

LE CONSEGUENZE DELLA TERAPIA

SESSIONE 4: L'IPOCORTICOSURRENALISMO

Il significato dell'ipocorticosurrenalismo dopo neurochirurgia

Antonio Stigliano

Dipartimento di Medicina Clinica e Molecolare Facoltà di Medicina e Psicologia Sapienza Università di Roma





guarigione



guarigione







guarigione







Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis

Ferdinand Roelfsema · Nienke R. Biermasz · Alberto M. Pereira



FOCUS ON PITUITARY TUMORS (11)

Management of Cushing disease

Nicholas A. Tritos, Beverly M. K. Biller and Brooke Swearingen

Surgical outcomes—remission criteria

in contrast to the diagnosis of Cushing disease, for which pertinent consensus criteria have been proposed, the criteria used to establish remission of Cushing disease are not universally agreed upon,





Consensus Statements

Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement

B. M. K. Biller, A. B. Grossman, P. M. Stewart, S. Melmed, X. Bertagna, J. Bertherat, M. Buchfelder, A. Colao, A. R. Hermus, L. J. Hofland, A. Klibanski, A. Lacroix, J. R. Lindsay, J. Newell-Price, L. K. Nieman, S. Petersenn, N. Sonino, G. K. Stalla, B. Swearingen, M. L. Vance, J. A. H. Wass, and M. Boscaro JCEM '08

Regressione dell'ipercortisolismo per:

- clinica
- residuo minima morbidità
- biochimica
- controllo a lungo termine dell'asse
- no recidiva





remissione clinica

















CLINICAL REVIEW: Cushing's Syndrome: Important Issues in Diagnosis and Management

James W. Findling and Hershel Raff

The most important treatment recommendation that an endocrinologist makes to a patient with Cushing's disease is referral to a neurosurgeon with extensive experience in operating on patients with corticotroph microadenomas. Even under the best circumstances, remission rates after transsphenoidal pituitary microsurgery range from 42 to 86% (70). Furthermore, even in patients who clearly have a clinical and biochemical remission (preceded by secondary adrenal insufficiency), there is a recurrence rate

of 5–25% (70). Consequently, there are many patients with Cushing's disease who either fail initial pituitary surgery or have a recurrence.





Endocrine Care

Outcome of Cushing's Disease following Transsphenoidal Surgery in a Single Center over 20 Years

Zaki K. Hassan-Smith, Mark Sherlock, Raoul C. Reulen, Wiebke Arlt, John Ayuk, Andrew A. Toogood, Mark S. Cooper, Alan P. Johnson, and Paul M. Stewart JCEM '12

pvibioon recidiva

Results: Median follow-up for clinical data was 4.6 yr. Three outcome groups were identified: <u>cure</u>, 72% (52 of 72); persistent disease, 17% (12 of 72); and disease recurrence, 11% (eight of 72). Median time to recurrence after initial remission was 2.1 yr (interquartile range, 1.3–3.1 yr). Mean follow-up for mortality was 10.9 yr.





Table 1 Outcome studies of transsphenoidal surgery for Cushing disease								
Study	Number of patients	Follow-up (mean or median in months)	Overall remission rate (% patients)	Recurrence rate (% patients)	Time to relapse (mean or median in months)			
Bochicchio et al.25	668	46	76	13	39			
Bakiri <i>et al.</i> 106	50	92	72	8	40			
Knappe et al.107	310	43	85		NA			
Sonino et al.19	103	72	77	26 (at 10 years)	72			
Blevins et al.29	106	62	85	16	8–142 (range)			
Invitti <i>et al.</i> 20	236	28	69	17	6-84 (range)			
Semple et al.14	105	NA	75	NA	NA			
Swearingen et al.15	161	96	85	7	68			
Barbetta et al.37	68	58	90	21	36			
Cavagnini et al.108	300	NA	70	15	NA			
Chee et al.27	61	88	79	15	76			
Estrada et al.34	109	61	69	21	12-110 (range)			
Rees et al.26	53	72	77	5	25			
Shimon et al.23	74	50	78	5	44			
Yap et al.30	89	92	69	11	36			
Chen et al.36	174	60	82	14	28			
Flitsch et al.109	147	61	98	5.5	44			
Pereira et al.41	78	86	72	9	84			
Hammer et al.21	289	133	82	9	59			
Rollin et al.22	48	58	88	5	60			
Salenave et al.110	54	19.9	82	19.5	19.9			
Atkinson et al.111	63	115	71	22	62			
Esposito et al.35	40	32	79.5	3	20			
Hofmann et al.112	100	18.8	75	4.8	NA			
Acebes et al.113	44	49	89	7.7	55			
Rollin et al.114	103	72	85	6.8	44			
Hofmann et al.115	426	72.3	68.5	15	73			
Prevedello et al.116	167	40	80	12.8	50			
Patil et al.18	215	45	85.6	17.4	39			
Fomekong et al.117	40	86	80	9.4	54			
Jagannathan et al.118	261	84	92	2	56			

All studies included 40 or more patients and were published since 1995. Abbreviation: NA, not available.

Tritos NA et al. Focus on Pituitary Tumors '11

ovibioon recidiva





Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis

Ferdinand Roelfsema · Nienke R. Biermasz · Alberto M. Pereira



SANT' ANDREA FACOLTÀ DI MEDICINA E

PSICOLOG1A



Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis

Ferdinand Roelfsema · Nienke R. Biermasz · Alberto M. Pereira



AZIENDA OSPEDALIERA SANT'ANDREA FACOLTÀ DI MEDICINA E PSICOLOGIA



SPECIAL FEATURE

Extensive Clinical Experience

Long-Term Predictive Value of Pos Concentrations for Cure and Risk Cushing's Disease

ALBERTO M. PEREIRA, MAARTEN O. VAN AKEN, HANS VAN NIENKE R. BIERMASZ, JAN W. A. SMIT, FERDINAND ROEI

0013-7227/01/\$03.00/0 Printed in U.S.A.

The Complete Normalization of th Function as the Criterion of Cure Surgery for Cushing's Disease



Diagnosis and Management of C Results of an Italian Multicentre

CECILIA INVITTI, FRANCESCA PECORI GIRALDI, MART							
FRANCESCO CATAGNINI, AND THE STUDY GROUP OF							
OF ENDOCRINODOGY ON THE PATHOPHYSIOLOGY OF							
HYPOTHALAMIC PITUITARY-ADRENAL AXIS†							

Transsphenoidal Microsurgery for Initial Outcome and Long-Term Re GARY D. HAMMER D BLAKE TYRRELL, KATHLEEN R. LAM ELIZABETH T. HAWKEGAN, SCOTT BELL, RIVA RAHL, AMY

European Journal of Endocrinology (2000) 143 227-234

CLINICAL STUDY

and Bruno Ambrosi

Cortisolo plasmatico h 8.00

- Cortisolo urinario 24 h
- Test al desametasone 1 mg
- Cortisolo salivare h 24
 - ACTH h 8.00
 - Test al CRH
- Test alla desmopressina

ISSN 0804-4643

f Cushing's Disease after Initial henoidal Surgery

lo, Shivanand P. Lad, Mary Lee Vance, Michael O. Thorner, R. Laws, Jr.

ORIGINAL ARTICLE

Endocrine Care

ter Transsphenoidal Surgery in 's Disease

Brooke Swearingen, Francesca Pecori Giraldi, as Hayden, Francesco Cavagnini,

t Salivary Cortisol Determination for g the Outcome of Transsphenoidal Surgery ng's Disease

asco, Joël Coste, Laurence Guignat, Lionel Groussin, Marie Annick Dugué, d, Xavier Bertagna, and Jérôme Bertherat

29-737

ISSN 0804-4643

hanges in 21 patients with recurrent successful pituitary surgery

Laurence Guignat 1, Carmen Carrasco $^{1,2},$ Jean Guibourdenche $^{3,5},$ and Jérôme Bertherat 1,2,3

ORIGINAL ARTICLE

Endocrine Care

Usefulness of the desmopressin test in the postoperative evaluation of patients with Cushing's disease

 0 , Chiara Dall'Asta, Laura Barbetta, Tiziana Re, Elena Passini, Giovanni Faglia

Postoperative Testing to Predict Recurrent Cushing Disease in Children

AZIENDA OSPEDALIERA SANT'ANDREA FACOLTÀ DI MEDICINA E PSICOLOGIA

Dalia L. Batista, Edward H. Oldfield, Margaret F. Kurst Constantine A. Stratakis





 Cortisolo h 8.00 dopo 24 h ultima dose idrocortisone: valutazione ripresa asse HPA

ACTH test: se cortisolo dosabile



Surgical management and outcomes in patients with Cushing disease with negative pituitary magnetic resonance imaging. *Yamada S, et al. World Neurosurg '12*

EUCORTISOLISMO

- Test al desametasone 1 mg
- ✓ Cortisolo < 2 µg/dl (< 50 nmol/L) nel 1° mese post-chirurgia
- ✓ Cortisolo < 3 µg/dl (< 84 nmol/L) per un periodo protratto
- ✓ Cortisolo > 5 μ g/dl (> 140 nmol/L)





EUCORTISOLISMO

- Cortisolo urinario 24 h
- Cortisolo plasmatico h 24
- Cortisolo salivare h 24



SANT' ANDREA

MEDICINA E

FACOLTA

Consensus Statements

Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement

B. M. K. Biller, A. B. Grossman, P. M. Stewart, S. Melmed, X. Bertagna, J. Bertherat, M. Buchfelder, A. Colao, A. R. Hermus, L. J. Hofland, A. Klibanski, A. Lacroix, J. R. Lindsay, J. Newell-Price, L. K. Nieman, S. Petersenn, N. Sonino, G. K. Stalla, B. Swearingen, M. L. Vance, J. A. H. Wass, and M. Boscaro JCEM '08

Cortisolo

- < 50 nmol/L (2 μg/dL)</p>
- 50 140 nmol/L (2 5 μg/dL)
- > 140 nmol/L (5 μg/dL)

Cortisoluria

- < 20 µg/24 h
- 20-100 μg/24 h
 - > 100 μg/24 h



PSICOLOGI/



remissione biochimica

ORIGINAL ARTICLE

The use of an ear function after tra

Nieke E. Kokshoorn · Johan Ferdinand Roelfsema · Anna Johannes W. A. Smit · Nien Alberto M. Pereira

The Postoperat Prediction of L Disease after T

EUCORTISOLISMO / IPERCORTISOLISMO

CRH test o DDAVP in:

✓ valutazione post-chirurgia: specificità e valore predittivo bassi

ר:

Rivalutazione per sospetta recidiva

John R. Lindsay, Edward H. Oldfield, Constantine A. Stratakis, and Lynnette K. Nieman

ing's disease Paolo Colombo¹, Chiara Dall'Asta, Laura Barbetta, Tiziana Re, Elena Passini, Giovanni Faglia

and Bruno Ambrosi

ISSN 0804-4643

est in the postoperative

in Response to

aghi, Massimo Giovanelli,

ng's Disease

stoperative Period

Vol. 84, No. 5 Printed in U.S.A

Cushing's Syndrome: tre Study*

ARTINA DE MARTIN, OF THE ITALIAN SOCIETY OF THE

European Journal of Endocrinology (20 CLINICAL STUDY

Sequential hormor Cushing's disease

Roula Bou Khalil¹, Camille Baud Stéphane Gaillard⁶, Xavier Berta

Managem

CRH	test	0	DDAVP	i

✓ Follow up







Nicholas A. Tritos, Beverly M. K. Biller and Brooke Swearingen

CLINICAL STUDY

Sequential hormonal changes in 21 patients with recurrent Cushing's disease after successful pituitary surgery

Roula Bou Khalil¹, Camille Baudry^{1,2,3,4}, Laurence Guignat¹, Carmen Carrasco^{1,2}, Jean Guibourdenche^{3,5}, Stéphane Gaillard⁶, Xavier Bertagna^{1,2,3} and Jérôme Bertherat^{1,2,3}

1. Aumento ACTH dopo CRH e DDVAP

2. Aumento cortisolo h 24

3. Aumento cortisolo urine 24 h







സ. remissione biochimica





Ipocortisolismo subclinico

SODClinico

Ipercortisolismo



Predictive factors for initial cure and relapse rate after pituitary surgery for Cushing's disease. *Pieters GF et al. JCEM* '89

Assessment of endocrine function after transsphenoidal surgery for Cushing's disease. McCance DE et al. Clin Endocrinol (Oxf) '93

Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. Trainer Pj et al. Clin Endocrinol (Oxf) '93

L'ipocortisolismo raggiunto entro due settimane dopo neurochirurgia rappresenta un criterio di remissione

'ipocortisolismo raggiunto entro due settimane d neurochirurgia rappresenta un criterio di remissio



Consensus Statements

Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement

B. M. K. Biller, A. B. Grossman, P. M. Stewart, S. Melmed, X. Bertagna, J. Bertherat, M. Buchfelder, A. Colao, A. R. Hermus, L. J. Hofland, A. Klibanski, A. Lacroix, J. R. Lindsay, J. Newell-Price, L. K. Nieman, S. Petersenn, N. Sonino, G. K. Stalla, B. Swearingen, M. L. Vance, J. A. H. Wass, and M. Boscaro JCEM '08

Part I: Criteria for Cure and Remission of ACTH-Dependent Cushing's Syndrome

In general, the initial treatment of choice for Cushing's disease is selective pituitary adenomectomy by a surgeon with extensive demonstrated experience in pituitary surgery. Tumor resection leads to corticosteroid deficiency because the remaining normal corticotroph cells have been suppressed by longstanding hypercortisolism. As a result, hypocortisolism provides an index of surgical success.



Consensus Statements

Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement

B. M. K. Biller, A. B. Grossman, P. M. Stewart, S. Melmed, X. Bertagna, J. Bertherat, M. Buchfelder, A. Colao, A. R. Hermus, L. J. Hofland, A. Klibanski, A. Lacroix, J. R. Lindsay, J. Newell-Price, L. K. Nieman, S. Petersenn, N. Sonino, G. K. Stalla, B. Swearingen, M. L. Vance, J. A. H. Wass, and M. Boscaro JCEM '08

Cortisolo



criteri di remissione

0013-7227/01/\$03.00/0 Printed in U.S.A. The Journal of Clinical Endocrinology & Metabolism 86(12):5695–5699 Copyright © 2001 by The Endocrine Society

The Complete Normalization of the Adrenocortical Function as the Criterion of Cure after Transsphenoidal Surgery for Cushing's Disease

JAVIER ESTRADA, JOSÉ GARCÍA-URÍA, CRISTINA LAMAS, JOSÉ ALFARO, TOMÁS LUCAS, SANTIAGO DIEZ, LUIS SALTO, AND BALBINO BARCELÓ

Transsphenoidal microsurgery is the standard treatment for patients with Cushing's disease. However, there is general lack of agreement regarding the definition of cure.





The Complete Normalization of the Adrenocortical Function as the Criterion of Cure after Transsphenoidal Surgery for Cushing's Disease

JAVIER ESTRADA, JOSÉ GARCÍA-URÍA, CRISTINA LAMAS, JOSÉ ALFARO, TOMÁS LUCAS, SANTIAGO DIEZ, LUIS SALTO, AND BALBINO BARCELÓ

TABLE 2. Postsurgical plasma cortisol, time of adrenal insufficiency and percentage of recurrences during follow-up in 58 patients with corrected hypercortisolism after transsphenoidal surgery for Cushing's disease

	Group I	Group II	Group III
Number of patients	33	8	17
Post-surgical plasma cortisol (nм)	46.9 ± 30.3	60.7 ± 38.6	306.2 ± 91
Months of adrenal insufficiency	18.2 (6–34)	¦ 10.4 (2–45)	г-Ө і
Recurrences, n (%)	1 (3.4)	4 (50)	11 (64.7)
Follow-up (months)	69.8 (18–175)	68.8 (15–198)	39.1 (6–103)
	-		



The complete normalization of the adrenocortical function, which is always preceded by postsurgical hypocortisolism, is associated with a very low recurrence risk and should be considered, in our opinion, the main criterion of surgical cure in Cushing's disease. (J Clin Endocrinol Metab 86: 5695–5699, 2001)



Long-Term Predictive Value of Postsurgical Cortisol Concentrations for Cure and Risk of Recurrence in Cushing's Disease

ALBERTO M. PEREIRA, MAARTEN O. VAN AKEN, HANS VAN DULKEN, PIETER J. SCHUTTE, NIENKE R. BIERMASZ, JAN W. A. SMIT, FERDINAND ROELFSEMA, AND JOHANNES A. ROMIJN







Extensive Clinical Experience

Late Recurrences of Cushing's Disease after Initial Successful Transsphenoidal Surgery

Chirag G. Patil, Daniel M. Prevedello, Shivanand P. Lad, Mary Lee Vance, Michael O. Thorner, Laurence Katznelson, and Edward R. Laws, Jr. JCEM '08



Recurrence rate in patients with postoperative serum Cortisol >2 micrograms/dl
Recurrence rate in patients with postoperative serum corisol <=2 micrograms/dl</p>





Endocrine Care

Delayed Remission after Transsphenoidal Surgery in Patients with Cushing's Disease

Elena Valassi, Beverly M. K. Biller, Brooke Swearingen, Francesca Pecori Giraldi, Marco Losa, Pietro Mortini, Douglas Hayden, Francesco Cavagnini, and Anne Klibanski JCEM '10





- Remissione prolungata: cortisolo basso per almeno 6 mesi con necessità di terapia sostitutiva
- Remissione ritardata: cortisolo/cortisoluria normale o elevata per 1-3-6 mesi successivi all'intervento chirurgico







- Cellule corticotrope non tumorali che continuano ad avere una normale secrezione senza indurre ipocortisolismo
- Cellule corticotrope tumorali residuali in numero basso per stimolare una dosabile secrezione di cortisolo sia basale che stimolata
- Macroadenoma (ruolo dell'ACTH)
- Interferenza degli inbitori della steroidogenesi
- Terapia steroidea
- Iperplasia surrenalica con parziale autonomia per la cronica esposizione all'ACTH



Necrosi tardiva delle cellule adenomatose residue



No linee guida

- Fattori rischio recidiva:
- ✓ Cortisolo post chirurgia
- Terapia sostitutiva
- ✓ Dimensioni adenoma, invasività, sede



follow

Cushing's disease. Bertagna X et al. Best Pract Res Endocrinol Metab '09

Follow up personalizzato:

- ✓ 1-7 gg post-chirurgia
- ✓ Dopo 1, 3 6 mesi
- ✓ Ogni 6 mesi per 5 anni
- ✓ Ogni anno dopo 5 anni dalla chirurgia



vollot

 Impossibilità di stabilire quali pz sono realmente "curati" nel periodo post-chirurgico

Attendere nadir del cortisolo (fino a 6 mesi)

Necessità di un follow up esteso (tutta la vita?)

"Remissione" termine più corretto rispetto a "guarigione"





AZIENDA OSPEDALIERA SANT' ANDREA FACOLTÀ DI MEDICINA E PSICOLOGIA



conclusioni

