CLINICAL STUDY

Factors influencing cure by transsphenoidal selective adenomectomy in paediatric Cushing's disease

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Abstract

Objective: Early diagnosis and effective treatment of paediatric 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 centres. In our paediatric CD patient group we have assessed the possible factors which may influence cure by TSS.

Subjects and methods: From 1983–2004, 27 paediatric patients (16 males, 11 females; mean age $\pm$ s.d., 13.1 $\pm$ 3.2 yr; range, 6.4–17.8 yr) with CD were managed in our centre and underwent TSS. Sixteen patients (59%), seven males and nine females (mean age $\pm$ s.d., 14.2 $\pm$ 2.5 yr; range, 8.2–17.8 yr), were cured (post-operative serum cortisol $<$ 50 nM). Eleven patients, nine males and two females (mean age $\pm$ s.d., 11.5 $\pm$ 3.6 yr; range, 6.4–17.8 yr) had post-operative cortisol levels above 50 nM (2–20 days), with mean serum cortisol levels at 09:00 h of 537 nM (range 269–900 nM) indicating a lack of cure. These 11 patients received external beam pituitary radiotherapy (RT). One patient with a pituitary macroadenoma had a post-operative cortisol level of $<$ 50 nM but 0.8 yr later showed an elevated cortisol and residual disease.

Results: The patients cured by TSS alone were significantly older than those not cured ($P = 0.038$; Student's *t* test). All patients had CT/MRI pituitary imaging: 14 were reported to have microadenomas and one macroadenoma, while 12 were reported as normal. Bilateral simultaneous inferior petrosal sinus sampling (BSIPSS) with i.v. corticotropin-releasing hormone (CRH) administration was introduced as a pre-operative investigation in 1986 and was performed in 21 patients (78%), on BSIPSS, 16 (76%) had evidence suggesting pituitary adrenocorticotrophic hormone (ACTH) secretion (central to peripheral (IPS:P) ACTH ratio after CRH of ≥ 3.0) and 16 (76%) showed lateralisation 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 16 patients showing lateralisation of ACTH secretion, 12 (75%) were cured by TSS. Of the four without lateralisation 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.

Conclusion: Over a 21-year period selective adenomectomy by TSS cured 59% of all paediatric CD patients, with higher age favouring cure. Introduction of BSIPSS resulted in the demonstration of a high rate of lateralisation of ACTH secretion consistent with the surgical identification of the adenoma, and therefore appears likely to have contributed to the higher surgical cure rate.

European Journal of Endocrinology 152 825–833

Introduction

Cushing's disease (CD) is defined as hypercortisolaemia due to a pituitary corticotroph adenoma. CD is the commonest cause (49–71%) of adult-onset Cushing's syndrome (CS) (1, 2, 3, 4) and also accounts for approximately 75% of paediatric CS (5, 6, 7). CD in childhood and adolescence is rare but associated with

significant morbidity (5, 6). Therapy directed towards the rapid normalisation of serum cortisol is essential (8), particularly in paediatric patients (9, 5). Transsphenoidal surgery (TSS) with selective removal of the adenoma is considered the first-line treatment of choice for adult and childhood-onset CD. TSS is regarded as safe with low reported rates of hypopituitarism in adults (8, 10, 11) and children (9, 12, 13).

Adult CD studies show variable surgical success rates depending on which definition of cure is adopted (14, 15, 16). In the few reported paediatric CD studies available, cure or remission rates after TSS have been reported as between 45% and 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 paediatric patients. We have therefore examined the possible factors, including age, length of history, clinical and endocrine features and investigations which may influence cure by TSS, in a series of paediatric-onset CD patients.

Subjects and methods

Patients

Twenty-seven patients, 16 males and 11 females (mean age $\pm$ S.D., 13.1 ± 3.2 yr; range, 6.4–17.8 yr) with CD were investigated and treated at St Bartholomew's and The Royal London Hospitals (London, UK) from 1983–2004 (Tables 1 and 2). The mean length of history of CD was 2.5 yr (range, 0.5–6.0 yr). Short stature (height S.D.S., ≤ -2.0) was present in 44% of patients (mean height S.D.S., -1.9 ; range, -4.2 – -1.2) and all the patients had a history of weight gain (mean BMI S.D.S., 2.4; range, 0.5–4.1) (Table 1).

Diagnosis of CD

The diagnosis of CD 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; 0.5 mg, 6 hourly for 48 h) (1). In addition, the patients either showed suppression of serum cortisol by more than 50% of the baseline value in a high-dose dexamethasone suppression test (2 mg, 6 hourly for 48 h) (1, 18) or an exaggerated response of serum cortisol during a CRH test (1 μ g/kg i.v.; range 106–554%) (18), or both.

Pubertal staging

Puberty was staged, at diagnosis, according to Tanner's criteria (19, 20). Prepubertal males had testicular volumes < 4 ml. Eleven were pre-pubertal, 14 patients were in puberty while two patients were post-pubertal at diagnosis (Table 1).

Protocol for BSIPSS

Bilateral simultaneous inferior petrosal sinus sampling (BSIPSS) with i.v. administration of 100 mcg CRH was introduced in 1986 and performed in 21 patients aged 8.2–17.8 yr. In four of the 21 patients, samples were obtained from the high jugular veins. BSIPSS was performed without sedation or systemic anaesthesia, as previously described (21). Informed written consent was obtained from the patients or their parents, or both, 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 ≥ 2.0 pre-CRH and ≥ 3.0 post-CRH stimulation were taken as indicative of pituitary ACTH secretion i.e. CD (1).

Evidence of lateralisation of ACTH secretion An inter-petrosal sinus gradient (IPSG) of ≥ 1.4 , between the ACTH values after CRH treatment, was taken as suggestive of lateralisation of the pituitary adenoma (1, 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 measured using a specific two-site immunometric assay from 2002, prior to which we used an inhouse extracted radioimmunoassay, using ACTH-(1–39) reference standards from Bachem Chemicals (Torrance, CA, USA); the assays were correlated at change-over and shown to be equivalent in the range assessed. The inter- and intra-assay coefficients of variation were less than 8% for both assays. Serum cortisol was determined by Bayer-Technicon Immuno 1 analyser (Newbury, UK).

Pituitary imaging

CT and/or MRI imaging was performed preoperatively in all patients, as previously described (21) (Table 2).

Transsphenoidal selective adenomectomy

TSS was attempted as first-line therapy in all 27 patients. The surgery was performed by the same surgeon (Farhad Afshar) in 24 of 27 patients. Operative findings of the localisation of the corticotroph microadenoma are based on the operation notes recorded at the time of surgery. Locations were categorised as right-sided, left-sided or midline. Hydrocortisone was given for a minimum of 24 h post-operatively. Eleven patients (nine males, two females) were not cured by

Table 1 Clinical features of paediatric adolescent Cushing's disease (CD).

Patient no.	Sex	Age at diagnosis (yr)	Diagnosis	Treatment	Length of history (yr)	Pubertal stage at diagnosis	Ht S.D.S	BMI S.D.S.	Hyper-tension	Acne	Hirsutism	Head-aches	Fatigue	Emotional lability
1	M	16.6	Micro-adenoma	TSS RT	5.0	G3 (12/10)	-4.2	2.8	+	-	+	+	-	-
2	M	6.4	Micro-adenoma	TSS RT	0.8	G2 (2/2)	-1.6	5.1	-	-	-	-	-	-
3	M	13.7	Micro-adenoma	TSS RT	2.0	G3 (3/3)	-1.8	2.3	+	+	+	-	-	+
4	M	17.8	Micro-adenoma	TSS RT	1.0	G4 (15/15)	-0.7	1.7	-	-	-	-	-	+
5	M	7.6	Micro-adenoma	TSS RT	2.0	G1 (2/2)	-3.7	4.0	+	-	+	-	+	-
6	F	10.6	Micro-adenoma	TSS RT	0.8	B1 M0	-1.1	2.3	+	-	+	-	-	-
7	M	9.4	Micro-adenoma	TSS RT	0.5	G2 (2/2)	1.2	1.9	+	-	+	-	+	+
8	M	8.4	Micro-adenoma	TSS RT	1.0	G2 (1/1)	-3.5	2.9	-	+	+	+	+	+
9	M	10.4	Micro-adenoma	TSS RT	2.5	G3 (4/4)	-0.7	3.3	+	-	+	-	+	-
10	F	11.9	Macro-adenoma	TSS RT	3.0	B2 P5	-2.0	2.5	-	+	+	+	-	+
11	M	13.4	Micro-adenoma	TSS RT	2.5	G3 (4/4)	-0.5	3.6	+	-	+	-	-	-
12	M	8.2	Micro-adenoma	TSS	2.0	G2 (2/2)	-1.5	3.0	+	-	+	-	-	+
13	M	10.8	Micro-adenoma	TSS	2.5	G1 (2/1)	-2.8	2.6	-	+	-	-	+	-
14	F	12.6	Micro-adenoma	TSS	2.0	B4 M0	-1.9	3.0	+	+	+	+	+	+
15	F	14.3	Micro-adenoma	TSS	0.5	B4 M0	-0.3	2.3	+	+	+	+	+	+
16	F	16.4	Micro-adenoma	TSS	3.5	B4 M0	-2.3	0.7	-	+	-	+	+	-
17	F	16.7	Micro-adenoma	TSS	4.0	Adult	-0.5	2.9	-	+	+	+	-	-
18	M	17.8	Micro-adenoma	TSS	1.0	Adult	-1.0	1.7	-	-	-	+	+	-
19	M	13.6	Micro-adenoma	TSS	4.0	G2 (3/3)	-3.6	2.1	-	+	-	+	+	-
20	F	14.8	Micro-adenoma	TSS	2.0	B3 M0	-2.9	0.8	-	-	-	+	+	+
21	M	11.7	Micro-adenoma	TSS	2.0	G1 (2/2)	-1.8	3.1	-	-	-	+	+	+
22	F	13.2	Micro-adenoma	TSS	4.0	B3 M0	-2.8	2.3	+	-	-	+	-	+
23	M	15.6	Micro-adenoma	TSS	4.0	G4 (12/12)	-1.1	3.0	-	+	+	-	+	-

Table 1 Continued

Patient no.	Sex	Age at diagnosis (yr)	Diagnosis	Treatment	Length of history (yr)	Pubertal stage at diagnosis	Ht s.d.s	BMI s.d.s	Hyper- tension	Acne	Hirsutism	Head- aches	Fatigue	Emotional lability
24	M	16.8	Micro-adenoma	TSS	2.0	G4 (8/8)	-3.3	1.6	+	-	+	-	-	-
25	F	15.9	Micro-adenoma	TSS	6.0	B4 M0	-2.7	1.2	-	+	+	+	+	-
26	F	13.8	Micro-adenoma	TSS	0.6	B5 M0	-0.5	2.2	-	+	+	+	+	+
27	F	14.6	Micro-adenoma	TSS	6.0	B3 M0	-4.2	0.5	+	+	+	-	-	+

F, female; M, male; TSS, transsphenoidal selective adenomectomy; RT, radiotherapy; Pubertal status: genitalia stage (G), breast stage (B), no menarche (M0). Values in parentheses indicate testicular volume in ml (right/left). Ht, height; BMI, body mass index; s.d.s, standard deviation score; +, clinical feature present at diagnosis; -, clinical feature absent at diagnosis.

TSS. These patients received external beam pituitary irradiation (RT) (23).

Definition of cure of CD

After TSS (1–8 days), serum cortisol levels were measured daily at 09:00 h at least 12 h after the last dose of hydrocortisone. A minimum of three post-operative serum cortisol levels of 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

Values are stated as mean $\pm$ s.d. 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%) (seven males and nine females; mean age $\pm$ s.d., 14.2 ± 2.5 yr; range, 8.2–17.8 yr; ten prepubertal, four pubertal, two post-pubertal) were cured by TSS. Eleven patients (nine males and two females; mean age $\pm$ s.d., 11.5 ± 3.6 yr; range, 6.4–17.8 yr; seven prepubertal; four pubertal) were not cured by TSS (mean post-operative (2–20 days) serum cortisol levels at 09:00 h of 537 nM; range 269–900 nM) and received second-line treatment with pituitary RT (Table 2). 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 MRI was consistent with a pituitary microadenoma in 14 patients; a macro-adenoma was reported in one patient and 12 were reported as normal. All the corticotroph micro-adenomas were small (< 5 mm) and there was no difference in adenoma size between the patients cured by TSS and those requiring RT. There was no invasive growth into the cavernous sinus noted on any of the pituitary images. Ten of 12 (83%) patients with a normal pituitary CT/MRI scan and 7 of 14 (50%) patients reported to have a pituitary micro-adenoma at diagnosis were cured by TSS alone (Table 2). One patient with a pituitary

Table 2 Details of patients, pituitary imaging, BSIPSS and TSS.

Patient no.	Sex	Age at diagnosis (yr)	Diagnosis	Treatment	CT/MRI	Results of pituitary imaging	Site of ACTH sampling	Lateralisation by ACTH sampling	Peak IPS/P ratio after i.v. CRH	IPS ratio after i.v. CRH	Adenoma position at surgery	Histology
1	M	16.6	Micro-adenoma	TSS RT	CT	N	–	–	–	–	Not seen	N
2	M	6.4	Micro-adenoma	TSS RT	MRI	ML	–	–	–	–	Not seen	N
3	M	13.7	Micro-adenoma	TSS RT	MRI	ML	–	–	–	–	R	adenoma
4	M	17.8	Micro-adenoma	TSS RT	MRI	N	IPS	L	13.5	7.1	R	N
5	M	7.6	Micro-adenoma	TSS RT	MRI	R	–	–	–	–	R	N
6	F	10.6	Micro-adenoma	TSS RT	MRI	L	IPS	R	28.6	20.8	R	N
7	M	9.4	Micro-adenoma	TSS RT	MRI	R	–	–	–	–	R	adenoma
8	M	8.4	Micro-adenoma	TSS RT	MRI	R	IPS	R	10.4	5.9	R	N
9	M	10.4	Micro-adenoma	TSS RT	MRI	ML	IPS	No	9.1	1.1	ML	adenoma
10	F	11.9	Macro-adenoma	TSS RT	MRI	–	–	–	–	–	–	adenoma
11	M	13.4	Micro-adenoma	TSS RT	MRI	R	IPS	R	2.1	1.7	ML	adenoma
12	M	8.2	Micro-adenoma	TSS	MRI	N	IPS	R	17.1	10.7	R	adenoma
13	M	10.8	Micro-adenoma	TSS	MRI	N	HJ	No	1.0	1.3	ML	adenoma
14	F	12.6	Micro-adenoma	TSS	MRI	N	IPS	R	6.0	3.3	R	N
15	F	14.3	Micro-adenoma	TSS	MRI	R	HJ	L	2.5	2.1	L	adenoma
16	F	16.4	Micro-adenoma	TSS	CT	N	IPS	R	157.2	7.1	R	adenoma
17	F	16.7	Micro-adenoma	TSS	MRI	R	HJ	L	21.1	8.5	L	adenoma
18	M	17.8	Micro-adenoma	TSS	MRI	R	IPS	R	7.5	5.3	R	adenoma
19	M	13.6	Micro-adenoma	TSS	MRI	N	HJ	R	4.7	2.7	R	N
20	F	14.8	Micro-adenoma	TSS	MRI	N	IPS	R	5.4	5.4	R	N
21	M	11.7	Micro-adenoma	TSS	MRI	R	HJ	L	10.0	10.5	L	N
22	F	13.2	Micro-adenoma	TSS	MRI	N	IPS	No	6.2	1.1	ML	adenoma
23	M	15.6	Micro-adenoma	TSS	MRI	L	IPS	No	3.0	–	ML	N

Table 2 Continued

Patient no.	Sex	Age at diagnosis (yr)	Diagnosis	Treatment	CT/MRI	Results of pituitary imaging	Site of ACTH sampling	Lateralisation by ACTH sampling	Peak IPS/P ratio after i.v. CRH	IPS ratio after i.v. CRH	Adenoma position at surgery	Histology
24	M	16.8	Micro-adenoma	TSS	MRI	N	IPS	R	1.1	1.4	R	adenoma
25	F	15.9	Micro-adenoma	TSS	MRI	N	IPS	No	1.6	1.3	L	adenoma
26	F	13.8	Micro-adenoma	TSS	MRI	ML	IPS	L	26.2	1.9	ML	adenoma
27	F	14.6	Micro-adenoma	TSS	MRI	N	IPS	L	19.5	3.3	L	adenoma

F, female; M, male; TSS, transsphenoidal selective adenomectomy; RT, radiotherapy; CT, computed tomography imaging; MRI, magnetic resonance imaging; N, normal; ML, midline; R, right side; L, left side; IPS, inferior petrosal sinus; P, peripheral; CRH, corticotrophin-releasing hormone; BSIPSS, bilateral simultaneous inferior petrosal sinus sampling; IPS, interpetrosal sinus; No, number; —, investigation not done.

macro-adenoma had 09:00 h serum cortisol of < 50 nM on three days post-surgery but 0.8 yr later showed elevated serum cortisol levels and recurrent disease. Subsequently, she achieved cure after RT. In seven of the 15 patients reported to have an adenoma (47%) the pituitary imaging correctly localised the position of the adenoma (Table 3).

Confirmation of central ACTH secretion and lateralisation of the pituitary adenoma by BSIPSS

BSIPSS with CRH administration was introduced in our paediatric 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 i.v. CRH, mean, 22.0; range, 3.0–157.2) (Table 2) while in 16 (76%) there was lateralisation of ACTH secretion (IPSG ≥ 1.4 after i.v. CRH, mean, 5.7; range, 1.4–20.8) (Table 4).

Sixteen of the 21 patients (76%) undergoing BSIPSS were cured by TSS (Table 4). Of the 16 patients with lateralisation of ACTH secretion, 12 (75%) were cured by TSS (Tables 2 and 4). In four patients without lateralisation of ACTH, suggesting a midline lesion (IPSG < 1.4 after i.v. CRH, mean, 1.2; range, 1.1–1.3), three (75%) were cured by TSS (Tables 2 and 4). In four patients, in whom samples were obtained from the high jugular veins, two demonstrated both central and lateralisation of ACTH secretion and only one ACTH lateralisation.

Operative and histological findings (Table 2)

An adenoma was visualised during surgery in all except two patients diagnosed with microadenomas. Of the microadenomas, 13 were right-sided (seven cured, six not cured by TSS), five left-sided (all cured by TSS) and six (four cured, two not cured by TSS) were in the central part of the gland (midline). The two patients without a tumour visualised at surgery were not cured by TSS and both had been operated on by a neurosurgeon other than Farhad Afshar. In addition, there seemed to be no association between the success of the transsphenoidal surgery and the length of experience of the surgeon, i.e. the patients were no more likely to be cured by TSS if they were operated on more recently. 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 4). In the three patients that demonstrated lateralisation from samples taken from

Table 3 Pituitary imaging, surgical identification of adenoma and cure by TSS.

Total patients (n)	Adenoma CT/MRI image (n)	Concordance of image with surgery (n)	Cure by TSS (n)
27	15 (56%)	7 (47%)	16 (59%)

n, number of patients; MRI, magnetic resonance imaging; CT, computed tomography imaging; TSS, transsphenoidal selective adenomectomy.

the high jugular veins, the correct lateralisation was confirmed at surgery.

Long-term outcome

The patients were followed-up for a mean $\pm$ S.D. period of 7.1 ± 5.3 yr (range 0.5–17.8 yr). 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 the patients that underwent TSS and RT, nine of 11 had only isolated GHD (17).

Discussion

Transsphenoidal surgery is recognised as the first-line treatment for Cushing's disease (CD) in adults and children. The main surgical goals are the localisation and selective removal of the ACTH-secreting tumour, 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 (4). In all age groups, micro-adenomas are the more common cause. Corticotroph macro-adenomas, although frequently reported in the adult literature, are much rarer in the paediatric age range (12, 24, 25). Many adult CD series report the efficacy of first-line TSS for the treatment of micro-adenomas 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). First-line TSS therapy, even when initially unsuccessful,

may confer protection against relapse following 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 (3, 14, 16). Reported cure rates using TSS in adult CD vary between 72–96%, but may be lower in paediatric series (3, 8, 13, 26, 29). In our centre, TSS had a current cure rate of 59% in paediatric CD, where cure was strictly defined as being reflected by a post-operative serum cortisol of less than 50 nM. Other paediatric series report cure rates ranging from 45% to 78% (12, 25, 27, 30, 31, 32), but few report rates of $> 90\%$ (5, 33).

Surgical failure is often attributed to technical difficulties in children. However, it has been suggested that CD in children may be a more aggressive disease (25). In our study we demonstrated that TSS performed in paediatric patients with CD by a single, experienced neurosurgeon is more likely to result in a successful surgical outcome. In adults, corticotroph macro-adenomas have lower cure rates of between 50–60% (8). Paediatric macro-adenomas are often not cured by TSS and require additional treatment (12, 24). This is consistent with our single macro-adenoma 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 discrete resection of the adenoma (34, 35, 36). More favourable 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 have included invasive tumour and macro-adenoma (8). Other authors, however, have reported that adenoma size had no effect on remission rates (26), while McCance and colleagues found that neither the operative findings nor the histology was related to the surgical outcome (11). No published paediatric CD studies attempt to identify specific prognostic factors, which may favour cure by TSS or identify

Table 4 BSIPSS results, surgical identification of adenoma and cure by TSS.

Total patients (n)	BSIPSS results		Concordance of BSIPSS result with surgery (n)	Cure by TSS (n)
	Lateralisation (n)	Non-lateralisation (n)		
21	16 (76%)	5	17 (81%)	16 (59%)

n, number of patients; BSIPSS, bilateral simultaneous inferior petrosal sinus sampling; TSS, transsphenoidal selective adenomectomy.

the high-risk patients who are more likely to require second-line therapy. In our research, patients cured by TSS alone were significantly older than those not cured. There was also a female preponderance in the group cured by TSS. However, this is more likely to reflect the previously described sex distribution of paediatric CD rather than gender itself directly affecting the surgical outcome (38). 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 micro-adenomas is often normal: 58% of tumours in adult CD were identified on CT or MRI scanning (2) or 60–70% on MR (10). In paediatric CD, only 22–23% of CT scans (13) and 33–72% of MRI scans indicated the presence of a micro-adenoma (5, 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/MRI is a poor predictor of surgical outcome. This might indicate that the smallest tumours, not readily imaged, are the most amenable to surgical cure.

Pre-operative localisation of the micro-adenoma has become part of the investigation of CD. BSIPSS with CRH administration is now routine in the investigation of adult patients (1, 8, 22) and experience in paediatric patients is growing (5, 13, 21). In approximately 90–95% of adult CD cases centralisation of ACTH secretion post-CRH is confirmed on BSIPSS (18). BSIPSS confirmed both central and lateralised ACTH secretion in a high percentage of patients. High-jugular vein sampling also gave positive information, as has been previously reported (21, 39). In several patients, there was a lack of centralisation of ACTH secretion on BSIPSS, but ACTH lateralisation was demonstrated, this might reflect the fact that BSIPSS is technically more challenging in children. However, in this group a negative catheter was associated with either positive suppression during a high-dose dexamethasone suppression test (HDDST) or a positive response to CRH, with no obvious ectopic ACTH source. Accordingly, pituitary exploration was still undertaken.

Corticotroph micro-adenomas 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 lateralise ACTH secretion on BSIPSS, may still be associated with a favourable surgical outcome.

Adenoma position was confirmed at surgery in a very high percentage of patients who demonstrated ACTH lateralisation. 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 tumour 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 micro-adenomas and the aim of the surgeon to leave normal pituitary tissue. This is consistent with other paediatric experience (12). The high rate of post-operative GH deficiency has been previously reported (40).

Our data support the current view that selective adenectomy is a safe and effective first-line treatment for paediatric CD. TSS cured 59% of 27 patients over a 21-year period, with a higher age favouring cure, as do an identifiable tumour seen at surgery and positive histology. Cure is also more likely to be achieved if the surgery is performed by an experienced neurosurgeon. In addition, the introduction of BSIPSS into the investigation of paediatric CD has been associated with an improvement in cure rate.

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Received 17 January 2005

Accepted 8 March 2005