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# Stalking the stalk: Isolated pituitary stalk thickening and predictive factors for proliferative disease

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**Abstract**

**Background**. Few studies have evaluated predictive factors of isolated pituitary stalk thickening (iPST) in children.

**Methods**. In this retrospective study, radiology, endocrinology, and neuro-oncology databases were interrogated to identify patients with iPST between January 2000 and June 2019. A blinded, longitudinal assessment of MRIs was performed using quantitative, semi-quantitative, and qualitative metrics. Neuroimaging parameters were correlated to clinical parameters.

**Results**. Forty-seven patients were identified, with 40 meeting the inclusion criteria. Median age at baseline MRI was 9.6 years (range 0.9–17.5) with median follow-up of 5.2 years (range 0.3–18.6). Twenty-five (63%) were female. Thirty-four (85%) had pituitary dysfunction, including 31 with central diabetes insipidus (cDI). cDI was not predictive of proliferative disease (PfD): 69% of those with presumed primary hypophysitis (PPH) versus 93% with PfD ($P = .1$). Fourteen (35%) patients were diagnosed with PfD (germinoma = 8, Langerhans cell histiocytosis = 5, lymphoma = 1) at median of 1.3 years (range 0.3–4.0) after initial MRI. Progressive thickening of the stalk over time was associated with PfD (86% vs 4% in PPH, $P < .0001$), as was thickening of the entire stalk (56% in PfD vs 27% in PPH, $P < .0001$) with different imaging trends over time observed in PfD versus PPH. A "sack of marbles" appearance with heterogeneous enhancement on post-contrast imaging was associated with germinoma.

**Conclusions**. In this cohort, 35% of children with iPST were diagnosed with PfD. The association of cDI and PfD was not statistically significant. Progressive thickening of the entire stalk was predictive of PfD and a "sack of marbles" pattern was found to be highly suggestive of germinoma.

## Key Points

- In children with isolated pituitary stalk thickening, progression of stalk thickening over time and thickening of the entire stalk are associated with the risk of proliferative disease.
- A contrast enhancement pattern described as a "sack of marbles" appearance was observed in patients with germinoma.

Isolated pituitary stalk thickening (iPST) is an imaging finding that is considered pathologic in children (Figure 1). It may represent a benign entity such as isolated hypophysitis, but can also be an early indicator of underlying proliferative disease (PfD) such as central nervous system (CNS) germinoma,[1,2] Langerhans cell histiocytosis (LCH),[3,4] or, rarely, lymphoma.[5,6] Given the precarious location along with the small size of the target, biopsy is difficult if not impossible to undertake, and additional workup or serial imaging surveillance is usually needed to ultimately establish a diagnosis with recent guidelines supporting this approach.[7]

Primary hypophysitis is a rare inflammatory condition of the pituitary gland and/or stalk, typically thought to be autoimmune in nature though current understanding is limited.[8]

## Importance of the Study

Few studies describe the outcome of children with isolated pituitary stalk thickening. Previous studies have identified predictors of future proliferative disease, including the presence of central diabetes insipidus, evolution of endocrinopathy, and imaging progression over time. Given that biopsy is technically challenging, may result in pituitary compromise, and may be nondiagnostic, further clinical predictors are needed to help distinguish malignant from benign etiologies. This institutional cohort study provides more insight into the rates of proliferative disease, as well as a structured quantitative, semi-quantitative, and qualitative neuroimaging review. Interestingly, likely due to the high rate of central diabetes insipidus (cDI) in our cohort, cDI was not found to be predictive of future proliferative disease. A contrast enhancement pattern described as a "sack of marbles" appearance was identified in patients ultimately diagnosed with germinoma which may assist in earlier diagnosis.

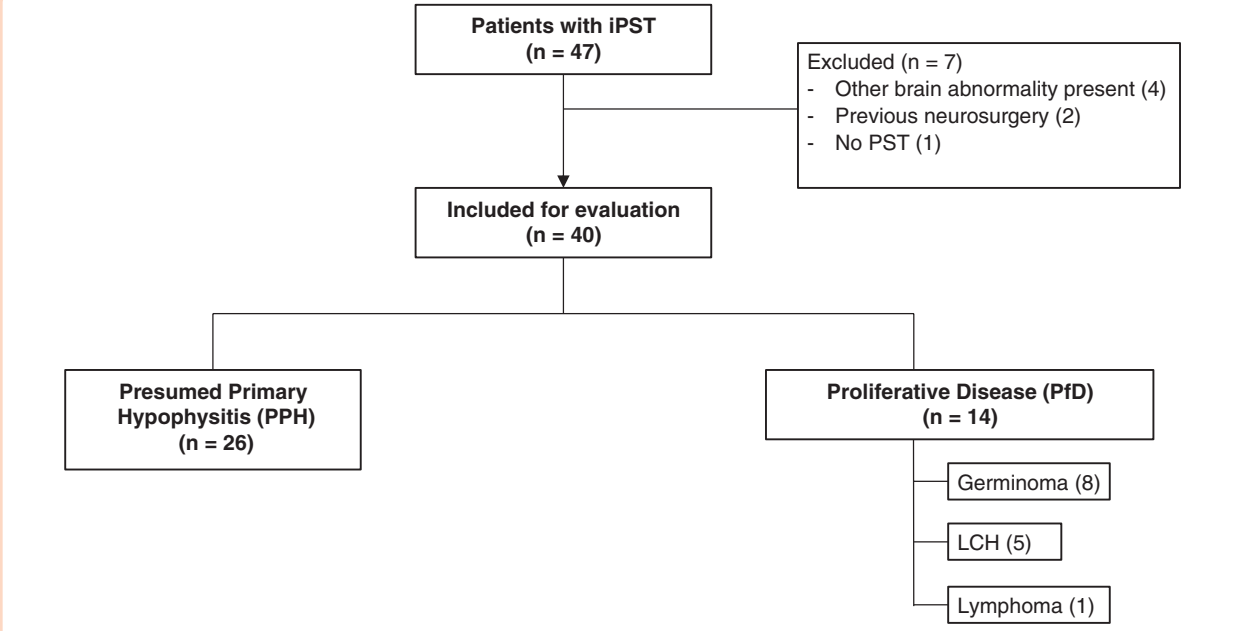


**Figure 1.** CONSORT diagram showing the cohort examined in this retrospective study. iPST, isolated pituitary stalk thickening.

It is most frequent in females of reproductive age. There are many secondary causes known including systemic inflammatory diseases, infections, medications such as immune checkpoint inhibitors, or the proliferative diseases mentioned above.[8] In children, it commonly presents with a lymphocytic infiltrate. Anterior and/or posterior pituitary function may be compromised by the inflammatory process. Presumed primary hypophysitis (PPH) is a diagnosis of exclusion with no confirmatory tests available.

PfDs may demonstrate additional features on MRI or clinical features suggestive of the underlying disease. CNS germinoma often presents with a suprasellar, pineal, or bifocal lesion that is avidly enhancing on post-contrast sequences on MRI, and can have a modest elevation of β-human chorionic gonadotropin (β-HCG) in either serum or cerebrospinal fluid (CSF).[9] LCH, in addition to pituitary stalk thickening, can demonstrate intrinsic T1 hyperintensity and/or abnormal T2/fluid-attenuated inversion recovery (FLAIR) signal in the cerebellum, especially in the dentate nuclei, and/ or basal ganglia, and rarely in other regions such as the pons, suggestive of neurodegeneration.[10] There may be additional systemic signs of LCH suggestive of multisystem disease. CNS lymphoma can demonstrate variable signal characteristics with almost half showing hyperintensity on T2-weighted imaging and most being hypo- or isointense on T1-weighted imaging.[11] CNS lymphomas universally demonstrate avid enhancement following administration of a gadolinium-based contrast agent (GBCA).[11] Other systemic findings may be present in patients with lymphoma. iPST is a rare presenting feature of all of these PfDs, and they may be difficult to distinguish from primary hypophysitis.[12]

Previous studies have demonstrated predictive factors, specifically the presence of central diabetes insipidus (cDI), that increase the likelihood of PfD, with a low probability of malignancy in those without cDI.[13,14] Additional clinical

factors including ≥2 hormonal deficiencies and evolution of new hormonal deficiencies were also associated with the risk of PfD.[14] In addition to clinical features, several imaging findings, including severe stalk thickening ≥6.5 mm or imaging progression of iPST over time are also harbingers of PfD.[7,12–15] To complicate matters, different cut-offs to define iPST have been used in different studies. To date, PPH is only diagnosed after excluding other causes of iPST, and further refinement is needed to accurately predict which patients are more likely to be diagnosed with PfD, given the risks associated with biopsy.

We therefore aimed to identify factors that can distinguish benign entities such as PPH from PfDs such as CNS germinoma, LCH, or lymphoma, by retrospective analysis of institutional data. This included a review of demographic, clinical and imaging features, outcomes, evolution of imaging findings, and analysis for additional predictive factors for future diagnosis of PfD.

## Methods

This study was approved by the Institutional Research Ethics Board. A waiver of consent was granted due to the retrospective nature of the study.

A search was performed using both the neuro-oncology and endocrinology clinical databases for patients with iPST. In parallel, a search of all radiology reports using the term "thick" combined with "infundibulum," "pituitary," and "stalk," along with "pituitary" combined with "germ" or "LCH" was performed. All patients <18 years of age found to have iPST with an axial stalk diameter ≥2.6 mm[13] from January 1, 2000, through June 30, 2019, were included. This list was then reviewed to include only patients who met the criteria for iPST. Patients with additional intracranial abnormalities were excluded. Clinical and imaging data were updated through August 31, 2023.

Longitudinal clinical data were collected by retrospective chart review including demographic data, dates of imaging, symptoms, endocrine function, any evaluation done including CSF analysis, imaging results, pathology, and outcome. If lumbar puncture (LP) was traumatic, this was corrected by subtracting WBC(blood)*RBC(CSF)/RBC(blood) from the CSF white blood cell (WBC) count.[16] The diagnosis of PfD was based on elevated tumor markers in CSF and/or blood or confirmatory pathology. Alpha-fetoprotein (AFP) levels in blood and/or CSF were required to be within normal institutional limits for those with a diagnosis of germinoma.

Neuroimaging evaluation was performed by 2 reviewers in consensus (U.B. [neuro-oncology] and B.E.-W. [neuroradiology], both with >20 years of experience) blinded to patient diagnosis and outcome. MRI was acquired using either 1.5 or 3 Tesla clinical MRI scanners (1.5T and 3T Achieva, Philips Healthcare; 3T Magnetom Skyra, Siemens Healthineers). Thin-slice coronal and sagittal T2-weighted sequences and thin-slice coronal and sagittal T1-weighted sequences before and after GBCA administration (maximum section thickness 2–3 mm), as well as axial FLAIR sequences (maximum section thickness 5 mm) of the brain were available for all included patients. Measurements of stalk thickening were performed in 3 planes, including anterior–posterior (AP), transverse, and craniocaudal dimensions. The location of the stalk thickening (ie, diffuse, upper portion, mid portion, lower portion of the stalk) and the contrast enhancement pattern were recorded. The avidity of contrast enhancement was graded on a semi-quantitative Likert scale with 1 being no enhancement and 4 being very avid contrast enhancement. The presence or absence of the posterior pituitary bright spot (PPBS) on T1-weighted images was documented. Extension of abnormal contrast enhancement into the infundibular recess or along the floor of the third ventricle was noted when present.

### Statistical Analysis

Descriptive analysis was performed for demographic and clinical variables. For quantitative variables, data were expressed as mean ± standard deviation or median (range), as appropriate. Dichotomous variables were reported as frequencies and percentages. All analyses were performed using the RStudio software (RStudio: Integrated Development for R. RStudio, PBC). The Welch Two-sample *t*-test was used to determine differences between 2 groups of normally distributed continuous variables. All categorical variables were compared between 2 groups using Fisher exact test. Generalized linear mixed-effects models (GLMMs) were conducted using lmer function in R to model radiographic changes over time incorporating both fixed and random effects to account for both within- and between-group variability. The model was used to determine which independent variables (time, diagnosis, and the interaction between the 2) could predict each outcome (transverse and AP pituitary stalk thickness). A random effect term is included for each participant. A *P*-value of <.05 was considered statistically significant.

## Results

Forty-seven patients between 0 and 18 years old with iPST were identified. Seven patients were excluded due to additional brain abnormalities (4), history of neurosurgery (2), and absence of iPST (1) (Figure 1). Forty patients met the eligibility criteria and were included in the final analysis. Median age at baseline MRI was 9.6 years (range 0.9–17.5) (Table 1). Twenty-five patients were female (63%). Median follow-up was 5.2 (0.3–18.6) years from the initial MRI. Indications for MRI included symptoms of diabetes insipidus in 29 patients, concerns for other endocrinopathy (6), headache (1), visual impairment (1), asymptomatic hypernatremia (1), and unknown (2) (Table 1). No patients in our cohort had been treated with immune checkpoint inhibitors. Fourteen (35%) patients were eventually diagnosed with a PfD, with germinoma (8), LCH (5), and lymphoma (1) diagnosed at an average of 1.6 (range 0.3–4.0), 4.3 years (range 0.3–9.4), and 1.1 years after initial MRI, respectively (Table 2). Overall, the median time to final diagnosis of PfD was 1.3 years (range 0.3–4.0) from baseline MRI. A total of 5 biopsies of the pituitary stalk were undertaken in the entire cohort (4 with PfD and 1 with PPH). Patients with germinoma were ultimately diagnosed based

**Table 1.** Demographic Data

| | Presumed Primary Hypophysitis (*n* = 26) | Proliferative Disease (*n* = 14) | *P*-value |
|---|---|---|---|
| Age at initial imaging (median, years) | 10.20 | 9.37 | .8 |
| Sex (%) | | | |
| Male | 9 (35) | 6 (43) | .9 |
| Female | 17 (65) | 8 (57) | |
| Indication for imaging (%) | | | |
| Symptoms of DI | 16 (61) | 13 (93) | .4 |
| Symptoms of other endocrinopathies | 5 (19) | 1 (7) | |
| Headache | 1 (4) | – | |
| Visual disturbance | 1 (4) | – | |
| Asymptomatic hypernatremia | 1 (4) | – | |
| Unknown | 2 (8) | | |
| Endocrinopathy at initial iPST diagnosis (%) | | | |
| cDI only | 13 (50) | 8 (57) | .3 |
| cDI plus anterior pituitary deficit | 5 (19) | 5 (36) | |
| Isolated anterior pituitary deficit | 2 (8) | 1 (7) | |
| None | 6 (23) | – | |
| Development of additional pituitary deficits (%) | | | |
| Developed cDI | – | – | .0012 |
| Developed anterior pituitary deficit | 2 (8) | 8 (57) | |
| No change over time | 24 (92) | 6 (43) | |
| Malignancy (%) | | | – |
| Germinoma | – | 8 (57) | |
| LCH | – | 5 (36) | |
| Lymphoma | – | 1 (7) | |
| CSF WBC > $5 \times 10^6$/L | | | |
| Yes | 3 (11.5) | 7 (50) | .1 |
| No | 7 (27) | 6 (43) | |
| Not done | 16 (61.5) | 1 (7) | |

**Abbreviations:** cDI, central diabetes insipidus; CSF, cerebrospinal fluid; iPST, isolated pituitary stalk thickening; LCH, Langerhans cell histiocytosis; WBC, white blood cell.

on biopsy (3), serum/CSF tumor markers (4), and CSF cytology (1). The pituitary stalk was not biopsied in any patient with LCH. Diagnosis of LCH was made based on biopsy of other suspicious lesions in 4/5 patients (3 bone lesions, 1 skin lesion) performed at a median of 1.4 years (range 0.3–9.4) from iPST diagnosis and CSF circulating tumor DNA (ctDNA) revealing BRAF p.V600E ($n = 1$). The diagnosis of CNS lymphoma was based on the biopsy of the pituitary stalk. Three patients underwent a nondiagnostic biopsy in the PPH cohort, 1 of the pituitary stalk and 2 of suspicious skin lesions. CSF was sent for sequencing with/without copy number analysis in 7 patients from this cohort, and sufficient for evaluation in 5 samples. Three patients had droplet digital PCR for BRAF p.V600E, one of which was positive, supporting a diagnosis of LCH. Two patients had panel sequencing and copy number analysis, one of which was supportive of germinoma with multiple copy number alterations in the context of rising β-HCG in the CSF (7 IU/L) and progressive thickening of the pituitary stalk. There was a predominance of females diagnosed with germinoma (75%) compared with a predominance of males with LCH (80%).

## Pituitary Dysfunction

Thirty-four (85%) patients had pituitary dysfunction at the time of initial diagnosis of iPST, including 31 with cDI (78%). Twenty-one (62%) patients had posterior pituitary deficits alone, with cDI as the only hormonal manifestation, 3 (9%) had exclusively anterior pituitary deficits (2 isolated growth hormone deficiency, 1 isolated central hypothyroidism), and 10 (29%) had mixed dysfunction with anterior and posterior pituitary deficits. Ten patients had more than 1 endocrinopathy identified at diagnosis, all of which were cDI coupled with 1 or more anterior pituitary deficits.

At the time of iPST diagnosis, 20/26 (77%) patients with PPH and 14 (100%) with PfD had an endocrinopathy ($P = .3$).

**Table 2.** Characteristics of Diagnosis for Those With Germinoma and LCH

| | Germinoma ($n = 8$) | LCH ($n = 5$) | *P*-value |
|---|---|---|---|
| Sex (%) | | | .1 |
| Male | 2 (25) | 4 (80) | |
| Female | 6 (75) | 1 (20) | |
| Median age iPST diagnosis, years (range) | 9.7 (6.2–15.8) | 7.1 (3.7–17.5) | .35 |
| Median age PfD diagnosis, years (range) | 12.6 (7.8–16.0) | 16.5 (4.3–17.8) | .87 |
| Average time to PfD Diagnosis, years (range) | 1.6 (0.3–4.0) | 4.3 (0.3–9.4) | .14 |

**Abbreviations:** cDI, central diabetes insipidus; iPST, isolated pituitary stalk thickening; LCH, Langerhans cell histiocytosis; PfD, proliferative disease.

All patients with LCH and germinoma had cDI at the time of iPST diagnosis. The presence of cDI with or without other pituitary deficiencies was not associated with the diagnosis of PfD (cDI 69% of PPH vs 93% PfD, $P = .1$). More than 1 endocrinopathy at diagnosis of iPST was not associated with the diagnosis of PfD (>1 endocrine deficit 19% of PPH vs 36% of PfD, $P = .28$).

Over the period of follow-up, 10 patients developed additional hormonal deficits, all of which were anterior pituitary hormonal dysfunction—6 patients had cDI alone and 4 had mixed anterior/posterior dysfunction at the time of diagnosis of iPST. Interestingly, 8/10 (80%) patients who had progressive endocrinopathy were ultimately diagnosed with PfD (6 with germinoma, 2 with LCH) compared to only 2 with PPH ($P = .001$) confirming prior observations.[14] Four patients with PfD with isolated cDI at time of diagnosis of iPST developed no further endocrinopathy identified during a median follow-up of 6.7 years (3 LCH, 1 germinoma, range 1.5–10.2).

## Neuroradiological Evolution

A total of 239 MRIs were reviewed (median 5.5 MRIs/patient, range 1–17) over a median of 3.3 years (range 0.2–10.8) prior to PfD diagnosis. All but 1 patient had a follow-up MRI. On neuroradiological review, the PPBS was absent in 32/40 (80%) patients at the time of initial MRI. All but 1 patient with absent PPBS had co-existent endocrinopathy (Table 3). Twenty of these 31 (64%) had isolated cDI, 8 (26%) had co-existing cDI with anterior pituitary dysfunction, and 3 (10%) had isolated anterior pituitary dysfunction. None of those with absent PPBS without cDI ($n = 4$) developed cDI over the period of follow-up. Thirteen patients with PfD (93%) had absent PPBS, compared to 19/26 (73%) of those with PPH ($P = .2$). Most patients with PPBS present on initial MRI ($n = 8$) had persistence of this on follow-up MRI (5/7) at a median of 2.2 years. Two patients lost PPBS over time at a median of 0.5 years after the first MRI, both of whom were diagnosed with cDI prior to that time. PPBS did not reappear in any patients with PfD following treatment.[17]

We observed differences in the growth pattern of iPST between those with PPH and PfD. For those with PPH, the pattern of growth of the pituitary stalk tended to be variable over time (14, 56%), decreasing (10, 40%), or, less likely, progressive (1, 4%, Figure 3) when AP and transverse measurements. This differed from those with PfD, as the growth pattern was more often progressive over time (12, 86%) and less likely variable over time (2, 14%, $P < .0001$). Importantly, all patients with germinoma showed progressive thickening of the pituitary stalk over time, with 2 of 5 patients with LCH showing variability over time. Linear mixed modeling was able to predict the growth trajectory over time in those with benign entities versus PfD (Figure 3).

Differences were observed in the contrast enhancement pattern of the pituitary stalk as well. Contrast enhancement tended to be homogeneous in patients with PPH (23, 88%, Figure 2A, B) and less likely variable over time (2, 8%) or heterogeneous (1, 4%). In patients with PfD, 6 (43%) patients had heterogeneous enhancement of the stalk (all with germinoma), 4 (28.5%) demonstrated homogenous enhancement (all with LCH, Figure 2C, D), and 4 (28.5%) demonstrated variability over time ($P < .0001$ compared to PPH). Of the patients with variability in enhancement pattern over time ($n = 6$), 3 evolved from homogeneous to heterogeneous enhancement (2 germinoma, 1 lymphoma) with the reverse observed in the remaining patients (2 PPH, 1 LCH). The finding of a heterogeneous enhancement pattern predominating in PfD was unexpected given that germinoma is typically an avidly enhancing tumor. On further review, an imaging pattern emerged for those with iPST who were eventually diagnosed with germinoma (Figure 2E, F). These had imaging features resembling a "sack of marbles" appearance with solid enhancing components interspersed with tiny nonenhancing cysts. This pattern was identified in 6/8 patients with germinoma, and not seen in any cases of PPH or LCH. This pattern may help with recognizing germinoma cases in the future.

We observed differences in the portion of the stalk that was thickened between patients with PPH and PfD. In those with PPH, only a portion of the stalk (upper, middle, and/or lower) was thickened in 19 (73%, Figure 2A, B) with variability over time in the remaining 7 (27%) patients. For those with variability in the portion of stalk thickening, it all started with the thickening of the entire stalk with progression to the thickening of only a portion of the stalk. None of the patients with PPH progressed from partial stalk thickening to entire stalk thickening. In contrast, 8 (57%) patients with PfD had thickening of the entire stalk on initial MRI (6 germinoma, 2 LCH), with 2 (14%) demonstrating only a portion of the stalk thickened (2 LCH) and 4 (29%) showing variability over time ($P < .0001$ compared to PPH). Of those with variability with PfD, all 4 evolved from partial stalk thickening to total thickening over time (2 germinoma, 1 lymphoma, and 1 LCH). This suggests patients with persistence of or evolution from partial stalk thickening to thickening of the entire pituitary stalk are at a higher likelihood of diagnosis of PfD.

Of those with PPH, 9 (35%) had normalization of iPST over time at a median of 1.3 years (range 0.3–3.9) after the initial MRI, 12 (46%) remained thickened, and 4 (15%) temporarily normalized and then demonstrated recurrence of iPST. Only 1 (7%) patient with PfD (LCH) had temporary normalization of stalk measurements followed by recurrence

**Table 3.** Summary of Imaging Findings

| | Presumed Primary Hypophysitis (*n* = 26) | Proliferative Disease (*n* = 14) | *P*-value |
|---|---|---|---|
| Posterior pituitary bright spot, absent (%) | 19 (73) | 13 (93) | .22 |
| Growth pattern* (%) | | | <.0001 |
| Progressive | 1 (4) | 12 (86) | |
| Variable | 14 (56) | 2 (14)† | |
| Decreasing | 10 (40) | 0 | |
| Resolution of iPST over time* | | | |
| iPST resolved | 9 (35) | 0 | |
| iPST persisted | 12 (46) | 13 (93) | |
| iPST recurred | 4 (15) | 1 (7) | |
| Enhancement pattern (%) | | | <.0001 |
| Homogeneous | 23 (88) | 4 (28.5) | |
| Heterogeneous | 1 (4) | 6 (43) | |
| Variable over time | 2 (8)‖ | 4 (28.5)¶ | |
| Portion of stalk thickened (%) | | | <.0001 |
| Upper | 3 (11) | 0 | |
| Middle | 14 (54) | 2 (14) | |
| Lower | 2 (8) | 0 | |
| Total | 0 | 8 (57) | |
| Variable over time | 7 (27)‡ | 4 (29)** | |

**Abbreviations:** iPST, isolated pituitary stalk thickening; LCH, Langerhans cell histiocytosis.
*One patient with only 1 MRI, pattern cannot be described.
†Both were LCH.
‡Both had heterogeneous enhancement initially that progressed to homogeneous enhancement pattern.
¶3/4 had homogeneous enhancement initially, progressing to heterogeneous.
‖All started with total stalk thickening and progressed to only a portion of the stalk being thickened.
**All progressed to total stalk thickening over time.

of iPST prior to ultimate diagnosis, with the remaining 13 (93%) of those with PfD showing persistence of iPST on all MRI done prior to ultimate diagnosis. This suggests that a pattern of waxing and waning of stalk measurements over time is possible, but normalization of stalk measurements at any point suggests PPH is the more likely etiology of iPST.

We identified 20 patients (13 PfD, 7 PPH) with transverse or AP pituitary stalk thickness of >5 mm. Using this as a cut-off, there was a 93% specificity (95% CI 68.5–99.6) of identification of PfD, with corresponding 73% sensitivity (95% CI 53.9–86.3). There were 13 patients (10 PfD, 3 PPH) with lateral or AP pituitary stalk thickness of >6.5 mm.[14] Using this as a cut-off, there was a 71% specificity (95% CI 49.7–91.8) of identification of PfD, with corresponding 88% sensitivity (95% CI 71.0–96.0). There were 8 patients with lateral or AP stalk diameters of >10 mm, with 7 with PfD (5 germinoma, 1 LCH, 1 lymphoma) and 1 with PPH. Using this as a cut-off, there was a 50% specificity (95% CI 26.8–73.2), with a corresponding 96% sensitivity (95% CI 81.1–99.8).

### Cerebrospinal Fluid Findings

LP was performed in 24/40 (60%) patients, with 7 patients undergoing multiple LPs. For those diagnosed with a PfD, LP was performed at a median of 0.50 years prior to diagnosis of neoplasia (range 0.07–5.3). Elevated CSF WBC (>5 × $10^6$/L) was found in 6 of 8 (75%) patients with germinoma, 1 (100%) patient with lymphoma, 0 of 4 patients with LCH, and 3 of 11 (27%) patients with PPH ($P = .1$, Figure 3). The majority of cells seen in those patients with elevated WBC were mature lymphocytes. Of the 8 patients with germinoma, 5 underwent more than 1 LP, with 3 of 5 showing elevated WBC in all specimens (range 7–56 × $10^6$/L), 1 patient with elevated WBC on 1 of 2 CSF specimens, and the remaining patient showing a normal CSF WBC count in 3 CSF specimens. Of those with PPH with elevated WBC, there was a mean follow-up time of 4.8 years after LP with no PfD identified in that time frame. LP was not repeated in these patients to evaluate the normalization of CSF WBC. There was no difference in CSF protein or glucose levels between those with PPH and PfD (Figure 3).

## Discussion

In our retrospective analysis of a cohort of patients with iPST from a single institution, we did not identify a predictive value of the presence of endocrinopathy, regardless of anterior or posterior pituitary involvement, with regards to future risk of a diagnosis of PfD, contrary to prior

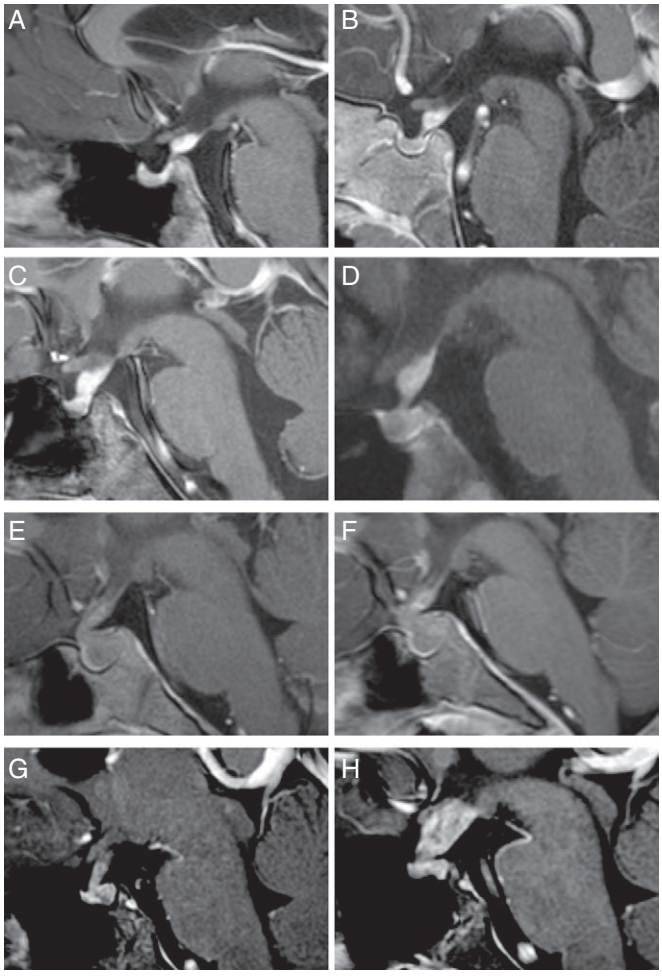


**Figure 2.** MRI demonstrating isolated pituitary stalk thickening (iPST) on sagittal post-contrast images. (A) and (B) are patients with primary hypophysitis (PPH) (13-year-old [y/o] M and 5 y/o M, respectively) showing diffuse enhancement with only partial stalk thickening. (C) is a patient with LCH (15 y/o M) with total stalk thickening and homogeneous enhancement. (D) is a patient (8 y/o M) with Langerhans cell histiocytosis (LCH) with upper/middle stalk thickening with homogeneous enhancement. (E) and (F) is a patient (7 y/o F) with an initial diagnosis of iPST (E) and final diagnosis of germinoma (F, 3 months later), and (G) and (H) is a patient (10 y/o M) with an initial diagnosis of iPST (G) and final diagnosis of germinoma (H, 2 years later) both showing a "sack of marbles" appearance and total stalk thickening.

reports.[13,14] Development of progressive anterior pituitary dysfunction over time was associated with the diagnosis of PfD. Imaging progression over time was predictive of future diagnosis of PfD, along with several neuroimaging features including thickening of the entire stalk and a pattern of enhancement described as a "sack of marbles" appearance in patients with a final diagnosis of germinoma. Results of CSF findings were also reviewed; while an elevated WBC in CSF tended to be associated with a diagnosis of germinoma, it was not conclusive in this limited patient population.

The female predominance found in those diagnosed with suprasellar germinoma is consistent with prior reports.[18,19] While not significant, this contrasts with the male predominance seen in those diagnosed with LCH. Notably, there was also a much longer time between diagnosis of iPST and PfD between those with LCH compared to CNS germinoma. The degree of stalk thickening in LCH was not as pronounced as observed in germinoma and there were cases with waxing/waning measurements over time. Although this did not achieve significance, taken together, it likely reflects the more indolent nature of LCH.

cDI was not found to be predictive of the development of PfD, conflicting with previously published reports.[13,14] It is unclear why our result varies from previous work, as there are similar numbers of total patients and those with PfD in each cohort. Of note, in our institutional cohort, the indication for imaging was significantly enriched for endocrinopathy compared to Robison et al.[13] with far fewer patients demonstrating vague complaints such as headache, suggesting potential differences in practice or indications for imaging. This enrichment of patients with cDI in our cohort may have a limited statistical association with PfD given the high overall prevalence. Importantly, all patients with PfD had endocrinopathy in our cohort, and while not statistically significant, the absence of cDI at diagnosis

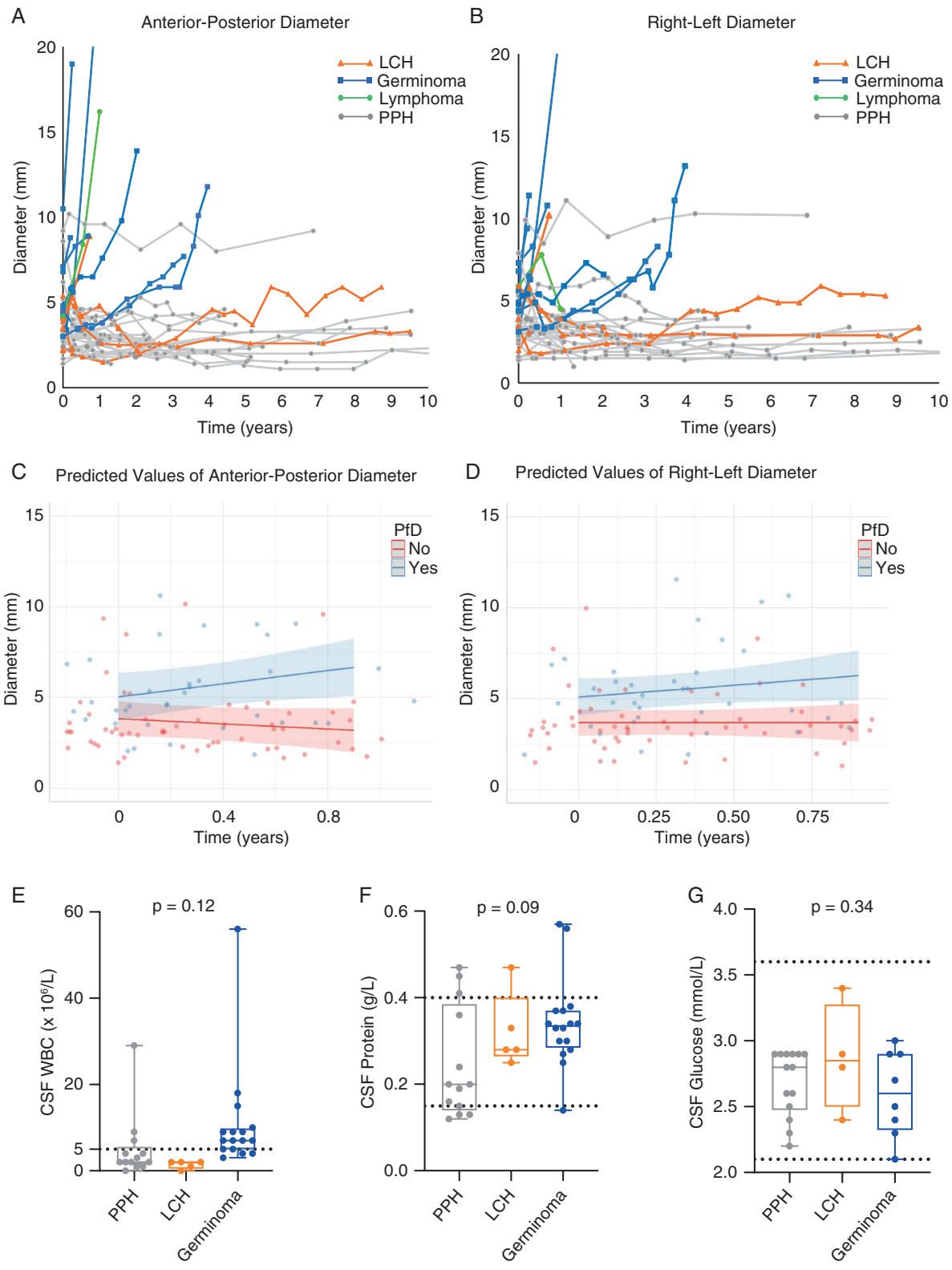


**Figure 3.** Imaging and cerebrospinal fluid (CSF) findings. Spider plot showing the (A) anterior–posterior (AP) and (B) transverse diameters of the pituitary stalk over time. Linear mixed modeling to predict the trajectory of growth of (C) AP and (D) transverse diameters over time stratified by proliferative disease status. Dot plots showing the distribution of (E) white blood cell (WBC), (F) protein, and (G) glucose levels in CSF. Normal range represented between dotted lines.

of iPST may be a reassuring feature. Those with cDI need ongoing follow-up to monitor for other signs of PfD. Given the association of progressive pituitary dysfunction with a diagnosis of PfD, earlier diagnosis may prevent further endocrine dysfunction. Given the risk of pituitary damage with biopsy, liquid biopsy should be considered early in the disease course.

To our knowledge, the CSF findings in our study have not previously been described. Patients who went on to develop germinoma or lymphoma tended to have elevated CSF WBC greater than 5. Due to the small number of samples, this was not statistically significant but may warrant further investigation in a larger cohort. The WBCs found were largely comprised of lymphocytes in all cases. Interestingly, germinoma tends to have a lymphocytic infiltrate while lymphoma consists of malignant mature or immature lymphocytes. This finding could allow for earlier detection of these entities, though further refinement is needed as there are rare cases of PPH that also demonstrate CSF pleocytosis.

The imaging review is one of the most comprehensive on this topic done to date. Assessment of specific imaging features including assessment of the portion of the stalk thickened, measurements, and enhancement patterns identified additional features that may give an earlier indication of malignancy. The "sack of marbles" enhancement pattern observed in patients with germinoma has not previously been described and may help distinguish this worrisome diagnosis from benign entities. Additionally, a model was developed that may help distinguish malignant behavior over time warranting closer follow-up or additional tests for workup. Certain parameters, such as AP or lateral diameter >10 mm may also be more suggestive of PfD.

Importantly, this study adds additional information regarding the ideal cut-off to meet the criteria for iPST. A recent consensus proposed a cut-off of 3 mm at pituitary insertion and 4 mm at the optic chiasm[7]; however, using this definition, 2 patients with LCH and 1 patient with germinoma in our cohort would have been interpreted as normal on initial MRI and would not have been followed up. Using a more conservative definition as we did in our study allowed identification and accurate diagnosis of a greater proportion of patients with PfD. In particular, we would advocate for ongoing surveillance of patients with cDI even if they are below these parameters.

There are several limitations to this study. First, it is a retrospective study. Certain data points, such as CSF evaluation, were not available for all patients. Second, due to the rarity of this finding, the cohort is small. The cohort is similar in size to previous publications; however, it represents the largest cohort described to date with co-existent cDI and iPST. A broad search strategy was used, including a search of clinical databases and through imaging reports for certain keywords, so it is unlikely that asymptomatic cases were omitted. The finding of CSF pleocytosis enriched in patients with germinoma needs further follow-up in a larger cohort. Additionally, new technologies using ctDNA including identification of biomarkers (such as micro-RNA or copy number alterations) or pathognomonic molecular alterations are currently being explored, which may allow earlier distinction of CNS germinoma or LCH.[20,21] Two patients in our cohort had ctDNA that was diagnostic or supported the presence of PfD—1 patient with LCH where BRAF p.V600E was found and 1 patient with germinoma with slight elevation of β-HCG (7 IU/L) with copy number alterations seen with ctDNA analysis. Given how many patients in our cohort underwent LP for CSF analysis, optimization of this testing may improve the diagnostic yield of this procedure, allow for earlier diagnosis of PfD, and differentiate germinoma from LCH. Indeed, patients with suspected LCH and iPST may benefit from BRAF p.V600E testing in the peripheral blood or CSF, which if positive, may aid in diagnostic differentiation and identify potential targets for inhibitor therapy.[22]

In conclusion, there are several imaging features that can be used to help determine the risk of PfD in patients with iPST, including a progressive increase in transverse and AP diameter and thickening of the entire stalk. A "sack of marbles" appearance on post-contrast MRI was associated with a germinoma diagnosis. Endocrinopathy, including cDI, was not found to be predictive of PfD, though progressive pituitary dysfunction was associated with PfD. Finally, patients with PfD were diagnosed up to 4 years after initial identification of iPST warranting ongoing follow-up of these patients, particularly in light of any of these imaging features.

## Keywords

CSF pleocytosis | germinoma | hypophysitis | LCH | pituitary stalk thickening

## Lay Summary

The pituitary stalk is a part of the brain that helps control hormones and growth. Thickening of the stalk can be associated with hormonal imbalances. Thickening of the stalk may be due to inflammation or certain neoplasms. Biopsy is very difficult in this area, meaning it may be difficult to diagnose a neoplastic process. The authors of this study wanted to understand risk factors associated with a neoplasms. To do this, they looked at MRI scans and medical records from 40 children with thickened pituitary stalks. Their results showed that about one-third of these children had neoplasms. They also found that if the stalk progressively got thicker over time, or looked like a "sack of marbles" on the MRI scan, the risk of developing a specific type of brain tumor called a germinoma was higher.

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## Conflict of interest statement

None declared.

## Authorship statement

J.B., E.B., and U.B. conceived of the idea. J.B., O.A., J.D.W., E.B., B.E.-W., and U.B. assisted with creating a list of patients. J.B. conducted data collection. B.E.-W. and U.B. conducted radiology review. J.B. and L.N. conducted analysis. J.B. and U.B. wrote the manuscript with input from all authors. All authors agreed upon the content of manuscript.

## Data availability

Data will be made available upon reasonable request by emailing the corresponding author.

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