NON-MODY MONOGENIC DIABETES: A VERY HETEROGENOUS AND PROBLEMATIC GROUP OF DIABETES

There is no conflict of interest

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Introduction: Monogenic diabetes represents a group of disorders resulting from a single gene defect leading to disruption of insulin secretion or a reduction in the number of beta cells.

Despite the classification of monogenic diabetes according to age of onset, with neonatal DM (<6 months of age) and maturity onset diabetes of young (MODY) (>6 months and <25 years of age); not every case can be classified into those groups.

It was aimed to evaluate non-MODY monogenic diabetes diagnosed in our clinic, and emphasize the characteristics of patients.

Cases: Admitted between 2006 to 2016
- Excluding criteria:
  - Type 1a DM
  - Genetically diagnosed MODY
  - Diabetic patients who had no mutaton on genetic analysis

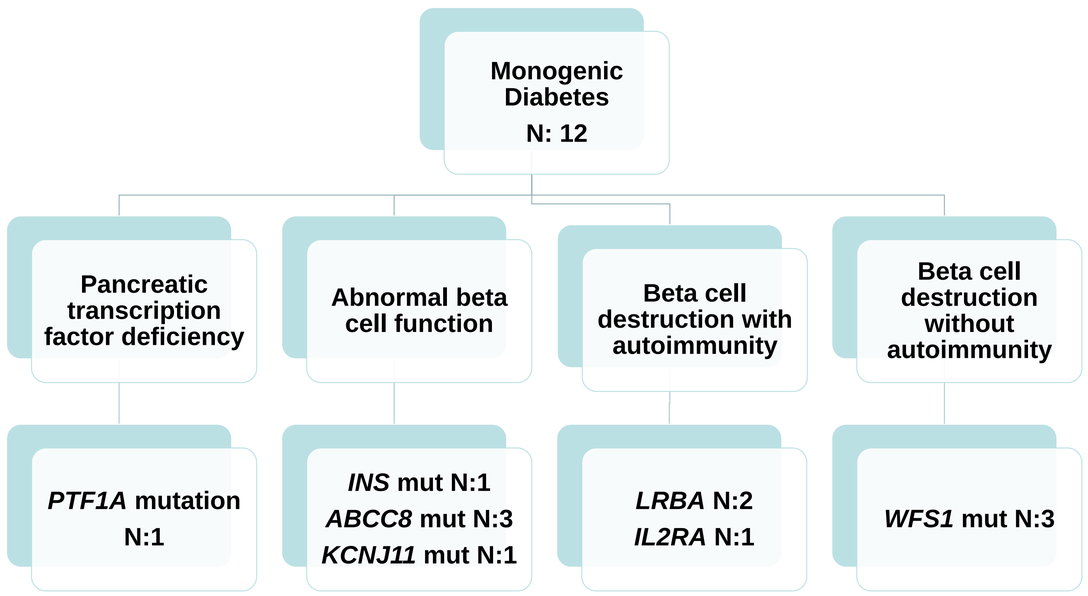

Table 1: Monogenic Diabetes with Immune Dysfunction

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
GENETIC LESION	*LRBA*	*LRBA*	*IL2RA*	*INS*
AGE OF DIAGNOSIS	4,5 months	9 years	5 months	1.5 months
PRESENTATION	Neonatal DM with DKA	Type 1 diabetes	Neonatal DM	Neonatal DM
IMMUNE DEFICIENCY	Low IgM, low lymphocyte activation with antiCD3	$CD21^{low}$ B cell depletion	$CD4^{+}CD25^{+}$cell depletion, neutropenia	Leukocyte adhesian defect type1
SYSTEMIC FEATURES	Inflammatory bowel disease, thrombocytopenia	Imflammatory bowel disease, autoimmune thyroiditis	Imflammatory bowel disease, autoimmune thyroiditis, thrombocytopenia	Meningomyelocel
PROGNOSIS	Died	Died	Died	On insulin treatment

Clinical pictures are similar in Treg cell related disorders with diabestes:

- Early onset hypogammaglobulinemia
- Autoimmunity
- Inflamatuar bowel disease
- Immune Dysfunction
- Recurrent infections

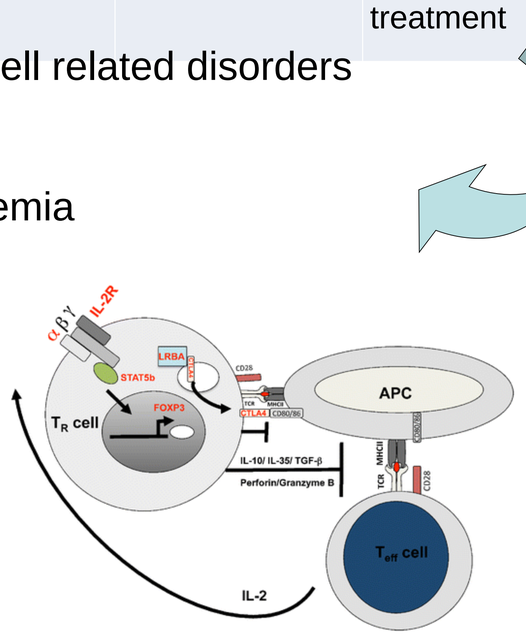

Table 2: Additional Systemic Findings of Cases:

Gruop of Diabetes	Diagnosis	Age of diagnosis	Sex	Additional features
Abnormal beta cell function	INS mutation	1.5 months	F	LAD type 1, meningomylocele
	ABCC8 mutation	25 days	M	Epilepsy
Beta cell destruction with autoimmunity	LRBA mutation	4.5 months	M	Inflammatory bowel disease, thrombocytopenia
	LRBA mutation	9 years	F	Imflammatory bowel disease, autoimmune thyroiditis
	IL2RA mutation	5 months	M	Imflammatory bowel disease, autoimmune thyroiditis
Beta cell destruction without autoimmunity	WFS1 mutation	1.7 years	M	Hydrocephalus, primary hypothyroidism, intestinal atresia

Conclusion: Monogenic diabetes due to a mutation in a non-MODY gene can be diagnosed after 6 months of age.Immune dysfunction was present in 50% in our cohort and should be investigated in all patients with early-onset monogenic diabetes.
Autoimmunity and immun dysfunction with diabetes should expand the spectrum of diagnosis from FOXP3 mutation to LRBA, IL2RA genes defect. Thes genes mutation have a role of NDM and showed very heterogenous phenotype. Mortality of patients with monogenic diabetes and additional autoimmunity was high in our cohort and is likely to reflect the multisystem nature of these diseases.

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