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First-line medical treatment include first generation long-acting somatostatin analogs: octreotide LAR and lanreotide autogel. Recently, pasireotide – a second generation somatostatin analog has been investigated in patients with acromegaly. The aim of this study was to compare the effectiveness of the single-dose of short-acting somatostatin analogs: octreotide vs pasireotide in patients with active acromegaly after surgical debulking who were resistant to first generation long-acting somatostatin analogs.
Eighteen patients after debulking surgery without biochemical control of acromegaly on medical therapy were enrolled in the study. All patients had short-acting octreotide and pasireotide administered on different days. GH concentration was measured before and 60, 120 and 180 min after drug administration. Nadir GH concentrations and decreases in GH concentrations were compared.
Nadir GH values in octreotide test were reached 60 min after drug administration, while in pasireotide test – 180 min after drug administration. The median nadir GH concentration was 2.765 μg/l (IQR: 1,885–4.07) vs 1.51 μg/l (IQR: 0.95–2.555) respectively, $P<0.001$. The decrease in GH concentration was more significant after pasireotide administration compared to octreotide administration ($P<0.001$). The median decrease in GH concentration in octreotide test was 1.255 μg/l (IQR: 0.918–1.75) vs 2.805 μg/l (IQR: 1.523–5.043) after pasireotide administration. Octreotide was generally better tolerated than pasireotide.
Short-acting pasireotide is more effective than short-acting octreotide in GH supression in patients with uncontrolled acromegaly. Pasireotide may be a promising alternative for patients resistant to first-generation somatostatin analogs.

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GP174

Efficacy and safety of switching to pasireotide LAR alone or in combination with pegvisomant in acromegaly patients controlled with combination treatment of first-generation somatostatin analogues and weekly pegvisomant (PAPE study): a prospective open-label 48 week study, preliminary results 24 weeks

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Background
Efficacy and safety of combination treatment of pasireotide LAR with pegvisomant (PEGV) has not been studied yet. Switching to Pasireotide LAR in patients previously controlled with long-acting somatostatin analogues (LA-SSAs) and PEGV could reduce the required PEGV dose to normalize serum IGF1 levels, while the effect on glucose metabolism is unknown.
Methods
We enrolled 60 acromegaly patients >18 years with acromegaly who had normal IGF1 levels ($\leq 1.2\times$Upper Limit of Normal (ULN)) using combination treatment of high dose LA-SSAs and weekly PEGV for ≥ 6 months. After enrollment LA-SSA treatment was continued, and the PEGV dose was reduced by 50% for 12 weeks. If IGF1 levels remained normal after 12 weeks, patients were switched to pasireotide LAR 60 mg monotherapy, every 4 weeks. If IGF1 levels $>1.2\times$ULN patients were switched to pasireotide LAR 60 mg and continued with the 50% reduced PEGV dose. The primary endpoint was the percentage of patients achieving normal IGF1 levels at 24 weeks. The key secondary endpoint was the frequency diabetes at 24 weeks.
Results
At baseline, median IGF1 was $0.94\times$ULN with a median PEGV dose of 80 mg/week, and 30.6% of patients had pre-existing diabetes. After the 50% dose reduction of PEGV, median IGF1 levels increased to 1.43 ULN, while IGF1 remained normal in 33% of patients. At 24 weeks, 73% of patients achieved normal IGF1 levels with a median IGF1 $0.98\times$ULN. Cumulative PEGV dose reduction between baseline and 24 weeks was 66%. At 24 weeks, IGF1 levels were normal in 88% of patients on pasireotide LAR monotherapy, and 68% of patients on combination treatment. Pasireotide LAR was well tolerated. At 24 weeks, the most common adverse event was diabetes which occurred in 70.2% of patients. Two patients withdrew prematurely due to hyperglycemia requiring insulin treatment.
Conclusion
Pasireotide LAR alone or in combination with pegvisomant controls IGF1 in 73% of patients after 66% reduction in cumulative dose of weekly pegvisomant. The frequency of diabetes was 70.2% and is in line with previous studies.

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GP175

Resistance to somatostatin analogues is associated with GSTP1 gene methylation and AHR rs2066853 variant in acromegaly patients

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Evidences suggest that environmental contaminants exposure and/or the impairment of intracellular xenobiotic metabolizing system could affect pituitary pathophysiology. Glutathione-S-transferase-P1 (GSTP1) gene encodes for an enzyme that is involved in cellular detoxification mechanisms. GSTP1 altered activity or expression has been reported in some tumours.
We aimed to assess the GSTP1 gene promoter methylation status in acromegaly patients and its contribution to their clinical features.
Seventy-seven WT AIP gene acromegaly patients (50 women) have been screened for germline AHR rs2066853 variant and GSTP1 promoter methylation. Epidemiologic, clinical, biochemical and radiological parameters at diagnosis have been compared after patients' stratification according to GSTP1 methylation status and the presence of AHR rs2066853 variant. We also evaluated the response to somatostatin analogues (SSA) administered either before or after surgery in 71 cases.
Seventeen patients were found to carry AHR rs2066853 variant and 26 methylated GSTP1 (GSTP1met). GSTP1met patients showed a higher prevalence of diabetes mellitus ($P=0.01$), colonic polyps ($P=0.05$), and were more resistant to SSA ($P=0.02$) as compared to GSTP1 unmethylated patients (GSTP1unmet).
On the basis of GSTP1 methylation status and the presence of AHR rs2066853 variant, we identified four groups: group 1, 40 patients GSTP1unmet and AHR WT; group 2, 20 patients only GSTP1met; group 3, 12 patients carrying only AHR rs2066853 variant; group 4, five patients with both GSTP1 methylation and AHR rs2066853 variant. Group 1 patients were more sensitive to SSA than other groups ($P=0.02$). Patients of group 4 were more resistant to SSA ($P=0.02$) and showed higher GH ($P=0.03$) and IGF1 ($P=0.04$) levels and lower percentage of GH decrease ($P=0.04$) after SSA than other groups.
In conclusion, GSTP1 methylation and AHR rs2066853 variant associate with resistance to SSA in acromegaly patients.

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GP176

Minimally Invasive Diagnosis and Direct Transnasal Surgery: a single centre series of 100 children with Cushing's Disease with long term follow-up

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Introduction
Trans-sphenoidal surgery (TSS) with minimally invasive techniques is the first choice in the treatment of paediatric Cushing's disease (CD). The question is how can high remission rates be achieved with less invasive investigations and TSS. The developments in our centre treating 100 pediatric Cushing patients with long-term follow-up may add some helpful ideas.
Material and methods
Data from our first series 1 ($n=55$) will be compared with new data from the recent series 2 ($n=45$) until 2009. All patients were operated by one surgeon by direct transnasal microsurgery (TNS). Special diagnostic methods such as inferior petrosal sinus sampling (IPSS) were replaced by ACTH measurement from the cavernous sinus (CSS) restricted to unclear cases without increase of salivary cortisol in the CRH-test, difficult sella anatomy and/or negative MRI. Multiple direct micro-cytology, micro-doppler and adequate visualization will be described.
Results
In our first series of 55 cases, IPSS was performed in 13 (24%) of whom 46% had false adenoma lateralization. All adenomas could be removed with extensive pituitary exploration and all had intraoperative pathology. Two patients had early successful re-surgery. Recurrence rate 15%. In the second series with more