Endocrine Manifestations Of Pediatric *HNF1β*-MODY (MODY 5)

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INTRODUCTION

HNF1β-MODY (MODY 5)

- Rare form of MODY (1% of all cases) with multi-system involvement including renal cysts and dysplasia, genital tract abnormalities, hyperuricemia, hypomagnesemia, gout, elevated LFTs, and pancreatic exocrine insufficiency.

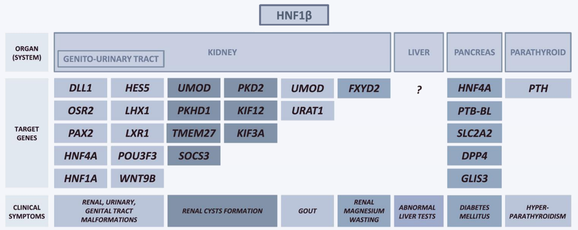
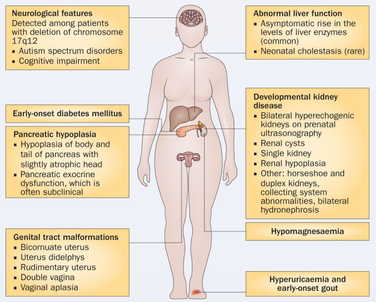


Figure 2. HNF1*β* as a promiscuous transcription factor. Target genes known to be regulated by the HNF1*β* transcription factor in several organ systems, responsible for the diverse multisystem clinical signs and symptoms, are depicted.

- Mutations often identified based on a history of renal disease and diabetes mellitus
- 50% of mutations are microdeletions of chromosome 17q12
- 50% of patients have de novo point mutations
- Other endocrine manifestations including dyslipidemia and hyperparathyroidism, not been well-defined in the literature
- No known correlation between site of mutation & clinical features; variable penetrance within families
- Few case series define the disease spectrum in children, which may have more a severe presentation than patients diagnosed with MODY5 as adults



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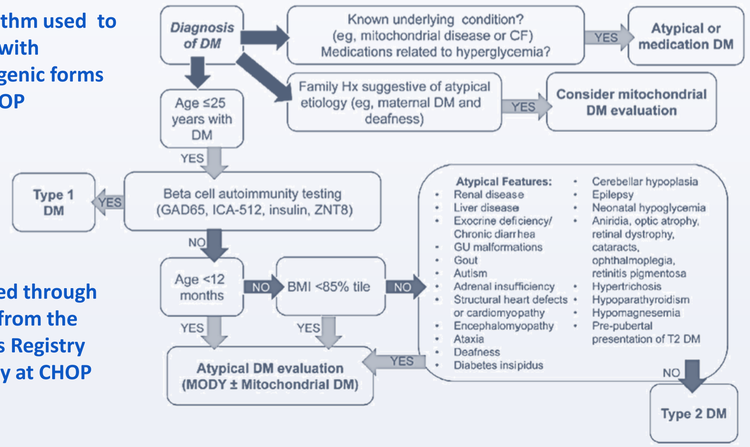
OBJECTIVE

- **To describe the clinical characteristics of HNF1B-related endocrine disorders in 9 pediatric patients at a single pediatric tertiary care center**

METHODS

The clinical algorithm used to identify patients with atypical or monogenic forms of diabetes at CHOP



Data was collected through chart extraction from the Atypical Diabetes Registry and Biorepository at CHOP

Table 1. Patient Demographics

Patient	Age at Diagnosis	Current Age	Sex	Type of Mutation	Birth Weight	BMI at diagnosis	Diabetes Mellitus	Abnormal Lipids	Hyper-parathyroidism
1	9 (2015)	14	F	17q12 del	SGA	19.25 (85%)	Yes	Yes	Yes
2	12 (2017)	15	F	17q12 del	SGA	16.93 (30%)	Yes	Yes	Yes
3	14 (2014)	20	F	17q12 del	AGA	19.92 (54%)	Yes	Yes	No
4	17 (2016)	22	F	17q12 del	SGA	16.52 (1%)	Yes	Yes	No
5	12 (2013)	21		HNF1B c.494G>A p.Arg165His	SGA	15.81 (9%)	Yes	Yes	No
6	12 (2018)	14	M	HNF1 c.1006delC p.His336Thrfs X40	AGA	32.23 (99%)	Yes	Yes	Yes
7	16 (2018)	18	F	HNF1B point mutation	SGA	19.18 (31%)	Yes	Yes	Yes
8	4 (2015)	10	F	HNF1B c.541C>T p.Arg181Ter	LGA	14.55 (26%)	No	No	No
9	15 (2019)	17	M	HNF1B c.1431G>C p.Gln477His	SGA	20.66 (53%)	No	Yes	Yes
Total							**78%**	**89%**	**55%**

RESULTS

Table 2. Glucose Homeostasis

Patient	Initial Presentation of Diabetes Mellitus						Current Treatment		
	Known Mutation	Age of Onset	Presentation	Peak Glucose at Diagnosis (mg/dL)	HbA1c at Diagnosis (%)	C-Peptide (ng/mL)	Recent HbA1C (%)	Treatment	TDD (U/kg/day)
1	No	9	Hyperglycemia	383	13.6	1.72	8.2	Basal Bolus	0.67
2	No	12	Hyperglycemia	378	7.0	9.5	6.1	Basal Bolus	0.96
3	No	14	Ketosis	>600	10.09	2.77	6.5	Basal Bolus	0.31
4	No	17	Ketosis	267	>14	0.6	7.2	Basal Bolus	0.9
5	No	12	Hyperglycemia	373	6.8	2.98	8.8	Basal Bolus	0.44
6	Yes	12	Hyperglycemia	214	6.1	19.1	6.3	Basal Only	0.05
7	Yes	17	Hyperglycemia	245	6.5	12.6	6.4	Lifestyle	-
8	Yes	No Known Diabetes Mellitus							
9	Yes	No Known Diabetes Mellitus							

Table 3. Lipid Profiles

Patient	Peak Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	HgbA1c* (%)	Creatinine* (mg/dL)	Management	Fecal Elastase (ug/g)
1	174	116	81	71	6.7	0.5	Dietary Changes	-
2	450	103	281	149	6.2	1.2	Pending Workup	-
3	210	741	86	34	5.9	0.6	Benefiber	>500
4	179	121	104	51	7.2	0.56	None	>200
5	227	162	140	55	8.8	1.46	Dietary Changes	54 (L)
6	323	493	185	37	6.3	2.74	Atorvastatin	-
7	176	142	78	70	6.4	1.84	Dietary Changes	-
8	160	78	90	54	5.2	0.69	None	>500
9	131	136	72	32	5.5	1.1	Dietary Changes	-

Table 4. Calcium Homeostasis

Patient	Peak PTH (pg/mL)	Calcium (mg/dL)	Phosphorous (mg/dL)	Magnesium (mg/dL)	Creatinine* (mg/dL)	Vitamin D 25-OH (ng/mL)	Current Management
1	95.5	10.2	4.2	1.4	0.6	24.2	None
2	312	10.3	5.3	2.0	1.6	14.7	Calcitriol, Ca Carbonate
3	20	9.9	3.0	1.4	0.75	27.9	None
4	14	9.9	2.9	1.1	0.56	-	Magnesium
5	52	9.6	2.6	1.3	1.23	21.1	Cholecalciferol
6	265	9.4	8.1	2.2	0.7	69.2	Cinacalcet
7	364	10.3	5.3	-	0.9	25.6	Calcitriol, Cholecalciferol
8	51.5	10.2	5.2	-	0.4	50.9	None
9	146	9.8	3.5	1.6	1.0	40.1	None

CONCLUSIONS

- One of the largest series describing the clinical characteristics of pediatric patients with HNF1B-MODY at a single center.
- Majority of patients have progressively declining beta-cell function, resulting in diabetes mellitus, with evidence of both insulin deficiency and insulin resistance.
- Nearly all had mixed hyperlipidemia with hypertriglyceridemia predominating
- Over half of the patients had elevated PTH levels preceding the decline in renal function concerning for primary hyperparathyroidism
- Additional research is needed to determine both ideal preventive approaches and optimal treatment plans for HNF1B-related endocrine disorders including diabetes and hyperparathyroidism