Impact of gsp mutations in somatotroph pituitary adenomas on growth horAmone response to somatostatin analogues: a meta-analysis

Z.A. Efstathiadou[1], A. Bargiota[2], A. Chrisoulidou[3], G. Kanakis[4], L. Papanastasiou[5], A. Theodoropoulou[6], S.K.Tigas[7], D.A. Vassiliadi[8], M. Alevizaki[9], and S. Tsagarakis[10]

[1]Department of Endocrinology, "Hippokration" General Hospital of Thessaloniki, Thessaloniki, Greece, [2]Department of Endocrinology, University of Thessaly, Larissa, Greece, [3]Department of Endocrinology-Endocrine Oncology, Theagenion Cancer Hospital, Thessaloniki, Greece, [4]Endocrine Unit, Athens Naval & VA General Hospital, Athens, Greece, [5]Department of Endocrinology and Diabetes Center, Athens General Hospital "G. Gennimatas", Athens, Greece, [6]Department of Endocrinology, University of Ioannina, Ioannina, Greece, [7]Department of Internal Medicine, Division of Endocrinology, University Hospital of Patras, Rio, Greece [8]Endocrine Unit, Second Department of Internal Medicine, University of Athens, Medical School, "Attikon" Hospital, Athens, Greece, [9]Endocrine Unit, Department of Medical Therapeutics, Athens University School of Medicine, [10]Department of Endocrinology, Evangelismos Hospital Athens, Greece

Introduction

Somatic mutations in the GNAS1 gene, which encodes the alpha-subunit of the G stimulatory protein (gsp) complex coupled to GHRH receptor, are detected in about 40% of somatotroph pituitary tumors.

Gsp mutations have been associated to specific clinical and histopathological characteristics such as:

- smaller, less invasive tumors occurring in older patients and
- densely granulated adenomas.

Methods

The aim of the present study was to investigate whether the presence of a gsp mutation in sporadic somatotroph adenomas is a prognostic factor of the response to somatostatin analog (SSA) treatment.

Following a literature search in MEDLINE and SCOPUS for a period up to January 2014, a meta-analysis was performed, including 8 eligible studies (***figure 1 & table 1***), in order to estimate the effect of gsp mutation on the percent reduction of growth hormone (GH) levels during an acute octreotide suppression test (OST).

OST was selected as the outcome measure because it was the test used most widely in the studies, with consistently available data. Furthermore, it has been validated as accurate predictor of the long term response of GH-secreting adenomas to SSAs.

No study addressing the research question in a prospective manner, with long term results of SSA treatment on GH and IGF 1 levels was found.
A total of 310 patients with acromegaly [126 gsp (+) and 184 gsp (-)] were included in the analysis.

Figure 1: **Flow diagram of study selection**

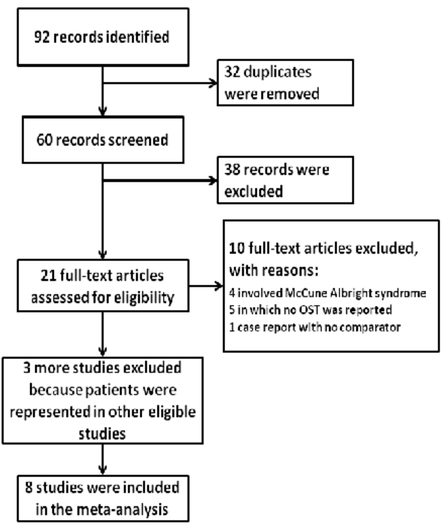


Table 1: **Characteristics of eligible studies for the meta-analysis.**

Study	Year of publication	Country	Study type	N tested for gsp	Age	Gender (female)	Frequency of gsp +(%)	OCT test methodology	N tested for gsp with an OST	Effect of Gsp mutation presence on clinical and tumor characteristics				
										age	sex	Basal GH levels	tumor size	tumor invasiveness
Spada et al. (9)	1990	Italy	retrospective	80	16-72	51	36,25	Serono Milan SRIF continuous infusion 3,33μg/min for 2h	33	no	no	higher	smaller	less
Yang et al. (10)	1996	Korean	prospective	21	NR	14	43	Sandostatin, Sandoz 100μg bolus	21	older	no	no	no	no
Barlier et al. (11)	1998	France	prospective	30	24-67	19	27	Sandostatin, Novartis 100μg bolus	25	no	no	higher for tumor size	no	less
Kim et al. (8)	2001	Korean	prospective	44	NR	27	15,9	Sandostatin, Sandoz 100μg bolus	44	no	no	no	smaller	trent for less
Park et al. (25)	2004	Korean	prospective	16	24-61	10	62,5	Sandostatin, Sandoz 100μg bolus	15	NR	NR	NR	NR	NR
Yasufuku-Takano et al. (3)	2006	Japan	retrospective	100	NR	60	53	Sandostatin, Sandoz 100μg bolus	58	no	no	no	NR	NR
Fougner et al.(26)	2012	Norway	retrospective	78	NR	NR	48,6	Sandostatin, Novartis 100μg bolus	70	NR	no	no	no	no
Larkin et al. (12)	2013	UK	retrospective	49	NR	30	53	Sandostatin, Novartis 100μg bolus	49	no	yes[a]	no	no	no

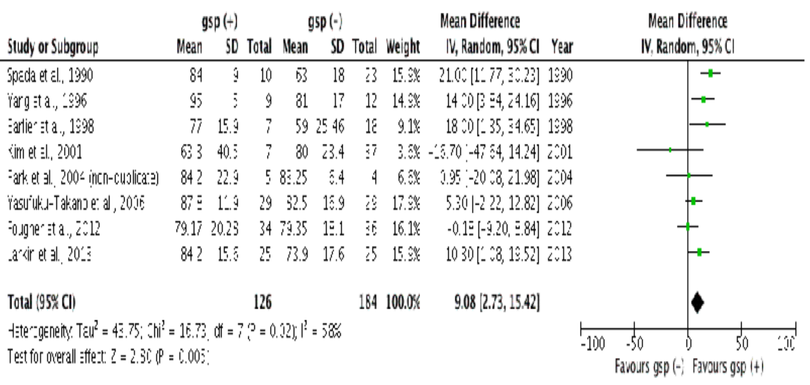
Results

The presence of the gsp mutation was related with a greater reduction in GH levels on OST [Weighted Mean Difference (WMD): 9.08% (95% CI, 2.73, 15.42; p=0.005; random effects model].

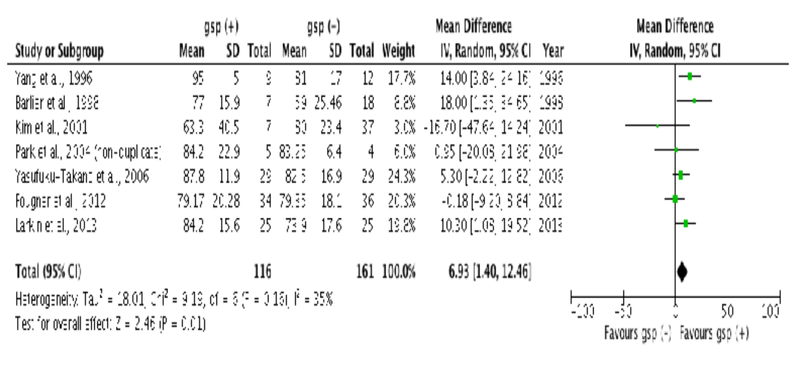
There was significant heterogeneity for this effect estimate (I2= 58%, *p* value for heterogeneity= 0.02) (***Forest plot 1***).

A sensitivity analysis after exclusion of a study with different methodology of OST provided similar estimates [WMD: 6.93% (95% CI, 1.40, 12.46); p=0.01), albeit with no significant heterogeneity (I2= 35%, *p* value for heterogeneity= 0.16) (***Forest plot 2***).

Forest plot 1: **percent reduction of GH on OST by gsp status.cv**



Forest plot 2: **sensitivity analysis; exclusion of one study with different methodology**



Conclusions

The present meta-analysis suggests a role for gsp mutations as a predictive factor of somatostatin analog treatment response in acromegaly.
In order to further clarify this position, studies evaluating the long term effect of treatment, using the combination of GH and IGF-1 measurements are needed.

References

- Colao et al. Resistance to somatostatin analogs in acromegaly. Endocr Rev 2011; 32:247
- Gadelha et al. Novel pathway for somatostatin analogs in patients with acromegaly. Trends Endocrinol Metabol 2013; 24:238
- Karavitaki et al. The value of an acute octreotide suppression test in predicting long-term responses to depot somatostatin analogues in patients with active acromegaly. Clin Endocrinol 2005; 62:282

17 ECE
728--EP
Pituitary clinical
Zoe Efstathiadou
DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY