Neuroendocrinology Letters Volume 46 No. 2 2025
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Endocrinological Differences Between Partial and Complete Primary Empty Sella: A Comparative Analysis

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Submitted: 2024-11-18 Accepted: 2025-08-13 Published online: 2025-08-23

Key words: **complete primary empty sella; partial primary empty sella; secondary adrenal insufficiency; secondary hypogonadism; secondary hypothyroidism**

Neuroendocrinol Lett 2025; **46**(2):86–90 **PMID:** 40929707 46022505

Abstract

OBJECTIVES: Empty sella is the herniation of the subarachnoid space into the sella turcica; either secondary to identifiable causes (e.g., surgery or radiotherapy); or spontaneously, which is termed primary empty sella (PES). The amount of cerebrospinal fluid (CSF) in the sella **on imaging** classifies PES as partial (<50% filling, pituitary >2 mm) or complete (≥50% filling, pituitary <2 mm). Few investigations have compared hormonal abnormalities in partial and complete PES.
DESIGN: This study aims to determine whether partial and complete PES differ endocrinologically.
MATERIAL AND METHODS: Fifty-eight PES patients underwent hormonal evaluation: morning corticotropin (ACTH), cortisol, thyrotropin (TSH), free thyroxine (fT4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (females), total testosterone (males), prolactin (PRL), growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Patients were divided into partial and complete PES groups and endocrinologically assessed.
RESULTS: The proportion of secondary adrenal insufficiency and secondary hypogonadism was significantly higher in the complete PES group ($p = 0.021$ and $p = 0.041$, respectively). The proportion of cases with two or more affected axes was higher in complete PES ($p = 0.010$). Secondary hypothyroidism was significantly more common among males ($p = 0.001$).
CONCLUSION: After a diagnosis of complete PES, clinicians should be cautious about secondary adrenal insufficiency and hypogonadism. It is advisable to perform hormonal testing for all PES patients, regardless of type, because affected-axis rates often exceed 10% and may reach 50%. Prospective multicenter trials are necessary.

INTRODUCTION

Empty sella (ES) occurs when the subarachnoid space herniates into the sella turcica under cerebrospinal fluid pressure, with or without sellar expansion (Lu *et al.* 2023). Sheehan and Summer (1949) first used the term to describe a hollow sella at autopsy due to pituitary contraction after postpartum necrosis. Subsequent autopsy series have shown ES in patients without pituitary disease (Giustina *et al.* 2010).

ES is classified as primary or secondary. The most frequent cause of primary empty sella (PES) is congenital absence of the diaphragm sella; other factors include fluctuating intracranial CSF pressure. Secondary ES may result from trauma, medications, infections, or radiotherapy (Ekhzaimy *et al.* 2020).

CT or MRI is necessary for diagnosis. The diagnostic criteria for partial and complete PES are as follows; **partial PES** = sella <50% CSF, pituitary >3 mm; **complete PES** = sella ≥50% CSF, pituitary <2 mm (Carosi *et al.* 2022).

Primary empty sella epidemiology data is greatly affected by the procedures used for data collection. PES is specifically reported as an incidental discovery. Epidemiologic data show PES in 5.5–12% of autopsies and 8–35% of imaging exams, with female:male ≈5:1. Hypopituitarism prevalence ranges 19–68%; somatotropic dysfunction is often most common, followed by gonadotropic; mild hyperprolactinemia is frequent (Ekhzaimy *et al.* 2020). A multidisciplinary approach (endocrinology, neurology, ophthalmology, primary care) is recommended, but no specific diagnostic/management criteria exist (Chen *et al.* 2021).

The aim of this study was to evaluate hormonal status in PES at our institution and determine the prevalence of hormonal dysfunction in each axis; and assess whether there is any endocrinological difference between partial and complete PES.

MATERIALS AND METHODS

Patient Selection

Retrospective review of 272 ES patients over 10 years (January 2014 to December 2023) was made. 188 with secondary ES were excluded. From 84 PES, 58 with complete endocrine data were analyzed.

Ethical Aspect of the Study

This study was approved by the Ethics Committee of Manisa Celal Bayar University Faculty of Medicine on 31.01.2024, with the approval number 20.478.486.

Hormonal Evaluation

Morning ACTH, cortisol, TSH, fT4, FSH, LH, estradiol, testosterone, PRL, GH, IGF-1 were measured. Dynamic tests were not performed. The relevant hormone deficiency diagnoses were made according to the following criteria:

- Secondary adrenal insufficiency: cortisol <3.0 μg/dL + low/normal ACTH.
- Secondary hypothyroidism: low fT4 + low/normal TSH.
- Secondary hypogonadism: low sex hormones + low/normal gonadotropins (criteria adjusted for menopausal status).
- Low age-adjusted IGF-1 was considered as affected GH axis.

ACTH, GH, and IGF-1 were evaluated using IMMULITE 2000 Systems ACTH Reagent, GH Reagent an IGF-1 Reagent respectively, with the electrochemiluminescence immunoassay method (IMMULITE 2000 XPi Immunoassay System). TSH, fT3, fT4, FSH, LH, estradiol, total testosterone and prolactin were evaluated using Beckman Coulter Access TSH Reagent, Free T3 Reagent, Free T4 Reagent, hFSH Reagent, hLH Reagent, Sensitive Estradiol Reagent, Testosterone Reagent and Prolactin Reagent respectively, with the chemiluminescence immunoassay method (Beckman Coulter UniCel DxI 800 Access Immunoassay System).

Radiological Evaluation

Diagnosis was made by pituitary MRI, pituitary CT, cranial MRI or cranial CT. The diagnostic criteria were as follows; complete PES: pituitary≤2 mm, ≥50% CSF filling; partial PES: pituitary ≥3 mm but less than 7 mm (the average adult pituitary gland diameter), <50% CSF filling (Carosi *et al.* 2022). For cases with pituitary height between 2 mm and 3 mm, the classification was made according to the closest category based on the criteria.

Statistical Analysis

Relevant statistical tests were applied; Kolmogorov–Smirnov for normality, t-test or Mann–Whitney U, Chi-square (significance at $p < 0.05$). The concordance of the quantitative data with the normal distribution was examined using the Kolmogorov-Smirnov test. In the comparison of normally distributed variables between groups, an independent samples t-test was used, and descriptive statistics were shown as mean ± standard deviation. Intergroup comparisons of non-normally distributed variables were made using the Mann-Whitney U test, and descriptive statistics were given as median (min-max). In the analysis of qualitative variables, Chi-square tests were used according to the groups, and the results were presented in the form of frequency (%). Results with a p value of < 0.05 were considered statistically significant. *P*-values are reported in tables.

RESULTS

Of 58 PES patients (81% diagnosed via MRI), 41 (70.7%) were female; 36 (62.1%) were partial PES, 22 (37.9%) were complete PES. Mean body mass index

Tab. 1. Demographic, clinical, and hormonal comparisons between partial and complete primary empty sella groups

	Partial empty sella n (%)	Complete empty sella n (%)	*p*-value
Average age (years)	49.22	56.41	
Gender			
Female	23 (63.9%)	18 (81.8%)	
Male	13 (36.1%)	4 (18.2%)	
Clinical manifestation			
Asymptomatic	6 (16.7%)	2 (9.1%)	
Neuro-ophthalmological symptoms	10 (27.8%)	7 (31.8%)	
Endocrinological symptoms	12 (33.3%)	4 (18.2%)	
Constitutional symptoms	8 (22.2%)	9 (40.9%)	
Hormonal assessment			
Secondary adrenal insufficiency	4 (11.1%)	8 (36.4%)	**0.021**
Secondary hypothyroidism	9 (25.0%)	7 (31.8%)	0.573
Secondary hypogonadism	10 (27.8%)	12 (54.5%)	**0.041**
Hyperprolactinemia	5 (13.9%)	0 (0.0%)	0.067
Growth hormone deficiency	11 (30.6%)	12 (54.5%)	0.070
Degree of hormonal deficiency			**0.010**
No axis affected	16 (44.4%)	8 (36.4%)	
One axis affected	13 (36.1%)	2 (9.1%)	
Two or more axes affected	7 (19.4%)	12 (54.5%)	

(BMI) (n = 29) was 30.76 ± 6.05 kg/m². Twenty-four had no hormonal axis affected, 15 had one axis affected, 19 had ≥2 affected. Twelve (20.7%) had secondary adrenal insufficiency, 16 (27.6%) secondary hypothyroidism, 22 (37.9%) secondary hypogonadism, 5 (8.6%) hyperprolactinemia, 23 (39.7%) GH deficiency.

The cases were divided into two groups as partial and complete PES and each group were assessed separately regarding the affected hormonal axes. Subgroup analysis revealed that secondary adrenal insufficiency and hypogonadism were significantly higher in complete PES compared to partial PES (rates 36.4% vs. 11.1% and 54.5% vs. 27.8%; $\boldsymbol{p = 0.021}$, $\boldsymbol{p = 0.041}$ respectively); the rate of 2 or more axes affected was also higher in complete PES (rates 54.5% vs. 19.4%; $\boldsymbol{p = 0.010}$) (Table 1). Analysis by gender showed that secondary hypothyroidism was more common in males compared to females (rates 58.8% vs. 14.6%; $\boldsymbol{p = 0.001}$) (Table 2).

DISCUSSION

Our study shows higher rates of secondary adrenal insufficiency and hypogonadism in complete PES patients. These conditions have serious implications and require clinician awareness. Moreover, even partial PES patients may have substantial hormonal dysfunction.

Since its discovery in 1949, various theories were postulated about the pathophysiology of PES; however, the etiology remains unknown to this date. In recent decades, the extensive use of MRI has revealed an unexpectedly high frequency of PES (Chen *et al.* 2021). No standardized guidelines exist for the diagnosis and management of PES, leading to case management by non-endocrinologists and insufficient hormone assessment (Ekhzaimy *et al.* 2020). Therefore, this situation requires further studies on this rare clinical condition.

Obesity plays a role in the pathophysiology of PES. Hypercapnia and obstructive sleep apnea may contribute to increased intracranial pressure; central obesity can raise intra-abdominal and pleural pressures, causing increased cerebral venous pressure. Additionally, obesity-related cytokines and 11β-hydroxysteroid dehydrogenase type 1 activity increase cortisol, which can further elevate CSF pressure by increasing its production and reducing outflow (Mehla *et al.* 2020). Our patients' BMI (30.76 ± 6.05 kg/m²) exceeded the national average (27.59 ± 4.61 kg/m²), which is consistent with previous PES cohorts (Hatemi *et al.* 2003); Poggi et al. reported 27.7 ± 4.9 kg/m², while Zuhur et al. found 29.2 ± 6.08 kg/m² (Poggi *et al.* 2012; Zuhur *et al.* 2014).

Previous studies show endocrine dysfunction in 19–68% of PES (Carosi *et al.* 2022); in our study the rate was 58.6%, with GH deficiency (39.7%) most common, then hypogonadism (37.9%). GH deficiency variation likely reflects dynamic testing use. The majority of the studies in literature point out growth hormone axis as the most frequently affected hormonal axis in PES; however, there are studies in which secondary hypogonadism surpasses GH deficiency (Carosi *et al.* 2022; Zuhur *et al.* 2014; Guitelman *et al.* 2013; Maira *et al.* 2005; Gasperi *et al.* 2002). The prevalence of GH deficiency in PES varies from 4% to 57.1% (Chiloiro *et al.* 2017). The reason for this wide variation may be as a result of the methods used for the assessment of GH axis. Some studies included dynamic tests in addition

Tab. 2. Comparison of the cases accoring to gender

	Female n (%)	Male n (%)	*p*-value
Average Age (years)	52.51	50.59	
Average body-mass index (kg/m²)	32.56	27.81	
Empty Sella Type			
Partial empty sella	23 (56.1%)	13 (76.5%)	
Complete empty sella	18 (43.9%)	4 (23.5%)	
Radiological imaging			
Pituitary MRI	31 (75.6%)	16 (94.1%)	
Pituitary CT	1 (2.4%)	1 (5.9%)	
Cranial MRI	6 (14.6%)	0 (0.0%)	
Cranial CT	3 (7.3%)	0 (0.0%)	
Clinical manifestation			
Asymptomatic	5 (12.2%)	3 (17.6%)	
Neuro-ophthalmological symptoms	15 (36.6%)	2 (11.8%)	
Endocrinological symptoms	8 (19.5%)	8 (47.1%)	
Constitutional symptoms	13 (31.7%)	4 (23.5%)	
Hormonal assessment			
Secondary adrenal insufficiency	8 (19.5%)	4 (23.5%)	0.731
Secondary hypothyroidism	6 (14.6%)	10 (58.8%)	**0.001**
Secondary hypogonadism	14 (34.1%)	8 (47.1%)	0.356
Hyperprolactinemia	4 (9.8%)	1 (5.9%)	0.632
Growth hormone deficiency	16 (39%)	7 (41.2%)	0.879
Degree of hormonal deficiency			0.304
No axis affected	19 (45.4%)	5 (29.4%)	
One axis affected	11 (26.8%)	4 (23.5%)	
Two or more axes affected	11 (26.8%)	8 (47.1%)	

to baseline GH and IGF-1 level assessment, while some studies, similar to ours, used only baseline hormone levels to assess the hormonal axis.

In this study, all four axes (adrenal, gonadal, thyroid, GH) were more often affected in complete PES, significantly so for adrenal insufficiency and hypogonadism. The ratio of hormonal deficiency was not statistically different among genders ($p = 0.304$); however, secondary hypothyroidism was significantly more frequent among male patients ($\boldsymbol{p = 0.001}$). When the patients were divided into two groups as partial and complete primary empty sella, the ratio of hormonal deficiency was significantly higher in the complete primary empty sella group ($\boldsymbol{p = 0.010}$). Moreover, secondary adrenal insufficiency and secondary hypogonadism were significantly more frequent in the complete PES group ($\boldsymbol{p = 0.021}$, $\boldsymbol{p = 0.041}$, respectively). There are only a few studies in literature comparing partial and complete PES patients in an endocrine approach. In one of the studies, Zuhur *et al.* pointed out that GH deficiency, secondary hypogonadism, secondary hypothyroidism and secondary adrenal insufficiency were all significantly more frequent in their complete PES group compared to partial PES group (Zuhur *et al.* 2014). The relevant results of our study reveal that hormonal deficiency is encountered in PES patients to some point. Four hormonal axes (adrenal, gonadal, thyroid and growth hormone) were more frequently affected in the complete PES group compared to partial PES group; with secondary adrenal insufficiency and secondary hypogonadism being significantly more frequent in complete PES group. Both secondary adrenal insufficiency and secondary hypogonadism have important clinical consequences and complications, so after the diagnosis of complete PES, clinicians should be more alerted about these two hormonal disorders. However, hormonal deficiencies, even in partial PES should be followed closely as they may exceed 10% or even 50%. As a result of our study, we recommend all PES patients to undergo hormonal assessment regardless of the type of PES.

This study has some limitations. Being a cross-sectional retrospective single center study, there was no follow-up of the patients to assess reversibility. Also, there may be potential differences in diagnostic procedures and imaging quality throughout the 10-year period. Moreover, dynamic tests were not perfomed, leading to a possible underestimation of GH and adrenal impairment.

In conclusion, the study highlights a significant predominance of adrenal insufficiency and hypogonadism in complete PES, supporting the recommendation for comprehensive pituitary hormonal assessment in all PES patients irrespective of classification. It calls for prospective multicenter studies to develop evidence-based management guidelines.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST/COMPETING INTERESTS

The authors declare they have no conflict of interest.

ETHICS APPROVAL

The study was approved by the Ethics Committee of Manisa Celal Bayar University, faculty of medicine.

INFORMED CONSENT

Not applicable.

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