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Recent perspective in neonatal diabetes

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Abstract
Over the past ten years, a plethora of research has shed light on the various hereditary reasons for a non-immunological kind of diabetes that is typically detected in the first six months of life. The genes involved in the whole series of processes that regulate glucose homeostasis are becoming better understood thanks to these investigations. It is now known that the cause of neonatal diabetes is abnormalities in genes that are essential for the pancreas' formation, β-cell apoptosis, insulin processing, and insulin release regulation. This work offers new tools for basic researchers to investigate basic molecular and cellular processes. These findings highlight the necessity for clinicians to determine the underlying genetic etiology of every occurrence. It is becoming more evident that in order to give the best possible care, a doctor's prognosis, therapeutic approach, and genetic counseling must be customized for each patient's unique gene.

Keywords: Neonatal diabetes, transient, permanant, gene etc.

Introduction

The Uncontrolled hyperglycemia in the first six months of life is a rare symptom of diabetes mellitus, which can affect people of all racial and cultural backgrounds. Intrauterine growth retardation (iugr), failure to thrive, decreased sc fat, and low or undetectable c-peptide levels are seen in most cases. Known as "early-onset" or neonatal diabetes mellitus (ndm), this kind of hyperglycemia is frequently inherited. While the diagnosis of these cases goes up to six months of age, the neonatal period is defined as the first four weeks of life; therefore, a reviewer noted that "congenital diabetes mellitus" is a more accurate term to describe a disorder that is present at birth but strategies have been created in recent years with the goal of increasing bioavailability, ~ 334 ~ The Pharma Innovation Journal convenience, and patient compliance. Some tablets, referred to as "true fast-dissolving tablets," are made to disintegrate in saliva in a matter of seconds. Glibenclamide (AAN, BAN, INN), commonly referred to as glyburide (USAN), is an antidiabetic medication that belongs to the sulfonylureas class of pharmaceuticals, which is closely connected to sulfa drugs. It was created in 1966 as a result of collaboration between Hoechst (now a part of Sanofi Aventis) and Boehringer Mannheim (now a part of Roche). Under the brand names Diabeta, Glynase, and Micronase in the United States, Daonil, Semi-Daonil, and Euglucon in the United Kingdom, and Delmide, Glybovin in India, it is available in dosages of 1.25, 2.5, and 5 mg. Additionally, it is available in Russia, Belarus, and other CIS nations as Glucovance, Benimet, and Glibomet, as well as Glucored and Glucored Forte (manufactured by Sun Pharmaceutical), when combined with metformin [2, 3].

History

In 1852, Kitselle wrote of his newborn son's polydipsia, polyuria, failure to thrive, and glycosuria. The boy passed away a few months later. When insulin was originally used to treat neonatal diabetes in the 1930s, the majority of the infants did not survive, but a small number had spontaneous remission. At postmortem, congenital islet tissue deficiencies were frequently visible. Two types of infancy-onset diabetes mellitus were identified in the 1960s: the first is insulin-sensitive diabetes mellitus with acidosis and ketosis in older infants, requiring lifelong insulin therapy; the other is known as "congenital temporary diabetes mellitus," which manifests at birth or shortly thereafter, is also insulin-sensitive, but does not include severe ketosis and may recover on its own.The term neonatal DM now refers to patients up to 1 year of age who present with monogenic DM. It is currently estimated that around 20% of cases still remain without a genetic diagnosis [1].

Advantages: Simultaneous administration to patients, including mental, pediatric, and elderly patients, who refuse to swallow a pill.

- Water is not required for swallowing the dose form.
- Quick medication absorption and disintegration.
- Easy administration and precise dosage in comparison to liquids.
- Good mouth feel property, especially for younger patients, helps to alter the common perception of medication as a "bitter pill."
- Enhanced steadiness
- Fit for both rapid and controlled release Inactives
- Permits a large drug loading 0.
- The capacity to offer solid preparation with the benefits of liquid medication.
- Cost-effective; flexible and compatible with current processing and packaging equipment.

Disadvantages: In most cases, the tablets' mechanical strength is inadequate. Consequently, handling must be done carefully during the manufacturing process.

- If the tablets are not made correctly, they may leave the oral cavity feeling gritty or tasting bad.
- More potent medications, such as rifampin (600 mg) and ethambutol (1000 mg), are more challenging to synthesize into FDT.

Types of Neonatal Diabetes

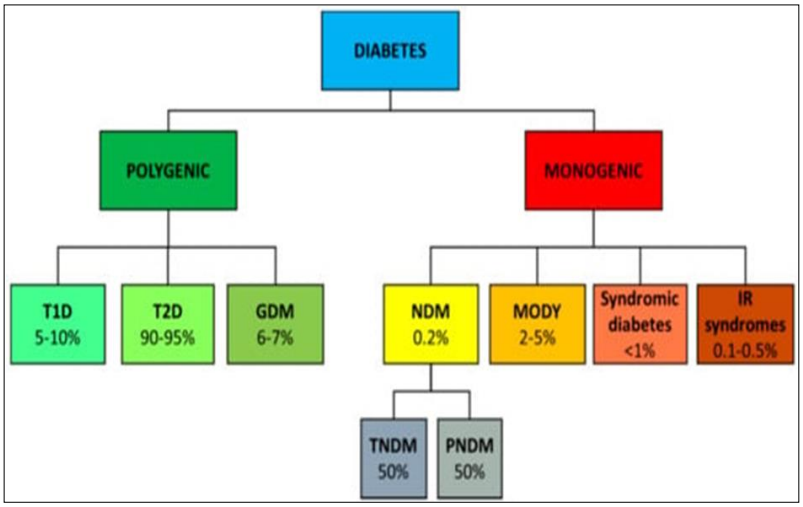

Fig 1: Types of Diabetes [3]

Hyperglycemia often resolves in infants with transitory neonatal diabetes mellitus (by 13–18 weeks of age). But it might come back in adolescence or adulthood.

Transient Neonatal Diabetes

Transient neonatal diabetes is most commonly caused by overexpression of genes on the 6q24 region. The loss of imprinting at 6q24 due to uniparental disomy, paternal duplication of this region, or loss of DNA methylation, which activates the maternal allele, are the causes of this. The ZAC and HYMAI genes are locate d in this area. ZAC is a C2H2 zinc-finger transcription factor that has a variety of roles. These roles include coactivating p53 in the transcription of Apaf1 (apoptotic protease activating factor, controlling p300's histone acetyltransferase activity, and coactivating or cor0epressing a number of nuclear hormone receptors. HYMAI is an untranslated RNA with an unknown purpose. Individuals with a 6q24 mutation typically exhibit symptoms before individuals with a KCNJ11/ABCC8 mutation. Children with newborn diabetes mellitus associated to mutation 6q24 may also have macroglossia or umbilical hernia. Insulin therapy is the initial treatment for patients with neonatal diabetes due to 6q24. Non-insulin treatments, like those for type 2 diabetes, might work well for elderly individuals. In a case series with transitory newborn diabetes mellitus associated to 6q24, up to 14% of patients experienced hypoglycemia following diabetes remission.

Mutations in either of the two genes that encode the voltage-dependent potassium channel subunits are the second most frequent cause of transitory neonatal diabetic DM. The KATP channel's inner subunit is encoded by KCNJ11, and its outer subunit (SUR1) is encoded by ABCC8. When any of the two genes is mutated, KATP channels are abnormally opened even in the presence of hyperglycemia, which prevents the cell membrane from depolarizing and releasing insulin.

Permanent Neonatal Diabetes

The most frequent cause of heterozygous mutations in KCNJ11 or ABCC8 that activate permanently in neonates is these conditions. Over half of all occurrences of neonatal diabetes mellitus are caused by these mutations. The second most frequent cause of temporary neonatal diabetes is likewise one of these two gene abnormalities. There are KATP channels in the brain as well. In a recent study, the median age of presentation was 9.6 weeks (IQR 6.1–18.3 weeks), and the majority of patients present before the age of six months, while reports of presentations after this age have been made.

Patients with KCNJ11 mutations may have a variety of neurocognitive impairments, including reduced reasoning, reading, vocabulary, and auditory working memory when compared to sibling controls, because KATP channels are expressed in the brain. In addition, patients may exhibit sleep difficulty, attention deficit hyperactivity disorder, learning disabilities, and delays in the development of social-emotional and behavioral skills. The DEND syndrome, which stands for developmental delay, epilepsy, and neonatal diabetes, is associated with severe cases of KCNJ11 mutation. The effects can range from slight delays to significant seizures-related delays. Individuals treated with sulfonylureas (SUs) are susceptible to mutations in these two genes.

Cause

1. Abnormal β Cell Function

ATP-dependent potassium channel gene mutations and 6q24 locus anomalies are the most common genetic causes of newborn diabetes with normal pancreatic shape.

2. 6q24 Gene

Abnormalities of the 6q24 locus, such as partial duplication of the paternal 6q24, relaxation of the maternal 6q24 imprinted locus, and paternal uniparental disomy of 6q24 (pUPD6), were the first genetic causes to be found. This locus has a CpG island, which exhibits varying levels of methylation based on the paternal and maternal alleles' respective origins (paternal alleles are non-methylated, whereas maternal alleles are methylated). The parents of the afflicted children have not yet been found to have the methylation issue.

The methylated allele's gene transcription is downregulated by methylation. The most "likely" candidate imprinted genes on 6q24, HYMAI (Hydatidiform mole-associated and imprinted transcript) and PLAGL1/ZAC (pleiomorphic

adenoma gene-like 1), are overexpressed as a result of all these disorders. The transcription factor encoded by PLAGL-1 is involved in the regulation of apoptosis and the termination of the cell cycle, as well as the induction of the receptor 1 gene for the human pituitary adenylate cyclase-activating polypeptide (PACAP1), a powerful inducer of insulin production. It is uncertain what the HYMAI gene does.

3. Mutations of the ABCC8 and KCNJ11 Genes Coding for the K_{ATP} Channel – [3, 4]

An essential function of the ATP-dependent potassium channel (KATP channel) is to stimulate the pancreatic β cell's release of insulin in response to glucose. The KATP channels are open (active) with low blood sugar levels (e.g., fasting), and their activity sustains a hyperpolarized resting membrane potential (around −70 mV).

An increase in blood sugar levels, such as those following a meal, results in more glucose entering the β cell. When glucose enters the glycolysis pathway, the concentration of ATP inside cells rises. This results in intracellular potassium buildup, which depolarizes the membrane by causing the KATP channels to close (inhibition). Depolarization causes the voltage-dependent calcium channels to open, allowing Ca2+ ions to enter the β cell and facilitating the secretion vesicles' exocytosis and subsequent release of insulin into the bloodstream [4, 5].

Two different subunit types combine to create the octamer that is the KATP channel: the Kir6.Within the SUR1 ion-channel regulator subunits, two subunits create the channel that is selective for the entering corrective potassium. The ABCC8 gene codes for them, and the KCNJ11 gene codes for them.

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4. Mutations of the Insulin Gene (INS) [6, 7]

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Adoptive mutations in one of these two genes cause newborn diabetes in cases where the pancreas is shaped normally. They cause the KATP channel to remain permanently open, blocking the event cascade that releases insulin because it is unable to regulate membrane potential in response to glucose.

5. Mutations of the Insulin Gene (INS) [8, 9]

Mutations in the insulin gene (INS) are, by frequency, the third cause of neonatal diabetes. Most of the mutations are heterozygous and impact the structure of preproinsulin; they are passed down autosomally dominantly. The aberrant proinsulin is broken down in the endoplasmic reticulum, which results in β cell death and extreme ER stress. Both in humans and in mice models, this mechanism has been documented. According to recent research, prolonged ER stress rather than INS mutations directly causes beta-cell mortality by obstructing their growth and development. Certain mutations change how the protein is expressed. They are mostly passed down through consanguineous families in a recessive fashion. These mutations either directly alter the insulin promoter or alter a component that increases its activity.

6. Pathogenesis [15, 16]

Approximately 80% of new born diabetic children have a genetic abnormality. There are currently around 20 recognized genetic reasons for neonatal diabetes (DM), and the number of genes present in infants with the disease is rising. Different inheritance patterns, phenotypes, and clinical aspects are linked to different genes. The growth of pancreatic beta cells, as well as the manufacture and secretion of insulin, are significantly influenced by the genes linked to neonatal diabetes. Following extensive genetic testing, which included Sanger sequencing, 6q24 methylation analysis, and targeted next-generation sequencing of all known neonatal diabetes genes, causal mutations were discovered in 82% of the cases in a large series of 1020 patients who were diagnosed with neonatal diabetes before the age of six months. While the most common cause of neonatal diabetes (38.2%) was mutations in the potassium channel genes (KCNJ11 and ABCC8), these mutations were found less frequently in consanguineous families (12% vs 46% in non-consanguineous families).

10% of patients from consanguineous and non-consanguineous families had mutations in the INS gene, which codes for insulin. In consanguineous families, a homozygous mutation in the EIF2AK3 gene was the most frequent genetic etiology (Wolcott-Rallison syndrome, 24%). Three categories can be used to group the underlying mechanisms for the different gene mutations that cause neonatal diabetes:

1. Modification of beta cell activity impacting insulin synthesis or secretion: KCNJ11, ABCC8, GCK, INS, RFX6, SLC2A2, SLC19A2.
2. Pancreatic hypoplasia or aplasia: NKX2-2, NEUROG3, NEUROD1, PAX6, GATA4, GATA6, HNF1B, MNX1, RFX6, GATA4, GATA6, GLIS3.
3. Damage to the IER3IPI, FOXP3, WFS, INS, and EIF2AK3 beta cells in the pancreas.

Recent Medication & Drug Delivery System [17, 18]

1. Management of acute hyperglycemia

Diabetic newborns may have severe hyperglycemia, electrolyte imbalance, dehydration, and ketoacidosis.18 The

first line of treatment for the dehydration caused by osmotic diuresis is fluid resuscitation using isotonic electrolyte solutions. To prevent cerebral edema from too quick correction, the needed fluid therapy is calculated individually and provided slowly over a 24-48-hour period. When a newborn or infant has diabetic ketoacidosis, they should be treated in an intensive care unit under the care of a pediatric endocrinologist. Their neurological condition, blood sugar, and electrolytes should all be regularly checked.

The same guidelines that govern the treatment of children and adolescents with diabetes mellitus also apply to the management of ketoacidosis.

2. Insulin treatment

Insulin therapy is essential for achieving adequate development and weight gain, particularly in infants with IUGR; however, because subcutaneous fat is scarce and low dosages of insulin are required, treating NDM is difficult. Insulin is delivered by continuous subcutaneous insulin infusion (CSII), intermittent subcutaneous therapy, or intravenous infusion. It is frequently started with an intravenous infusion since this allows for more accurate dose titration according to blood glucose levels.

3. Basal Insulin

Insulin glargine or insulin detemir are examples of long-acting insulin, whereas NPH (isophane) insulin is an example of an intermediate-acting insulin. Similar to NPH, intermediate-acting insulin causes notable fluctuations in blood sugar levels and hypoglycemia since it does not offer insulin delivery profiles that match eating schedules. The issues with intermediate acting insulin would be resolved by insulin glargine, which has a virtually flat action profile and a 24-hour duration of action. However, the safety and efficacy of glargine insulin in individuals younger than 6 years old have not been proven.

4. Bolus insulin

Either rapid-acting insulin, such as insulin lispro or insulin aspart, or short-acting insulin, such as normal insulin, is used to administer bolus. The insulin groups should be used with caution since, even at extremely low dosages, their peak effect can cause substantial hypoglycemia. Newborns and infants can get the high-blood glucose correction and the carbohydrate bolus using an insulin to carbohydrate ratio and an insulin to blood glucose level (insulin sensitivity factor), just as children with type 1 diabetes [15, 16].

5. Diluted insulin

It is necessary to use diluted insulin because newborns and infants typically require very small doses of insulin, with gradations in fractions of a unit, which can be challenging to quantify with a regular insulin syringe [17].

6. Continuous subcutaneous insulin infusion

One of the main challenges in NDM continues to be the delivery of tiny doses of insulin and changing insulin requirements along with regular blood glucose monitoring. Low insulin administration rates appropriate for neonates with diabetes are made possible by CSII. Furthermore, CSII offers more flexibility to account for variations in oral intake and shifts in energy expenditure as the kid develops [18, 19].

7. Continuous glucose monitoring sensor

An electrode sensor in a continuous glucose monitoring sensor (CGMS) catalyzes glucose oxidation, producing an electric current that is recorded by a monitor. The interstitial fluid's glucose can be continuously measured with the CGMS, which is placed subcutaneously. The sensor is particularly helpful for small-for-gestational-age babies and preterm infants who are susceptible to significant fluctuations in blood glucose levels [20].

8. Oral sulfonylurea

Because NDM patients have little to no endogenous insulin, it was once thought that they would need to take insulin continuously for the rest of their lives. The way NDM is treated has changed dramatically after KATP channel mutations were found in these patients. When treating people with type 2 diabetes mellitus, oral sulfonylureas have shown effective in treating non-diabetic NDM resulting from mutations in the KCNJ11 and ABCC8 genes. Sulfonylurea causes membrane depolarization and insulin release by binding to the KATP channel's SUR1 subunits and closing the channel without the need for ATP [21, 22]. Similarly, by attaching to the SUR subunits in the mutant KATP channels, sulfonylurea triggers insulin release. Only patients with activating KCNJ11 or ABCC8 gene mutations respond to treatment among the recognized genetic subgroups of NDM [22].

Future Directions

Even after relevant genes are sequenced, a significant portion of patients with phenotypic monogenic diabetes do not have a genetic diagnosis. Modern technologies like whole exome and perhaps whole genome sequencing may make it possible to find gene mutations in a significant number of people whose diabetes is most likely monogenic in nature. These technologies are probably going to become sufficiently sensitive and affordable in the coming years to be used as first-line diagnostic instruments for determining the molecular genetic origins of monogenic diabetes [23].

It is obvious that the development of systems to manage the amount of data produced and enhancement of quality control procedures will be crucial first steps for a broader use of these technologies. It's debatable at what age "neonatal diabetes" is best defined. The age at which to consider genetic testing will be extended as cases accumulate with diagnoses after 6 months of age, after infancy, and even into early childhood, as notably illustrated by diagnoses of KCNJ11-related diabetes at 22 months of age (Greeley SA, Worrell H, Naylor R, Paz V, Philipson LH, Bell GI, 2010, unpublished data) and at 4 years of age. The relevant elder cases for screening will be selected with the assistance of HLA haplotyping and antibody testing. Through longterm monitoring of these patients using monogenic diabetes registries, new classifications of what is now known as neonatal diabtes will emerge [24, 25].

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