Research Article

Pituitary Stalk Germ Cell Tumors: Retrospective Case Series and Literature Review

Han Chen,1 Ming Ni,2 Yun Xu,3 and Li-Yong Zhong1

1Department of Endocrinology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
2Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
3Department of Obstetrics and Gynaecology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China

Correspondence should be addressed to Li-Yong Zhong; zhongliyong@bjtth.org

Received 3 November 2021; Revised 11 January 2022; Accepted 17 February 2022; Published 26 March 2022

Academic Editor: Marek Bolanowski

Copyright © 2022 Han Chen et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. Intracranial germ cell tumors with isolated pituitary stalk involvement are rare. Early recognition and long-term monitoring deserve further exploration.

Methods. A retrospective study reviewing eleven intracranial germ cell tumor patients with isolated pituitary stalk involvement was performed.

Results. Seven boys and four girls who presented with a hyperintense pituitary stalk on postcontrast T1-weighted magnetic resonance imaging without a posterior pituitary signal were included. The average maximum width of the pituitary stalk was 5.2 ± 1.6 mm. Polydipsia and polyuria occurred in all patients, followed by growth retardation, fatigue, and amenorrhea. Eight patients (72%) had concomitant partial anterior pituitary hormone deficiency. Seven patients initially had elevated human chorionic gonadotropin levels. After chemoradiotherapy, ten patients attended follow-up. Central diabetes insipidus remained in all survivors, and four (40%) of them had concomitant partial anterior pituitary hormone deficiency, primarily of growth hormone and insulin-like growth factor-1. The causes of the delayed diagnosis of previous studies were mainly negative tumor markers and the initial pathological diagnosis of autoimmune diseases.

Conclusion. Isolated pituitary stalk lesions could be a signal of intracranial germ cell tumors, especially coexisting with diabetes insipidus, hypopituitarism, and a worse response to glucocorticoid therapy. Negative results of tumor markers and pathology could not exclude the diagnosis. Chemoradiotherapy is an effective therapy, leaving mild-t-moderate hypothalamus-pituitary dysfunction. This rare neuroimaging feature may be used as a factor to predict long-term neuroendocrine outcomes.

1. Introduction

Intracranial germ cell tumors (iGCTs) are malignant neoplasms [1, 2] that are common in children and young adolescents [3]. iGCTs are considered a mismigrated progenitor during early embryogenesis, with distribution along the midline of body development [4]. The hypothalamic-pituitary region is the second primary site of iGCTs after the pineal region, and a solitary suprasellar lesion is possible. Compared to an enlarged pituitary, suprasellar mass, hypothalamic involvement, and synchronous bifocal lesions, iGCTs with isolated pituitary stalk involvement are rare and difficult to diagnose, accounting for 13% of pediatric idiopathic pituitary stalk involvement [5–7] and/or diabetes insipidus cases [8]. However, identifying the underlying condition often requires a long period of observation, which can worsen nervous system damage and pituitary defects and increase the risk of dissemination [9–11].

Generally, the diagnostic flow charts and the treatment strategies for pituitary stalk involvement caused by iGCTs are described as follows. (1) Consideration of pathological thickening of the pituitary stalk: the imaging measurement of the pituitary stalk was 3–4 mm or more, indicating potential pathological thickening [8]. The coexistence of diabetes insipidus and hypopituitarism supports the diagnosis of neoplastic diseases [8, 12]. (2) Consideration of germ cell tumors: significant hyperintense intrasellar or pituitary stalk on postcontrast T1-weight magnetic resonance imaging (MRI) with an absent bright spot in the posterior pituitary.
lobe suggested the possible diagnosis of iGCT. Elevated concentrations of human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) in serum and/or cerebrospinal fluid (CSF) are specific evidence. Pathological examination is the gold standard, and a good response to chemoradiotherapy is a supplementary diagnosis. (3) Treatment of germ cell tumors: as a local lesion, whole-brain or whole-ventricle radiation with adjuvant chemotherapy has been considered the optimized therapeutic strategy for iGCTs with isolated pituitary involvement. After tumors are removed, sequelae should also be highlighted. Theoretically, chemoradiotherapy without surgical damage to the pituitary gland and pituitary stalk may preserve the partial neuroendocrine function of patients with isolated pituitary stalk involvement. However, research has thus far proven inconclusive.

The clinical management of iGCTs with isolated pituitary stalk involvement remains questionable as follows: (1) How can germinomas be distinguished from other pituitary stalk lesions to decrease the risk of progression or dissemination? (2) Combined with rarely isolated pituitary germ cell tumors, what is the role of the negative tumor marker? (3) Can the diagnosis of iGCTs be ruled out based on the pathological result of autoimmune diseases? (4) Would survivors of isolated pituitary stalk involvement need long-term or even lifelong multiple hormone replacements as common sellar/suprasellar disease? To better describe iGCTs with isolated pituitary stalk involvement, this retrospective study was performed. Previously published cases and updated management were also reviewed. Published studies related to the management of iGCTs with pituitary stalk lesions and advanced multidisciplinary therapy were also analyzed.

2. Materials and Methods

The present retrospective study was conducted in accordance with the Declaration of Helsinki for human research on humans, and the protocol was approved by the Ethics Committee of Beijing Tiantan Hospital affiliated with Capital Medical University (Beijing, China).

Medical records of eleven outpatients with iGCT with a radiographic presentation of isolated pituitary stalk involvement diagnosed at our institution between 2015 and 2021 were collected for every outpatient visit. The inclusion criteria were as follows: (1) isolated pituitary stalk involvement was defined as a width of the pituitary stalk of > 3 mm or a mass on the pituitary stalk on the MRI scan; (2) postcontrast T1-weighted MRI was received; (3) germ cell tumors were confirmed by elevated tumor markers (hCG > 2.6 mIU/ml and/or AFP > 7 ng/ml), good response to chemotherapy (tumor significantly shrank after the first course of chemotherapy), or pathological result; and (4) exclusion of coexistence with other sellar/suprasellar lesions or presentation of metastases.

The neuroendocrine disturbance was demonstrated by the pituitary-target hormone profile, which included basal adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone, free triiodothyronine, free thyroxine, gonadotropin, testosterone, estradiol, prolactin, growth hormone, and insulin-like growth factor-1 (IGF-1). Central diabetes insipidus (CDI) was defined as elevated plasma osmolality (≥300 mOsm/kg H2O) and hypoosmolar urine (≤200 mOsm/kg H2O). Short stature was defined as height below -2 standard deviation score by gender and age based on population data of Chinese children. Delayed puberty was defined as the absence of any pubertal signs at the age of 13 years in girls and 14 years in boys. Hypogonadism was defined as amenorrhoea in women and the presence of hypogonadal symptoms along with low serum testosterone levels in men.

3. Results

3.1. Case Series. Seven boys and four girls with an average age of 10.6 ± 4.2 years (range, 5–17) were included in this study. All patients presented with polydipsia and polyuria at the first outpatient visit, with a median symptom interval of 10 (range, 2–48) months (see Table 1). Furthermore, four patients presented with short stature, four with fatigue, one with secondary amenorrhoea, and one with delayed puberty. At the initial MRI scan, marked enhancement of the pituitary stalk on postcontrast T1-weighted MRI with an absent posterior pituitary bright spot was observed. No signs of multiple lesions or metastasis were reported. The average maximum diameter of the pituitary stalk was 5.2 ± 1.6 (range, 3.4–8.6) mm in the patients enrolled. Four patients had a maximum diameter at the upper site of the pituitary stalk, while seven had a maximum diameter at the middle site (see Table 1). Slight optic chiasma involvement was present in one patient, but no visual change occurred (patient 1, see Figure 1). All patients received the detection of tumor markers, at least hCG and AFP, in serum, and three of them synchronously received the CSF test. Seven patients showed an increase in serum hCG and/or AFP levels, and three of them also showed synchronously higher CSF levels. Nine patients, including seven with elevated hCG and two with normal hCG levels, were clinically diagnosed with iGCTs through a good response to chemotherapy. Another two patients with negative tumor markers were diagnosed with germinomas by pituitary stalk biopsy.

Further laboratory assessment indicated that nine patients had concomitant partial anterior pituitary hormone deficiency. Six had impairments to the growth hormone/insulin-like growth factor (GH/IGF) axis, six had hyperprolactinemia, and two had hypogonadotropic hypogonadism. No case involving a deficiency of adrenocorticotrophic hormone or central hypothyroidism was reported (see Table 2). Except for hypernatremia related to uncontrolled CDI, biochemical and hematological tests, including blood cell count, electrolyte, kidney, and liver function tests, were almost normal. After being diagnosed, the patients received radiation therapy combined with adjuvant chemotherapy in the oncology department, and all achieved complete responses after chemoradiotherapy (see Figure 1). Re-evaluation of the neuroendocrine function indicated that CDI and impairments to the GH/IGF axis persisted, although the tumor had been eliminated (see
| No. | Patient | Manifestations (month) | \(D_{\text{max}}\) (mm) | Sagittal MRI (mm) | Coronal MRI (mm) | Tumor markers | Diagnosis |
|-----|---------|------------------------|--------------------------|------------------|------------------|--------------|-----------|
|     |         |                        | OC | M | PI | OC | M | PI | hCG\(^a/b\) mlU/ml | AFP\(^a/b\) ng/ml |         |
| 1   | 16M     | PD/PU and fatigue (6)  | 6.5 | 5.3 | 5.6 | 3.7 | 6.5 | 5.6 | 5.2 | 62.1 | 66.8 | iGCT (tumor marker) |
| 2   | 6M      | PD/PU (18)             | 4.7 | 3.0 | 4.4 | 3.1 | 3.4 | 4.7 | 2.2 | 0.1  | 1.25 | iGCT (chemotherapy)  |
| 3   | 8M      | PD/PU (2)              | 4.3 | 2.9 | 2.2 | 1.7 | 4.3 | 2.2 | 0.9 | 0.1  | 1.22 | iGCT (chemotherapy)  |
| 4   | 13M     | PD/PU and SS (48)      | 4.3 | 3.7 | 4.0 | 2.5 | 2.2 | 4.3 | 2.2 | 0.1  | 1.82 | Germinoma (pathology) |
| 5   | 13F     | PD/PU, DP, and SS (10) | 8.6 | 7.0 | 6.6 | 5.0 | 6.9 | 8.6 | 3.4 | 42.51| 1.71 | iGCT (tumor marker)  |
| 6   | 9F      | PD/PU (12)             | 4.7 | 3.6 | 4.6 | 3.6 | 3.8 | 4.7 | 3.8 | 204  | 1.63 | iGCT (tumor marker)  |
| 7   | 5M      | PD/PU and fatigue (6)  | 6.5 | 4.9 | 6.5 | 4.2 | 1.8 | 3.6 | 3.1 | 11.52 | 1.71 | iGCT (tumor marker)  |
| 8   | 12F     | PD/PU and SS (10)      | 6.6 | 3.9 | 4.2 | 2.3 | 4.2 | 6.6 | 2.8 | 26.11/26.61 | 0.605/1.36 | iGCT (tumor marker)  |
| 9   | 12M     | PD/PU and fatigue (4)  | 3.9 | 1.5 | 3.0 | 1.9 | 2.6 | 3.9 | 2.6 | 6.64/22.65 | 1.55/2.15 | iGCT (tumor marker)  |
| 10  | 17F     | PD/PU, fatigue, and amenorrhoea (24) | 3.4 | 3.4 | 1.8 | 1.1 | 3.3 | 1.9 | 1.4 | 2.51 | 1.39 | Germinoma (pathology) |
| 11  | 5M      | PD/PU and SS (9)       | 3.9 | 3.9 | 2.8 | 2.6 | 3.6 | 2.7 | 2.3 | 14.8/34.72 | 2.16/2.13 | iGCT (tumor marker)  |

Patient: M, male; F, female; manifestations: PD/PU, polydipsia and polyuria; SS, short stature; DP, delayed puberty; HH, hypogonadotropic hypogonadism; MRI: \(D_{\text{max}}\), maximum diameter of the pituitary; OC, optic chiasma; M, median of the pituitary stalk; PI, pituitary insertion; tumor markers: \(^a\), tumor markers in serum; \(^b\), tumor markers in cerebrospinal fluid; hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; diagnosis: iGCT, intracranial germ cell tumor (without pathological type).
Three patients with hyperprolactinemia at diagnosis spontaneously normalized, and two remained elevated. For two patients with hypogonadotropic hypogonadism before, a girl restored menstruation (patient 10) while another girl remained in a state of delayed puberty (patient 5).

A boy who reached age 14 years at the end of chemoradiotherapy was also considered to have delayed puberty secondary to hypogonadotropic hypogonadism (patient 4).

Ten patients received a follow-up visit for a median period of 1 year (range, 1–4). At the last visit, all patients

**Table 2: Neuroendocrine disturbance of the patients.**

| No. | Patient | Pre-CRT | Post-CRT | Final follow-up (age/year) |
|-----|---------|---------|----------|---------------------------|
| 1   | 16M     | CDI, HPA, HPRL, and GH/IGF | CDI, HPRL, and GH/IGF | CDI and GH/IGF (21) |
| 2   | 6M      | CDI     | CDI      | CDI (11) |
| 3   | 8M      | CDI and HPRL | CDI and GH/IGF | CDI (11) |
| 4   | 13M     | CDI, GH/IGF, and HPRL | CDI, GH/IGF, HPG, and HPRL | CDI, GH/IGF, HPG, HPT, and HPRL (15) |
| 5   | 13F     | CDI, GH/IGF, and HPG | CDI, GH/IGF, and HPG | CDI, GH/IGF, and HPG (15) |
| 6   | 9F      | CDI and HPRL | CDI and GH/IGF | CDI (11) |
| 7   | 5M      | CDI     | CDI      | CDI (7) |
| 8   | 12F     | CDI and GH/IGF | CDI and GH/IGF | CDI, GH/IGF, and HPG (14) |
| 9   | 12M     | CDI and HPRL | CDI      | CDI (14) |
| 10  | 17F     | CDI, GH/IGF, and HPG | CDI and GH/IGF | CDI (18) |
| 11  | 5M      | CDI, GH/IGF, and HPRL | CDI and GH/IGF | - |

Patient: M, male; F, female; neuroendocrine disturbance: CDI, central diabetes insipidus; HPA, hypothalamic pituitary adrenal axis; HPG, hypothalamic pituitary gonadal axis; HPT, hypothalamic pituitary thyroid axis; HPRL, hyperprolactinemia, GH/IGF, growth hormone/insulin-like growth factor axis; CRT, chemoradiotherapy.

[Figure 1: Contrast-enhanced brain magnetic resonance imaging of patients: (a) coronal/sagittal-enhanced brain magnetic resonance imaging at diagnosis and (b) coronal/sagittal-enhanced brain magnetic resonance imaging after chemoradiotherapy (tumor is marked with the arrow).]
maintained a complete response, but neurohypophysis dysfunction, presenting as polydipsia and polyuria, persisted. Four patients (40%) had concomitant partial hypopituitarism (see Table 2). Only one of the four patients with low concentrations of GH and IGF-1 developed short stature (patient 4), although the other patients also presented with growth retardation. Three patients had delayed puberty at the last visit (patients 4, 5, and 8). Only one patient developed new central hypothyroidism and constant hyperprolactinemia (patient 4).

3.2. Literature Review. A literature search was performed in the PubMed/Medline electronic databases for articles published before September 1, 2021, applying the following search terms: pituitary stalk thickening, germinomas, and intracranial germ cell tumors. The criteria for papers to be included in this study were as follows: (1) patients were definitively diagnosed with iGCTs by pathology or good response to chemoradiotherapy; (2) brain imaging revealed isolated pituitary involvement, with a description of pituitary function; (3) studies published in English; and (4) exclusion of reviews, expert opinions, or clinical guidelines. In addition, clinical trials with the purpose of analyzing the etiology of pituitary stalk lesions without neuroimaging details were also excluded.

A total of 16 original articles involving 28 patients were included [9–24] (Table 3), with an average age of 13.4 ± 7.6 (range, 4.5–40) years. Fifteen of them were females, five were males, and the remaining eight patients were of unclear gender. Polydipsia and polyuria were the most common initial manifestations of cases included, followed by short stature, hypogonadism, including delayed puberty and amenorrhea, and other atypical manifestations related to hypopituitarism such as fatigue and loss of appetite. In addition to CDI, hypopituitarism was observed in 68% of the patients, including growth hormone and IGF-1 deficiency, hypogonadotropichypogonadism, central hypothyroidism, hyperprolactinemia, and cortisol deficiency. The primary neuroimaging features are a thickening pituitary stalk with an absent bright spot in the posterior pituitary gland, followed by the combination of an enlarged pituitary or sellar/suprasellar change. Only three patients had elevated hCG levels in the CSF, and the other had elevated serum hCG levels. No cases of elevated AFP levels were reported. Among all patients included, only four were directly diagnosed with germ cell tumors through biopsy and pathology results. Nine patients chose to wait, and their extended lesion on rescan MRI or an increase in the hCG level indicated possible germ cell tumors after a period of observation. They were further diagnosed as iGCTs on pathology. In addition to patients who received observation, the other 15 patients were initially misdiagnosed as having other pituitary stalk lesions by CSF examination or biopsy testing; ten had lymphocytic hypophysitis, three had granulomas, and one had Langerhans cell histiocytosis. Among those patients, nine received a high dose of glucocorticoids as an anti-inflammatory treatment for pathologically autoimmune diseases, but their lesions showed no significant regression on MRI. Four patients received growth hormone replacement for short stature, but it also promoted tumor progression. Rescan magnetic resonance imaging indicated an enlarged lesion in these patients and even intracranial metastases. Reassessment of tumor markers was performed in twelve patients, eight of whom presented with increased hCG levels, and the remaining four patients were still negative as before. Finally, all patients, except one, were pathologically diagnosed with iGCTs. The other patient with an elevated CSF hCG level was diagnosed with germinomas through a good response to chemoradiotherapy. Twenty patients reported sequelae of neuroendocrine disturbance after chemoradiotherapy; eight patients reported hormone replacement or pituitary hormone deficiency without details; and the remaining 12 patients primarily presented with persistent CDI, followed by central hypothyroidism, adrenocorticotropic and basal cortisol deficiency, growth hormone and IGF-1 deficiency, and hypogonadotropic hypogonadism.

4. Discussion

iGCTs with isolated pituitary stalk involvement are rare. IGCTs have a typical midline distribution, and the sellar region was regarded as the second primary site of iGCTs occurrence, following the pineal region. Even among sellar iGCTs, isolated pituitary stalk lesions are rare [13, 16, 17, 19, 21, 24, 25]. Bifocal lesions with a pituitary stalk and the pineal region or basal ganglia region are more easily valued, while isolated pituitary stalk lesions may be ignored in the early stage. As a malignancy, delayed diagnosis can increase the risk of progression and even metastasis [10, 11]. Given that the initial clinical manifestations usually involve neuroendocrine disorders, multidisciplinary teams are highlighted to pay more attention to the neuroendocrine management of iGCTs with isolated pituitary stalks. To our knowledge, the present study involving 11 patients is the largest series of iGCT patients with isolated pituitary stalk involvement.

The patients included in the present case series and the review studies were mostly children and young adolescents, with no significant differences in sex. Unlike other suprasellar masses with a significant mass effect, presentations related to severe headache, persistent vomiting, visual impairment, disorders of movement, and cognitive decline have rarely been reported. Polydipsia and polyuria are the most common clinical manifestations that occur in almost all patients. Other common manifestations included growth retardation, hypogonadism, atypical fatigue, and loss of appetite. The longest symptom interval is related to polydipsia and polyuria coexisting with growth retardation. Neuroimaging is highly recommended for further etiological diagnosis. The most important neuroimaging predictor of germinomas is an absent signal of the posterior pituitary with a well-enhanced lesion on postcontrast T1-weighted MRI, perhaps presenting with a homogeneous solid mass, irregular cystic mass [17, 19], and thickening pituitary stalk. However, regarding the physiological variation in the size of the pituitary stalk, it seems difficult to diagnose these faintly visible lesions of the pituitary stalk. Most studies evaluating
| Study | Patient Manifestation | Initial Initial | Manifestation (duration) | Initial | Diagnosed (method) | Rep. MEI | Repettent markers | Initial therapeutic strategy (observation duration) | Diagnosed (method) | Repettent markers | Initial therapeutic strategy (observation duration) |
|-------|-----------------------|----------------|--------------------------|--------|-------------------|--------|------------------|------------------------------------------------|-------------------|----------------|------------------------------------------------|
| 1997  | 5.8F PU/PD (5 months) | Normal         | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (8 months) | Normal            | NA               | Normal (8 months) | Normal mass         |
|       | 1997  | 10.5F PU/PD and SS (12 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (3 months) | Normal            | NA               | Normal (3 months) | Normal mass         |
|       | 1997  | 11.8F PU/PD (2 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (11 months) | Normal            | NA               | Normal (11 months) | Normal mass         |
|       | 1997  | 12.9F PU/PD (2 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (14 months) | Normal            | NA               | Normal (14 months) | Normal mass         |
|       | 1997  | 18.1F PU/PD and DP (17 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (8 months) | Normal            | NA               | Normal (8 months) | Normal mass         |
|       | 1999  | 8F PU/PD, SS, and appetite (2 years) | CDI, GHD, and HPT, and PRL | Neuroendocrine disturbance | Normal | LYPH (pathology) | NA     | Normal           | CDI, GHD, and HPT, and PRL | LYPH (pathology) | NA               | CDI, GHD, and HPT, and PRL |
|       | 1999  | 12F PU/PD and SS (12 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (3 months) | Normal            | NA               | Normal (3 months) | Normal mass         |
|       | 1999  | 13F PU/PD and SS (18 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (3 months) | Normal            | NA               | Normal (3 months) | Normal mass         |
|       | 1999  | 7F PU/PD and SS (12 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (1 year) | Normal            | NA               | Normal (1 year)   | Normal mass         |
|       | 1999  | 13F PU/PD and SS (12 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (1.8 years) | Normal            | NA               | Normal (1.8 years) | Normal mass         |
|       | 1999  | 8F PU/PD and SS (12 months) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (1.8 years) | Normal            | NA               | Normal (1.8 years) | Normal mass         |
|       | 1999  | 12M PU/PD, SS, and appetite (17 years) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (6 months) | Normal            | NA               | Normal (6 months) | Normal mass         |
|       | 1999  | 8F PU/PD, SS, and appetite (17 years) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (6 months) | Normal            | NA               | Normal (6 months) | Normal mass         |
|       | 1999  | 12M PU/PD, SS, and appetite (17 years) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (6 months) | Normal            | NA               | Normal (6 months) | Normal mass         |
|       | 1999  | 18F PU/PD, SS, and appetite (17 years) | Normal | Neuroendocrine disturbance | Initial MRI | Normal mass         | NA     | NA               | Normal (6 months) | Normal            | NA               | Normal (6 months) | Normal mass         |
| Study       | Patient | Manifestation (duration) | Neuroendocrine disturbance | Initial MRI | Initial tumor markers | Initial diagnosis (method) | Initial therapeutic strategy (observation duration) | Aggravated manifestations | Repeat MRI | Repeat markers | Diagnosis (method) | Neuroendocrine disturbance |
|-------------|---------|--------------------------|---------------------------|-------------|----------------------|---------------------------|------------------------------------------------|---------------------------|-------------|----------------|---------------------|---------------------------|
| Edouard 2009 [19] | 10F | PU/PD, headache, and DP (3 years) | CDI, HPT, and GHD | PST and absent posterior pituitary | Normal | LYH (pathology) | GHRT for 5 months (9 months) | NA | Enlarged mass in the pituitary stalk and hypothalamus | NA | GE (pathology) | CDI and HPT |
| 4.5M | PU/PD and SS (1 year) | CDI and GHD | Isolated PST | Normal | LYH (pathology) | GHRT for 3 years (6 years) | Progressive PST | Enlarged infundibular, pineal mass | Elevated CSF hCG | GE (pathology) | CDI, HPA, HPT, and GHD |
| Jevalikar 2012 [21] | 10M | PU/PD (6 months) | CDI and GHD | Absent signal of posterior pituitary | Normal | LYH (pathology) | GHRT for 2 months (16 months) | Headache and Parinaud’s sign | Elevated CSF hCG | GE (pathology) | CDI, HPA, HPT, and GHD |
| Guzzo 2012 [23] | 24F | PU/PD, amenorrhea, and fatigue (1 year) | CDI, HPA, HPT, and HPRL | PST and suprasellar mass | Normal | LYH (pathology) | NA | NA | NA | NA | GE (pathology) | NA |
| Terasaka 2012 [20] | 40F | PU/PD, amenorrhea, polyalactasis, headache, and VI (3 years) | CDI, HPA, HPT, and HPG | PST and intrasellar mass | Normal | LYH (pathology) | Hydrocortisone (1000mg with gradient decrease) for 2 weeks | Deteriorated | Enlarged mass | Elevated CSF hCG | GE (pathology) | APD |
| 5 | PU/PD | CDI | Isolated PST | Normal | LYH (pathology) | NA (6 years) | NA | NA | NA | NA | GE (pathology) | GE (pathology) |
| Robison 2013 [12] | 19 | PU/PD | CDI and hypopituitarism | Isolated PST | Elevated CSF hCG | — | — | — | — | — | — | APD |
| 10 | PU/PD | CDI | Isolated PST | Normal | — | — | — | — | — | — | — | — | APD |
| 11 | PU/PD | CDI | Isolated PST | Normal | — | — | — | — | — | — | — | — | APD |
| Zilbermint 2014 [22] | 13F | PU/PD, fatigue, and amenorrhea (1 year) | CDI, HPA, HPT, HPG, and HPRL | PST and extending to hypothalamus | Normal | — | — | — | — | — | — | GE (pathology) | CDI, HPA, and HPT |
| Graaf 2020 [9] | 12F | PU/PD (3 years) | CDI, HPA, HPT, and HPG | PST, suprasellar mass, and absent posterior pituitary | Elevated CSF hCG | Granuloma (pathology) | Glucocorticoid (1mg/kg/d) for 3 months (36 months) | CDI, VI, headache, and vomiting | Sellar mass and enhancement of the ependyma and pineal gland | Elevated CSF hCG | GE (pathology) | CDI, HPA, and HPG |
| Dias 2020 [24] | 27M | PU/PD (1 year) | CDI | PST, absent posterior pituitary, and pineal cyst | Elevated CSF hCG | Neurohypophysis (clinical) | Methylprednisolone (500mg/week to 250mg/week) for 3 months (1 month) | Anejaculation | Enlarged PST, absent posterior pituitary, and pineal cyst | Elevated CSF hCG | GE (pathology) | CDI, HPA, HPT, and GHD |

Patient: M, male; F, female; manifestations: PU/PD, polydipsia and polyuria; SS, short stature; DP, delayed puberty; HH, hypogonadotropic hypogonadism; VI, visual impairment; neuroendocrine disturbance: CDI, central diabetes insipidus; HPA, hypothalamic pituitary adrenal axis; HPT, hypothalamic pituitary thyroid axis; HPG, hypothalamic pituitary gonadal axis; HPRL, hyperprolactinemia; GHD, growth hormone deficiency; APD, anterior pituitary hormone deficiency; MRI, PST, pituitary stalk thickening; tumor markers: hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; CSF, cerebrospinal fluid; diagnosis: LYH, lymphocytic hypophysitis; LCH, Langerhans cell histiocytosis; GE, germinomas; NGGCT, nongerminomatous germ cell tumors; therapy: GHRT, growth hormone replacement treatment; NA, not applicable.
pituitary stalk imaging consider a maximum diameter equal to or greater than 2.5–3 mm as thickening [12, 26, 27], 4 mm at the optic chiasm, 3 mm at the pituitary insertion, or both as pathological thickening [8]. In the present study, the mean diameter of the pituitary stalk was 5.2 ± 1.6 mm as neoplastic diseases, which is commonly larger than nonneoplastic lesion [5, 6, 28]. Although elevated hCG and AFP levels in serum and CSF are the specificity of iGCTs, the problem of low sensitivity remains in the early stage of iGCTs. In this study, only seven patients had significantly elevated hCG levels, and most of the cases with delayed diagnoses in published studies also had initially negative tumor markers. From present cases and published studies, a delayed diagnosis of iGCT with isolated pituitary stalk involvement may be related to (1) a lack of awareness of neuroimaging features of pituitary stalk thickening caused by neoplastic diseases, (2) overestimation of the sensitivity of tumor markers, and (3) the initial pathological results of lymphocytic hypophysis or granulomatous disease leading to misdiagnosis [20, 21, 23]. Early diagnosis and appropriate treatment of iGCT before the occurrence of giant mass effect and metastasis is a key factor for reducing mortality and complications. For patients with manifestations but atypical neuroimaging and/or negative tumor marker, CNS MRI and tumor marker tests should be re-evaluated within a shorter interval than regular observation. For patients with typical neuroimaging, assessing the response of tumors to chemoradiotherapy is highly recommended due to its great effect and relative safety. Although some studies suggested that patients with a pituitary stalk of 6–7 mm receive a pathological examination [8], whether to perform a surgical biopsy deserves careful weighing. On the one hand, although safe [29], pituitary biopsy is a difficult operation, especially for a small lesion, clinical diagnosis based on significant tumor size regression after a low dose of irradiation or a short course of chemotherapy is easier to perform. [30, 31] On the other hand, partial cases of iGCTs were pathologically diagnosed as hypophysitis [10, 11, 13, 17–20, 24] or granuloma disease [9, 15] at the initial biopsy due to the immune response of the host to germinomas. Hence, for patients diagnosed with autoimmune diseases who do not respond well to glucocorticoids, iGCTs should be taken into consideration.

There is not much controversy about the therapeutic strategy in local iGCTs, using a reduced dose of whole-brain or whole-ventricle radiation with adjuvant chemotheraphy. Tumors shrank on MRI, and tumor markers normalized indicated remission. Evaluation of the neuroendocrine function after chemoradiotherapy indicated that most of the pituitary defects of the survivors had occurred before therapy rather than newly developed. Meanwhile, the neuroendocrine function of survivors with isolated pituitary involvement is better than that of most sellar/suprasellar lesions. In the present study, only one of the six patients with impairments to the GH/IGF axis, developed short stature at the last outpatient visit. This patient refused to receive a growth hormone supplement due to the uncertain risk of recurrence. For patients with gonadotropin deficiency before, menstruation or erection may sometimes be spontaneously relieved in adults and adolescents. Hyperprolactinemia usually normalizes spontaneously after tumor elimination. Only one patient presented with panhypopituitarism following biopsy, craniospinal plus primary boosting radiotherapy combined with six chemotherapy courses. In this case, the cause of panhypopituitarism may come from the lesion itself or treatment-related damage. Combined with a systematic review of previously published studies, the grade of anterior pituitary hormone deficiency varied greatly, and the risk factors are still unclear, while CDI usually persists. Overall, the neuroendocrine disturbance caused by isolated pituitary stalk iGCTs, as well as manifestations caused by a hypothalamus-pituitary hormone deficiency, are still milder than those caused by other sellar iGCTs. Therefore, whether isolated pituitary stalk involvement could be used as an independent risk factor for predicting long-term neuroendocrine function in patients with iGCT is worth further exploration. With the increasing awareness of this rare disease, future studies may try to take pituitary stalk involvement as a separate subtype of image classification to optimize the prediction of the neuroendocrine outcomes of patients with sellar/suprasellar iGCTs on the classification of initial neuroimaging.

In conclusion, children with diabetes insipidus should be advised to receive enhanced MRI, whether they coexist with hypopituitarism. A hyperintense pituitary stalk with an absent bright signal of the posterior pituitary is a strong signal of neoplasms. Elevated levels of hCG and/or AFP in serum or cerebrospinal fluid indicated iGCTs; however, the negative results could not exclude the diagnosis. If rescanning neuroimaging is also suspected, a referral to the oncology department and an evaluation of the response to chemotherapy or radiation therapy are highly suggested. Surgery biopsy should be weighed carefully to protect neuroendocrine function. Germinomas should also be considered in patients diagnosed with autoimmune diseases without a good response to glucocorticoids. After the tumor is completely removed, partial anterior pituitary function damage can spontaneously reverse, while CDI commonly persists. Current studies suggested that, from the perspective of initial imaging estimation, the neuroendocrine outcome of isolated pituitary stalk involvement may be one of the best among all sellar iGCTs; however, whether isolated pituitary stalk involvement could become an independent imaging classification still needs more research in the future.

**Data Availability**

The datasets that were used or analyzed during the current study are available from the corresponding authors on reasonable request.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this article.
References

[1] S. Cheng, J.-P. Kilday, N. Laperriere et al., “Outcomes of children with central nervous system germinoma treated with multi-agent chemotherapy followed by reduced radiation,” Journal of Neuro-Oncology, vol. 127, no. 1, pp. 173–180, 2016.

[2] A. Takada, N. Li, M. Hirayama et al., “Long-term follow-up of intensive chemotherapy followed by reduced-dose and reduced-field irradiation for intracranial germ cell tumor,” Journal of Neurosurgery. Pediatrics, vol. 23, no. 3, pp. 317–324, 2018.

[3] P. D. Q. P. T. E. Board, “Childhood central nervous system germ cell tumors treatment,” Health Professional Version. PDQ Cancer Information Summaries, National Cancer Institute (US), Bethesda, MD, USA, 2002.

[4] J. Oosterhuis, H. Stoop, F. Honecker, and L. Looijenga, “Why human extradural germ cell tumours occur in the midline of the body: old concepts, new perspectives,” International Journal of Andrology, vol. 30, no. 4, pp. 256–263, 2007.

[5] X. Zhou, H. Zhu, Y. Yao et al., “Etiological spectrum and pattern of change in pituitary stalk thickening: experience in 321 patients,” Journal of Clinical Endocrinology & Metabolism, vol. 104, no. 8, pp. 3419–3427, 2019.

[6] F. Jian, L. Bian, S. Sun et al., “Surgical biopsies in patients with central diabetes insipidus and thickened pituitary stalks,” Endocrine, vol. 47, no. 1, pp. 325–335, 2014.

[7] S. C. Yoon, C. H. Shin, S. W. Yang, and S. Y. Lee, “Clinical and radiological features of pituitary stalk lesions in children and adolescents,” Annals of Pediatric Endocrinology & Metabolism, vol. 19, no. 4, pp. 202–207, 2014.

[8] M. Cerbone, J. Visser, C. Bulwer et al., “Management of children and young people with idiopathic pituitary stalk thickening, central diabetes insipidus, or both: a national clinical practice consensus guideline,” The Lancet Child & Adolescent Health, vol. 5, no. 9, pp. 662–676, 2021.

[9] R. Pal, A. Rai, K. Vaiphei et al., “Intracranial germinoma masquerading as secondary granulomatous hypophysitis: a case report and review of literature,” Neuroendocrinology, vol. 110, no. 5, pp. 422–429, 2020.

[10] M. Bettendorf, M. Fehn, J. Grulich-Henn et al., “Lymphocytic hypophysitis with central diabetes insipidus and consequent panhypopituitarism preceding a multifocal, intracranial germinoma in a prepubertal girl,” European Journal of Pediatrics, vol. 158, no. 4, pp. 288–292, 1999.

[11] M. Fehn, M. Bettendorf, D. K. Lüdecke, C. Sommer, and W. Saeger, “Lymphocytic hypophysitis masquerading as a suprasellar germinoma in a 12-year-old girl—a case report,” Pituitary, vol. 1, no. 3–4, pp. 303–307, 1999.

[12] N. J. Robison, S. P. Prabhu, P. Sun et al., “Predictors of neoplastic disease in children with isolated pituitary stalk thickening,” Pediatric Blood and Cancer, vol. 60, no. 10, pp. 1630–1635, 2013.

[13] S. L. Mootha, A. J. Barkovich, M. M. Grumbach et al., “Idiopathic hypothalamic diabetes insipidus, pituitary stalk thickening, and the occult intracranial germinoma in children and adolescents,” Journal of Clinical Endocrinology & Metabolism, vol. 82, no. 5, pp. 1362–1367, 1997.

[14] J. Leger, A. Velasquez, C. Garel, M. Hassan, and P. Czernichow, “Thickened pituitary stalk on magnetic resonance imaging in children with central diabetes Insipidus,” Journal of Clinical Endocrinology & Metabolism, vol. 84, no. 6, pp. 1954–1960, 1999.

[15] T. Endo, T. Kumabe, H. Ikeda, R. Shirane, and T. Yoshimoto, “Neurohypophyseal germinoma histologically misidentified as granulomatous hypophysitis,” Acta Neurochirurgica, vol. 144, no. 11, pp. 1233–1237, 2002.

[16] H. Prosch, N. Grois, J. Bökerink et al., “Central diabetes insipidus: is it Langerhans cell histiocytosis of the pituitary stalk? A diagnostic pitfall,” Pediatric Blood and Cancer, vol. 46, no. 3, pp. 363–366, 2006.

[17] Y. Mikami-Terao, M. Akiyama, T. Yanagisawa et al., “Lymphocytic hypophysitis with central diabetes insipidus and subsequent hypopituitarism masking a suprasellar germinoma in a 13-year-old girl,” Child’s Nervous System, vol. 22, no. 10, pp. 1338–1343, 2006.

[18] N. Oz bey, A. Sencer, S. Tanyolac et al., “An intrasellar germinoma with normal cerebrospinal fluid β-HCG concentrations misdiagnosed as hypophysitis,” Hormones, vol. 5, no. 1, pp. 67–71, 2006.

[19] T. Edouard, D. E. J. Stafford, I. Oliver et al., “Isolated lymphocytic infiltration of pituitary stalk preceding the diagnosis of germinoma in 2 prepubertal children treated with growth hormone,” Hormone Research, vol. 72, no. 1, pp. 57–62, 2009.

[20] S. Terasaka, M. Kawabori, H. Kobayashi et al., “Lymphohypophyseal germinoma with abundant fibrous tissue,” Brain Tumor Pathology, vol. 29, no. 1, pp. 58–62, 2012.

[21] G. Jevalikar, S. C. Wong, and M. Zacharin, “Rapidly evolving hypopituitarism in a boy with multiple autoimmune disorders,” Journal of Paediatrics and Child Health, vol. 49, no. 9, pp. 783–785, 2013.

[22] M. Zilbermint, M. S. Ramnitz, M. B. Lodish et al., “Pituitary stalk lesion in a 13-year-old female,” Journal of Pediatric Endocrinology & Metabolism: Journal of Pediatric Endocrinology & Metabolism, vol. 27, no. 3–4, pp. 359–362, 2014.

[23] M. F. Guzzo, C. B. F. Bueno, T. T. Amancio et al., “An intrasellar germinoma with normal tumor marker concentrations mimicking primary lymphocytic hypophysitis,” Arquivos Brasileiros de Endocrinologia & Metabologia, vol. 57, no. 7, pp. 566–570, 2013.

[24] D. Dias, H. Vilar, J. Passos, and V. Leite, “Central diabetes insipidus caused by a pituitary stalk germinoma resembling infundibuloneurohypophysitis,” BMJ Case Reports, vol. 13, no. 9, 2020.

[25] K. J. Shin, J. Y. Lee, J. N. Kim, J. Y. Yoo, C. Shin, and W. C. Song, “Quantitative analysis of the cochlea using three-dimensional reconstruction based on microcomputed tomographic images,” The Anatomical Record, vol. 296, no. 7, pp. 1083–1088, 2013.

[26] M. Suzuki, T. Takashima, M. Kadoya et al., “Height of normal pituitary gland on MR imaging,” Journal of Computer Assisted Tomography, vol. 14, no. 1, pp. 36–39, 1990.

[27] N. Di Iorgi, A. E. M. Allegri, F. Napoli et al., “Central diabetes insipidus in children and young adults: etiological diagnosis and long-term outcome of idiopathic cases,” Journal of Clinical Endocrinology & Metabolism, vol. 99, no. 4, pp. 1264–1272, 2014.

[28] E. Saberrada, R. N. Joseph, B. Jafar-Mohammadi, A. M. Isidori, S. Cudlip, and A. B. Grossman, “Pituitary stalk thickening: the role of an innovative MRI imaging analysis which may assist in determining clinical management,” European Journal of Endocrinology, vol. 175, no. 4, pp. 255–263, 2016.

[29] E. L. Day, E. R. Smith, and K. P. Fehnel, “Single-institution case series of pituitary biopsy for suspected germinoma in the pediatric population: diagnostic utility, operative risks, and
biopsy approaches,” *Scientific Reports*, vol. 10, no. 1, pp. 15257–2020.

[30] Q.-Y. Yang, C.-C. Guo, M.-L. Deng et al., “Treatment of primary intracranial germ cell tumors: single center experience with 42 clinically diagnosed cases,” *Oncotarget*, vol. 7, no. 37, pp. 60665–60675, 2016.

[31] M. Kanamori, T. Kumabe, and T. Tominaga, "Is histological diagnosis necessary to start treatment for germ cell tumours in the pineal region?" *Journal of Clinical Neuroscience*, vol. 15, no. 9, pp. 978–987, 2008.