

성인 쿠싱병의 치료성적과 예후인자*

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= Abstract =

Treatment Outcome and Prognostic Factors of Cushing's Disease in Adults

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Objectives : The authors analyzed the surgical series of Cushing's disease to evaluate the proper treatment policy and to verify the possible prognostic factors.

Material and Methods : Of 50 patients diagnosed as Cushing's disease and operated at Department of Neurosurgery of our institute between 1988 and 1999, 48 patients with available medical records were analyzed retrospectively. Mean follow-up period was 48 months(3 to 109 months). Preoperative diagnosis was made after evaluating the patients with multiple-stage endocrinological studies and 31 selective patients were evaluated with inferior petrosal sinus sampling(IPSS). Magnetic resonance imaging(MRI) and/or high resolution computerized tomography(CT) was done in all patients. A total of 51 transsphenoidal adenomectomy(TSA) were performed including 3 revision for initial surgical failure cases. Remission was decided on the basis of both endocrinological criteria and clinical status. Radiation and/or ketoconazole therapy were applied to failed cases. For the verification of prognostic factors, the authors evaluated the statistical significance of multiple variables over remission rate by chi-square test.

Result : Sensitivity of IPSS for central localization was 93.5% which was better than that of MRI(87.5%). But for lateralization, it was 72.4% for IPSS versus MRI 90.5%. Success rate of TSA was 82%(42/51) and recurrence rate was 9%(4/48). When including adjuvant treatments for surgically failed cases, overall success rate was 89.6% and all of 3 reoperated cases(TSA) due to recurrence were successful. Significant complication occurred in 7.8%(4/51) after TSA including hypopituitarism, diabetes insipidus, and visual loss. Non-existence of tumor in MRI and prolonged symptom duration(>3 years) were significant prognostic factors.

Conclusion : TSA can be considered as initial treatment for Cushing's disease. In surgically failed cases, multiple treatment modality may improve the overall outcome and repeated TSA for recurrent cases seem to provide similar success.

KEY WORDS : Cushing's disease · Transsphenoidal adenomectomy · Surgical outcome · Prognostic factor.

서론

(Adrenocorticotrophic hormone, A-CTH) (Cushing's disease) (cortisol) 가 1 (Cushing syndrome) 가 100 0.7 2.4 5 50% 9). (transsphenoidal adenectomy, TSA) 1969 Hardy 가 TSA 63 83% (magnetic resonance imaging, MRI) TSA가 가 12-15) 48 10 가

(high dose dexamethasone suppression test, HDDST) 가 10mm (microadenoma), 10mm (macroadenoma) . MRI (dynamic MRI) , 31 (inferior petrosal sinuses sampling, IPSS) . IPSS ACTH ACTH 가 1.4 TSA 4 3 TSA 51 TSA (selective adenectomy), (partial adenectomy), (hemihypophysectomy) (total hypophysectomy) 1) , 2) , 3) LDDST 가

대상 및 방법

1988 1997 10 ACTH 50 가 48 6.6% 3 109 48 24 cortisol 60pg/ml , 3 25g/dl, 30 130g 가 (low dose dexamethasone suppression test, LDDST)

가 , MRI 가 chi-square test

결과

1. 역학적 분석

48 14 60 (32) 20 , 20 40 가 13 : 35 가 3

(Fig. 1).

2. 임상증상 및 징후

(Table 1).

30 (63%), 9 (24%)

40

(2 108) 가

가

3. 수술 전 내분비학적 검사

ACTH 65.9pg/ml

(10 201) cortisol 24 cortisol

32.4g/dl(13.1 59.8) 820 µg(106 4590)

. 40

LDDST HDDST LDDST

(2.5%) 가 39 (97.5%)

, HDDST 34 (85%)가

6 (15%)가

4. 신경방사선학적 검사

MRI

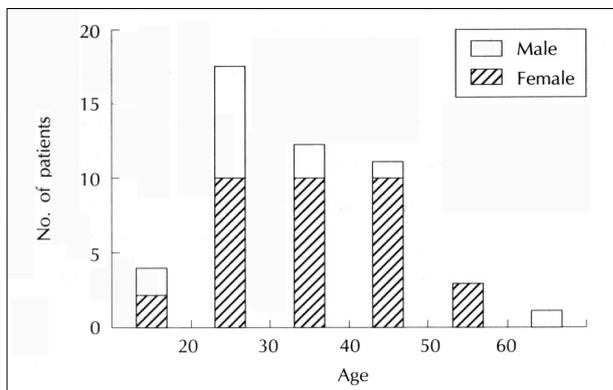


Fig. 1. Distribution of gender according to age.

Table 1. Presenting symptoms of Cushing's disease (N = 48)

Symptom	Patient	(%)
Obesity	40	(83%)
Hypertension	30	(63%)
Headache	21	(44%)
Easy bruise	17	(35%)
Fatigability	14	(29%)
Irregular menstruation	13	(27%)
Hirsutism	9	(19%)
Diabetes mellitus	9	(19%)
Visual acuity	8	(17%)
Palpitation	6	(13%)
Mental change	3	(6%)
Loss of libido	2	(4%)

42 (87.5%)

38 (18 , 20)

, MRI 가

MRI 90.5%(38/42)

100% . MRI

6.9mm ,

. MRI 6 41

가 7 1cm

. 31 IPSS 가

29 (93.5%)

MRI

29 21 (72.4%)

MRI가 IPSS

5. 치료

51 TSA 가 42

82% . 34

32 가 , 4

4

12 9 가 ,

1 가 (Table 2).

가 9

1) 가 7 , 2) MRI

IPSS 가 가 6 , 3)

가 가 5 , 4)

4 가

42 4 (9%)가

8, 10, 28, 54 . 4

30 , MRI 가

가 가 2 .

9 ketoconazole 3 가

, 2 ketoconazole 1

1 가 .

4 3 TSA , 1

(Table 3).

Table 2. Outcome according to operation method

Operation	Remission (%)	Failure (%)
Selective adenomectomy	32(94)	2(6)
Partial adenomectomy	0(0)	4(100)
Hemihypophysectomy	9(75)	3(25)
Total hypophysectomy	1(100)	0(0)

Table 3. Treatment and its result after surgical failure

Treatment	Number of cases	Result
Initial failure(N = 9)		
Radiation + Ketoconazole	6	3 remission(50%)
Ketoconazole only	2	1 remission(50%)
Follow-up loss	1	?
Recurrence(N = 4)		
Revision TSA	3	3 remission(100%)
Radiation	1	1 remission(100%)

Table 4. Analysis of possible prognostic factors and outcome

Prognostic factors	Remission(%)	Failure(%)	Statistics*
MRI localization			
Localized	36(86)	6(14)	p = 0.036
Unlocalized	3(50)	3(50)	
Symptom duration			
Under 36months	28(90)	3(9)	p = 0.030
Over 36months	11(64)	6(35)	
Tumor size			
Microadenoma	35(85)	6(14)	p = 0.077
Macroadenoma	4(57)	3(43)	
Preop s-ACTH level			
Below 65.9pg/ml	22(82)	5(18)	p = 0.963
Above 65.9pg/ml	17(81)	4(19)	
Preop s-cortisol level			
Below 32.4ug/dl	13(81)	3(19)	p = 1.000
Above 32.4ug/dl	26(81)	6(19)	
Preop u-cortisol level			
Below 820ug	13(68)	6(32)	p = 0.065
Above 820ug	26(90)	3(10)	
HT or DM			
Present	23(74)	8(26)	p = 0.091
Absent	16(94)	1(6)	

* : Chi-square test

48 43
89.6%

6. 합병증

2
1 4 7.8%

7. 예후인자

(Table 4).

3

Table 5. Surgical outcome of TSA in literature

Authors(year)	Success rate(%)	Recurrence rate(%)	Follow up (months)
Salassa, et al. (1978)	16/18(89)	0/16(0)	18
Hardy(1982)	63/75(84)	0/63(0)	21
Semple, et al.(1984)	17/19(89)	1/17(6)	40
Tagliaferri, et al.(1986)	19/23(76)	2/19(11)	39
Chandler, et al.(1987)	24/34(71)	-	-
Nakane, et al.(1987)	86/100(86)	8/86(9)	38
Guihaume, et al.(1988)	42/61(69)	6/42(14)	24
Mampalam, et al.(1988)	171/216(79)	9/171(5)	46
Arnott, et al.(1990)	24/28(86)	3/24(13)	22
Burke, et al.(1990)	44/54(82)	2/44(5)	56
Tindall, et al.(1990)	46/53(87)	1/46(2)	57
Robert, et al.(1991)	60/78(77)	5/60(8)	77
Tahir, et al.(1992)	34/45(76)	7/34(21)	69
Trainer, et al.(1993)	39/48(81)	3/39(8)	-
Ram, et al.(1994)	205/222(92)	-	-
Bochicchio, et al(1995)	510/668(76)	65/510(13)	-
Present series(2000)	42/51(82)	4/42(10)	48
Total	1418/1759(80.6)	116/1213(9.6)	

, MRI 가

, , 24
cortisol 820g 가

ACTH cortisol ,
가 .

7 가 1
가 4 가 .
2 가 가 .

고 찰

TSA가

가 20

가

(Table

5)^{1)2)5)11)12)17)18)20 - 23)25)26)28)29)}

82%

. MRI

가 , (2) 1 13 가
, (3) , (4) 가
corticotropin , (5) TSA 가
, (6) 2 가
, (7) 50%, 85% 가
4)7)8)11)18)25)28). 8)16)20).
ketoconazole
가 , MRI 가
가 가 20). TSA
MRI 가 가 71% , Friedman 10) 73%
26% Nel -
son 가 TSA
, MRI, IPSS 가
IPSS 가 93.5% 가 가
MRI IPSS 가
가 가
5 20% 2)18)24)28). , MRI
가 2 4 2)11)15). Bo -
chicchio 2) 104 ,
(1) cor - 3)8)24). MRI 가
tisol , (2) 가
, (3) cortisol 가
, (4) 가
2)18)24)28). 9% 가 24 cortisol 가
54 가
30
결 론
가 , 1 48
2 TSA가
, (82%) 1
가

TSA

MRI IPSS
MRI가 100%

MRI 가

(>3)

- : 2000 3 9
- : 2000 7 25
- :

110 - 744 28

: 02) 760 - 2358, : 02) 744 - 8459

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References

- 1) Arnott RD, Pestell RG, McKelvie PA, et al : *A critical evaluation of transsphenoidal pituitary surgery in the treatment of Cushing's disease. Acta Endocrinol* 123 : 423-430, 1990
- 2) Bochicchio D, Losa M, Buchfelder M, et al : *Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery. J Clin Endocrinol Metab* 80-11 : 3114-3120, 1995
- 3) Boggan JE, Tyrrell JB, Wilson CB : *Transsphenoidal microsurgical management of Cushing's disease. Report of 100 cases. J Neurosurg* 59 : 195-200, 1983
- 4) Burch WM : *Cushing's disease-a review. Arch Intern Med* 145 : 1106-1111, 1985
- 5) Burke CW, Adams CB, Esiri MM, et al : *Transsphenoidal surgery for Cushing's disease. Clin Endocrin(Oxf)*33 : 525-537, 1990
- 6) Chandler WF, Scheingart DE, Lloyd RV, et al : *Surgical treatment of Cushing's disease. J Neurosurg* 66 : 204-212, 1987
- 7) Dyer EH, Civit T, Visot A, et al : *Transsphenoidal surgery for pituitary adenomas in children. Neurosurgery* 34-2 : 207-212, 1994
- 8) Estrada J, Boronat M, Mielgo M, et al : *The longterm outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med* 336 : 172-177, 1997
- 9) Extabe J, Vazquez JA : *Morbidity and mortality in Cushing's disease : An epidemiologic approach. Clin Endocrin(Oxf)*40 : 479, 1994
- 10) Friedman RB, Oldfield EH, Nieman LK, et al : *Repeat transsphenoidal surgery for Cushing's disease. J Neurosurg* 71 : 520-527, 1989
- 11) Guilhaume B, Bertagna X, Thomsen M, et al : *Transsphenoidal pituitary surgery for the treatment of Cushing's disease. J Clin Endocrinol Metab* 66 : 1056-1064, 1988
- 12) Hardy J : *Cushing's disease : 50 years later. Can J Neurol Sci* 9 : 375-380, 1982
- 13) Kim ES, Hong SC, Han DH, et al : *Cushing's disease Clinical analysis and surgical outcome in 16 cases. J Korean Neurosurg* 21(1) : 14-22, 1992
- 14) Kim JS, Jung HW, Kim HJ, et al : *Diagnosis and treatment outcome in ACTH-producing pituitary adenomas. J Korean Neurosurg* 24(7) : 814-819, 1995
- 15) Lee YY, Kim JS, Mun BS, et al : *The results of transsphenoidal microsurgery for pituitary microadenoma in Cushing's disease. Korean J Medicine* 53(6) : 811-816, 1997
- 16) Leinung MC, Kane LA, Scheithauer BW, et al : *Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. J Clin Endocrinol Metab* 80(8) : 2475-2479, 1995
- 17) Mampalam TJ, Tyrrell JB, Wilson CB : *Transsphenoidal microsurgery for Cushing's disease. Ann Intern Med* 15 : 487-493, 1988
- 18) Nakane T, Kuwayama A, Watanabe M, et al : *Long term results of transsphenoidal adenomectomy in patients with Cushing's disease. Neurosurgery* 21 : 218-225, 1987
- 19) Post FA, Soule SG, De Villiers JC, et al : *Pituitary function after selective adenomectomy for Cushing's disease. Br J Neurosurg* 9 : 41-46, 1995
- 20) Ram Z, Nieman LK, Cutler GB, et al : *Early repeat surgery for persistent Cushing's disease. J Neurosurg* 80 : 37-45, 1994
- 21) Robert F, Hardy J : *Cushing's disease : A correlation of radiological, surgical and pathological findings with therapeutic results. Pathol Res Pract* 187 : 617-621, 1991
- 22) Salassa RM, Laws ER Jr, Carpenter PC, et al : *Transsphenoidal removal of pituitary microadenoma in Cushing's disease. Mayo Clin Proc* 53 : 24-28, 1978
- 23) Semple CG, Thomson JA, Teasdale GM : *Transsphenoidal microsurgery for Cushing's disease. Clin Endocrin(Oxf)*21 : 621-629, 1984
- 24) Sonino N, Zielesny M, Fava GA, et al : *Risk factors and long term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab* 81 : 2647-2652, 1996
- 25) Tagliaferri M, Berselli ME, Loli P : *Transsphenoidal microsurgery for Cushing's disease. Acta Endocrinol* 113 : 5-11, 1986
- 26) Tahir AH, Sheeler LR : *Recurrent Cushing's disease after transsphenoidal surgery. Arch Intern Med* 152 : 977-981, 1992
- 27) Thomas JP, Richards SH : *Long-term results of radical hypophysectomy for Cushing's disease. Clin Endocrin(Oxf)*19 : 629-636, 1983
- 28) Tindall GT, Herring CJ, Clark RV, et al : *Cushing's disease : results of transsphenoidal microsurgery with emphasis on surgical failures. J Neurosurg* 72 : 363-369, 1990
- 29) Trainer PJ, Lawrie HS, Verhelst J, et al : *Transsphenoidal resection in Cushing's disease : undetectable serum cortisol as the definition of successful treatment. Clin Endocrin(Oxf)* 38 : 73-78, 1993