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Destroyed thyroid by acidic blood during subarachnoid hemorrhage: Experimental study

Subaraknoid kanama sırasında asidotik kanla oluşan tiroid harabiyeti: Deneysel çalışma

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Abstract

Aim: Metabolic acidosis can negatively affect thyroid functions. The aim of this study is to show the damage in the thyroid gland caused by acidosis following subarachnoid hemorrhage (SAH).

Methods: Twenty rabbits were chosen from our recent SAH studies. Five healthy rabbits were included in the control group, five were included in the SHAM group, which received 1 ml of saline, and ten rabbits, chosen from SAH-induced animals with decreased blood pH, constituted the study group. TSH, T3, T4 and blood pH values were recorded before, during and after the experimental procedures. Densities of the normal and degenerated epithelial cell of thyroid glands were estimated using stereological methods. The relationship between blood pH and thyroid hormone values, and degenerated epithelial cell densities were analyzed statistically.

Results: pH values of blood were measured as 7.35 (0.037), 7.32 (0.05), and 7.21 (0.012) in the control, SHAM and SAH groups, respectively. The estimation of normal and degenerated epithelial cells per square millimeter of follicles was calculated as wall surface/cell surface. The mean normal epithelial cell count was 5,000 (750) in normal thyroid follicles. Mean degenerated epithelial cells counts were 50 (9) in the normal group, 154 (30) in the SHAM group and 460 (80) in the study group. For all results there was statistically significant difference between the control, SHAM and SAH groups (P<0.001).

Conclusions: Acidosis, one of the most fatal complications of SAH, may damage the thyroid gland with neurovascular network degeneration.

Keywords: Subarachnoid hemorrhage, Acidosis, Destroyed thyroid gland

Öz

Amaç: Metabolik asidoz tiroid fonksiyonlarını olumsuz etkileyebilir. Bu çalışmanın amacı subaraknoid kanama (SAK) sonrası oluşan asidozun tiroid bezinde yaptığı harabiyeti göstermektir.

Yöntemler: Çalışma, son SAK deneylerinden seçilen yirmi tavşan verilerinden seçildi. Tiroid bezlerini analiz etmek için kontrol grubu olarak beş tavşan (n=5) seçildi; 1 cc salin enjekte edilen SHAM grubu (n=5) ve SAK sonrası asidoz oluşan tavşanlardan seçilen on tavşandan oluşan çalışma grubu (n=10) saptadı. Deney prosedürleri öncesinde, deney sırasında ve sonrasında TSH, T3, T4 ve düşük pH değerleri kaydedildi. Tiroid bezlerinin normal ve dejenere epitel hücresinin yoğunlukları stereolojik yöntemler kullanılarak hesaplandı. pH ve tiroid hormon değerleri, dejenere epitel hücre yoğunlukları arasındaki ilişki istatistiksel olarak analiz edildi.

Bulgular: Kanın pH değerleri kontrolde 7,35 (0,037), SHAM'da 7,32 (0,05), SAK grubunda 7,21 (0,012) SAH grubunda tespit edildi. Duvar yüzeyi/hücre yüzeyi olarak hesaplanan foliküllerin milimetre kare başına normal/dejenere epitel hücre sayısı hesaplandı. Normal tiroid foliküllerinde normal epitel hücre sayısı 5.000 (750) idi. Dejenere epitel hücre sayısı normal grupta 50 (9) idi; SHAM grubunda 154 (30) ve çalışma grubunda 460 (80) olarak hesaplandı. Tüm sonuçlar için kontrol grubu ile SHAM ve SAH grupları arasında istatistiksel olarak anlamlı fark bulundu (P<0,001).

Sonuç: SAK'ın en ölümcül komplikasyonlarında biri olan asidoz nörovasküler ağ dejenerasyonuyla tiroid bezinde hasar oluşturabilir.

Anahtar kelimeler: Subaraknoid kanama, Asidoz, Tiroid bezi harabiyeti

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Introduction

Current literature has not mentioned that hypothyroidism is the most dangerous complication of acidosis during subarachnoid hemorrhage (SAH). The acidotic injury was first sampled with choroid plexus in acidotic cerebrospinal fluid of brain ventricles by Ozmen et al. [1]. All body fluid pH is mainly regulated by the Carotid body network [2]. Carotid body network injury is the most accountable factor for acidosis following SAH [3]. Binuclear neuronal denervation injury of the carotid body can result in decreased pH in all compartments. In this study, we showed that acidic blood could destroy the thyroid gland, which may lead to untreatable hypothyroidism during or following SAH. Acidosis could cause multiple endocrinopathies [4]. It is known to decrease thyroid hormone levels in newborns , result in encephalopathy complicated with myxedema [5-7]. Thyrotoxicosis is also frequently seen during acidosis [8]. Treatment of metabolic acidosis reportedly improves thyroid function [9]. Hypothyroidism resulting from thyroid gland injury induced by acidic blood was firstly described by that study.

Materials and methods

Twenty rabbits were used in this study. Animal care and the study design followed the guidelines of the Guide for the Care and Use of Laboratory Animals. The study design was approved by the Committee of Animal Research in Ataturk University.

Five rabbits were used to analyze the normal structure of CN_{IX}-Carotid body. Five rabbits were included in the SHAM group, and received injection of 1 ml saline into cisterna magna. The remaining ten rabbits received 1 ml of autologous arterial blood injection into the cisterna magna to create subarachnoid hemorrhage. Blood pH values were recorded by using a pH meter (Mettler Toledo MP 220 pH Meter, Schwarzenbach, Switzerland) before the experiment, three times a week, for two weeks and just before sacrification. Then, they were sacrificed under general anesthesia after all thyroid glands were excised and fixed in 10% formalin solution. Fixed brain tissues were embedded in paraffin blocks, and twenty consecutive sections of 5 µm were obtained for stereological examinations. Thyroid gland preparates were stained with hematoxylene&eosin (H&E) and TUNEL methods as well as Aldehyde Fuchsin. All sections were examined under the light microscope, and the stereological method was used for the determination of epithelial cell density of the thyroid follicles: Cytoplasmic darkening, nuclear narrowing, angulated cells, and peri-cytoplasmic halo development were considered neuronal degeneration criteria. Follicular cell density was estimated by dividing the follicle's inner surface area into the cell sectional surface area.

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 22.0 (IBM, Armonk, NY, USA). Blood pH, thyroid hormone levels, thyroidal follicles cell density were analyzed with the statistical method. Normal distribution of data was assessed with the Kolmogorov–Smirnov or Histogram test. Continuous variables were expressed as mean (standard deviation) (SD). The groups were compared using the One-Way ANOVA test for independent variables. Kruskal Wallis test was used for the non-normally distributed data. *P*-value of less than 0.05 was considered statistically significant.

Results

Clinical and electrophysiological results

In physical examination, consciousness, meningeal irritation, heart rhythm, and respiration disorders returned to normal after one week. Ischemic autonomic network findings were recorded as heart rhythm disorders with depressed ST, bi/trigeminal pulses, separated QRS, and atrioventricular fibrillations in electrocardiograms of animals with SAH. Acidotic respiratory parameters were detected as frequent respiration with decreased respiration amplitude, shortened inspiration/prolonged expiration, apnea-tachypnea intervals, diaphragmatic respiration, and respiratory arrest in animals with fatal SAH. Mean heart rates were 252 (23) beats/min in control, 224 (14) beats/min in SHAM, and 182 (15) beats/min in SAH groups. Heart rhythm was 143 (12) /min in animals with respiratory acidosis. Acidotic respiration patterns increased with decreasing pH values.

Histological findings in the thyroid gland

Figure 1 shows the histological appearance of the thyroid gland with follicles of a normal rabbit and hyperplastic lymph node, decreased thyroid follicles along with degenerated thyroid follicles of a rabbit with acidosis. Figure 2 presents the histological appearance of the thyroid gland with destructed-collapsed follicles, condensed amorphous acellular colloid materials, and apoptotic follicular cells of an acidotic rabbit. Follicular cell counts and thyroid follicle surface estimation method is seen in a normal rabbit. Each follicle is considered to be in ellipsoid form. Follicular surface, total follicle surface, each follicular cell surface and total follicular cell count are calculated by formulas I, II, III, and IV, respectively, as shown in Figure 3.

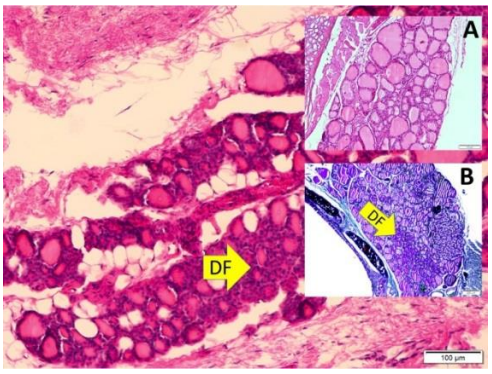

Figure 1: Histological appearance of the normal thyroid gland with follicles (LM, H&E, x10/A) in a healthy rabbit, hyperplastic lymph node and decreased thyroid follicles (DF) (LM, Aldehyde Fuchsine, x4/B) and degenerated thyroid follicles (LM, H&E, x10/Base) in an acidotic rabbit

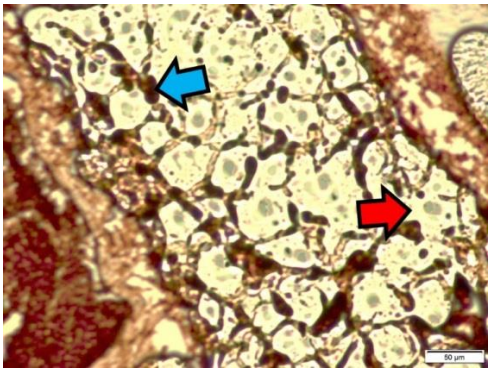

Figure 2: Histological appearance of the thyroid gland with destructed-collapsed follicles, condensed amorphous acellular colloid materials (red arrow), and apoptotic follicular cells (blue arrow) (LM, H&E, x20) of an acidotic rabbit

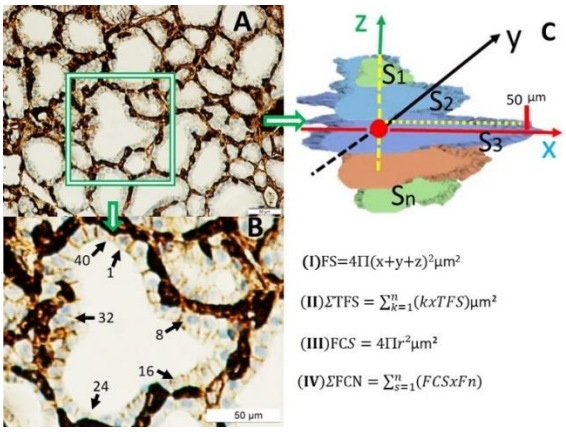

Figure 3: Follicular cell counts and thyroid follicle volume estimation method is demonstrated in a normal rabbit. Each follicle is considered as an ellipsoid form (LM, GFAP, x20/A-B). Cell count estimation method in a slice (S1-n), and both cell and follicle volume estimation method is formulated in C. Follicular volumes (FV), total follicular volumes (TFV), each follicular cell volume (FCV) and total follicular cell counts (FCC) were calculated with Formulas I, II, III and IV, respectively (C)

Numerical results of study

Mean blood pH, T3, T4, TSH values and degenerated epithelial cell counts per follicle are 7.353 (0.037), 108 (10) µg/dl, 1.40 (0.29) µg/dl, <0.5 ng/dl, 50 (9), respectively in the control group, 7.32 (0.05), 94 (9) µg/dl, 1,16 (0.76) µg/dl, >0.5 ng/dl, 154 (30), respectively, in the SHAM group, and 7.21 (0.012), 53 (5) µg/dl, 1.01 (0.12) µg/dl, >0.5 ng/dl, 460 (80), respectively, in the study group. For all results, statistically significant differences were detected between the control group versus SHAM and SAH groups (P<0.001). Numerical and statistical results are summarized in Table 1.

Table 1: Numerical statistical values of study

	Study	Control	SHAM	*P*-value for study vs. control	*P*-value for study vs. SHAM
Blood pH	7.21 (0.012)	7.353 (0.037)	7.32 (0.05)	<0.001	<0.001
T3 level (µg/dl)	53 (5)	108 (10)	94 (9)	<0.001	<0.001
T4 level (µg/dl)	1.01 (0.12)	1.40 (0.29)	1.16 (0.76)	<0.001	<0.001
TSH level (ng/dl)	>0.5	<0.5	>0.5	<0.001	<0.001
DECC	460 (80)	50 (9)	154 (30)	<0.001	<0.001

All values presented as mean (standart deviation). DECC: Degenerated epithelial cell count per follicles

Discussion

Acidosis has been considered a biochemical problem and treatment modalities aim to correct biochemical abnormalities. We believe that acidosis should be accepted as the most troubling complication in intensive care units. In contrast to current explanations, all of our authors think that acidosis should be accused of destroying neuroendocrinological circuitry and related metabolic disorders. Thyroid hormones affect other hormones and regulate the energy metabolism of the body [10]. Thyroid hormone release is influenced by ketoacidosis [11]: Diabetic ketoacidosis disrupts thyroid hormone synthesis and hormone metabolism [12]. Although the article of Valimaki et al. [4] discusses the cause or effect of metabolic disorders in patients with acidosis, we have drawn the conclusion that most of the endocrinological disorders may be secondary to acidosis. Ketoacidosis has a direct effect on thyroid hormone catabolism [13]. Some authors declared that dangerous effects of diabetes mellitus arise from pituitary-thyroid-peripheral tissue axis injury [14]. However, our study showed that acidotic thyroid gland destruction was just as responsible as the explained central mechanism.

Enhanced glucose metabolism in high-grade non-Hodgkin's lymphoma cause lactic acidosis [15] related to multiple endocrine deficiencies in intensive care units. Metabolic acidosis could also destruct the parathyroid gland [16]. In chronic acidosis, the parathyroid gland comes into play and releases bicarbonate from bone to correct acidosis [17]. Also, tachycardia may arise from increased thyroid hormone levels in blood secondary to released hormones by destroyed thyroid gland [8]. Acidosis-based hypothyroidism [12] inducing myxedema [7] may also contribute to edema and coma of the patient. In contrast to common belief some authors indicated that increased thyroid functions could result in renal tubular necrosis [18]. However, this mechanism, which seems to be contrary to the basic philosophy of the paper, can be a negative feedback reaction to protect the organism from the crisis of hyperthyroidism. Encephalopathy associated with Hashimoto thyroiditis [6] should also be attributed to acidosis. Intracellular acidosis may promote atherosclerosis [19]. Maternal hypothyroidism due to acidosis also affects the fetus [5]. Pediatricians should not forget that acidosis-induced maternal hypothyroidism affects the child in the same way.

Acidosis could cause multiple endocrinopathies [4], such as decreased thyroid hormone levels in newborns [5] and encephalopathy [6]. Chronic metabolic acidosis forces the parathyroid glands to obtain bicarbonate from bones to maintain blood pH homeostasis [17]. Especially metabolic acidosis has a provocative role in bone resorption [16]. Metabolism of thyroid hormones is influenced by diabetic ketoacidosis, which results in "low T3 syndrome" [11] and is usually complicated with myxedema [7]. Thyrotoxicosis is frequently seen following stored thyroid hormone release from destructed thyroid gland during acidosis [8]. Correction of metabolic acidosis results in improved thyroid function [9]. Decreased blood pH could be the undetermined cause of hypothyroidism in intensive care units. Parasympathetic denervation and/or decreased blood pH induces hypothyroidism. If the fluid in the thyroid follicles is acidic, it can burn thyroid follicular cells from the inside. The thyroid hormones stored in the follicles can also be denatured in acidic pH in both stored or circulating thyroid hormones. Although thyroid gland destruction occurs, lymphocytes are resistant to pH changes, which may lead to lymphoid hyperplasia in the thyroid. The destruction of follicles in diabetic ketoacidosis may explain the thyrotoxicosis clinic, independent of thyroid hormone levels. We advise urgent correction of metabolic acidosis to improve thyroid functions, prevent local/generalized complications of acidosis in adults, children and most importantly, in both pregnant women and fetuses. Physicians should not forget that body fluids could be hell for organs, and acidosis could write an invitation letter to the angel of the death in intensive care units.

Limitations

This study has been devoid of biochemical, radiological, and electrophysiological data and will not be extended to human studies.

Conclusion

Acidosis should be considered as the most troubling complication and the cause of thyroid gland destruction in SAH.

References

1. Ozmen S, Altinkaynak K, Aydin MD, Ahiskalioglu A, Demirci T, Özlü C, et al. Toward understanding the causes of blood pH irregularities and the roles of newly described binuclear neurons of carotid bodies on blood pH regulation during subarachnoid hemorrhage: Experimental study. Neuropathology. 2019;39(4):259-67.
2. Bederson JB, Germano IM, Guarino L. Cortical blood flow and cerebral perfusion pressure in a new noncraniotomy model of subarachnoid hemorrhage in the rat. Stroke. 1995;26(6):1086-92.

3. Demirci T, Aydin MD, Caglar O, Aydin N, Ozmen S, Nalci KA, et al. First definition of burned choroid plexus in acidic cerebrospinal fluid-filled brain ventricles during subarachnoid hemorrhage: Experimental study. Neuropathology. 2020.
4. Välimäki M, Liewendahl K, Nikkanen P, Pelkonen R. Hormonal changes in severely uncontrolled type 1 (insulin-dependent) diabetes mellitus. Scandinavian journal of clinical and laboratory investigation. 1991;51(4):385-93.
5. Chan LY-S, Fok WY, Sahota D, Lau TK. Cord blood thyroid-stimulating hormone level and risk of acidosis at birth. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2006;124(2):173-7.
6. Takahashi S, Mitamura R, Itoh Y, Suzuki N, Okuno A. Hashimoto encephalopathy: etiologic considerations. Pediatric neurology. 1994;11(4):328-31.
7. Mallipedhi A, Vali H, Okosieme O. Myxedema coma in a patient with subclinical hypothyroidism. Thyroid. 2011;21(1):87-9.
8. Mayfield RK, Sagel J, Colwell JA. Thyrotoxicosis without elevated serum triiodothyronine levels during diabetic ketoacidosis. Archives of Internal Medicine. 1980;140(3):408-10.
9. Molfino A, Beck GJ, Li M, Lo JC, Kaysen GA, Investigators F. Association between change in serum bicarbonate and change in thyroid hormone levels in patients receiving conventional or more frequent maintenance haemodialysis. Nephrology. 2019;24(1):81-7.
10. Akarsu M, Yoldemir ŞA, Altun Ö, Dikker O, Özcan M, Çil EÖ, et al. The effects of overt hypothyroidism on adipose tissue and serum betatrophin levels. Journal of Surgery and Medicine. 2019;3(9):631-4.
11. ahmad Mirboluk A, Rohani F, Asadi R, Eslamian MR. Thyroid function test in diabetic ketoacidosis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017;11:S623-S5.
12. Rashidi H, Ghaderian SB, Latifi SM, Hoseini F. Impact of diabetic ketoacidosis on thyroid function tests in type 1 diabetes mellitus patients. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017;11:S57-S9.
13. Schlienger J, Anceau A, Chabrier G, North M, Stephan F. Effect of diabetic control on the level of circulating thyroid hormones. Diabetologia. 1982;22(6):486-8.
14. Castells S. Thyroid function in juvenile diabetes. Pediatric Clinics of North America. 1984;31(3):623-34.
15. Dürig J, Fiedler W, De Wit M, Steffen M, Hossfeld D. Lactic acidosis and hypoglycemia in a patient with high-grade non-Hodgkin's lymphoma and elevated circulating TNF-α. Annals of Hematology. 1996;72(2):97-9.
16. Kawashima H, Kraut JA, Kurokawa K. Metabolic Acidosis Suppresses 25-Hydroxyvitamin D 3-1α-Hydroxylase in the Rat Kidney: Distinct Site And Mechanism Of Action. The Journal of Clinical Investigation. 1982;70(1):135-40.
17. Bronner F. Calcium homeostasis. Disorders of mineral metabolism: Elsevier; 1982. p. 43-102.
18. Mizuno J, Yonenaga K, Mimura Y, Arita H, Hanaoka K. Hyperthermia and metabolic acidosis during subtotal thyroidectomy for a patient with Basedow's disease. Masui The Japanese journal of Anesthesiology. 2008;57(7):897-900.
19. Haas M, Reinacher D, Li J, Wong N, Mooradian A. Regulation of apoA1 gene expression with acidosis: requirement for a transcriptional repressor. Journal of Molecular Endocrinology. 2001;27(1):43-57.

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