CHAPTER 27

Neonatal Diabetes

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Chapter Outline

INTRODUCTION

Diabetes mellitus (DM) presenting as hyperglycemia during the first 6 months of life is a rare disorder that affects all races and ethnic groups and is increasingly being recognized as a separate entity. This form of insulin sensitive hyperglycemia has been termed "congenital diabetes mellitus" or "neonatal diabetes mellitus (NDM)" and is usually of genetic origin. Though technically, the neonatal period limits itself to the first 4 weeks of life, the term NDM has been used for diabetes with onset up to 6 months of life and most of these cases appear to have a monogenic form of inheritance due to a single gene mutation.[1-4] Although rarely NDM may present after 6 months of age, we propose the term infantile onset for those with onset more than 6 months of age. NDM presents as hyperglycemia, failure to thrive and in some cases, dehydration and ketoacidosis, which may be severe often with coma in an infant and occurs within the first few months of life.[5] NDM is rare with an incidence of 1:100,000–300,000 newborns.[5-9] Neonatal diabetes is heterogeneous and can be transient neonatal diabetes mellitus (TNDM) or permanent neonatal diabetes mellitus (PNDM). Insulin production is inadequate and therefore exogenous insulin therapy is required although some neonates with specific mutations in the *ABCC8* or *KCNJ11* genes may respond to sulfonylurea agents. Hyperglycemia in a neonate could be due to other factors like sepsis, higher infusion rates of glucose or prematurity. However, these conditions are transient and usually resolve with correction of the underlying process and do not need insulin therapy for long. The incidence, etiopathogenesis, presentation and management of NDM are discussed in this chapter.

CLASSIFICATION OF NEONATAL DIABETES MELLITUS

Neonatal diabetes is classified into two types: (1) TNDM and (2) PNDM. In addition, there are other forms with other genetic syndromes.

Transient Neonatal Diabetes Mellitus

Transient neonatal diabetes mellitus usually presents within the first few weeks of life. It needs insulin for at least 2 weeks and resolves by a median 12 weeks.

Table 27.1: Mutations in transient neonatal diabetes mellitus

Chromosome 6q related
• Paternal uniparental disomy
• Duplication defects
• Hypomethylation related
ABCC8 (SUR) mutation
KCNJ11 (Kir6.2) mutation

Rarely, it lasts until 12 months of age. In the west, TNDM represents 50–60% of cases of neonatal diabetes.[5] In our series of NDM, 5% had TNDM.[6] The commonest genetic mutation is the chromosome 6q24-related (*PLAGLI, HYMAI, ZFP57* gene), which accounts for nearly 70% of all the TNDM cases.[10-12] Two imprinted genes *ZAC* (zinc finger protein associated with apoptosis and cell cycle arrest) and *HYMAI* (imprinted in hydatidiform mole) present in the 6q region were identified as potential candidates for this imprinting disorder. Paternal uniparental disomy of chromosome 6, duplication of 6q24 region on the paternal allele and hypomethylation of the maternal differentially, methylated region (a CpG island overlapping exon 1of *ZAC/HYMAI*) account for the 6q related TNDM.[12] K_{ATP} channel mutations account for 25% of TNDM.[13-17] The mutations seen in TNDM are summarized in Table 27.1.

The cardinal features of TNDM are severe intrauterine growth retardation, hyperglycemia, dehydration, and absence of ketoacidosis. Neonates may present with breathlessness, lethargy and poor feeding. Insulin is required for fetal growth, and severe growth retardation could be due to insulin deficiency. Hyperglycemia is usually identified during routine investigations. Infants with 6q 24 related mutations may have macroglossia. Though transient, DM may recur in the pediatric age range, or later in adulthood in over 50% of cases. Annual evaluation for hyperglycemia is therefore mandatory in all children with TNDM during the remission phase. During relapse initial management may be by diet modification but subsequently, they may need insulin, as the response of oral sulfonylurea is uncertain. Women who have had 6q24-TNDM are at risk of relapse of diabetes during pregnancy. Thus, the "transient" form of the disease is most likely a permanent β-cell defect with variable expression during growth and development. Considerable overlap occurs between TNDM and PNDM and hence they cannot be distinguished based on clinical features alone and can only be differentiated based on genetic testing. However, in general, those with TNDM have lower insulin requirement in comparison to PNDM.[5]

Permanent Neonatal Diabetes Mellitus

This is a form of NDM which does not go into remission. Unlike western literature, in our series of 33 NDM children from India, we noted that 61% had PNDM and only 5% had TNDM.[6] About 60–75% of the PNDM with onset less than 6 months of age were found to be of genetic origin.[2] Based on the genetics of neonatal diabetes, they could be either syndromic or non-syndromic. The etiology of PNDM is summarized in Table 27.2.

ABCC8 Gene

The adenosine triphosphate (ATP) binding cassette sub family C member 8 (*ABCC8*) gene which encodes the four sulfonylurea receptors of the ATP sensitive potassium channels that regulates insulin secretion. It is located at 11p 15.1. Mutations in *ABCC8* can lead to both hyperinsulinism and hypoinsulinism. Activating mutations of the *ABCC8* gene lead to decreased insulin secretion and neonatal diabetes. About 20% of permanent neonatal DM is due to *ABCC8* mutation, which is inherited either as autosomal dominant or recessive pattern. *ABCC8* gene mutations that cause permanent neonatal DM result from single amino acid changes in the protein sequence, leading to K_{ATP} channels that do not close and reduced insulin secretion from beta cells. Babies with this mutation usually present with low birth weight and DM during the first 6 months of life. Neurological dysfunction may be a key feature in some with PNDM due to *ABCC8* mutation.[16,17] Transient hyperglycemia in neonatal period may be followed by permanent diabetes later in life.

KCNJ11 Mutations

KCNJ11 is the potassium inwardly rectifying channel subfamily J member *11* gene located at the 11p 15.1 chromosome. Mutations in the *KCNJ11* gene encoding the *Kir6.2* subunit of the beta-cell K_{ATP} channel accounts for the majority of children with diabetes diagnosed in the first 6 months of life.[18] The mutations are predominantly spontaneous but may be due to autosomal dominant inheritance and paternal mosaicism. Nearly, 30% of them present with ketoacidosis and developmental delay is reported in 20–40% of children.[6,18,19] In a few patients, *KCNJ11* mutations cause a triad of developmental delay, epilepsy, and neonatal diabetes which is called DEND syndrome. It probably results from mutated K_{ATP} channels in muscle, nerve and brain. The variant without epilepsy is called iDEND.[6] Studies have been performed to identify

Table 27.2: Types of permanent neonatal diabetes mellitus based on genetic mutations

Genetic defect	*Associated features*
Heterozygous mutations of the *ABCC8* gene (SUR)	Developmental delay
KCNJ11 (Kir6.2)	
Wolcott-Rallison syndrome with *EIF2AK3* mutation	Epiphyseal dysplasia, renal and hepatic failure
IPEX syndrome with autoimmunity with *FOXP3* mutation	Diarrhea, eczema, thyroiditis
Homozygous glucokinase mutation	Heterozygote parents
IPF mutation	Heterozygote parents
PTF1A mutation	Cerebellar hypoplasia, pancreatic involvement
GLIS3 mutation	Hypothyroidism, glaucoma
HNF 1β mutation	Renal cysts, genital malformations
Enteroviral related diabetes	
Others type A Insulin resistance syndrome	Features of androgen excess with hyperinsulinemia
Leprechaunism	
Rabson-Mendenhall syndrome	

(IPEX: Immune dysregualtion polyendocrinopathy enteropathy X-linked)

the association between potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*) gene and type 2 diabetes mellitus (T2DM) and the results have been inconsistent.[20]

Treatment with oral sulfonylurea results in good glycemic control and improvement in epilepsy and psychomotor abilities. Hence there is a need for a definitive genetic diagnosis in children with neonatal DM.

INS Gene

Mutations in the insulin gene (*INS* gene) account for another 20% of permanent neonatal DM. The genetic location of this gene is 11p 15.5. The precursor form of insulin, pro insulin is produced as single chain of amino acids, which is cleaved chains A and B, bound by the disulfide bonds, forming insulin. The mutation in *INS* gene disrupts the cleavage or the binding of the two chains leading to hypoinsulinemia and diabetes. These mutations are inherited in an autosomal dominant pattern. The homozygous mutations of *INS* gene account for the most common type of PNDM among consanguineous families. They manifest with severe intrauterine growth retardation and diabetes within few days or weeks of life. Some may present later, from 6 months to 1 year of age. Patients with *INS* mutations do not have other associated extrapancreatic features. Some patients have complications secondary to longstanding diabetes such as neuropathy and retinopathy. Mutations in *INS* gene may have diverse phenotypes from hypoinsulinemia and hyperinsulinemia to neonatal diabetes.

Glucokinase Mutation

Glucokinase (GCK) mutation accounts for 5–10% of PNDM.[21] Glucokinase is a key regulating enzyme in regulating pancreatic beta cell insulin synthesis. Being the glucose sensor, it plays a major role in insulin release. Mutations in the gene encoding GCK can lead to hypo or hyperglycemia. Heterozygotic mutation leads to milder phenotype presenting as MODY and the homozygotic mutations are with severe phenotype with presentation as PNDM.[22] Children with neonatal diabetes born of consanguineous parents, who have hyperglycemia, must be screened for *GCK* mutations. They present in the first few days of life with hyperglycemia with ketoacidosis usually requiring insulin therapy. Though sulfonylureas can enhance insulin release the response is not satisfactory. It may be used to reduce the insulin requirement.[23]

Syndromes of Insulin Resistance

Rarely insulin resistance syndromes like type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome and lipodystrophy can present with diabetes in the first few months of life. Generalized lipodystrophy in insulin resistance manifest by acanthosis nigricans, hyperandrogenism, muscular hypertrophy, hepatomegaly, glucose intolerance or diabetes and hypertriglyceridemia. In the generalized form, both subcutaneous and visceral adipose tissues are nearly absent. The congenital form is called the Berardinelli-Seip Congenital Lipodystrophy (BSCL). Berardinelli-Seip syndrome is a rare autosomal

recessive disease. Two loci for BSCL have been identified recently on chromosome 9 (*AGPAT2*) and chromosome 11 (Seipin). The high degree of insulin resistance makes metabolic control of diabetes very difficult despite high doses of insulin.[24] We have identified a novel mutation Val67Met in *AGPAT2* gene in one of our NDM patient with Berardinelli-Seip syndrome.[6]

Wolcott-Rallison Syndrome

Wolcott-Rallison Syndrome (WRS) is the most common cause of permanent neonatal DM seen in children born of consanguineous parents.[25] It was named after Wolcott and Rallison, who first described this syndrome in three affected siblings. WRS is a rare autosomal recessive condition characterized by early onset diabetes, epiphyseal dysplasia with multisystem involvement in the form of renal impairment, acute hepatic failure, developmental delay and hypothyroidism. Central hypothyroidism is usually noted during the acute presentation; it may be a reflection of euthyroid sick syndrome occurring during stress and is not part of the syndrome. They may have associated exocrine pancreatic dysfunction. WRS is associated with mutations in the Eukaryotic initiation factor 2 alpha kinase 3-EIF2AK3 (PKR like endoplasmic reticulum kinase PERK).[26-28] EIF2AK3 regulates the protein synthesis during stress by phosphorylating the α subunit of the eukaryotic initiation factor 2 (e IF 2). Four protein kinases: phosphorylate eIF2: GCN2, Heme regulated inhibitor, Double stranded RNA activated protein kinase (PKR) and EIF2AK3/PERK.

Though WRS commonly presents as neonatal diabetes, it can present as late as 30 months of age. *EIF2AK3* mutations are considered as the most common cause of NDM in regions where consanguineous marriages are more prevalent. In our experience, five families with different *EIF2AK3* mutations were identified. As the inheritance is recessive, children with homozygous mutations were affected whereas their unaffected parents were heterozygous. Skeletal dysplasia is usually diagnosed by 2 years and hepatic failure can occur at any time. Defective mineralization or dysplastic changes affect the long bones, pelvis and vertebra. The skull is usually spared. Hepatic involvement can be mild with hepatomegaly or severe and life threatening. Other features include renal dysfunction, exocrine pancreatic insufficiency, hypothyroidism, neutropenia and recurrent infections. WRS must be suspected in any child with diabetes onset at less than 2.5 years who presents with hepatic failure. Parents and heterozygous siblings of WRS patients do not have any distinctive features. Management includes close monitoring for hypoglycemia and ketoacidosis as both are frequent. Insulin pumps may be useful because of the brittle nature of diabetes. However, one should not target a very tight metabolic control in these children. Early diagnosis is recommended, in order to ensure rapid intervention for episodes of hepatic failure, which is the most life-threatening complication. Clinical course of this disease is variable due to the variable age of onset, varied clinical involvement and the associated complications. Prognosis is poor and these children usually die at a young age although a few can survive up to the age of 35. Death often results from multiorgan failure with renal dysfunction and hepatic failure sometimes associated with encephalopathy.

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

The *FOXP3* gene defect leading to immune dysregualtion, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is an autoimmune endocrinopathy associated with diarrhea, anemia, eczema and thyroiditis.[29,30] It is inherited as an X-linked disorder affecting only boys. Presentation is most commonly the clinical triad of watery diarrhea, eczematous dermatitis, and endocrinopathy (most commonly type 1 DM). Coombs-positive anemia, hypo- or hyperthyroidism, autoimmune thrombocytopenia, autoimmune neutropenia, and tubular nephropathy are some of the other autoimmune manifestations. Molecular testing confirms the diagnosis. Bone marrow transplantation can resolve clinical symptoms. Majority of the affected males die in the first few years of diagnosis due to sepsis or severe metabolic derangements. Milder phenotypes survive into second or third decade. Children presenting in late childhood have been reported.[31]

GLIS 3 Syndrome

Permanent neonatal diabetes mellitus can present due to mutations in *GLIS 3* associated with congenital hypothyroidism, congenital glaucoma, hepatic fibrosis and polycystic kidneys. It is rarely associated with osteopenia, bilateral sensorineural deafness and pancreatic exocrine insufficiency.[32,33] Gli-similar (GLIs) 1-3 proteins constitute a subfamily of Krüppel-like zinc finger proteins and the mutations have been implicated in many disorders.

Table 27.3: Glycemic levels of Indian children before and after sulfonylurea treatment[6]

S. no	Gene	Mutation	Zygosity	HbA_{1c} Levels		Fasting plasma glucose levels	
				Before SU treatment	After SU treatment	Before SU treatment	After SU treatment
1.	*KCNJ11*	Cys42Arg	Heterozygous	14.3%	7.0%	461 mg/dL	120 mg/dL
2.	*KCNJ11*	Arg201Cys	Heterozygous	10.8%	7.4%	275 mg/dL	110 mg/dL
3.	*KCNJ11*	Arg201Cys	Heterozygous	11.0%	7.2%	300 mg/dL	105 mg/dL
4.	*ABCC8*	Val86Ala	Heterozygous	7.8%	6.4%	250 mg/dL	92 mg/dL
5.	*ABCC8*	Asp212Tyr	Heterozygous	7.0%	6.2%	235 mg/dL	100 mg/dL

(SU: Sulfonylurea)

GENETIC STUDIES OF NEONATAL DIABETES MELLITUS IN INDIA

Neonatal diabetes mellitus is thus a form of monogenic diabetes where genetic testing currently has clinical application. *KCNJ11* and *ABCC8* mutations have been identified in Indian NDM children with onset of diabetes below 6 months of age (Table 27.3).[6] Children who are not harboring mutations in *KCNJ11* and *ABCC8* should be considered for screening of *INS, GCK, PDX1* and *HNF4A* genes, as the mutations in these genes were previously seen in children with neonatal diabetes.[34] Screening of additional clinical features is very important in case of NDM children because some of the syndromic features present in the later part of neonatal period. Hence, a proper diagnosis will help in appropriate genetic testing to aid for treatment regimen. Screening of *EIF2AK3, GCK, SLC2A2, SLC19A2, IPF1, PTF1A, HNF1B, FOXP3, ZFP57, GLIS3, GATA6, NEUROD1, NEUROG3, IER31P1, PAX6* and *RFX6* genes should be considered in case of NDM children with clinical features like hepatic failure, skeletal abnormalities, optic atrophy and developmental delay etc.[35] A number of homozygous mutations have been identified in children with syndromic forms of diabetes (Arg1065X in *EIF2AK3*, Val67Met in *AGPAT2*, and Leu19Arg in *SLC2A2* etc.) in Indian children.[6] Splice and frame shift mutations were identified in the genes associated with NDM in Indian children and these mutations are certainly pathogenic as they can disturb the normal protein synthesis mechanism (unpublished data).

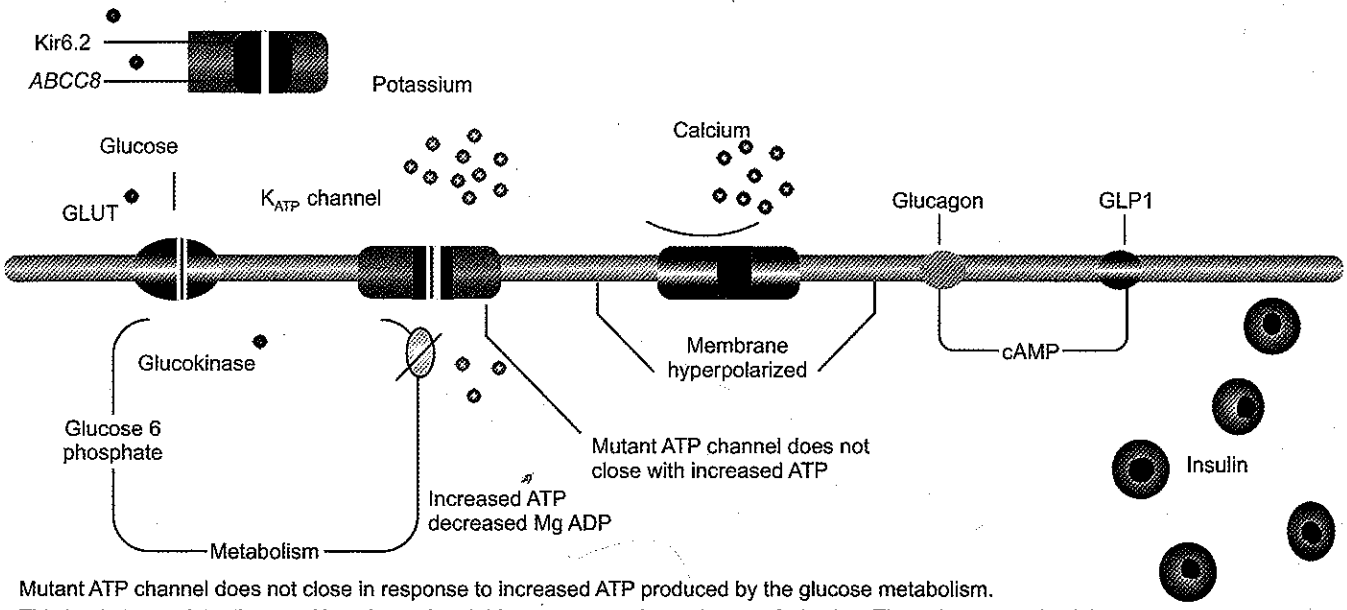
As the K_{ATP} mutations are sulfonylurea (SU) responsive, children with *KCNJ11* (Cys42Arg and Arg201Cys) and *ABCC8* (Val86Ala, Asp212Tyr and Pro254Ser) gene mutations have been successfully shifted to oral SU drugs from insulin injections.[17] Family genetic studies should be conducted to check the co-segregation of mutation with the disease which will help in predicting the risk for subsequent pregnancies.

PATHOPHYSIOLOGY OF NEONATAL DIABETES MELLITUS

While a few do not respond to oral suphonylurea, the majority of neonates respond to oral sulfonylurea therapy. The diagrammatic representation of the pathophysiology in pancreatic cells is shown in Figures 27.1 and 27.2.

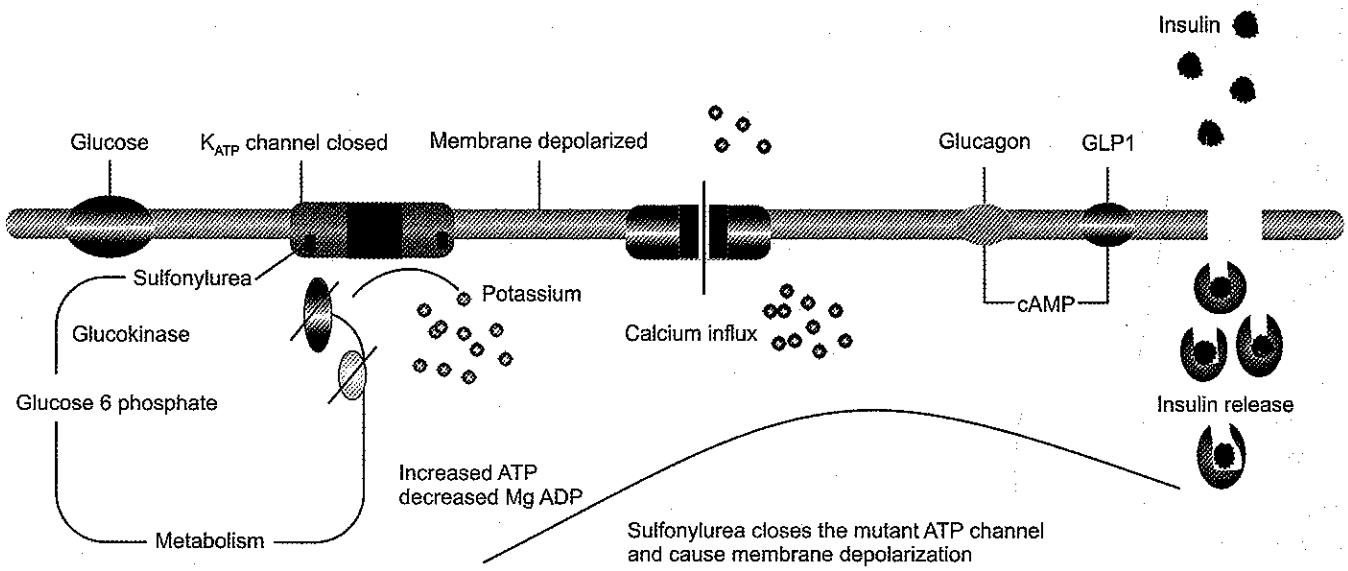
CLINICAL PRESENTATION AND DIAGNOSIS OF NEONATAL DIABETES MELLITUS

Neonatal DM in the immediate newborn period is usually diagnosed incidentally. Hyperglycemia in the neonatal period is more common and this usually resolves once the underlying disease process is treated. Differentiating this stress hyperglycemia from that of neonatal DM is challenging. One needs to wait for the resolution of the underlying diseases process and the C peptide levels may give some useful information. Neonatal DM can present as diabetic ketoacidosis with classical features of acidosis with hyperglycemia especially in KCNJ11 mutations.[18] It is not uncommon to misinterpret this acidosis as sepsis related lactic acidosis and delay the management of DM. In older infants, beyond 6 months of age, history of polyuria and polydipsia may be elicitable and a diagnosis of type 1 diabetes may be considered. This is usually confounded by presence of insulin autoantibody like the glutamic acid decarboxylase (GAD) antibody. Missed diagnosis of diabetes in not uncommon in diagnosis of DKA in infants. Since autoimmune etiology is less common in infants, all infants with diabetes should be carefully examined for any syndromic features and should undergo genetic evaluation for monogenic diabetes.



Mutant ATP channel does not close in response to increased ATP produced by the glucose metabolism. This leads to persistently open K_{ATP} channel and this causes membrane hyperpolarization. The voltage gated calcium channels remain closed and the intracellular calcium does not increase. This absence of cytosolic calcium prevents insulin exocytosis.
Note: Black dots represent the mutations

Fig. 27.1: Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations
(ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; GLP1: Glucagon like peptide 1; GLUT: Glucose transporters)
Pearson ER, et al. N Engl J Med 2006; 355:467-77



Sulfonylurea causes closure of the Mutant K_{ATP} channel in response to the increased ATP. This causes membrane depolarization and opens the voltage gates calcium channels. Intracellular calcium influx leads to exocytosis of insulin. The non ATP mediate mechanisms of insulin release are also augmented.

Fig. 27.2: Proposed model of the action of sulfonylurea (SU) on beta cells expressing mutations in the Kir6.2 subunit of the K_{ATP} channel
(ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; GLP1: Glucagon like peptide 1)
Pearson ER, et al. N Engl J Med 2006; 355:467-77

Confirmation of blood glucose more than once is mandatory to diagnose neonatal diabetes. A thorough clinical examination should include anthropometry, dysmorphic features, features of androgen excess, evidence of bony abnormalities, features of hypothyroidism and a detailed developmental assessment. Laboratory evaluation should include serum C-peptide levels, HbA_{1c}, thyroid function tests, serum uric acid, serum ammonia levels, ultrasonogram of the abdomen and genetic studies. It may not be feasible to obtain fasting and post-meal C-peptide samples as the feeding schedule in infants are inconsistent. Genetic studies are mandatory in all infants with onset of diabetes below 6 months of age and if possible in all children with DM whose onset is less than one year of age. It is prudent to evaluate all children with onset at less than 2.5 years of age with history of liver failure for WRS.

Management of Neonatal Diabetes Mellitus

The specific management includes insulin therapy and in genetic mutations responsive to oral sulfonylurea oral medications are used. The inconsistent feeding pattern and the requirement of insulin in very small doses pose difficulty in day to day management. However, if the requirement is very low, once or twice a day dose of intermediate acting insulin may be useful. Insulin pumps have been successfully used in neonatal DM as early as the first month of life.[36,37] In case of requirement of insulin being less than 0.5 units/dose it is ideal to use the insulin diluent provided by the insulin manufacturers. Caution must be provided as accidental overdose of insulin can be hazardous. Some infants may be very sensitive and develop rapid hypoglycemia with rapid or short acting insulin. Analog insulin like Glargine has been successfully used in extremely low birth weight neonates with DM.[38]

Switching over to Oral Drugs in Neonatal Diabetes Mellitus

Most of the *KCNJ11* and *ABCC8* mutations are responsive to oral sulfonylurea therapy. Drugs that have been successfully tried include oral glibenclamide and oral gliclazide. The SUR 1 selective sulfonylurea drugs will close β-cell K_{ATP} only while the non-selective sulfonylurea drugs like glibenclamide will also act on muscle and brain K_{ATP} channels. The mutated channels in nerve, muscle and brain are responsible for the neurological symptoms. Thus, a non-selective sulfonylurea may be a better choice in attempting to alleviate the neurological symptoms in infant with this mutation. A successful dose is likely to be much higher than the adult dose of the drug.[39-41] The process of switch to oral medications can be done as a rapid in-hospital procedure over a period of one week or it can be done as a slow process as outpatient therapy over a period of 4 weeks. Infants may need very high doses of sulfonylurea for switch. In view of altered renal clearance of sulfonylurea in infants, they may develop hypoglycemia during subsequent days of switch therapy. Hence, out patient protocol for transfer done over a few weeks would be better if home circumstances are appropriate for therapy. Prior to the switch, the following parameters are recorded—HbA_{1c} levels, general physical examination including height and weight, developmental age, gross motor, fine motor, verbal, neurological examination if any developmental delay (ideally with a quantitative, repeatable method), IQ (age appropriate test), electroencephalogram (EEG) if epilepsy and MRI if neurological features are present. A complete neurological evaluation is mandatory. To initiate the switch process begin with 0.1 mg/kg of the sulfonylurea given twice daily. The increment of dosage is to be done with simultaneous reduction of the insulin until the infant or the child is free of insulin. The commonest known side effects are skin allergies in 1.5% and they usually resolve, GI side effects including diarrhea in 1-2% and hematological features like anemia, leucopenia and thrombocytopenia.[42] Short term follow-up in these children has not revealed any untoward complications, however long term follow-up is awaited. Periodic monitoring of complete blood counts and liver function tests are advised. Table 27.4 summarizes the different switch protocol.[43]

While insulin therapy in these genetic mutations can only control the hyperglycemia, studies have shown that oral sulfonylurea therapy can also bring some improvement in the neurological impairment.[44] This switch over from insulin to oral sulfonylurea can be done at any age irrespective of the duration of diabetes. However, the chances of successful switch to oral therapy are reduced in adults especially if over 30 years where there has been poor glycemic control prior to switch. The dose required in neonatal diabetes may range from 0.5 mg/kg/day to 1.0 mg/kg/day.[39,41] Among the infants with *Kir6.2* mutation and SUR mutations, the insulin requirement and later sulfonylurea requirement was found to be significantly lower in the SUR mutation group.[5,45,46] The role of oral therapy is presently limited to the *KCNJ11* and

Table 27.4: Summary of the switch protocol from insulin to oral sulfonylurea

Slow out-patient switch protocol	*Rapid out-patient switch protocol*
Height, weight and complete neurological examination to be documented prior to switch	Height, weight and complete neurological examination to be documented prior to switch
Day 1: Fasting HbA_{1c}, C peptide levels. Give 0.1 mg/kg/dose of oral glibenclamide with breakfast. Continue evening dose with insulin, if blood glucose is more than 126 mg/dL	*Day 1:* Fasting HbA_{1c}, C-peptide levels taken. Give 0.1 mg/kg/dose of oral glibenclamide with breakfast. Continue evening dose with insulin if blood glucose is more than 126 mg/dL
Reduce the insulin slowly keeping the sulfonylurea constant for 1 week	*Day 2:* Omit the isophane insulin and continue only short or rapid acting insulin throughout therapy. Oral sulfonylurea is increased to 0.2 mg/kg/dose given twice daily and reduce insulin by 50%
Increase sulfonylurea to 0.2 mg/kg/dose twice daily during week 2 with decreasing insulin doses	*Day 3:* Increase the sulfonylurea to 0.3 mg/kg/dose given twice daily with reduction of insulin if the blood glucose is more than 126 mg/dL. Do not increase sulfonylurea, if sugars are less than 126 mg/dL
Increase the sulfonylurea to 0.3 mg/kg/dose in the 3rd week and to 0.4 mg/kg/dose in the 4th week and later up to 0.5 mg/kg/dose twice daily	Increase sulfonylurea to 0.3 mg/kg/dose on Day 4 and then to 0.4 mg/kg/dose to a maximum of 0.5 mg/kg/dose (1 mg/kg/day). Doses up to 2 mg/kg/day have been used in literature
Continue to monitor the blood glucose with every meal until the switch is complete by coming off insulin	Continue to monitor the blood glucose with every meal until the switch is complete by coming off insulin
Subsequent follow-up at 3 months with height, weight, a complete neurological assessment with HbA_{1c} levels and serum C-peptide levels	Subsequent follow-up at 3 months with height, weight, a complete neurological assessment with HbA_{1c} levels and serum C-peptide levels

ABCC8 mutations. The same has been successfully used in transient neonatal DM and in relapse of TNDM at 15 years of age in a child (glimepiride).[47,48] Sulfonylurea therapy has not been found to be useful in homozygous GCK mutation, Wollcott Rallison syndrome and other types of neonatal diabetes. However, there are some recent reports where homozygous GCK mutation had showed partial responsiveness to repaglinide, glibenclamide or glyburide.[32,49] The associated co-morbid states like pancreatic dysfunction, hypothyroidism, anemia and eczema need to be treated. Parental evaluation for heterozygote status may help to plan future pregnancies and antenatal genetic counseling and diagnosis. As the mother is the immediate caregiver in NDM, the role of these painful injections being given by the mother with whom the infant is developing bonding, needs to be addressed.

CASE STUDY

A 45-day-old male child was brought to the emergency room with a history of breathlessness of 1 day duration, lethargy and refusal of feeds noted since 8 hours. The child was the first born of consanguineous parents and was delivered as a full term baby by Cesarean section with a birth weight of 2.3 kg and had an uneventful neonatal period. The baby was exclusively breast fed and the present weight was 3 kg; the mother was concerned that the weight gain was very minimal despite being exclusively breast fed. The infant was initially evaluated by a physician and was referred to a tertiary care facility as suspected bronchopneumonia. Clinical examination at the emergency room revealed that the child was afebrile with lethargy, tachypnea and tachycardia with hepatomegaly of 7 cm. Other systems were normal. The infant was admitted with a provisional diagnosis of sepsis with bronchopneumonia. The investigations revealed normal chest X-ray, serum sodium of 130 mEq/dL, potassium of 5 meq/dL, and a bicarbonate of 10 mEq/dL. His urea was 98 mg/dL and creatinine was 2.1 mg/dL. Routine blood sugar done at the bed side was high. The blood glucose was subsequently confirmed in the laboratory to be 550 mg/dL. Urine sugars were +++ and ketones were mildly positive. Retrospectively, a history of polyuria was obtained, which the mother was not able to recognize as abnormal being a neonate. There was also a history of white patches over the external genitalia, which were noticed for 2 weeks prior to the illness. There was no dehydration clinically but blood gases revealed metabolic acidosis with a wide anion gap. The child was treated as per DKA protocol and stabilized after 72 hours of hospital stay and switched over to subcutaneous insulin injections. His HbA_{1c} level was 9%. Serum C-peptide was low and GAD antibodies were negative. Baby required 1 unit/kg/day

of insulin to start with and was stabilized after 10 days on 1 unit of intermediate insulin in the morning and 0.5 units of intermediate acting insulin in the evening. Genetic analysis was done 2 weeks later and the child was found to have a homozygous *ABCC8* mutation. Both the parents were heterozygous carriers for the mutation. Following genetic reports, the baby was readmitted for an in-hospital transfer process to oral sulfonylurea. The child had a successful switch over to oral glibenclamide at the dose of 1.5 mg/kg/day given in two divided doses. There was no episode of hypoglycemia and after 3 months of the switch, the HbA_{1c} reduced to 7.8% and at the end of 6 months, to 6.5%. The serum C-peptide levels improved. At 3 years of age, the child had good metabolic control and normal growth and development.

PROGNOSIS AND LONG-TERM OUTCOME IN NEONATAL DIABETES MELLITUS

Neonatal diabetes is very different from other forms of diabetes in that the course of disease is variable. In some infants it is transient, in some it remits after varying periods of insulin dependency only to recur later in life, in some infants it continues to be permanent DM. Outcome in the immediate neonatal period depends on the presentation, severity of dehydration and acidosis and how early it is recognized and treated appropriately. In the post neonatal period the prognosis is determined by associated conditions like neurological involvement or hepatic involvement.

Though it resolves in a few weeks, transient neonatal diabetes can later lead to diabetes over the years. Some of these genetic mutations predispose the pregnant mother who had TNDM in the past to develop DM during pregnancy. Hence, the infants with TNDM need to be followed up for relapse later. Follow-up studies on children on oral sulfonylurea has shown good metabolic control and improvement of developmental delay and are safe in the short term.[2,19] Reports from literature mention the incidence of hypoglycemia with oral medications to be rare.[2] Frequent monitoring is advised during intercurrent illness. Those with WRS frequently develop acute hepatic failure and frequently die in the earlier years of life. Though not much therapy is available for WRS, recent reports mention an insulin free life for a 6-year-old who underwent a quadruple organ transplant with both kidneys, pancreas and liver. Except for these occasional case reports the long-term outcome for WRS is poor. Some of the PNDM may require replacement therapy for the exocrine functions of the pancreas as well. Finally, the level of metabolic control determines the timing of appearance of the long-term complications like any other diabetes. The management in insulin resistance syndromes is much difficult. The impact of insulin sensitizers is very limited in severe insulin resistance states. In partial lipodystrophy, metformin may be useful. In total lipodystrophy, leptin therapy may be useful though presently it is for research purposes only.[50] Response of NDM subjects with *Kir6.2* and SUR-1 (*ABCC8*) mutations to sulfonylurea therapy represents one of the best examples of the benefits of genetic testing in the field of medicine.

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