CLINICAL STUDY

Diagnosis, management and therapeutic outcome in prepubertal Cushing’s disease

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Abstract

Objectives: Cushing’s disease (CD) in prepubertal children is very rare and presents important diagnostic and therapeutic challenges. We report experience of the management of this subpopulation of CD patients.

Study design/methods: Retrospective patient case note review.

Results: Between 1985 and 2008, 17 prepubertal children (13M, 4F), aged 5.7–14.1 years presented to our centre for diagnosis and management of CD. All children had subnormal linear growth and excessive weight gain at presentation. A high proportion (85% of males, 75% of females) had evidence of excessive virilisation. Striae and hypertension were seen in 41% of patients. The investigation with highest sensitivity (100%) for CD was excessive increase of serum cortisol to i.v. CRH (mean increase 113%). Pituitary imaging performed in all the patients showed poor concordance with findings at surgery (31%). In contrast bilateral simultaneous inferior petrosal sinus sampling (BSIPSS), performed in 11/16 subjects showed a high correlation with surgical findings (91%). In 16 patients, transsphenoidal selective adenomectomy (TSS) achieved a cure rate of 44%. However, in the 11 patients who had pre-operative BSIPSS, the cure rate was 64%. Of the 16 patients, 9 patients who were not cured by TSS received external pituitary radiotherapy.

Conclusions: Prepubertal CD had distinctive features with increased frequency in males, abnormal auxology and excessive virilisation. The cortisol response to i.v. CRH administration was particularly exuberant and contributed to diagnosis. BSIPSS was much more helpful than pituitary imaging in localisation of the microadenoma and was associated with improved cure rate by TSS.

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Introduction

Cushing’s disease (CD) is caused by excess ACTH secretion by a pituitary corticotroph tumour. In all age groups, microadenomas are the most common cause. In childhood and adolescence, CD accounts for ~75–80% of paediatric Cushing’s syndrome cases, but is still rare (1). In children, the hypercortisolaemia of CD can cause severe morbidity, so early diagnosis, based on a series of standardised biochemical and radiological investigations, is essential (1–5).

Children with CD who are prepubertal, defined by the absence of gonadotrophin-dependent secondary sexual characteristics, comprise a rare subgroup, as most paediatric CD patients are pubertal at the time of diagnosis (3). There are very few reports describing the diagnosis and management of prepubertal children with CD.

The diagnosis and management of young children with CD poses a significant challenge to the paediatric endocrinologist. Firstly, the clinical features of CD in children may be relatively subtle with growth failure and abnormal puberty being two of the most common features (6–8). Secondly, the microadenomas are usually very small and pituitary imaging may fail to detect the lesion (9, 10). In addition, transsphenoidal microadenomectomy may be technically very difficult in children and requires a highly skilled and experienced neurosurgeon (11, 12).

Here we review the diagnostic features, management and therapeutic outcomes of all the prepubertal CD patients managed in a single centre during a 23-year period.

Subjects and methods

Patients

Between 1985 and 2008, 17 prepubertal children (13 males, 4 females), aged 5.7–14.1 years with CD, were treated in the paediatric endocrine unit at St Bartholomew’s and the Royal London Hospitals, London, UK.
Puberty was staged according to the criteria of Tanner (13, 14). Prepubertal status in males was defined as testicular volumes <4 ml and in females breast development <Tanner stage 2. Evidence of virilisation, shown by genital and/or pubic hair Tanner stage ≥2, was present in 10/17 patients. In all cases, however, testicular volumes or breast development were prepubertal.

Clinical features and auxology

Parental reports of timing of onset of symptoms including weight gain, change in facial appearance, fatigue, headaches and emotional lability were ascertained on direct questioning. Hypertension was defined as a diastolic or systolic blood pressure >95th centile for age and sex on more than two occasions (15). Auxological observations consisted of measurement of height, height velocity and weight using standardised anthropometric techniques (16). Body mass index (BMI) was calculated and converted to SDS using the method of Cole (17). Height was converted to SDS using the method of Tanner (16, 18). Bone age (BA) was determined using the TW3 RUS method (Tanner–Whitehouse 3 radius, ulna and small bones), and BA delay was calculated as the difference between chronological age and BA (19).

Diagnosis of CD

CD was diagnosed on the basis of detectable 0900 h plasma ACTH (normal range 10–50 ng/l), loss of serum cortisol circadian rhythm (elevated sleeping 0000 h cortisol >50 nmol/l) and failure of serum cortisol to suppress to <50 nmol/l during a low-dose dexamethasone suppression test (LDDST: 0.5 mg every 6 h for 48 h, corrected to 30 μg/kg per day in children <30 kg) (3). Additionally, the patients showed suppression of serum cortisol to <50% of baseline in a high-dose dexamethasone suppression test (HDDST: 2 mg every 6 h for 48 h, corrected to 120 μg/kg per day in children <30 kg) (3, 4) and/or an exaggerated (≥20% of baseline) rise in serum cortisol during a corticotrophin releasing hormone (CRH) test (100 μg human serum recombinant i.v. CRH) (20).

Pituitary imaging

All the patients underwent pre-operative pituitary magnetic resonance imaging (MRI), as previously described (21). MRI was performed at 1.5 Tesla. T1-weighted sequences were acquired in sagittal and coronal planes with a 3-mm slice thickness. After gadolinium administration, further acquisitions were made in the coronal plane; a dynamic sequence within 60 s of contrast and then a gradient-echo volume acquisition, reconstructed in both sagittal and axial planes. In all the cases, radiologists were blinded to the results of inferior petrosal sinus sample (IPSS). Patients had MRI within the same centre. During the study period of 23 years, MR scanners were changed twice with improved spatial resolution, most importantly in 2000.

Bilateral simultaneous inferior petrosal sinus sampling

Bilateral simultaneous inferior petrosal sinus sampling (BSIPSS) with i.v. administration of 100 μg CRH was introduced in our centre for paediatric patients in 1986 (22). BSIPSS was performed in 11/17 patients (65%), all with microadenomas, without complications. In a total of six patients, BSIPSS was not attempted; in two patients this was for technical reasons, another two patients presented before the introduction of the technique, one patient had a macroadenoma and one patient was too unwell due to respiratory failure. In nine children, BSIPSS was performed without sedation, but two young patients (aged 5.6 and 6.6 years) required general anaesthesia. Written informed parental consent was obtained for BSIPSS in every child.

The central to peripheral (IPS/P) ACTH ratio was defined as the highest right or left IPS value after the administration of CRH compared with the concurrent level in a peripheral blood sample (P). A basal or CRH-stimulated IPS/P ratio of >2 was taken as indicative of pituitary ACTH secretion (4). The interpetrosal sinus ACTH gradient (IPSG) was calculated by taking the highest IPS ACTH value (right or left) after CRH administration divided by the value at the same time point in the contralateral IPS. Lateralisation of ACTH secretion was defined as an IPSG of >1.4, while an IPSG of <1.4 was suggestive of a midline lesion, as previously described (23).

Transsphenoidal selective adenomectomy and histological analysis

Sixteen patients underwent transsphenoidal selective adenomectomy (TSS) as first-line treatment. Two patients underwent TSS in other centres prior to referral to our unit. In our centre, the same neurosurgeon (F A) performed TSS in 14 patients, as previously described (12). The location of the adenomas was categorised as right-sided, left-sided or midline, based on the operation notes. Parenteral hydrocortisone was given perioperatively and for a minimum of 24 h post-operatively. Data on histological analysis of pituitary tissue were available for all but one patient, who underwent TSS in another country.

Bilateral adrenalectomy was performed in one patient because of extreme illness with respiratory failure; this child is excluded from further analysis in the results.
Pituitary radiotherapy

In our centre, pituitary radiotherapy (RT) is the second-line treatment for paediatric CD after unsuccessful TSS. All the patients who were not cured by TSS (n = 9) received external beam pituitary irradiation, with 6 MeV photons from a linear accelerator to deliver 45 Gy in 25 fractions over 35 days. A three-field technique (two lateral and one superior oblique) was used to localise radiation to the pituitary, as previously described (24).

Definition of cure of CD

Post-TSS, serum cortisol levels were measured daily at 0900 h at least 12 h after the last dose of hydrocortisone (mean 2.1 days post-operatively; range 1–7 days). Cure was defined as an undetectable serum cortisol level (< 50 nmol/l) (25). Cure of CD after second-line pituitary RT was defined as a mean serum cortisol on a 5-point day curve of < 150 nmol/l after discontinuation of medical therapy, in addition to a midnight serum cortisol < 50 ng/l and suppression of serum cortisol to < 50 nmol/l on the LDDST, as previously described (26).

Hormone assays

ACTH was measured using two-site chemiluminescent immunometric assays on an Immulite semi-automated analyser (DPC Ltd, Llanberis, Wales, UK), with an assay imprecision < 8% (25). Serum cortisol was determined historically on the Bayer Technicon Immuno-I automated immunoassay analyser (Bayer Diagnostics) and, since 2004, on the Roche E170 automated immunoassay analyser. Assay imprecision of both the systems has been calculated as < 6%.

Table 1 Auxological features and puberty staging in 17 patients at diagnosis of Cushing’s disease.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Pubertal stage (testicular volume in ml)</th>
<th>Height SDS</th>
<th>Height velocity (cm/years)</th>
<th>BMI SDS</th>
<th>BA (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.7</td>
<td>F</td>
<td>A1 B1 P1</td>
<td>-0.2</td>
<td>NA</td>
<td>6.9</td>
</tr>
<tr>
<td>2</td>
<td>6.2</td>
<td>M</td>
<td>A1 G3 P2 (3/2)</td>
<td>-1.4</td>
<td>NA</td>
<td>9.2</td>
</tr>
<tr>
<td>3</td>
<td>6.4</td>
<td>M</td>
<td>P2 G2 (2/2)</td>
<td>-1.6</td>
<td>2.4</td>
<td>5.1</td>
</tr>
<tr>
<td>4</td>
<td>6.6</td>
<td>M</td>
<td>A1 G2 P2 (2/2)</td>
<td>-3.2</td>
<td>2.5</td>
<td>3.8</td>
</tr>
<tr>
<td>5</td>
<td>7.6</td>
<td>M</td>
<td>P2 G1 (2/2)</td>
<td>-3.7</td>
<td>2.2</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>8.2</td>
<td>M</td>
<td>G2 P1 (2/2)</td>
<td>-1.5</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>8.4</td>
<td>M</td>
<td>P3 G2 (1/1)</td>
<td>-3.5</td>
<td>NA</td>
<td>2.9</td>
</tr>
<tr>
<td>8</td>
<td>8.8</td>
<td>M</td>
<td>G1 P1 (3/3)</td>
<td>-1.1</td>
<td>0</td>
<td>3.2</td>
</tr>
<tr>
<td>9</td>
<td>9.4</td>
<td>M</td>
<td>P2 G2 (2/2)</td>
<td>1.2</td>
<td>NA</td>
<td>1.9</td>
</tr>
<tr>
<td>10</td>
<td>10.6</td>
<td>F</td>
<td>B1 P2 A1</td>
<td>-1.1</td>
<td>NA</td>
<td>2.3</td>
</tr>
<tr>
<td>11</td>
<td>10.8</td>
<td>M</td>
<td>G1 P1 (2/1)</td>
<td>-2.8</td>
<td>NA</td>
<td>2.6</td>
</tr>
<tr>
<td>12</td>
<td>11.6</td>
<td>M</td>
<td>A1 G1 P2 (2/3)</td>
<td>-1.6</td>
<td>0.8</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>11.7</td>
<td>M</td>
<td>G1 P2 (2/2)</td>
<td>-1.8</td>
<td>2.2</td>
<td>3.1</td>
</tr>
<tr>
<td>14</td>
<td>11.9</td>
<td>F</td>
<td>B1 P5 A3</td>
<td>-2.0</td>
<td>2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>15</td>
<td>13.6</td>
<td>M</td>
<td>P3 G2 (3/3)</td>
<td>-3.6</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>16</td>
<td>13.7</td>
<td>M</td>
<td>P3 G3 (3/3)</td>
<td>-1.8</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>17</td>
<td>14.1</td>
<td>F</td>
<td>A3 B1 P4</td>
<td>-2.1</td>
<td>2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

F, female; M, male. Pubertal staging: A, auxiliary hair; G, genitalia; B, breast and P, pubic hair. Height velocity during ≥ 0.5 years. Numbers in parentheses indicate testicular volumes in millilitres; BMI indicates body mass index score. BA, bone age (TW3 RUS method); NA, data not available.
patients, with 12 (87%) patients suppressing their serum cortisol to >50% of baseline. All 17 patients underwent a CRH test and 100% of them had an increase of serum cortisol from baseline of >20% (mean change 113%; range 30–438%).

**Table 2** Clinical signs and symptoms in 17 Cushing’s disease patients at diagnosis.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Percentage (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>29 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (7)</td>
</tr>
<tr>
<td>Striae</td>
<td>41 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>52 (9)</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>59 (10)</td>
</tr>
</tbody>
</table>

Percentage of children who demonstrated the clinical sign or reported symptom at diagnosis, figure in parentheses indicates actual number of patients.

Radiological imaging studies and concordance with findings at TSS

Pituitary MRI reported an adenoma in 10/17 (59%) of patients. The percentage concordance of imaging with the findings at surgery was only 31% (5/16), including the patient with the macroadenoma. Furthermore, in 6/7 (86%) patients who were reported to have normal imaging, a tumour was visualised during TSS. There have been some changes in neuroradiology personnel and MR technology and equipment over a 23-year period. Within our service, 8/17 (47%) children were scanned prior to the latest scanner installation in 2000 and 2/8 (25%) patients showed concordance with surgical findings which is similar to the overall findings.

**Table 3** Results of pituitary imaging, bilateral simultaneous inferior petrosal sinus sampling, transsphenoidal surgery and histology.

<table>
<thead>
<tr>
<th>MRI</th>
<th>IPSS site/ lateralisation</th>
<th>Adenoma at surgery</th>
<th>Histology</th>
<th>Treatment</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>IPS/R (under GA)</td>
<td>R</td>
<td>Adenoma</td>
<td>TSS  Y</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>ND</td>
<td>NA</td>
<td>–</td>
<td>Adrenalectomy Y</td>
</tr>
<tr>
<td>3</td>
<td>ML</td>
<td>ND</td>
<td>Not seen</td>
<td>N</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>IPS/L (under GA)</td>
<td>L</td>
<td>Adenoma</td>
<td>TSS Y</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>ND</td>
<td>R</td>
<td>N</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>IPS/R</td>
<td>R</td>
<td>N</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>IPS/R</td>
<td>R</td>
<td>N</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>8</td>
<td>L</td>
<td>ML</td>
<td>L</td>
<td>N</td>
<td>TSS RT N</td>
</tr>
<tr>
<td>9</td>
<td>R</td>
<td>ND</td>
<td>R</td>
<td>Adenoma</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>10</td>
<td>L</td>
<td>IPS/R</td>
<td>R</td>
<td>N</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>11</td>
<td>N</td>
<td>HJV/ML</td>
<td>ML</td>
<td>Adenoma</td>
<td>TSS Y</td>
</tr>
<tr>
<td>12</td>
<td>R</td>
<td>IPS/R</td>
<td>NA</td>
<td>NA</td>
<td>TSS ×2, RT (in Poland) N</td>
</tr>
<tr>
<td>13</td>
<td>R</td>
<td>IPS/L</td>
<td>L</td>
<td>N</td>
<td>TSS Y</td>
</tr>
<tr>
<td>14</td>
<td>Macroadenoma</td>
<td>ND</td>
<td>Macroadenoma</td>
<td>Adenoma</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>15</td>
<td>N</td>
<td>HJV/R</td>
<td>R</td>
<td>N</td>
<td>TSS Y</td>
</tr>
<tr>
<td>16</td>
<td>ML</td>
<td>ND</td>
<td>R</td>
<td>Adenoma</td>
<td>TSS RT Y</td>
</tr>
<tr>
<td>17</td>
<td>N</td>
<td>IPS/R</td>
<td>R</td>
<td>Adenoma</td>
<td>TSS Y</td>
</tr>
</tbody>
</table>

N, normal; L, left-sided lesion; R, right-sided lesion; ML, midline; NA, not available; ND, not done; IPS, inferior petrosal sinus sample; HJV, high jugular vein sample; TSS, transsphenoidal surgery alone; TSS ×2, two transsphenoidal operations performed; TSS RT, transsphenoidal surgery and pituitary radiotherapy.

Results of BSIPSS

BSIPSS was performed in 11/16 (69%) patients (8M, 3F, mean age 11.0 years, range 5.7–14.1 years). Sampling for ACTH was performed from the inferior petrosal sinuses bilaterally in 9/11 patients and from both high internal jugular veins (HJV) in 2/11 (18%) patients. The peak IPS/P or HJV/P ACTH ratio after CRH was ≥2 (mean 13.2, range 2.0–28.6) in 10/11 (91%) patients. One patient who underwent HJV sampling had a peak central to peripheral ratio post-CRH of ≤2 (0.95). TSS was performed in this child as all the other biochemical investigations were entirely consistent with a diagnosis of CD.

In 9/11 (82%) patients, the IPSG after CRH was >1.4 (mean 9.95, range 1.7–20.8) indicating ACTH lateralisation (to the right-side in seven patients and to the left-side in two patients). In the two patients who did not demonstrate lateralisation, TSS revealed a left-sided adenoma in one case and a midline adenoma in the other.

Concordance of the results of BSIPSS with findings at TSS

In 10/11 (91%) patients who underwent BSIPSS, the site of ACTH secretion was consistent with the position of the adenoma seen during surgery. Of note, bilateral HJV sampling correctly identified the adenoma position in both patients.

Cure of CD and results of histological analysis

An adenoma was confidently identified by the neurosurgeon during TSS in 14/16 (88%) patients. Histological analysis confirmed a corticotroph adenoma in 8/15 (53%) patients (Table 3).
Cure by TSS

Overall, 7/16 (44%) patients were cured by TSS alone. One of the patients in whom TSS was unsuccessful had a pituitary macroadenoma. In the patients who underwent BSIPSS prior to TSS, 7/11 (64%) were cured. Of the ten patients in whom BSIPSS findings concurred correctly with the surgical findings, seven (70%) were cured.

Cure by radiotherapy

Pituitary RT was curative in 8/9 (89%) patients. One patient responded initially to RT and was considered to be cured but then relapsed.

Post-cure anterior pituitary function

Patients were followed up for a median period of 3.2 years (range 0.18–16.7 years), after TSS or RT. GH provocation testing was performed in 11/15 patients. Two patients were operated on within the last 6 months and so no GH provocation data are available. The main post-operative pituitary hormone deficiency in the patients cured by TSS alone was isolated GH deficiency (GHD) in 40% (2/5), mean peak GH 33 mU/l, range <0.5–42.5. One child developed GHD prior to TSS which was transient (reassessment post RT showed recovery). In the patients who underwent TSS and RT, 83% (5/6) had isolated GHD although this was transient in two children. Two male children who had TSS and pituitary RT, developed early puberty with a pubertal response on GnRH test and were treated successfully with GnRH analogue. In the nine patients for whom data are available, none had evidence of thyroid dysfunction following TSS alone or in combination with pituitary RT.

Discussion

We have reviewed the characteristics of diagnosis, management and long-term outcome in a prepubertal CD cohort managed in a single centre. Some features at diagnosis are worthy of comment. The predominance of males has previously been described (27). Magiakou et al. noted a similar phenomenon in a large series of children and adolescents (3). All the prepubertal CD patients presented with excessive weight gain and change in facial appearance with frequent growth failure highlighting the importance of accurate auxological assessment. Excessive virilisation in the majority of our patients was striking and has been previously reported (3). Clinical signs of hypercortisolaemia including hypertension and striae were common, as reported in a large series of patients from early childhood to late adolescence (3). However, despite the abnormal virilisation seen in most children, almost half had delayed BA. Suppression of gonadotrophin secretion has previously been described as a complication of chronic hypercortisolaemia (7).

Biochemical investigations in our patients showed a markedly increased cortisol response following CRH administration in all the subjects. The CRH test can therefore be of real diagnostic value in young children with CD. In a previously reported series of 51 children and adolescents, 75% showed an excessive increase in cortisol (mean 34%) after CRH, (3). However, this cohort was different to ours and included patients across a large age spectrum. The dose and type of CRH used was also different (1 µg/kg of ovine CRH).

Paediatric CD is predominantly caused by corticotroph microadenomas (defined as <5 mm in diameter) which are usually hypodense on MRI and usually fail to enhance with gadolinium contrast (4). Although pituitary MRI is part of our pre-operative protocol, both the rate of visualisation of a tumour and concordance with the findings at TSS were low. This is comparable to the ~20% correlation between MRI and surgical findings reported in a series of children and adolescents by Batista et al. (9). In adult CD, the detection rate was reported to be 56% with contrast-enhanced MRI (28). The most likely explanation for this difference is the relatively smaller size of ACTH-secreting tumours in children. There have been improvements in MR technology, particularly over the last 15 years with markedly enhanced spatial resolution. Improved imaging techniques have reported higher detection rates in children, most importantly reducing false-negative results (9). Within our series, concordance between MR findings and surgery remained constant during the duration of the study.

In contrast, BSIPSS was, in our experience, highly informative with identification of the site of ACTH secretion showing 91% concordance with surgical findings. Our localisation rates in this group compare favourably with the large paediatric series from NIH, which reported 60% concordance between BSIPSS and operation findings in patients showing lateralisation (29). Furthermore, localisation of tumour site by BSIPSS appears to improve cure rate by TSS. In experienced hands, as evidenced by our results, BSIPSS is feasible and can be performed without complications in children. Performance of BSIPSS under general anaesthetic (GA) has been reported to give valid results (9). In the two patients in our series where BSIPSS was performed under GA, IPS/P and IPSG ratios were conclusive. Our cure rate from TSS in this prepubertal group was less (44%) than in all our paediatric CD patients grouped together (65%). This probably reflects the technical difficulty of complete removal of very small microadenomas. Differences between the percentage cure and positive histological evidence of a microadenoma have previously been reported (29). Overall, our results for cure following TSS compare favourably with other published paediatric and adult series (8, 30–32).
TSS in young children is complicated by the small size of the adenomas, a small pituitary fossa and lack of sphenoid sinus aeration in some cases, as the sphenoid sinus does not achieve adult pneumatisation until approximately age 12 years. A highly skilled neurosurgeon is more likely to achieve a successful surgical outcome (11). We accept that over a 23-year period the accumulated experience of the surgeon may have influenced our results.

Post-therapeutic anterior pituitary function in children and adolescents following TSS alone and in combination with pituitary RT shows that isolated GHD is the most common anterior pituitary hormone defect seen, occurring in 56 and 83% respectively, although this can be transient (10, 33). Our results are comparable to this. Other anterior pituitary defects appear to be much less common.

In conclusion, presentation of CD in prepubertal children can be subtle with growth failure, weight gain and change in appearance being the most common presenting features. Diagnosis requires careful investigation, ideally in an experienced centre. The marked CRH response in this subgroup of paediatric patients was notable and of diagnostic value. Pituitary imaging correctly identified the microadenoma in only a low percentage of patients, but we believe this should remain as part of the investigation protocol. Although BSIPSS can be technically demanding and required the skill of an experienced radiologist, it was highly informative in terms of tumour localisation and appeared to contribute to optimal surgical outcome and cure.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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