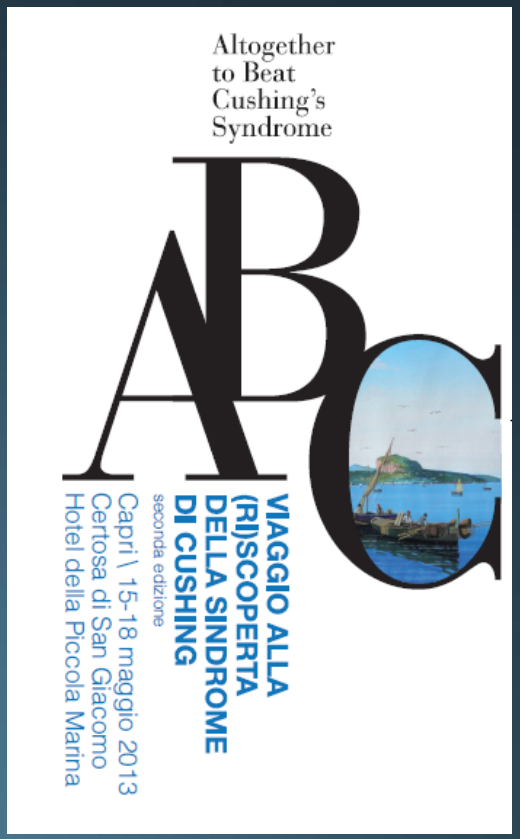

Sindrome di Nelson: Approccio terapeutico

Giuseppe Reimondo
Medicina Interna 1 ad Indirizzo Endocrinologico
AOU San Luigi Gonzaga Orbassano
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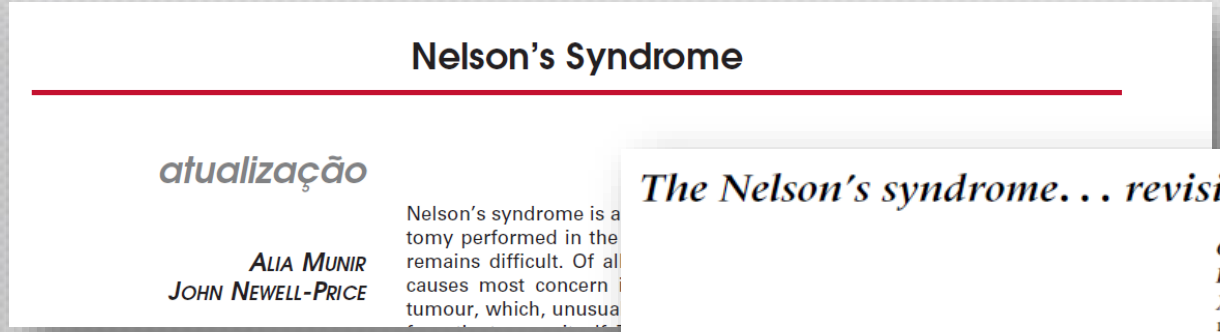
La storia del paziente

- Neurochirurgia non efficace
- Terapia medica non efficace
- Radioterapia non efficace
- Surrenectomia bilaterale

I problemi terapeutici

- Tumore refrattario/resistente
- Terapie pregresse
- Invasione/aggressività della lesione

Early treatment vs. observation

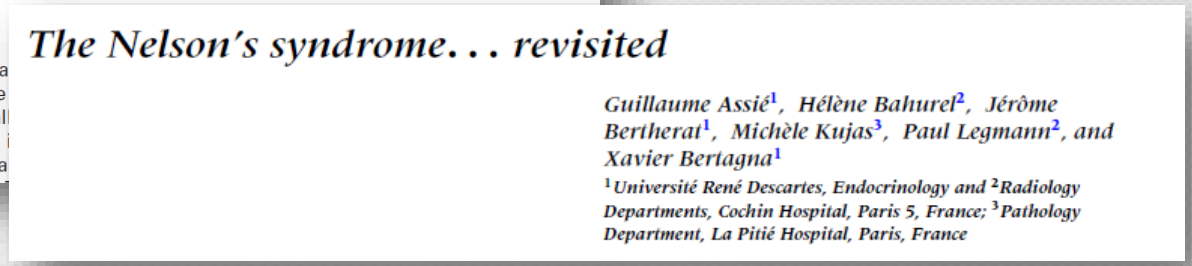


Nelson's Syndrome

atualização

ALIA MUNIR
JOHN NEWELL-PRICE

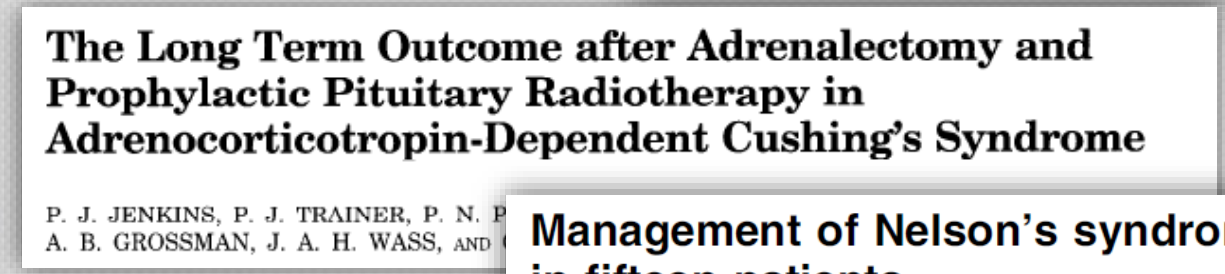
Nelson's syndrome is a
tomy performed in the
remains difficult. Of al
causes most concern i
tumour, which, unusua



The Nelson's syndrome... revisited

Guillaume Assié[1], Hélène Bahurel[2], Jérôme Bertherat[1], Michèle Kujas[3], Paul Legmann[2], and Xavier Bertagna[1]

[1]Université René Descartes, Endocrinology and [2]Radiology Departments, Cochin Hospital, Paris 5, France; [3]Pathology Department, La Pitié Hospital, Paris, France



The Long Term Outcome after Adrenalectomy and Prophylactic Pituitary Radiotherapy in Adrenocorticotropin-Dependent Cushing's Syndrome

P. J. JENKINS, P. J. TRAINER, P. N. P
A. B. GROSSMAN, J. A. H. WASS, AND

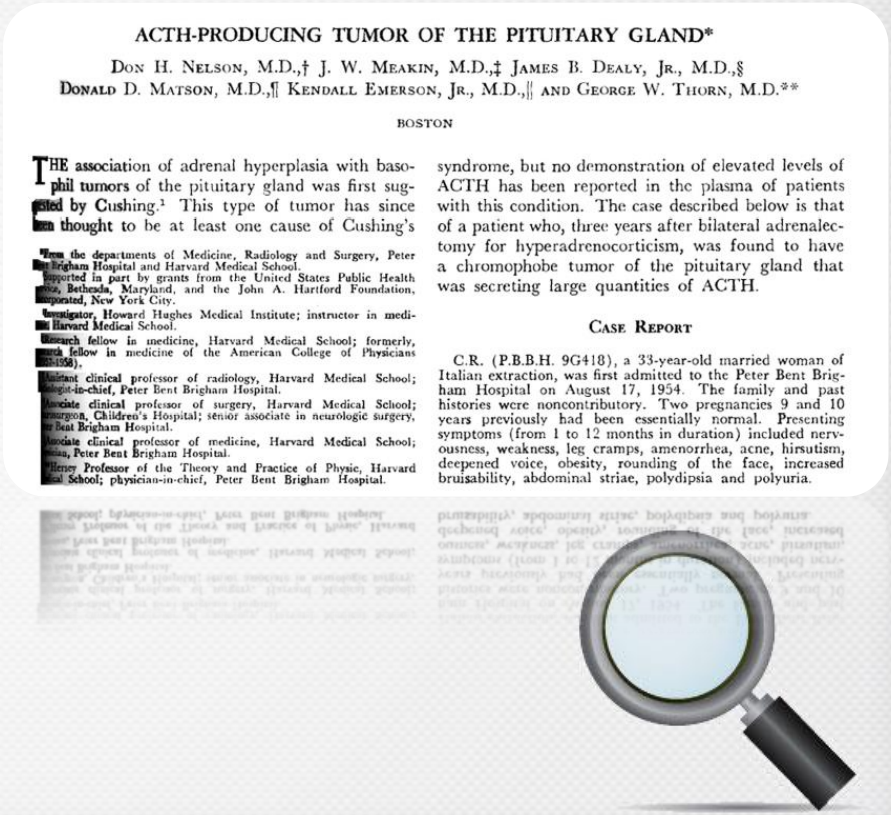
Management of Nelson's syndrome: observations in fifteen patients

S. A. G. Kemink*, J. A. Grotenhuis†, J. De Vries†, G. F. F. M. Pieters*, A. R. M. M. Hermus* and A. G. H. Smals*

Elective pituitary surgery was performed in 11 patients, of whom three were operated twice. Clinical remission was documented in five patients in the first

I cardini del trattamento

- ✓ Neurochirurgia
- ✓ Radioterapia
- ✓ Terapia medica



ACTH-PRODUCING TUMOR OF THE PITUITARY GLAND*

DON H. NELSON, M.D.,† J. W. MEAKIN, M.D.,‡ JAMES B. DEALY, JR., M.D.,§
DONALD D. MATSON, M.D.,¶ KENDALL EMERSON, JR., M.D.,‖ AND GEORGE W. THORN, M.D.**

BOSTON

THE association of adrenal hyperplasia with basophil tumors of the pituitary gland was first suggested by Cushing.[1] This type of tumor has since been thought to be at least one cause of Cushing's syndrome, but no demonstration of elevated levels of ACTH has been reported in the plasma of patients with this condition. The case described below is that of a patient who, three years after bilateral adrenalectomy for hyperadrenocorticism, was found to have a chromophobe tumor of the pituitary gland that was secreting large quantities of ACTH.

CASE REPORT

C.R. (P.B.B.H. 9G418), a 33-year-old married woman of Italian extraction, was first admitted to the Peter Bent Brigham Hospital on August 17, 1954. The family and past histories were noncontributory. Two pregnancies 9 and 10 years previously had been essentially normal. Presenting symptoms (from 1 to 12 months in duration) included nervousness, weakness, leg cramps, amenorrhea, acne, hirsutism, deepened voice, obesity, rounding of the face, increased bruisability, abdominal striae, polydipsia and polyuria.

NEUROCHIRURGIA

…la prima linea del trattamento

Pituitary surgery should be the first-line treatment option for Nelson's syndrome, particularly if there is compression of the optic apparatus

Barber et al. 2010

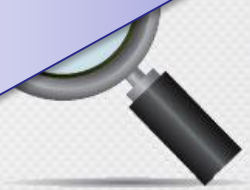
Transsphenoidal surgery is usually performedas a first-line treatment in these patients. Yet there is no discussion also that it does not always work

Assiè et al. 2004

Pituitary surgery may be performed for corticotroph tumour progression if the anatomy is favourable for such an approach

Newell Price et al 2007

Still the best hope for cure in cases of NS, surgery is the treatment of choice for large tumors that produce acute compression of the optic apparatus and other vital structures.
Banasiak et al. 2007



Obiettivi e fattori predittivi di successo

- L'obiettivo non è necessariamente la guarigione, ma evitare le complicanze compressive
- L'intervento è maggiormente efficace quando:
  - Le dimensioni dell'adenoma sono minori
  - L'intervento è eseguito precocemente
  - Minor grado di invasione tumorale
  - Elevata esperienza del neurochirurgo

Risultati

Authors	# of patients	Control of the mass	Stable disease	Tumor progression	Negative post-operative MRI	Recovered normal pigmentation	Reduced ACTH levels
Kelly et al 2002	13	70%	15%	15%	85%	85%	100%
Xing B et al 2002	23	57%	26%	17%			100%
De Tommasi et al. 2005	6	17%	83%				

Complicanze

- 69% · Hypopituitarism
- 38% · Permanent Diabetes Insipidus
- 15% · Cerebrospinal fluid leak
- 8% · Meningitis
- 5% · Cranial nerve deficits
- 5% · Mortality rate
- None · Visual loss

Kelly et al. 2002, Xing et al. 2002,
De Tommasi et al. 2005, Banasiak et al. 2007

Radiation is another alternative treatment for patients in whom surgery has been unsuccessful or is not an option

Banasiak 2007

RADIOTERAPIA

Radioterapia frazionata

Radiochirurgia

Terapia neo-adiuvate

Terapia adiuvate

The Long Term Outcome after Adrenalectomy and Prophylactic Pituitary Radiotherapy in Adrenocorticotropin-Dependent Cushing's Syndrome

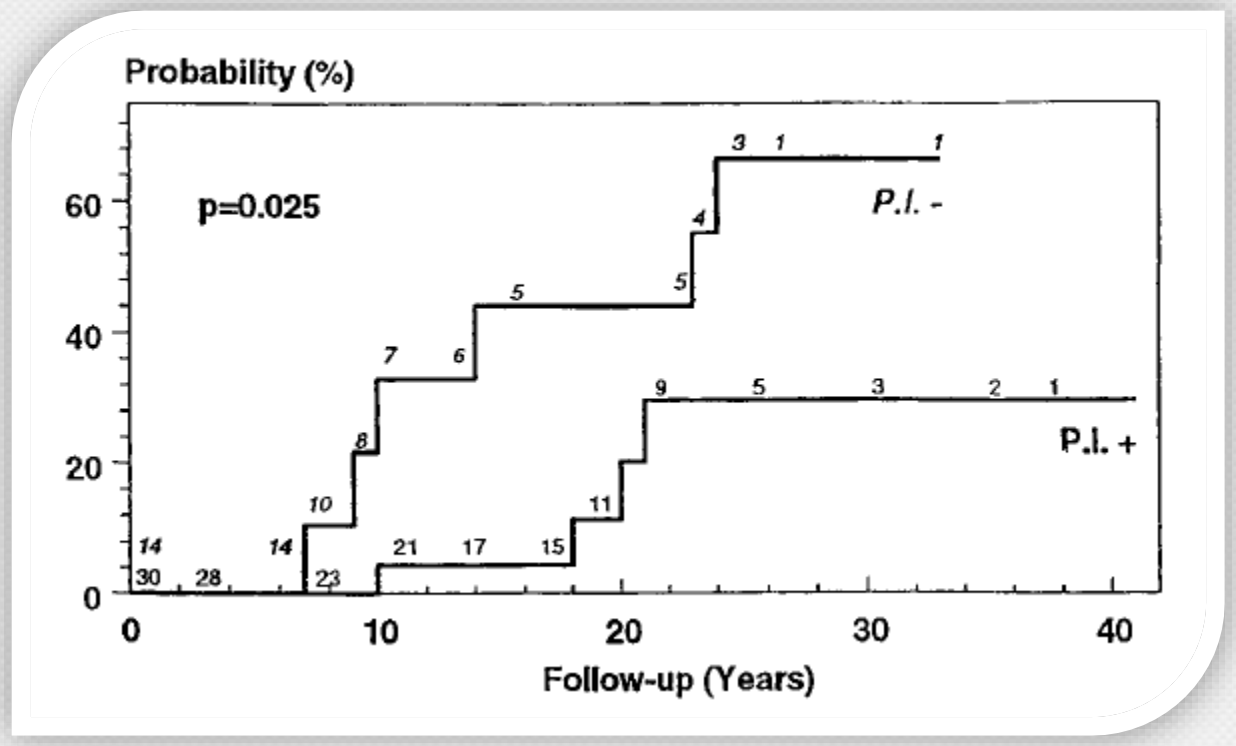
P. J. JENKINS, P. J. TRAINER, P. N. PLOWMAN, W. S. SHAND,
A. B. GROSSMAN, J. A. H. WASS, AND G. M. BESSER

TABLE 4. Patients receiving prophylactic pituitary radiotherapy

Nelson's syndrome	Previous TPS (yr)	TPS after RT (yr)	Max ACTH (ng/L)	Anterior pituitary deficiency (yrs after radiotherapy)			Length of F/U after RT (yr)
				LH/FSH	GH	TSH	
N	N	N	160	16	5	12	20
N	N	N	101	N	N	N	10
N	N	N	150	N	NR	N	6
N	N	N	196	N	NR	N	15
N	N	N	146	N	10	N	16
N	N	N			12	N	12
N	N	N			N	N	5
N	N	N			NR	N	15
N	N	N			NR	N	10
Y	N	11			N	N	11
Y	N	10			N	N	10
Y	N	4			N	N	4
Y	N	11	905	N	N	N	11
Y	3.2	N	1,2430	N	N	N	3
N	8	N	141	N	7	N	13
N	1	N	189	N	NR	N	3
N	2	N	237	N	NR	N	3
N	0.75	N	155	N	NR	N	2
N	0.5	N	241	0.5	NR	0.5	5
N	0.5	N	330	2	NR	2	8

Long-term Results of Total Adrenalectomy for Cushing's Disease

Suresh K. Nagesser, M.D.,[1] Arnoud P. van Seters, M.D., Ph.D.,[2] Job Kievit, M.D., Ph.D.,[1] Jo Hermans, Ph.D.,[3] H. Michiel J. Krans, M.D., Ph.D.,[2] Cornelis J.H. van de Velde, M.D., Ph.D.[1]



Neurosurg Focus 23 (3):E13, 2007

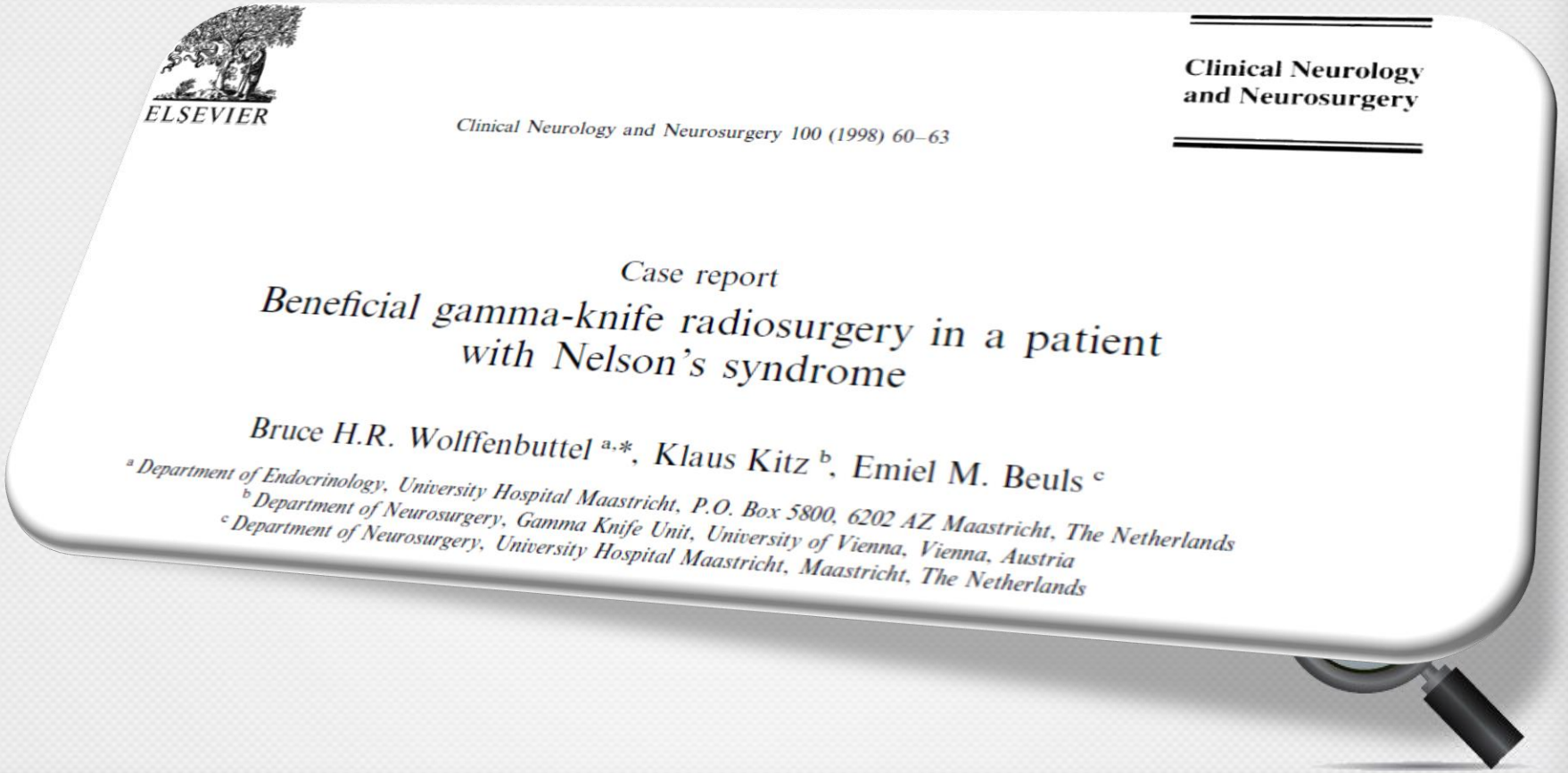
Nelson syndrome: comprehensive review of pathophysiology, diagnosis, and management

MAGDALENA J. BANASIAK, M.D., AND ALI R. MALEK, M.D.

Department of Neurosurgery, University of South Florida, Tampa, Florida

- ✓ While the use of prophylactic radiotherapy at the time of adrenalectomy has been proposed, the suggestion has not been translated into common practice.
- ✓ Given the risks of sellar radiation, the inconsistent protective relationship, and the relatively low rates of NS in patients who have undergone adrenalectomy, routine prophylactic irradiation is not justified based on currently available data.
- ✓ Thus far there has been no agreement on the optimal time of intervention in patients with NS.

1998



ELSEVIER

Clinical Neurology and Neurosurgery 100 (1998) 60–63

Clinical Neurology and Neurosurgery

Case report

Beneficial gamma-knife radiosurgery in a patient with Nelson's syndrome

Bruce H.R. Wolffenbuttel [a,*], Klaus Kitz [b], Emiel M. Beuls [c]

[a] Department of Endocrinology, University Hospital Maastricht, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands
[b] Department of Neurosurgery, Gamma Knife Unit, University of Vienna, Vienna, Austria
[c] Department of Neurosurgery, University Hospital Maastricht, Maastricht, The Netherlands

2008–2009

	# of patients	follow-up	Controlled mass volume	ACTH reduction	complications
Einar Osland Vik-Mo 2009	10	7 yrs	100%	90%	Hypopit 40%
Mauermann 2007	23	22 mo	91%	67%	Hypopit 40% 1 case cranial nerve palsy
Petit 2008	5	9 yrs	100%	100%	2 patients hypopit
Pollock 2002	11	37 mo	82%	91%	36% visual defects + Hypopit

Quale ruolo?

- ✓ Several concerns in planning radiosurgery for NS arise from the propensity of NS adenomas to grow faster and invade more readily than do most ACTH-secreting tumors in CD.
- ✓ Tumor progression can occur before the delayed effect of radiosurgery (mean 1 year) takes place.
- ✓ Proximity to the optic nerves or chiasm may exclude some larger tumors from radiosurgical treatment, unless the nerve is already nonfunctional.
- ✓ Cavernous sinus invasion can be subtle even on MR images, and the borders of an invasive adenoma, particularly the borders of a subtotally resected tumor admixed with postoperative fibrosis, can be difficult to delineate with enough certainty to protect adjacent brain from radiotoxicity.
- ✓ A history of prior irradiation of the sella, commonly encountered in patients with NS, may limit the dose possible in radiosurgery

Unfortunately, none of the drugs tested thus far have consistently provided reproducible efficacy in the treatment of NS and no well-established medical therapy for CD or NS currently exists

TERAPIA MEDICA

Analoghi della somatostatina

Dopamino agonisti

PPARγ

Temozolomide

Effect of an oral serotonin antagonist, ketanserin, on plasma ACTH concentrations in Nelson's syndrome

R W G PRESCOTT, W A RATCLIFFE, P KENDALL TAYLOR

Endocrinol. Japon. 1984, 31 (3), 619-626

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Journal of
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Acute Effects of Bromocriptine, Cyproheptadine, and Valproic Acid on Plasma Adrenocorticotropin Secretion in Nelson's Syndrome

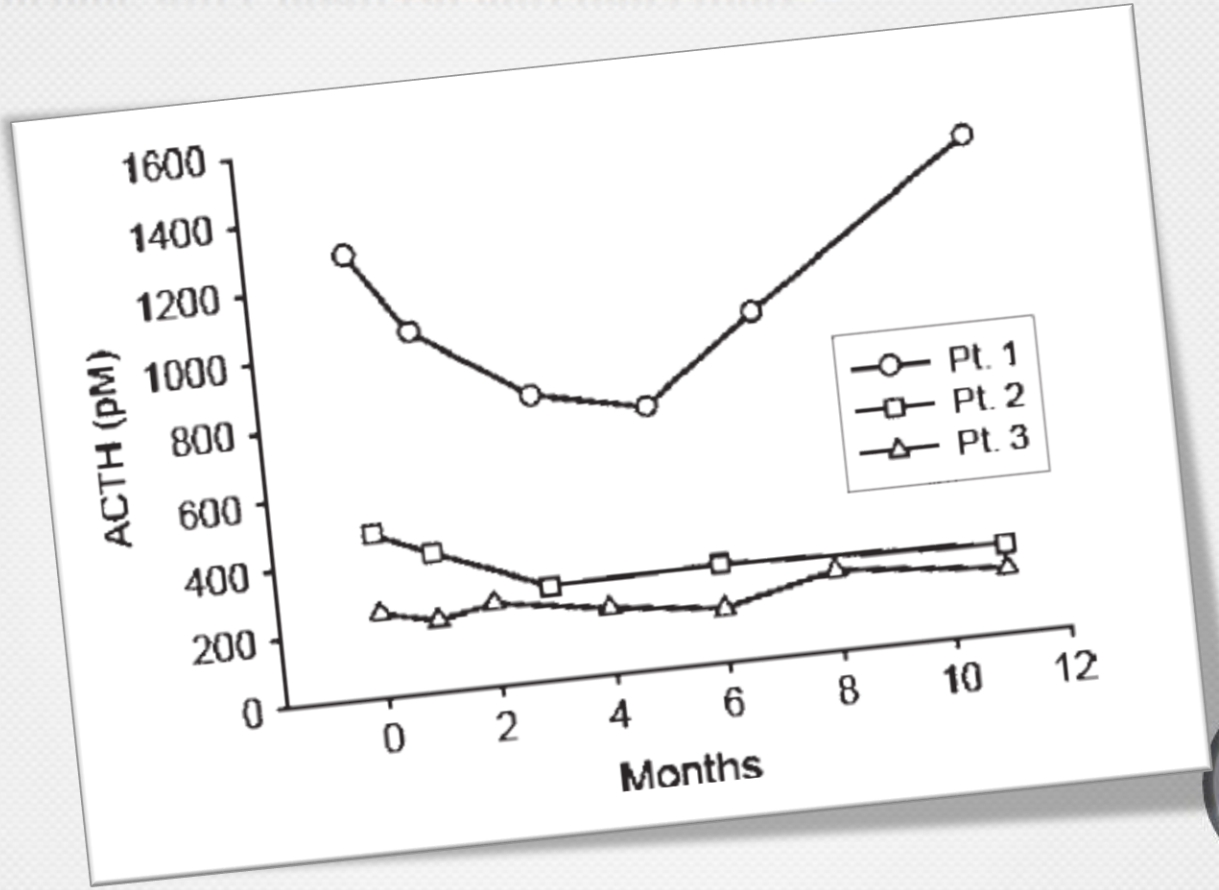
LEILANI B. MERCADO-ASIS*, JACK A. YANOVSKI†, HOWARD L. TRACER‡, CONSTANCE L. CHIK§, AND GORDON B. CUTLER, JR.†

European Journal of Endocrinology (2005) **153** 503–505 ISSN 0804-4643

CASE REPORT

Rosiglitazone for prevention or adjuvant treatment of Nelson's syndrome after bilateral adrenalectomy

Mikkel Andreassen and Lars Østergaard Kristensen



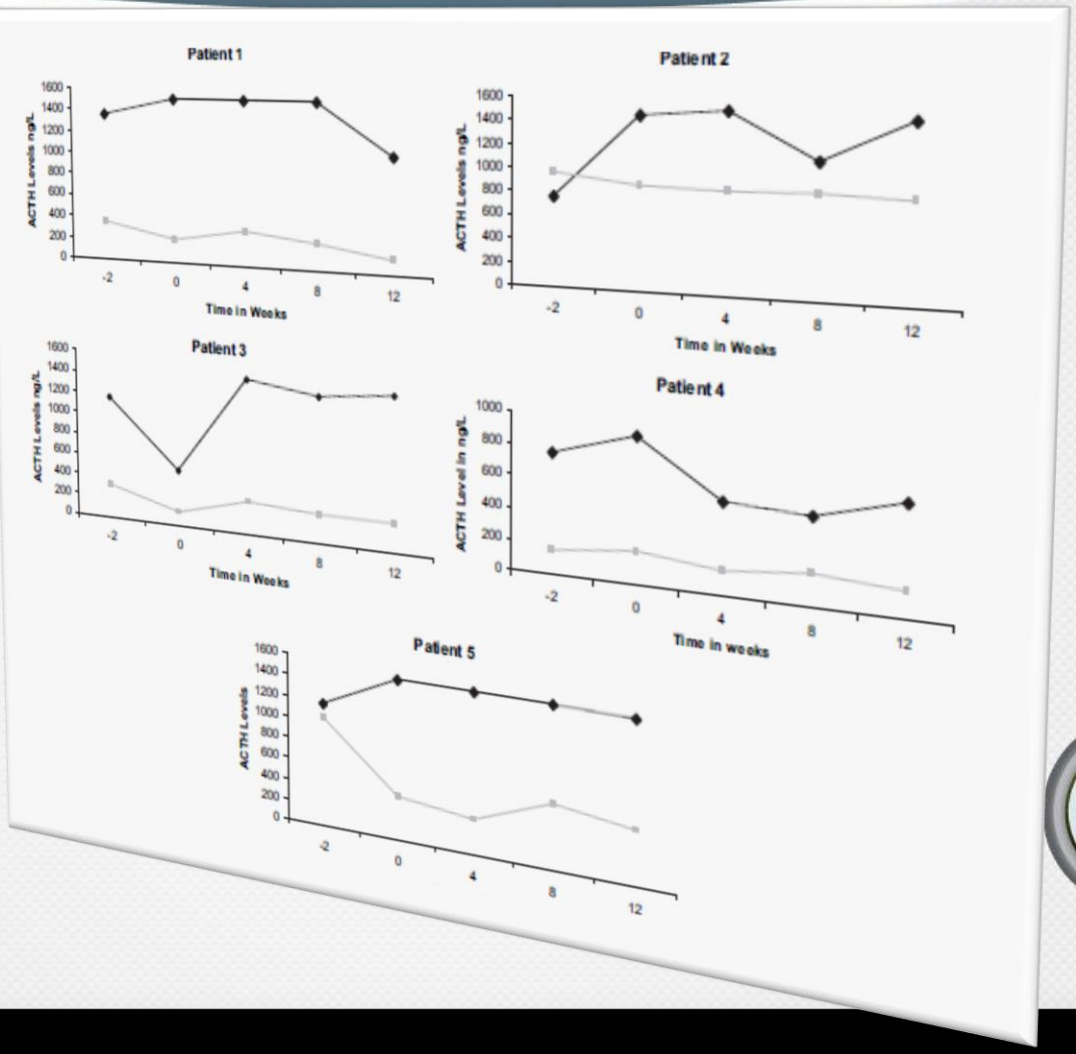
0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(5):1758–1763

doi: 10.1210/jc.2006-2005

Ineffectiveness of Rosiglitazone Therapy in Nelson's Syndrome

A. Munir, F. Song, P. Ince, S. J. Walters, R. Ross, and J. Newell-Price

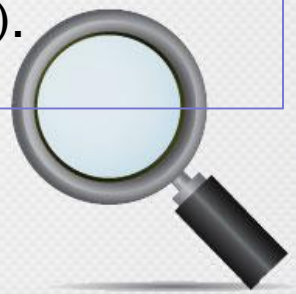


J Endocrinol Invest. 1999 Dec;22(11):860-5.

Complete remission of Nelson's syndrome after 1-year treatment with cabergoline.

Pivonello R, Faggiano A, Di Salle F, Filippella M, Lombardi G, Colao A.

- Cabergoline dose was then increased up to 2 mg a week.
- Six months later plasma ACTH levels were normalized (22 ng/l) and MRI demonstrated the disappearance of the pituitary adenoma.
- In order to investigate on the direct effect played by cabergoline treatment on the remission of Nelson's syndrome, the treatment was withdrawn.
- Plasma ACTH levels significantly increased (119 ng/l) after 3 months of treatment withdrawal.
- At the last follow-up, during cabergoline treatment at the dose of 2 mg/week plasma ACTH levels were normalized (40.4 ng/l).

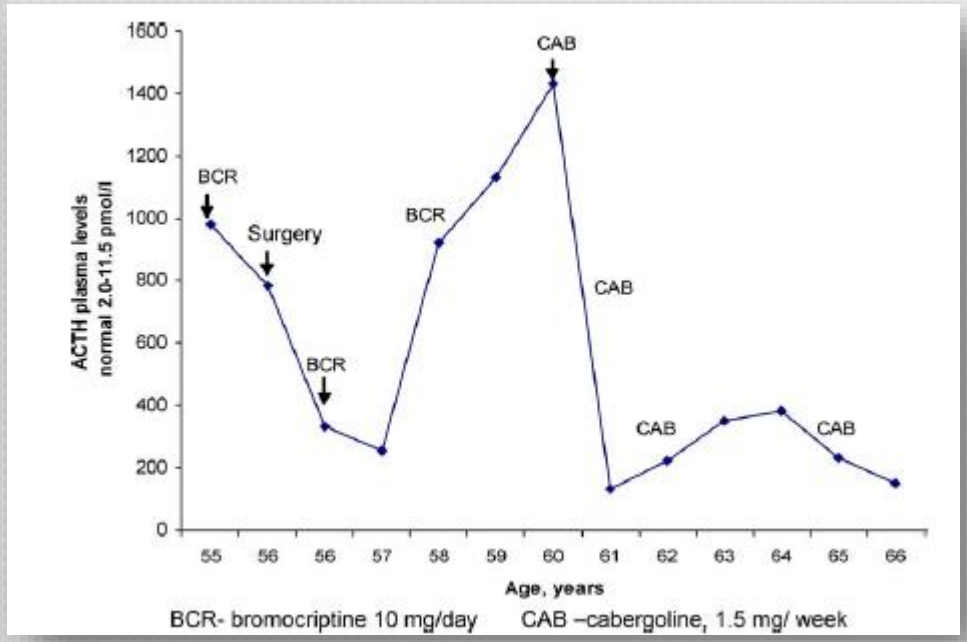


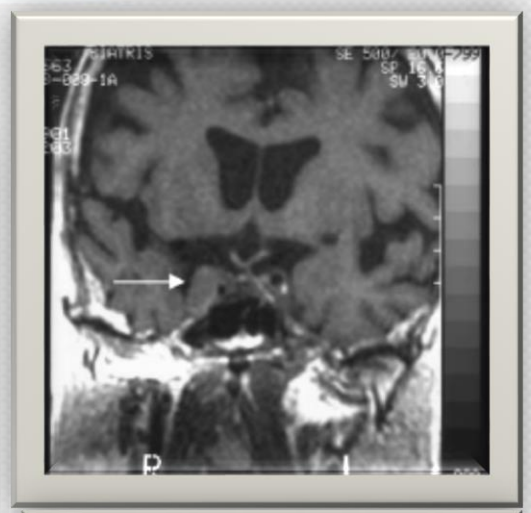
Pituitary (2006) 9:151–154
DOI 10.1007/s11102-006-9290-4

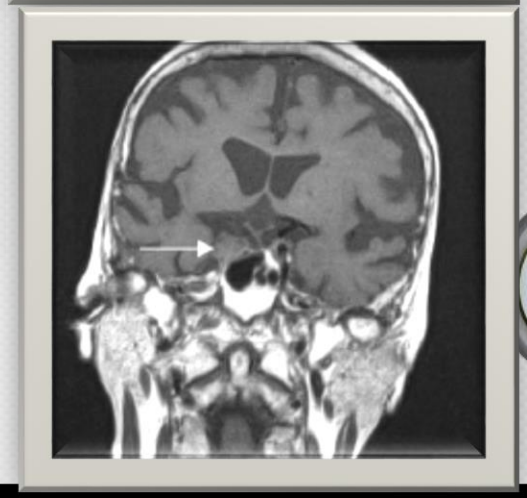
CASE REPORT

Clinical and biochemical stabilization of Nelson's syndrome with long-term low-dose cabergoline treatment

Ilana Shraga-Slutzky · Ilan Shimon · Ruth Weinshtein







J Endocrinol Invest. 1994 Feb;17(2):135-9.

Long-term treatment of Nelson's syndrome by octreotide: a case report.

Petrini L, Gasperi M, Pilosu R, Marcello A, Martino E.

- We report here on the results of long-term (2 yr) treatment with the somatostatin analogue octreotide (300 micrograms daily sc) in one patient affected by Nelson's syndrome occurring after bilateral adrenalectomy for Cushing's syndrome.
- During treatment, skin hyperpigmentation and serum ACTH levels decreased dramatically and a slight (about 10%) reduction in tumor size, as assessed by computerized tomography, was also observed.

Am J Ther. 2012 Jul 19. [Epub ahead of print]

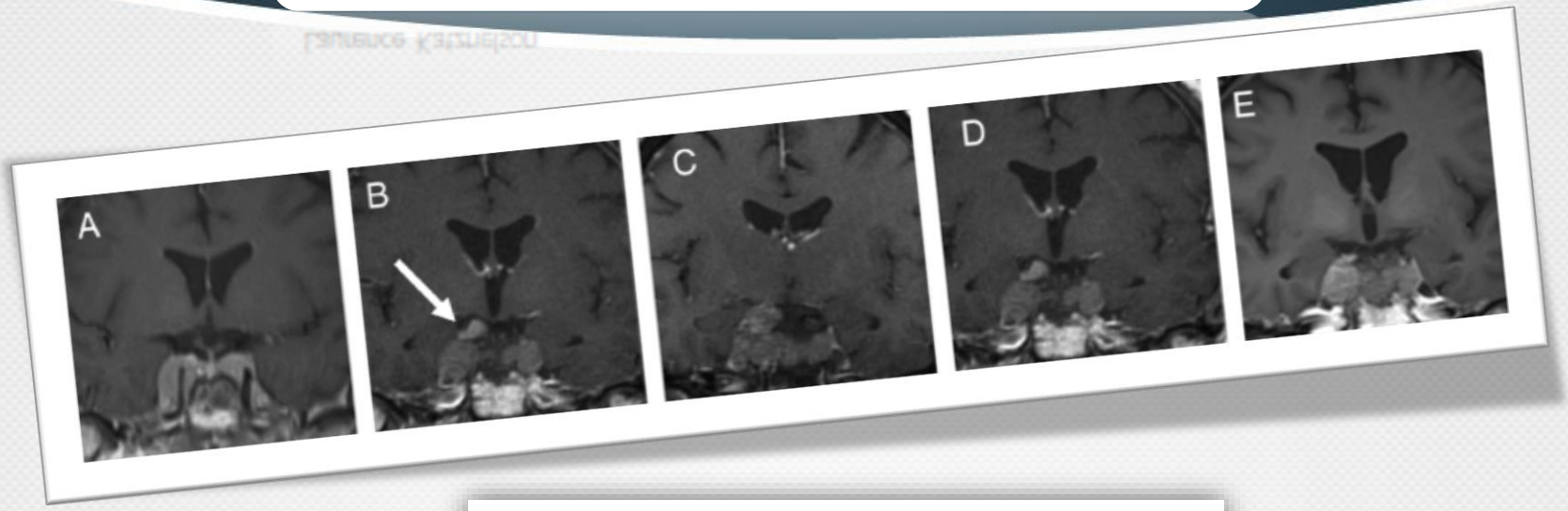
Hormonal Secretion and Quality Of Life in Nelson Syndrome and Cushing Disease After Long Acting Repeatable Octreotide: A Short Series and Update.

Arregger AL, Cardoso EM, Sandoval OB, Monardes Tumilasci EG, Sanchez R, Contreras LN.

- ✓ To our knowledge, there are no reports on the effect of long-acting repeatable octreotide (oct-lar) on hormonal secretion and quality of life in patients with NS and CD who failed conventional therapy.
- ✓ Herein, we describe the effects of treatment with oct-lar (20 mg/month intramurally) in 1 woman with NS and 2 women with persistent CD. Oct-lar therapy reduced ACTH secretion and improved the quality of life in NS patient.
- ✓ By contrast, in CD patients, it failed to control ACTH and cortisol secretion, and the quality of life remained unchanged.

Sustained Improvements in Plasma ACTH and Clinical Status in a Patient With Nelson's Syndrome Treated With Pasireotide LAR, a Multireceptor Somatostatin Analog

Laurence Katznelson



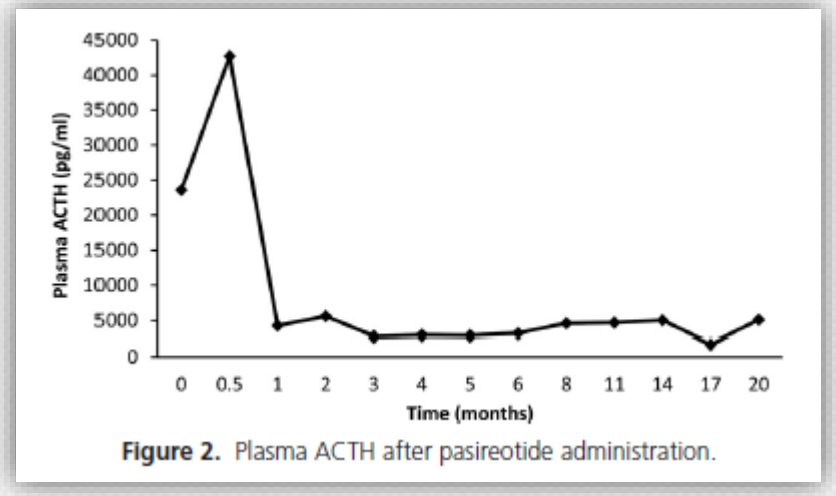


Figure 2. Plasma ACTH after pasireotide administration.

Pasireotide 2014

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Pasireotide Therapy in Patients With Nelson's Syndrome

This study is currently recruiting participants.

Verified June 2012 by Sheffield Teaching Hospitals NHS Foundation Trust

Sponsor:
Sheffield Teaching Hospitals NHS Foundation Trust

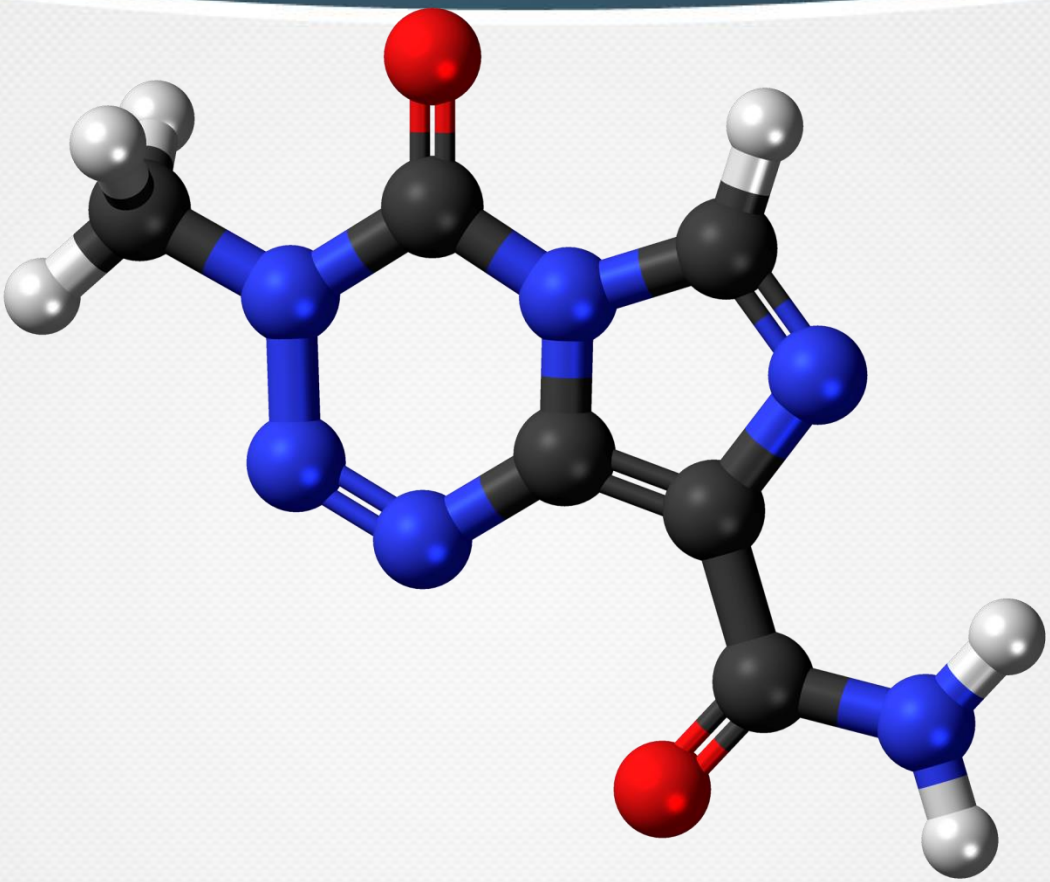
Collaborators:
Novartis
Christie Hospital NHS Foundation Trust
Oxford University Hospitals NHS Trust
Barts & The London NHS Trust

Information provided by (Responsible Party):
Sheffield Teaching Hospitals NHS Foundation Trust

ClinicalTrials.gov Identifier:
NCT01617733

First received: June 8, 2012
Last updated: NA
Last verified: June 2012
History: No changes posted

Temozolomide

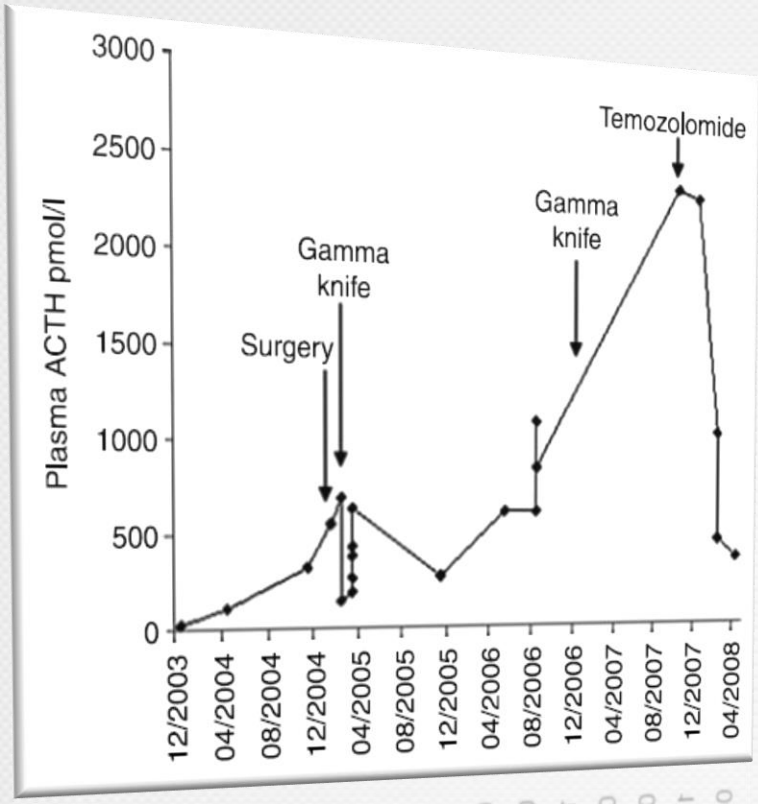


European Journal of Endocrinology (2009) **160** 115–119 ISSN 0804-4643

CASE REPORT

Treatment of Nelson's syndrome with temozolomide

V J Moyes[1], G Alusi[2], H I Sabin[3], J Evanson[4], D M Berney[5], K Kovacs[7], J P Monson[1], P N Plowman[6] and W M Drake[1]



- ✓ dose of 320 mg (200 mg/m2 per day) orally for 5 days of a 28-day cycle.
- ✓ Symptomatic response was noted following the first month of treatment, with the resolution of the persistent ear discharge and significant improvement in the severity of headaches. Persistent nausea was experienced 5 days after treatment but without vomiting.
- ✓ Repeated MRI imaging, post-fourth cycle, has confirmed marked shrinkage of tumour, most evident in the occipital area.
- ✓ Plasma ACTH levels have fallen from 2472 to 389 pmol/l.

Donna 51 anni – Sindrome di Cushing da macroadenoma ipofisario

Primo intervento NCH luglio 2004

Persistenza malattia

Secondo intervento NCH maggio 2005

IPOPITUITARISMO

Persistenza malattia

2006: Radioterapia stereotassica (Gamma – Knife)

Iniziale risposta poi
Ripresa di attività secernente

Ketoconazolo

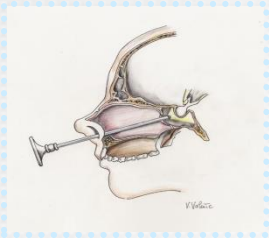
Mancata risposta

Surrenectomia bilaterale marzo 2010

Comparsa di cefalea
(circa 1 mese dopo l'intervento)

ACTH: 895 pg/ml

RMN: crescita dell'adenoma con espansione sovrasellare e nel seno cavernoso destro.



Intervento NCH settembre 2010

asportazione parziale
Istologico: Ki-67: 10%

Cabergolina

Non possibile effettuare Pasireotide

CEFALEA – DIPLOPIA – ALGIE BULBO OCULARE DESTRO

RMN a distanza di 1 e 2 mesi:
progressivo incremento della massa, che ora occupa entrambi i seni cavernosi, con masse di circa 2.5 cm bilateralmente; il tessuto neoplastico coinvolge anche il chiasma e il peduncolo.

ACTH: > 2000 pg/ml

TERAPIA MEDICA:

- Cortone 1/2 co al risveglio e ½ co verso le 14.30
- *Decadron 0.5 mg, 1 co all'ora dell'addormentamento*
- *Dostinex 1 co a stomaco pieno*
- Florinef 1 co al mattino
- Lansoprazolo 1 co la mattino
- Fosamax 70 1/settimana
- Dibase 20 gtt/settimana
- Eutirox 50 per 5 gg, poi Eutirox 75 per 2 gg

Decadron serale → "aumentare" l'effetto feedback nel tentativo di tenere sotto controllo la crescita dell'adenoma.

ALTRE POSSIBILITA’

TERAPIA RADIOMETABOLICA

PASIREOTIDE

TEMOZOLAMIDE

OCREOSCAN

Eventuale captazione del tessuto tumorale, che si potrebbe utilizzare per “rinforzare” la richiesta del Pasireotide o, anche, per un’eventuale terapia radiometabolica

→ NEGATIVO

TEMOZOLAMIDE (3 CICLI)

ACTH: Netta riduzione da > 2000 → 800 pg/ml

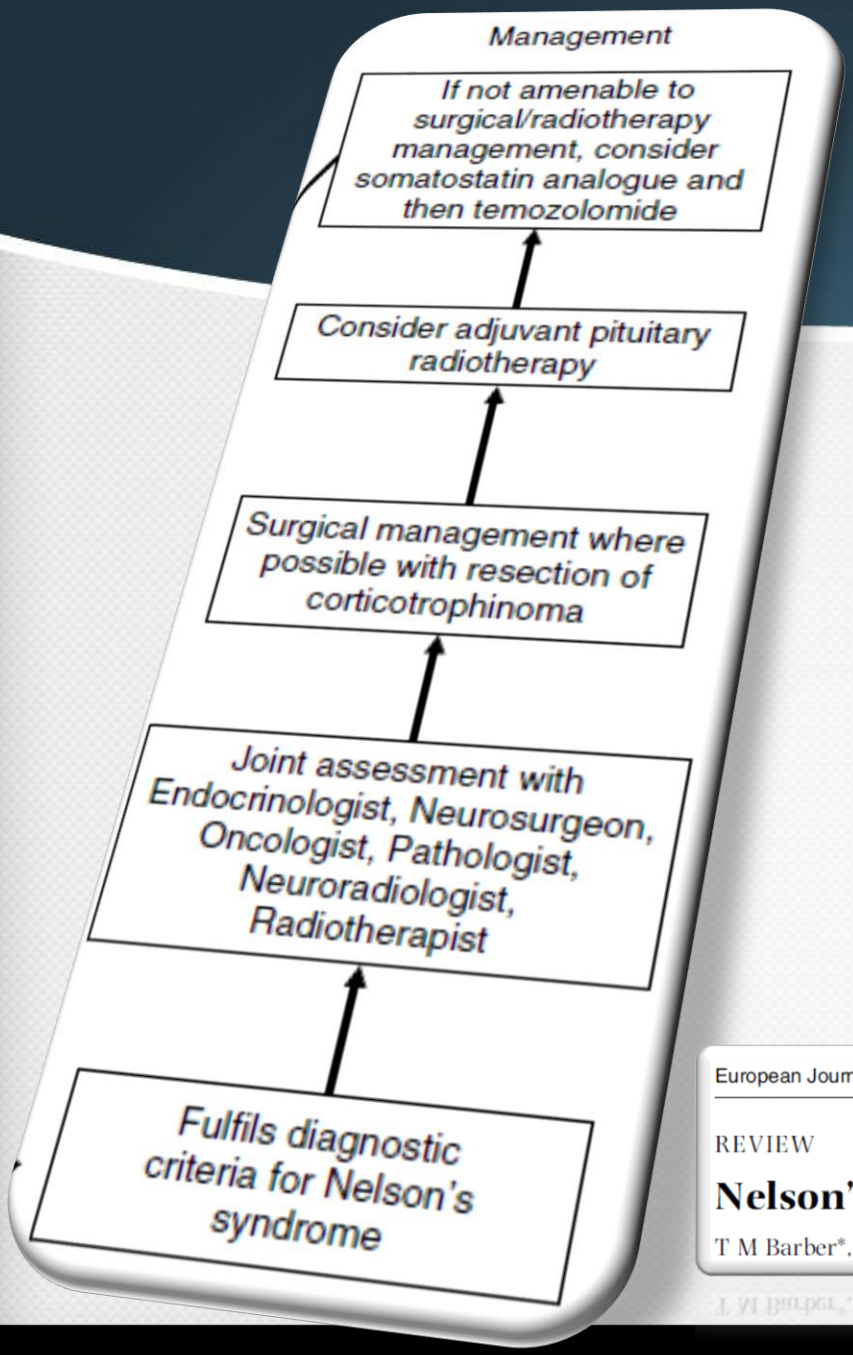
RMN:

Netta riduzione del diametro complessivo della nota formazione espansiva sellare (diametri complessivi attuali di 23 x 34 x 20 mm Vs 30 x 42 x 22 mm). Permane il coinvoglimento di entrambi i seni cavernosi con reperto prevalente a sinistra e risultata tuttora apprezzabile, anche se ridotta di dimensioni, la nodulazione craniale dx che determina modica impronta sul giro retto frontale omolaterale. I tratti ottici sono nei limiti, mentre la lesione si appoggia sull'emiporzione sinistra del chiasma senza determinane una significativa dislocazione

Effetti collaterali:

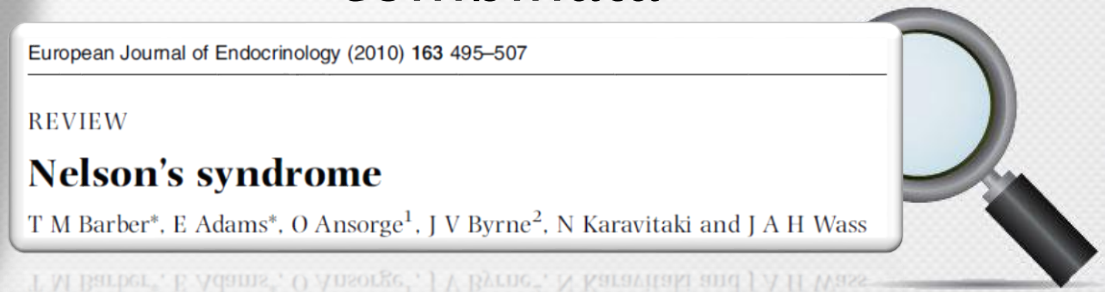
Trattamento molto ben tollerato

Piastrinopenia con valori attorno a 46.000



Prospettive

- Caratteristiche anatomo-patologiche
  - Rischio di progressione
  - Target therapy
  - Radioterapia neo-adiuvante
- Terapia medica combinata


European Journal of Endocrinology (2010) **163** 495–507

REVIEW

Nelson's syndrome

T M Barber*, E Adams*, O Ansorge[1], J V Byrne[2], N Karavitaki and J A H Wass

Grazie per l'attenzione

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