

Original Article



Vagosympathetic imbalance induced thyroiditis following subarachnoid hemorrhage: a preliminary study

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Abstract

Introduction: This preliminary study evaluates the possible responsibility of ischemia-induced vagosympathetic imbalances following subarachnoid hemorrhage (SAH), for the onset of autoimmune thyroiditis.

Methods: Twenty-two rabbits were chosen from our former experimental animals, five of which were picked from healthy rabbits as control (nG-I=5). Sham group (nG-II=5) and animals with thyroid pathologies (nG-III=12) were also included after a one-month-long experimental SAH follow-up. Thyroid hormone levels were measured weekly, and animals were decapitated. Thyroid glands, superior cervical ganglia, and intracranial parts of vagal nerve sections obtained from our tissue archives were reexamined with routine/immunohistochemical methods. Thyroid hormone levels, hormone-filled total follicle volumes (TFVs) per cubic millimeter, degenerated neuron density (DND) of vagal nuclei and neuron density of superior cervical ganglia were measured and statistically compared.

Results: The mean neuron density of both superior cervical ganglia was estimated as $8230 \pm 983/\text{mm}^3$ in study group animals with severe thyroiditis, $7496 \pm 787/\text{mm}^3$ in the sham group and $6416 \pm 510/\text{mm}^3$ in animals with normal thyroid glands. In control group (group I), T3 was $107 \pm 11 \mu\text{g/dL}$, T4: $1.43 \pm 0.32 \mu\text{g/dL}$ and TSH < 0.5 , while mean TFV was $43\%/\text{mm}^3$ and DND of vagal nuclei was $3 \pm 1/\text{mm}^3$. In sham group (group II), T3 was $96 \pm 11 \mu\text{g/dL}$, T4: $1.21 \pm 0.9 \mu\text{g/dL}$ and TSH > 0.5 while TFV was $38\%/\text{mm}^3$ and DND of vagal nuclei was 13 ± 4 . In study group, T3 was $54 \pm 8 \mu\text{g/dL}$, T4: $1.07 \pm 0.3 \mu\text{g/dL}$ and TSH > 0.5 , while TFV was $27\%/\text{mm}^3$ and DND of vagal nuclei was $42 \pm 9/\text{mm}^3$.

Conclusion: Sympathovagal imbalance characterized by relative sympathetic hyperactivity based on vagal insufficiency should be considered as a new causative agent for hypothyroidism.

Introduction

Thyroid gland is innervated by vagal parasympathetic, cervical chain sympathetic and cervical somatosensitive fibers. Parasympathetic insufficiency or sympathetic overactivity may cause autoimmune thyroid disease. Its most frequently detected form is Hashimoto thyroiditis, more frequently diagnosed in women¹ with characteristically increased anti-thyroglobulin antibodies,² elevated thyroid-stimulating hormone, and low thyroxine levels.³ Lymphocytic/eosinophilic infiltration, follicular atrophy,⁴ fibrosis, and scar fibrosis are commonly found in Hashimoto's thyroiditis.⁵ The suprachiasmatic nucleus (via

TSH release),⁶ superior cervical/intrathyroidal ganglia of vagal nerves, trigeminal nerve, and cervical dorsal root ganglia regulate thyroid gland functions.⁷ Cervical sympathetic fibers decrease vascular conductance⁸ and parasympathetic system increases secretory activity.⁹ Based on the studies of Sundler et al,⁷ we postulated that vagal insufficiency triggering relative adrenergic hyperactivity could be an important underestimated cause of autoimmune thyroiditis following subarachnoid hemorrhage (SAH). This has not yet been reported in the literature.

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Methods

This study was conducted on 26 rabbits chosen from former SAH experiments. All rabbits were male hybrid at the age of 3 ± 0.4 years and weighed 4.2 ± 0.3 kg. Five healthy rabbits were included as controls (group-I), five were included in the sham group (group-II) and twelve rabbits diagnosed with severe hypothyroidism in former experiments were included in the study group (group-III). Among the study group, six rabbits were chosen from the group with severe hypophyseal ischemia (GIII-A) and six were picked from the vagal ischemia group (GIII-B). All animals were followed in special metal cages at normal living room standards.

All animals were examined as four groups: Five rabbits were selected for the control group (group I, n=5) without surgical application. Five rabbits were used as sham group (group-II, n=5) chosen from animals with one mL of serum saline injection in their cisterna magna. Our experimental procedure as follow; to reduce pain and mortality, 0.2 mL/kg of isoflurane with ketamine HCL 150 mg/1.5 mL, xylazine HCL 30 mg/1.5 mL, and distilled water 1 mL was used. After bringing the head to a hyperflexed position to identify the foramen magnum, a 22-gauge needle was inserted in the cisterna magna and cerebrospinal fluid was aspirated. Half a milliliter of autologous blood was injected over about one minute to induce a SAH condition (G III, n=12). Surgical techniques related to autologous blood injection into cisterna magna were represented on a 3-D computerized tomography of the rabbit (Figure 1). They were monitored for vital signs with ten minutes periods two times a week and hormone levels were evaluated during the experiment. The thyroid glands, vagal nerves and their ganglia, together with other brainstem nerves, were kindly removed from all rabbits. The brains, vagal networks, cervical sympathetic chains, and thyroid tissues were washed with a graded alcohol series and embedded in liquid paraffin.

Histopathological procedures

The thyroid glands, superior cervical ganglia, and intracranial parts of vagal nerves sections were stained with hematoxylin and eosin (H&E) and TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) method to determine SAH-related damages. The thyroid glands were cut in 5 μm -thick slices every 30 μm . Fractionation method was used for the estimation of the total number and volumes of thyroid follicles. Tissue

sections of each consecutive specimen were placed on glass-slides for histopathological examination after H&E and TUNEL staining, and were examined under a light microscope.

For the analysis of vagal nuclei lesions, brain specimens were sectioned parallel to the long axis of these nuclei to examine both brainstems at that level and were stained with H&E and TUNEL dyes. To estimate the neuron density of the vagal nucleus, all of the vagal nerves together with their extensions, were embedded in paraffin blocks. Stereological method was used to analyze vagal neuron density, as in our previous studies.¹⁰

Stereological analysis

Stereological methods were used to provide good tools to estimate the total volume of thyroid follicles, sympathetic ganglia, and vagal web elements. The first sampled sections pair was selected randomly from a starting point within the first 30-section interval. Thereafter, every 30th section and its neighbor were sampled. The follicular sections sampling fractions of thyroid gland (f1) were therefore, $f1=1/30$. Section pairs not containing the thyroids cells and vagal neuron nuclei were discarded. This sampling fraction yielded on average 10 to 11 section pairs. Area of sampling fraction (f2) was 1/1. We preferred to use the physical dissector method to evaluate the number of thyroid follicles, sympathetic ganglia neurons, and vagal complex particles to minimize bias, as in our former studies.^{11,12}

Numerical results of all specimens were estimated as in our previous studies. Vagal circuitry neuron densities

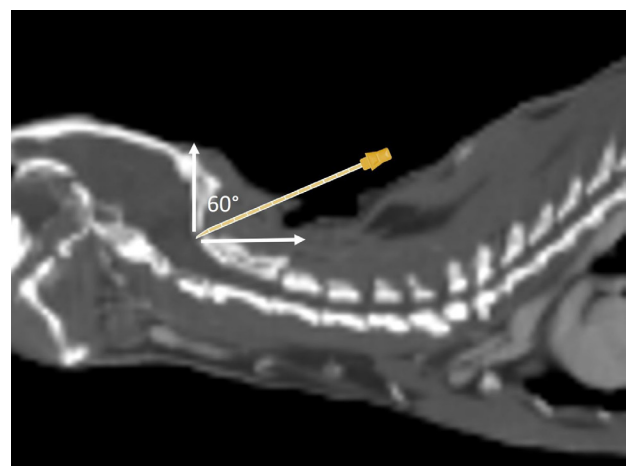


Figure 1. Needle insertion and blood/saline injection technique is represented

were calculated with the method described by Aydin et al¹³ and the thyroid gland was examined as described by Aydin et al.¹¹ Vasospasm index calculation method was used to determine the severity of the thyroidal artery spasm, as described by Ozoner et al.¹⁰ The data were analyzed using a commercially available statistics software package (SPSS® for Windows v. 12.0, Chicago, USA). The data were analyzed with the Kruskal-Wallis and Mann-Whitney U tests. Differences were considered significant at $P < 0.05$.

Results

Meningeal irritation signs, unconsciousness state, epileptic attacks, respiratory disturbances, electrocardiographic abnormalities such as ventricular extrasystoles, ST depression, QRS separation, bigeminal, or trigeminal extrasystoles and fibrillations were detected in animals with severe thyroiditis. Brain edema, stiffness, leptomeningeal thickness, brain swelling, and increased brain weight were seen in all animals which developed hyperthermia. Generally, basal cisterns and rarely fourth and lateral ventricles were filled with blood. Arachnoidal membranes of the lower cranial parts were stuck to lower cranial nerve roots. Especially the arterial supply of the nerve roots and ganglia were more vasospastic, and apoptotic neuronal changes and degenerated neuron density (DND) of the vagal nerve were more abundant in GIII than the others. Hypophyseal cisterns were filled with blood. The thyroid glands were decreased in size in SAH models. Lost acinar cells, decreased number of hormone-filled vesicles, total volume reduction of thyroid follicles, injury-related ductal closing of ductal epithelial cells, degenerative changes of extrathyroidal parasympathetic ganglia neurons and apoptotic changes in acinar cells, tubular cells and supporting cells were detected. Vagosympathetic imbalance was evaluated by thyroid hormone levels and histopathological examination. Decreased vagal activity and increased sympathetic activity caused a decrease in thyroid hormone values. Histopathologically, the destruction of thyroid follicles supports these findings.

Anatomical and histopathological results

Macroscopic appearance of a SAH-created brain, histopathological appearance of SAH just over the hypophyseal stalk, internal carotid arteries, and spastic cortical branch of hypophyseal artery are seen in a rabbit with SAH in Figure 2. Figure 3 shows histopathological appearance of the optic chiasm, hypophysis, and

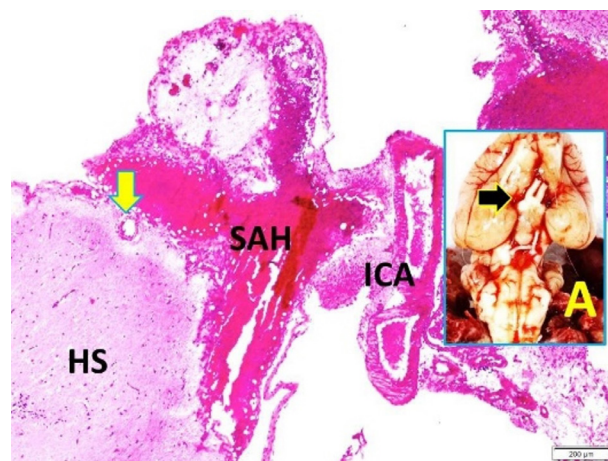


Figure 2. Macroscopic appearance of a brain with SAH (Black arrow/A). Histopathological appearance of subarachnoid hemorrhage (SAH) just over the hypophyseal stalk (HS), internal carotid arteries (ICA), spastic cortical branch of a hypophyseal artery (Yellow arrow) (LM, H&E, x4/Base) are seen in a rabbit with SAH.

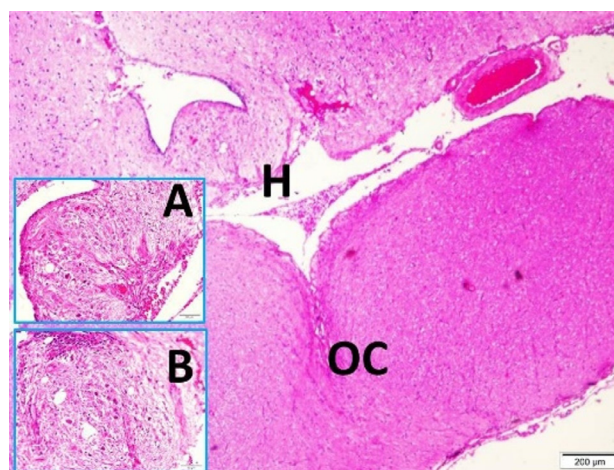


Figure 3. Histopathological appearance of the optic chiasm (OC) (LM, H&E, x4/Base), hypophysis (H), and magnified form of normal (LM, H&E, x10/A) and ischemic (LM, H&E, x20/B) hypophyses are seen.

magnified forms of normal and ischemic hypophyses. Histopathological appearances of vagal nuclei and normal/degenerated neurons are presented in a rabbit with SAH in Figure 4.

In Figure 5 the histopathological appearance of normal thyroid gland follicles and thyroid artery of a normal rabbit are shown. Histopathological view of superior cervical ganglia, and interconnected nerve fibers are presented in Figure 6. The normal structure of a thyroid gland is seen in a rabbit with normal vagal nuclei but partial hypophyseal ischemia (Figure 7). Figure 8 represents partially atrophic lessened thyroidal follicles and minimally lymphocytic invasion to follicles, and severe lymphocytic infiltration

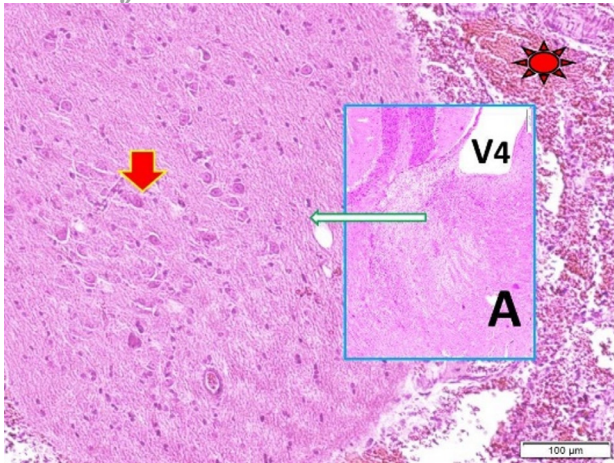


Figure 4. Histopathological appearance of vagal nuclei (LM, H&E, x4/A) and normal/degenerated neurons (Red arrow), subarachnoid hemorrhage (red sun) (LM, H&E, x10/Base) in a rabbit with SAH.

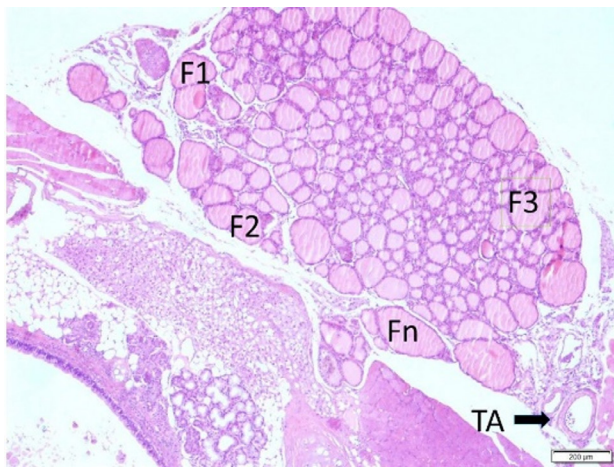


Figure 5. Histopathological appearance of normal thyroid gland follicles (F1-n) and thyroid artery (TA) of a normal rabbit (LM, H&E, x20).

from intrathyroidal lymphatic tissues to thyroid gland with follicular destruction. Figure 9 shows lessened/atrophic thyroid follicles in severe thyroidal arterial vasospasm, immunologic staining of the same thyroid gland, and the atrophic/fibrotic thyroid gland.

Numerical results

The mean neuron density of both superior cervical ganglia was estimated as $8230 \pm 983/\text{mm}^3$ in animals with severe thyroiditis, $7496 \pm 787/\text{mm}^3$ in the sham group and $6416 \pm 510/\text{mm}^3$ in animals with normal thyroid glands. In the control group (Group-I), T3 was $107 \pm 11 \mu\text{g/dL}$, T4: $1,43 \pm 0.32 \mu\text{g/dL}$ and TSH < 0.5 , while mean thyroid follicles volume (TFV) was $43\%/\text{mm}^3$ and DND of vagal nuclei was $3 \pm 1/\text{mm}^3$. In the sham group (group-II), T3

was $96 \pm 11 \mu\text{g/dL}$, T4: $1,21 \pm 0.9 \mu\text{g/dL}$ and TSH > 0.5 while TFV was $38\%/\text{mm}^3$ and DND of vagal nuclei was 13 ± 4 . In the study group (group-III), T3 was $54 \pm 8 \mu\text{g/dL}$, T4: $1,07 \pm 0.3 \mu\text{g/dL}$ and TSH > 0.5 , while TFV was $27\%/\text{mm}^3$ and DND of vagal nuclei was $42 \pm 9/\text{mm}^3$. The numerical and statistical results of the study are presented in Table 1.

Discussion

Autoimmune thyroiditis is the most frequent autoimmune disease, described by Hashimoto in 1912, by reviewing 15000 thyroidectomized patients' archives from May 1889 to October 2012 at Johns Hopkins Hospital. Papillary thyroid cancer was the most commonly reported

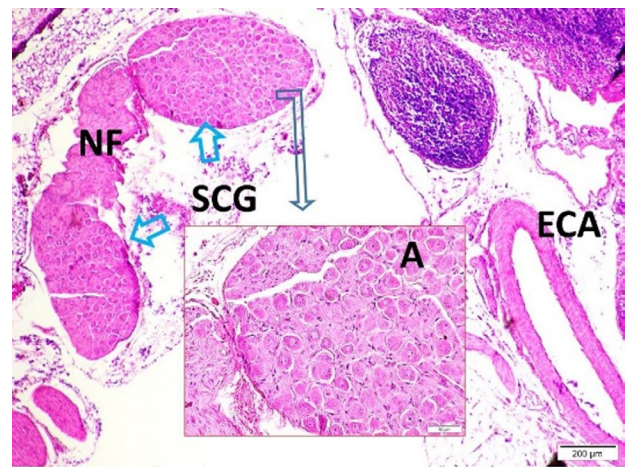


Figure 6. Histopathological view of superior cervical ganglia (SCG), interconnected nerve fibers (NF) of both ganglia around of external carotid artery (ECA) (LM, H&E, x4/Base), and magnified form of SCG (LM, H&E, x20/A).

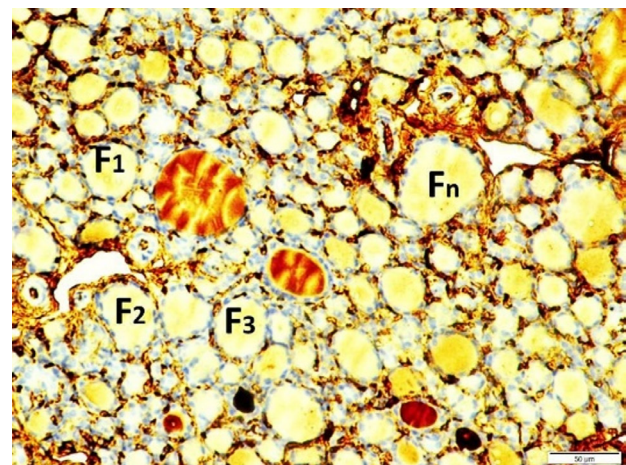


Figure 7. The normal structure of the thyroid gland is seen in a rabbit with normal vagal nuclei but partially ischemic hypophysis. Profound neurofibrillary networks are seen among interfollicular spaces (LM, TUNEL, x20).

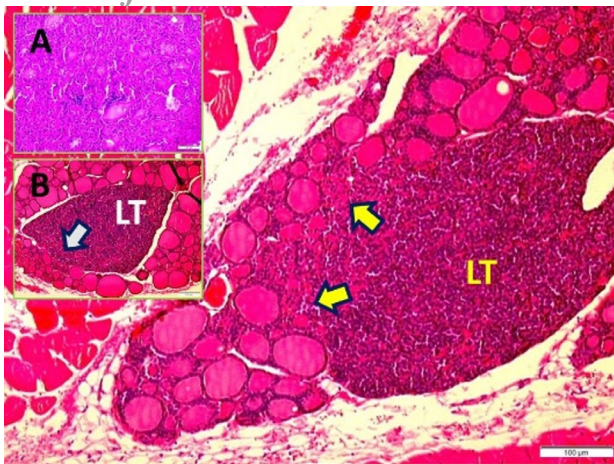


Figure 8. Partially atrophic lessened thyroidal follicles and minimal lymphocytic infiltration (LM, H&E, x20/A), moderate lymphocytic infiltration (white arrow) in enlarged intrathyroidal lymphatic tissue (LT) (LM, H&E, x10/B), and severe lymphocytic infiltration in intrathyroidal lymphatic tissue (LT) causing follicular destruction (yellow arrows) are seen (LM, H&E, x10/Base)

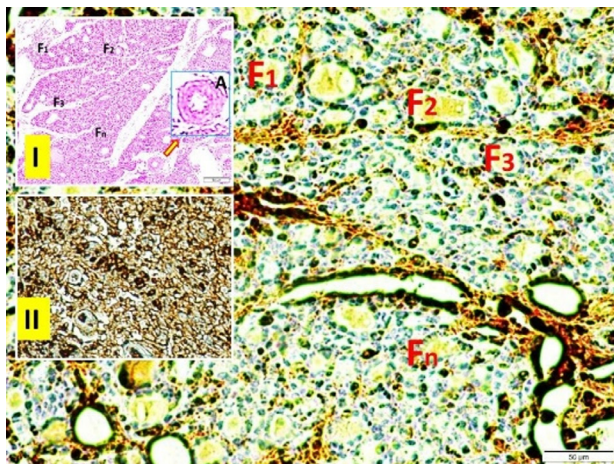


Figure 9 Lessened/atrophic thyroid follicles in severe thyroidal artery (A, x40) vasospasm (LM, H&E, x40/I), and the same immunologically stained thyroid gland. Poor neurofibrillary networks are seen among spaces of degenerated follicles within the thyroid gland (LM, GFAP, x20/Base) and atrophic/fibrotic thyroid gland (LM, TUNEL, x10/II).

pathology,¹⁴ predominantly in women. Radiodiagnostic features are multilobulated¹ and hypoechoic nodules.¹⁵ The most common laboratory findings are elevated TSH, low thyroxine, and increased anti-thyroid peroxidase antibodies.³ Histopathologically, severe lymphoplasmacytic infiltration, follicular degeneration, and giant histiocytic infiltration, interfollicular fibrosis, interlobular fibrosis, and scar fibrosis are the most specific diagnostic pathological criteria of Hashimoto or autoimmune thyroiditis.⁵

Table 1. The numerical and statistical results of the study

	Control	SHAM	Study
T3 µg/dL	107 ± 11 ^a	96 ± 11 ^b	54 ± 8 ^c
T4 µg/dL	1.43 ± 0.32 ^a	1.21 ± 0.9 ^b	1.07 ± 0.3 ^c
TSH	<0.5	>0.5	>0.5
TFV	43% ^a	38% ^b	27% ^c
DND Vg/mm ³	3 ± 1 ^a	13 ± 4 ^b	42 ± 9 ^d

TFV, thyroid follicles volume; DND Vg, degenerated neuron density of vagal nucleus.

^a P>0.05 Control vs SHAM; ^b P<0.005 SHAM vs Study; ^c P<0.0001 Control vs Study; ^d P<0.0005 Control vs Study.

Autonomic innervation of thyroid gland

Generally, the thyroid gland is controlled by the suprachiasmatic nucleus via their TSH release,⁶ superior cervical ganglia, intrathyroidal ganglia of vagal nerves, trigeminal ganglia, cervical dorsal root ganglia which their fibers project to the thyroid gland and control of thyroid activity.⁷ The thyroid gland and blood vessels have double innervation arising from the sympathetic and parasympathetic fibers.¹⁶ They are located in the periphery of arterioles under the fibrous capsule and around secretory vesicles.¹⁷ Cervical sympathetic trunk stimulation decreases vascular conductance.⁸

Central innervation

The thyroid gland is generally controlled by the suprachiasmatic nucleus via their TSH release.⁶

Parasympathetic innervation

The thyroid gland receives parasympathetic innervation from the inferior laryngeal nerve of the vagal nerve. Bilateral inferior laryngeal nerve section generally decreased circulating T4 for up to four weeks after surgery, but unilateral section caused a transient T4 decrease in the first postoperative week. Electrical stimulation of parasympathetic superior laryngeal nerve increased thyroid blood flow. Parasympathetic superior laryngeal nerve stimulation resulted in increased thyroidal blood flow and secretory activity by causing vasodilation.¹⁸

Sympathetic innervation

Cervical sympathetic ganglia send their axons around external carotid arteries to the thyroid gland.¹⁹ Sympathetic innervation of the thyroid gland is provided by superior cervical ganglion,²⁰ which contributes to gland enlargement and may modulate tissue/TSH interactions.²¹ The sympathoadrenal system interacts with thyroid

hormone levels. Exaggerated responses to catecholamines dominate the manifestations of thyrotoxicosis.²² Neuron number of superior cervical ganglion are important in sympathetic overactivity of the thyroid gland.²³

Effect of sympathicovagal network imbalance on thyroid gland

Hypothalamo-hypophyseal axis injury causes TSH insufficiency induced thyroid dysfunctions,⁶ extirpation of the nodose ganglion, and decrease of parasympathetic effect on thyroid gland.²⁴ The unilateral superior cervical ganglion section leads to a decrease in the size of the thyroid gland. Postganglionic nerve transection causes various histomorphological abnormalities on related glands.²³ The unilateral superior cervical ganglion section leads to a decrease in the size of the thyroid gland. Acutely superior cervical ganglionectomy has a significant role on the depression of the thyroid economy.²⁵

Evaluation of our results in the light of current literature

Although hypothalamo-hypophyseal axis pathologies have been the scapegoat following SAH, this study has revealed that various neurophysiological mechanisms may be responsible additionally, because it is shown that hypothalamo-hypophyseal axis injuries do not cause the expected biochemical/histopathological deterioration. This astonishing finding led us toward examining the peripheral autonomic neural network that innervates the thyroid.

Our histopathological examinations showed that ischemic degeneration in vagal nuclei and nodose ganglia could result in thyroid gland dysfunction due to parasympathetic denervation deficiency. In the meantime, a large number of neurons included cervical sympathetic ganglia or vagal network ischemia-induced indirect sympathetic overactivity could be responsible for excessive catecholamine release induced thyrotoxicosis likely described by previous authors.²²

In conclusion, we could say with a great insight that the damage of the peripheral autonomic network innervating the thyroid gland can be as responsible or even more than the hypothalamic-pituitary axis in the pathology of autoimmune thyroiditis.

Rationale of the study

Vagosympathetic circuitry plays an essential role on thyroid anatomy, histology and physiology with

parasympathetic metabolism and sympathetic catabolism functions. Vagal insufficiency causes decreased blood flow and immunological disorders of thyroid. Sympathetic discharges have catabolic and inflammatory effects. SAH models dangerously affect lower cranial nerves, such as the vagal nerves. Our macroscopic and microscopic examinations revealed that blood clots and inflammation in needle insertion sites have compressive effects on vagal nerves. Histopathological examinations have also shown pia-arachnoid adhesion, inflammation, and spasm in vagal nerve root supplying arteries and vagal network result in ischemia. However, SAH rarely results in sympathetic ischemia secondary to external carotid artery spasm.²⁶ For that reason, SAH induced vagal ischemia and relatively augmented sympathetic overactivity may be responsible for thyroiditis. As seen in Figure 8, lymphoid cells infiltrating the thyroid follicles is our most prominent histopathological evidence.

Limitations

Stronger data would be available if radiological analyzes were also performed.

Future insight

Although sympathetic hyperactivity has been accused of the etiology of Hashimoto's thyroiditis within the last century, vagal insufficiency induced sympathetic hyperactivity has not been mentioned, and even regrets of that reality initiates the dark age in medical science. We are expecting future researchers to consider the mentioned histopathological mechanism and to conduct critical studies in the future. Vagal stimulation may be a new treatment method for autoimmune thyroid diseases.

Conclusion

Vagal network ischemia based relative sympathetic overactivity may cause thyroid tissue destruction. Destructed follicular cell remnants are considered foreign antigenic materials, and the thyroidal lymphocytic cells are stimulated to exterminate them. As a result, thyroid tissue enlarges with activated intrathyroidal lymphatic nodes, which causes the nodular thyroid gland appearance. In the progression of that neuropathological war, the thyroid gland becomes atrophied and sclerosed like as Hashimoto's thyroiditis. We concluded that sympathovagal imbalance following SAH might be considered the unpublished neuropathological mechanism of Hashimoto thyroiditis,

which has not been mentioned in the literature so far.

Conflict of Interest

Authors declare no conflict of interest in this study.

Ethical Approval

Ethical approval was obtained from the Ethics Committee of Medical Faculty, Ataturk University Animal Experiments laboratory, Erzurum/Turkey (19.09.2017/1700254064).

Authors contribution

OC, EK, and MDA carried out the design, coordinated the study, and participated in the experiments. I.A. participated in anesthesia and follow ups. SO participated in the examination of histopathological data. MDA aided in statistical analysis and manuscript preparation. OC and MDA assisted in data gathering and participated in manuscript editing.

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