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 cases 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.

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,
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 (Benvenega et al., 2003). Drugs producing hypothyroidism are lithium and amiodrone. Lithium is used for treatment of bipolar disorders (Klein et al., 1999). Amiodrone 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.
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
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 (Chaubé 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 (Farsett et al., 1992). Researchers also found down-regulation of myelin related genes in postmortem schizophrenic brain, including cyclic nucleotide phosphodiesterase, 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

**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**
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). Pfieffer 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 (Pfieffer 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 Mendelian 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 Kaj, 1979; Parnas, 1986; Lewis 1987; Murray and Lewis 1987) viral infections before and after delivery and traumatic injury to head (DeLisi 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).

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(Received: 2015; Revised: 2016)