Abstract: Neonatal diabetes mellitus (NDM) is one of the rarest forms of the diabetes, which can be characterized by the hyperglycaemic condition. This is usually witnessed at the early stages of life. This condition can be categorized into two types namely transient neonatal diabetes mellitus (TNDM) or permanent neonatal diabetes mellitus (PNDM). Transient neonatal diabetes mellitus (TNDM) is a medical condition which can be treated within few months of the onset of the disease where as permanent neonatal diabetes mellitus (PNDM) will persist life long and intense care should be given to treat and manage the condition. The root cause of the Neonatal diabetes mellitus (NDM) was unclear until the recent development in the field of molecular and genetic diagnosis techniques which illuminated the molecular basis of the disease. The primary objective of this study is to get an overview of the molecular basis of the Neonatal diabetes mellitus (NDM) and to understand the diagnosis, treatment & management of this medical condition and to spread awareness.

Keywords: NDM, TNDM, PNDM

1. Introduction

Diabetes mellitus is a medical condition which is characterized by the hyperglycaemia condition were the glucose concentration is high in blood flow due to low insulin production, lack of sensitivity of insulin receptor in the cells or a condition in which the liver releases more insulin.

The most common symptoms are Increase in thirst, Loss weight, Frequent urination, Loss of vision, Reduce in wound healing capacity, Fatigue and Frequent infection [1].

Diabetes is classified into two groups according to the molecular basis as Polygenic and Monogenic. Polygenic diabetes is a class of medical condition which is caused due to the mutation of combination of genes were as monogenic diabetes is caused due to the mutation of a single genes.

1.1 Polygenic Diabetes:

It is a medical condition caused due to mutation of a combination of genes. There are two class of polygenic diabetes namely type 1 & type 2 diabetes.

Type 1 diabetes: it is a medical condition caused due to the low production of the insulin by pancreas.

Type 2 diabetes: it is a medical condition which is caused due to development of insulin resistance cells [2].
1.2 MONOGENIC DIABETES:
Monogenic diabetes is one of the rare medical condition, which arises due to mutation occurred at the molecular level of transcription factor or other proteins that are involved in the endocrine regulation of pancreas.

There are two forms of monogenic diabetes which are Neonatal diabetes mellitus (NDM) and Maturity onset diabetes of the young (MODY) [3].

1.3 NEONATAL DIABETES MELITUS:
Neonatal diabetes mellitus is a type of the monogenic diabetes which is caused to a mutation in a single gene. This can be of two types, Transient neonatal diabetes mellitus and Permanent neonatal diabetes mellitus [4].

1.4 TRANSIENT NEONATAL DIABETES MELLITUS (TNDM)
It is a type of medical condition which occurs at the early stage of life, which can be treated at initial stage within 15-18 months, there are chances of re-appearing at later stage of life. Mutation of these gene cause transient neonatal diabetes mellitus (TNDM) are chromosome 6q24, KCNJ11, ABCC8 & HNF1B mutation [5].

1.5 PERMANENT NEONATAL DIABETES MELLITUS (PNDM)
Permanent neonatal diabetes mellitus is a type of diabetes that first appears within 6 months of birth and persist throughout life. Mutation of KCNJ11, ABCC8, INS, IPF1, PDX1, GLIS3, HNF-1B, FOXP3, SLC19A, SLC2AZ, RFX6 & PTF1A lead to PNDM [6].

Neonatal diabetes mellitus can lead to late development, epilepsy & neurological disorders, Improper development of pancreas, Improper digestion capacity and Inability to absorb fat soluble vitamins.

1.6 GENES INVOLVED IN NEONAL DIABETES MELLITUS
There has been a major progress in uncovering the molecular basis of neonatal diabetes mellitus. Till date 20 genes have been discovered which plays a major role in manifestation of the disease. The most common genes which are involved in neonatal diabetes mellitus are K-ATP, KCNJ11, ABCC8 & INS [7][8].

According to a case study 30 % of NDM cases was caused due to the mutation of KCNJ11 gene, 20% due to the mutation of ABCC8 gene and 20 % due to the mutation of INS gene.

KCNJIII gene and ABCC8 gene are involved in providing the signals for making the different sub units of ATP sensitive potassium channel (K-ATP). This channel is found across the cell membranes of beta cell of pancreas, these channels open and close as a response to the concentration of glucose in blood stream.

When the concentration of glucose is high in the blood these channels will close and as a response the beta cells of pancreas produce insulin to maintain the blood glucose concentration.

INS gene is involved in producing the signals required for releasing insulin. The insulin is produced as a precursor pro-insulin which is a single polypeptide, which breaks down into chain A & chain B bound together with disulphide bonds, mutation in this gene will disrupt the release of insulin [9].
<table>
<thead>
<tr>
<th>GENE</th>
<th>PHENOTYPE/SYNDROME</th>
<th>PHENOTYPE/SYNDROME INHERITANCE</th>
<th>INHERITANCE</th>
<th>ONSET</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLAGLIHYMAI (6q24)</td>
<td>Over expression of paternally expressed genes within the impaired region of chromosome 6q24</td>
<td>TNDM</td>
<td>Autosomal recessive</td>
<td>Within few days of birth</td>
<td>[10]</td>
</tr>
<tr>
<td>ZFP57</td>
<td>Zinc finger protein 57 is a transcription factor with a role in maintenance of imprinted DNA methylation.</td>
<td>TNDM</td>
<td>Autosomal recessive</td>
<td>Within few days of birth</td>
<td>[11]</td>
</tr>
<tr>
<td>KCNJ11</td>
<td>K (+) channel sub unit of K-ATP</td>
<td>PNDM</td>
<td>Autosomal dominant</td>
<td>&lt;6months, Rarely late</td>
<td>[12]</td>
</tr>
<tr>
<td>ABC28</td>
<td>Sulfonylurea receptor 1 sub unit of K-ATP</td>
<td>PNDM</td>
<td>Autosomal dominant</td>
<td>&lt;6months, Rarely late</td>
<td>[13]</td>
</tr>
<tr>
<td>INS</td>
<td>Insulin hormone</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
<td>&lt;6months, Rarely late</td>
<td>[14]</td>
</tr>
<tr>
<td>EIF2AK3</td>
<td>Eukaryotic translation initiation factor involved in translation</td>
<td>Wolcott-rallison syndrome</td>
<td>Autosomal recessive</td>
<td>2-28 weeks of birth</td>
<td>[15]</td>
</tr>
<tr>
<td>FOXP3</td>
<td>Forkhead box protein P3 transcription factor</td>
<td>Immunodysregulation Poly endocrinopathy enteropathy, x linked syndrome</td>
<td>X-linked recessive</td>
<td>3days-5months</td>
<td>[16]</td>
</tr>
<tr>
<td>GCK</td>
<td>Glucokinase</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
<td>After onset of PNDM</td>
<td>[17]</td>
</tr>
<tr>
<td>PDXI</td>
<td>Pancreas duodenum home-box protein transcription factor</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
<td>12-15 days on birth</td>
<td>[18]</td>
</tr>
<tr>
<td>PTF1A</td>
<td>Pancreas transcription factor 1</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
<td>Within 2-3 days of birth</td>
<td>[19]</td>
</tr>
<tr>
<td>NEUROD 1</td>
<td>Transcription factor</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
<td>2months</td>
<td>[20]</td>
</tr>
<tr>
<td>NEUROD</td>
<td>Transcription factor</td>
<td>PNDM</td>
<td>Autosomal</td>
<td>Within</td>
<td>[21]</td>
</tr>
</tbody>
</table>
From the above table we infer that mutation in the above 20 genes lead to the neonatal diabetes in the first few years of life. However only 60-70% of the medical condition is due to the mutation caused in those 20 genes, in other cases the molecular basis is not still clear hence further research will pave way for identifying the cause and to understand the molecular basis.

2. DIAGNOSIS

2.1 Clinical condition should be suspected, in individuals with the following clinical symptoms:

- When the plasma glucose concentration > 150-200mg/dl in infants younger than 6 months.
- When there are clinical symptoms of glucosuria, ketonuria, hyper-ketonuria in infants.
- Low or undetectable plasma insulin c peptide related to hyperglycaemia.
- High blood fat in infants having hypoplasia [30].

2.2 Based on the onset of the symptoms the diagnosis can be carried out in two different ways:

1. Genetic testing
2. Radiographic examination

Genetic testing is a type of the test which is carried out to determine if there is any variation or mutation that has occurred in the molecular and genetic level which can be the root cause for the onset of the neonatal diabetes mellites, they also reveal the details of a person’s chance of developing or passing a genetic disorder. More than 1000 test protocol are currently in use and some more are being developed to increase the efficiency of molecular diagnosis of diseases. Based up on the clinical symptoms genetic testing can be carried out as serial single gene testing, multi gene testing or comprehensive genome testing [31].

<table>
<thead>
<tr>
<th>3</th>
<th></th>
<th>recessive</th>
<th>days to 9 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFX6</td>
<td>DNA binding protein winged helix transcription factor</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>IER3IP1</td>
<td>Immediate early response 3 interacting protein 1</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>HNF1B</td>
<td>Hepatocyte nuclear factor transcription factor</td>
<td>TDNM</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>GLIS3</td>
<td>Glioma associated oncogene- similar family zinc finger 3 transcription factor</td>
<td>NDH</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>PAX6</td>
<td>Paired box 6 transcription factor</td>
<td>PNDM</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>WFS1</td>
<td>Wolframin membrane glycoprotein</td>
<td>Wolfram syndrome</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>SLC19A2</td>
<td>Thiamine transporter 1</td>
<td>TRMA syndrome</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>SLC2A2</td>
<td>Glucose transporter</td>
<td>Fanconi bickel syndrome</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>
Radiographic features such as CT scan, ultrasound and MRI scan examination can be carried out for identification of the pancreatic hypoplasia. But one of the major drawbacks of this method is visualization of the pancreas in neonatal is very difficult [32].

3. TREATMENT AND MANAGEMENT

The management of neonatal diabetes mellitus in infants is insulin therapy [33], irrespective of the root cause of the clinical significance. Oral sulfonylurea is an alternative treatment for treating the medical complication according to the genetic diagnosis of K-ATP channel mutation [34][35]. Treatment is always initiated as immediate response after the diagnosis of the medical complication.

4. MANAGEMENT

4.1 ACUTE HYPERGLYCEMIA

Infants showing significant hyperglycaemia is also related with electrolyte disturbances, dehydration and ketoacidosis [36]. The initial management includes fluid resuscitation with electrolytic solutions and to treat dehydration using osmotic diuretics. The fluid therapy is done according to the individual basis over a period of 24-48 hrs to avoid edema.

4.2 INSULIN THERAPY

Insulin therapy is initial treatment given to the babies with IUGR, but the procedure is complex due to paucity of subcutaneous fat and low dose treatment requirement. Intravenous infusion and intermittent subcutaneous therapy are the route of administration of insulin [37].
4.3 BASAL INSULIN
Basal insulin is a type of insulin which is used as a background insulin to maintain blood-glucose level in between the duration of meal time. They have a 24hr action, but not an appropriate option for patients less than 6 years of age. this is usually used to treat toddlers and children with type 1 diabetes and infants to maintain glucose level and less hypoglycaemia. Glargine and insulin detemir used as basal insulin [38].

4.4 BOLUS INSULIN
Bolus insulin is a type of insulin which is used to manage the blood glucose after a meal. Lispro and insulin aspart are used as medication. The dose level should be maintained accurately so that their peak action can result in hypoglycaemia even at low dose. This medication is used for high glucose blood correction in infants.

4.5 DILUTED INSULIN
A very small dose of insulin is needed to treat new born and infants with gradation in fractions of unit, this can be difficult to measure using standard insulin syringe, hence diluted insulin is used as a source for treatment [39]. The diluents appropriate for each insulin is given by pharmaceutical company. The dilute insulin is prepared in aseptic condition and due to its instability issues, it loses its potency and hence discarded within 30 days according to the manufacturer recommendation [40].

4.6 ORAL SULFONYLUREA
Sulfonylurea is a class of oral hypoglycaemic agents. It is usually used to treat type two diabetes. They increase the secretion of insulin by pancreas. Two generation of sulfonylurea is produced, according to the mechanism of elimination from the body [41].

5. MAJOR OBSTACLES IN TREATING NEONATAL DIABETES MELLITUS
- Preparation of very low dose insulin.
- Route of administration of insulin
- Difficulty in predicting milk intake.
- Consequent and multiple blood sticks to test blood sugar and frequent blood draws that could theoretically cause anaemia.
- Physical and physiological factors that affected the family members of the patient during day to day management.

6. CONCLUSION
Neonatal diabetes mellitus is one of the rarest diseases that is either transient neonatal diabetes mellitus (TNDM) or permanent neonatal diabetes mellitus (PNDM). With advances in molecular and genetic diagnosis paved a bright way towards treatment of the neonatal diabetes to decrease the complexity of diabetes management and to provide a better quality of life.
7. REFERENCES


