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Research Article

Case-control Study to Evaluate the Association Between Reinke's Edema and Central Hypothyroidism

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Abstract

Objective: To evaluate the association between Reinke's Edema and central hypothyroidism in the population from the state of Bahia.

Methods: It was held a longitudinal observational study of the type of case control study. The case group was formed by patients with Reinke's Edema, aged 40 years or more. Control group was made by female patients aged 40 years or more with other benign pathologies of the larynx. The diagnosis of central hypothyroidism is based on the biochemical analysis: the patients show low circulating concentrations of free T4, associated to normal to low serum levels of TSH.

Results: The study had 26 patients in the case group and 26 in the control group. Central hypothyroidism was found in 17,6% of the case group; as it had not been found in the control group, it was not possible to calculate the OR; however, data showed statistical significance (p 0,034).

Conclusion: When compared to the primary one, and, usually, it does not show goiter, and the TSH values, in most the cases, are not high; these characteristics seem to make it difficult the clinical suspicion, and it can cause controversies regarding the association between hypothyroidism and Reinke's edema.

Keywords: Reinke's Edema; Hypothyroidism; Central Hypothyroidism

Abbreviations

TSH: Thyroid Stimulating Hormone; T4: Thyroxine; SPSS: Statistical Package for the Social Sciences; MRI: Magnetic Resonance Imaging

Introduction

The voice is essential to man as an individual, because, beyond differentiating him in the other ones in the animal scale, it is a valuable adjuvant in his social, intellectual and emotional life. From birth to old age, the phonatory function continually changes, due to changes of growth, hormonal action and structural deterioration of the larynx. The are many the alterations in the larynx that compromise the individual's good phonation. Among them there is the Reinke's edema, which corresponds to the increase of the fluid in the superficial layer of the blade itself, that had been described for the first time, in 1891, as larynx's edema [1].

The larynx shows specific receptors for the action of hormones. Some authors identified thyroid receptors in larynx of corpses [2], giving important information on how the thyroid hormones act in the larynx.

Was reported higher incidence in females, in the reports that associated the Reinke's edema to Middle-aged women and to hypothyroidism [3]. In another study Reinke's edema was recorded in patients from 31 to 74 years old, with mean age of 49,4 years and almost double the incidence in females [4]. Was also reported higher incidence of thyroid disfunctions in these patients [5]. Through the stimulation of the thyroid gland held a study in 28 patients with Reinke's edema, being 5 (18%) males and 23 (82%) females, in which They observed that subclinical hypothyroidism is the organic pathology that is more frequently correlated with Reinke's edema, determined by the accumulation of mucopolysaccharides in the subepithelial area of the vocal folds [6].

In a more recent study it was observed, in some patients, the decrease of free T4, without the increase of TSH [7], as it is observed from the primary hypothyroidism [8].

Central hypothyroidism is characterized by a default in the secretion of thyroiodin hormone, which results from the insufficient stimulation of TSH by a healthy thyroid gland [9-14]. This condition can be a consequence of a disorder in the anatomy or role of the pituitary and/or hypothalamus.

The global prevalence of central hypothyroidism varies from 1 in 20,000 to 1 in 80,000 individuals in the general population [15], and it is a rare cause of hypothyroidism (1 in 1,000 patients with hypothyroidism) [9].

Central hypothyroidism can be congenial (i.e., caused by genetic disorders) or acquired (i.e., They result from lesions as tumors, traumas, or cerebrovascular accidents that affect the axis hypothalamus-pituitary) [13].

Disorders in the secretion of TSH can be quantitative (reduced reserve of TSH r), qualitative (i.e., reduction of bioactivity of the released molecules of TSH) or both [16-23]. The qualitative disorder in the secretion of TSH could explain the lack of correlation between circulating levels of thyroiodin hormone, and concentrations of TSH, in patients with central hypothyroidism. Also, the post-traditional processing of TSH, especially the glycosylation of TSH, is fundamental for the modulation of the bioactivity of TSH [17,24-26].

The objective of this study was to evaluate the association between Reinke's Edema and central hypothyroidism in the population from the state of Bahia-Brazil.

Materials and Methods

It was held a longitudinal observational study of the type of case control study. The case group was formed by patients with Reinke's Edema, aged 40 years or more who had been attended in the ambulatory of otorhinolaryngology at Santo Antônio Hospital, in Salvador-BA. Control group was made by female patients aged 40 years or more who had been attended in the ambulatory of otorhinolaryngology, with other benign pathologies of the larynx.

The approval of the protocol was submitted to the Ethics Committee and all the guest patients had declared their written consent, being free to give up the study at any time. Data was extracted from the work "Evaluation of the metabolic profile of female patients with Reinke's edema" (CAAE (Ethics Committee in Research): 73297317.5.0000.0047). An epidemiologic questionnaire was handed in asking for information on smoking, and the following laboratory exams were dosed: TSH, Free T4 and Total T4.

The diagnosis of central hypothyroidism is based on the biochemical analysis: the patients show low circulating concentrations of free T4, associated to normal to low serum levels of TSH [27].

For the two groups, the laboratory results were classified as normal or altered exams, based on the 'Case records of the Massachusetts General Hospital. Weekly Clinicopathological Exercises. Laboratory Reference Values' [28].

In the statistical analysis it was used the odds ratio, and for the estimator's accuracy it was used the confidence interval of 95%. The quantitative variables with normal distribution were reported as mean and standard deviation and, for the variables with non-normal distribution, according to the median and interquartile range. The normal variables were identified through Shapiro-Wilk test. The categorical variables were related as frequencies and percentages. The bivariate comparisons among the groups were held by using the t-Student test for numerical variables with normal distribution. The categorical variables were compared through

Pearson's chi-square or through Fisher's exact test, whenever necessary.

The statistical analysis was held using the software SPSS (v.25, Chicago, IL), R Program (v.3.6.1) and Microsoft Excel 2016.

Associated risks with blood collection include: pain, hematoma or any other discomfort in the area of the collection. Rarely, there may be fainting or infection in the area of the punction. There was taken all the needed care to minimize these risks.

There is not a direct benefit for the participant in this study. It is a case control study that tests the hypothesis that central hypothyroidism shows association with Reinke's edema. Only after the holding of new studies and discussions with the academic community, we can perceive some benefits. However, the obtained results in this study can help in the disease management, in question, through the knowledge of possible associated co-morbidity. The results of the exams were handed in to the participants, and the found amendments were sent to the endocrinology team.

Inclusion Criteria: case group – female patients, older than 40 years old with Reinke's edema that had been attested by two otorhinolaryngologists, and who had been attended in the otorhinolaryngology ambulatory, in the study hospital, in the period from January 2018 to February 2020. Control group – female patients, older than 40 years old with other benign laryngeal pathologies (except for Reinke's edema), attested by two otorhinolaryngologists, and who had been attended in the otorhinolaryngology ambulatory, in the study hospital, in the period from January 2018 to February 2020.

The patients who had agreed to participate in the study, had read and signed the form of free and informed consent.

The exclusion criteria were: age lower than 40 years old, does not accept to participate, withdrawal during the study, non-collection of exams, problems in the implementing of the evaluation and on achieving results and, finally, if the patient even die during the study.

Results and Discussion

The study had 26 patients in the case group and 26 in the control group, totaling 52 patients. The mean age in the case group was 59,5 years and 52,5 years in the control group. The groups were homogeneous, from the point of view of ethnicity, schooling, alcohol consumption, sedentarism and vocal abuse (Table 1). The case group showed higher association with the presence of comorbidities (OR 16, p0,002), higher average of comorbidities ($p < 0,001$) (Table 2), and also higher association with anxiety and/or insomnia (OR 7,8, p0,037) as well as smoking (OR 54, $p < 0,001$). See tables 1 and 2 below.

Variables	Groups			OR	p-value
	Category	Case (26)	Control (26)		
		n (%)	n (%)		
Ethnicity	White	6 (26,1)	7 (35,0)	-	0,765
	Black	9 (39,1)	6 (30,0)		
	Brown	8 (34,8)	7 (35,0)		
Sedentarism	Yes	22 (88,0)	19 (73,1)	2,70 (0,61 - 11,93)	0,180
Schooling	Illiterate	4 (16,0)	1 (4,2)	-	0,50
	Complete Elementary School	1 (4,0)	2 (8,3)		
	Incomplete Elementary School	12 (48,0)	12 (50,0)		
	Complete High School	7 (28,0)	5 (20,8)		
	Incomplete High School	1 (4,0)	0 (0,0)		
	Complete Superior Course	0 (0,0)	4 (16,7)		
Vocal abuse	Yes	20 (80,0)	20(76,9)	1,20 (0,31 - 4,58)	0,789
Comorbidity	Yes	24 (96,0)	15 (60,0)	16,00 (1,86 - 137,97)	0,002
Anxiety/ Insomnia	Yes	6 (24,0)	1 (3,8)	7,8 (0,88 - 71,21)	0,037

Systemic Arterial Hypertension	Yes	11 (44,0)	9 (52,9)	1,48 (0,48 - 4,59)	0,493
Diabetes mellitus	Yes	6 (37,5)	3 (14,3)	3,60 (0,74 - 17,60)	0,103
Alcoholism	Yes	11 (44,0)	13 (52,0)	0,725 (0,24 - 2,21)	0,571
Smoking	Yes	24 (96,0)	8 (44,4)	54,00 (6,19 - 417,45)	< 0,001
Source: Survey's Data.					

Table 1: Univariate analysis of participants' epidemiologic data.

Variables	Patient's group		
	Case (26)	Control (26)	p-value
	Average (IIQ)	Average (IIQ)	
Age (years)	59,5 (56 - 66)	52,5 (46 - 60)	< 0,001
Number of comorbidities	2 (1 - 3)	1 (0 - 1)	< 0,001
Number of comorbidities in the family	2 (1 - 2,5)	1 (0,5 - 1)	< 0,001
Smoking time (years)	40 (30 - 45)	26,5 (17 - 41)	0,052
Vocal abuse time (years)	20 (6,5 - 35)	13 (10 - 17)	0,345
Source: Survey's Data.			

Table 2: Univariate analysis of participants' sociodemographic data.

Central hypothyroidism was found in 17,6% of the case group; as it had not been found in the control group, it was not possible to calculate the OR; however, data showed statistical significance (p 0,034).

Variables	Groups			
	Case	Control	OR	p-value
	n (%)	n (%)		
Central hypothyroidism (Free T4 < 0,8 and TSH < 4,7)	3 (17,6)	0 (0)	-	0,034
Source: Survey's Data.				

Table 3: Univariate analysis of participants' laboratory data.

The clinic characteristics of central hypothyroidism depends on etiology, seriousness of the hypothalamic-pituitary extension, seriousness of associated hormonal disorders, and the patient's age in the beginning of the disease [29,30]. The symptoms and signs of hypothyroidism include fatigue, depression, intolerance to coldness, hoarseness, dry skin, constipation, bradycardia and hyporeflexia, and they are usually the same, but less serious than the ones of primary hypothyroidism, and goiter is rarely present.

As in patients with primary hypothyroidism, the ones with central hypothyroidism that had not been treated, can show, as consequences, adverse cardiovascular effects [31]. The doppler echocardiogram is a sophisticated method to investigate the cardiac function, and it is even useful to record minimum signs of disorders that can be secondary to central hypothyroidism.

Central hypothyroidism is usually diagnosed when measuring the circulating levels of T4, because this is a clinically difficult condition to be recognized [27,32]. Also, the serum levels of TSH are usually from low to normal, or, even, slightly high, in patients with tertiary hypothyroidism (hypothalamic).

An evaluation through MRI of the hypophysis, and an evaluation of the hypothalamic- pituitary axis must be taken into consideration after the biochemical diagnosis of central hypothyroidism, if there is family history of confirmed central hypothyroidism, a suggestive clinical history including trauma, subarachnoid hemorrhage, previous cerebral irradiance or confirmed surgery, or if there are confirmed symptoms as headaches or disorders in the visual field [33].

As in the primary hypothyroidism, the objective of the treatment of hypothyroidism is the restoration and maintenance of euthyroidism [34].

The therapy with levothyroxine is the main treatment for central hypothyroidism. The treatment and following up are difficult to be personalized, because in the central defects, the analysis of circulating levels of TSH is not a reliable indicator in the action of the thyroiodin hormone. Nevertheless, the only measure than can be used to monitor if the dose with levothyroxine is efficient, the used one is of the circulating concentrations of free thyroid hormones, particularly free T4. In general, it is assumed that serum levels of free T4, from the medium area to the superior one, represents an appropriate target in patients with central hypothyroidism that make use of levothyroxine [35].

Conclusion

As herein discussed, central hypothyroidism has more discrete symptomatology When compared to the primary one, and, usually, it does not show goiter, and the TSH values, in most the cases, are not high; these characteristics seem to make it difficult the clinical suspicion, and it can cause controversies regarding the association between hypothyroidism and Reinke's edema. Since the minority of patients with Reinke's edema have hypothyroidism (17,6%), this pathology is probably presented as an associated type and not as the cause. However, other populations need to be studied in order to evaluate if there is a replicability of results.

Conflict of Interest

There is no conflict of interest on the part of the authors in the study carried out.

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