Brief Communication

# Rathke's cyst with ectopic neurohypophysis presenting as severe short stature with delayed puberty

**Deep Dutta, Ajitesh Roy, Sujoy Ghosh, Pradip Mukhopadhyay, Ranen Dasgupta, Satinath Mukhopadhyay, Subhankar Chowdhury**

*Department of Endocrinology & Metabolism, IPGMER & SSKM Hospital, Kolkata, India*

## ABSTRACT

Ectopic neurohypophysis (EN) is found in nearly half of children with growth hormone deficiency (GHD). Rathke's cyst (RC) is uncommon in children and when present, hypopituitarism is found in nearly half of them. We present a fourteen and half-year-old girl with severe short stature and delayed puberty who on evaluation was found to have GHD, secondary hypocortisolism, and hypogonadism. Imaging revealed hypoplastic anterior pituitary, stalk agenesis, EN at tuber cinereum and intrapituitary RC. This is perhaps the first report of simultaneous occurrence of EN and RC, which was seen in a girl with multiple pituitary hormone deficiency. A primary defect in pituitary development may explain this simultaneous occurrence of EN and RC and hence this severe anterior pituitary function deficit.

**Key words:** Ectopic neurohypophysis, multiple pituitary hormone deficiency, Rathke's cyst, short stature

## Introduction

Ectopic neurohypophysis (EN) has been associated with isolated growth hormone deficiency (GHD) and multiple pituitary hormone deficiency (MPHD). Traumatic birth, breech delivery, and genetic factors may have some role in the ectopic location of the neurohypophysis.[1] Inadequate obliteration of the Rathke's pouch, which embryologically gives rise to the anterior and intermediate lobes of the pituitary, results in cystic remnants between the anterior and posterior lobe of pituitary known as Rathke's cyst (RC), and is found in 20% of pituitary at autopsy in adults.[1] RC is uncommon in children.[1]

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## Case Report

A fourteen and half-year-old chirpy active girl with good scholastic performance having a small face with low set ears without any midline defects, born term of breech delivery of a non-consanguineous marriage presented to us with concerns of lack of height gain and puberty since 6 years age. There was no history of headache, visual defects, polyuria or polydypsia. Her height was 107.5 cm, height standard deviation score (SDS) was -7.8 (target height SDS: -0.24) with a height age of 5.5 years Sexual maturity rating was prepubertal. Her bone age was 6-7 years (Greulich-Pyle method). Hormonal evaluation revealed low insulin like Growth factor-1 (IGF-1), GHD, secondary hypocortisolism, low luteinizing hormone (LH) and follicle stimulating hormone (FSH) with increased prolactin [Table 1]. Magnetic resonance imaging (MRI) brain revealed hypoplastic anterior pituitary with stalk agenesis (partial empty sella), with intrapituitary cyst measuring 0.3 cm in diameter, with ectopic posterior pituitary located in tuber cinereum of the hypothalamus [Figure 1a-c]. Optic nerve, olfactory bulbs, corpus callosum, and septum pellucidum were normal. A diagnosis of MPHD with intrapituitary

**Corresponding Author:** Dr. Deep Dutta, Department of Endocrinology & Metabolism, Room-9, 4th Floor, Ronald Ross Building, IPGMER & SSKM Hospital, Kolkata - 700 020, West Bengal, India. E-mail: deepdutta2000@yahoo.com

**Table 1: Hormonal parameters**

| Baseline | | Post-stimulation | |
|---|---|---|---|
| Serum LH (mIU/L) | <0.1 | LH: 40 min post-triptorelin (100 mcg) | 0.38 |
| Serum FSH (mIU/L) | 0.56 | FSH: 40 min post-triptorelin (100 mcg) | 2.23 |
| Serum 8 am cortisol (mcg/dl) | 3.8 (5-25) | Cortisol: 1 h post-ACTH (250 mcg) | 9.4 |
| Serum prolactin (ng/ml) | 94.6 (1.2-29) | GH: 30 min post-clonidine (100 mcg) | 2.2 |
| Serum GH (ng/ml) | 2.1 | GH: 60 min post-clonidine (100 mcg) | 2.0 |
| Serum IGF-1 (ng/ml) | 142 (237-996) | GH: 90 min post-clonidine (100 mcg) | 3.4 |
| Plasma ACTH (pg/ml) | 2.8 | GH: 120 min post-clonidine (100 mcg) | 1.8 |
| Serum fT3 (pg/ml) | 3.3 (1.5-4.1) | | |
| Serum fT4 (ng/dl) | 1.12 (0.8-1.9) | | |
| Serum TSH (mU/L) | 7.6 (0.35-4.9) | | |

LH: Luteinizing hormone, FSH: Follicle stimulating hormone, GH: Growth hormone, ACTH: Adrenocorticotropic hormone, fT3: Free triiodothyronine, fT4: Free tetraiodothyronine, TSH: Thyroid stimulating hormone

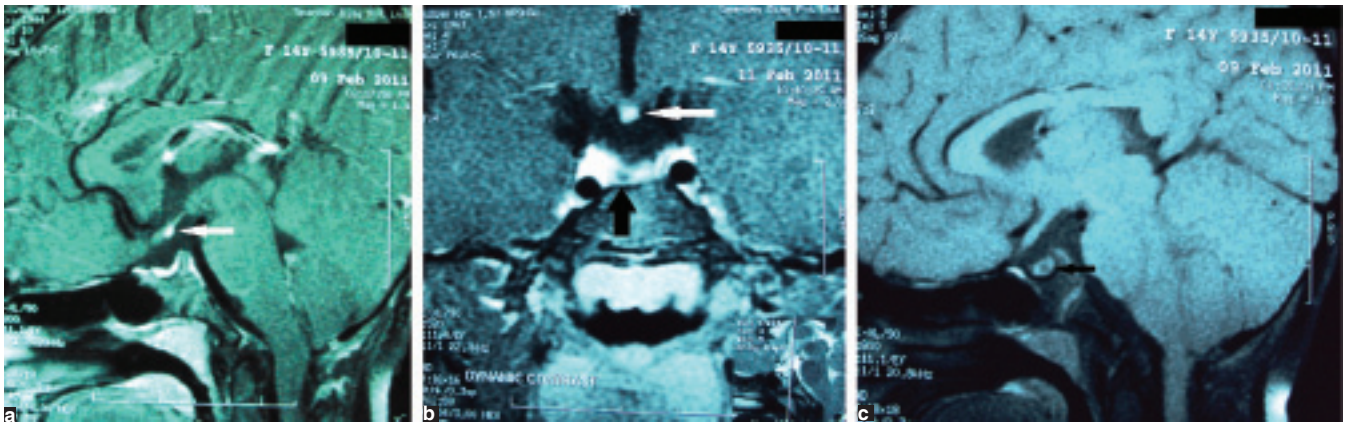

**Figure 1:** (a) T1W magnetic resonance imaging (MRI) showing hypoplastic anterior pituitary, stalk agenesis with ectopic posterior pituitary (white arrow); (b) Intrapituitary cyst (Rathke's cyst) seen on T1W MRI coronal sections (black arrow); (c) Intra-pituitary cyst (black arrow)

RC and EN was made in a teenage girl who had presented with severe short stature and delayed puberty.

## Discussion

Ectopic posterior pituitary is found in up to 43% of children presenting with short stature due to GHD, and is more common in children with MPHD.[1,2] Abnormal development of pituitary is thought to be responsible for the ectopic location of the neurohypophysis as well as for the anterior pituitary defects, and the perinatal difficulties are a consequence rather than a cause of this defect.[2] EN is believed to occur due to incomplete downward growth and fusion of the neurohypophysis with the adenohypophysis in the sella due to a defect in various transcription factors and may be associated with midline cranio-facial anomalies (e.g., Lhx4, HESX1).[2]

Causes of cysts in the sella include RC mainly, rarely dermoid cyst and acquired cysts secondary to hemorrhage in an adenoma. Arachnoid cysts, epidemoid and dermoid cysts mainly develop at the cerebellopontine angle and are uncommon in sella.[1] Dermoid cysts usually have calcified walls and contain hair follicles and sebaceous material.[1] RC are uncommon in children, prevalence of 1.2% in MRI brain in 341 children less than 15 years age,[3] as compared to 12-33% of normal adult pituitaries during autopsy.[4] Hypopituitarism has been reported in up to 45% of children with RC and growth delay in 29% children[5] RC may appear hyper-intense or hypo-intense on T1W MRI depending on the protein content of the cyst fluid, have a median size of 1.2 cm. Suprasellar extension is more common in adult (34%) as compared to pediatric patients (15%).[5] Our child had a hypointense homogenous intrapituitary cyst of 0.3 cm diameter on T1W MRI. Craniopharyngioma is unlikely as they are predominantly suprasellar tumors with extension into the sella, and they usually have evidence of calcification and local invasion. Furthermore, a long indolent clinical profile since 6 years of age goes against craniopharyngioma. Cystic pituitary adenomas have rarely been reported. However, it is unlikely in our child in the absence of visualization of any adenoma

on the pituitary imaging. On the contrary, our child has partial empty sella.

One of the limitations of this report is the lack of genetic testing to rule out transcription factor defects causing structural defects in the pituitary along with MPHD. It may be said that most of the transcription factor defects present early unlike our child. However, *PROP1* mutation is known to have a delayed clinical presentation and may even be associated with an enlarged pituitary. However, elevated serum prolactin with normal free triiodothyronine (fT3) and free tetraiodothyronine (fT4) virtually rules out a *PROP1* defect in our child.[5] The clinical and biochemical profile of our child is not suggestive of any known transcription factor defect. Hence RC is the most likely explanation of the anatomical defect seen in the pituitary imaging.

RC are usually clinically asymptomatic as in our child. Cyst evacuation along with removal of the cyst wall is the definitive therapy in symptomatic patients. Outcomes are variable with a relapse rate of 0-42% on follow up.[3,5]

The occurrence of RC with hypoplastic anterior pituitary can be explained by their common embryologic origin (vide supra). However, the simultaneous occurrence of RC and EN has not been previously reported. Their simultaneous occurrence may be incidental or may be reflective of a more extensive primary embryological development anomaly of the pituitary due to a defect in the transcription factors which are involved in the very early stages of development of pituitary like BMP4, BMP2, FGF8, Wnt4, Wnt5, HESX1, Lhx3, Lhx4.[3-5] Of these, the only transcription factor which is both involved in the early stages of pituitary development and is known to be associated with anterior and posterior pituitary defect is HESX1 mutation causing septo-optic dysplasia.[5] However, HESX1 mutation is unlikely in our child given the clinical and biochemical profile. Both RC and EN are independently associated with anterior pituitary defect, and their simultaneous occurrence in our patient may explain the pituitary hypoplasia, stalk agenesis, and the severe anterior pituitary hormonal deficit.

## Conclusion

To conclude it may be said that though the simultaneous occurrence of RC and EN is uncommon and not reported previously, it is not unexpected as the origin of both lie in a primary defect in the pituitary development early in gestation. Their presence together may signify a more severe anterior pituitary defect as was in our patient.

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