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Respiratory adenomatoid hamartoma must be suspected on CT-scan enlargement of the olfactory clefts*

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SUMMARY

Objective: *To demonstrate that Respiratory Epithelial Adenomatoid Hamartoma (REAH) of the nose, a recently individualized benign tumour, is characterized by a significant widening of the CT-scan width of the olfactory clefts.*

Patients and methods: *Retrospective study comparing, in the axial and coronal planes, the CT-scan maximum width of the olfactory clefts, i.e. the maximum distance between both turbinal ethmoidal walls, of 15 REAH patients, 36 Nasal Polyposis (NPS) and 49 normal individuals.*

Results: *In axial and coronal planes, respectively, the medians of the olfactory clefts width were of 12.2 mm and 12.1 mm for REAH, and 5.6 mm and 5.4 mm for NPS, compared to 4.5 mm and 4.2 mm for normal individuals (both $p < 0.0001$). Total nasal width (i.e. the distance between both medial orbital walls) was not found to be different between groups in both planes. The median ratios "olfactory cleft width / total nasal width" were, for the axial and coronal planes respectively, of 53.1% and 44.7 for REAH, and 23.5% and 22.9% for NPS, compared to 19.2% and 19.1% for normal controls (both $p \leq 0.001$).*

Conclusion: *Compared to normal and nasal polyposis CT-scans, REAH significantly enlarges the olfactory clefts width. Bilateral REAH represent a genuine differential diagnosis of Nasal Polyposis; the CT-scan appears as a major clue to differentiate the two diseases. Endoscopic surgery of REAH definitely confirms their origin in the olfactory cleft, and opens a new field of endoscopic surgery of the olfactory cleft.*

Key-words: respiratory hamartoma, CT-scan, olfactory cleft, nasal polyposis, endonasal endoscopic surgery

INTRODUCTION

The Respiratory Epithelial Adenomatoid Hamartoma (REAH) of the nose, paranasal sinuses and nasopharynx [(1)] is a benign tumor arising from the lining mucosa, which has been individualized in 1995 by Wenig and Heffner [(2)]. REAH seem to be rare as only about fifty cases have been reported in the literature [(2-14)]. They may occur isolated or associated with Nasal Polyposis. Surgical resection seems curative for REAH [(1,2)].

Since our first case in 1998, we have been paying more attention to this entity, and until January 2006, we have evaluated 15 patients with a histological diagnosis of REAH. While the literature is vague concerning the site of implantation within the nose and paranasal sinuses [(1,2,6-9,11,12)], our REAHs were constantly found implanted on the anterior half of the olfactory clefts, bilaterally. No other paper, as far as we know, reports that REAH constantly originate in the olfactory clefts. Besides an appropriate observation through endoscopy, a thorough analysis of the CT-scan images revealed a characteristic and constant enlargement of the width of both olfactory clefts, which led us to suspect their diagnosis pre-operatively.

The aims of this study were (1) to retrospectively measure the CT-scan olfactory clefts maximum width in subjects with REAH, Nasal Polyposis (without REAH) and normal controls; and (2) to demonstrate that the width of the olfactory clefts in the REAH group was significantly larger that the one of the two other groups. The knowledge that REAH originate in the

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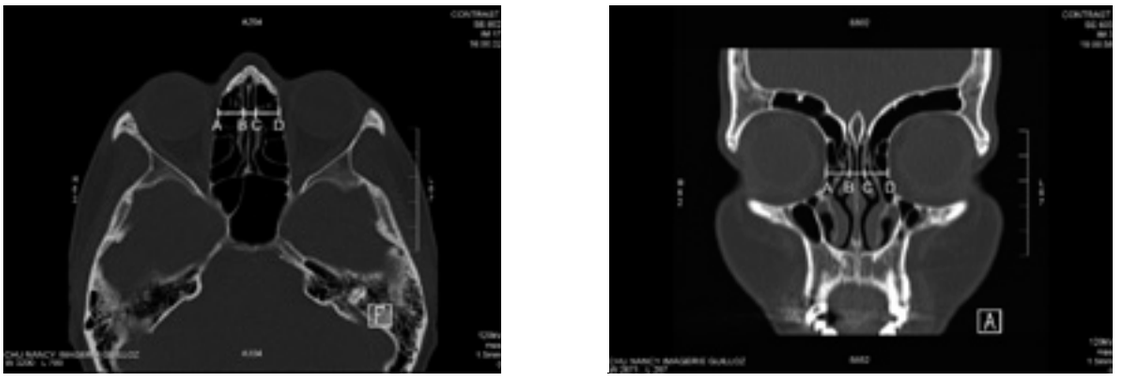

Figure 1. Normal Sinus CT-scan showing measurement method, in the axial and coronal planes. For each image slice on the axial and coronal planes containing the ocular globe (i.e. the anterior olfactory area) measurements were taken. BC distance corresponds to the maximum olfactory clefts width (MOC) in that image, within the plane of the ocular globe. AD distance corresponds to the total nasal width (TN). BC/AD is the proportion of the maximum olfactory cleft width to total nasal fossa width (MOC/TN).

olfactory clefts modifies the surgical approach, as no ethmoidal sinus surgery is mandatory, but rather endonasal endoscopic surgery of the olfactory clefts.

PATIENTS AND METHODS

We designed a retrospective study to compare the CT-scan olfactory clefts maximum width in normal controls, Nasal Polyposis, and REAH patients.

Patients

Nasal and Paranasal Sinus CT-scans of three groups of patients were selected as follows: the first group was formed by all our cases of histologically proven REAH (n=15); all cases were reviewed by two independent pathologists and classified as REAH according to the WHO criteria [(1)]; for the second group we randomly collected 40 patients among the 189 cases operated on Nasal Polyposis (NPS), without REAH on pathological examination, between 2003 and 2005 (Nasalization [(17)] with or without Septoplasty); and the third group consisted of 50 randomly collected normal CT-scans of patients from the database of our Institution's Radiology Department, likely being representative for the general normal population.

The olfactory cleft is anatomically described as being limited superiorly by the cribriform plate of the ethmoid bone, medially by the nasal septum and laterally by the turbinate wall of the ethmoidal labyrinth [(15)]; as REAH, as well as Nasal Polyposis, are bilateral diseases, we considered the olfactory clefts width as the maximum distance between their lateral boundaries, i.e. the maximum distance between both turbinate walls of the ethmoidal labirynths; we considered the total nasal width as the distance between both laminae papyracea, i.e. the distance between both medial orbital walls. In the three groups, only the CT-scans on which both turbinate walls of the ethmoidal labirynths [(15)] and both laminae papyracea could clearly be identified were included. This provided 15 patients for the REAH group, 36 patients for the NPS group and 49 patients for the Normal group.

Methods

The CT-scans of all these patients were blinded (a number was allocated to each patient's CT-scan), mixed up and analyzed in random order.

For each patient, we measured the maximum olfactory clefts width (MOC) and the total nasal width (TN) on each CT slice containing the ocular globe (which corresponds to the anterior olfactory cleft area), both in the axial and coronal planes (Figure 1). The mean slice thickness was 1 mm (range: 0.5 – 1.5 mm). The measurements were made on film CT-scans, using a millimeter ruler, and normalized according to the scale provided on the films. The ratio olfactory clefts width to total nasal width (MOC/TN) was calculated. A total of 2212 measurements were performed: 428 for the REAH group, 730 for the NPS group and 1054 for the Normal group. The mean value of measurements performed on all slices in a given individual was calculated to produce each outcome individual value.

Statistical analysis

The outcomes (MOC, TN and MOC/TN, in both axial and coronal planes) were described using median, quartiles and range.

Group pairwise comparison of outcomes was conducted using the non-parametric Wilcoxon rank test. To protect against multiple testing between the three groups, the type I error was set at alpha = 0.01. The statistical analysis used the SAS system V8.02.

RESULTS

The REAH group was composed by 8 men and 7 women, with a median age of 57 years (38 to 93 years). Symptoms of chronic nasal dysfunction going on from 2 to 20 years, combining major nasal obstruction and hyposmia/anosmia, were present in the majority of cases. Anterior rhinoscopy showed bilateral polypoid lesions (stage II to IV; i.e. up to the superior limit of the inferior turbinate, and exteriorizing through the nasal vestibule, respectively)* in all cases; in one case a bigger unilateral polyp clinically evoked a diagnosis of malignancy. CT-scan

images showed characteristic large olfactory clefts in all cases (Figure 3). The medians of maximum olfactory clefts widths (MOC) were 12.2 mm (7.3-19.4) and 12.1 mm (7.3-18.3) in the axial and coronal planes, respectively (Table 1a).

The NPS group consisted of 23 men and 13 women, ranging from 11 to 68 years, with a median age of 48 years. All patients complained of chronic nasal dysfunction. Observation showed bilateral nasal polyps with the usual macroscopic appearance (pale white-pink masses arising from the middle meatus, smooth surfaced and soft elastic on touch). CT-scan images showed typical features (Figure 4). The medians of MOC were 5.6mm (2.8-8.9) and 5.4mm (3.2-9.1) for the axial and coronal planes, respectively (Table 1a).

In the normal control group, the medians of MOC in the axial plane were 4.5mm (3.1-6.5) and in the coronal plane 4.2mm (3.1-6.8) (Table 1a and Figure 1).

The total nasal width (TN) was very similar in all groups (median around 24 mm), ruling out important differences of the size of the nose between patients ($p > 0.01$) (Figure 2a). In the patient group outcomes pairwise comparison, the Wilcoxon tests found statistically significant differences for all outcomes (other than TN) between all groups for 0.01 threshold ($p \leq 0.001$) (Table 2b). Not only were REAH and NPS greater than normal, but also REAH was significantly greater than NPS: in patients with REAH, the median MOC was more than twice (around 12 mm) the one of NPS (around 5mm) and Normal (around 4 mm) (Figure 2b). As a consequence, the ratios MOC/TN were significantly greater in REAH than in NPS and normal (Figure 2c): on axial planes, median MOC/TN were 53.1% for REAH, versus 23.5% in NPS ($p < 0.0001$) and 19.2% in Normal ($p < 0.0001$); on coronal planes, median MOC/TN were 44.7% in REAH versus 22.9% in NPS ($p < 0.0001$) and 19.1% in Normal ($p < 0.0001$).

Table 1a. Descriptive statistics for the three groups. MOC – maximum olfactory clefts width; TN – total nasal fossa width; MOC/TN – relationship of olfactory clefts width to total nasal width; LQ: lower quartile; UQ: upper quartile. Note the higher values of MOC and MOC/TN of REAH patients relatively to the other two groups.

	REAH patients (n=15)					
	Variable	LQ	Median	UQ	Min	Max
Axial	MOC (mm)	9.0	12.2	15.7	7.3	19.4
	TN (mm)	18.7	24.6	25.7	15.5	30.7
	MOC/TN (%)	36.5	53.1	68.8	28.9	100
coronal	MOC (mm)	9.5	12.1	15.0	7.3	18.3
	TN (mm)	22.3	25.5	28.7	21.5	31.5
	MOC/TN (%)	36.7	44.7	60.1	31.3	69.2
	Nasal Polyposis patients (n=36)					
	Variable	LQ	Median	UQ	Min	Max
Axial	MOC (mm)	4.9	5.6	6.6	2.8	8.9
	TN (mm)	22.3	24.5	26.8	17.7	33.1
	MOC/TN (%)	18.4	23.5	28.7	10.0	44.6
coronal	MOC (mm)	4.4	5.4	6.3	3.2	9.1
	TN (mm)	22.6	23.5	25.0	20.0	31.1
	MOC/TN (%)	19.7	22.9	27.1	15.7	37.7
	Normal controls (n=49)					
	Variable	LQ	Median	UQ	Min	Max
Axial	MOC (mm)	4.2	4.5	5.2	3.1	6.5
	TN (mm)	21.8	24.4	26.6	16.6	33.8
	MOC/TN (%)	17.4	19.2	21.9	11.9	29.2
coronal	MOC (mm)	3.8	4.2	4.9	3.1	6.8
	TN (mm)	21.7	23.9	27.4	15.9	30.8
	MOC/TN (%)	17.0	19.1	21.8	11.7	34.5

Table 1b. Non-parametric Wilcoxon rank test (one-sided Pr > Z).
p values for the comparisons between groups for all variables; the threshold value was considered 0.01.

	axial			coronal		
Comparison	MOC	TN	MOC/TN	MOC	TN	MOC/TN
REAH - Normal	<0.0001	0.33	<0.0001	<0.0001	0.07	<0.0001
NPS – Normal	<0.0001	0.34	0.0013	<0.0001	0.42	0.0003
REAH - NPS	<0.0001	0.25	<0.0001	<0.0001	0.048	<0.0001

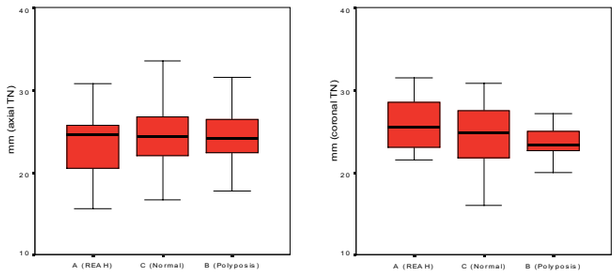

Figure 2a

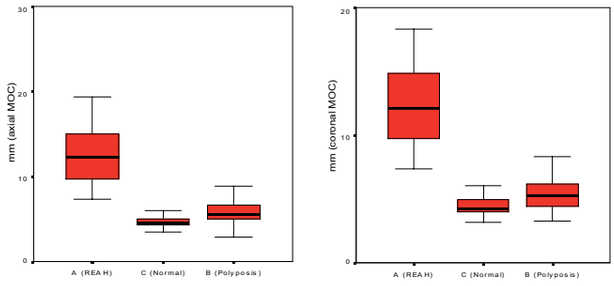

Figure 2b

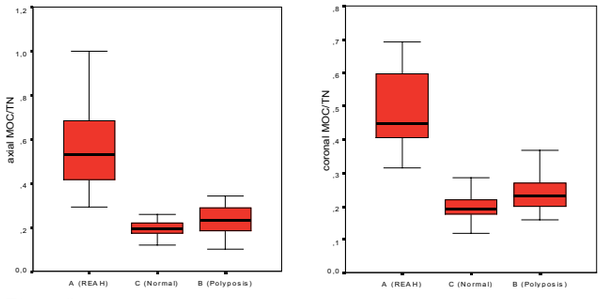

Figure 2c

Figure 2. Descriptive statistics boxplots for the variables in the axial and coronal planes. (a) total nasal width (TN) – no statistical difference was found between groups. (b) maximum olfactory clefts width (MOC) – note the degree of difference between group A and the other two groups. (c) ratio olfactory clefts width to total nasal width (MOC/TN) – like MOC, there is also a larger MOC/TN in group A.

DISCUSSION

Hamartomas of the sinonasal tract seem relatively uncommon, with only about 50 cases described in the literature [1,2-14]. The majority of them are of pure epithelial type (REAH), although pure mesenchymal hamartomas or mixed epithelial-mesenchymal hamartomas may also occur. Unlike teratomas, they are devoid of ectodermal, neurectodermal and/or mesodermal elements [1].

The REAH is a pathological entity individualized by Wenig and Heffner in 1995 in a series of 31 cases [2]. It is a benign overgrowth of the surface respiratory epithelium, which leads to pseudoglandular development in the lamina propria. REAH has been described as being similar to an inflammatory polyp, but with a macroscopically polypoid-exophytic appearance, indurated and rubbery quality and tan-white to red-brown color. Histologically these lesions are characterized by a prominent glandular-like structure proliferation, lined by ciliated respiratory epithelium originating from the surface epithelium; typical features, but not well known to every pathologist. They may arise and co-exist in the setting of inflammatory polyps [1,2,10], raising a possible developmental induction secondary to the inflammatory process. They can also develop primarily, favoring secretion retention in the ethmoid and other paranasal sinuses. Clinically they might present as a differential diagnosis of neoplasic lesions like Inverted Papilloma or Adenocarcinoma [2].

REAH predominantly occur in adult patients, with a male predominance, from the 3rd to the 9th decade of life, with a median age on the 6th decade [1,2,9].

They can present uni- or bilaterally, with non-specific symptoms like nasal obstruction, nasal stuffiness, hyposmia, epistaxis and recurrent or chronic rhinosinusitis. The site of implantation in the sinonasal tract is not precisely described in the literature, with the majority of them being found in the nasal cavity, particularly on the nasal septum; they were also seen to arise along the middle meatus, ethmoid, maxillary and frontal sinuses, inferior turbinates, and the nasopharynx [1,2,6-,9,11,12,16]. Conservative surgical resection seems to be curative, with no recurrences reported in variable follow-up periods (from 4 months to 5 years) [1,2,5-7,9,12,14].

No data regarding the CT-scan characteristics of sinonasal hamartomas was found in the literature.

Our first case, in 1998, was a pathological finding in a patient treated through endoscopic endonasal surgery for what was thought to be an Inverted Papilloma or Esthesioneuroma. Five more cases were then diagnosed sporadically between 1998 and 2004. The remaining 9 cases were found between 2004 and 2006. It is our impression that since we know how to recognize and diagnose this tumor, its frequency is increasing. Our series is epidemiologically according to the literature; the symptoms described by the patients are the same, and very like those of Nasal Polyposis. Anterior rhinoscopy showed bilateral nasal polyps stage II to IV in all patients, but a close inspection of the mass lesions, especially with an endoscope with the patient under general anesthesia, before starting the surgical procedure, revealed some differences to the inflammatory polyps: a more red-brown color, papillomatous surface, indurated and fibrotic to the touch and, most importantly, a different site of implantation. In our series, the REAHs were bilateral and found to constantly originate in the anterior half of the olfactory grooves, contrary to the polyps of Nasal Polyposis which are developing in the ethmoidal labyrinths and protruding from the middle or superior meatus into the nasal cavities. No other case series report was found in the literature describing such a characteristic location of the REAH in the olfactory clefts.

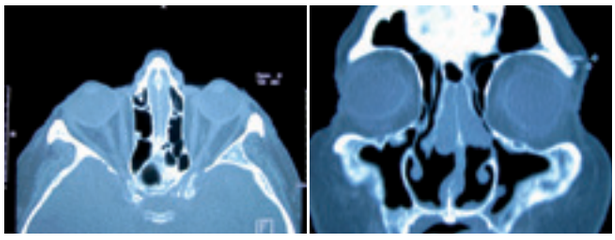

Figure 3a

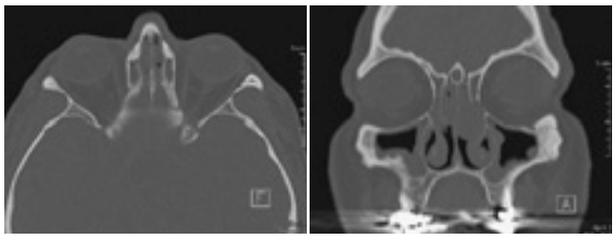

Figure 3b

Figure 3. CT-scans of two patients with REAH, showing the characteristic widening of the olfactory clefts in both axial and coronal planes. Observe the lateral displacement of the turbinate walls of the ethmoidal labyrinths. (a) CT-scan of a patient with REAH of the olfactory clefts and normal sinus ventilation. (b) CT-scan of a patient with REAH of the olfactory clefts and bilateral ethmoidal opacities.

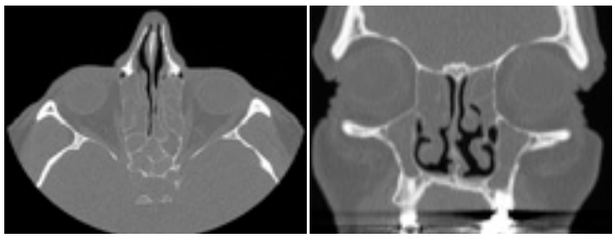

Figure 4. CT-scan of a patient with Nasal Polyposis. Observe the presence of bilateral ethmoido-maxillary opacities and the small width of the olfactory cleft.

The CT-scan is an essential tool in the evaluation of a patient with chronic nasal dysfunction. In our REAH series, the CT-scans show an enlargement of the olfactory clefts in all patients, particularly on its most anterior part, displacing the turbinate wall of the ethmoidal labyrinth [15] laterally, narrowing the ethmoidal space (which can lead to secretion retention), which is clearly viewed either on the axial or coronal planes (Figure 3), raising the hypothesis of not just common Nasal Polyposis. In fact, in our last eight cases, the diagnosis of REAH was evoked in the pre or per-operative setting, based on these characteristics.

Fourteen patients were given indication for surgical treatment; one patient was not operated because of his debilitating general condition, but the diagnosis was confirmed histologically, with a biopsy. In most cases, a complete resection was possible, thanks to a meticulous dissection of the olfactory cleft and cribriform plate. A nasalization procedure [17] was undertaken in 8 cases, due to the finding of associated polyps in the middle meatus. In these 8 cases, the surgical specimens coming from the olfactory clefts were always addressed separately from those coming from the ethmoids and the pathologist could clearly make the distinction between classical polyps and REAH. In 2 cases with ethmoidal opacities on the CT-scan but no polyps found intra-operatively, only retained secretions could be aspirated from the ethmoids. The four remaining cases had only surgery of the olfactory clefts. No per-op or late complication has to be reported in this series.

Our study shows that REAH significantly enlarges the CT-scan olfactory clefts, confirming in our series of 15 consecutive cases, its origin in the olfactory cleft. REAH patients also show an increment of MOC/TN that is statistically bigger than in the other 2 groups. In Nasal Polyposis (without REAH), MOC and MOC/TN were also significantly bigger than in Normal, but the difference in widths was only about 1 mm. This small widening can be explained by the inflammatory and edematous swelling of the mucosa covering the turbinate wall of the ethmoid labyrinth in NPS patients. The enlargement of the olfactory clefts seen on CT-scans of NPS patients is almost imperceptible to the naked eye, whereas that seen in REAH is outstanding (Figures 3 and 4).

This characteristic bilateral widening of the CT-scan olfactory clefts permits a high degree of diagnostic suspicion; combined to the characteristic endoscopic presentation, the diagnosis of bilateral REAH of the olfactory clefts can be suggested to the pathologist before histological examination. The diagnosis of REAH can, however, be difficult for the pathologist who has no knowledge about this recently individualized tumor (1995) [1,2]. The pathologist might easily differentiate REAH from inverted papilloma or adenocarcinoma (which are the two other clinical differential diagnosis), but the risk is he might conclude, by default, with common inflammatory polyps.

Surgical treatment is reported to be curative for REAH [1,2,5-7,9,12,14] and we have also not experienced any recurrence of REAH after total resection, in the short follow-up of our patients. As in many cases of REAH, the ethmoidal opacities might be secondary to ostio-meatal obstruction due to compression by the REAH tumour, the surgical approach should be directed primarily towards the olfactory clefts and not the ethmoid sinuses. The true prevalence of the association between REAH and nasal polyposis is currently difficult to approach, as many REAHs have probably until today not been recognized and were operated as nasal polyposis (i.e. polypectomy or ethmoidectomy). More attention needs to be paid from now to differentiate REAH of the olfactory clefts from nasal polyposis, as not only the recurrence rate seems different but also the surgical approach. Our current experience with

REAH surgery has convinced us that endoscopic surgery of the olfactory cleft with dissection of the cribriform plate is possible without complication. To plan safe endoscopic olfactory cleft surgery needs, however, that the diagnosis of REAH has been suspected on the CT-scan.

CONCLUSION

The REAH is a well defined pathological entity, but unknown to many clinicians and pathologists. Despite being reported as a rare occurrence, REAH are probably underdiagnosed. Our series differs from others already published by the site of implantation, characteristically found in the anterior half of the olfactory clefts, which is clearly seen on CT-scan images as a widening of the most anterior part of both olfactory clefts. This widening of the olfactory clefts, clearly seen with the naked eye, leads to a high degree of suspicion of REAH. Its recognition is extremely important, as a different surgical approach should be advised; inappropriate diagnosis could lead to extensive and unnecessary surgery.

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