Screening of PROP-1, LHX2 and POU1F1 mutations in patients with ectopic posterior pituitary gland

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Introduction:

Ectopic posterior pituitary gland (EPP) is characterized by an abnormal pituitary stalk and hypoplasia of the anterior hypophysis. The genetic mechanisms involved in the development of EPP remain uncertain. The aim of this study is to determine whether mutations in the three genes, PROP-1, LHX2, and POU1F1, are associated with the risk for and the characteristics of EPP.

Methods:

In the Endocrinology Outpatient Clinic of Dr. Behcet Uz Children's Hospital, 27 patients with EPP were submitted to sequencing analyses of the PROP-1, LHX2, and POU1F1 genes.

Results:

Growth hormone, thyrotropin, corticotropin, gonadotropin, and vasopressin deficiency were observed in 22 (81.5%), 23 (85.2%), 17 (63%), 14 (51.9%), and two (7.4%) patients. Thirteen patients (48.1%) presented with hyperprolactinemia. Fourteen patients (51%) had a history of birth dystocia, and 12 cases (42.1%) had a history of breech presentation. Central nervous system abnormalities in EPP patients included five cases with corpus callosum agenesis, one case with schizencephaly, and one case with Chiari type 1 malformation. We identified a homozygous p.S109* mutation in exon 2 in one male patient with EPP and two different PROP1 gene polymorphisms (A142T or c.109+3 G>A polymorphism) in thirteen patients.

Table-1: Baseline characteristics of patients with Ectopic posterior pituitary gland

	(n=27)
Median Age at Diagnosis, y (IQR) *	8,5(4,5)
Male/Female	15/12
Number of patients who had Caesarean Delivery (%)†	15(%55)
Number of patients who had Breech Presentation (%)†	12(%44)
Number patients with difficult Birth (%)†	14(%51)
Median Weight, kg (IQR)*	18 (8)
Median Weight SDS (IQR) *	-2,4(2,3)
Height (cm)**	110 ± 18
Height SDS*	-3,2 (1,4)
BMI**	16,3 ± 3,3
BMI SDS*	-0,34 (1,6)
Height Age*	5,1 (3)
Bone Age*	5 (4)
Height Velocity*	3(1,4)
Height Velocity SDS**	-2,7 (1,7)
Target Height**	163 ± 7,6
Target Height SDS*	-1,1 (0,6)
IGF-1*	25(12)
IGF-1 SDS*	-2,2 (0,7)
IGFBP-3*	1300 (930)
IGFBP-3 SDS*	-2,6 (1,5)

* Data are presented as median(interquartile range)
** Data are presented as mean ± standard deviation
† Data are presented as number (percentege)
BMI: Body mass index, IGF: Insulin-like growth factor-1, IGFBP-3: Insulin-like growth factor-binding protein-3

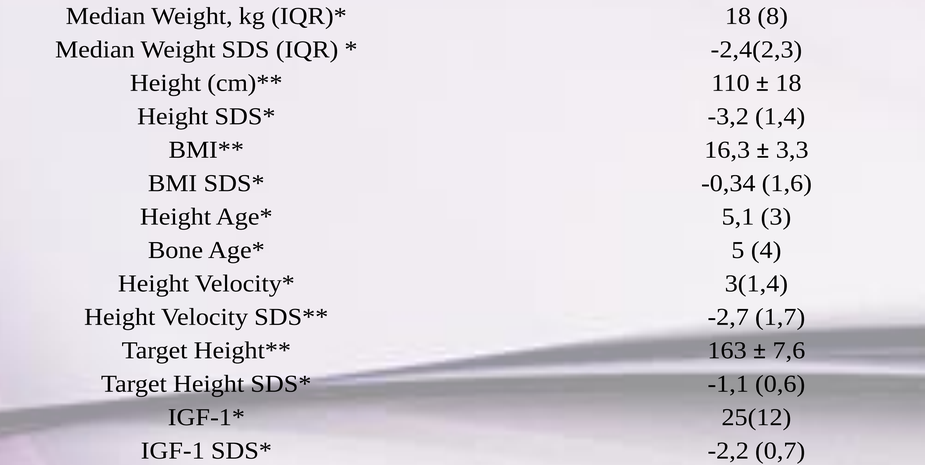

Figure 1: Brain magnetic resonance imaging findings in patients with ectopic posterior pituitary gland

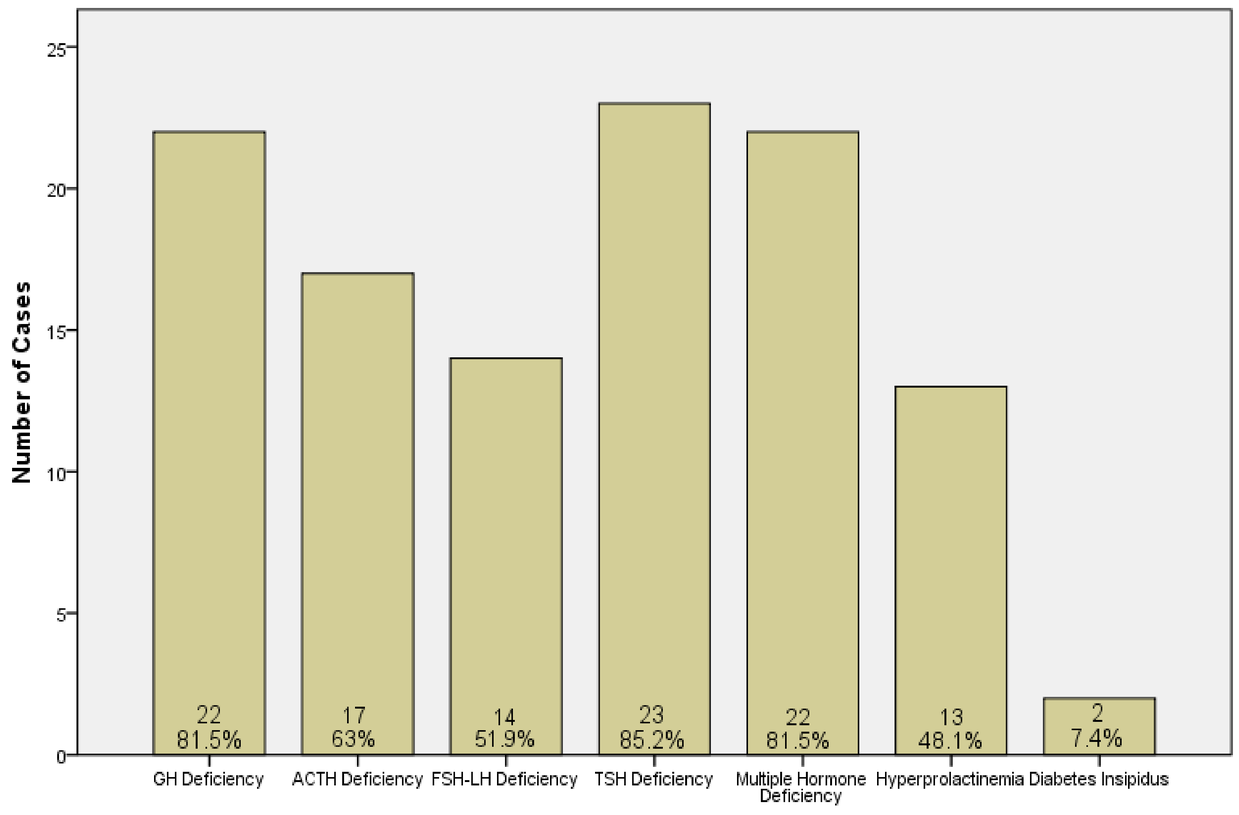

Figure 2: Pituitary hormonal deficits in patients with ectopic posterior pituitary gland

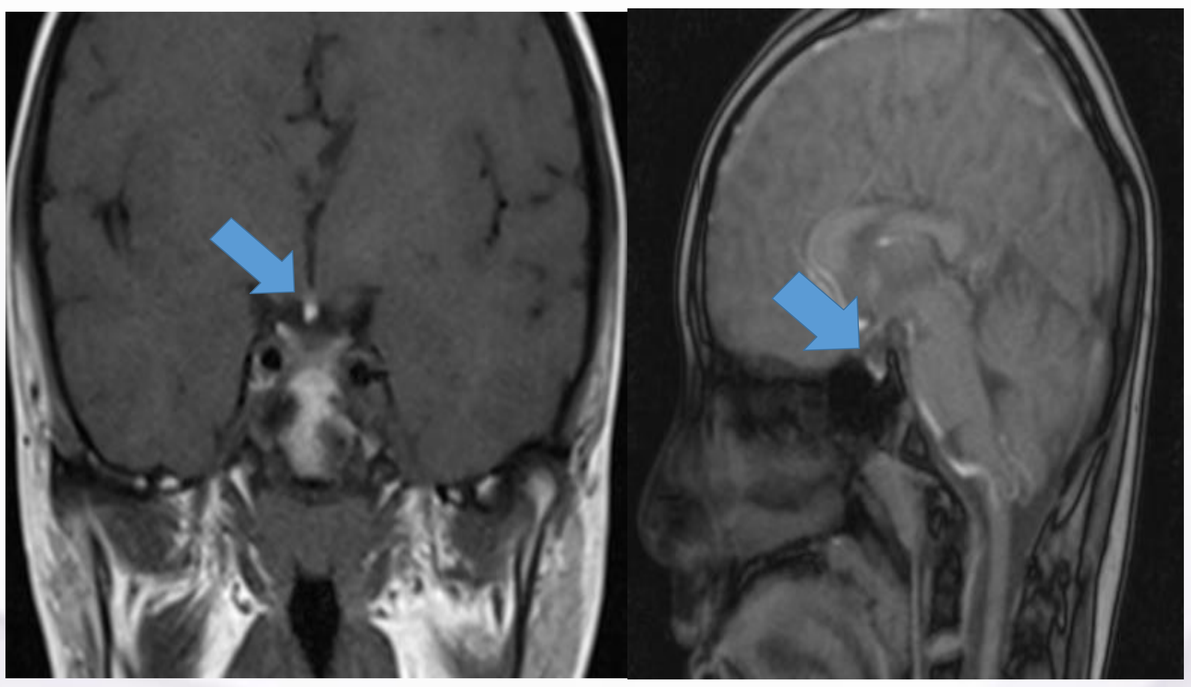

Figure 3: Ectopic posterior pituitary gland of magnetic resonance imaging in two cases

Conclusions:

We performed mutational analysis of the PROP-1, LHX2, and POU1F1 genes in a cohort of 27 patients with EPP. In thirteen patients with EPP, we identified two different PROP1 gene polymorphisms (A142T or c.109+3 G>A polymorphism) and found a homozygous p.S109* mutation in the second exon. However, we found no mutations in the LHX2 and POU1F1 genes.

We found PROP-1 gene abnormalities in 37% of patients with EPP. The results of this study further indicated that rare gene variants in patients with EPP could provide novel insights into the development of the pituitary gland. Further studies of PROP-1 gene variants and clinical EPP cases are needed to explore genetic disorders involving hypothalamic–pituitary abnormalities.

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