
18. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF: Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet 1997, 15(1):106-110.
19. Jonsson J, Carlsson L, Edlund T, Edlund H: Insulin-promoter-factor 1 is required for pancreas development in mice. Nature 1994, 371(6498):606-609.
20. Njolstad PR, Sovik O, Cuesta-Munoz A, Bjorkhaug L, Massa O, Barbetti F, et al: Neonatal diabetes mellitus due to complete glucokinase deficiency. N Engl J Med 2001, 344(21):1588-1592.
21. Peake JE, McCrossin RB, Byrne G, Shepherd R: X-linked immune dysregulation, neonatal insulin dependent diabetes, and intractable diarrhoea. Arch Dis Child Fetal Neonatal Ed 1996, 74(3):F195-9.
22. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al: The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001, 27(1):20-21.
23. Wolcott CD, Rallison ML: Infancy-onset diabetes mellitus and J Pediatr 1972, 80(2):292-297.
24. Delepine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C: EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat Genet 2000, 25(4):406-409.
25. Christen HJ, Hanefeld F, Duley JA, Simmonds HA: Distinct neurological syndrome in two brothers with hyperuricaemia. Lancet 1992, 340(8828):1167-1168
26. Yorifuji T, Matsumura M, Okuno T, Shimizu K, Sonomura T, Muroi J, et al: Hereditary pancreatic hypoplasia, diabetes mellitus, and congenital heart disease: a new syndrome? J Med Genet 1994, 31(4):331-333.
27. Hoveyda N, Shield JP, Garrett C, Chong WK, Beardsall K, Bentsi-Enchill E, et al: Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of a new recessive syndrome. J Med Genet 1999, 36(9):700-704.
28. Senee V, Chelala C, Duchatelet S, Feng D, Blanc H, Cossec JC, et al: Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. Nat Genet 2006, 38(6):682-687.
29. Cave H, Polak M, Drunat S, Denamur E, Czernichow P: Refinement of the 6q chromosomal region implicated in transient neonatal diabetes. Diabetes 2000, 49(1):108-113.
30. Gardner RJ, Mackay DJ, Mungall AJ, Polychronakos C, Siebert R, Shield JP, et al: An imprinted locus associated with transient neonatal diabetes mellitus. Hum Mol Genet 2000, 9(4):589-596.
31. Mitamura R, Kimura H, Murakami Y, Nagaya K, Makita Y, Okuno A: Ultralente insulin treatment of transient neonatal diabetes mellitus. J Pediatr 1996, 128(2):268-270.
32. Siri AW: KATP Neonatal Diabetes, Pediatric Diabetes 2012, 13(4):354
33. Shepherd M, Cropper J, Flanagan S, Ellard S, Hattersley A. A diagnosis of monogenic neonatal diabetes can improve treatment and glycaemic control. J of Diabetes Nursing.2011;15(Suppl):25-9