FACTORS INFLUENCING CURE BY
TRANSSPHENOIDAL SELECTIVE ADENOMECTOMY
IN PEDIATRIC CUSHING'S DISEASE

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Short Title: Factors influencing cure of Pediatric Cushing’s disease.

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Abstract

Early diagnosis and effective treatment of pediatric Cushing's disease (CD) is necessary to minimise associated morbidity. Accepted first-line treatment is selective transsphenoidal microadenomectomy (TSS), which can be technically difficult, and cure rates vary considerably between centers. In our pediatric CD patient group we have assessed the possible factors, which may influence cure by TSS.

From 1983-2004, 27 pediatric patients (16 males, 11 females; mean age ± SD 13.1 ± 0.4 yr; range, 6.4-17.8 yr) with CD were managed in our center and underwent TSS. Sixteen patients (59%), 7 males and 9 females (median age 14.2 yr; range, 8.2-17.8 yr), were cured (post-operative serum cortisol < 50 nM). Eleven patients, 9 males and 2 females (median age 11.5 yr; range, 6.4-17.8 yr) had detectable post-operative (2-20 days) mean serum cortisol levels at 9am of 537 nM (range 269-900 nM) indicating lack of cure. These 11 patients received external beam pituitary radiotherapy (RT). One patient with a pituitary macroadenoma had a post-operative cortisol of <50nM but 0.8 yr later showed an elevated cortisol and residual disease. The patients cured by TSS alone were significantly older than those not cured (P=0.038).

All patients had MR/CT pituitary imaging: 14 were reported to have microadenomas and one macroadenoma, while 12 were reported as normal. Bilateral simultaneous inferior petrosal sinus sampling with iv CRH administration (BSIPSS) was introduced as a pre-operative
investigation in 1986 and was performed in 21 patients (78%). On BSIPSS, 16 (76%) had evidence suggesting pituitary ACTH secretion (central to peripheral (IPS:P) ACTH ratio after CRH of >3.0) and 17 (81%) showed lateralization of ACTH secretion (IPSG of >1.4). There was concordance between the BSIPSS finding and the position of the microadenoma at surgery in 17/21 (81%) patients. Of the 17 patients showing lateralization of ACTH secretion, 13 (76%) were cured by TSS. In 4 without lateralization of ACTH, suggesting a midline lesion, 3 (75%) were cured by TSS. Post-operative pituitary hormone deficiencies in the patients cured by TSS were: pan-hypopituitarism 1/16, isolated growth hormone deficiency (GHD) (peak GH on glucagon/ITT <1-17.9 mU/l) 9/16 and diabetes insipidus 3/16.

In conclusion, over a 21-year period selective adenomectomy by TSS cured 59% of all pediatric CD patients, with higher age favoring cure. Introduction of BSIPSS resulted in demonstration of a high rate of lateralization of ACTH secretion consistent with the surgical identification of the adenoma and therefore appears to have contributed to the higher surgical cure rate.
Cushing's disease (CD) is defined as hypercortisolemia due to a pituitary corticotroph adenoma. CD in childhood and adolescence is rare but is associated with significant morbidity (1;2). CD is the commonest cause (49-71%) of adult-onset Cushing's syndrome (3-6) and also accounts for approximately 75% of pediatric Cushing's syndrome (1;2;7). Therapy which provides prompt and effective normalization of serum cortisol is essential as prolonged excessive cortisol secretion leads to significant morbidity (8). This is especially important in pediatric patients (1;9). Transsphenoidal surgery with selective removal of the adenoma is generally considered the first-line treatment of choice for adult and childhood-onset CD. TSS is considered safe with low reported rates of subsequent hypopituitarism in adults (8;10;11) and children (9;12;13). Adult CD series show variable surgical success rates depending on which contentious definition of cure is adopted (14-16). In the few reported pediatric CD series available, cure or remission rates after TSS have been reported as between 45-98%, but again different definitions of cure were used in these various studies (17).

In childhood CD, TSS can be technically difficult and there is a considerable failure rate in the hands of even the most experienced neurosurgeons. However, there are no published series evaluating factors that affect surgical outcome in pediatric patients. We have therefore examined numerous factors, including age, length of history, clinical and endocrine features and investigations which may influence cure by TSS in a series of pediatric-onset CD patients.
Patients and Methods

Patients

Twenty-seven patients, 16 males and 11 females (mean age ± SD 13.1 ± 0.4 yr range, 6.4-17.8 yr) with CD were investigated and treated at St. Bartholomew’s and The Royal London Hospitals, London, United Kingdom, from 1983-2004 (Table 1).

Diagnosis of CD

The diagnosis of Cushing’s disease was based on the following biochemical criteria: detectable plasma ACTH (mean 09.00 h value, 46 ng /L; range, 15-125 ng /L; normal range, 10-50 ng /L), loss of serum cortisol circadian rhythm i.e. elevated sleeping midnight cortisol of more than 50 nM (mean 470 nM; range 165-930 nM); and failure of serum cortisol to suppress to <50 nM during a low-dose dexamethasone suppression test (LDDST; 0.5mg, 6 hourly for 48 h) (3). In addition, the patients either showed suppression of serum cortisol to more than 50% of the baseline value in a high-dose dexamethasone suppression test (2mg, 6 hourly for 48 h) (3;18) or an exaggerated response of serum cortisol during a CRH test (1μg/kg iv; range 106%-554%) (18), or both.

Pubertal Staging

Puberty was staged, at diagnosis, according to Tanner’s criteria (19;20). Pre-pubertal males had testicular volumes < 4 ml. Eleven were pre-pubertal, 14 patients were in puberty and 2 patients were post-pubertal at diagnosis.
Protocol for BSIPSS

Bilateral simultaneous inferior petrosal sinus sampling with iv administration of 100mg CRH (BSIPSS), was introduced in 1986 and performed in 21 patients aged 8.2–17.8 yr. In 4 of the 21 patients samples were obtained from the high jugular veins. BSIPSS was performed without sedation or systemic anesthesia, as previously described (21). Informed written consent was obtained from the patients or their parents before the procedure.

Interpretation of data from BSIPSS

Evidence for central ACTH secretion A central to peripheral (IPS/P) ACTH ratio, i.e. the highest right or left IPS value, compared with the level simultaneously measured from the peripheral vein of more than 2.0 pre-CRH or more than 3.0 post CRH stimulation were taken as indicative of pituitary ACTH secretion i.e. Cushing’s disease (3).

Evidence of lateralization of ACTH secretion An inter-petrosal sinus gradient (IPSG) of more than 1.4, between the ACTH values after CRH treatment, was taken as suggestive of lateralization of the pituitary adenoma (3;22). An IPSG ratio of less than 1.4 was taken as suggestive of a midline lesion.

Assay for ACTH and cortisol

Plasma ACTH was determined by Diagnostic Products Corporation (DPC) immunolite 2000 analyser (Lanberis, Wales) according to the manufacturers
Instructions. Serum cortisol was determined by Bayer-Technicon Immuno 1 analyser (Newbury, UK).

*Pituitary imaging*

CT and/or MR imaging was performed preoperatively in all patients, as previously described (21).

*Transsphenoidal selective adenomectomy (TSS)*

TSS was attempted as first-line therapy in all 27 patients. The surgery was performed by the same surgeon (F.A) in 24 of 27 patients. Operative findings of the localization of the corticotroph microadenoma are based on the operation notes recorded at the time of surgery. Locations were categorized as right-sided, left-sided or midline. Hydrocortisone was given for a minimum of 24 hours post-operatively.

*Pituitary Radiotherapy*

Eleven patients (9 males, 2 females) were not cured by TSS. These patients received external beam pituitary irradiation (RT), using a 6-MV linear accelerator, with a dose of 45 Gy in 25 fractions over 35 days (23) at median 0.1 yr (range 0.2-8.0) post -TSS.

*Definition of cure of CD*

After TSS, serum cortisol levels were measured daily at 09 00h at least 12 hours after the last dose of hydrocortisone. Post-operative serum cortisol
levels less than 50 nM (set as the detection limit in our assay) were taken to indicate 'cure' (15). Cure of CD after RT, was defined as mean serum cortisol on a 5-point day curve of less than 150 nM as previously reported (17). All 27 patients were cured of CD according to these criteria.

Statistical Analysis

Student's 't' test was used for data analysis, with significance taken as $P < 0.05$.

Results

Clinical parameters at diagnosis in patients cured and not-cured by TSS

Sixteen of 27 patients (59%) (7 males and 9 females; mean age, 14.2 ± 2.5 yr; range, 8.2-17.8 yr; 10 prepubertal; 4 pubertal; 2 postpubertal) were cured by TSS. Eleven patients (9 males and 2 females; mean age, 11.5 ± 3.6 yr; range, 6.4-17.8 yr; 7 prepubertal; 4 pubertal) were not cured by TSS and received second-line treatment with pituitary RT (Table 1). Patients cured by TSS alone were older than those not cured ($P=0.038$). The clinical features of CD at diagnosis and the length of history of CD between the cured /not-cured groups were comparable (mean 2.9 yr, range 0.5-6.0 yr in the patients cured by TSS and 1.9 yr, range 0.5-5.0 yr, in patients treated by RT).

Radiological imaging at diagnosis in patients cured and not-cured by TSS

Pituitary imaging using CT or MR was consistent with a pituitary microadenoma in 14 patients; a macroadenoma was reported in one patient.
and 12 were reported as normal. Ten of 12 (83%) patients with a normal
pituitary MR/CT scan and 6 of 14 (43%) patients reported to have a pituitary
microadenoma at diagnosis were cured by TSS alone (Table 1). One patient
with a pituitary macroadenoma had a 09.00 h serum cortisol of <50nM post-
surgery but 0.8 yr later showed elevated serum cortisol levels and recurrent
disease. Subsequently she achieved cure after RT. In 7 of the 15 patients
reported to have an adenoma (47%) the pituitary imaging correctly localized
the position of the adenoma (Table 2).

*Confirmation of central ACTH secretion and lateralization of the pituitary
adenoma by BSIPSS*

BSIPSS with CRH administration was introduced in our pediatric patients in
1986 and performed in 21 patients as part of the investigation of CD. Sixteen
(76%) demonstrated central ACTH secretion (peak IPS / P ratio >3.0 after iv
CRH, mean, 22.0; range, 3.0-157.2) (Table 1) and in 17 (81%) there was
lateralization of ACTH secretion (IPSG >1.4 after iv CRH, mean, 5.7; range,
1.4-20.8) (Table 3).

Sixteen of the 21 patients undergoing BSIPSS (76%) were cured by TSS
(Table 3). Of the 17 patients with lateralization of ACTH secretion, 13 (76%)
were cured by TSS (Tables 1 and 3). In 4 patients without lateralization of
ACTH, suggesting a midline lesion (IPSG <1.4 after iv CRH, mean, 1.2;
range, 1.1-1.3), 3 (75%) were cured by TSS (Tables 1 and 3). In 4 patients, in
whom samples were obtained from the high jugular veins 3 demonstrated
both central and lateralization of ACTH secretion.
Operative and histological findings (Table 1)

An adenoma was visualized during surgery in all except 2 patients diagnosed with microadenomas. Of these, 13 were right-sided (7 cured, 6 uncured by TSS), 5 left-sided (all cured by TSS) and 6 (4 cured, 2 uncured by TSS) were in the central part of the gland (midline). The 2 patients without a tumor visualised at surgery were not cured by TSS. In 16 (59%) patients the adenoma was confirmed histologically, 5/11 (45%) in the not-cured and 11/16 (69%) in the cured group.

Concordance between BSIPSS ACTH sampling and adenoma position at surgery

There was concordance between the position of the adenoma at surgery with the BSIPSS finding in 17 of 21 (81%) patients (Table 3). In the 3 patients that demonstrated lateralization from samples taken from the high jugular veins, the correct lateralization was confirmed at surgery.

Long-term outcome

Post-operative pituitary hormone deficiencies in the patients cured by TSS were: pan-hypopituitarism 1/16, isolated growth hormone deficiency (GHD) (peak GH on glucagon/ITT <1-17.9 mU/l) 9/16 and diabetes insipidus 3/16.
Discussion

Transsphenoidal surgery is recognised as the first-line treatment for Cushing’s disease in adults and children. The main surgical goals are the localization and selective removal of the ACTH-secreting tumor, whilst preserving normal anterior and posterior pituitary function. TSS also provides a confirmatory tissue diagnosis.

Pituitary corticotroph micro and macro-adenomas are recognised causes of CD (6). In all age groups, microadenomas are the more common cause. Corticotroph macroadenomas, although frequently reported in the adult literature, are much rarer in the pediatric age range (12;24;25). Many adult CD series report the efficacy of first-line TSS for the treatment of microadenomas with low levels of mortality and morbidity (8;10;26). TSS is also safe and effective in children. Surgical morbidity is rare and there is a low reported rate of long-term hypopituitarism (12;13;25;27). Even when TSS is unsuccessful first-line treatment, it may confer protection against relapse following either repeat TSS or pituitary irradiation (28).

The failure rate of TSS for ACTH-secreting adenomas is significant even in the most experienced hands. Post-operative cure and remission rates vary considerably between the reported series. Part of this discrepancy may be due to varying definitions of ‘cure’ or ‘remission’ after TSS, which remain contentious in CD (5;14;16). Reported cure rates using TSS in adult CD vary between 72-96%, but may be lower in pediatric series (5;8;13;26;28;29). In
our center, TSS had a current cure rate of 59% in pediatric CD defining 'cure' strictly as being reflected by a post-operative serum cortisol of less than 50 nM. Other pediatric series report cure rates ranging from 45% to 78% (12;25;27;30-32) but few report rates of greater than 90% (1;33).

Surgical failure is often attributed to technical difficulties in children. However, it is has been suggested that CD in children may be a more aggressive disease (25). In adults, corticotroph macroadenomas have lower cure rates of between 50-60% (8). Pediatric macroadenomas are often not cured by TSS and require additional treatment (12;24). This is consistent with our single macroadenoma patient who required pituitary irradiation in addition to TSS to achieve cure.

Good prognostic features of TSS in adult-onset CD include classic biochemical data, a positive MRI scan and a clean resection of the adenoma (34-36). More favorable cure rates after TSS have also been attributed to a smaller-sized pituitary adenoma and pathological confirmation of the adenoma after resection (29;37). Surgical failure has been associated with a lack of neuroradiological or surgical evidence of a pituitary adenoma, a severe clinical picture and the presence of major depression (28). Other negative prognostic factors include invasive tumor and macroadenoma (8). Other authors have reported that adenoma size had no effect on remission rates (28); however McCance found that neither the operative finding nor the histology was related to the surgical outcome (11). No published pediatric CD series attempt to identify specific prognostic factors, which may favor cure by
TSS or identify the high-risk patients who are more likely to require second-line therapy. In our series, patients cured by TSS alone were significantly older than those not cured. There was no difference in clinical features of CD at diagnosis or the length of the history between the cured and not-cured groups.

Pituitary imaging in CD due to microadenomas is often normal: 58% of tumors in adult CD were identified on CT or MR scanning (4) or 60-70% on MR (10). In pediatric CD, only 22-23% of CT scans (13) and 33-72% of MRI scans indicated the presence of a microadenoma (1;12;13). In our series pituitary imaging was relatively unhelpful, showing a normal appearance in over half of the patients. Paradoxically, a higher cure rate was noted in the patients with a normal pituitary image suggesting that identification of an adenoma by CT/MR is a poor predictor of surgical outcome. This might indicate that the smallest tumors, not readily imaged, are the most amenable to surgical cure.

Pre-operative localization of the microadenoma has become part of the investigation of CD. Bilateral simultaneous inferior petrosal sinus sampling with CRH administration is now routine in the investigation of adult patients (3;8;22) and experience in pediatric patients is growing (1;13;21). BSIPSS confirmed both central and lateralized ACTH secretion in a high percentage of patients. High-jugular vein sampling also gave positive information, as has been previously reported (21;38). Corticotroph microadenomas are commonly found intra-operatively to lie in the midline in the central mucoid wedge of the pituitary (8). We demonstrate that the presence of a midline lesion, which
does not lateralize ACTH secretion on BSIPSS, may still be associated with a favorable surgical outcome. Adenoma position was confirmed at surgery in a very high percentage of patients who demonstrated ACTH lateralization. It is possible, though not proven by our findings, that identification of the site of ACTH secretion contributed to successful surgical outcome. While the numbers are small and not statistically significant, our data suggest that both the apparent presence of tumor at operation, and a positive histology for a corticotroph adenoma, are associated with an increased cure rate.

Post-operative hypopituitarism was uncommon in our series. This reflects the small size of the microadenomas and the aim of the surgeon to leave normal pituitary tissue. This is consistent with other pediatric experience (12). The high rate of post-operative GH deficiency has been previously reported (39).

Our data support the current view that selective adenomectomy is a safe and effective first-line treatment for pediatric CD. TSS cured 59% of 27 patients over a 21-year period, with a higher age favoring cure, as do an identifiable tumor seen at surgery and positive histology. In addition, the introduction of BSIPSS into the investigation of pediatric CD has been associated with an improvement in cure rate.
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F, female; M, male; TSS, transphenoidal selective adenomectomy; BSIPSS, bilateral simultaneous inferior petrosal sinus sampling; IPSG, inferior petrosal sinus gradient; CRH, corticotrophin-releasing hormone; Neg, negative; ML, midline; R, right side; L, left side.
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<th>Total patients (n)</th>
<th>Adenoma MR / CT image (n)</th>
<th>Concordance of image with surgery (n)</th>
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<td>15 (56%)</td>
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n, number of patients; MR, magnetic resonance imaging; CT, computed tomography scanning; TSS, transphenoidal selective adenomectomy.
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n, number of patients; BSIPSS, bilateral simultaneous inferior petrosal sinus sampling; TSS, transphenoidal selective adenomectomy.
References


