SRI RAMACHANDRA
UNIVERSITY
Chennai

NEONATAL DIABETES MELLITUS (Case from Unit I – Dr. Padmasani's Unit)

November 15, 2017

Presentor : Dr. Reshma Ramesh, MD I year
Guide : Dr. Padmasani L.N, Professor – Paediatrics
Unit I Faculty : Dr. Arun Prasath,Dr. Rajesh, Dr. Vidya, Dr. Ram Mohan
Co-guide : Dr. J. Dhivyalakshmi, Paediatric Endocrinologist

Introduction

- Neonatal Diabetes Mellitus is diabetes diagnosed in the first 6 months of life.
- Rare disease. It can occur in isolation or as a part of multi organ disease.
- It can be transient or permanent.
- Treatment of neonatal diabetes can be insulin or sulfonylureas depending on the mutation.

Clinical History

- 4 months old girl child

Decreased oral intake reduced activity	**1 day**
Passing increased amounts of urine	1 day

Clinical History – Details

- **HOPI :**
  - Previously well thriving child presented with complaints of decreased oral intake and reduced activity for a day
  - Passing increased amounts of urine since 1 day (Increased frequency of diaper change)
  - No complaints of fever/breathing difficulty/seizures
  - No complaints of loose stools / vomiting

Clinical History – Details

- **Birth History**
  - Antenatal : No history of GDM / PIH
  - Natal : Term, NVD, Birth weight – 3.1 Kgs. Cried immediately after birth.
  - Postnatal : No NICU admissions
- **Development History**
  - Gross motor : Partial head control attained
  - Language : Cooing present
  - Social : Recognises mother, social smile present.
- **Immunization History** : Immunized for age
- **Nutrition History** : On exclusive breast feeds

Family History

- First Born to non - consanguineous parents
- No family history of Diabetes Mellitus

Examination

Temperature	Afebrile
PR	156 / minute
RR	72 / minute, acidotic breathing
CBG	High

- No Pallor / Icterus/Cyanosis/Clubbing/Lymphadenopathy/Edema
- No Neurocutaneous markers
- Head to Foot examination was normal

CVS	S1S2 +. No added sounds Peripheral pulses feeble. CFT < 3 seconds
RS	NVBS +. BAE +
P/A	Soft. Bowel sounds + No organomegaly present
CNS	Child was drowsy GCS : 11/15 B/L PERL +

Anthropometry

	OBSERVED	EXPECTED	INTERPRETATION
WEIGHT	4.6 Kgs	6.5 Kgs	0 to -1 Z score
HEIGHT	56 cm	62 cm	0 to -1 Z score
MAC	11 cm	13 cm	0 to -2 Z score
HC	36 cm	40 cm	0 to -2 Z score

Child is of normal weight and height for age

Diagnosis

Infant Onset Diabetes Mellitus

(? Type 1 Diabetes Mellitus)

? Diabetic Ketoacidosis

Investigations

Hemoglobin	11.2
TC	13300
Platelet	4.56

C-Peptide	**0.06 ng/ml**

Urine ketones	**3+**

Sodium	132 mEq/L
Potassium	5.6 mEq/L
Chloride	101 mEq/L
Bicarbonate	**4** mEq/L

Course in Hospital : PICU STAY

- Child was managed as per standard DKA protocol .
- Insulin infusion was gradually stopped and child was started on subcutaneous insulin (Regular insulin initially)
- Child was changed to NPH insulin in view of poor glycemic control with regular insulin.
- Since child is 4 months old, the possibility of Neonatal Diabetes Mellitus was considered
- Samples for genetic testing were sent to Royal Devon and Exeter Hospital, UK.
- Child was discharged with NPH insulin (4-0-3 units)

Follow Up

- Genetic testing report –
  - Heterozygous novel ABCC8 missense variant p.(Val587Asp).
  - Parents are negative for this mutation

- Hence, insulin was gradually tapered and child was started on Oral Hypoglycemic Agents (glibenclamide).

Diagnosis

NEONATAL DIABETES MELLITUS

- ABCC8 a novel missense mutation

DISCUSSION

Neonatal Diabetes Mellitus

INCIDENCE	**1 in 89000 births (Germany & Italy)** **1 in 260000 births (Other European countries)**

TRANSIENT

Occurs more often in premature or very low birth weight infants

PERMANENT

More often due to mutations.
Less commonly due to disorders of pancreas

Causes

TRANSIENT(6q24)

- ZAC
- HYAMI

(70%)

- ABCC8 (15%)
- KCNJ11 (10%)
- HNF – 1β (5%)

PERMANENT

- KCNJ11 (50%)
- INS (30%)
- ABCC8 (15%)
- GCK
- PDX-1
- HNF – 1β

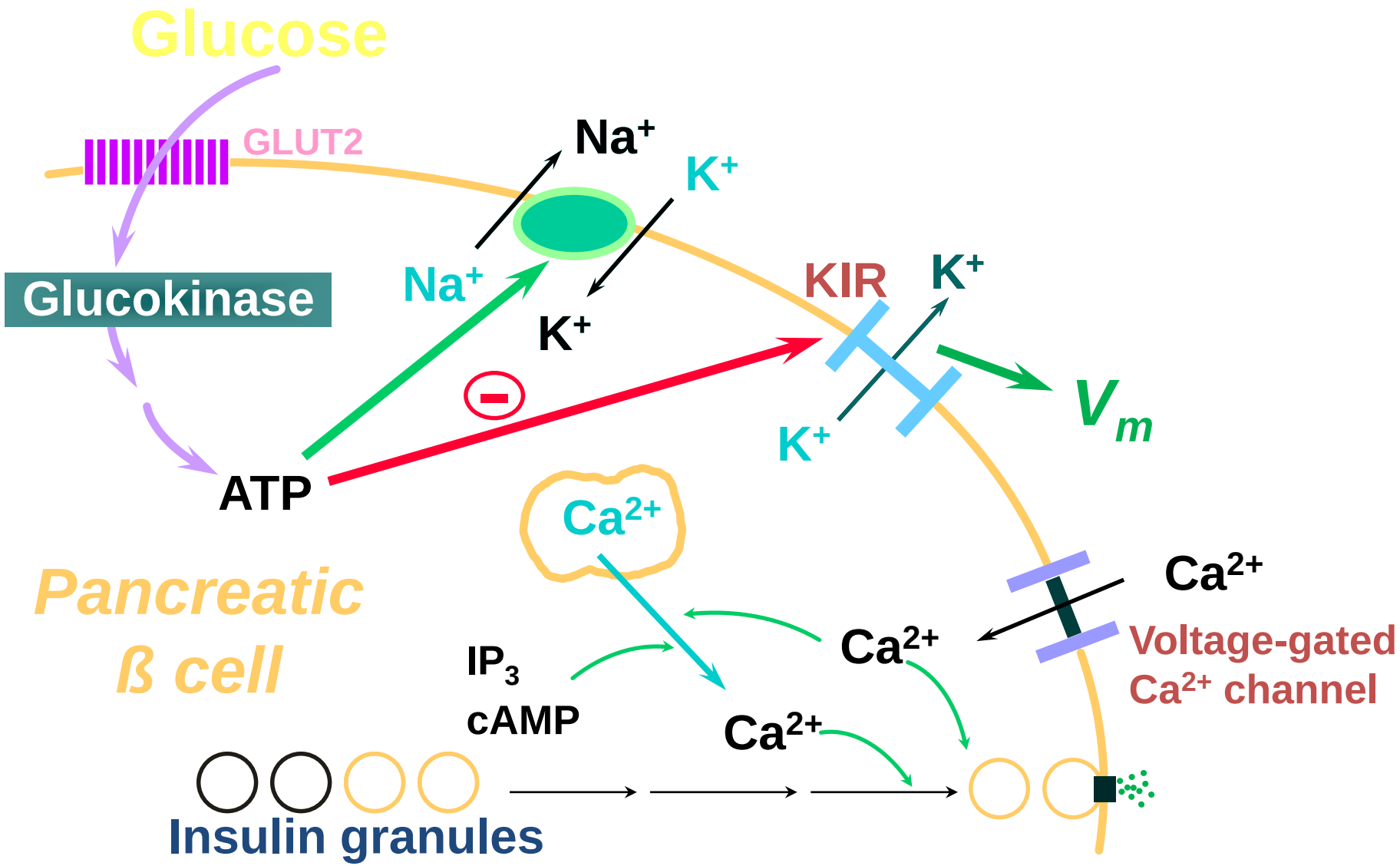
SYNDROMIC (rare)

- EIF2AK3 – Walcott-Rallison Syndrome
- FOXP3-IPEX syndrome
- GLIS3
- PTF1A
- RFX6 - Mitchell-Riley Syndrome
- NEUROG3
- GATA6

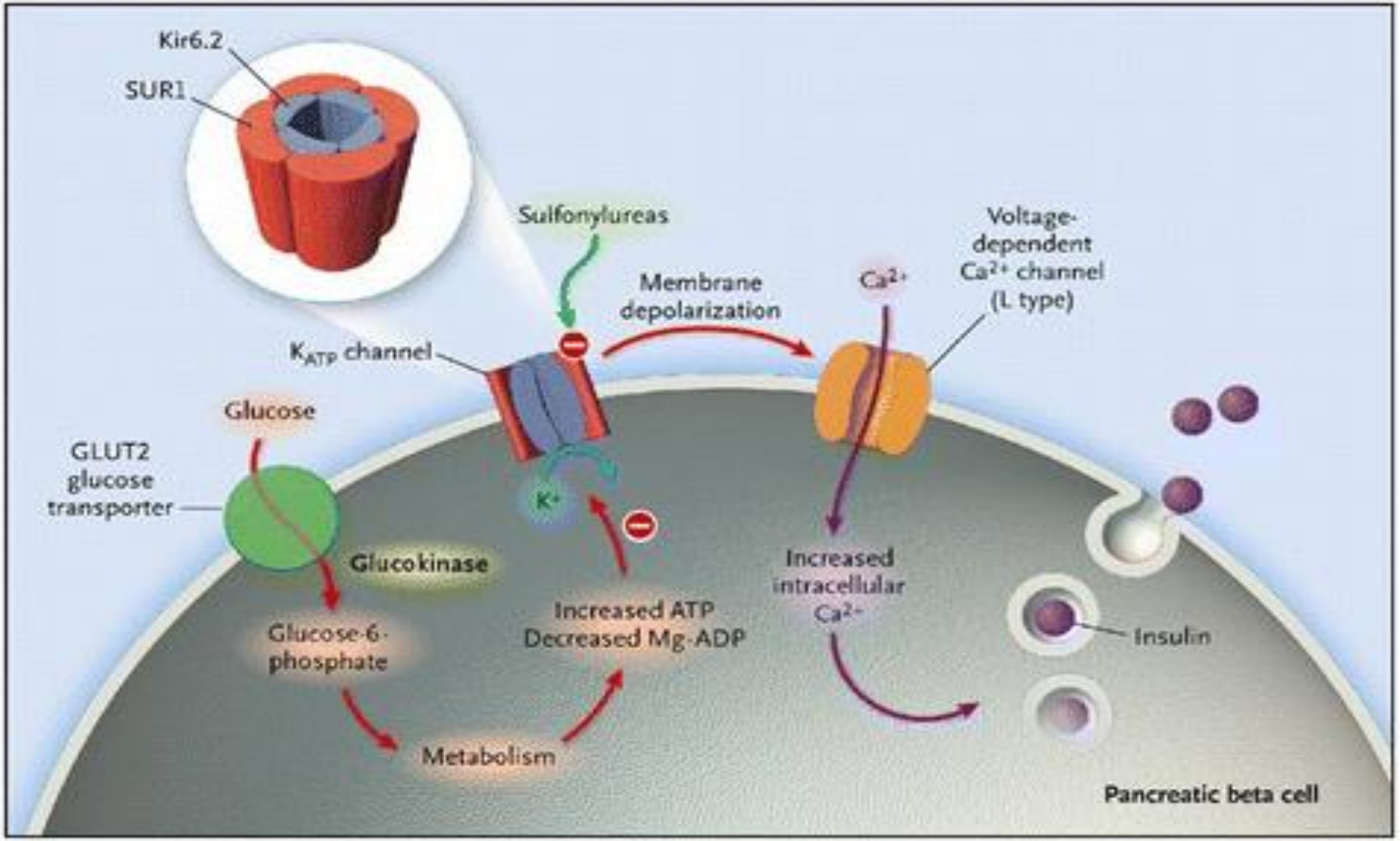
When a diagnosis of Type I DM can be incorrect

- A diagnosis of diabetes within the first 6 months of life
- Family history of diabetes with an affected parent
- Evidence of endogenous insulin production (C- peptide) outside the honeymoon phase (> 3 years)
- Absence of pancreatic islet autoantibodies

Glucose-stimulated insulin secretion



INSULIN MECHANISM



Initial Management of Neonatal diabetes

- Management of DKA is almost similar as that of children and adolescents

- Newborns are very sensitive to insulin, hence careful monitoring and adjustment of insulin doses is required to avoid hypoglycemia

- Complexities involved with subcutaneous insulin

Less subcutaneous fat
Need for low doses of insulin (may require dilution)
Frequent monitoring of CBG

Challenges in delivering insulin

Identifying a suitable insulin regimen is challenging because

- Carbohydrate content of breast feed cannot be quantified
- Insulin titration should be based on CBG levels

Insulin regimen

BASAL INSULIN

NPH/Glargine/detemir is used

Glargine is preferred since NPH and detemir have peaks and risk of hypoglycemia

BOLUS INSULIN

Given by rapid or regular insulin

May require insulin dilution

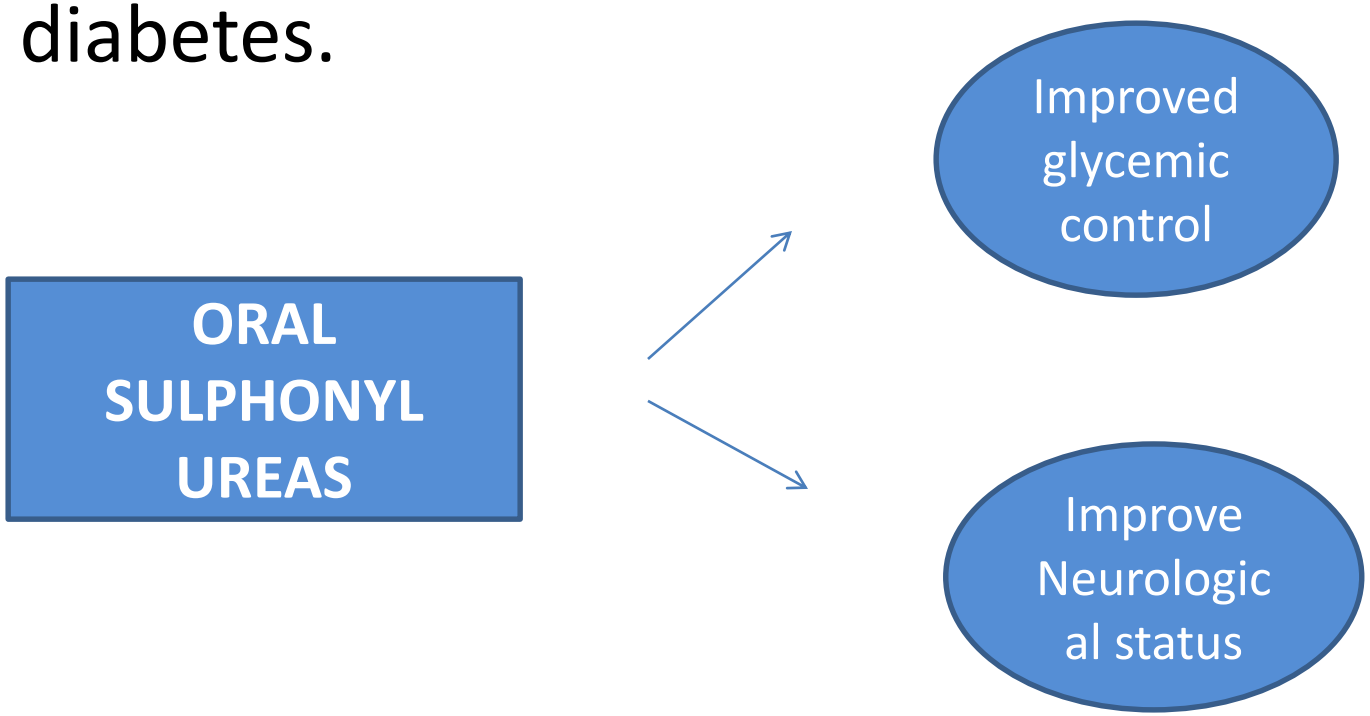
- Usage of insulin pumps have shown promising results in recent studies.
- Use of Continuous Glucose Monitoring is yet to be validated in newborns.

Importance of Genetic Testing

- A genetic analysis will be of immense help in guiding treatment.
- The application of pharmacogenetics to NDM allows for transition from insulin injections to sulfonylureas in most patients.
- This in turn provides better control of HbA1c levels and sugar control.
- Of equal importance to therapeutic considerations are the genetic implications for parents, sibling and offspring of an identified subject.

Insulin Vs Sulphonylureas

- Insulin alone may not be able to reverse the neurological impairment in infantile onset diabetes.



Use of Sulphonylureas

- 90% of patients with *KCNJ11* gene mutations and 85% of patients with *ABCC8* gene mutations can successfully transit from insulin to sulfonylurea

- Dose has to be individualised. Usually dose is higher than that used in patients with type 2 diabetes mellitus

- Preferred drug is glibenclamide, given usually in 2 divided doses, along with feeds

ADR

Nausea and vomiting
Abdominal pain and diarrhoea
Hypoglycemia
Transient allergic skin reactions
Tooth discolouration

TREATMENT FAILURE

- ✓Trial of sulfonylurea for a period of at least 3 months, with a dose as high as 1.5 mg/kg/day

- ✓10 to 15% of children with KCNJ11 and ABCC8 gene mutations may not respond to sulfonyureas

Indian Setting

- A study done by Poovazhagi Varadarajan et al in Chennai in 2013 studied 40 infants with IODM. Results showed that

Most common syndromic form : **Walcott Rallison syndrome**
Most common genetic mutation : **ABCC8 mutation**
followed by
KCNJ 11 mutation
Berardinelli Seip congenital lipodystrophy
Fanconi Bickel syndrome

- Among the IODM with onset below 6 months of age, 85% were monogenic, hence it is mandatory to perform genetic testing in all IODM.

Management of this case

- Child was on exclusive breast feeding.
- Carbohydrate content of breast feeds that child has consumed cant be quantified.
- Hence becomes essential to check sugars.
- Pre feed CBG was checked and insulin dose was titrated accordingly.

CURRENT STATUS

- Child is 6 month old.
- CBG - 100's to 200's
- Doses of Glibenclamide gradually increased (currently on 0.1 mg/kg/day)
  - Has loose stools, hence glibenclamide dose increased very slowly
- Insulin doses (currently on 0.8 U/kg/day) are gradually reduced.
- Complimentary feeds initiated.
- Child has novel mutation, hence needs to be followed up for transient / permanent NDM nature

Take home message

- ✓ A high index of suspicion is required to diagnose Neonatal Diabetes Mellitus since presentation is atypical.
- ✓ If there is a suspicion, it is mandatory to perform genetic testing.
- ✓ Genetic testing is essential because in specific mutations, it allows to switch over from Insulin to Sulphonyl ureas.

Acknowledgements

- Dr. Shuba & Dr. Rajakumar (PICU Team)
- Dr. Sriram (Endocrine department)

References

- Hattersley A, Bruining J et al. The diagnosis and management of monogenic diabetes in children and adolescents.Pediatric Diabetes 2009: 10 (Suppl. 12): 33–42.

- Poovazhagi Varadarajan, Senthil Senniappan et al. Clinical Presentation and long term outcome of 40 children with Infantile onset Diabetes Mellitus in South India. Indian Pediatrics Feb 2013.

Thank you!