Movement Disorders
CLINICAL PRACTICE
REVIEW

Thyroid Disorders and Movement Disorders—A Systematic Review

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Abstract: Background: There is overlap between movement disorders and neuroendocrine abnormalities.
Objectives and methods: To provide a systematic review on the association of thyroid dysfunction and movement disorders. Thyroid physiological function and classical thyroid disorders highlighting typical and atypical manifestations including movement disorders, as well as diagnostic procedures, and treatments are discussed.
Results: Hypothyroidism may be associated with hypokinetic and hyperkinetic disorders. There is debate whether their concomitance reflects a causal link, is coincidence, or the result of one unmasking the other. Hypothyroidism-associated parkinsonism may resemble idiopathic Parkinson's disease. Hypothyroidism-associated hyperkinetic disorders mainly occur in the context of steroid-responsive encephalopathy with autoimmune thyroiditis, that is, Hashimoto disease, mostly manifesting with tremor, myoclonus, and ataxia present in 28–80%, 42–65% and 33–65% in larger series. Congenital hypothyroidism manifesting with movement disorders, mostly chorea and dystonia, due to Mendelian genetic disease are rare.
Hyperthyroidism on the other hand mostly manifests with hyperkinetic movement disorders, typically tremor (present in three quarters of patients). Chorea (present in about 2% of hyperthyroid patients), dystonia, myoclonus, ataxia and paroxysmal movement disorders, as well as parkinsonism have also been reported, with correlation between movement intensity and thyroid hormone levels.
On a group level, studies on the role of thyroid dysfunction as a risk factor for the development of PD remain non-conclusive.
Conclusions: In view of the treatability of movement disorders associated with thyroid disease, accurate diagnosis is important. The pathophysiology remains poorly understood. More detailed case documentation and systematic studies, along with experimental studies are needed.

An overlap between movement disorders and neuroendocrine abnormalities is widely recognized, including in the context of thyroid dysfunction. Shared pathogenic features and underlying mechanisms including hormonal deficiency or inflammation may contribute to their development, the clinical presentation and influence treatment responses.

In this paper, we review the borderland between movement disorders and thyroid dysfunction. We start with an overview of thyroid physiological function and classical thyroid disorders highlighting their typical and atypical manifestations including movement disorders, diagnostic procedures, and treatments. Ataxia and other cerebellar disorders associated with thyroid dysfunction are beyond the scope of this review, for which we refer to the recent comprehensive paper by Ercoli and colleagues[1] who identified 65 cases of ataxia published in the literature, often associated with atrophy of vermis and often of both cerebellar hemispheres as the main imaging abnormality.

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Methods

We searched the literature using PubMed to identify relevant articles published between 1965 to 2021. To select a preliminary list of articles, we used the (combinations of) terms movement disorder, parkinsonism, dystonia, chorea, tics, myoclonus, thyroid dysfunction/disease, hypothyroidism, hyperthyroidism, autoimmune thyroiditis, Grave's disease (GD), Hashimoto encephalopathy (HE), steroid-responsive encephalopathy associated with autoimmune thyroiditis. Further articles were identified by cross-referencing, ie, searching the bibliographies of identified articles. For the purpose of our review, we selected those studies reporting patients diagnosed with thyroid disorders AND a movement disorder including single case reports and case series. Overall, 129 papers were selected. As mentioned above, ataxia and other cerebellar disorders associated with thyroid dysfunction are not explicitly included in this review.

Results

Thyroid Function

The thyroid gland secretes the two thyroid hormones—triiodothyronine (T3) and thyroxine (T4)—and calcitonin. While T3 is the biologically active thyroid hormone, T4 is considered a prohormone and functions as a depot form. The thyroid hormones control the metabolic rate and protein synthesis and, in children, growth and development. This is reflected by the spectrum of manifestations in infancy- and early-onset neurodevelopmental disorders associated with thyroid dysfunction.[2] Calcitonin influences calcium homeostasis. Secretion of the former are regulated by thyroid-stimulating hormone (TSH), which is secreted from the anterior pituitary gland (hypophysis), a protrusion off the bottom of the hypothalamus. TSH in turn is regulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus.

Causes of thyroid dysfunction are multifold (Table 1). The diagnosis of a thyroid disorder is made based on the clinical findings, biochemical assessment (eg, TSH and free T4 (FT4) and T3 (FT3) assays, thyroid antibodies) and imaging, eg, thyroid ultrasound. For specific questions, additional diagnostic tools such as scintigraphy or functional tests of the thyroid gland can be performed. In a nutshell, elevated levels of TSH indicate hypothyroidism; low TSH levels indicate hyperthyroidism (Table 2). Increased antibody levels are characteristic of autoimmune/inflammatory thyroid disease. The major four antibodies are anti-thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), THS receptor simulating *antibodies* (TSAb) and TSH receptor blocking antibodies (TBAb) (see below and Fig. 1). Their precise pathogenic role, however, is not well understood, as thyroid antibodies have been shown to be present in the normal population without clinical or laboratory evidence of thyroid disease at the time of data collection.[4] Levothyroxine is the standard treatment of hypothyroidism. Treatment of hyperthyroidism depends on the etiology. Reversible causes of thyroid dysfunction (eg, autoimmune diseases, iodine deficiency, drug-related causes) should be carefully excluded or treated appropriately. Regular monitoring is advised.

Some movement disorder drugs influence thyroid hormone levels and may lead to disturbance of thyroid metabolism as a side effect. The intake of dopamine or its derivatives, for example may cause difficulty in the interpretation of TSH serum levels.[5] Most prominently, dopamine and dopamine agonists (such as bromocriptine), via the activation of dopamine D2 receptors, have a suppressive effect on the hypothalamic–pituitary-thyroid axis and lead to inhibition of TSH secretion.[6,7] While in healthy controls dopamine infusions reduce TSH pulse amplitude without significantly altering TSH pulse frequency,[6] in critically ill patients dopamine infusions can cause iatrogenic central hypothyroidism. Cessation of dopamine infusions leads to rapid reversal of TSH suppression within hours.[8] In euthyroid patients with Parkinson's disease therapeutic doses of levodopa, however, have no significant effect on thyroid function.[9] Another example from the neuropsychiatric spectrum is lithium which can induce hypothyroidism but also less commonly, transient hyperthyroidism (similar to silent thyroiditis).[10]

Laboratory assays are sensitive to influential factors, including variations to sample handling, temperature, drug-intake etc. This includes serum thyroid function tests which are complex and dependent on medication or agents. The intake of dopamine or its derivatives, for example may cause difficulty in interpreting serum TSH levels.[6,11] To elaborate, levodopa treatment can

TABLE 1 *Common thyroid disease and their clinical manifestation*

Pathology	Thyroid function
Iodine deficiency	Hypothyroidism (euthyroidism)
Hashimoto thyroiditis	Hypothyroidism (rarely with euthyroidism)
Autonomous thyroid, Graves' disease	Hyperthyroidism (rarely with euthyroidism)
Subacute thyroiditis (de Quervain)	(Self-limited) hyperthyroidism, (euthyroidism, hypothyroidism)
Malignancy	Euthyroidism
Cyst	Euthyroidism
Drug-induced (see Table S1)	Euthyroidism, hypothyroidism, hyperthyroidism

TABLE 2 *Interpretation of basic thyroid function tests*

TSH	Free T4	Interpretation
Normal	Normal	Euthyroidism
High	Low	Primary hypothyroidism
High	Normal	Subclinical hypothyroidism
Low	High	Primary hyperthyroidism
Low	Normal	Subclinical hyperthyroidism

Note: Normal range of TSH = 0.5 to 5.0 mIU/L; normal range of free T4 = 0.7 to 1.9 ng/dL.
Abbreviation: TSH, thyroid-stimulating hormone.

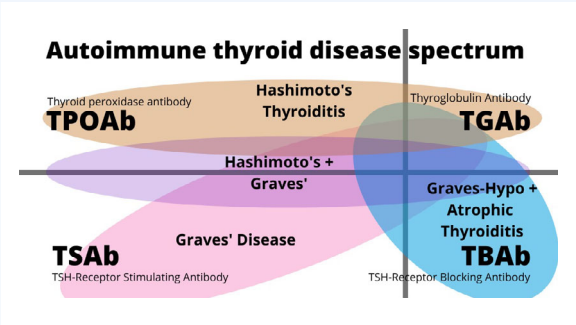

FIG. 1. Main antibodies associated with thyroid disease and their overlap (reproduced from[3]). TPOAb, Anti-thyroid peroxidase antibody; TGAb, Thyroglobulin antibodies, TSAb, THS receptor simulating antibody; TBAb, TSH receptor blocking antibody.

result in lowered TSH levels with blocking action exerted at the hypothalamic as well as at the pituitary level.[12] For about 2 hours after levodopa/carbidopa intake, TSH levels can show a small but significant reduction. Blood for TSH studies should thus be collected prior to drug intake.[9] This effect is more pronounced in PD patients compared to healthy controls[13,14] and may lead to discordant results of thyroid function tests (eg, fully or partly suppressed TSH with normal FT3/FT4 levels).[9,15] Propranolol on the other hand can diminish T4 to T3 conversion and tests may show hyperthyroxinaemia with nonsuppressed TSH (ie, elevated FT4 with normal TSH, and usually normal FT3 levels).[15]

Autoimmune Thyroid Disorders and Movement Disorders

Autoimmune thyroid diseases, that is, when autoantibodies, such as TPOAb, *TGAb*, TSAb and TBAb, target the thyroid gland and lead to hormonal imbalance, can be associated with neurological symptoms. The two most common forms of autoimmune thyroid diseases are GD and HE, both T-cell mediated and characterized by lymphocytic infiltration of the thyroid parenchyma.[16] The prevalence of autoimmune thyroid diseases is estimated to be 5%. Subclinical autoimmune thyroid inflammation can be found in around 15% of the biochemically euthyroid population.[5] Traditionally, both GD and HE belong to the group of steroid-responsive encephalopathies which have in common a diffuse brain injury, high titers of anti-thyroid peroxidase antibodies and responsiveness to corticosteroids or other immunosuppressive therapies such as IV immunoglobulin and plasmapheresis.

Graves' disease is the leading cause of hyperthyroidism in areas with adequate iodine intake. In GD TSAb lead to excessive stimulation of the thyroid gland and thus increased release of thyroid hormones and hypertrophy of the thyroid gland. Women are up to five times more likely to be affected by GD, with a mean age at onset of 30–50 years.[17] Typical GD clinically presents with thyroid enlargement, hyperthyroidism-related symptoms (eg, palpitations, tachycardia, weight loss, heat intolerance, tremor and fatigue as the most common symptoms occurring in 50% of the patients[17]) and endocrine ophthalmopathy (bulging eyes, also known as proptosis). The latter is caused by additional antibodies targeting the eye muscles and surrounding connective tissue causing exophthalmos with protruding eyeballs, strabismus and, in some cases, permanent visual disorders.[18] Up to 50% of people with GD develop Graves' ophthalmopathy.[17] Thyroid dermopathy (myxoedema), typically localized pretibially, occurs in up to 4% of GD patients.[19] Unusual clinical presentations of GD including neurological symptoms (eg, encephalopathy, seizures or myelopathy) including movement disorders (see below) have been described and pose a diagnostic dilemma.[18]

Hashimoto's thyroiditis is the most common form of autoimmune thyroiditis leading to hypothyroidism[20] due to elevated TPOAb and, to a lesser degree, TGAb.[21,22] Hashimoto's thyroiditis typically manifests with subclinical hypothyroidism or hypothyroidism[23]; in the early course temporary hyperthyroid state, called Hashitoxicosis, can occur.[21–25] In severe cases patients develop HE,[26–28] also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) the prevalence of which is estimated to be 2:100,000. Mean age at onset is between 50–60 years of age.[29,30] Almost one quarter of cases, however, are 18 years or younger[30] with middle-aged women having the highest risk of developing Hashimoto's thyroiditis.[31] A broad clinical spectrum of HE has been described including behavioral changes cognitive decline, confusion, stroke-like episodes and seizures.[24,26] A substantial proportion develop late sequelae, mostly epilepsy.[32] Notably, the existence of the nosological entity of HE remains widely debated with some doubt of the existence of this type of encephalopathy and its features that have long been considered characteristic of it, including response to steroids. The reader is referred to Mattozzi et al.[27] for further reading.

Autoimmune thyroid disorders are often part of an autoimmune predisposition. Thus, thyroid autoimmune disease can serve as a clue towards autoimmunity which in turn may be linked with a broad spectrum of autoimmune-associated movement disorders that are caused by other autoantibodies.[33]

Hypothyroidism

Worldwide, primary hypothyroidism is very prevalent, particularly in iodine-deficient regions. The prevalence of subclinical

hypothyroidism alone is thought to be around 4% to 8% in the general population, with women being more frequently affected.[34]

Hypothyroidism and Parkinsonism

Generally, parkinsonism is not typical of mild hypothyroidism. However, the disorders share clinical features.[35,36] For instance, in patients with myxedema, which is a manifestation of advanced stage hypothyroidism, the face descry may appear "expressionless," "masklike" and "apathetic" similar to facial characteristics of PD[37] which is characterized by a reduced blink rate resulting in a staring expression, reduced smiling and unintentional lips separation resulting in an open mouth. Likewise, the speech in advanced hypothyroidism may appear slow, low-pitched, and coarse with difficulty in articulation—similar to the speech in PD. This may lead to diagnostic confusion[38] with a delay in making the diagnosis[35] and drug-resistant PD patients should be investigated for co-existing hypothyroidism and vice versa.

Several papers in the literature discuss the relationship between hypothyroidism and parkinsonism and in how far their presence in the same patient may coincide, whether these disorders may be unmasked by another or are causatively linked. The number of detailed reported cases, however, remains scarce in the literature[35,38,39] (Table S1). Hypothyroidism-associated parkinsonism is accompanied by globally reduced brain activity as indicated by brain imaging which showed generalized decrease in regional cerebral blood flow of 24% and in cerebral glucose metabolism of 12% in severe hypothyroidism in one study involving 10 patients who had undergone thyroidectomy for thyroid carcinoma.[40]

As mentioned above, one cause of hypothyroidism is Hashimoto thyroiditis where parkinsonism may occur.[41]

In a broader context, the role of thyroid disorders as a risk factor for the development of PD has been investigated[42–48], (Table S2). Findings remain non-conclusive: Some studies found that hypothyroidism was more common in PD and potentially increases the susceptibility for PD development,[42,44,45] whereas others did not.[49,50] Yet other studies found an association of hypothyroidism between TSH levels and the motor subtype of PD and disease severity.[51] To elaborate, albeit all had hormone levels within the normal range the authors found relatively lower levels in the tremor-dominant patients compared to akinetic-rigid patients.[51] FT3 was negatively correlated with disease severity.[51]

In MSA, a form of atypical parkinsonism, no significant differences in basal or post-levodopa levels of TSH were found compared to controls.[52]

Hypothyroidism and Hyperkinetic Movement Disorders

There are rare reports of hyperkinetic movement disorders associated with hypothyroidism (Table S3). This includes hypothyroidism due to structural/functional damage of the thyroid, e.g. induced by papillary thyroid cancer and parathyroid adenoma presenting with focal dystonia.[53] There are also several reports of patients with hypothyroidism who developed drug-induced dyskinesia following the intake of neuroleptics ([sulpiride[54]], antidepressants [nomifensine[55]], or gamma-aminobutyric acid type B (GABA-B) receptor agonists [baclofen[56]]) leading to the debate about a possible interaction of thyroid hormone and the targeted receptors, that is, dopamine or GABA-B, in the emergence of tardive dyskinesia.

Notably, a broad spectrum of hyperkinetic disorders has been observed in patients with steroid-responsive encephalopathy with autoimmune thyroiditis, i.e. Hashimoto disease, mostly tremor,[57] myoclonus,[57] and ataxia, sometimes mimicking Creutzfeldt–Jakob disease.[58–60] In larger series and reviews involving 13 to 130 patients assessing the clinical features of SREAT, tremor and myoclonus (typically, stimulus-sensitive without correlation of the electroencephalogram (EEG) activity) were present in 28%–80% and 42–65% of cases, respectively.[21,24,28,61,62] Ataxia was similarly common (33–65%). Other hyperkinetic disorders have rarely been reported, including chorea,[63,64] tics,[65] facial movements[66] and painful leg moving toe syndrome.[67] Notably, HE (with movement disorders) may even occur with euthyroid states.[21,66,68,69]

Movement disorders may also occur after abrupt change of thyroid medication. Recently, Ehm and colleagues[70] reported a hypothyroid patient with reversible myoclonus and encephalopathy which developed after accidentally stopping levothyroxine.

Genetic Hypothyroidism and Hyperkinetic Movement Disorders

Mendelian genetic disorders causing congenital hypothyroidism and movement disorders, mostly chorea and dystonia, are rare (Table S4).

This includes mutations in *NKX2-1* causing Brain-Lung-Thyroid Syndrome, also referred to as Benign Hereditary Chorea (OMIM 118700), an early-onset autosomal dominantly inherited neurodevelopmental disorder.[2] Children have delayed motor milestones with late walking or a "clumsy" or "ataxic" gait. Chorea is the predominant movement phenotype and is classically generalized, affecting the trunk and limbs which often stabilizes or resolves in early adulthood. Limb/axial dystonia, "jerky" dystonia, motor or vocal tics, tremor, myoclonus and drop attacks may also be present. Comorbid psychiatric symptoms of depression, psychosis, cognitive impairment and attention-deficit–hyperactivity disorder have been reported and may lead to poor school performance. As many as two thirds of patients develop hypothyroidism. This manifests as either congenital hypothyroidism in the neonatal period or as compensated hypothyroidism detected later in childhood or even adulthood.[71–73] Since *NKX2-1* is one of the genes involved in regulating thyroid development, its mutation can lead to thyroid dysembryogenesis.[71,72] In some cases, athyreosis has been observed.[74] Treatment of hypothyroidism can improve neurological symptoms as demonstrated in a case with L-thyroxine responsive drop attacks.[75]

Another genetic cause of congenital hypothyroidism and movement disorders is Allan-Herndon-Dudley syndrome

(OMIM 300523), an X-linked intellectual disability syndrome due to mutations in the *SLC16A2* gene encoding the monocarboxylate transporter 8 (MCT8). Onset is right after birth or in early infancy; dysmorphic features become apparent over time. While the most characteristic neurological features are early-onset hypotonia and spastic paraplegia, movement disorders including dystonic posturing, chorea and paroxysmal dyskinesia may occur.[2,76] Hypothyroidism in Allan–Herndon–Dudley syndrome may be characterized by low serum total and free thyroxine (T4), highly elevated total and free triiodothyronine (T3) and normal thyrotropin (TSH) with blunted response to TRH.[77] Since MCT8 is a thyroid hormone transporter in target cells, including neurons, it is assumed that the defect in the transporter disturbs the uptake of T3 and thus leads to reduced T3 activity and metabolism. This would also explain the high T3 serum levels due to accumulation.[78]

Mutations in the *SLC30A10* gene encoding a Mn transporter, are associated with hereditary manganese toxicity which leads to elevated manganese in the blood and brain and subsequent neurotoxicity. The clinical presentation encompasses hepatic cirrhosis, dystonia ("cock-walk" gait), polycythemia, and hypermanganesemia. Animal studies revealed elevated thyroid manganese results in blocks of thyroxine production, clinically manifesting with hypothyroidism.[79]

Hyperthyroidism

Hyperthyroidism occurs when the thyroid is overactive. Typical symptoms are nervousness, twitching and trembling, irritability and anxiety, tiredness and weakness, sensitivity to heat, tachycardia, palpitations and weight loss, as described before. The most common cause in non-iodine deficient regions is GD, accounting for about 50–80%; Other causes include excessive intake of iodine or thyroid hormones [thyrotoxicosis factitia], while non-cancerous tumors of the pituitary gland are very rare. As mentioned above, GD is an immune system disorder associated with elevated levels of TRAb which bind to the TSH receptor on the thyroid gland and stimulate it to increase thyroid hormone production.

Severe cases of excessive release of thyroid hormones lead to a thyroid storm or thyrotoxicosis which a potentially life-threatening disorder characterized by high fever, hypertension, tachycardia, vomiting and agitation. Bilateral basal ganglia lesions as complication of thyroid storm have been reported.[80]

Hyperthyroidism and Parkinsonism

There are few case reports of hyperthyroidism and parkinsonism where thyrotoxicosis led to an exaggeration of akinesia, tremor,[81,82] rigidity and on–off phenomena[83] in pre-existent parkinsonism and showed improvement after restoration of euthyroidism.[84,85] Hemiparkinsonism[86] as a manifestation of hyperthyroidism due to GD has also been described. (Table S3) Notably, in newly diagnosed PD patients with concomitant hyperthyroidism[87] the response to dopaminergic medication may be masked and thus, in treatment-refractory PD patients thyroid disorders should be excluded.

Thyroid function in PD has also been studied on a group level. While early studies in relatively few patients ($n < 100$) reported normal thyroid function in PD,[36] more recent studies (with more than 5500 and more than 8700 patients) found hyperthyroidism may be associated with an increased risk for parkinsonism[42,45] (Table S2).

Hyperthyroidism and Hyperkinetic Movement Disorders

Hyperthyroidism may be associated with hyperkinetic movement disorders, most typically with tremor or chorea, but dystonia, myoclonus, ataxia and paroxysmal movement disorders have also been reported (Table S3). For ataxia associated with thyroid dysfunction we refer to Ercoli et al.[1]

Tremor is a commonly recognized symptom of hyperthyroidism, observed in 76% of patients with thyrotoxicosis.[88] Tremor typically presents as high-frequency and low-amplitude bilateral action tremor of the arms and hands resembling enhanced physiologic tremor. Tremor may be the presenting or an isolated sign in the absence of other systemic symptoms. Atypical manifestation of tremor have been described including orthostatic tremor,[89] isolated, position-specific leg tremor[90] and abdominal tremor.[91] Pathophysiologically, upregulation of beta-adrenoceptor has been postulated as a contributing factor to the mechanism of tremorgenesis in hyperthyroidism.

Tremor improves with correction of thyroid function. In addition, propranolol may be used as adjunct therapy.[92] In a placeco-controlled trial, during the first month treatment with carbimazole *plus* propranolol resulted 59% improvement, compared to 31% in the carbimazole plus placebo group.[92]

Among the other hyperkinetic disorders associated with a hyperthyroid state, chorea is by far the most common form; yet the overall incidence is rare. In an Israeli national study evaluating 800 hyperthyroid patients over the course of 15 years, only one patient developed chorea demonstrating the rarity of this entity.[93] Arifi and colleagues[94] postulate chorea occurs in less than 2% of patients with hyperthyroidism. On the other hand, the incidence may be underestimated, as—particular in the older literature—chorea may have been mistaken as "nothing more than an exaggerated form of psychomotor restlessness"[95,96] or thyrotoxic tremor.[97–99]

Our literature search identified 55 reports with detailed descriptions (Table S3). Chorea primarily affects young females with only a few affected men described in the literature. This may be partly due to the higher incidence of GD in women which is one of the main underlying thyroid disorders associated with hyperthyroid chorea.[97] Clinically, there is variable onset, distribution, severity and temporal relation between the emergence of chorea and symptoms and signs of thyroid dysfunction. To elaborate, onset of chorea may be insidious over months or abrupt developing within days.

Chorea may present as persistent generalized, bilateral chorea or sometimes hemichorea,[100] affecting limbs, trunk, face or the oral-lingual region, symmetrically or asymmetrically.[100] There

may be violent proximal movements, that is, ballism.[101,102] Generalized chorea, however, is the most common manifestation. Paroxysmal kinesigenic choreoathetosis has also been reported.[103–107] Severity of chorea ranges from mild to violent, sometimes requiring self-protection.[100,101,108,109] As mentioned above, the underlying thyroid disorder most commonly is GD, but Hashimoto encephalitis and iatrogenic thyrotoxicosis secondary to thyroxine replacement therapy[103,110] have also been reported. Chorea typically develops simultaneously with or after the onset of thyrotoxicosis, but preceding chorea has also been observed.[97,111] As mentioned above other signs of hyperthyroidism include weight loss, tachycardia, anxiety, sweating and more obvious signs such as thyromegaly or Graves' ophthalmopathy which, if present in a patient with chorea, should alert the clinician to this differential diagnosis.[97]

There is a close temporal relationship between attainment of a euthyroid state and cessation of chorea.[97] Thus, within a few weeks chorea typically improves with normalization of thyroid function, followed by a gradual further improvement until complete cessation. Rarely chorea may persist for months to years despite normal thyroid function.[102,112] Chorea may also reoccur with poor compliance to antihyroid medication.

The exact pathophysiological underpinnings of hyperthyroid chorea are not fully understood. Dopaminergic dysregulation and functional modification of dopaminergic receptors have been suggested to play a primary role. Early studies from the 1970s reported changes in the levels of homovanillic acid, a metabolite of dopamine, in cerebrospinal fluid, which was reduced in hyperthyroid patients (and reduced in hypothyroid patients).[113] Animal studies in hyperthyroid guinea pigs demonstrated an increased sensitivity of striatal dopamine receptor sites to simulation with a dopamine agonist.[114] A hypersensitivity of dopaminergic receptors resulting in a decrease in dopamine turnover was thus hypothesized.[100,113] An increased sympathetic response has also been proposed.[99] To our knowledge there are no recent experimental studies exploring the nature of hyperthyroid chorea.

Hyperthyroidism may also manifest with dystonia. Our literature research identified six reports with detailed descriptions including truncal, generalized[115] or focal, task-specfic[116] dystonia (eg, writing dystonia with bilateral postural 8- to 10-Hertz hand tremor). Lingual dystonia presenting as irregular jerky lingual and lip movements suggestive of dyskinesia in a patient with GD has also been described.[117] In the latter, diffuse increased uptake of technetium was present on nuclear imaging. Movements disappeared with treatment with carbimazole and propranolol.

Complex phenotypes have also been observed, eg, complex dyskinesia, with prominent high-amplitude myoclonic jerks, ataxia, mild chorea and associated postural tremor.[118,119] Behavioral, emotional or psychiatric disorders, weakness, myopathy and other neurological signs and symptoms may be associated signs.

A correlation between the intensity of the hyperkinetic movements and the serum levels of thyroid hormones,[120] but not between the movement disorders and thyroid autoantibody concentrations has been demonstrated.

Genetic Variations in Thyroid-Associated Genes and Movement Disorder Syndromes

Monogenetic causes of syndromes encompassing thyroid dysfunction (ie, hypothyroidism) and movement disorders are discussed above. In addition, genetic variations in thyroid-associated genes have been identified to influence the phenotype of genetic movement disorders. For example, loss of the thyroid hormone-binding protein Crym increases the vulnerability of striatal neurons in Huntington's disease, the most common type of genetic chorea.[121]

Treatment Implications

Movement disorder symptoms improve with normalization of thyroid hormone levels in both idiopathic and genetic forms thyroid function.[75,83] As a general rule, in patients presenting with a new movement disorder or an unexpected lack of or unexpected response to the standard drug regime (eg, levodopa-resistant PD secondary to hypothyroidism[38]) or unexpected worsening of a pre-diagnosed movement disorder, thyroid function should be checked and corrected. Similar conclusions were drawn by Ercoli et al.[1] for ataxia in the context of thyroid dysfunction. The choice of thyroid treatment is based on the underlying type of thyroid dysfunction. The standard treatment of care for hypothyroidism is with L-thyroxine. For hyperthyroid, thyreotoxic states due to GD first line treatment in Europe consists of thyrostatic drugs drugs including carbimazole, methamizole, thiamazole or propylthiouracil. Thyroidectomy is a second line option which is often the first choice in the US. Hyperthyroidism due to autonomous adenomas is treated by surgery or radioiodine. Hashimoto thyroiditis and SREAT are characterized by an exquisite response to steroids or—if unresponsive—to plasma exchange, albeit this is debated.[27]

If the rational approach does not fully abandon the movement disorder, symptomatic movement disorder drugs may further alleviate these. For example, propranolol may be used as an adjunct therapy to ameliorate hyperthyroid tremor.[92] Dopamine antagonists (mainly haloperidol) have been mentioned in the literature for the treatment of hyperthyroid chorea.[97,112]

Several studies report the high frequency of relapse in case of poor compliance. Thus, regular follow-up is an important part of management,[97] also to monitor for side effects which may include worsening of movement disorders (eg, parkinsonian tremor increasing with thyroxine[122]) and allow for treatment adjustment. For the effect of drugs (including those commonly used in movement disorder patients) on thyroid function see the section on "Thyroid function". These should be kept in mind as potential side effects.

Conclusion

As summarized in this review, thyroid dysfunction may manifest or be associated with a variety of hypo- and hyperkinetic

movement disorders. In view of the treatability of movement disorders associated with thyroid disease, accurate diagnosis is important. The pathophysiology of movement disorders associated with thyroid disease remains poorly understood, and more detailed case documentation and systematic studies, along with experimental studies of the relationships between thyroid and movement disorders and the brain regions involved would be desirable.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

S.A.S.: 1A, 1B, 1C, 3A.

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N.R.: 3B.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Hypokinetic disorders associated with thyroid dysfunction, listed by publication date.

Table S2. Studies exploring the association between thyroid disorders and Parkinson's disease.

Table S3. Hyperkinetic disorders associated with thyroid dysfunction, listed by publication date.

Table S4. Causes of hypothyroidism and associated clinical clues.