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Review

Neonatal Diabetes Mellitus: Clinical and Genetic Approach

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Neonatal diabetes mellitus (NDM) is monogenic diabetes occurs in the first 6 month of age with an incidence of one in 20,000 to 500,000 newborn. This form of diabetes can be either transient (TNDM) resolves within a few months to relapse mainly at pubertal age or permanent (PNDM) stays for life.Abnormalities in the chromosome 6q24 region is present in approximately 70% of TNDM cases, mutations in the KCNJ11 genes, encoding the Kir6.2 subunit of the pancreatic KATP channel is the main case of PNDM, while mutations in the ABCC8 genes encoding the SUR1 subunit of the pancreatic KATP channel can be present in both TNDM and PNDM. Patients with TNDM usually presented earlier and have lower birth weight than PNDM, but there is a considerable overlapping in clinical features between the two groups necessitate molecular genetic tests for accurate diagnosis which has important therapeutic impacts on patients leading to transfer most of PNDM patients with activating mutations in KCNJ11 and ABCC8 genes, from insulin therapy to oral sulfonylurea. This review about NDM focuses on clinical presentation, genetic etiologies,diagnosis, acute treatment and long-term management. We describe a diagnostic algorithms for assessment of suspected neonatal diabetes to increase the yield of positive tests (Figure 2,3).

Keywords: Neonatal diabetes, Permanent neonatal diabetes, Transient neonatal diabetes, KATP channel mutations, Molecular genetic testing, Sulfonylurea.

INTRODUCTION

Monogenic diabetes is a heterogeneous disease with more than 30 subtypes results from different genes mutations affect mostly β-cell function, growth or insulin transcription. It is prevalence is estimated to account for 2–5% of all patients with diabetes (Ledermann, 1995; Fendler et al., 2012; Irgens et al., 2013). Neonatal diabetes mellitus (NDM) is one form of monogenic diabetes with a reported incidence of one in 20,000 to 500,000 newborn (Habeb et al., 2012; Grulich-Henn et al., 2010; Wiedemann et al., 2010; Globa et al., 2015; Iafusco et al., 2012). It develops mainly in the first 6 months of age. Iafusco et al. (Iafusco et al., 2002) found that 76% of 36 children who developed diabetes before 180 days had a protective HLA antigen and no autoimmune markers. Many studies indicate that diabetes before 6 months of age is NDM, (Iafusco et al., 2002; De Franco et al., 2015; Naylor et al., 2011; Edghill et al., 2010; Sperling, 2005; Rubio-Cabezas et al., 2014; Flanagan et al., 2006; Flanagan et al., 2007; Shield et al., 1997) with absent of autoimmune markers of B-cell destruction, (Edghill et al., 2006; Edghill et al., 2004) but its prevalence is lower than type1diabetes after 6 months of age (Iafusco et al., 2002; Iafusco et al., 2014). Sporadic, recessive, dominant and X-linked inheritance has been reported (Garin et al., 2010; Gloyn et al., 2004; Wildin et al., 2001). Early molecular genetic diagnosis of NDM has been helped in confirming the diagnosis, appropriate treatment, and prognostic information. Neonatal diabetes is classified into two subgroups, transient NDM (TNDM) which represents 50-60% of neonatal diabetes, mainly due to abnormalities in the chromosome 6q24 region and requires insulin for the transient period. Permanent PNDM does not go into remission, mainly due to activating mutations of KATP channels (Gloyn et al., 2004; Babenko et al., 2006; Augilar-Bryan et al., 1995; Inagaki et al., 1995; Edghill et al., 2008) and usually respond to oral sulfonylurea (Pearson et al., 2006; Rafiq et al., 2008).

Types of neonatal diabetes mellitus

TRANSIENT NEONATAL DIABETES MELLITUS

TNDM accounts for 50-60 % of all cases of NDM results mainly from overexpression of genes in the 6q24 region, which contains two major TNDM genes, HYMA1 (hydrogenase subunit HymA) and ZAC 1 (zinc finger, apoptosis, and cell cycle) (Gardner et al., 2000; Mackay and Temple, 2010). In the normal situation these genes at 6q24 region is imprinted in such a way that the paternal allele is expressed actively while the maternal allele remains silent. About 70% of TNDM results from loss of imprinting at 6q24 region and the subsequent overexpression of TNDM genes (Gardner et al., 2000; Abdollahi, 2007; Metz et al., 2002) by duplication of this 6q24 region (paternal duplication) which accounts for the majority of familial cases (Cavé et al., 2000), paternal uniparentalisodisomy (UPD), which is common in sporadic cases (Temple et al., 1995; Gardner et al., 1998; Hermann et al., 2000; Hermann and Soltész, 1997; Whiteford et al., 1997), or maternal hypomethylation which also present in sporadic cases (Metz et al., 2002) (Table) 1. Activating mutations of the KATP channel genes (KCNJ11 or ABCC8) encoding the Kir6.2 and SUR1 subunits respectively are present in 20% of TNDM (Flanagan et al., 2007; Gloyn et al., 2004; Inagaki et al., 1995). (Table 1) Few cases of TNDM attribute to mutations in hepatocyte nuclear factor-1beta (HNF1beta) (Table 1) that causing two form of monogenic diabetes, TNDM in Homozygous condition and maturity-onset diabetes of the young (MODY5) in Heterozygous state (table1) (Yorifuji et al., 2004; Edghill et al., 2006). NDM is characterized by low insulin which cloud be from delayed maturation of pancreatic B-cells as a result of the overexpression of imprinted genes on the 6q24 region that leads to reducing insulin or from defects in glucose sensing that resulting from B-cell dysfunction. It is responding to insulin therapy and resolves spontaneously within a few months the maximum reported the age of remission is 18 month (Docherty et al., 2013; Temple et al., 2000), to relapse years later usually during adolescence or early adulthood with features of type 2 diabetes mellitus. (Flanagan et al., 2007; Murphy et al., 2008; Hattersley and Ashcroft, 2005) Thus a relapse may be a consequence of variable expression β -cell defect during growth and development (Mackay and Temple, 2010; Murphy et al., 2008; Aguilar-Bryan and Bryan, 2008)

PERMANENT NEONATAL DIABETES MELLITUS

PNDM has no remission period characterized by absent or low insulin as a result of B-cell dysfunction or decrease in B-cell mass (Aguilar-Bryan and Bryan, 2008). KATP channels play important roles in glucose homeostasis by regulating insulin secretion from pancreatic β cells (Ashcroft et al., 1984; Ashcroft and Rorsman, 1989). It composed of four SUR1 and four KIR6.2 subunits that found across cell membranes of beta cells of the pancreas. It responds to fluctuating changes in blood glucose concentrations by regulates insulin secretion to keep normal blood glucose (Seghers et al., 2000; Henquin, 2000). In normal B-cells function, intracellular production of ATP from glucose metabolism increased and bound to KIR6.2 subunit, resulting in closing the KATP channels and inhibiting potassium efflux resulting in depolarization of cell membrane, the influx of calcium and raise intracellular calcium concentration resulting in exocytosis of insulin granules (Figure 1). Mutations of the KCNJ11 gene encoding Kir6.2 subunit-inhibit closure of the potassium channel and depolarization cell membrane resulting in prevention of insulin secretion (Hattersley and Ashcroft, 2005). Also, mutations of ABCC8 gene encoding SUR1 subunits inhibit channel closure and insulin release (Babenko et al., 2006). Activating mutations in the KCNJ11 gene is the most common cause of PNDM account for 31% of cases (Gloyn et al., 2004; Inagaki et al., 1995; Babenko et al., 2006) however mutations in the insulin (INS) gene and ABCC8 account for 12% and 10% of cases of TNDM, respectively (Augilar-Bryan et al., 1995; Augilar-Bryan et al., 1995; Babenko et al., 2006). A few cases of PNDM are attributed to mutations in other genes that encoding pancreas transcription factor 1α (Sellick et al., 2004), glucokinase (GCK), (Njolstad et al.,2001) eukaryotic translation initiation factor 2-alpha kinase (EIF2AK3) (Delepine et al., 2000) insulin promoter factor 1 (Stoffers et al., 1997), or forkhead box P3 protein (FOXP3) (Peake et al., 1996; Bennett et al., 2001), which are important for B-cell function and development (Naylor et al., 2011). Identification of these mutations help in knowing accurately the etiology of NDM, establish long term management, and genetic counseling. PNDM in 20% of cases of Kir6.2 mutation is associated with developmental delay and epilepsy (DEND syndrome) (Shimomura et al., 2007; Proks et al., 2005) (table1). The less severe form of DEND without epilepsy has been described and is known as (iDEND) (Fendler et al., 2013). Also, Mutations in the ABCC8 gene (11p15.1) have been reported rarely with DEND (Proks et al., 2007).

Table 1. Causes of neonatal diabetes mellitus

Gene	Inheritance	Pancreatic Pathology	Clinical features	Treatment
Transient NDM				
6q24 abnormalities ZAC (PLAG1), HYMA1	variable	Reduced Β-cell mass	± macroglossia ± umbilical hernia	Insulin, relapsed cases respond to oral medication
KCNJ11	S, AD	Reduced β-cell function	± DEND	Responsive to sulfonylureas
ABCC8	S, AD	Reduced β-cell function	Low birth weight	Responsive to sulfonylureas
INS	Variable	Reduced β-cell function	Low birth weight	insulin
Permanent NDM				
KCNJ11	S, AD	Reduced β-cell function	± DEND	Responsive to sulfonylureas
ABCC8	S, AD	Reduced β-cell function	Low birth weight	Responsive to sulfonylureas
INS	Variable	Reduced β-cell function	Low birth weight	Insulin
GCK	AR	Reduced β-cell function	Low birth weight	Insulin ± sulfonylureas
Syndromic NDM				
FOXP3 IPEX syndrome	X-linked	Destruction of β-cells	PNDM, autoimmune enteropathy thyroid disease, eczema	Insulin
EIF2AK3 Wolcott–Rallison Syndrome	AR	Destruction of β-cells	PNDM, Spondyloepiphyseal dysplasia, recurrent liver dysfunction renal failure, mental retardation	Insulin
GLIS3	AR	Reduced Β-cell mass	PNDM, Congenital hypothyroidism glaucoma, hepatic fibrosis, renal cysts	Insulin
NEUROD1	AR	Reduced Β-cell mass	PNDM, Cerebellar hypoplasia, visual impairment, sensorineural deafness, developmental delay	Insulin
PAX6	AR	Abnormal pancreatic development	PNDM, microphthalmia, brain malformations	Insulin
HNF1B	S, AD	Abnormal pancreatic development	PNDM, TNDM, pancreatic hypoplasia renal cysts	Insulin
PTF1A	AR	Abnormal pancreatic development	PNDM, Pancreatic hypoplasia cerebellar hypoplasia	Insulin
PDX1	AR	Abnormal pancreatic development	PNDM, Pancreatic agenesis	Insulin

Clinical presentation

Intrauterine growth retardation (IUGR) is The most common presentation of NDM, seen in 95% of cases (Mackay and Temple, 2010). IUGR was found in 74% of cases of TNDM and 36% of cases of PNDM in French cohort study. This growth retardation has happened as a result of a failure of insulin production by the fetus and at the same time the maternal insulin cannot cross to the fetus through the placental (Metz et al., 2002). Hyperglycemia is anther common presenting symptom that reported in several case reports and cohort studies (Gloyn et al., 2004; Metz et al., 2002; Woolley and Saranga, 2006; Lee et al., 2003). It is usually severed and associated with low insulin and C-peptide levels, can rarely progress to ketoacidosis or presents as classical symptoms of diabetes of polyuria and polydipsia, but more common the presentation mimic sepsis (Shield et al., 1997; Babenko et al., 2006; Woolley and Saranga). Early age of presentation is a characteristic feature of NDM and one of the diagnostic criteria. The median age of diagnosis of TNDM and PNDM is (6 days; range 1−81 days) and (27 days; range 1−127 days) respectively. Extrapancreatic manifestations are present in a few patients with PNDM in whom NDM is not isolated but associated with multiorgan syndromes (Table 1). Such Wolcott-Rallison syndrome which is an autosomal recessive disorder characterized by NDM, spondyloepiphyseal dysplasia, mental retardation, renal failure hepatomegaly, and early death (Wolcott and Rallison, 1972). IPEX syndrome is rise a suspicion of mitochondrial diabetes (Maassen et al., 2004).

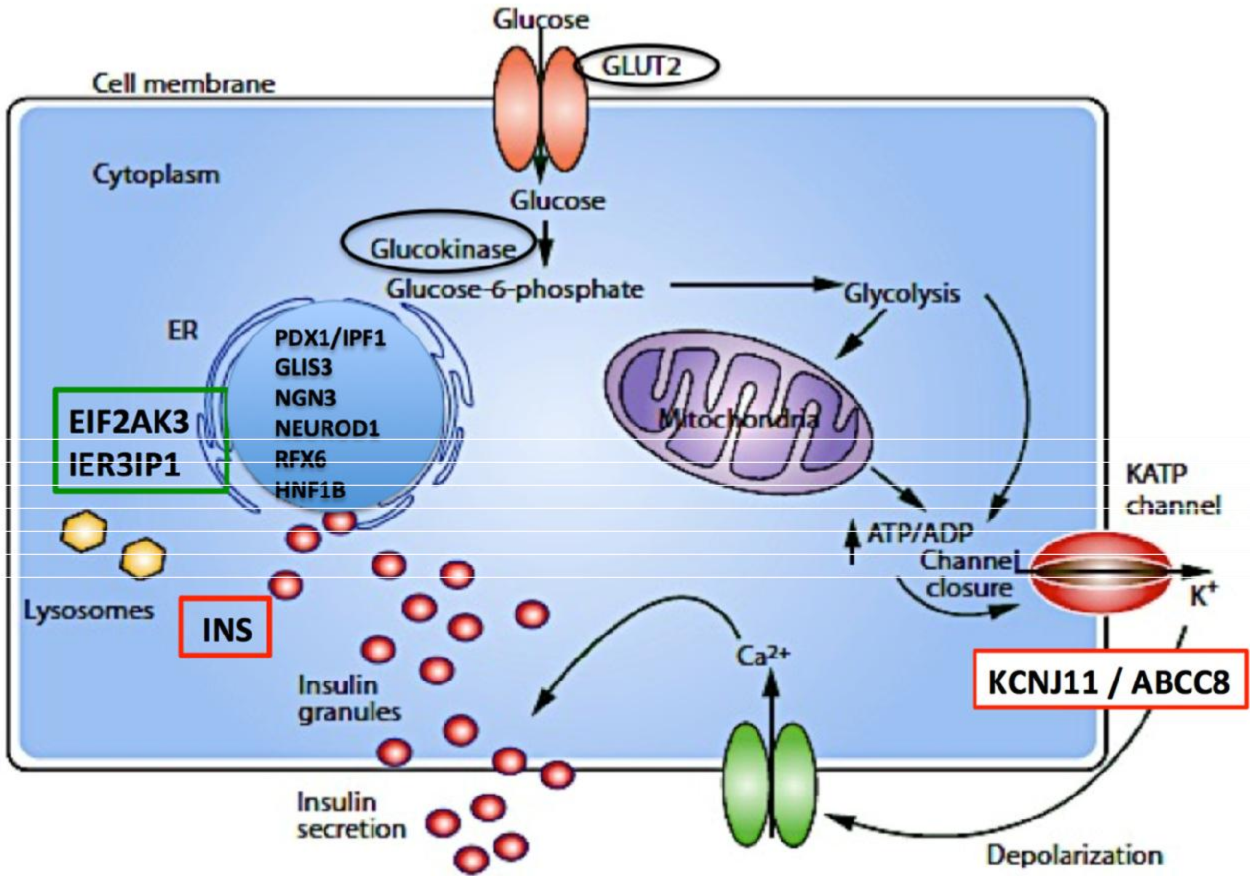

Figure 1. Regulation of Insulin Secretion and Genetic Defects that Cause Neonatal Diabetes

Normally glucose inters into B cell by GLUT2 transporter, then phosphorylates by the glucokinase enzyme to form glucose-6-phosphate that metabolise by glycolysis results in generation of ATP/ADP which leads to closure of KATP channels, depolarization of the plasma membrane, calcium influx results in fusion of insulin secretory granules withthe cell plasma membrane and the release of insulin into the circulation. Mutations of KATP charnel with the KIR6.2 subunits and SUR1 subunits or INS gene (red box) will inhabit insulin secretion, causes usually non-syndromic NDM. Single gen defect of transcription factors located inside the nucleus (blue circle) will lead to the syndromatic NDM. Gene defects of EIF2AK3 or ER3IP1 gene located in the endoplasmic reticulum (green box) leads toWollcot-Rallison syndrome (WRS) or microcephaly, epilepsy and permanent neonatal diabetes (MEDS) syndrome respectively and finally Cell membrane and cytoplasm gene defects (brown box) can also cause NDM

Abbreviations: GLUT2, glucose transporter 2; ATP, adenosine triphosphate; ADP, adenosine diphosphate; KATP, ATP-sensitive potassium channel; KIR6.2, ATP-sensitive inward rectifier potassium channel; SUR1, sulfonylurea receptor; INS, insulin; PDX1/IPF1, Pancreas/duodenum homeobox protein 1; GLIS3, Gli-similar 3 protein (zinc finger protein); NGN3, Neurogenin 3 NEUROD1, neuronal differentiation 1; PAX6 Paired box protein Pax6; HNF-1B, hepatocyte nuclear factor-1-beta;EIF2AK3, eukaryotic translation initiation factor 2-alpha kinase; IER3IP1 Immediate early response 3interacting protein 1

Diagnostic algorithm Overlapping and Lack of specific clinical features to differentiate between transient and permanent NDM nauseated molecular genetic tests for accurate diagnoses, proper management, genetic consoling and prognostic information. Genetic diagnosis should be cost effectiveness, as it is not available or affordable by every medical center. Clinical and genetic tests approach for patient with NDM (Figure 2,3) help in minimize negative results and improve the cost effectiveness of the test.

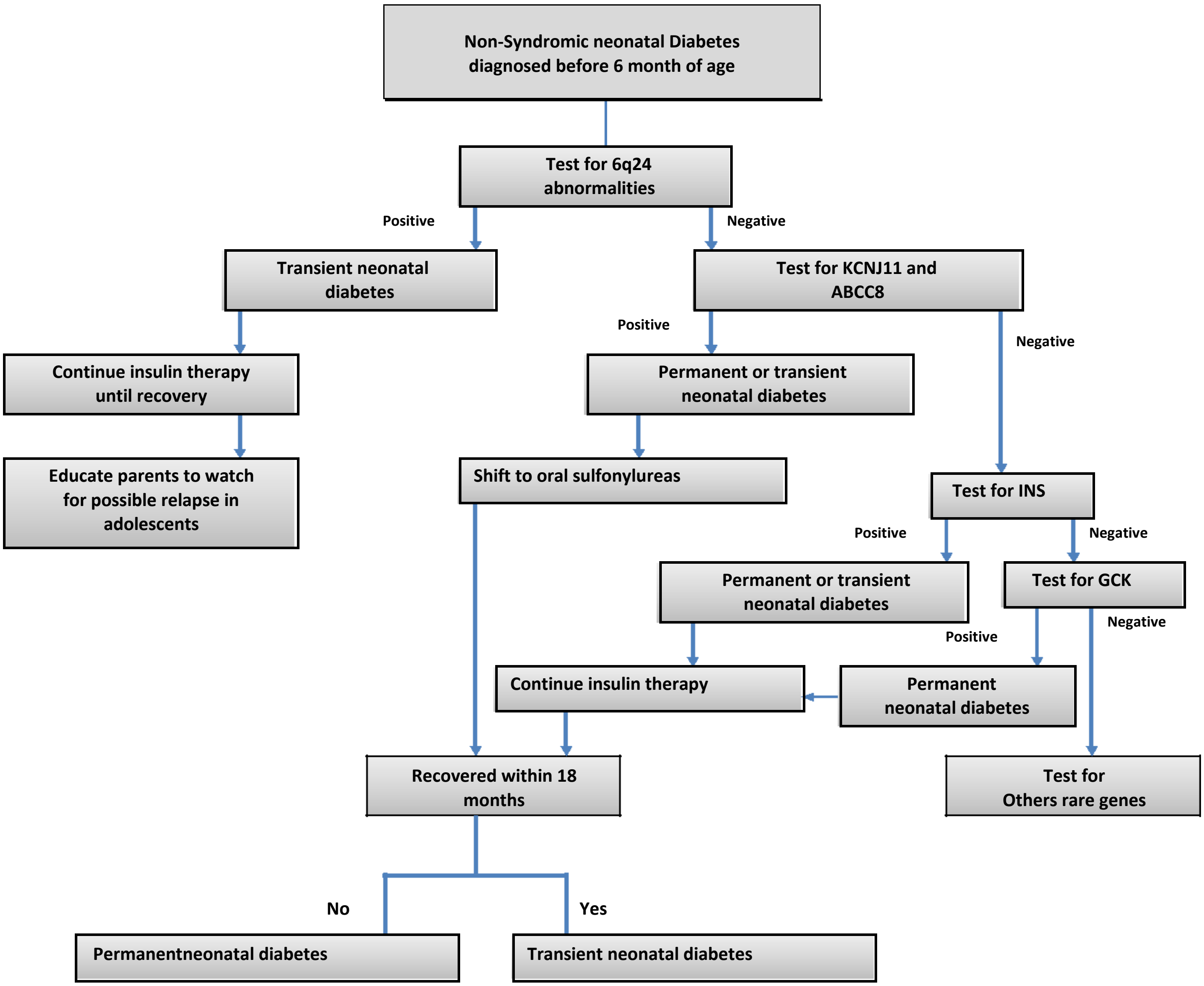

Figure 2. Clinical and genetic approach of non-syndromic neonatal diabetes

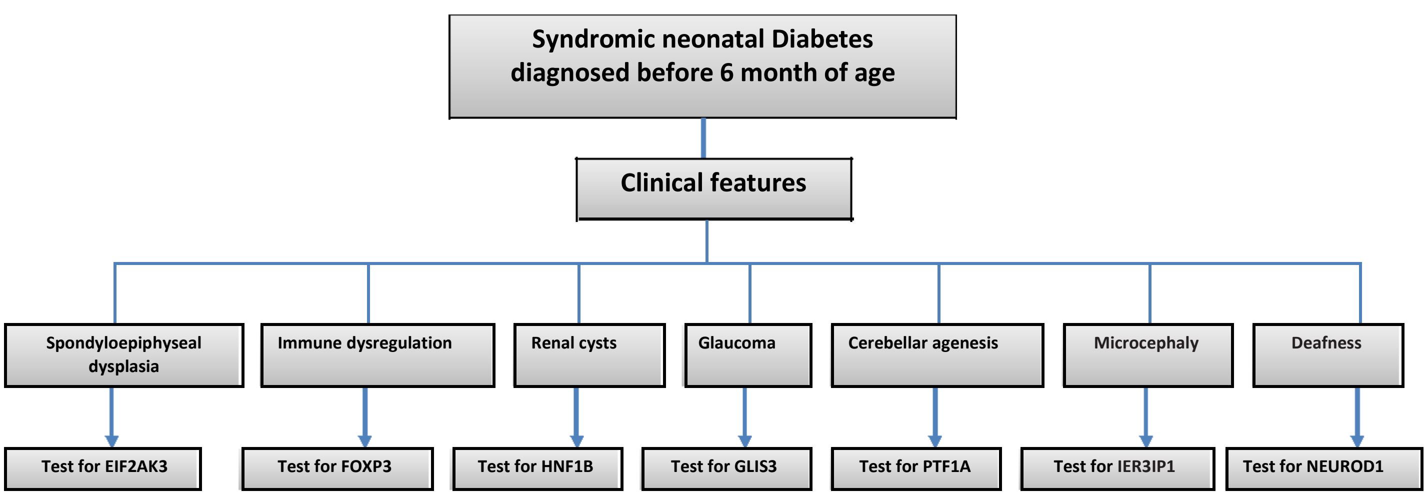

Figure 3. Clinical and genetic approach of syndromic neonatal diabetes

Genetic counseling

Genetic counseling for patients with NDM depends on the genetic etiology, as the mode of inheritance is widely variable. The majority of TNDM cases are sporadic due to UPD with low recurrence risk to sibling and offspring. The children of affected males with paternal duplication of the chromosome 6q24 region have a 50% chance to have the disease from their fathers, but women with maternal duplication will not affect their children, however, sons can transmit TNDM to their offspring (Maassen et al., 2004). On the other hand, most of the affected children with KATP channel mutations (KCNJ11 and ABCC8 genes) in PNDM have a negative family history as the mutations are the result of spontaneous de novo heterozygous mutations. However, these mutations can be transmitted as an autosomal dominant mode of inheritance with a 50% chance of the offspring of affected individuals to have the disease (Gloyn et al., 2004). The ABCC8 gene mutations in 40% of PNDM cases inherited in an autosomal recessive pattern with 25% risk of affected offspring for a carrier parents (Flanagan et al., 2007; Ellard et al., 2007; Sagen et al., 2004; Temple et al., 2000). The recurrence risk of a spontaneous de novo mutation is not negligible as germlinemosaicism, where mutations may be present in the gonads but not in blood that has been found in several families (Gloyn et al., 2004; Edghill et al., 2007). PNDM secondary to PDX1, INS or GCK, gene mutations are inherited in an autosomal recessive pattern, which means that both parents are heterozygote for the mutation and their children have 25% risk of having the disease.

Management

The initial management of all cases of NDM is insulin to control hyperglycemia and avoid acute complications then patients can be shift to oral sulfonylurea-based on the results of genetic testing. The discovery of KATP channel mutations had a great impact on the management of patients with PNDM. These mutations inhibit endogenous insulin secretion in patients with PNDM by preventing KATP channel closure, however, oral sulfonylurea restores normal insulin secretion in PNDM patients with mutated KATP channels by binding to the SUR subunits, causing membrane depolarization, closing KATP channel and insulin secretion (Gribble and Reimann, 2003). The NDM patients with activating mutations in KCNJ11 or ABCC8 genes respond to treatment with a sulfonylurea which should be started after established the genetic diagnosis (Chakera et al., 2013). Several studies confirmed the efficacy and safety of sulfonylurea in PNDM patients Chan and Laffel, 2007; Gurgel et al., 2007; Malecki et al., 2007; Bremer et al., 2008; Koster et al., 2008; Mohamadi et al., 2009; Monaghan et al., 2009; Wambach et al., 2009; Landau et al., 2007; Stanik et al., 2007; Rica et al., 2007; Suzuki et al., 2007; Stoy et al., 2008). Most of the patient with KCNJ11 gene mutations or ABCC8 gene mutations (90% and 85% respectively) are successively metabolic controlled with sulfonylurea (Pearson et al., 2006; Rafiq et al., 2008) and continue to maintain control without hypoglycemia (Hattersley and Ashcroft, 2005; Wambach et al., 2009; Shah et al., 2012; Begum-Hasan et al., 2008; Kir6.2Klupa et al., 2009), they can be treated as inpatients or outpatients based on specific treatment protocols (Pearson et al., 2006; Rafiq et al., 2008) and transitioned to sulfonylurea as young as 1 month of age (Ješic´ et al., 2011). Although the requirement doses sulfonylurea for patients with NDM are higher than those used in type 2 diabetes mellitus patients (Greeley et al., 2010). The side effects of sulfonylurea are mild (Kumaraguru et al., 2009) and temporary. The most common side effects are abdominal pain, nausea, vomiting, and diarrhea (Sellick et al., 2004). Tooth discoloration and allergic skin reactions are rare side effects (Shah et al., 2012; Kumaraguru et al., 2009).

The minority of patients has not responded to sulfonylurea therapy due to either late transition or sever DEND syndrome (Pearson et al., 2006; Malecki et al., 2007; Monaghan et al., 2009; Landau et al., 2007; Stoy et al., 2008). The studies on mouth models have shown that in absence of sulfonylurea therapy the functional β -cell mass decreased which may explain the lack of response to sulfonylurea therapy in late transition (Girard et al., 2009; Remedi et al., 2009). Although patients with less severe DEND syndrome have shown a good responsiveness to sulfonylureas and improved motor and cognitive function (Mohamadi et al., 2009; Stoy et al., 2008; Slingerland et al., 2006; Ting et al., 2009) others with the sever DEND syndrome have not responded to sulfonylurea (Masia et al., 2007; Sumnik et al., 2007; Della Manna et al., 2008). All other causes of PNDM required Long-term insulin therapy although the patient with GCK gene mutations have shown mild metabolic improvement with sulfonylurea therapy (Turkkahraman et al., 2008).

CONCLUSIONS

Diagnosed diabetes in first 6 months of age is neonatal diabetes as type 1 diabetes is unlikely to present during this period. Neonatal diabetes is one of monogenic diabetes with unknown prevalence, which could be due to misdiagnosis with type 1 diabetes. However, increase NDM awareness and use a clinical algorithm for molecular genetic testing should minimize misdiagnosis and increase the yield of positive results. Knowing the etiology of NDM based on molecular genetic testing has an important impact on diagnosis, counseling, management and prognosis. Such the discovery of KATP channel mutations responses to oral sulfonylurea makes a huge life changing on the management of NDM from insulin injection to oral sulfonylurea that is controlling diabetes. Genetic counseling of families with NDM and understand the future risk of recurrence are essential.

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