Dysthyroid Optic Neuropathy: Short- and Long-Term Effects on Brain Circuitry

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Commentary

Dysthyroid optic neuropathy is one of the most serious complications of thyroid-associated ophthalmopathy, occurring in 5–9 percent of cases. It is diagnosed by edema of the optic disc, i.e., the exit of retinal ganglion cell axons, and relative afferent pupillary defect (reduced pupil constriction in response to light, a clinical sign of optic nerve damage). In addition, patients suffer from impaired visual acuity and visual field, color recognition [11], and eventually even blindness. Damage to the optic nerve can lead to retinal damage, particularly in the ganglion cell layer, as well as orbital blood flow impairment and optic nerve atrophy. As reported by Jiang et al. [5], symptoms in dysthyroid optic neuropathy occur predominantly in regions involved in or related to visual processing, or are related to consciousness and behavioral parameters. Notably, regional homogeneity scores were negatively correlated with the “Hospital Anxiety and Depression Scale” along with disease duration. These findings suggest that patients with dysthyroid optic neuropathy are more prone to anxiety and depression, and that reduced parietal lobe/middle frontal gyrus function is observed with disease duration and progression. Because subclinical dysthyroid optic neuropathy is common in patients with autoimmune thyroid disease, there is agreement that early diagnosis and medical treatment of this disease are helpful in these patients [12].

In the healthy visual system, the optic nerve transmits the signal by fiber tracts primarily to the image-forming structures such as the lateral geniculate body, superior colliculus, and Brodmann areas 17–19. Not surprisingly, the middle frontal gyrus mediates interactions between the dorsal and ventral streams (“what” = form and color information, inferotemporal stream) [7].

In the few studies that have examined the human brain in patients with thyroid-associated ophthalmopathy, thinning of gray matter has been observed in several brain regions. Compared to healthy controls, regional homogeneity scores were decreased in parts of the visual pathway, such as the occipital lobe, superior temporal gyrus, and cuneus [8,9]. These regions host and connect striate (V1) and extrastriate visual cortices and are involved in visual information processing. In addition, evidence of reduced connections between brain hemispheres [10] may reflect dysfunction within the visual pathway.

Reduced regional homogeneity levels have also been found in the parietal lobe/middle frontal gyrus in dysthyroid optic neuropathy patients [5]. The parietal areas are part of the dorsal visual pathway that mediates motion and spatial visual information (“where” = parietal stream), and...
Fig. 1. Some aspects of the complex interactions between brain and thyroid gland. Solid black lines: axonal projections. Open arrows: hormonal influences. Broken red lines: feedback regulation. Abbreviations: B, basophil cells; C, colloid; CSG, cervical sympathetic ganglia; E, epithelium; F, follicle; H, hypothalamus; LGN, lateral geniculate nucleus; OEM, outer eye muscle; ON, optic nerve; PFC, prefrontal cortex; PVN, paraventricular nucleus; SC, superior colliculus; T3, triiodothyronine; T4, tetraiodothyronine = thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone.

The occipital (visual) cortex is among the regions found to be affected in all of the studies mentioned. The study by Jiang et al. [5], the first to differentiate patients with thyroid-associated ophthalmopathy with and without dysthyroid optic neuropathy, also shows that rfMRI combined with regional homogeneity analysis demonstrates clear differences between the two groups of patients. These results were recently confirmed by similar analysis methods based on rfMRI data [13]. Although the study by Jiang et al. [5] has limitations such as small sample size, the results indicate a risk of regional brain dysfunction in dysthyroid optic neuropathy. It also demonstrates that regional homogeneity analysis may be useful for the early diagnosis of dysthyroid optic neuropathy and thus be helpful for the prevention of the disease.

It is important to determine what factors cause damage to the visual system in the course of immune hyperthyroidism. A likely pathophysiological mechanism involves the recruitment of B-cells to the thyroid gland, and the production of antibodies against thyroid antigens, leading to an inflammatory response. These autoantibodies bind to receptors on thyroid cells, mediating a chronic growth stimulus that eventually leads to hyperthyroidism, but also bind to receptors on pluripotent connective tissue cells in the orbit. This leads to inflammation, fibroblast activation, proliferation of orbital fat, and swelling of the external eye muscles, dislocating the eye and often compressing the optic nerve.

Although the pathophysiological progression of the disease appears to be unidirectional from the thyroid to the eye to the visual system, the overall situation is rather complex. It is characterized by bidirectional and parallel connections between the thyroid and brain that should be mentioned. A schematic overview of the basic anatomical and functional relationships (Fig. 1) shows neural interfaces and relay stations, as well as hormonal feed-forward and feed-back pathways that are likely to work in concert under physiological conditions. First, a humoral pathway activates thyroid metabolism. Thyrotropin-releasing hor-
mone is produced by neuroendocrine cells of the paraventricular hypothalamus and secreted into the portal blood. This peptide hormone stimulates basophil cells of the anterior pituitary to release thyrotropin into the vasculature, from where it exerts its stimulatory influence on the thyroid gland. The thyroid effector hormones triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine) act on their target organs and also provide feedback inhibition to the anterior pituitary and hypothalamus. Second, the gland is subject to nervous control via its autonomic innervation. Notably, the autonomic nervous system plays a key role in integrating signals related to the body’s energy homeostasis [14]. Parasympathetic vagal fibers, with acetylcholine as the main transmitter, enter the gland as branches of the laryngeal nerve [15]. Sympathetic fibers arise from the cervical ganglia [16], and there is evidence that the sympathetic nervous system controls human thyroid function via adrenergic innervation of follicular cells. Complementary to its role in hormonal stimulation of the pituitary gland, the paraventricular nucleus also sends fibers to the intermediolateral column of the spinal cord which in turn innervates the cervical sympathetic ganglia [17], which provide the adrenergic stimulation of the thyroid gland. Interestingly, the paraventricular nucleus is under the direct control of the prefrontal cortex [18], a mechanism responsible for psychological influences on endocrine and autonomic parameters. The prefrontal cortex itself receives information from cortical areas such as the striate and peristriate cortices (the regions affected by thyroid-associated ophthalmopathy and dysthyroid optic neuropathy) through extensive connections provided by association fibers.

An interesting approach would be to investigate non-image-forming pathways originating in the retina. It is not known whether additional optic fiber targets serving other needs, such as the hypothalamic suprachiasmatic nucleus (endogenous clock), the pretectal area (pupillary reflexes, optokinetic response), or the tegmental terminal nuclei of the optic tract (control of eye movements), are also functionally impaired by dysthyroid optic neuropathy. It cannot be excluded that the spatial resolution of the current methods utilized is not sufficient to image these relatively small structures. In the context of possible hypothalamic damage in dysthyroid optic neuropathy, it would be interesting to know whether the distinct circadian rhythm of pituitary thyrotropin secretion [2] persists in dysthyroid optic neuropathy.

In summary, the effects of thyroid-associated ophthalmopathy and dysthyroid optic neuropathy on functional parameters of visual and further brain regions have been investigated by Jiang and colleagues (2021) [3] and by studies from other groups. The structural changes in the human brain detected by MRI and regional homogeneity analysis are consistent with and explain many clinical signs in these patients. The complex mechanisms underlying thyroid-brain interactions are emerging. Further studies are needed to clarify these interactions and other related issues, such as the putative associations between autoimmune thyroiditis and movement disorders and dementia [19,20] and their underlying pathological mechanisms.

Author Contributions

SR wrote the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

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