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Inter-Relationship of Thyroid Disorders and Schizophrenia: An Extended Review

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ABSTRACT

Psychiatric patients, particularly those having mood disorders show a certain signs and symptoms of hypo and hyperthyroidism which in turn are responsible for the aggravation of autoimmune thyroiditis. Schizophrenia is considered as one of the most common psychiatric disorders with prevalence of about 0.7-1.0% of the total world's population. It is a chronic form of disease which in most of the case represents poor response to the provided treatment. Moreover, it leads to loss of productivity and has very expensive treatment. Its important features include cognitive impairment, delusions, hallucinations as well as emotional reactivity and behavioral abnormality. It is not a simple disease it is a multifaceted disorder that may arise from a range of various genetic and environmental exposures it is also found to be acting at prenatal life. Molecular mechanism of schizophrenia is still not very clear and no biological markers have been identified. In this context modulators of transcriptional activity and their carriers or receptors are the only one which can bridge between genetic and environmental determinants of schizophrenia. Thyroid hormones are important among them. Thyroid hormones are necessary for the development of an adult brain. Instabilities in the levels of thyroid hormones during various phases of life and development can lead to a psychiatric disease manifestation. In this review we have emphasized that there is a relationship between disturbed pituitary-thyroid-axis and schizophrenia not only at genetic level but also at the level of different brain neurotransmitters (serotonin, GABA, and glutamate), myelination and pro-inflammatory responses.

Keywords: Hypothyroidism, hyperthyroidism, neuropsychiatric disorders, thyroiditis, T3 and T4 hormones, Hashimotos encephalopathy, neurotransmitters, GABA, 5-hydroxy tryptamine, depression.

INTRODUCTION

Thyroid is a large ductless gland present in the neck region and has its own significance in secreting different hormones which regulate the metabolism, growth, heart rate, blood pressure, body temperature *etc.* Physiologically there are two main disorders found to be associated with the thyroid with its up and down regulation *i.e.,* hypothyroidism and hyperthyroidism.

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Hypothyroidism

Hypothyroidism is a clinical condition that results from low thyroid hormone levels in the body. There are variable manifestations of hypothyroidism which are mostly age dependent. In this syndrome physical symptom includes cold intolerance, fatigue, and constipation, irregularities in menstrual cycle, dry skin and hair loss. There can be hoarse voice, non-pitting edema, bradycardia, facial puffiness, myxedema, slow speech and delayed reflexes. Psychiatric symptoms may range from mild attention deficit to significant agitated delirium or psychosis (Heinrich and Grahm, 2003; Geracioti,

2006). Face is puffy in the morning but in the evening lower legs are edematous .There is slow relaxation of deep tendon reflexes. Vascular resistance is increased but hypertension is uncommon. There is compensatory increase in noradrenergic activity. In severe cases there is paranoia, tremendous agitation and aggressiveness. As far as metabolism is concerned there is hyperprolactinemia leading to galactorrhea probably due to increase thyrotropin releasing hormone (TRH) release from hypothalamus which stimulates prolactin secretion from anterior pituitary. There can also be oligomenorrhea, amenorrhea or even infertility (Geracioti, 2006). In rare cases there can be macroglossia and uvular hypertrophy leading to dysarthria (Stollberger *et al*., 2001).

Hypothyroidism, may present with psychiatric symptoms among many other (Davidoff and Gill, 1977). Prevalence of hypothyroidism is 0.5-18%. Its pathophysiology includes, a; hypothalamus or pituitary disease, clinical disorders and tissue resistance to explained thyroid hormone is found to affect thyroid gland directly whereas, more commonly In women of older ages while about ten times more commonly in females (Heinrich and Grahm, 2003). Gull (1874) was the first man to describe the term adult hypothyroidism. After few years the term Myxedema was used to describe non-pitting edema which was observed in some patients of hypothyroidism (Ord, 1878). In 1888 for the first time hypothyroidism was linked with psychosis in committee on Myxedema of the clinical society of London. Committee reported that half of total 109 patients with Myxedema had delusions and hallucinations. In 1949 Asher used the terminology of myxedema madness.

Hypothyroidism is common in 4-10 % of females increasing with age (Redmond, 2002). Eight percent of women and thirty five percent of men have subclinical hypothyroidism (Vanderpump *et al*., 2002; Potesta *et al*., 1996). In a study done, on elderly in-patient population, about 4.9% of the patients executed primary hypothyroidism, while 8.2% had secondary hypothyroidism and rest 17.9% were through sick euthyroid syndrome. Causes of the disease were divided into three common classes named as primary, secondary and iatrogenic. Primary hypothyroidism is due to failure of gland to respond to Thyroid Stimulating Hormone (TSH) and is released from pituitary (Chuo *et al*., 2003). It can be due to Hashimotos thyroiditis, atrophy of thyroid gland after autoimmune attack. In Iatrogenic causes there can be surgical destruction of gland, radioactive destruction of gland and overtreatment of gland by antithyroid medications. Among Secondary causes there can be disease of pituitary gland which does not secrete adequate TSH (Heinrich and Grahm, 2003). Overtreatment of thyroid with antithyroid drugs produces hypothyroidism with concurrent psychiatric disturbances (Benvenga *et al*., 2003). Drugs producing hypothyroidism are lithium and amiadrone. Lithium is used for treatment of bipolar disorders (Klein *et al*., 1999). Amiadrone is an antiarrythmic agent contains iodine and thus overtreatment with it can lead to hypothyroidism (Harjai *et al*., 1997) as shown in the Figure 1.

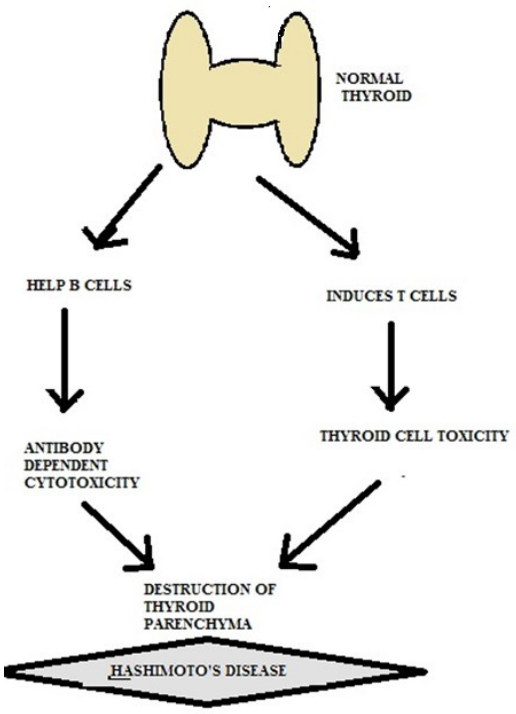

Fig. 1: Induction of Hashimoto's Thyroiditis by Immune cells.

Hyperthyroidism

As regards hyperthyroidism, according to Hall (1983) it is considered to be most frequently occurring endocrine disease. Its incidence is more in

females between the ages of 20-40. At the initial ages most commonly encountered symptoms are irritability, fatigue, anxiety, fine tremors, cold intolerance, insomnia, mood labiality, nervousness, increased sweating, impaired coordination, palpitation, doubts and fear. They have weight loss despite increased appetite. There can also be difficult eye focusing, pressure symptoms which are found related to goiter and tachycardia which is considered as a condition for irregular heart rate. Graves' disease usually represents ocular disturbances and diffused goiter (Hall, 1999).

Causes of hyperthyroidism remains iodine induced hyperthyroidism and toxic adenoma, in the group of patients diagnosed with multinodular goiter, exogenous thyroid hormone Ingestion, iatrogenic hyperthyroidism, hydatiform mole and TSH secreting tumor of pituitary gland. It has been observed that 1-20% hyperthyroid patients present with psychosis, between 30-40%, complain of anxiety, nervousness, apprehension, depression, decreased concentration, restlessness, forced thinking, emotional liability and hyperkinesia (Hall, 1999).

Schizophrenia is a disease/disorder which includes abnormal neurodevelopment characterized with minor physical anomalies, abnormalities of brain function and structure and neurological soft signs (John, 2009). Such abnormalities are found to cause several abnormalities in all the cases that may be working memory and long term memory tasks (Van Snellenberg, 2009). Hence it is tagged as disturbance in emotional or social reaction or disturbances like incapable of thinking properly or encounter illusions and hallucination.

Brain is considered to be novel/unique when it concerned with sensitivity to thyroid hormones and it utilization of thyroid hormones differently than any other organ systems of body (Thompson *et al*., 2000). Hormone receptors are located in all parts of CNS. High concentration of T3 receptors is present in amygdala and hippocampus. These receptors can influence neural activity. Thyroid dysfunction effects brain functions differently at different stages of development. Thyroid hormones have definite role in maturation of CNS and maintenance of homeostasis (Heinrich and Grahm, 2003). Metabolic activities in every cell of the body require normal thyroid hormones level in body. Diagnosis of hypothyroidism is made keeping in mind biochemical as well as clinical data. There may be severe biochemical hypothyroidism but mild clinical symptoms or there may be mild biochemical hypothyroidism with severe clinical manifestations (Zulewski *et al*., 1997). Whenever patient develops abnormal symptoms related to disturbance in hypothalamo-pituitary-thyroid axis, he first of all consults a psychiatrist (Geracioti, 2006). These patients with psychiatric symptoms are often diagnosed with depressive spectrum syndrome (Geracioti, 2006). Common of all the symptoms in case of disorder remains bipolar nature, premenstrual syndrome, cyclothymia, mixed mania, borderline personality disorders or paranoid psychosis (Geracioti, 2006). There is also psychomotor slowing and mental dullness, easy fatigue ability and lethargy. Among the major depressive symptoms is lassitude, concentration difficulties, decreased libido and sometimes sadness. Symptoms usually improve after continuous thyroid hormone replacement therapy (Gunnarsson *et al*., 2001). It is also seen that women with mild hypothyroidism but no psychiatric symptoms, still show mood improvement after six months therapy with levothyroxine (Bono *et al*., 2004).In some patients with no biochemically or clinically significant hypothyroidism, mood symptoms still improve after augmentation of antidepressants by thyroid hormones (Iosifescu *et al*., 2006). Occasionally patients presenting with thyroid dysfunction found to have anxiety disorders like panic disorder agoraphobia, social phobia, post-traumatic stress disorder and generalized anxiety disorders (Tancer *et al*., 1990).

It is somewhat surprising that hypothyroidism is as common as hyperthyroidism in patients with anxiety disorders (Geracioti, 2006). Both hypo- as well as hyperthyroidism is common in patients with panic level anxiety (Geracioti, 2006). Figure 2 shows a brief representation of the hyper and hypothyroidism.

Schizophrenia and thyroid interrelationship at neurotransmitter level

Thyroid hormones are very important in development of adult brain. Oscillations in the

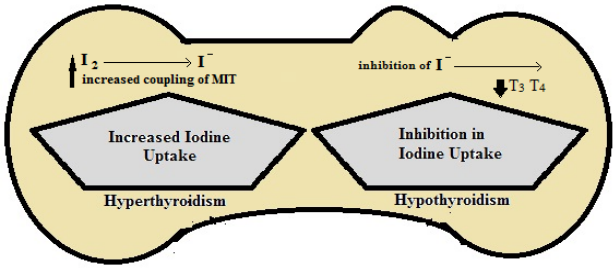

Fig. 2: Mechanism of hypothyroidism and hyperthyroidism. Hypothyroidism can be stated as the inhibition of iodine uptake while increased uptake can be termed as hyperthyroidism**.**

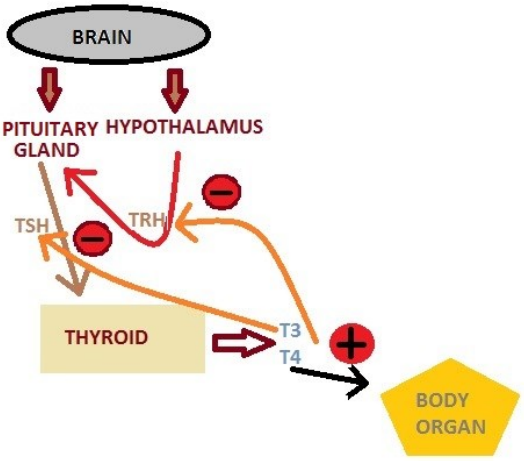

Fig. 3: Stimulus from hypothalamus to pituitary gland causes release of T3 and T4 from thyroid

levels of thyroid hormones at any stage in development can lead to manifestation of psychiatric disease and respond to treatment (Santos *et al*., 2012). There is definitely a relationship between pituitary-thyroid axis and major signaling systems involved in pathophysiology of schizophrenia. Roca *et al.* (1990) suggested that most of hyperthyroid patients showed psychosis (positive symptom in Schizophrenia) while hypothyroid patients showed depression and decreased motivation. Thyroid hormones modulate crucial brain neurotransmitter systems *i.e.,* dopaminergic, serotonergic, glutamatergic and GABAergic system. Moreover, they also participate in brain myelination and inflammatory processes (Santos *et al*., 2012). Regarding Dopaminergic system, it is now known that antipsychotic drugs that block dopamine D2 receptors alleviate hallucinations and delusions (Geyer *et al*., 2008). Thyroid hormones regulate levels of dopamine receptors (Crocker *et al*., 1986) and activity of tyrosine hydroxylase rate limiting step in catecholaminergic pathway (Chaube *et al*., 2003). Figure 3 shows the cascade of signaling in between brain and thyroid. Another hypothesis in the case of schizophrenia is serotonin which suggests enhanced serotonergic signaling, especially via serotonin type 2A receptor, is involved in pathophysiology of schizophrenia (Shin *et al*., 2011). Similarly deficient central 5HT function may underlie some negative symptoms of schizophrenia (Abi Dargham *et al*., 2007). Cleare *et al*. (1995) suggested that there is reduced 5HT activity in hypothyroid patients.

As far as glutamatergic pathway is concerned, Mohn *et al*. (1999) suggested that reduced NMDA receptor (glutamate receptor) leads to schizophrenia like symptoms. Later on Mendes (2008) studied the role of T3 in CNS, especially on glutamate uptake. Researchers in 2002 treated male rat with glutamate receptor agonists and found that they develop raised TSH in blood with antagonistic decrease in TSH and TH serum levels (Mendes, 2008). Up-regulation of postsynaptic GABA –A receptors was described in schizophrenia (Akbarian *et al*., 2006). Thyroid hormones are found to effect enzymes involved in synthesis and metabolism of GABA and glutamate, GABA release and reuptake and GABA receptors (Berbel *et al*., 1996). Hypothyroidism is associated with delayed myelination in several regions of brain (Farsetti *et al*., 1992). Researchers also found down-regulation of myelin related genes in postmortem schizophrenic brain, including cyclic nucleotide phosphodiestrase, myelin associated glycoprotein, transferring and V-erb-b2 erythroblastic leukemia, viral oncogenes homolog 3 (Hakak *et al*., 2001) are all regulated by thyroid hormones. Katsel *et al*. (2008) observed changes in identified cell cycle genes, doing microarray analysis of schizophrenic patients, showing that two genes cyclin D1 and cyclin dependent kinase inhibitor1C (P57), which are among early regulated cell cycle genes after exposure to thyroid hormones and are essential for

oligodendrocyte differentiation (Dugas *et al*., 2007; Dugas *et al*., 2006).

In neurological or psychiatric diseased brain, myelin abnormalities are often presented with inflammation. In schizophrenia for example, there is a potential pathogenic role of elevated cytokines expression. There is elevated expression of IL-6, TNF-α in CSF along with altered creatine kinase and creatin kinase receptor expression (Potvin *et al*., 2008; Fan *et al*., 2007). Their induction in immune and glial cells such as astrocytes and microglia play a significant role in neural cells homeostasis, especially at the level of oligodendrocyte functions and myelination (Schmitz and Chew, 2008). Normally thyroid hormones are found to play a significant role in regulation of de-iodinase activity, but some other regulating mechanisms may also show their action in thyroid hormone metabolism during some pathophysiological conditions, they may also overlap with those known to be relevant for development of schizophrenia (Santos *et al*., 2012). There is schizophrenia-thyroid hormone-inflammation interrelationship as in sites of local inflammation, with enhanced de-iodenase type 3 activity and local degradation of T3 (Boelen *et al*., 2005).

The role of thyroid hormones in pathophysiology of schizophrenia is clearer when possible function of thyroid hormone as neurotransmitter was considered. This hypothesis of neurotransmitter role of T3 was put forward in 1970s (Dratman *et al*., 1976). The T3 has a vast role in brain as it promotes differentiation in astrocytes, mediates cerebellar astrocytes, neuronal proliferation and organization of extracellular matrix molecule via astrocytes (Mendes *et al*., 2008; Trentin *et al*., 2006). Similar neurotransmitter function of 3-iodothyronamine, a product which is formed in decarboxylation of T4 or rT3 (reverse T3) has been reported (Scanlan *et al*., 2009).

The hormone T3 accumulates in nerve endings, reaching a high concentration in synaptic vesicles (Kastellakis and Valcana, 1989; Dratman *et al*., 1978) and releases from it in calcium dependent mechanism (Mason *et al*., 1993). *In vitro* studies T1AM have been reported to block the transporters for neurotransmitters, dopamine, serotonin and nor-epinephrine. It also binds strongly with associated receptor (Scanlan *et al*., 2009) which is a G-protein coupled receptor and genetic studies show a strong linkage between TAAR gene and schizophrenia (Zucchi *et al*., 2006).

Hashimotos encephalopathy (HE) is a rare neuropsychiatric syndrome which is more common in women. The term Hashimotos encephalopathy was first used by Brain *et al*. (1966) and since then it is considered to be an important differential diagnosis of encephalopathy of unknown origin. There is usually serological evidence of presence of antithyroid antibodies in blood of the patient (Chong *et al*., 2003). Onset of disease is usually acute with episodes of cerebral ischemia, seizures and psychosis or it may present as depression, cognitive decline, myoclonus, tremors and fluctuations in consciousness (Chong *et al*., 2003; Sanchez *et al*., 2004). The relationship of HE and Hashimotos thyroiditis (HT) is still not clear because there is no evidence of thyroid autoantibodies reacting with brain tissue and affecting neuronal functions. Similarly level of circulating antibodies do not correlate with severity of symptoms or response of treatment. Good response to steroid and association with other autoimmune diseases point that it may be an inflammatory or immunological dysfunction (Sanchez *et al*., 2004; Chong *et al*., 2003). Some authors suggest that despite of HE, it can be called as steroid-responsive encephalopathy associated with autoimmune thyroiditis (Castillo *et al*., 2006; Tamago *et al*., 2010). Chaves *et al*. (2011) reviewed all cases of HE that has been published since it was first described.

They reported that HE has a variable clinical spectrum, due to which there is difficulty in diagnosis and early treatment of the disease. There is also wide variation in age of onset of the disease but they found it to occur most commonly between fifth and sixth decade of life. Most common manifestations of all these cases were cognitive deficit and generalized seizures (Chaves *et al*., 2011). Pathogenesis of the disease includes autoimmune cerebral vasculitis (George *et al*., 2007; Nolte *et al*., 2000) toxic effects of TSH on CNS (Brain *et al*., 1966) and neuronal reaction mediated by antibodies (Blanchin *et al*., 2007; Oide *et al*., 2004; Takahashi *et al*., 1994). Chaves *et al*. (2011) further reported that 86% patients presented positive

serum anti-thyroid peroxidase (TPO) antibodies whereas 48% presented with anti-thyroglobulin (Tg) antibodies. Blanchin *et al*. (2007) have reported that anti TPO antibodies could be sufficient to cause disease by interacting with CNS tissue although the pathogenic role of other antibodies could not be ruled out.

Researchers while finding the role of some common antigens against thyroid and brain tissue, demonstrated the role of an antigen (amino terminal enolase), which is found to be highly prevalent in population studies. It might help to explain the pathophysiology of HE (Chaves *et al*., 2011). Nineteen percent of HE are reported in patients of Graves' disease. With this finding it is clear now that HE is not exclusively associated with HT but also with other autoimmune thyroid diseases. For this reason it is more appropriate to use the term SREAAT instead of HE (Chaves *et al*., 2001). CSF analysis of patients of both Graves' disease and HT who develop SREAAT, showed nonspecific inflammatory status with normal or increased cellularity at the expense of lymphocytes (Tamagno *et al*., 2010). Important findings were presence of anti Tg and anti TPO antibodies in CSF and high CSF protein concentration in these patients. These findings if found in patients of encephalitis of unknown etiology, should reinforce the diagnosis (Chaves *et al*., 2011). In the end Chaves *et al*. (2011) concluded that if neuropsychiatric manifestations are found in any patient and any other cause of encephalopathy is excluded, then diagnosis of HE can be made easily if following findings are there: A high concentration of antithyroid antibodies in CSF or serum, no change in CSF indicative of vascular infection or neoplastic etiology, nonspecific MRI or CT scan and a good response to immune suppressive therapy (Chaves *et al*., 2011).

Numerous reports have explained psychiatric consequences of hypothyroidism (McGaffee *et al*., 1981; Westphal, 1997; Tachman *et al*., 1984). Pfeiffer included hypothyroidism as one of 29 medical causes of schizophrenia. According to this report about 10% of schizophrenics showed hypothyroidism. The mental state includes changes in perception such as aural and visual hallucinations, disorders of thought such as obsession, suspiciousness and mood swings. All these symptoms fit into the category of schizophrenia (Pfeiffer and Holdford, 1996). Hoffer, (2001) reported that thyroid hormones improve cure rates in most of the patients of schizophrenia. In many studies it was found that if treatment with thyroid hormones was maintained, many patients of schizophrenia were rendered free of signs and symptoms. This is true not only for periodic catatonics but also for other schizophrenics who had no regular periodicity (Hoffer, 2001). Hoffer in his review in 2001, reported a case of a 16 year old girl who was classic adolescent schizophrenic, with changes in perception, gross thought disorder, inappropriate affect and activity. She was treated with different modes of treatment like ECT (electro convulsive therapy), penicillamine and nicotinic acid but she did not recover. Ultimately when she was started with heavy doses of thyroid and nicotinic acid with strict monitoring of her pulse rate she almost recovered completely and started leading normal social life. Keeping these dramatic results in mind, twelve more schizophrenics were started with high doses of thyroid hormones with nicotinic acid. From this group of 12, only 3 were not improving out of which one had discontinued treatment. Out of remaining 9, 6 were improving a lot and 3 were recovering as the dose of thyroid hormone was being increased (Hoffer, 2001). Thus he concluded that all schizophrenic patients should be examined for hypothyroidism. Finding symptoms, high doses of thyroid hormone should be added to treatment program. Low TSH can sometimes be misleading patients can have low T3 despite of low TSH. It can be because of decreased peripheral conversion of T4 to T3 (Hoffer, 2001). Hypothyroidism is a disorder which has varying degree of presentations. This is the reason why diagnosis is difficult in most of the cases. Keeping this in mind Heinrich and Grahm (2003), reviewed the literature describing relationship of hypothyroidism with various psychiatric presentations. In one of their articles they described a case of 75 years old female who suddenly started having episodes of visual and auditory hallucinations without any previous medical illness. Upon GP examination it was found that she had normal thyroid but dry skin with brittle nails. Upon neurological examination she had delay

in relaxation phase of deep tendon reflex. The patient was admitted in hospital and after lab investigations was found have raised TSH and low T3 and T4.When she was started low-dose of thyroid replacement therapy (TRT) together with risperidone (a medicine to treat hallucinations), she slowly began to recover and by 2-3 weeks of therapy she had no further hallucinations. Afterwards she herself discontinued risperidone but no recurrence of symptoms was seen with maintenance dose of TRT.

Thyroid, schizophrenia and associated pathophysiology

There is definitely a genetic etiology for schizophrenia. It has usually a Mandelian characteristic of inheritance and has a higher chance of incident in monozygotic twins. Thus appearance of disease may depend upon the presence of other risk factors in genetically susceptible individuals (DeLisi *et al*., 1991). Previous studies have explained some factors associated with psychosis. They are obstetric and perinatal complications (McNeil and Kaij, 1979; Parnas, 1986; Lewis 1987; Murray and Lewis 1987) viral infections before and after delivery and traumatic injury to head (De-Lisi *et al*., 1986; Wilcox and Nasrallah, 1987).

Onset and development of schizophrenia can be determined by the presence of any previous brain insult such as head injury or substance abuse or any previous brain insult (DeLisi *et al*., 1991). Several studies have been conducted on individuals having high risk of developing schizophrenia. These studies have showed that some childhood problems like delayed neuromotor development and attention deficit (Watt *et al*., 1984; Parnas and Mednick, 1991) are associated with later development of schizophrenia. In a survey conducted by DeLisi *et al*. (1991), on 100 consecutive first admission patients with DSM-III-R diagnosis of schizophrenia, they did not find increased risk of schizophrenia subsequent to head injuries during childhood. Hall (1983) reported that psychosis occur in 1-15% of hypothyroidism patients. In patients with acute hypothyroidism anxiety disorders occur in 30-40% hypothyroidism patients. Patients in acute myxedema, usually develop progressive anxiety with agitation. They can also experience disorientation (deteriorating with time), delusion hallucinations and lethargy alternating with restlessness. Patients in extreme cases may complain of auditory and visual hallucination increased sexual activity, irritability, delusion, lack of concentration and decreased memory are all sign of acute thyroid disease. This increased fatigue ability, psychomotor slowing and chronic anxiety is more likely to be due to progressively changing thyroid hormone levels in these patients. Elderly patients and patients with rapidly changing thyroid hormone level have more severe mental symptoms (Hall, 1983).

When treatment is started, the initial symptom *i.e*., anxiety, disappears within days to months but the main effect of hypothyroidism cannot be cleared until 2-12 months of successful therapy. Sleep disturbance and growth hormone levels during sleep take weeks to months to normalize and it is related to complete cure of anxiety in these patients (Hall, 1983). Trepacz *et al*. (1988) reported a higher rate of anxiety in the patients who were not given any treatment for the Graves' disease. There is behavioral inhibition system in the brain within which neuroanatomical circuits modulate response to stress stimuli. If these systems are overstimulated, there is a persistent anxiety state in human beings. Among these systems one is Septo-hippocampal system, discharge from which increases arousal. Noradrenergic and serotonergic stimulation to this system send a lot of impulses to limbic system and prefrontal cortex. Medical conditions which alter hypothalamo-hypophyseal axis or which alter neurotransmitter levels in brain may produce anxiety.

Wells *et al*. (1988) reviewed 2554 patients with one of 8 chronic medical conditions and estimated that significant anxiety is present in 10-20% of patients. He also noted that more than 11% of patients of chronic medical conditions have experienced an episode of recent anxiety disorder. He found that 10-40% of patients with anxiety have some organic cause of their psychiatric symptoms (Wells *et al*., 1988). He also suggested that among many psychiatric disorders, anxiety disorders are the one which have a strong association with chronic medical conditions. It was reported that patients who experienced common anxiety issues had higher

plasma catecholamine levels than controls. Their catecholamine receptors down regulates and thus they experience reduced receptor sensitivity in their adrenergic nervous system (Mathew *et al*., 1990). In another report it was found that patients with generalized anxiety have decreased growth hormone response to clonidine stimulation (alpha-2 partial agonist) suggesting decrease sensitivity of alpha-2 receptors which again may be due to increased catecholamine levels in these patients (Abelson *et al*., 1991). Wu *et al*. (1991) reported that in patients of generalized anxiety disorders, there is increased relative metabolic rate in occipital, temporal and frontal lobe and cerebellum. They also noted decreased absolute metabolic activity in areas of basal ganglia, cingulate gyrus, temporal lobe, amygdala and hippocampus of the patients. Popkin, (1993) stated that endocrine disorders presenting with anxiety are due to adrenal dysfunction, Cushing's syndrome, pancreatic tumors, pheochromocytoma and thyroid diseases (hyperthyroidism, hypothyroidism and thyroiditis (Popkin, 1993).

A similar study was carried out on 711 patients at Harvard Brawn Anxiety Disorders Research Program (HARP). where it was found that anxiety disorder patients, with associated panic disorders and depression had higher rates of reported medical illness like peptic ulcer, angina and thyroid diseases. In the current study about two percent of males were included and out of them about nine percent females were suffering through thyroid disease (Rogers *et al*., 1994). Afterwards, Sherbourne *et al*. (1996) studied a group of 2494 patients with hypertension, heart diseases and diabetes, assessing them for depression, panic disorders, general anxiety disorders and phobia. He found that depressed medical patients have higher incidence of developing panic disorders than non-depressed medical patients. Similarly phobia and anxiety disorders were found to be 14.6% higher in patients with depression as compared to non-depressed patients. They found that 14-66% patients in care unit had medical care and were encountered with at least one of the anxiety disorder (Sherbourne *et al*., 1996). According to Brawman-Mintzer and Lydiard (1997), patients at risk of developing generalized anxiety disorders may have some problem in regulation of hypothalamo-hypophyseal axis. Such patients are more sensitive than control in terms of numbers and intensity of symptoms. Brawman-Mintzer and Lydiard suggested that there may be several abnormalities in cellular structures and in regulatory mechanism that may be important in production of anxiety. In response to stressful stimuli, a maladaptive response occurs in locus ceruleus-norepinephrine – sympathetic nervous system, the hypothalamic – pituitary – axis and cholecystokinin (CCk) system. Abnormalities are also noted in GABAergic and 5-HT systems (Brawman-Mintzer and Lydiard, 1997). Meredith *et al*. (1997) studied 2189 general medical patients and concluded that patients with primary medical conditions with associated anxiety disorders are more likely to receive treatment for their anxiety than patients with primary anxiety disorders. He also found that if anxiety disorder occur with another disease like any medical illness or depression, patient is more likely to receive counseling or to be treated with psychotropic medication.

When it is established that anxiety mostly associates medical illness, we should be able to differentiate between primary anxiety disorder and anxiety associated with medical illness certain questions in this regard would be helpful. Is there any association between exacerbation and remission of medical illness with aggravation or depletion of anxiety symptoms? Do the anxiety symptoms disappear, when primary medical condition is treated? Whether the atypical features of primary anxiety disorders are present. Such as usual age and type of onset, initial presentation or absence of family history. Following extensive studies it was concluded that neurological and endocrine disorders are responsible for half of medically induced anxiety symptoms encountered. Certain characteristics differences between patients of anxiety disorder and patients of medically induced anxiety disorders are: a, Patients with medically induced anxiety disorders show fluctuations in severity and duration of their attacks. b, There is a definite association between progression of their anxiety state and their underlying disease. c, Medically induced anxiety disorder has its onset before the age of 14 and after the age of 35 and

patient usually do not have any background family history or history of any previous attack. On the other hand patients with primary anxiety disorders present with history of other psychiatric symptoms like phobia and conversion symptoms and give history of recent severe psychological stress.

Symptoms of patient with primary anxiety disorder are acute as compared to more chronic symptoms in patients with medically induced anxiety disorders (Hall, 1999).Psychiatric presentations are usually the first sign of hypothyroidism and considered as initial symptoms in 2-12 % of reported cases together with organic mental deficits (Hall, 1986). Initial symptoms then progress as mental slowing associated with decreased recent memory, speech deficits, decreased learning etc. In women between ages of 40 and 60 spontaneous hypothyroidism occurs. They show symptoms of weakness, fatigue, cold intolerance, diminished libido, lethargy, dry skin, headache and menorrhagia. Signs include thin course hair, brittle nails, diminished pulse rate, pallor and diminished deep tendon reflexes. Delayed symptoms include changes in sense of taste, smell, vision and hearing, weight gain and sweating, pallor, hoarseness of voice, peripheral edema, muscle cramps, angina and dyspnea. Menstrual irregularities can also be seen. Development of severe anxiety disorders in hypothyroid patients is due to rapidly changing levels of thyroid hormones in these patients. No matter what is the cause of hypothyroidism, it may be due to thyroidectomy autoimmune disease, gland ablation by radioactive iodine due to thyroid cancer, neuropsychiatric symptoms are same in all cases.

CONCLUSION

There is definitely a relationship between thyroid dysfunction and schizophrenia as characterized by strong family history of thyroid disease in patients of schizophrenia and interaction between pituitary-thyroid axis and dopamine, serotonin, glutamate and GABA systems together with myelin and proinflammatory response which are strongly implicated in patients of schizophrenia. All schizophrenic patients should be investigated for their thyroid profiles as thyroid dysfunction is associated with depression (a negative symptom of schizophrenia) and psychosis (a positive symptom of schizophrenia).

REFERENCES

Abelson JL, Glitz D and Cameron OG. Blunted growth hormone response to clonidine in patients with generalized anxiety disorder. *Arch Gen Psychiatry*, 1991; 48(2): 157-62.

Abi-Dargham A. Alterations of serotonin transmission in schizophrenia. *Int Rev Neurobiol*., 2007; 78: 133-64.

Akbarian S and Huang HS. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. *Brain Res Rev*., 2006; 52(2): 293-304.

Arufe MC, Duran R, Perez-Vences D, and Alfonso M. Endogenous excitatory amino acid neurotransmission regulates thyroid-stimulating hormone and thyroid hormone secretion in conscious freely moving male rats. *Endocrine*., 2002; 17(3): 193-7.

Asher R. *Report of the Committee of the Clinical Society of London to investigate the subject of myxoedema.* Trans Clinical Society of London, 1888; 21: 1-215.

Bauer MS, Whybrow PC and Winokur A. Rapid Cycling Bipolar Affective Disorder I: Association with Grade I Hypothyroidism. *Arch Gen Psychiatry*, 1990; 47(5): 427-32.

Benvenga S, Lapa D and Trimarchi F. Don't forget the thyroid in the etiology of psychoses. *Am J Med.*, 2003: 115.

Berbel P, Marco P, Cerezo JR and DeFelipe J. Distribution of parvalbumin immune-reactivity in the neocortex of hypothyroid adult rats. *Elsevier*, 1996; 204: 65-68.

Blanchin S, Coffin Cm and Viader F. Anti-thyroperoxidase antibodies from patients with Hashimoto's encephalopathy bind to cerebellar astrocytes. *J Neuroimmunol*., 2007; 192(1-2): 13-20.

Boelen A, Kwakkel J, Alkemade A. Induction of type 3 deiodinase activity in inflammatory cells of mice with chronic local inflammation. *Endocrinology*, 2005; 146(12): 5128-34.

Bono G, Fancellu R, Blandini F, Santor G and

Mauri M. Cognitive and affective status in mild hypothyroidism and interactions with L-thyroxine treatment. *Acta Neurol Scand*., 2004; 110(1): 59-66.

Brann DW. Glutamate: a major excitatory transmitter in neuroendocrine regulation. *Neuroendocrinology*, 1995; 61(3): 213-25.

Brawman-Mintzer O and Lydiard RB. Biological basis of generalized anxiety disorder. *J Clin Psychiatry*, 1997; 31: 16-25.

Castillo P, Woodruff B and Caselli R. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol*., 2006; 63(2): 192-202.

Chaube R and Joy KP. Thyroid hormone modulation of brain *in vivo* tyrosine hydroxylase activity and kinetics in the female catfish Heteropneustesfossilis. *J Endocrinol*., 2003: 179(2): 205-15.

Chaves NP, Dantas D, Taciana BC, Cynthia SL and Francisco B. Hashimoto's Encephalopathy: Systematic Review of the Literature and an Additional Case. *J Neuropsychiatry Clin Neusci*., 2011; 23: 4.

Chong JY, Rowland LP and Utiger RD. Hashimoto encephalopathy: syndrome or myth? *Arch Neurol*., 2003; 60(2): 164-71.

Cleare AJ, McGregor A and Keane VO. Neuroendocrine evidence for an association between hypothyroidism, reduced central 5-HT activity and depression. *Clin Endocrinol*., 1995; 43(6): 713-9.

Cleare AJ, McGregor A, Chambers SM, Dawling S and O'Keane V. Thyroxine replacement increases central 5-hydroxytryptamine activity and reduces depressive symptoms in hypothyroidism. *Neuroendocrinology*, 1996; 64(1): 65-9.

Crocker AD and Overstreet DH. Modification of the behavioural effects of haloperidol and of dopamine receptor regulation by altered thyroid status. *Pharmacology (Berl)*, 1984; 82(1-2): 102-6.

Crocker AD, Overstreet DH and Crocker JM. Hypothyroidism leads to increased dopamine receptor sensitivity and concentration. *Pharmacol Biochem Behv*., 1986; 24(6): 1593-7.

Davidoff F and Gill J. Myxedema madness: psychosis as an early manifestation of hypothyroidism. *Conn Med*., 1977; 41(10): 618-21

DeLisi LE, Boccio AM, Riordan H, Hoff AL, Dorfman A, McClelland J, Kushner M, Van Eyl O and Oden N. Familial thyroid disease and delayed language development in first admission patients with schizophrenia. *Psychiatry Res*., 1991; 38(1): 39-50.

Diarra A, Lefauconnier JM, Valens M, Georges P and Gripois D. Tyrosine content, influx and accumulation rate, and catecholamine biosynthesis measured in vivo, in the central nervous system and in peripheral organs of the young rat. Influence of neonatal hypo- and hyperthyroidism. *Arch IntPhysiol Biochem*., 1989; 97(5): 317-32.

Dratman MB and Crutchfield FL. Synaptosomal [125I] triiodothyronine after intravenous [125I] thyroxine. *Am J Physiol*., 1978; 235(6): 638-47.

Dratman MB, Crutchfield FL and Axelrod J. Localization of triiodothyronine in nerve ending fractions of rat brain. *Proc Natl Acad Sci USA*., 1976; 73(3)941-4.

Dugas JC, Ibrahim A, and Barres BA.A crucial role for p57*Kip*2 in the intracellular timer that controls oligodendrocyte differentiation. *J Neurosci*., 2007; 27(23): 6185-96.

Dugas JC, Tai YC, Speed TP, Ngai J, and Barres BA. Functional genomics analysis of oligodendrocyte differentiation. *J Neurosci*., 2006; 26(43): 10967-83.

Esposito S, Prange AJ and Golden RN. The thyroid axis and mood disorders: overview and future prospective. *Psychopharmacol Bull*., 1997; 33(2): 205-17.

Fan X, Goff DC and Henderson DC. Inflammation and schizophrenia. *Expert Rev Neurother*., 2007; 7(7): 789-96.

Farsetti A, Desvergne B, Hallenbeck P, Robbins J and NikodemVM. Characterization of myelin basic protein thyroid hormone response element and its function in the context of native and heterologous promoter. *J Biol Chem*., 1992; 267(22): 15784-8.

Fountoulakis KN, Iacovides A**,** Grammaticos P,

Kaprinis GS and Per Bech. Thyroid function in clinical subtypes of major depression: a major study. *BMC Psychiatry*, 2004; 15(4): 6.

George A, Abdurahman P and James J. Spastic paraparesis, abnormal muscle biopsy and positive antithyroid antibodies. *J Assoc Physicians India*, 2007; 55: 585-6.

Geracioti TD. Identifying hypothyroidism's psychiatric presentations. *J Assoc Physicians India*, 2006; 55: 585-6.

Geyer MA and Vollenweider FX. Serotonin research: contributions to understanding psychoses. *Trends Pharmacol Sci*., 2008; 29(9): 445-53.

Gull WW. On cretinoid state supervening in adult life in women. *Trans Clin Soc Lond*., 1874; 7: 180-85.

Gunnarsson T, Sjoberg S, Eriksson M and Nordin C. Depressive symptoms in hyothyroid disorder with some observations on biochemical correlates. *Neuropsychobiology*, 2001; 43(2): 70-4.

Haggerty JJ, Silva SG and Marquardt M. Prevalence of antithyroid antibodies in mood disorders. *Depress Anxiety*, 1997; 5(2): 91-6.

Hakak Y, Walker JR and Li C. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci USA*., 2001; 98(8): 4746-51.

Hall RCW. Anxiety and endocrine disease. *Semin Clin Neuropsych*., 1999; 4(2): 72-83.

Hall RCW, Popkin MK and DeVaul R. Psychiatric manifestations of Hashimoto's thyroiditis. *Psychosomatics*, 1982; 23(4): 337-42.

Hall RCW, Stickney S and Beresford TP. Endocrine disease and behavior. *Integrative psychiatry*: 1986.

Hall RCW. Psychiatric effects of thyroid hormone disturbance. *Psychosomatics*., 1983; 24(1): 7-11.

Hall RCW. Psychiatric Presentations of Medical Illness. *SP Medical and Scientific Books*, NY, 1980.

Harjai KJ and Licata AA. Effects of amiodarone on thyroid function. *Ann Intern Med*., 1997; 126(1): 63-73.

Harris B, Othman S and Davies JA. Association between postpartum thyroid dysfunction and thyroid antibodies and depression. *Biomed J.*, 1992; 305(6846): 152-156.

Heinrich TW and Grahm G. Hypothyrodism presenting as sychosis. *J Clin Psychiatry*, 2003; 5(6): 260-266.

Hoffer A. Thyroid and schizophrenia. *Orthomolecular Medicine*, 2001; 16(4).

Ibarrola N and Rodr´ıguez-Pe˜na A. Hypothyroidism coordinately and transiently affect myelin protein gene expression in most rat brain regions during postnatal development. *Brain Res*., 1997; 275(1-2): 285-93.

Iosifescu DV. 'Supercharge' antidepressants by adding thyroid hormones: Why hormones help, and new data on SSRI augmentation. *Current Psychiatry*, 2006; 5(7).

Jefferson JW and Marshall JR. Neuropsychiatric Features of Medical Disorders. *Critical Issue in Psychiatry*, 1981; ISBN 978-1-4684-3920-5.

John JP. Fronto-temporal dysfunction in schizophrenia, a selective review. *Indian J Psychiatry*, 2009; 51(3): 180-90.

Kales A, Heuser G and Jacobson A. All night sleep studies in hypothyroid patients before and after treatment. *Clinical endocrinology and Metabolism*, 1967; 27(11).

Kastellakis A and Valcana T. Characterization of thyroid hormone transport in synaptosomes from rat brain. *Mol Cell Endocrinol*., 1989; 67(2-3): 231-41.

Katsel P, Davis KL and Li C. Abnormal indices of cell cycle activity in schizophrenia and their potential association with oligodendrocytes. *Neuropsychopharmacology*, 2008; 1999: 2993-3009.

Kleiner J, Altshuler L and Hendrick V. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *J Clin Psychiatry*, 1999; 6(4): 249-55.

Kung AW. Life events, daily stresses, and coping in patients with Graves' disease. *Clin Endocrinol*., 1995; 42(3): 303-8.

Lacovides A, Fountoulakis KN, Grammaticos P and Ierodiakonou C. Difference in symptom profile between generalized anxiety disorder

and anxiety secondary to hyperthyroidism. *Int J Psychiatry Med*., 2000; 30(1): 71-81.

Lewis SW. obstetric complications, neuro developmental deviance and risk of schizophrenia. *J Psychiatr Res*., 1987; 21(4): 413-21.

Lord B, Jellied EH and Ball K. Hashimoto's disease and encephalopathy. *Lancet*, 1966; 2(7462): 512-4.

MacDonald AW and Schulz SC. What we know: findings that every theory of Schizophrenia should explain. *Oxford*, 2009; 493-508.

Mason GA, Walker CH and PrangeJr AJ. L-triiodothyronine: is this peripheral hormone a central neurotransmitter? *Neuropsychopharmacology*, 1993; 8(3): 253-8.

Mathew RJ, Ho BT and Francis DJ. Catecholamines and anxiety. *Acta Psychiatr Scand*., 1982; 65(2):142-7.

Mathew RJ, Ho BT and Kralik P. Catechol-o-methyltransferase and catecholamines in anxiety and relaxation. *Psychiatry Res*., 1980; 3(1): 85-91.

McGaffee J, Barnes MA and Lippmann S. Psychiatric presentations of hypothyroidism. *Am Iam Physician*, 1981; 23(5): 129-33.

McNeil TF and Kaij L. Etiological relevance of comparisons of high risk and low risk groups. *Acta Psychiatrica Scandinavica*, 1979; 545-560.

Mendes-de-Aguiar CB, Alchini R, Decker H, Alvarez- Silva M, Tasca CI and Trentin AG. Thyroid hormone increases astrocytic glutamate uptake and protects astrocytes and neurons against glutamate toxicity. *J Neurosci Res*., 2008; 86(14): 3117-25.

Meredith LS, Sherbourne CD and Jackson CA. Treatment typically provided for co-morbid anxiety disorder. *Arch Fam Med*., 1997; 6(3): 231-7.

Mohn AR, Gainetdinov RR, Caron MG and Koller BH. Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. *Cell*, 1999; 98(4): 427-36.

Murray GR. Note on the treatment of myxoedema by hypothermic injections of an extract of the thyroid gland of a sheep. *Br Med J*., 1891; 2(1606): 796-7.

Murray RM and Lewis SW. Is schizophrenia a neuro developmental disorder.*Arch Gen Psychiatry*, 1987; 44(7): 660-9.

Musselman DL and Nemeroff CB. Depression and endocrine disorders: focus on the thyroid and adrenal system. *Br J Psychiatry Suppl*., 1996; (30): 123-8.

Nicol-Smith L. Causality, menopause, and depression: a critical review of the literature. *BJM*., 1996; 313(7067): 1229-32.

Nolte KW, Unbehaun A and Sieker H. Hashimoto encephalopathy: a brainstem vasculitis? *Neurology*, 2000; 54(3): 769-70.

O'Hara MW. Postpartum depression, Causes and consequences. *Psychology*, 1995; ISBN 978-1-4613-8416-8.

Oide T, Tokuda T and Yazaki M. Anti-neuronal autoantibody in Hashimoto's encephalopathy: neuropathological, immunohistochemical and biochemical analysis of two patients. *J Neurol Sci*., 2004; 217(1): 7-12.

Oomen HA, Schipperijn AM and Drexhage HA. The prevalence of affective disorder and in particular rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. *Clin Endocrinol*., 1996; 45(2): 215-23.

Orenstein H, Peskind A and Raskind MA. Thyroid disorders in female psychiatric patients with panic disorder or agoraphobia. *Am J Psychiatry*., 1988; 145(11): 1428-30.

Palha JA and Goodman AB. Thyroid hormones and retinoids: a possible link between genes and environment in schizophrenia. *Brain Res Rev*., 2006; 51(1): 61-71.

Parnas J and Mednic SA. Early predictors of onset and course of schizophrenia and schizophrenia spectrum. *Causes of Schizophrenia*, 1991; 11: 34-47.

Parnas J. Risk factors in development of schizophrenia. *Danish Medical Bulletin*, 1986; 33(3): 127-133.

Pfeiffer C and Holford P. Mental Illness: The Nutrition Connection. *Medical Health*, 1996; 200.

Pop VJ, de Rooy HA and Vader HL. Postpartum thyroid dysfunction and depression in an

unselected population. *N Engl J Med*., 1991; 324: 1815-1816.

Pop VJ, de Rooy HA, Vader HL, Heide van der D, van Son MJ and Komproe I. Microsomal antibodies during gestation in relation to postpartum thyroid dysfunction and depression. *Acta Endocrinol*., 1993; 129(1): 26-30.

Pop VJ, Maartens LH, Leusink G, van Son MJ, Knottnerus AA, Ward AM, Metcalfe R and Weetman AP. Are autoimmune thyroid dysfunction and depression related? *J Clin Endocrinol Metab*., 1998; 83(9): 3194-7.

Popkin MK, Mackenzie TB, Sadock BJ, Baltimore MD and Williams W. Psychiatric presentations of endocrine dysfunction. *Psychiatric Presentation of Medical Illness*, 1980; 139-156.

Popkin MK. Consultation-Liaison Psychiatry, in Comprehensive Textbook of Psychiatry. *Kaplan HI*., 1993; 1592-1605

Potesta P, Murolo R. and Costantini S. High prevalence of asympto-matic hypothyroidism and hyperthyroidism in hospitalized elderly females. *Ri Eur Sci Med Farmacol*., 1996; 18(3): 129-33.

Potvin S, Stip E, Sepehry AA, Gendron A, Bah R and Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry*., 2008; 63(8): 801-8.

Redmond GP. Hypothyroidism and women's health. *Int J FertilWomens Med*., 2002; 47(3): 123-7.

Roca RP, Blackman MR, Ackerley MB, Harman SM, and Gregerman RI. Thyroid hormone elevations during acute psychiatric illness: relationship to severity and distinction from hyperthyroidism. *Endocr Res*., 1990; 16(4): 415-47.

Rogers MP, White K and Warsaw WMG. Prevalence of medical illness in patients with anxiety disorders. *Int J Psychiatry Med*., 1994; 24(1): 83-96.

Sa´nchez Contreras A, Rojas SA and Manosalva A. Hashimoto encephalopathy. *J Clin Rheumatol*., 2004; 10(6): 339-43.

Santos NC, Costa P, Ruano D and Macedo A. Revisiting Thyroid Hormones in Schizophrenia. *J Thyroid Res*., 2012; 569147.

Scanlan TS, Suchland KL and Hart ME. 3-Iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat Med*., 2004; 10(6): 638-42.

Scanlan TS. Minireview: 3-iodothyronamine (T1AM): a new player on the thyroid endocrine team? *Endocrinology*, 2009; 150(3): 1108-11.

Schmitz T and Chew LJ. Cytokines and myelination in the central nervous system. *Scientific World J*., 2008; 8: 1119-47.

Sherbourne CD, Jackson CA and Meredith LS. Prevalence of co-morbid anxiety disorders in primary care outpatients. *Arch Fam Med*., 1996; 5(1): 27-34.

Shikaeva FV and Koreneva GP. Functional interrelations of monoamines, thyrotropic hormone and thyroid hormones in hyperprolactinemia. *Prob Endokrinol (Mosk)*., 1987; 33(4): 27-30.

Shin JK, Malone DT, Crosby IT and Capuano B. Schizophrenia: a systematic review of the disease state, current therapeutics and their molecular mechanisms of action. *Curr Med Chen*., 2011; 18(9):1380-404.

Stollberger C, Finsterer J, Brand E and Tschabitscher D. Dysarthria as the leading symptom of hypothyroidism. *Am J Otolaryngol*., 2001; 22(1): 70-2.

Sullivan GM, Hatterer JA and Herbert J. Low Levels of Transthyretin in the CSF of Depressed Patients. *Am J Psychiatry*, 1999; 156(5): 710-5.

Tachman ML and Guthrie GP Jr. Hypothyroidism: diversity of presentation. *Endocr Rev*., 1984; 5(3): 456-65.

Takahashi S, Mitamura R and Itoh Y. Hashimoto encephalopathy: etiologic considerations. *Pediatr Neurol*., 1994; 11(4): 328-31.

Tamagno G, Celik Y and Simo´ R. Encephalopathy associated with autoimmune thyroid disease in patients with Graves' disease: clinical manifestations, follow-up, and outcomes. *BMC Neurol*., 2010; 28: 10-27.

Tancer ME, Stein MB, Gelernter CS and Uhde TW. The hypothalamic-pituitary-thyroid axis in social phobia. *Am J Psychiatry*., 1990;

147(7): 929-33.

Thompson CC and Potter GB. Thyroid hormone action in neural development. *Cereb Cortex*., 2000; 10(10): 939-45.

Trentin AG. Thyroid hormone and astrocyte morphogenesis. *J Endocrinol*., 2006; 189(2): 189-97.

Trepacz PT, McCue M and Klein I.A psychiatric and neuropsychological study of patients with untreated Graves' disease. *Gen Hosp Psychiatry,* 1988; 10(1): 49-55.

Van Snellenberg JX. Working memory and long term memory deficits in schizophrenia; is there a common substrate? *Psychiatry Res*., 2009; 174(2): 89-96.

Vanderpump MP and Tunbridge WM. Epidemiology and prevention of clinical and subclinical hypothyroidism. *Thyroid*, 2002; 12(10): 839-47.

Washington DC. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. *American Psychiatric Press*, 1994; 438.

Washington DC. Diagnostic and Statistical Manual of Mental Disorders. *American Psychiatric Press*, 1994; 7.

Watt NF, Anthony EJ, Wynne LC and Rolf JE. Children at risk for schizophrenia. 1984.

Wells KB, Golding JM and Burnam NA. Chronic medical conditions in a sample of the general population with anxiety, affective and substance use disorders. *Am J Psychiatry*, 1989; 146(11): 1440-6.

Wells KB, Golding JM and Burnham NA. Psychiatric disorder in a sample of the general population with and without chronic medical conditions. *Am J Psychiatry*, 1988; 145(8): 976-81.

Wilcox JA and Nasrallah HA. Childhood head trauma and psychosis. *Psychiatry Res*., 1987; 21(4): 303-6.

Winsa B, Adami HO and Bergstrom R. Stressful life events and Graves' disease. *Lancet*, 1991; 338(8781): 1475-9.

Wu JC, Buchsbaum MS and Hershey TG.PET in generalized anxiety. *Biol Psychiatry*, 1991; 29(12): 1181-99.

Zucchi R, Chiellini G, Scanlan TS and Grandy DK. Trace amine-associated receptors and their ligands. *Br J Pharmacol*., 2006; 149(8): 967-78.

Zulewski H, Muller B and Exer P. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. *J Clin Endocrinol Metab*., 1997; 82(3): 771-6.

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