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CLINICAL STUDY

Diabetes insipidus in pediatric germinomas of the suprasellar region: characteristic features and significance of the pituitary bright spot

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Abstract The pituitary bright spot is acknowledged to indicate functional integrity of the posterior pituitary gland, whilst its absence supports a diagnosis of central diabetes insipidus (DI). This feature was evaluated, together with the incidence and clinical characteristics of DI in children with suprasellar/neurohypophyseal germinomas. We performed a review of all suprasellar (SS) or bifocal (BF) germinoma pediatric patients treated in Toronto since 2000. Demographics, symptomatology, treatment outcome and imaging were evaluated. Nineteen patients fulfilled inclusion criteria (10 SS, 9 BF; median age 12.5 years (6.2–16.8 years)). All remained alive at 6.4 years median follow-up (1.2–13.7 years) after receiving chemotherapy and radiotherapy (13 focal/ventricular, four whole brain, two neuraxis), with only one progression. All had symptoms of DI at presentation with a symptom interval above one year in eight cases (42 %). Desmopressin was commenced and maintained in 16 patients (84 %). The pituitary bright spot was lost in most diagnostic interpretable cases, but was appreciated in three patients (18 %) who had normal serum sodium values compared to 'absent' cases ($p = 0.013$). For two such cases, spots remained visible until last follow-up (range 0.4–3.3 years), with one still receiving desmopressin. No case of bright spot recovery was observed following therapy. Protracted symptom intervals for germinoma-induced central DI may reflect poor clinical awareness. Explanations for persistence of the pituitary bright spot in symptomatic patients remain elusive. Desmopressin seldom reverses the clinical features of germinoma-induced DI to allow discontinuation, nor does treatment cause bright spot recovery.

Keywords Diabetes insipidus · Pediatric · Germinoma · Suprasellar · Bifocal · Pituitary bright spot

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Introduction

In Western society, intracranial germ cell tumors comprise less than five percent of childhood tumors of the central nervous system [1, 2]. The incidence rises to over ten percent in parts of Eastern Asia [3, 4]. Within this heterogeneous tumor group, germinomas represent the most common histological subtype, accounting for approximately 65 % of all cases [5, 6]. Germinomas arise in midline, diencephalic brain structures. The two most common locations are the pineal and suprasellar (neurohypophyseal) regions, reported at an incidence of 2:1 respectively [7, 8]. Simultaneous primary involvement of both such sites, termed bifocal germinoma, has been observed in up to one-quarter of cases [9].

Central diabetes insipidus (DI) is a recognized, often solitary presenting feature of intracranial germ cell tumors [10, 11]. Along with anterior pituitary dysfunction and visual disturbances, DI is typically associated with suprasellar/bifocal germinomas, where it has been described in over 80 % of comparable subgroup analyses [9, 12–25].

It is widely acknowledged that the clinical and biochemical diagnosis of central DI is supported by an absence of hyperintense signal on T1-weighted MR imaging of the posterior pituitary gland [25–28], stemming from hypotheses that this pituitary 'bright spot' reflected functional integrity of the gland by representing arginine vasopressin accumulation [26, 29–31]. Indeed, loss of the pituitary bright spot has been reported as a cardinal or universal feature of tumor-induced central DI [10, 15]. However other studies refute this, reporting persistence and even recovery of the bright spot in patients with symptomatic central DI from a variety of etiologies including malignancy [29, 32], thereby questioning the biochemical composition and functional relevance of the bright spot. To date, evaluation of this imaging characteristic in a substantial cohort of pediatric germinoma patients is lacking.

In order to address these issues, we performed an analysis of DI in cases of childhood suprasellar and bifocal germinoma. We specifically explored the incidence and symptom characteristics of DI in this tumor cohort, whilst attempting to ascertain the frequency, clinical significance and implications of retaining or losing the pituitary bright spot for these patients.

Methods

Patients

A retrospective review of all patients either diagnosed or treated at the Hospital for Sick Children, Toronto (Sickkids) from 2000 to 2013 was performed. Sickkids is the principal referral center for childhood brain tumors in Southern Ontario, encompassing a population of approximately one million children and adolescents (aged less than 18 years). In turn, cohort analyses can be considered population-based. Secondary to a large Asian population, the incidence of intracranial germ cell tumors in Toronto is relatively high [33]. Data on patient demographics, presenting symptomatology, therapy, outcomes and imaging were collated from institutional clinical and imaging databases which are regularly maintained for such work [34–36]. The study received approval from the local Research Ethics Board.

Patients with either suprasellar or bifocal germinomas were included for evaluation. Patients had to have demonstrated normal institutional levels of alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (βhCG) levels $\leq$100 IU/Lin serum and/or cerebrospinal fluid (CSF). Except for bifocal cases, histological confirmation of germinoma was required in the presence of normal markers. Patients with focal pineal germinomas or intracranial non-germinomatous germ cell tumors (the latter with AFP and βhCG levels exceeding aforementioned thresholds) were excluded from the study to enable analysis of a homogenous cohort with regards to tumor location and histopathological diagnosis.

Diabetes insipidus was diagnosed by attending endocrinology colleagues on the basis of clinical assessment, abnormal serum and urine electrolytes and osmolality results (using institutional normal ranges), urine specific gravity analysis and, in selected cases, water deprivation. Complete DI was characterized by a serum osmolality above 300 mOsm/kg combined with a urine osmolality below 200 mOsm/kg, and partial DI by the urine osmolality being above 200 mOsm/kg yet less than 300 mOsm/kg.

Imaging

MRI imaging was performed at SickKids, Toronto using a GE LX 1.5-tesla MRI scanner with 8 channel head coil (General Electric Healthcare, Milwaukee, WI, USA). Evaluation of the pituitary bright spot was performed independently and blinded from other analyses on both the diagnostic and most recent follow-up brain MRI scans. All patients in the study underwent sagittal, 3D-T1 weighted images without contrast at 1.5 mm slice depths. If no bright spot was identified, sagittal T1 FLAIR sequences and dedicated sellar sequences were subsequently performed. Whole brain imaging using contrast and non-contrast T1 sequences in standard planes (sagittal, axial, coronal) at 1.5 mm slice depths was also performed (Fig. 1).

Statistical analysis

Analyses were performed using SPSS (version 21.0, SPSS Inc, IBM, NY, USA). Comparison of parametric continuous variables was performed by Independent sample t-testing with 95 % confidence intervals (CIs), while categorical variables were compared using Fisher's exact testing. Symptom interval was defined as the time lapsed from initial complaint to diagnostic scan. Survival analysis was performed by the Kaplan–Meier method. Progression-free survival (PFS) was defined in years from the date of tumor diagnosis to the date of further disease progression, death or censorship if alive. Median follow-up was estimated by the inverse Kaplan–Meier method [37]. Significance was achieved with p-values below 0.05.

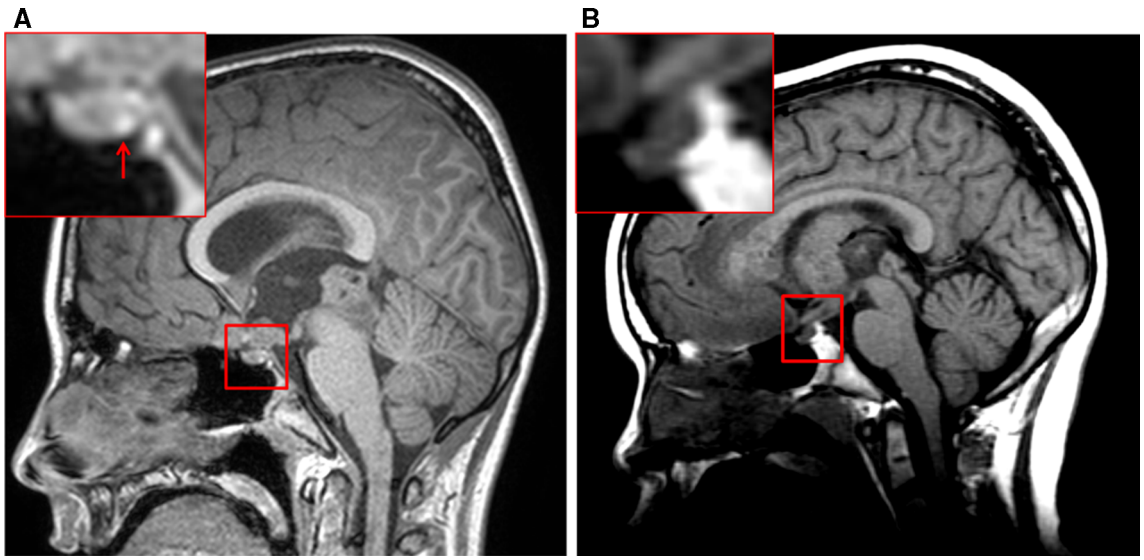

Fig. 1 Variable presence of the pituitary bright spot at diagnosis in cases of pediatric suprasellar/bifocal germinoma. **a** diagnostic, non-contrast enhanced sagittal-T1 MRI of patient G12 who presented with bifocal germinoma and acute hydrocephalus (with ventricular dissemination noted at subsequent endoscopic biopsy). Note the presence of the posterior pituitary bright spot, distinguishable from the dorsum sellae (*red arrow* in magnified image of pituitary gland (*outlined box*)). This is in contrast to the corresponding diagnostic image for patient G7 (B), where the posterior pituitary spot is typically absent

Results

Demographics

Among the 46 patients with intracranial germ cell tumors treated from January 2000 until December 2013, 19 children fulfilled inclusion criteria (summarized in Table 1). The median age of the group was 12.5 years (range 6.2–16.8 years) with a female: male ratio of 1.7:1. Tumors were localized SS lesions (n = 9), non-metastatic bifocal disease (n = 5), or tumors with neuraxial dissemination which was observed either by MRI (n = 4; all BF) or as "ventricular studding" at the time of endoscopic ventriculostomy (n = 1; SS). A histological diagnosis of germinoma was made for twelve patients, whilst seven bifocal cases were diagnosed by a combination of imaging and tumor marker analysis.

Clinical presentation

All 19 patients demonstrated symptoms of DI at diagnosis with increased frequency of micturition being a universal finding (Fig. 2). Polydipsia was described by almost the entire cohort (n = 18, 95 %), with five patients drinking in excess of five liters of fluid per day. Symptoms of raised intracranial pressure and visual disturbance were also frequent complaints. The median symptom interval across the group was protracted at 6 months (range 1–48 months) and was over one year in eight cases (42 %). Endocrinology assessment and investigations at diagnosis confirmed DI (n = 17) or partial DI (n = 2) across all patients. Hypopituitarism was also identified at this point in the majority of the cohort (n = 16, 84 %). The most common signs on initial physical assessment of the group included papilledema (n = 9, 47 %), and visual impairment (field cut, Parinaud's syndrome or loss of acuity; n = 8, 42 %).

Treatment and outcomes

All 19 children were treated with both chemotherapy, followed by radiotherapy which was either focal (n = 1) ventricular ± boost (n = 12), whole brain (n = 4) or craniospinal (n = 2) (Table 1). The chemotherapy regimens used were predominantly platinum and etoposide based, incorporating ifosfamide for patients treated until 2008. At a median follow-up of 6.4 years (range 1.2–13.7 years), all patients remain alive. Five-year progression-free survival was 93 % as a result of localized tumor recurrence in patient G5 who had been treated for SS disease with 3 cycles of chemotherapy (carboplatin, etoposide) followed by ventricular radiotherapy (2,340 cGy). This patient relapsed below the level of the ventricular radiation field at the foramen of Luschka, 9 months post completion of therapy and was successfully salvaged with chemotherapy including high dose carboplatin, thiotepa, autologous stem cell rescue and craniospinal radiation at a dose of 2,340 cGy.

Several clinical sequelae were reported during the follow-up period of this germinoma cohort. Pituitary dysfunction, already present in most of the children at

Table 1 Patient and treatment characteristics

Variable	Patient cohort (n = 19)
Median age	12.5 years (6.2–16.8 years)
Median follow-up	6.4 years (1.2–13.7 years)
Gender	
Male	7 (37 %)
Female	12 (63 %)
Ethnicity	
Caucasian	12 (63 %)
Asian	4 (21 %)
African	1 (5 %)
Other	2 (11 %)
Location	
Suprasellar	10 (53 %)
Bifocal	9 (47 %)
Dissemination on MRI	
Yes	4 (21 %)
No	15 (79 %)
Markers	
Median AFP	
Serum	1.5 IU/L (range 0–4 IU/L)
Lumbar CSF	1.0 IU/L (range 0–1 IU/L)
Median βhCG	
Serum	2.0 IU/L (range 0–38 IU/L)
Lumbar CSF	2.0 IU/L (range 0–96 IU/L)
Largest tumor diameter	
Less than 2 cm	8 (42 %)
Greater than 2 cm	11 (58 %)
Treatment	
Surgery	
Biopsy	10 (53 %)
PR	2 (11 %)
Plus temporary EVD	3 (16 %)
Plus ETV	5 (26 %)
Plus VP Shunt	1 (5 %)
No CSF diversion required	10 (53 %)
Chemotherapy	19 (100 %)
Radiotherapy	
Focal	1 (5 %)
Ventricular ± boost	12 (63 %)
Whole brain	4 (21 %)
CS	2 (11 %)
Status	
Alive without progression	18 (95 %)
Alive with progression	1 (5 %)

MRI magnetic resonance imaging, *AFP* alpha fetoprotein, *βhCG* beta human chorionic gonadotrophin, *CSF* cerebrospinal fluid, *IU* international units, *L* liter, *cm* centimeters, *PR* partial resection, *CS* craniospinal, *EVD* external ventricular drainage, *ETV* endoscopic third ventriculostomy ± septostomy

diagnosis, was the most frequent (n = 18, 95 %). Encouragingly, vision either remained stable or improved across the cohort. Other late effects included behavioral difficulties or psychiatric disorders (n = 4, 21 %), memory impairment (n = 4, 21 %) and high frequency hearing loss (n = 3, 16 %).

Pituitary bright spot presence, serum sodium values and desmopressin use

An evaluation of brain imaging, laboratory electrolyte results and DI therapy, both at diagnosis and most recent follow-up, was performed for all patients in the cohort (Fig. 3). Bright spot interpretation could not be performed for two patients in the cohort (G2 and G15) as their MRI images did not include T1, non-contrast enhanced sequences. Furthermore, one patient (G6) began treatment overseas and did not have documented diagnostic serum or urine electrolytes.

The pituitary bright spot was absent in the majority of cases at diagnosis (n = 14/17, 82 %), but was identified in three patients (G12, G14, G16; 18 %) (Fig. 3a). These three patients had serum sodium values within the institutional reference range (135–145 mmol/L) when compared to cases with bright spot loss ($p = 0.013$, Fisher's exact test), although direct comparison of mean serum sodium values between groups did not reach significance (143 mmol/L (bright spot present) versus 155 mmol/L (bright spot absent); $p = 0.148$, Independent t test). Despite the serum sodium values, all three bright spot cases had a reduced urine: serum osmolality ratio in keeping with a diagnosis of DI, which was no less pronounced than the group demonstrating bright spot loss (ratio mean 0.62 (bright spot present) versus mean 0.66; $p = 0.817$, Independent t test). Desmopressin (DDAVP) was commenced in the vast majority of the cohort (n = 17, 90 %), including two of the three patients with a diagnostic bright spot (G12, G14). The two children not treated with DDAVP (G13 (bright spot absent), G16 (bright spot retained)) were diagnosed with partial DI and had symptoms deemed manageable through education, without the need for medication.

At most recent patient follow-up, the pituitary bright spot remained detectable in two of the three originally visualized cases (G12 and G16), at 0.4 and 3.28 years from diagnosis respectively (Fig. 3b). The third patient (G14) lost the pituitary bright spot on imaging, 9 months after diagnosis. Intriguingly, this occurred despite the patient discontinuing DDAVP after 3 months as her symptoms had resolved. For the remaining cohort, DDAVP use was ongoing for all those who had initially received it, as it had brought about electrolyte stability and reduced both the

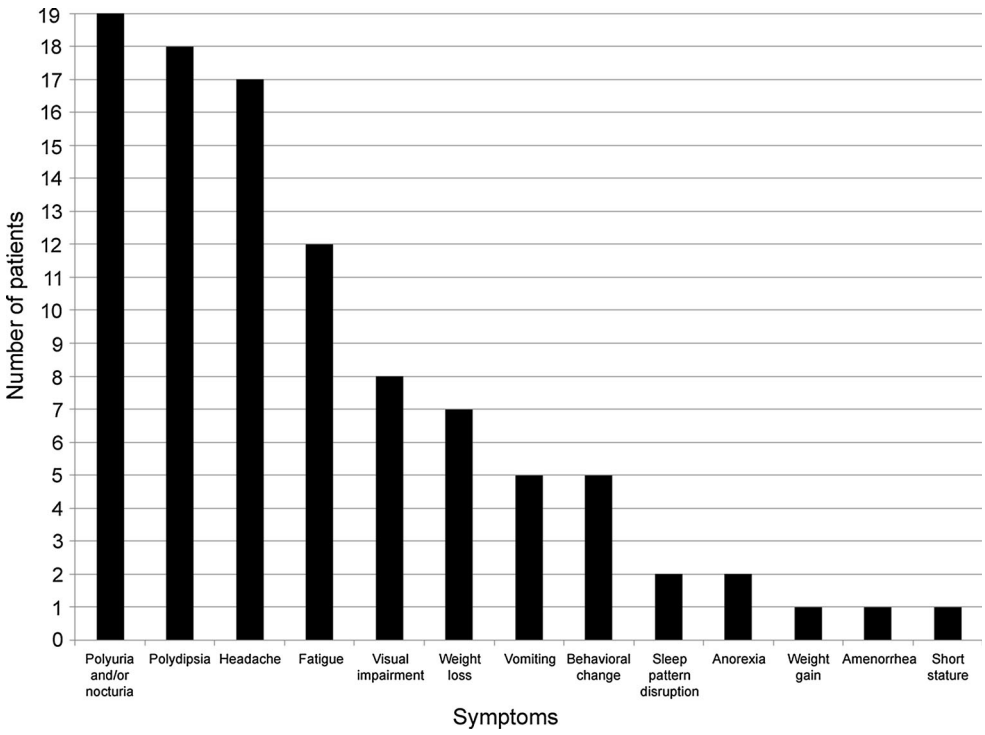

Fig. 2 Presenting symptoms of the suprasellar/bifocal germinoma cohort. The median patient symptom interval (time from initial complaint to diagnostic scan) was 6 months (range 1–48 months). Visual impairment included upward gaze palsy (n = 4), diplopia (n = 3), visual field deficit (n = 2), monocular visual loss (n = 2) and photophobia (n = 1) with symptom overlap in certain patients

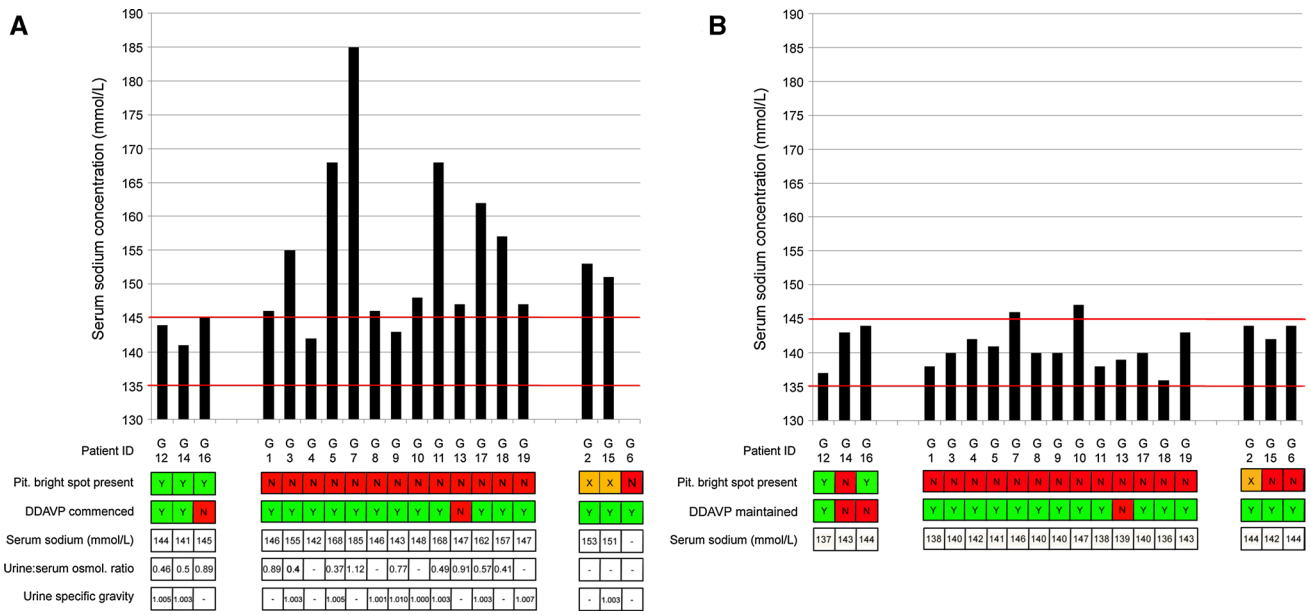

Fig. 3 Serum sodium values, pituitary bright spot presence and desmopressin (DDAVP) usage at diagnosis (**a**) and last follow-up (**b**) for the suprasellar/bifocal germinoma cohort. In both figures, cases are grouped according to presence of the pituitary bright spot at diagnosis (*left group*, n = 3), absence of the bright spot at diagnosis (*middle group*, n = 13), and those with inadequate diagnostic imaging (patients G2 and G15) or absent serum sodium results (patient G6 who was treated initially overseas) (*right group*, n = 3). The left and middle groups are ranked by age at diagnosis. The normal institutional range for serum sodium (135–145 mmol/L) is highlighted by the two *horizontal red lines* on the *graph*. Where available, the diagnostic urine: serum osmolality ratios and urine specific gravities are demonstrated. *Y* yes, *N* no, *X inadequate* imaging (no T1, non-contrast enhanced MRI images available)

frequency of micturition and consequent lifestyle disruption for affected patients. Pituitary bright spot recovery was not observed for any patient where it had been absent at diagnosis.

Discussion

This retrospective, population-based regional study identified symptoms of central DI in all children with

suprasellar or bifocal germinoma. Significantly protracted symptom intervals were observed for over one-third of patients, albeit with excellent survival outcomes following treatment strategies incorporating chemotherapy and radiotherapy. This is the first study to evaluate the incidence and clinical significance of pituitary bright spot visualization in a sizeable cohort of symptomatic DI patients with suprasellar pediatric germinomas, demonstrating that while bright spot loss was the archetypal finding, its presence was identified in almost 20 % of diagnostic cases. Desmopressin was commenced and maintained in over 80 % of the cohort but oncological management seldom reversed the clinical features of germinoma-induced DI, nor did it result in bright spot recovery for cases of initial absence.

This analysis represents one of the larger single-institution cohort studies of suprasellar and bifocal germinomas in childhood. The demographics of the population analyzed were consistent with preceding pediatric intracranial germinoma analyses with respect to median patient age [13, 15–17, 19, 20, 38] and the female predominance that is apparent in suprasellar cases [12, 15, 17, 18, 20, 38, 39]. The finding that our entire cohort presented with symptoms of central DI is also comparable when reviewing recent published data on the presenting features of pediatric and adolescent patients with suprasellar germinomas, where DI was diagnosed in 84 % of patients (n = 150/178), often accompanied by visual impairment and anterior pituitary anomalies as was observed from our experience [9, 12–24].

The prolonged median symptom interval of 6 months in our study cohort remains an ongoing concern amongst neuro-oncologists, as most other brain tumors of childhood have a shorter time to diagnosis [18]. This was originally highlighted in 1985 by a meta-analysis of 215 intracranial germ cell tumors [6], where over a third of germinoma patients had been symptomatic for greater than 6 months before diagnosis. Evidence from our work and that of comparable studies suggests little improvement has been made in reducing this symptom interval over the past 30 years [14, 18, 20, 22, 40, 41]. The insidious, non-specific symptomatology of neurohypophyseal lesions undoubtedly underpins this issue, including the gradual modification of fluid balance to counteract impaired osmoregulation in cases of DI. Symptoms observed in our cohort, ranging from polyuria and polydipsia to delayed puberty and anorexia in adolescence, can also be attributable to a range of etiologies, the majority of which are encountered far more frequently than a suprasellar tumor.

As a consequence, awareness of the existence of such lesions among primary healthcare professionals is lacking [42]. Educational programs are now being launched to address this [43], as evidence suggests delays in diagnosing intracranial germ cell tumors may increase the risk of dissemination and aggravate long-term consequences [18]. Supportive interventions advocated by this group would be to perform brain MRI with dedicated pituitary sequences in all cases of new onset, idiopathic pediatric DI, and incorporate MRI into the initial panel of investigations for suspected cases. Moreover, serial scans may prove an invaluable surveillance tool for detecting occult lesions causing endocrinological imbalance and subtle imaging anomalies which precede eventual radiological evidence of tumor growth [18, 25, 41]. Indeed, work analyzing 26 children with idiopathic DI, loss of the pituitary bright spot and pituitary stalk thickening concluded that performing MRIs every 3–6 months until 3 years from DI diagnosis represented a comprehensive method of capturing cases of inconspicuous suprasellar germinoma [25].

The pituitary bright spot is typically evident on unenhanced T1-weighted MRI sequences with mean dimensions of 4.8 × 2.4 mm, varying according to patient age [44]. Its etiology, composition, and therefore functional role, remain uncertain. Whilst the signal intensity has been ascribed to a high concentration of the neuromodulator oxytocin in the posterior pituitary [45], or lipid accrual in pituicytes and neurosecretory vesicle membranes [26, 29], the most common belief is that the signal intensity represents a protein complex incorporating arginine vasopressin and its transporter neurophysin [26, 30, 31, 46, 47]. Depending on the cause, central DI is typically thought to be associated with vasopressin depletion through either excessive excretion, storage impairment or production failure, and is assumed to underpin the loss of pituitary bright spot frequently observed [26].

Our findings confirm that absence of the pituitary signal on MRI is the typical finding in central DI secondary to germinomatous neurohypophyseal infiltration. However, the bright spot can be retained in a proportion of patients, substantiating reports of signal persistence following therapy in cases of familial, idiopathic and lesional central DI [29, 48–51]. Explanations for this phenomenon remain theoretical. Since it has been proposed that lesion-induced central DI appears to manifest clinically after destruction of 90 % of hypothalamic nuclei [29], it could be argued that residual functioning pituitary tissue was responsible for the diagnostic bright spots observed in three of the patients from our cohort. This appears substantiated by all three children having normal serum sodium values and intact thirst mechanisms at presentation, albeit with impaired urine concentrating ability. Such a hypothesis would require verification in a larger cohort of patients since the difference in serum sodium values between groups with or without a diagnostic bright spot in this analysis, whilst considerable, did not reach statistical significance. An alternative, unsubstantiated hypothesis for bright spot persistence despite clinical DI is the aforementioned

presence of oxytocin containing granules because oxytocin is less affected by changes in osmolality [45].

From our analysis, any theoretical germinoma-induced neurohypophyseal injury appears irreparable since no cases of bright spot recovery were observed and desmopressin was unable to be discontinued for almost all of those commenced on it. This appears to contrast other neoplastic processes such as Langerhans Cell Histiocytosis, where bright spot recovery has been reported with chemotherapy and desmopressin [32]. In addition, Japanese colleagues have suggested that the ongoing requirement of desmopressin maintenance therapy in suprasellar germinomas is paradoxically related to the size of the tumor at presentation, with smaller lesions (less than 2 cm maximum diameter) requiring more sustained therapy following tumor disappearance [13]. Our study refutes this theory, as DDAVP was unable to be discontinued in all six patients with small suprasellar lesions or the 10/11 patients with larger lesions (Table 1; $p = 1.0$, Fisher's exact testing).

As stated, due to the rarity of this tumor subgroup, our study was limited in the number of cases accrued. Indeed, validation of our findings in larger, cohort would be of benefit to verify the hypothesized functional significance of the pituitary bright spot. This would undoubtedly require international collaboration. Whilst not specifically examined in this analysis, the incorporation of both germinomas and non-germinomatous lesions from all intracranial locations should be considered for inclusion in future studies as central DI secondary to germ cell tumors of the pineal region and third ventricle has also been reported [52]. Radiological evaluation of pituitary stalk thickening by MRI has also been purported to be of use in discerning lesional neurohypophyseal infiltration [15, 25]. Our analysis did not incorporate this measure into the radiological evaluation as the evidence for its statistical sensitivity has proven inconsistent when compared to bright spot analysis [28]. In addition, germinomas often present as large suprasellar masses which consequently obscure the pituitary stalk, making accurate assessment impossible.

In summary, loss of the pituitary bright spot appears typical for central DI secondary to childhood suprasellar and bifocal germinomas, but this is not universal and DI can still occur despite a visible pituitary signal. Indeed, explanations for persistence of the bright spot in patients with symptomatic DI remain elusive, although it may reflect a degree of functionality to the posterior pituitary gland which requires investigation in larger collaborative cohorts. Treatment of DI in suprasellar/bifocal germinoma cannot typically be withdrawn once commenced and does not result in bright spot recovery. We have demonstrated a protracted symptom interval persists for central DI secondary to intracranial germinomas, which is likely to be the case for non-germinomatous counterparts too, despite its diagnostic regularity amongst this tumor population. This potentially reflects ongoing poor clinical awareness amongst both medical professionals and the public which warrants consideration by global health authorities. In the interim, surveillance MRI scanning that incorporates sagittal, non-enhanced T1 weighted images and dedicated pituitary sequences to optimize bright spot identification is advocated to support the imperative endocrinological evaluation of all cases of new onset, idiopathic DI.

Conflict of interest All authors declare no conflict of interest.

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