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Primary pancreatic insulinomas: Clinical, morphological and genetic characteristics of 12 children

ЭНДОКРИНОЛОГИЧЕСКИЙ НАУЧНЫЙ ЦЕНТР

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Background

Insulinomas are extremely rare tumors in children and an uncommon first manifestation of the Multiple Endocrine Neoplasia Syndrome type 1 (MEN1). An early clinical and genetic diagnosis is very important for the appropriate medical assessment and family counseling. In children, insulinomas are usually benign tumors with only a few reports of malignant insulinomas.

Objectives

To investigate clinical features, genetic and morphological characteristics of 12 children with primary pancreatic insulinomas.

Materials and Methods

Insulinomas were diagnosed biochemically and by imaging and verified histopathologically. Detailed clinical and biochemical examination was performed in all children. Sequencing of the *MEN1* gene was performed in 11 patients using bidirectional direct sequencing and MLPA deletion analysis. Families of the mutation carriers were studied after the molecular genetics verification. Follow up (mean age 16.6 y) included screening for signs of MEN1 (hormonal, imaging) and screening for metastases in case of malignant tumors.

Results

- ❑ Twelve children aged 8-16 years were diagnosed to have primary pancreatic insulinoma.
- ❑ Seizures and weight gain were the most common symptoms of hyperinsuliemic hypoglycemia (83.3% and 66.6% respectively).
- ❑ Five children (42%) had hypoglycemic coma before the diagnosis was established. Clinical features are summarized in ***table 1***.

Table 1

Characteristics		Results
Gender (n)	m:f	6:6
Age at onset of the first symptoms (years)	mean±SD	9.45±2.75
Age at diagnosis (years)	mean±SD	11.25±2.18
Serum insulin at hypoglycemia (mU/l)	Median (min-max)	30 (10.1-149)
Major symptoms	Seizures (n, %)	10 (83.3%)
	Weight gain (n,%)	8 (66.6%)
	Hypoglycemic coma (n,%)	5 (41.6%)
Initial erroneous diagnosis	Epilepsy (n, %)	8 (66.6%)
	Schizophrenia (n,%)	1 (8.3%)
Number of insulinomas pr patient	Solitary (n,%)	8 (66.6%)
	Multiple (n,%)	4 (33.3%)
Tumor size (cm)	<1 cm (n)	6
	1-2 cm (n)	7
	>2 cm (n)	6

- ❑ Four out of eleven children investigated (36%) were found to have mutations in the *MEN1* gene and developed hyperparathyroidism and hyperprolactinemia during the following 10 years. One patient with normal *MEN1* analysis developed hyperparathyroidism. In the two patients with *MEN1* mutations, where family biochemical testing was possible, relatives revealed the biochemical spectrum of MEN1 components, but with no clinical symptoms. Clinical, genetic features and family history of the patients with MEN1 syndrome are shown in ***table 2.***
- ❑ Histopathological studies revealed G2 differentiation stage (ENETs grade) in 5 of 12 cases (41.6%), distant metastases were seen during follow up in two patients.

Table 2

Patient	Age (yrs)	Histology (N of pancr tumors)	Family history	*MEN1* sequencing	Results of the investigations in relatives	Findings at follow up of index patient (age)
1	8	Benign (1)	Gastric cancer in grandmother, thyroid cancer in aunt. Mother is healthy	c.1547insC	ND	Hyperprolactinemia (21 y)
2	11	Malignant G2 (3)	None	w/t	ND	HPTH, PTH adenoma, liver + mesogastric metastases (21 y) Lung carcinoid (23 y)
3	11	Malignant G2 (2)	Ulcer in father and father`s brother	c.830C>G, p.P277R	Father: HPTH, prolactinoma, pancreatic adenoma	Pituitary microadenoma (13 y)
4	13	Benign (1)	None	c936 del C	HPTH, parathyroid adenoma in brother, hyperprolactinemia	HPTH, PTH adenoma, prolactinoma, adrenal nodular hyperplasia (19 y)
5	8	Benign G1 (3)	Ulcer in father and father`s brother, thyroid cancer in grandmother	c.625_628delACAG, p.S210fxX222	ND	HPTH, PTH adenoma (9 y)

HPTH – hyperparathyroiditis, PTH – parathyroid, ND-no data

Conclusions

- ❑ **Late diagnosis of insulinoma is typical, probably due to unspecific symptoms and disease rareness**
- ❑ **MEN1 syndrome should be suspected in all cases of pediatric insulinomas, even in cases with no other clinical features of MEN1 and absence of suspicious family history**
- ❑ **A high incidence of malignant insulinomas was seen at follow up**

The authors have nothing to disclose