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Original Article

Renal Anomalies Associated with Ectopic Neurohypophysis

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ABSTRACT

Objective: Although the etiology of ectopic neurohypophysis that leads to pituitary hormone deficiencies is not yet clearly understood, birth trauma or genetic factors have been considered responsible. Concurrent cranial and extracranial congenital anomalies have been reported in such cases. The aim of the present study was to investigate the frequency of renal anomalies in nonsyndromic cases with ectopic neurohypophysis.

Methods: We retrospectively evaluated the medical records of 20 patients with ectopic neurohypophysis who were followed up between January 1990 and December 2007 in a tertiary University Hospital.

Results: Renal anomalies were identified in three (15%) cases including unilateral renal agenesis in one case, renal hypoplasia in one case, and double collecting system and unilateral renal agenesis in one case.

Conclusions: In the present study, the increased frequency of renal anomalies in cases of ectopic neurohypophysis was highlighted, and it was emphasized that there might be common genetic factors that lead to such associations.

Key words: Ectopic neurohypophysis, renal anomalies, pituitary hormone deficiency

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Introduction

Ectopic neurohypophysis is frequently associated with anterior pituitary hormone deficiencies. Isolated growth hormone deficiency (GHD) or multiple pituitary hormone deficiency (MPHD), in which GHD is associated with one or more other anterior pituitary hormone deficiencies, may develop in these cases. Although the etiology is unclear, traumatic birth, breech delivery and genetic factors have all been considered as possible factors (1,2). Some of the genetic factors include LHX4, HESX1, GLI2, GH-1, GH releasing hormone (GHRH) receptor, POU1F1, PROP-1and SOX3 mutations and have been shown to be important in the development of the pituitary gland. However, studies have failed to implicate a genetic factor in 95% of cases of ectopic neurohypophysis associated with GHD (1,2,3,4,5). In the present study, nonsyndromic cases with ectopic neurohypophysis were evaluated with respect to renal developmental anomalies, while the etiology of GHD was being investigated.

Materials and Methods

Patients

Two-hundred and thirteen cases followed between January 1990 and December 2007 at the Pediatric Endocrinology Department of Ege University Faculty of Medicine with the diagnosis of GHD were included in

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this study. The medical records of the patients were retrospectively evaluated. Of the total group, 20 (9.3%) cases (7 girls and 13 boys), in whom ectopic neurohypophysis was detected via magnetic resonance imaging (MRI), were included in this study. We analyzed the data regarding chronologic age at the time of diagnosis, standard deviation scores (SDSs) for height and body mass index (BMI) at the time of diagnosis, history of parental consanguinity, difficult birth history, family history of short stature, presence of other pituitary hormone deficiencies or additional anomalies other than ectopic neurohypophysis and presence of renal anomalies.

Sagittal and coronal 3-mm-thick slices of the pituitary area were obtained via MRI. All MRI scans were assessed by pediatric neuroradiologists who were not blinded to the clinical information.

Two standard GH stimulation tests were performed with insulin and levodopa (L-DOPA). In one neonate, plasma GH levels were measured during spontaneous hypoglycemia. A peak value of less than 10 ng/mL in two tests was regarded as confirmatory for the diagnosis of GHD. Adrenocorticotropic hormone (ACTH) deficiency was diagnosed based on a cortisol level of less than 5 µg/dL and a peak cortisol level of less than 25 µg/dL on ACTH test. The diagnosis of thyroid-stimulating hormone (TSH) deficiency was based on a free thyroxine (fT_4) level of less than 0.8 ng/dL in combination with a normal TSH level. Moreover, patients with TSH levels below the normal range were also diagnosed as having TSH deficiency. Thyrotropin-releasing hormone (TRH) stimulation test (7 µg/kg) was also used in the diagnosis of TSH deficiency. Hypogonadotropic hypogonadism was suspected when both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responses to LH-releasing hormone (LHRH) stimulation test (100 µg/m^2) were flat in pubertal patients. Basal and stimulated levels of cortisol, ACTH, TSH, prolactin (PRL), FSH, and LH were measured at sequential time points (15, 30, 60 and 90 minute after stimulation). Each hormone was measured by immunochemiluminescent assay and radioluminescence. Renal anomalies were examined by experienced radiologists via ultrasonography (US). In case of pathological findings on US, the presence of renal anomalies was confirmed via renal scintigraphy and intravenous pyelography (IVP).

This study was conducted according to the principles of the Declaration of Helsinki.

Results

The mean age of the patients at the time of diagnosis was 11.3±4.7 years (range, 0.2-18.1 years). The mean SDS for height at the time of diagnosis was -4.2±1.5 and the mean SDS for BMI at the time of diagnosis was -0.2±1.2. Five (20%) of the cases had a family history of short stature and two (10%) had a history of parental consanguinity. Two cases had a history of difficult birth.

Endocrinological evaluation of the patients, in whom ectopic neurohypophysis was detected on MRI, revealed that five (20%) cases had isolated GHD and 15 (80%) had MPHD. GHD was followed by TSH deficiency (13/20; 65%), FSH-LH deficiency (9/20; 45%) and ACTH deficiency (4/20; 20%), in decreasing order.

MRI scans revealed stalk formation in three cases. One of these cases had isolated GHD and two had MPHD. MPHD was determined in all of the 17 cases without stalk formation on MRI.

Examination of the patients for renal anomalies revealed renal anomalies in three (15%) cases: unilateral renal agenesis in one case, renal hypoplasia in one case, and double collecting system and unilateral renal agenesis in one case. All of the cases with renal anomalies had also MPHD.

Two patients had testicular hypoplasia, one case had chromosomal abnormality [46, XX/47, XX + mar (6) karyotype], and one case had Fanconi anemia. Table 1 shows the clinical characteristics, endocrinological deficiencies of the patients as well as the presence of renal and additional anomalies. None of the patients had a family history of renal anomalies.

Discussion

Ectopic positioning of the posterior lobe of the pituitary gland is a developmental anomaly and may lead to pituitary hormone deficiencies. Ectopic neurohypophysis has generally been reported as sporadic cases and, in the majority of cases the etiology is unknown (1,2,3,4,5). However, perinatal trauma, such as difficult birth and breech delivery, has been considered responsible. These traumatic factors may cause pituitary stalk transection and ectopic posterior lobe formation after axonal reorganization (6). In this study, two cases had a history of difficult birth. Many studies have reported concurrent cranial anomalies such as craniofacial dysmorphism, septo-optic dysplasia and Pallister-Hall syndrome, Chiari 1 malformation, Dubowitz syndrome and Worster-Drought syndrome in cases with ectopic neurohypophysis (3,4,5,6,7). LHX4, HESX1, GLI2 and SOX3 mutations were detected in some of these cases (1,2,3,4,5,6,7). Moreover, previous studies have also reported concurrent extracranial anomalies such as arthrogryposis multiplex congenita (8), Fanconi anemia (9), and situs inversus totalis (10). In a study performed by Simon et al (7), unilateral renal hypoplasia and ectopia was found in one of 60 patients with ectopic neurohypophysis.

In the present study, renal anomalies were found in three (15%) out of 20 cases of ectopic neurohypophysis.

Recently, a number of transcription factors that are involved in the development of the pituitary gland both in humans and in animals have been identified. However, the underlying genetic factor still remains to be determined in the majority of cases with ectopic neurohypophysis (2,3,4,5,6). In humans, mutations in transcription factors including PIT1, PROP1, HESX1, LHX3 and LHX4 have been associated with a broad spectrum of clinical phenotypes (11). Among these genes, the mutations of LHX4 (12), HESX1 (13,14), GLI2 and SOX3 (4,15) have been reported in patients with pituitary hormone deficiency and ectopic neurohypophysis.

In the present study, the high frequency of renal anomalies including renal agenesis and hypoplasia in patients with ectopic neurohypophysis was noteworthy. In the general population, the frequency of renal anomalies is three to six per 1 000 live births (16). Previous studies have reported mutations in various genes, such as LHX1 (17), LIM 1(18), SALL1 (19), FGFR1, FGFR2 (20), SIX1 (21), SIX2 (22), EYA1 (23), and GLI3 (24), leading to renal developmental anomalies. It is well-known that a mutation during the early stages of embryonic development is likely to affect more than one system. Common genes may be responsible for the development of ectopic neurohypophysis and renal anomalies. In a study conducted by Johnston et al (24), GLI3 mutations were identified in Pallister-Hall syndrome cases with pituitary developmental anomalies and renal agenesis or dysplasia, and it was suggested that this single gene mutation affected both the pituitary gland and the renal system. Furthermore, renal agenesis/dysplasia has been reported in Kallmann syndrome caused by KALL1 or FGFR1 gene mutations. Unilateral renal agenesis has been described in patients with Kallmann syndrome. Kirk et al (25) reported a systematic study of kidneys in 17 affected individuals from six families with Kallmann syndrome, including a family with Kallmann syndrome associated with ichthyosis and interstitial deletion within the short arm of the X chromosome. In that particular study, unilateral renal agenesis was found in six males from four families. Moreover, in two families (including a family in which all four patients had normal kidneys), there were male infants who died because of bilateral renal agenesis. In the family with Kallmann syndrome associated with ichthyosis, unilateral renal agenesis was found in two of four affected individuals. These four individuals all had the same

Table 1. Clinical features, endocrinological deficiencies, renal and other additional anomalies of the patients

Case	Gender	Age at diagnosis (years)	Endocrinological deficiency	Additional anomalies	Renal anomalies
1	M	13.8	TSH, GH	None	None
2	F	15.4	TSH, GH	None	None
3	M	4.4	ACTH, GH, FSH-LH	Fanconi anemia	Right renal agenesis
4	M	11.5	GH	Right hypoplastic testis	None
5	M	10.4	TSH, GH	None	None
6	F	10.1	TSH, GH, FSH-LH	None	None
7	M	0.16	GH, ACTH, TSH	None	Renal agenesis
8	F	9.7	GH	46, XX/47, XX + mar (6)	None
9	M	17.1	GH, TSH, FSH-LH	None	None
10	F	15.6	GH, TSH, FSH-LH	None	None
11	M	13.2	GH, TSH, FSH-LH	None	None
12	F	11.7	GH, TSH, FSH-LH	None	None
13	F	18.1	GH, FSH-LH	None	None
14	M	8.3	GH, TSH	None	None
15	M	7.9	GH, TSH, FSH-LH	None	None
16	M	17.3	GH, TSH, ACTH, FSH-LH	Hypoplastic testis	Renal hypoplasia
17	F	9.7	GH	None	None
18	M	6.7	TSH, FSH-LH	None	None
19	M	14.1	GH	None	None
20	M	14.2	GH	None	None

F: female; M: male; LH: luteinizing hormone; FSH: follicle-stimulating hormone; ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone; GH: growth hormone

X-chromosome deletion. Presumably, normal renal development requires expression of the Kallmann product (Kalig1/AMDLX), but mutation or absence of this product is not invariably associated with renal agenesis (25,26,27).

LHX1 gene is expressed in the primitive streak and prechordal mesoderm and, later, in the developing kidney and in portions of the central nervous system. A knockout experiment showed that LHX1 is an essential regulator of the vertebrate head organizer (17).

In conclusion, ectopic neurohypophysis is a diagnosis that should not be disregarded in cases with GHD. Further detailed studies are warranted to elucidate the etiology of ectopic neurohypophysis and other anomalies that may accompany this entity. The probability of the association of pituitary development anomalies with LHX1, LIM 1, BMP 4, AGTR2, SALL1, FGFR1, FGFR2 and SIX 1 gene mutations that have been shown to cause renal development anomalies and/or mutations of one of these gene families should be taken into consideration, and further studies should be planned. In the present study, increased prevalence of renal anomalies associated with ectopic neurohypophysis was highlighted and, the probability of the presence of common underlying genetic factors was emphasized.

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