Insulin-like growth factor-1 as predictive factor of difficult laryngoscopy in patients with GH-producing pituitary adenoma: A pilot study

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ABSTRACT

Background: Growth hormone (GH)-producing pituitary tumors account for 10 to 15% of pituitary tumors. The hypersecretion of GH may induce changes in the airway anatomy through the activation of Insulin-like Growth factor 1(IGF-1) pathway. We sought investigate the role IGF-1 as a potential predictive factor of difficult laryngoscopy in patients with GH-producing pituitary adenoma.

Methods: This study was a single center retrospective study. We included 33 patients undergoing transsphenoidal resection of GH-producing pituitary. We recorded demographic data, el-Ganzouri risk index (EGRI) and modified Look-Evaluate-Mallampati-Obstruction-Neck mobility (mLEMON) score, and pituitary hormone plasma levels. We performed ordinal logistic regression to analyze the relationship between IGF-1 and EGRI, mLEMON, and Cormack-Lehane Grade score and a multiple logistic regression to test the capability of EGRI, mLEMON and IGF-1 levels to predict Cormack-Lehane score. Receiver operating curve (ROC), area under the curve (AUC), and cut-off value of IGF-1 were calculated.

Results: Only 14 (42.8%) and 12 (36.36%) patients showed predictive factors of difficult intubation according to EGRI and mLEMON score, respectively. IGF-1 significantly correlated with Cormack-Lehane ($p = 0.005879$) but not with mLEMON and EGRI ($p = 0.3080$ and 0.4146, respectively). In multiple regression model IGF-1 correlated only with Cormack-Lehane grade ($p = 0.0089$). Area under ROC was 0.8571 and cut-off value of IGF-1 was 186.15 ng/ml.

Conclusion: Higher IGF-1 levels correlate with the probability of having a higher Cormack-Lehane score; classical bedside scores, such as mLEMON and EGRI, were not able to predict difficult laryngoscopy in our population.

1. Introduction

Pituitary adenoma can be classified according to the hormones that they produce and their size: microadenomas (<10 mm in diameter) and macroadenomas (>10 mm in diameter) [1,2]. Most of the clinical manifestations of pituitary adenomas are related to the hypersecretion of hormones. However, the mass effects of the enlarging tumor can also lead to specific signs and symptoms.

The most commonly occurring pituitary adenomas are growth hormone (GH)-secreting adenomas (somatotropinoma), prolactin-secreting adenomas (prolactinoma), growth hormone and prolactin co-secreting adenomas (somatomammotropinoma),

and non-functioning pituitary adenomas [3]. GH-producing pituitary tumors account for 10 to 15% of pituitary tumors and are frequently mixed tumors that secrete more than one hormone; possible clinical manifestations range from anatomofunctional alterations to acromegaly in adults and gigantism in children. The biochemical goals of therapy are to reduce basal GH levels with pharmacological therapy based on somatostatin analogues and/or antagonists of the GH-receptor, but transsphenoidal surgery remains the primary treatment for these adenomas [4].

The constellation of physical manifestations, especially heart and lung disease, combined with upper airway modifications, makes patients with GH-secreting adenoma a particular challenge for anesthesiologists [5,6]. Patients develop hypertrophy of the facial bones, mandible thickening, and significant prognathism. Soft tissues of nose, mouth, and tongue are affected too [7]. Significant macroglossia and hypertrophy of the laryngeal and pharyngeal soft tissues have been well documented, and may reduce the glottic opening's size and contribute to airway obstruction

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[8]. These changes are the result of Insulin-like Growth factor 1 (IGF-1) pathway hyperactivation. After GH binding to its receptor at target tissues (such as liver, muscle, adipose tissue, bone, and kidney) the production and secretion of IGF-1 is increased, through Jak-Stat pathway [9]. IGF-1 has similar insulin activity and promotes cell proliferation and differentiation, especially at the cartilage and muscle level [10]; for example, it stimulates the activity of chondrocytes, the cells responsible for the synthesis of new cartilage, and promotes the activity of osteoblasts, increasing bone tropism. Therefore, it is a powerful cell growth factor with strong anabolic properties whose mechanisms of action have not yet been fully clarified [10].

Three published retrospective series documented an incidence of 12% and 30% of difficult intubation in GH-linked diseases: difficult airways were more common in acromegalic patients but no authors correlated so far, the levels of biochemical markers with laryngoscopy or intubation outcomes [11–13]. Only the Mallampati test showed a moderate predictive validity as yet [14,15].

We sought to evaluate the strength of known predictive scores such as el-Ganzouri risk index (EGRI) and modified Look-Evaluate-Mallampati-Obstruction-Neck mobility (mLEMON) score, and investigate the role of IGF-1 as a potential predictive factor of difficult laryngoscopy in patients with GH-producing pituitary adenoma [16].

2. Materials and Methods

This study was a single center retrospective pilot study. The requirement for written informed consent was waived by the Medical Ethics Committee of University of Naples Federico II. We screened medical records of patients undergone transsphenoidal resection of GH-producing pituitary tumors from April 2019 to January 2020.

Inclusion criteria were: [1] American Society of Anesthesiologists (ASA) class I or II; [2] age 18–65 years old; and [3] GH-producing pituitary adenoma, treated or not with pharmacological therapy, and eligible to surgery. We selected patient records whose airway management was handled by an anesthesiologist with at least ten years of experience.

Exclusion criteria were: [1] high level of prolactin hormone; [2] complete remission of the disease after pharmacology therapy.

Thirty-three patients met the inclusion criteria. We collected demographic data, EGRI and mLEMON score, and IGF-1 level corrected for gender and age. The EGRI score includes mouth opening, thyroid-chin distance, Mallampati score, neck mobility, prognathism, body weight, and history of difficult intubation. The mLEMON score takes into account for the interincisive distance, the presence of facial trauma or beard and mustache, protruding incisors, thyrohyoid distance, thyromental distance, short and reduced mobility of the neck and obstructive conditions (laryngitis, tonsillar abscesses, OSAS, dysphonia, dysphagia) [17,18].

On arrival to the operating room, each patient was monitored blood pression, ECG continous wave and oxygen saturation. Therefore, premedication is perfomed with Midazolam 0.03 mg/Kg, Atrophine 0.01 mg/Kg and Fentanyl 2 mcg/Kg. We started with pre-oxygenation for 5 min while being administred Propofol 2 mg/Kg as hypnotic drug. Then we proceeded to curarization with rocuronium 0.8 mg/Kg. After the drop of ToF ratio we started to laringoscopy. Airway management and Cormack-Lehane evaluation were handled by a single anesthetist with more than ten years of experience. The first laringoscopy was performed using Macintosh direct laryngoscope. Based on first glottic plane view our phisycian decided how to continue intubation procedure.

The primary outcome was the correlation of IGF-1 level with Cormack-Lehane grade. The secondary outcome was the correlation of IGF-1 with EGRI and mLEMON score.

2.1. Statistical analysis

We presented normally distributed data as mean and standard deviation, and non-parametric data as median and interquartile range. Differences between groups were analyzed by Student *t*-test for parametric data and by Mann-Whitney test for non-parametric data. To assess the correlation between IGF-1 levels and Cormack-Lehane, EGRI, or mLEMON, we performed simple ordinal logistic regression assuming the three score as dependent variable and IGF-1 as the independent variable. We also performed a multiple logistic regression to test the capability of EGRI, mLEMON, and IGF-1 levels to predict Cormack-Lehane score. Moreover, we performed an ordinal logistic regression to investigate the dependence between IGF-1 and Mallampati score. All the results were considered statistically significant when p-value < 0.05.

Receiver operating curve (ROC) and area under the curve (AUC) were calculated to assess the accuracy of IGF-1 to predict Cormack-Lehane grade along with IGF-1 cut-off value.

A post-hoc analysis of mean and SD among population with Cormack-Lehane grade ≤ 2 versus grade 3 showed a power of 76.2% with $\alpha = 0.05$.

This manuscript adheres to the applicable STROBE guidelines.

3. Results

We enrolled 33 patients. Table 1 reports the demographic and clinical characteristics of patients. Fig. 1 shows the different scatter plots of Cormack-Lehane, EGRI, and mLEMON score and IGF-1: the relationship between EGRI score and IGF-1 (A2 cell) present higher density towards lower IGF-1 values despite it presents an increasing correlation trend. These classic preoperative scores cannot explain by itself the difficulty of airway management of patient with GH-adenoma. Only 14 (42.8%) and 12 (36.36%) patients showed predictive factors of difficult intubation according to EGRI

Table 1

Demographic data. BMI = Body Mass Index; IGF-1 = Insulin-like Growth Factor 1 serum level; EGRI = el Ganzouri risk index; LEMON = Look-Evaluate-Mallampati-Obstruction-Neck mobility score. None of the patients had a LEMON score ≥ 5 and a Cormack-Lehane grade 4.

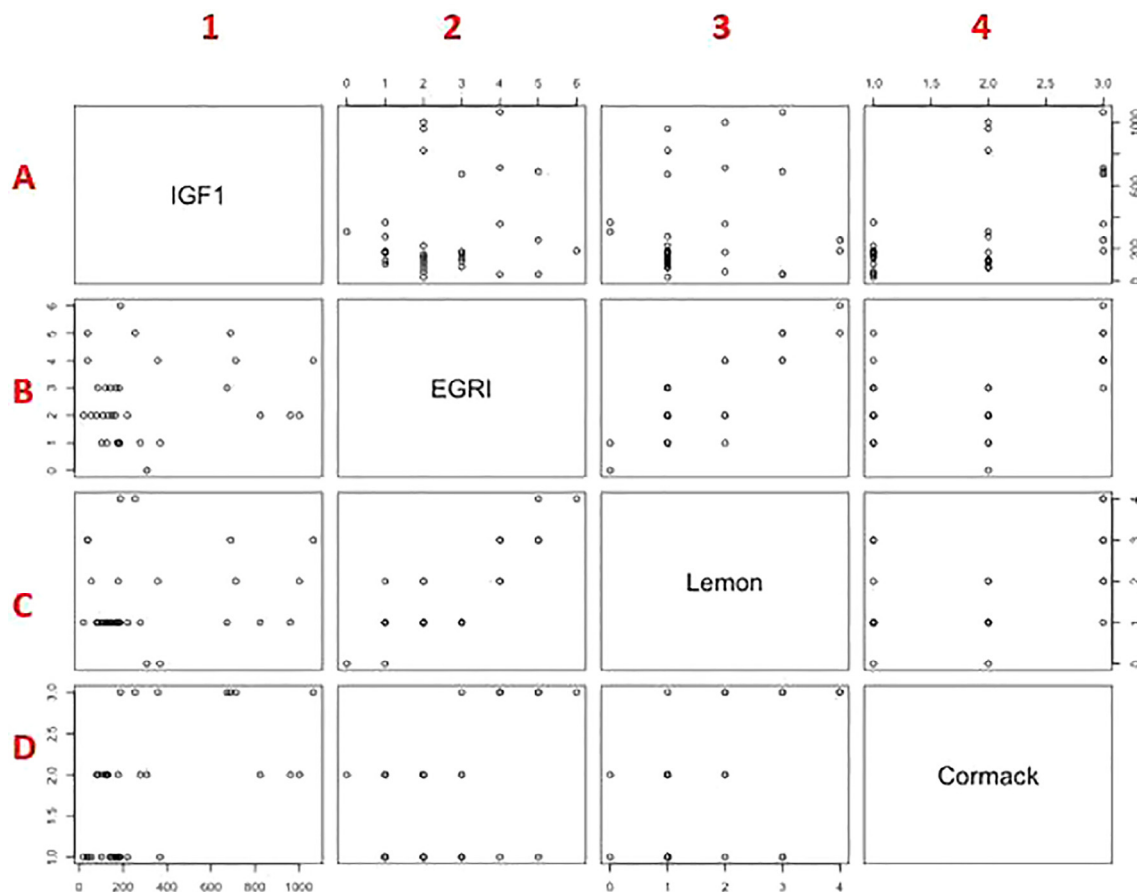|	Male	Female	p value
	n = 20	n = 13	0.223
BMI (kg/m^2) mean (sd)	27.082 (3.578)	27.29 (5.531)	0.8962
IGF-1 (ng/ml) median (IQ range)	145.3 (107.3–193.2)	308.5 (174.9–673.2)	0.06216
Cormack-Lehane			
Grade 1	10	4	0.4073
2	8	4	0.6674
3	2	5	0.08281
LEMON			
Score 0	0	2	0.079
1	14	6	0.3899
2	2	3	0.3457
3	4	0	0.07941
4	0	2	0.1067
EGRI			
Score 0	0	1	0.2148
1	5	1	0.2546
2	6	5	0.6808
3	5	2	0.5579
4	2	2	0.6642
5	2	1	0.8299
6	0	1	0.2148

Fig. 1. Ordinal logistic regression with EGRI, mLEMON and IGF-1.

and mLEMON score, respectively. Eight patients (24.24%) showed a Mallampati score $\geq$ 3. Our patients presented an average value of IGF-1 of 307.24 ng/ml (range 55–205 mg/ml). No significant differences were registered in Cormack-Lehane, EGRI, mLEMON score, Body mass index, and IGF-1 levels between males and females. Table 2.A shows that IGF-1 significantly correlated with Cormack-Lehane (p = 0.005879) but not with mLEMON and EGRI (p = 0.3080 and 0.4146, respectively); interestingly, in multiple regression model both mLEMON and EGRI did not correlate with Cormack-Lehane grade (p = 0.3865 and 0.3205, respectively); conversely, IGF-1 correlation with Cormack-Lehane grade was statistically significant (p = 0.0089) (Table 2.B).

The correlation between IGF-1 and Mallampati score was not significant (p = 0.8653).

Fig. 2 shows ROC accuracy of IGF-1 to discriminate Cormack-Lehane grade 1 and 2 versus grade 3. AUC was 0.8571; cut-off value of IGF-1 serum level was 186.15 ng/ml (CI 95%: 183–520.7 ng/ml). According to ROC analysis, IGF-1 is a moderately accurate test to distinguish the probability to find Cormack-Lehane grade 1 and 2 versus grade 3.

4. Discussion

Our study found a statistically significant correlation between IGF-1 levels and Cormack-Lehane score in patients undergoing transsphenoidal resection of GH-secreting adenoma. In our knowledge, this is the first study that highlighted such a correlation. Furthermore, our findings did not show a relationship between classical predictive scores (i.e. mLEMON and EGRI) and Cormack-Lehane score.

mLEMON and EGRI are two of the most used scores for airways evaluation, and they include classical predictive factors that can be influenced by GH action, such as Mallampati class or body mass index [16,17]. Even if these two scores have been validated in the general population, no studies have been so far conducted to investigate their applicability in patients with GH-producing tumors.

Only a few authors tried to study predictive indices for patients with acromegaly and GH-linked disease to identify a potentially difficult airway.

Schmidt et al. proposed Mallampati as the most important predictive factors to evaluate difficult airways, while, Seidman et al., focused the attention on the anatomic changes due to acromegaly
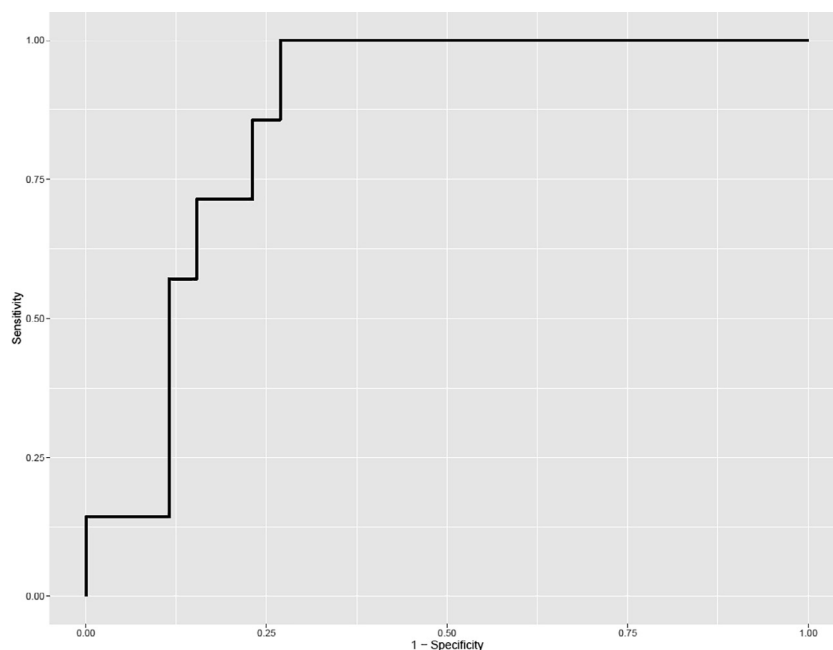
Table 2
A Simple ordinal logistic regression between IGF-1 (Insulin-like Growth Factor-1), Cormack-Lehane grade (CL), LEMON (Look-Evaluate-Mallampati-Obstruction-Neck) mobility score, EGRI (el-Ganzouri index). B. Multiple logistic regression between Cormack-Lehane Grade and IGF-1 (Insulin-like Growth Factor-1), EGRI (el-Ganzouri index), and LEMON (Look-Evaluate-Mallampati-Obstruction-Neck) mobility score.

A	Beta coefficient	p-value
CL-IGF1	0.003583	0.005879
LEMON-IGF1	0.001104	0.3080
EGRI-IGF1	0.0008119	0.4146
B	**Beta coefficient**	**p-value**
IGF1	0.0038	0.0089
LEMON	0.5351	0.3856
EGRI	0.4276	0.3205

Fig. 2. Receiver operating curve (ROC) of Insulin-like growth factor-1 (IGF-1) plasma level to predict Cormack-Lehane grade 1 and 2 versus 3.

which could reasonably affect patient airway such as vocal cord hypertrophy, macroglossia and thyromental distance [14,19].

Khan et al. questioned the usefulness of these single factors, in particular, they stated that Mallampati did not effectively predict difficult airway and proposed the upper lip bite test as an adequately predictive test. Furthermore, they underlined the importance of mandibular length: the longer the jaw is, the larger is the space to displace the tongue [20].

Zhang et al. analyzed some predictive factors and indices of difficult intubation in acromegalic patients. They found that degree of neck extension and circumference, total time of the tracheal intubation, and Mallampati score were higher in acromegaly patients compared to general population. Nevertheless, they did not investigate the relationship between the IGF-1 levels and the above-mentioned factors [21]. Instead, we clearly showed the increasing probability of having a higher Cormack-Lehane grade as the IGF-1 raises.

Our study confirms that current bedside tests are not so effective to discriminate between difficult and easy laryngoscopy; Vannucci et al., in a systematic review highlighted the limits of predictive factors such as Mallampati test, thyro-mental distance, upper lip bite test, inter-incisors gap, and sterno-mental distance [22].

Given these considerations, we strongly believe that standard tests should be integrated with more specific elements to take different pathophysiological conditions into account. IGF-1 represents a paradigmatic example that not only anatomic or biometric examination but even biouomoral markers can help identify patients with potentially difficult intubation. One of the advantages to using a biomarker is that it is a factor which is not subject to personal interpretation; moreover we determined a cut off for IGF-1 level in order to determine the probability to find Cormack-Lehane grade 1 and 2 versus grade 3.

According to our results, IGF-1 could be used as a parameter of a novel score to predict difficult laryngoscopy which should take into account not only anthropometric and clinical factors but also biochemical ones: this could improve patient safety and reduce unexpected difficult intubation. For example, ASA guidelines in the case of unexpected difficult intubation, suggests the use of the video-laryngoscope after failure of the direct laryngoscopy [18]; higher preoperative IGF-1 levels could lead anesthesiologist to use video-laryngoscope as a first line device [23,24]. Moreover, a higher level of IGF-1 could suggest a preoperative otorhinolaryngology evaluation of upper airways to program an awake intubation with fibrobronchoscope. In addition to our findings, it is important to underline that patients with alterations of GH/IGF-1 pathway have a higher incidence of apnea syndrome and a lower functional oxygen reserve and consequently an increased risk of desaturation during intubation [6]. Consequently, IGF-1 can be considered a marker of both anatomical and functional anomalies which could negatively interfere with intubation.

Our findings should be interpreted in the context of some limitations: first it is a pilot study so the sample size is small, nevertheless these are preliminary results in order to conduct a prospective study on a larger population; furthermore, GH-secreting adenoma is a relative rare intracranial tumor. Second, given the retrospective design of the study, some outcomes as successful first attempt, number of attempts, time needed to tube placement, need of larynx external manipulation or to change intubation strategy have not been recorded.

In conclusion, this is the first study investigating the relationship between IGF-1 and Cormack-Lehane grade. We showed that IGF-1 level, unlike EGRI and mLEMON score, significantly correlate with Cormack-Lehane grade.

Further researches are needed to confirm our findings and to investigate the potential role of other hormones secreted by pituitary secreting adenomas to predict difficult laryngoscopy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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