DISSERTATION ON

A COMPARATIVE STUDY OF VISUAL EVOKED POTENTIALS IN HYPOTHYROID AND HYPERTHYROID INDIVIDUALS

SUBMITTED TO

THE TAMILNADU DR MGR MEDICAL UNIVERSITY

In partial fulfillment of the requirements

For the award of degree of

MD PHYSIOLOGY (BRANCH V)

DEPARTMENT OF PHYSIOLOGY

GOVT.STANLEY MEDICAL COLLEGE
CHENNAI – 600 001

APRIL - 2017

CERTIFICATE

This is to certify that this dissertation entitled **"A COMPARATIVE STUDY OF VISUAL EVOKED POTENTIALS IN HHYPOTHYROID AND HYPERTHYROID INDIVIDUALS"** by the Post Graduate **Dr. V.VENGADESH PRABHU** for **M.D. (PHYSIOLOGY), BRANCH – V** is a bonafide record of the research done by her in the Department of Physiology, Government Stanley Medical College hospital, Chennai in partial fulfilment of regulations of the Tamilnadu Dr MGR Medical University for the award of degree of MD (Physiology) Branch –V during the academic period 2014 – 2017.

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DECLARATION

I, Dr. V.VENGADESH PRABHU, solemnly declare that this dissertation entitled, **"A COMPARATIVE STUDY OF VISUAL EVOKED POTENTIALS IN HYPOTHYROID AND HYPERTHYROID INDIVIDUALS"** is a bonafide and genuine research work done by me in the Department of Physiology, Govt. Stanley Medical College and Hospital during 2014– 2017 under the guidance and supervision of **Dr VIJI DEVANAND, M.D.,** Professor and Head, Department of Physiology, Stanley Medical College, Chennai – 600 001.

The dissertation is submitted to the The Tamilnadu, Dr. M.G.R. Medical University, towards partial fulfilment of the University regulations for the degree of M.D. (Physiology), Branch V, examination to be held in April 2017.

Place : Chennai – 600 001

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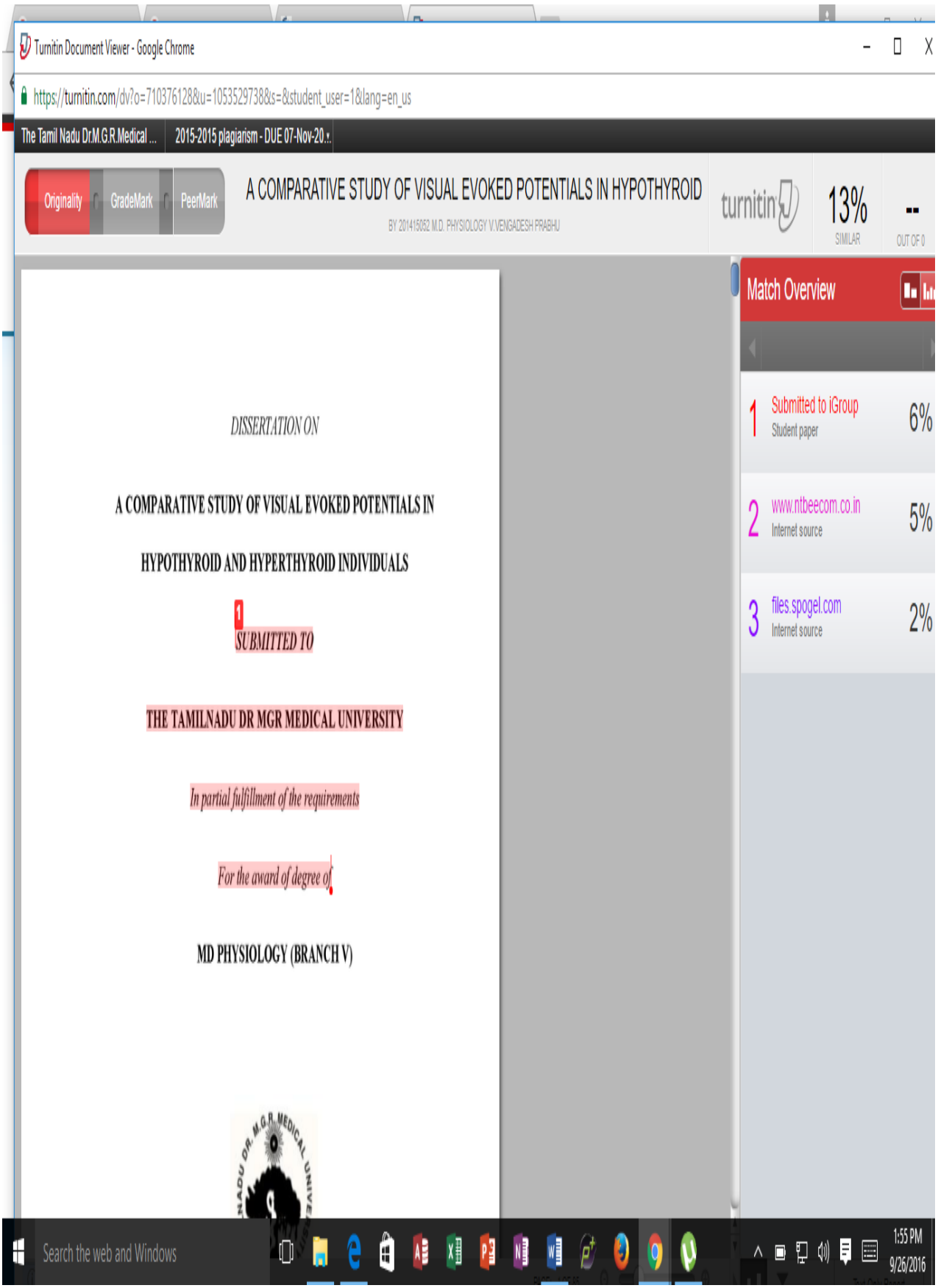
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The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 13.01.2016 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

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LIST OF ABBREVIATIONS

TSH : Thyroid Stimulating Hormone

FT_3 : Free tri iodo thyronine

FT_4 : Free tetra iodo thyronine

LATS : Long Acting Thyroid Stimulator

TRH : Thyrotropin Releasing Hormone

ANS : Autonomic Nervous System

BMI : Body Mass Index

BP : Blood Pressure

EP : Evoked Potentials

VEP : Visual Evoked Potentials

N75 : Latency of the N75 wave in milli second(ms)

P100 : Latency of the P100 wave in milli second(ms)

N145 : Latency of the N145 wave in milli second(ms)

P100-N75 : Amplitude of the P100N75 wave in microvolt(µv)

SD : Standard Deviation

HPA axis : Hypothalamo-Pituitary-Thyroid axis

ms : Millisecond

TAO :Thyroid associated Opthalmopathy

TMB : Tetra Methyl Benzidine

DON : Dysthyroid Optic Neuropathy

CMCT : **Central Motor conduction Time**

INTRODUCTION

The normal growth and development of an individual is profoundly influenced by the hormones produced by the Thyroid gland. Thyroid hormones are very much essential for the maintenance of the vital functions of life, their deficiency causes profound severe deficits in the mental and physical growth of an individual associated with an extreme decrease in body metabolism(1).Thyroid hormones are known to be involved in many processes and functions of the nervous system. Thyroid hormones play a very important role in the development and differentiation of the neuromuscular system and brain in foetal and neonatal life (2). Thyroid hormones affect the central and peripheral nervous system through its role in gene expression, myelin production and its effects on the neurotransmitter system and axonal transportation (3). Thyroid hormones also regulate protein synthesis by affecting gene transcription and mRNA stabilization (4,5,6).

Hypothyroidism affects both central and peripheral nervous system. The peripheral nerve involvement may be due to the defect in axons, nerve cell body or myelin sheath (4).

The central effects of Hyperthyroidism on are most pronounced, during the development of the central nervous system Thyroid hormones affect myelination. Therefore increased levels of thyroid hormones lead to oxidative damage of the myelin sheath and /or the oligodendroglial cells(4)

The Visual Evoked Response(VER) is the visual response to the specific alterations in the electroencephalogram caused by the sensory stimuli (7). Visual evoked potentials provide a reliable and objective measure of function of the anterior visual pathway which refers to the structures in the anterior part of visual pathway up to the lateral geniculate nucleus. Visual evoked response is an objective technique available to assess the functional state of the visual system beyond retinal ganglion cells (8). Since VEP is a relatively easy and safe technique, it can be used for early assessment of defects caused in the anterior visual pathway by alteration in the functions of thyroid gland

AIMS &OBJECTIVES

AIM & OBJECTIVE

AIM:

To assess and compare the neurological dysfunction of anterior visual pathway in Hypothyroidism and Hyperthyroidism using Visual Evoked Potential(VEP).

OBJECTIVES:

- To record VEP and compare the latencies and amplitude of visual evoked potential in hypothyroid and hyperthyroid patients with that of normal subjects.
- To correlate the duration of thyroid disease with the P100 latencies and P100-N75 amplitude of visual evoked potential in hypothyroid and hyperthyroid patients.
- To correlate the thyroid function tests with the P100 latencies and P100-N75 amplitude of visual evoked potential in hypothyroid and hyperthyroid patients

REVIEW OF LITERATURE

THYROID HISTORY – A TIMELINE REVIEW:

2700 BC : Emperor **Shun Nung's** prescriptions mentions the seaweed for the treatment of Goiter in his book Pen-Ts'ao Tsing (**A treatise on herbs & roots**)

300 BC : Hindu holy text, **Ayurveda** discusses about **Goiter**

40 BC : **Pliny, Vitrivius and Juvenal** described the prevalence of Goiter in Alps and the use of Seaweed for treatment of Goiter (11)

138 AD : Greek Physician **Soranus** mentioned neck swelling following `Pregnancy

340 AD : Chinese alchemist **Ko-Hung** recommends seaweed for the treatment of goiter among people living in Mountains

650 AD : Chinese physician, **Sun Ssu-Mo** used dried powdered Mollusc shells and chopped thyroid gland for the treatment of Goiter

961 AD : **Abul Kasim** , personal physician to Caliph El Hakin III of Colaboda was the first to describe **Thyroidectomy for Goiter** and to perform a **needle biopsy** of the thyroid

1500 AD **: Leonardo Da Vinci** was the first person to recognize and draw the thyroid gland (13)

1540 : Andreas Vesalius provided first anatomic description and illustration of the thyroid gland(15)

1563 : **Eustachius** used the term **Isthmus** to describe the tissue connecting two lobes of the gland

1602 : **Felix Patter** first described **Cretins** who were found in Valais region of Switzerland.

1656 : **Thomas Wharton** names the gland as THYROID after the shape of an ancient Grecian Shield. (12).

1669 : **Albert Van Healer** decribed constipation as a complication of Cretinism

1754 : First use of the term **CRETIN** in medical literature (term derived from latin word **Christianus** as affected individuals are incapable of committing sin)

1835 : **Thyrotoxicosis** was described for the first time by **Robert Graves** in women presenting with Goitre, rapid heartbeat and exophthalmos

1848 : **C Von Bosedow** describes **Exophthalmic Goiter**

1862 : **Armond Trousseau** introduces the term **Graves disease**

1874 : Gull considered that hypothyroidism could be either a neurological or a skin disorder

1891 : **Sheep thyroid extract** was used to cure myxedema

1914 : **Kendell and Osterberg** isolated the active substance in this extract and named it thyroxine

1924 : **H.S.Plummer** at the Mayo clinic report on the preoperative use of iodine for the treatment of Graves disease

1927 : **Harrington** determines the **chemical structure of thyroxine**

1936 : **Dr.Saul Hertz** first proposes the use of **radioactive iodine** for the study of thyroid

1949 : **RG Hoskins** reports about the **negative feedback mechanism** of thyroid on pituitary, which he described as **SERVO mechanism**

1956 : **Roitt and Danioach** demonstrated autoantibodies in Hashimotos disease

1960 : **Adams , Purves and Mckenzie** discover **LATS** in the serum of Graves disease patients

1970 : **A.Schally** identifies **TRH** and was awarded **Nobel prize** for it in 1977

1970 : T4 – T3 conversion was described by **L.Braverman, S.Ingar, and K.Sterling**

1998 : **Recombinant human TSH** approved for clinical use in humans in United states

PHYSIOLOGICAL ANATOMY OF THYROID GLAND:

The thyroid gland is a reddish brown, highly vascular endocrine gland located in the anterior part in the lower neck lying opposite the fifth cervical vertebra to the 1st thoracic vertebra (17).

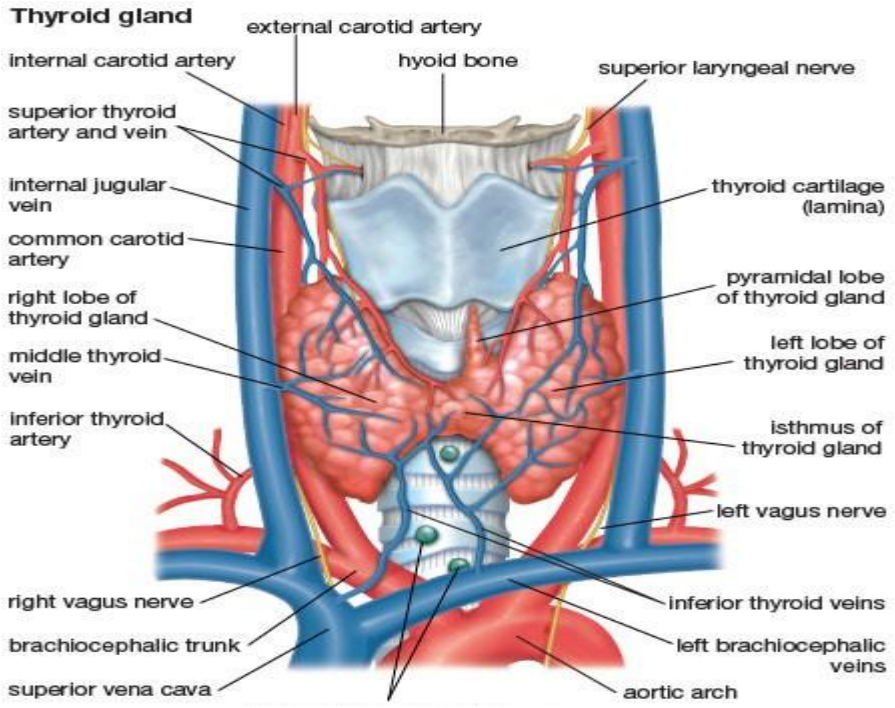


Fig.-1: Anatomy of Thyroid Gland

The gland usually weighs about 25 grams. The gland enlarges during pregnancy and menstruation (17). The thyroid gland consists of two lateral lobes connected by isthmus in the lower part. The isthmus usually lies anterior to the second and third tracheal rings but may lie above or below depending on its size. A conical lobe arises from the isthmus

ascending towards the hyoid bone but it may also arise from either of the two lobes – the left side being more common

The superior and inferior thyroid arteries supply on each side of the thyroid gland. The venous drainage is by three pairs of thyroidal veins namely superior, middle and inferior thyroid veins. The lymphatic drainage goes to pre and para tracheal and the deep cervical lymph node. The thyroid gland is innervated by both the recurrent and superior laryngeal nerves.

The thyroid gland is covered by covering called Capsula Glandulae Thyroideae. It is a thin fibrous sheath and is made up of inner and outer layer.

DEVELOPMENT:

In the developing embryo by 3 – 4 weeks of gestation, the isthumus and major portions of the lateral lobes develop from the median thyroid diverticulum which arises from the endoderm of the primitive pharynx at the base of the tongue. The gland reaches the base of neck few weeks later by passing ventral to the hyoid. The thyroglossal duct attaches the thyroid gland to the tongue.

The foetal pituitary and hypothalamus begins to secrete TSH and TRH respectively by about 18-20 weeks of gestation.

The thyroid gland starts synthesizing hormones by 11 weeks of gestation. The levels of thyroxine produced by the foetus reach a significant levels by around 20 weeks of

gestation whereas the T_3 levels remain low till 30 weeks of gestation after which it starts to increase reaching 50ng/dl at term(18)

The parafollicular cells of the thyroid gland derived from the neural crest cells produce calcitonin, a calcium lowering hormone. These parafollicular or C cells , seen between the thyroid follicular cells are maximum at the junction of the superior 1/3rd and inferior 2/3rd of the gland.

About 3% of the metabolically active hormones secreted by the thyroid gland is thyroxine and 7% is tri-iodothyronine. However almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so that both are functionally important.

Synthesis of thyroid hormones:

To form normal quantities of thyroxine about 150 gms of ingested iodine in the form of iodides is required each day. To prevent iodine deficiency common table salt is iodised with 1 part sodium iodide to every 1 lakh parts of sodium chloride

Orally ingested iodides are absorbed from the gastrointestinal tract in the blood, from which they are rapidly excreted by the kidney. About one fifth are selectively removed by cells of the thyroid gland and used for synthesis of thyroid hormones

The basal membrane of the thyroid cell has the specific ability to pump the iodine actively to the interior of the cell. This is called iodide trapping. This is done by transmembrane transporters which has eight membrane spanning domains. The transport is an active process.in a normal gland the iodide pump concentrates the iodide to about

thirty times its concentration in the blood. The concentration ratio can rise as high as 250 when maximally active.

Thyroglobulin and chemistry of the thyroxine and triiodothyronine

The endoplasmic reticulum and Golgi apparatus of the thyroid gland cells synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin with a molecular weight about 33500. Each molecule of thyroglobulin contains 70 tyrosine amino acids, and they are the major substrate that combine with iodine to form the thyroid hormones, which form within the thyroglobulin molecule.

The thyroxine and tri - iodo thyroxine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis and even afterward and stored as hormones in the follicular colloid

Storage of thyroglobulin:

After synthesis of thyroid hormones each thyroglobulin molecule contains 1 to 3 thyroxine molecules and an average of 1 triiodothyronine for every 14 molecules of thyroxine. The amount stored is sufficient to supply the body for 2to 3 months. Therefore, when synthesis ceases, effects of deficiency are not observed for several months

Release of thyroxine and triiodothyronine:

Thyroglobulin itself is not released into the circulation in measurable amounts. Instead thyroxine and triiodothyronine are first cleaved from the thyroglobulin molecule and then these two hormones are released. This occurs via pinocytosis of the colloid by the follicular cells, formation of pinocytic vesicles which fuse with the lysosomes to form digestive vesicles, and digestion and release of thyroxine and triiodothyronine, which then diffuses into the surrounding capillaries.

Transport of thyroid hormones:

On entering the blood, all but a fraction of 1 percent of the thyroxine and triiodothyronine combine immediately with several of the plasma proteins. They combine mainly with thyroxine binding globulin, much less with thyroxine binding pre albumin and albumin

The glycosylation of thyroid binding globulin influences its clearance from the plasma. Because of the high affinity of the plasma binding proteins for the thyroid hormones, these substances in particular thyroxine, are released into the cells slowly. Half of the thyroxine in the blood is released into the tissue cells about every 6 days, whereas half of triiodothyronine because of its lower affinity is released to the cells in about 1 day.

Metabolism of thyroid hormones:

The most important pathway for metabolism of T4 is the mono de-iodination of its outer ring to form the active thyroid hormone T_3. T_3 and T_4 are deiodinated in the liver, kidneys and many other tissues. These deiodination serves two purpose namely

1. Catabolism of hormones

2.Provide a local supply of T_3

Inner ring deiodination reactions deactivates the hormones. Three de-iodinases have been identified in mammalian tissues. Deiodinase 1 and 2 (D1 and D2) catalyzes outer ring deiodination to produce active T_3. D1 also catalyses the inner ring deiodination. Type 3 deiodinase (D3) is obligate inner ring monoiodinase with a preference for T3 as substrate. All three deiodinases contain selenocysteine in the active center.

The deiodinases also convert some of the T_3 and T_4 to deiodotyrosines. T_3 and T_4 are also conjugated in the liver to form sulfates and glucuronides. They enter the bile and pass into the intestine where they are hydrolyzed and some are reabsorbed - Entero hepatic circulation while the others are excreted in stool. Some T_3 and T_4 pass directly from the circulation into the intestine. The iodides lost by these accounts to about 4% of the daily iodide loss.

Cellular action of thyroid hormones:

Thyroid hormone enters inside the cell by diffusion. They then bind to specific high affinity receptors in the target cell nucleus. T_3 binds with approximately 10 times the affinity of T_4 and has proportionately greater biological activity. Thyroid hormones also bind to low affinity sites in the cytoplasm, this cytoplasmic binding may serve to keep the thyroid hormones in the neighbourhood.

The nuclear receptors are either attached to the genetic strands or in proximity to them. On binding, the receptors become activated and initiate transcription process. Then large numbers of mRNA are formed, followed within minutes to hours by RNA translation of the cytoplasmic ribosomes to form hundreds of new types of proteins.

Physiological effects of thyroxine:

The thyroid hormones increase the metabolic activities of all or almost all tissues of the body. The basal metabolic rate increases to 60-100% above normal when large quantities of the hormones are secreted.

Effect on Mitochondria:

Increase in the size and number of mitochondria occurs. The total surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate.

The mitochondria in turn increases the rate of formation of ATP to energize cellular functions.

Effect of thyroid hormones on ion transport

One of the enzymes that become increased in response to thyroid hormones is Na+K+ATP ase. This in turn increases the rate of transport of both sodium and potassium through the cell membrane of some tissues. Because this process uses energy and increases the amount of heat produced in the body, it has been suggested that this might be one of the mechanisms, by which thyroid hormones increases the metabolic rate. Thyroid hormones also cause the cell membrane to become leaky to sodium ion, which further activates the sodium pump and further increases heat production.

Effect of thyroid hormone on growth:

Thyroid hormones have both general and specific effects on growth. For instance, it has long been known that thyroid hormone is essential for the metamorphic change of the tadpole to the frog.

The rate of growth is highly retarded in hypothyroid children. In those who are hyperthyroid excessive skeletal growth often occurs causing child to be considerably taller at an earlier age.

However premature closure of epiphysis and bone maturation also occurs, so that the duration of growth and eventual height of the adult may actually be shortened.

An important effect of thyroid hormone is to promote growth and development of the brain during foetal life and for the first few years after postnatal life. Therefore, an infant with hypothyroidism will remain mentally deficient throughout life. T_3 has been shown to enhance transcription of growth hormone gene so that more Growth hormone is produced. This may be also one of the explanations for short stature in hypothyroid children.

Effects of thyroid hormone on Carbohydrate metabolism:

Thyroid stimulates most aspects of carbohydrate metabolism.

1.Increased uptake of glucose by the cells

2.Enhances glycolysis

3.Enhances gluconeogenesis

4.Increases rate of absorption of glucose from the GIT

5.Increases insulin secretion

6.Increase insulin degradation

Effect on body weight:

Greatly increased thyroid hormone almost always decreases the body weight and greatly decreased hormone almost always increases the body weight.

Effect on cardiovascular system:

Thyroid hormones increase blood flow, cardiac output, heart rate and blood volume. Mild excess of thyroid hormone increases the strength of heart because of enzymatic activity. However marked increase causes weakness of cardiac muscle because of excessive protein catabolism.

Blood pressure – mean arterial pressure is unchanged. Systolic blood pressure increases while diastolic pressure decreases.

Effect on Respiratory system:

It increases rate of metabolism, increases rate of oxygen utilization and formation of carbon dioxide. This leads to activation of respiratory centre and causes increase in rate and depth of respiration.

Effect on Gastro-intestinal tract:

On GIT – increases appetite, increases food intake, increases enzyme secretion and increases motility.

Effect on Central Nervous system:

Thyroid hormone increases rate of cerebration, increases nervousness and many psychoneurotic tendencies such as anxiety complexes, extreme worry and paranoia.

On muscle function, slight increase in thyroid hormone causes increased vigour, Excessive increase produce excessive protein catabolism and cause muscle weakness, On the other hand, lack of thyroid hormone causes the muscle to become sluggish and slow relaxation after a contraction.

Increase in thyroid hormone level also cause muscle tremor which is supposed to be due to increased reactivity of neuronal synapses in the areas of spinal cord that control muscle tone.

Effect on Sleep:

Hyperthyroid patients often have a feeling of constant tiredness, but because of the excitable effects of thyroid hormone on the synapses, it is difficult to sleep. Extreme somnolence is characteristic of hypothyroidism.

Effect on sexual functions:

Lack of thyroid hormones causes loss of libido. Great excess on the other hand causes impotence.

In women lack of thyroid hormone cause menorrhagia and polymenorrhoea. Thyroid excess causes oligomenorrhoea or amenorrhoea.

These effects probably result from a combination of direct metabolic effect on the gonads and excitatory and inhibitory feedback effects operating through the anterior pituitary hormones.

Regulation of Thyroid hormone secretion:

Since both the excess as well as decrease in thyroid hormones leads to derangement in body functions, their levels are well controlled in the body by the following regulatory mechanisms existing in our body

1.Hypothalamo – Pituitary – Thyroid axis (HPT axis):

It is a classical example of Endocrine negative feedback mechanism and is the major regulator of thyroid gland. The HPT axis depends upon the Hypothalamus, pituitary and the thyroid gland. The hypothalamus secretes Thyrotropin Releasing Hormone which acts on the anterior Pituitary gland to produce Thyroid Stimulating Hormone(TSH) which acts on the thyroid gland to produce its hormones namely T_3 and T_4. TRH and TSH release are controlled by negative feedback mechanism of the thyroid hormones.

The circulating thyroid hormones acts on the anterior lobe of Pituitary gland to reduce secretion of TSH primarily by reducing TSH β subunit gene expression. Thyroid hormones also act on the hypothalamus TRH secreting neurons. T_3 acts on the hypothalamus by inhibiting the pre-pro TRH gene. This clearly shows the role of thyroid hormones in regulating the production of TSH by means of its feedback control on anterior pituitary and Hypothalamus (41).

TSH:

The thyrotropes in the anterior pituitary gland secrete this hormone. It has two components α and β. The α part is also shared by other hormones such as LH, FSH and HCG while the β component is specific for TSH.

TSH regulate the HPT axis by acting on the thyroid cells (42). It acts by binding of TSH with specific cell surface receptors, activation of enzyme adenylate cyclase, increasing the cellular concentration of cyclic Amp and thus increasing the production of thyroid hormones. Thus assessment of serum TSH serves as an indicator regarding the functional capacity of thyroid gland. It increases the entire pathway of hormone biosynthesis. Growth hormone inhibiting hormone, glucocorticoid and increased amounts of iodide concentration and sex hormone decrease TSH.

2.Autoregulation:

The important regulator in autoregulation is the iodide concentration. It has a biphasic action. At low levels of iodide intake, the rate of hormone synthesis is directly proportional to the availability of iodide. If the intake of iodide is greater than 2 mgs/day, the hormone biosynthesis is suppressed – WOLFF CHAIKOFF EFFECT. If there is excess iodide intake, then the thyroid gland adapts by decreasing transport of iodide into the cell (43). Thus the plasma concentration of thyroid hormones is maintained.

3.Other factors:

Besides TSH, the major regulator of thyroid gland, many substances produced locally also play in the regulation of hormone secretion by thyroid gland namely

- Insulin like Growth factor
- Epidermal growth factor
- Transforming growth factor - β
- Cytokines
- Endothelins

Hypothyroidism:

Hypothyroidism is a common medical condition in the general population. Common systemic manifestations include fatigue, constipation, cold intolerance, weight gain, hair loss, dry skin and hoarseness of voice. A variety of central and peripheral nervous system manifestations are common in patients with hypothyroidism (23).

Symptoms are generalized initially. Neurologic signs appear after months to years. the brain, peripheral nerves and muscular systems can be affected. The neurological manifestations occur in conjunction with the systemic features of the disease and may be noted only incidentally. However, symptoms and signs may be presenting feature in some patients and can contribute significant disability. Most of these complications are partially/ fully responsive to thyroid replacement.

Neuromuscular symptoms are present in 30-80% of patients with hypothyroidism (33). Symptoms improve or disappear with correction of hypothyroid state. With thyroid myopathy, slowness of muscle relaxation is noted, as is slowness of muscle contraction. Deep tendon reflexes are delayed in approximately 85% of patients with hypothyroidism. Muscle enlargement, stiffness and cramping are a constellation of findings seen in individuals with hypothyroidism. In adults these findings are known as Hoffman syndrome. In children these findings are called as Kocher-Debre-Semelaigne syndrome. In peripheral nerves segmental demyelination has been observed with decreased conduction velocities. Patients develop polyneuropathy with loss of reflexes and weakness. Decrease in vibration, joint position and touch-pressure sensations are also seen (3) .

Causes of hypothyroidism:

Hypothyroidism can be primary, secondary, or due to tissue resistance to thyroid hormone.

Primary causes:

- Destructive lesions such as Hashimoto's thyroiditis
- Radioactive iodine therapy for hyperthyroidism
- Subtotal thyroidectomy (ex.- surgery for Graves disease)
- Defects in enzymes that are necessary for thyroid hormone synthesis
- Endemic goiter (Iodine deficiency)
- Drug induced thyroid agenesis

- Thyroid dysgenesis or ectopy
- Anti-thyroid drugs

Secondary causes:

- Hypothalamic dysfunction due to neoplasm
- Eosinophilic granuloma or therapeutic irradiation
- Pituitary dysfunction due to neoplasm
- Pituitary surgery or irradiation
- Idiopathic hypopituitarism
- Sheehan syndrome (Postpartum pituitary necrosis)
- Dopamine infusion

Histological findings in hypothyroidism:

Pale central regions on nicotinamide adenine dinucleotide with accumulation of periodic acid Schiff positive material are seen. Decreased number of beta adrenergic receptors are observed, accompanied by glycogenolysis. Some muscle fibre atrophy is noted and increased number of internal nuclei, glycogen aggregates and occasionally, deposition of mucopolysaccharides in the connective tissue are characteristic of hypothyroid myopathy. Hypothyroidism – Nonspecific type II muscle fibre atrophy, occasionally with glycogen storage. The electron microscopic findings of affected nerve are focal micro fibrillary disorganization and mitochondrial accumulation.

HYPERTHYROIDISM:

Hyperthyroidism occurs due to excessive production of thyroid hormone by the thyroid gland. Thyrotoxicosis is a condition that occurs due to excessive thyroid hormone. The most common causes of thyrotoxicosis are hyperthyroidism caused by Graves disease (76%), toxic multinodular goitre (14%), thyroid adenoma (5%). Other less common causes of thyrotoxicosis are transient thyroiditis (De Quervain's, post-partum), iodide induced (drugs, supplementation), factitious and TSH-secreting pituitary tumour.

The terms primary and secondary hyperthyroidism are sometimes used to classify hyperthyroidism arising from an intrinsic thyroid abnormality and that arising from disease processes outside of the thyroid gland, such as a TSH-secreting pituitary tumour, respectively.

CAUSES OF THYROID ENLARGEMENT:

Associated with Hyperthyroidism

Primary

- Diffuse hyperplasia (Graves disease)
- Hyperfunctioning ("toxic") multinodular goiter
- Hyperfunctioning ("toxic") adenoma
- Iodine-induced hyperthyroidism
- Neonatal thyrotoxicosis associated with maternal Graves disease

Secondary

- TSH-secreting pituitary adenoma (rare)

Not Associated with Hyperthyroidism

- Granulomatous (de Quervain) thyroiditis (*painful*)
- Subacute lymphocytic thyroiditis (*painless*)
- Struma ovarii (ovarian teratoma with ectopic thyroid)
- Factitious thyrotoxicosis (exogenous thyroxine intake)

The clinical manifestations of thyroid are large and it includes changes due to the hypermetabolic state induced by excess thyroid hormone and due to over activity of sympathetic adrenergic tone – increased beta adrenergic tone

The most common symptoms are:

- Weight loss with a normal appetite
- Heat intolerance.
- Palpitations.
- Tremor.
- Irritability

Other symptoms include sweating, palpitations, tremor, dyspnoea, fatigue, Irritability, emotional lability, tremor, palmar erythema, sinus tachycardia,.

All causes of thyrotoxicosis can cause lid retraction and lid lag, but only Graves disease causes exophthalmos, ophthalmoplegia, and papilledema

Other less common symptoms include osteoporosis, diarrhoea, steatorrhoea, Angina, Ankle swelling, Anxiety, psychosis, Muscle weakness, Periodic paralysis, pruritus, alopecia, Amenorrhoea / oligomenorrhoea, infertility, spontaneous abortion, Loss of libido, impotence, Excessive lacrimation, Goitre with bruit, atrial fibrillation, Systolic hypertension, increased pulse pressure, Cardiac failure, Hyper-reflexia, Ill-sustained clonus, Proximal myopathy, Bulbar myopathy.

Visual evoked potential

Any neuronal response triggered by stimulating sensory receptors or peripheral nerves and also neuronal activity time related to cognitive process or motor programming, can be viewed as Evoked Potential(EP)

Clinical application of Visual Evoked Potential(VEP):

The clinical application of evoked potentials began to emerge shortly after Halliday demonstrated for the first time in 1970, that VEP's can identify silent lesions of the optic nerve tracts in patients with multiple sclerosis or a previous history of optic neuritis(47)

Evoked Potentials proved to be useful in

- To test sensory functions when clinical examination is not reliable.

- To investigate subjective symptoms and detect whether they are related to any dysfunction of organic origin
- To appraise the causative mechanisms of neurological deficits
- To monitor the degree of functional recovery.
- To monitor various cerebral functions when patient's condition is critical

Responses and EP components:

The term "response" refer to any change in brain electrical activity related to the processing of information by nervous system, and for each of the sequential electrical waves recorded at the exploring electrodes the term EP "component" is used.

Each EP component is characterized by features such as latency, amplitude and topography, and is influenced by extrinsic factors such as the particular stimulus by which it is elicited or the particular montage used for the recording.

This distinction between the response, viewed as a physiological concept and the EP component considered as the electrical field phenomenon is distinguished by four main arguments.

1.Surface recordings may be blind to some elements of neuronal response.

2. Some EP components may not correspond to any discrete synaptic or axonal response and are due to the physical changes of the volume conductor in which an axonal

valley is propagating or to changes in the direction of propagation with respect to the site of the recording electrode.

3.A single surface component may result from the combination of separate cell populations activated through parallel pathways and overlapping in time.

4. An EP component is a composite signal resulting from the difference between activities picked up separately by the so called “active” and “reference” electrodes.

INSTRUMENTATION

BASIC INSTRUMENTS FOR DATA ACQUISITION:

1.AMPLIFIERS:

Equipment for recording Eps must be suitable for amplifying electrical signals with amplitudes down to 0.1 microvolt and bandwidth from below 1Hz to 10 Hz.

The first stage of amplification uses Pre-amplifiers which can be placed close to the patient so that the leads to the electrodes can be kept short and the cable between the pre and main amplifiers carries signals from a low impedance source – both features help to reduce pick-up mains and other interferences. The impedance of the skin electrodes is less than 10k ohms and the input impedance of the amplifiers 10 milli ohms or more.The amplifiers have a wide range of stepped gain control.

2.FILTERS:

Both low and high pass filters have a number of set positions so that the upper frequency can be reduced from 10 or 20 KHz to 30Hz and the lower frequency limit raised from 0.01Hz to 300 Hz.

3.ELECTRODES:

Electrodes are attached to the skin by means of a special paste, which serves as an adhesive, but also establishes a good contact with the skin. Electrodes made from dissimilar metals must be avoided. A system is available to measure the impedance of each electrode.

4.STIMULATORS:

All Eps investigations require sensory stimulation. Stimulators are an integral part of the equipment. The stimuli are synchronized to the sampling epoch and the trigger point advanced or delayed from the start of the epoch to facilitate viewing the data on the screen.

5.DISPLAY:

The Eps are displayed on an oscilloscope after averaging. The data are manipulated by digital techniques before being displayed in color on visual display unit (VDU). Further adjustment can be done in the display mode before the data are stored. Several traces can be displayed on the VDU at the same time, so that comparisons can be made. Latencies and amplitude can be obtained from the displayed data either automatically or by cursor measurements.

6.STIMULATION:

Visual stimulation:

Flash:

The most used type of visual stimulation is the stroboscope flash. The stroboscope produces an intense, brief pulse of light and is used in clinical neurophysiology to evoke the VEP & ERG. It can be used as a single flash or repetitively.

Patterns and pictures:

Stationary pictures or patterns can be projected onto a screen. High quality pictures can be displayed on a monochrome or colour VDU under software control

Moving or changing patterns such as checkerboard reversal can be generated on a VDU and switched electromechanically at the required rate (2/sec). the latency of the pattern reversal EP is dependent on the luminance of the pattern.

Recording procedures:

VEPs can be evoked by brief changes either in the luminance or in the pattern within the field of vision; both type of changes can also be combined into a single stimulus.

Analysis time & Sampling rates:

Scalp VEPs are obtainable in all normal adults peak with latencies in 70-150 millisecond range. Consequently, an analysis time of 300 msecs is suitable.

In children a slightly longer analysis time up to 500 msecs is used.

Filters:

Filters are set between 1 to 100 Hz. The filters must be kept constant in the laboratory for the recording of the control subjects and the patients.

SPECIAL CONTROLS FOR RUNNING VEP TEST:

Gaze fixation:

Recording VEPs require active co-operation of the subject who is instructed to gaze at a dot at the center of the pattern. The most elaborate means of controlling fixation is to record eye movements and automatically reject all sweeps contaminated by eye movement potentials.

Patients with visual defects involuntarily shift their gaze into the good visual field, a phenomenon related to the formation of pseudo fovea. Thus they will have a small response to stimulation of the blind half field when the fixation dot is placed at the edge of the pattern.

MONOCULAR STIMULATION:

Monocular stimulation is obtained by covering the non-stimulated eye with a patch. This patch must be made of opaque material and light should not leak around its edges.

NORMAL FINDINGS IN VEP:

Pattern VEPs contain three main components labelled N75, P100and N145 which are recorded in the mid occipital region when the pattern is presented in the central part of the visual field, when it subtends an angle of 5 degrees at the eye

Of the three components, the positive one peaking at the latency of 100 msec (P100) has the largest amplitude and can be obtained with a wide range of patterns although its amplitude and latency are affected by changing the stimulus/parameters. Hence the clinical interpretation of pattern VEPs is based mainly on the measurement of P100 latency.

LATENCY AND AMPLITUDE MEASUREMENT:

The latency of P100 is universally accepted as the most useful measure for interpreting the pattern VEPs. P100 latencies from 100-120 msecs have been reported in normal subjects with S.D not exceeding 8% of the mean

The difficulties encountered in choosing the point at which the peak of P100 should be taken are

1.Irregular shape of the component in abnormal wave forms

2.The blind pattern of this peak in some subjects

3.Identification of the peak when it is delayed

Irregular shape of P100 results from the admixed and superimposition of 2 or 3 averaged traces recorded in the in the same conditions is the most reliable means of differentiating the peak from the background noise.

The bifid pattern of the P100 peak is encountered when stimulating with bright or highly contrasted checkerboard. This can be prevented by reducing the contrast between bright and dark squares to 50% or 20%. This causes the latter of the 2 positivities to disappear.

AMPLITUDE MEASUREMENTS:

The amplitude of the P100 measured from the baseline or from the peak of the N75 negativity, shows the greater inter-individual variability. Values between 2-20 microvolts fall in the normal range of the most laboratories and the study of inter ocular differences is crucial for interpreting the waveforms.

INTEROCULAR DIFFERENCES OF LATENCIES AND AMPLITUDES:

In healthy individuals the latencies and amplitudes of the P100 potentials from each eye are almost identical. Inter ocular P100 amplitudes and latencies differences over 8 microvolts and 10 msec respectively are reported as beyond the upper limits of normality as is an amplitude ratio greater than 2:3

NON PATHOLOGICAL SOURCES OF VEP VARIATION:

SUBJECT FACTORS:

AGE:

The P100 latencies is decreased in children and adult values are reached only after 5 years. There is absence of age related changes of the P100 latency in adults until the 5^{th} decade. After the 5^{th} decade the mean value and the variance of the P100 latency increases

with the age in females between 50-70 years whereas in the males it remains fairly stable. No major changes occur in the amplitude of P100 during adult life

GENDER:

P100 is shorter latency and greater amplitude in female than in males within the 20-50 years age range. Due to the increase of P100 latency in females over 50 years the sex difference was not obvious beyond this age.

VISUAL ACUITY:

With a checkerboard containing large checks, P100 latency is insensitive to refractory errors, but with a smaller checks represented foveally, it increases when the retinal image is not correctly focused. Therefore visual acuity must be measured and refractive errors corrected before recording VEPs and patient should wear glasses during testing. Poor visual acuity causes prolonged and low amplitude pattern VEPs.

BODY TEMPERATURE AND PHYSICAL EXERCISE:

Temperature does not affect the latency or amplitude of P100. Physical exercise immediately before VEP recording produces significant reduction of P100 amplitude

ATTENTION AND ACCOMODATION:

When a subject is engaged in a mental task not related to visual stimulus itself there is no significant change in P100 latency

TECHNICAL FACTORS:

LUMINANCE:

There is a decrease in amplitude and increase in the latency of 18 % and 15 msec respectively/log unit diminution of the mean luminance of the screen

STIMULATOR TYPE:

The P100 latency is influenced by the time taken to reverse the pattern. An increase of 1 msec in the reversal time causes a 0.6 msec increase in P100 latency

In a study published in New England Journal of Medicine by Vermon Sanders M D et al titled "Neurological manifestations in Myxedema"(19),Clinical and sural nerve biopsy findings were described in four hypothyroid patients with manifestations of diffuse neuropathy. Clinical examination of them revealed distal sensory impairment, ataxia and decrease of deep tendon reflexes with total ankle jerk loss. Electron microscopic findings of the sural nerve biopsy of the subjects reveal a marked reduction of myelinated fibres, affecting mainly the large myelinated axons.

In a study by by Kudrajavec T et al titled "Neurologic complications of Thyroid dysfunction"(20), the morbidity rates for thyroid dysfunction has been cited. In England and Wales, the incidence of thyroid dysfunction, among outpatients were 1.1 per 1000 for thyrotoxicosis and 1.7 per 1000 for myxedema. In United states the incidence was 0.16 per 1000 for thyrotoxicosis and 0.13 for myxedema. 50% of hyperthyroid patients have clinical evidence of mild or moderate muscle weakness which was confirmed by electromyography. This comprehensive study was done without apparent patient selection and it reported 2% of patients with carpal tunnel syndrome, 6% with myopathy and 18% with polyneuropathy.

In a study by Schutt P, Muche H, Gallenkamp U, Lehmann H J et al titled "Reversible alterations of peripheral nerve function in Thyroid dysfunction"(21)**,** seven patients with hyperthyroidism and nine patients with hypothyroidism before treatment and after a period of normal thyroid function of at least one year duration were evaluated. There was no difference in hyperthyroid patients and normal persons, whereas in hypothyroidism the conduction velocity was shown to be significantly reduced and a decline in the nerve action potential were found. These alteration of peripheral nerve function interpreted as evidence of neuropathy, proved to be reversible, when the thyroid function returned to normal.

IN a study by Rao SN, Katiyar BC, Nair KR, Misra S et al titled "Neuromuscular status in Hypothyroidism" (22), twenty patients with hypothyroidism were evaluated by

clinical and neurophysiological techniques for neuromuscular dysfunction. The electromyograms were abnormal in 14 patients. The average duration of motor unit potentials and the mean amplitude in these patients were reduced, compatible with myopathy. No denervation potentials were found. The nerve conduction abnormalities were found in 13 patients, predominantly affecting the median than the peroneal nerve..

In this study by Abott RJ O'Malley BP, Barnett DB et al titled, " Central and peripheral nerve conduction in thyroid dysfunction" (23), the latencies of visual evoked responses, Indices of central nerve conduction and peripheral nerve conduction were slowed in patients with primary hypothyroidism compared with controls. In thyrotoxic patients there were no change in in the latencies of the visual evoked responses and peripheral nerve conduction compared with the control group. The abnormalities seen in hypothyroidism were reversed by L-thyroxine therapy. Warming untreated hypothyroid patients significantly improve both central and peripheral nerve conduction.

In also this study, the sensory thresholds of perception along with motor responsiveness in hypothyroid, thyrotoxic and euthyroid subjects were also measured by employing a simple and readily reproducible technique. Sensory thresholds were elevated and motor responsiveness was impaired in hypothyroid subjects as compared to euthyroid controls. In thyrotoxic subjects motor responsiveness was significantly enhanced but sensory thresholds did not differ from control values. This study suggests that sensory thresholds would be a reliable reflectors of tissue thyroid status in hypothyroidism whereas

motor responsiveness seems to be a better guide to thyroid status across the whole spectrum of thyroid function.

In a study by Torres C F. Moxley R T et al titled “Hypothyroid Myopathy”(24), the clinical and electro diagnostic findings before and during 6 years of therapy were reported in a 59 year old man with severe hypothyroidism. He had severe sensory neuropathy, carpal and tarsal syndromes, mild motor neuropathy and moderately severe myopathy. The study suggests that thyroid hormone replacement eliminates the neuropathic manifestations of severe hypothyroidism in contrast to the myopathic features such as weakness and muscle wasting which may persist despite the maintenance of the euthyroid state.

In a study by Lai CL, Tai CT, Liu CK, Lin RT et al titled “The changes of Central and Peripheral Nerve conduction and the effect of Thyroxine replacement in Thyroidectomised rats”(25) were studied. In this study BAEP and PNCs were performed in two groups of the hypothyroid animals 1 and 3 months after thyroidectomy. In BAEP study prolonged I-V inter peak latency was the most consistent abnormal finding in all hypothyroid rats. Delayed peak latencies as well as prolonged I – III and III-IV inter peak intervals occurred when the hypothyroid status was longer than one month. It was noted that the longer the hypothyroid status, the more severe was the central conduction

dysfunction. All these abnormalities returned to normal after replacement therapy if the hypothyroid state was shorter than three months duration. For the PNCs study all group of thyroidectomised rats showed the normal results. Musculoskeletal function was analyzed with respect to the thyroid function and thyroid antibody status. The prevalence of carpal tunnel syndrome was highest in hypothyroid group. So this study suggests that patients with thyroid dysfunction should be questioned for musculoskeletal complaints and referred to specialists.

In a study by Lai CL, Tai CT, Liu CK, Lin rt et al titled " A longitudinal study of central and peripheral nerve conduction hypothyroid rats" (26),a series of BAEP and PNCs was conducted and compared with age matched controls' and PNCs were performed in three groups of hypothyroid animals 1.3.5 months after thyroidectomy respectively. For BAEP prolonged I-V inter peak latency was the most consistent abnormal finding in all groups of hypothyroid rats, and longer hypothyroid states correlated well with more severe conduction disorder. These abnormalities return to normal after thyroxine replacement if the duration of hypothyroidism was less than 5 months. Regarding PNCs all group of thyroidectomised rates showed normal conduction before and after thyroxine therapy. This study indicates that PNS seems to be more resistant to changes in thyroxine level.

In a study by Khedr EM, E1 Toony LF,Tarkhan MN et al, titled "Peripheral and central nervous system alterations in hypothyroidism: electrophysiological findings"(27), 23 patients (17-64 years old) with biochemical evidence of hypothyroidism, with thyroxine less than 4 microgram/dl and thyrotropin above 4.5 mu/mi and 20 age and sex matched normal subjects were studied. The electrophysiological measurements included electromyography, motor conduction velocity, visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs) and event related potentials. Of the hypothyroid patients 52% had peripheral system involvement.35% had Entrapment neuropathy, 9% had Axonal neuropathy and 9% had myopathy. The central nervous system(CNS) was affected in 78% of the cases. 52% had abnormal VEPs and BAEPs. No significant correlation was observed between hormonal levels and different electrophysiological parameters. Thus CNS is more vulnerable to the effect of hypothyroidism than PNS. Therefore, electrophysiological studies were suggested to be performed in hypothyroid patients, even in asymptomatic ones, early in the course of disease in order to detect the nervous system involvement.

In this study by Devon I Rubin, MD et al titled," Neurological manifestations of Hypothyroidism"(28), the following features about hypothyroidism were described. Hypothyroidism is a common medical condition in the general population. Common systemic manifestations include fatigue, constipation, cold intolerance, weight gain, hair loss, dry skin and hoarseness. A variety of central and peripheral nervous system

manifestations are common in hypothyroidism. Symptoms and signs of neurologic dysfunction may be the presenting feature in some patients and can contribute significant disability.

In a retrospective study by Weik R, Ruprecht KW et al titled "Value of electrophysiology in ophthalmic monitoring of patients with endocrine myopathy"(29), 27 patients with ophthalmopathy were examined. Best corrected visual acuity, intra ocular pressure, visual field, motility and thickness of ocular muscle were determined. Registration of visual evoked cortical potentials and pattern electro retinograms were performed regularly. Regular controls of P-VEPs reveal optic nerve involvement at an early stage, at which visual acuity might not be altered. Therefore, this electrophysiological examination should be used in controlling patients suffering from opthalmopathy.

In a study by Rulecka- debnaik A, Lubinski W, Krzystolik Z et al titled " Visual evoked potentials in diagnosis and monitoring of optic neuropathy in the course of thyroid opthalmopathy"(30), PVEP (UTAS E-1000) were recorded in 74 patients with thyroid opthalmopathy including 12 patients with clinically evident DON – Group I, 13 patients with subclinical DON (prolongation of latency of P100 wave in PVEP)-Group II. Thirty-six healthy subjects served as controls. The latencies of P100 and N75 waves were examined. In 50 thyroid opthalmopathy patients they recorded changes in PVEP before

and after treatment. The mean LP100 and LN 75 were significantly longer in TO patients compared to the control group. Prolongation of LP100 above the upper limit of normal values was observed in all patients with clinically evident DON. After treatment in patients with clinically evident DON the latencies of both waves were significantly shorter in comparison to values obtain after therapy. PVEP is a useful method in the diagnosis and monitoring of dysthyroid optic neuropathy. It can reveal asymptomatic optic nerve dysfunction. Detection of subclinical neuropathy using PVEP enables early – thus more effective treatment. The most important factor in PVEP is the latency of P100 wave, the latency of N75 wave is less useful.

In a study Salvi M, Spaggiari E, Maculuso C, Gardini E, Ferrozi F, Minelli r, Wall JR, Roti E et al titled "The study of visual evoked potentials with thyroid associated opthalmopathy identifies asymptomatic optic nerve involvement" (31), Visual Evoked Cortical potentials were recorded in 88 patients affected by auto immune thyroid disease and thyroid associated opthalmopathy (TAO) without clinical signs of optic neuropathy. At the time of ophthalmological examination 37 of these were hyperthyroid, 41 were euthyroid and 8 were hypothyroid. Twenty-nine normal subjects served as controls. The p100 latency was recorded, there was no difference in the mean P100 amplitude of TAO patients and normal subjects. The P100 latency in euthyroid patients did not differ significantly from the either of the hypo or hyperthyroid patients. A prolongation of the latency of visual evoked cortical response was observed in patients with TAO patients

without optic nerve compression. The study of VEP in TAO patients is complimentary to the study of visual field examination in identifying optic nerve dysfunction in the absence of visual acuity.

In a study by Osterwll D, Syndulko K, Cohen SN,Pettler-Jennings PD, Hershman JM, Cummings JL, Tourtellote WW, Solomon DH et al titled "Cognitive function in Non demented older adults with Hypothyroidism"(32) , fifty four non demented hypothyroid patients with biochemical evidence of hypothyroidism and 30 euthyroid controls were studied . Attention, orientation, memory, learning, visual spatial abilities calculation, language, visual scanning and motor speed were evaluated in them using standardized non psychological tests. The P300 component of the auditory event related potentials and the conduction speed from eye to cortex and the P100 latency of the patterned visual evoked potential was recorded and it shows significant longer P100 latencies in the hypothyroid subjects

In a study by Avramides A, Papamargriyis K, Mavomartis I, Saddic G, Vyzantiadis A, Milonas I et al titled "Visual Evoked Potentials in Hypothyroid patients before and after achievement of Euthyroidism"(33), the visual evoked potentials (latency and amplitude) was studied in12 hyperthyroid and 15 hypothyroid patients. VEP was recorded in them before treatment and after they had become euthyroid status with treatment. In four

hyperthyroid, the p100 latencies were prolonged and the amplitude was lower than normal in 6 of them. In the hypothyroid patients there was change in the amplitude and latencies which was reversible to a greater extent with thyroxine. They state that, the Evoked Potentials is another method of studying in humans the metabolic effects of thyroxine deficiency in CNS

In a study by Ozata M, Ozkardes A, Dolu H, Corakci A, Yardim M, Gudagan MA et al titled "Evaluation of central motor conduction in Hypothyroid patients" (34), the motor evoked potentials following the magnetic stimulation of the motor cortex and spinal roots 20 hypothyroid and 19 hyperthyroid patients and 20 age, sex, height matched controls were studied. Central motor conduction time (CMCT) was determined as the differences between MEP latencies after cortical and spinal stimulation. The mean CMCTs before treatment in both hypothyroid and hyperthyroid was significantly prolonged as compared with the controls. The mean CMCT values in both groups were not significantly reduced after they had become euthyroid but a tendency to a decrease in CMCT was observed. Further no correlation was observed between CMCT and free T3, free T4 and TSH levels as on the onset age, the severity of disease or disease duration in both hypo and hyperthyroidism. They finally state that CMCT abnormality could be documented in few of these patients and these alterations could not be improved completely after attaining euthyroid status.

In a study by Nazliel B, Akbay E, Irkeç C, Yetkin I, Ersoy R, Toruner F et al titled "Pattern visual evoked potential (PVEP) evaluation in hypothyroidism" (35), pattern-shift VEP (PVEP) recordings were recorded on 48 newly diagnosed hypothyroid patients. Twenty-four had sub-clinical and 24 had overt hypothyroidism and none had clinical symptoms or signs referable to CNS dysfunction. There was a triphasic response with a prominent positive wave (P100) There was no statistically significant difference in the P100 latency. Delays above the average latency +/-2.5 SD of the mean of the control subjects was defined as a criterion for an abnormality. In their study, 6 patients demonstrated abnormal PVEP in at least on one tested side.

In a study by Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JG, Wiersinga WM et al titled "Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for Primary Hypothyroidism" (36) with an aim to assess neurocognitive functioning and well-being in euthyroid patients with primary hypothyroidism on adequate thyroxine (T4) treatment. Their study was conducted on 141 hypothyroid patients. Assessment of neurocognitive functioning of the subjects included tests for cognitive or psychomotor speed, attention, working memory as well as learning and memory. Well-being was measured with the Symptom Check List-90 total score and the Rand 36-item Health Survey subscales for 'mental health' and 'vitality'. Patients showed poor performance on various domains of neurocognitive functioning compared with mean standard reference values, especially on a complex attention task and on verbal memory

tests. The results of their study suggest that neurocognitive functioning as well as psychological well-being may not be completely restored in patients with hypothyroidism, despite T4 treatment.

In a study by Ashwini A Mahadule, Pravin S Jadhao, and Mrunal S Phatak et al titled "Motor Conduction Parameters in recently diagnosed and untreated Hypothyroidism" (37), the motor nerve conduction parameters viz. Distal latency (DL), amplitude of compound muscle action potential (CMAP) and motor nerve conduction velocity (MNCV) were recorded bilaterally in median, ulnar and posterior tibial nerves using standard protocols and settings. The study was conducted among 60 newly diagnosed hypothyroid and 60 euthyroid subjects. Their study revealed significantly prolonged distal motor latencies, reduced CMAP amplitudes and slowed MNCV in the peripheral nerves in hypothyroid.

In a case report published by Sahni V, Gupta N, Anuradha S, Tatke M, Kar P et titled "Thyrotoxic neuropathy – An under diagnosed condition"(38), they have reported a case of thyrotoxic neuropathy presenting in 45 year old female with progressive weakness of both lower limbs and slowly increasing swelling on the anterior aspect of the neck for three months and have concluded that thyroid function tests can be helpful in the diagnosis of neuropathy which is treatable and thyroid function tests should be included in the routine work up.

In a study by Adikesavan Balaraman, Gowdhaman Natarajan, Vishwanath Rao B, Balasubramaniam Kabali et al titled" A study of Nerve conduction velocity in newly diagnosed Hypothyroid females" (39), 20 newly diagnosed hypothyroid females and 20 euthyroid females were studied for sensory and motor nerve conduction in median, peroneal and sural nerves. Their study showed significant decrease in conduction velocity in median and sural nerve showing subclinical nerve involvement in newly diagnosed hypothyroidism

In a study by Satish Waghmore, Shoha pajai, Chaudhari AR, Sachin Pawar and Vinod Shende et al to "Evaluate the efficiency of Nerve Conduction parameters in the early diagnosis and management of Hypothyroidism"(40), 100 newly diagnosed hypothyroid females and 100 euthyroid females were studied for compound muscle action potential, distal motor latency and conduction velocity were evaluated. Their study showed significant prolongation of latencies and conduction velocity and amplitude were significantly reduced in median and peroneal nerve when compared with controls. They conclude that Nerve conduction study is one of the simple effective tests for early diagnosis of neuropathy in hypothyroid patients

In a study by Ladenson PW, Stakes JW, Ridgway EC et al titled" Reversible alteration of the visual evoked potential in hypothyroidism"(46), the pattern-shift evoked potential was measured in 19 hypothyroid patients before treatment, and after short- (one week) and long-term (12 to 24 weeks) thyroid hormone replacement therapy. Before treatment, nine patients had an abnormally prolonged visual evoked potential latency. After one week of therapy, the mean visual evoked potential latency for the entire group was unchanged, But after long-term therapy, significantly shortened latency of the P100 wave of visual evoked potential was observed. In eight of the nine patients with initially abnormal results, the visual evoked potential latency was completely restored to normal. Since visual evoked potential was reversibly altered in hypothyroidism they concluded that this neurophysiologic parameter (P100) permits quantitation of the effects of hypothyroidism on the central nervous system and the extent and rate of response to thyroid hormone replacement therapy

MATERIALS AND METHODOLOGY

MATERIALS AND METHODOLOGY:

STUDY DESIGN:

Cross sectional study

STUDY SETTING:

The present study was conducted in the Neurophysiology Research Laboratory, Department of Physiology and Outpatient department of Endocrinology, Stanley Medical College, Chennai

STUDY TIME:

The study was conducted during the time period from January 2016 to August 2016.

INCLUSION CRITERIA:

1. Hypothyroidism patients of age between 18-45 years.

2. Hyperthyroidism patients of age between 18-45 years

EXCLUSION CRITERIA:

1. Hypothyroid and hyperthyroid patients of age less than 18 years or greater than 45 years

2.Individuals with known Diabetes, Systemic hypertension ischemic heart disease, renal failure, liver failure

4.Individuals with epilepsy, brain tumour and other space occupying brain lesions.

5.Individuals on treatment for Tuberculosis.

6.Individuals with neurological disease like multiple sclerosis

7.Individuals with Corneal opacity, squint, color blindness, on miotic or mydriatic drugs

SUBJECT GROUP:

30 willing hypothyroid patients & 30 hyperthyroid patients were recruited from Medicine - Endocrinology OPD of Stanley Medical college.

CONTROL GROUP:

30 age and gender matched individuals with normal thyroid profile attending the Master Health Checkup Program in Stanley Medical College were selected for the study

MATERIALS USED FOR STUDY:

1. Proforma was used to record the anthropometric measurements and clinical findings of the subjects
2. A portable weighing machine was used to record the weight of the patient in kilograms
3. A Stadiometer was used to measure the standing height of the subjects in cenimetres

4. A standardized mercury sphygmomanometer was used to record the blood pressure of the subjects.
5. RMS polyrite EMG EP Mark-II analyser in the Neurophysiology Research Laboratory in the Department of Physiology, Stanley Medical College was used to record the VEP of subjects using standard procedures.
6. Materials (Disposable syringe, vacutainer, spirit swab, cotton) for drawing blood from the subjects under aseptic precautions for thyroid function tests

Ethics committee approval was obtained from the Ethical committee, Stanley Medical College for the study

Written informed consent (Annexure I) was obtained individually from each individual after explaining to them about the procedure in detail and the purpose of the study

The recordings were done between 10 AM and 1.00 PM in the morning in sitting position. All the techniques of measurement, duration and instruments were maintained uniformly throughout the study.

METHODOLOGY:

The participant was made to relax and be comfortable prior to the tests. Detail clinical history about hypothyroidism and hyperthyroidism were collected.

Measurement of anthropometric indices:

The subjects were asked to stand erect without their footwear with arms relaxed and hanging by their side and the following were measured

- Weight of the subjects in kilograms was recorded using a portable weighing machine to the nearest 0.5 Kgs
- Height of the subjects to the nearest 0.5 cm was measured using a Stadiometer
- Body Mass Index of the subjects was calculated using the **Quetelets Index**

BMI= weight in kgs / Height in metres^2

The vitals signs – pulse rate, temperature, respiratory rate and blood pressure of the subjects were recorded and documented.

VEP RECORDING – PROCEDURE:

Visual evoked potentials were analysed using RMS polyrite EMG EP Mark-II analyser in the Neurophysiology Research Laboratory in the Department of Physiology, Stanley Medical College using standard procedures

PRE-REQUISTES:

1.Hair spray or oil to be avoided after hair wash

2. The individuals were asked to wear the spectacles or contact lenses during the test if they were using them for refractive errors

3.Any miotic or mydriatic drug is avoided 12 hours before the test

4. Individuals were advised to avoid intake of drugs or foods containing caffeine on the test day and the previous day

5. Individuals were advised to take adequate sleep on previous night

RECORDING CONDITIONS:

1.Filter: High cut filter - 100-300 hg

2.Amplification between 20000 -100000

3.Sweep duration: 300 msecs

4.Number of epochs: 100 are averaged.

5. Electrode impedance kept below 5 kilo ohms

STIMULATION:

Black and white checkerboard was used.

Average distance between subject and screen – 100 cms

Contrast: 80 %

Size of the pattern element:14 x 16 minute

Rate of stimulation : 4-8 Hz

Subjects was instructed to fix gaze at the centre of the screen

PROCEDURE:

The subject was asked to sit comfortably on the chair.

Each eye was tested separately. Other eye was covered with an opaque eye shield which prevents entry of light into that eye

Using 10-20 International system, the electrodes were placed. Before placement of electrodes, the skin at the point of placement was cleansed with spirit.

Three surface disc type electrodes were used namely

1.Recording electrode

2.Reference electrode

3.Ground electrode

The recording electrode was placed at Oz – 5cms above the inion using an electrode paste .

The reference electrode was placed at FP_Z -12cms above the nasion using an electrode paste.

The ground electrode is placed at the midline in forehead using an electrode paste.

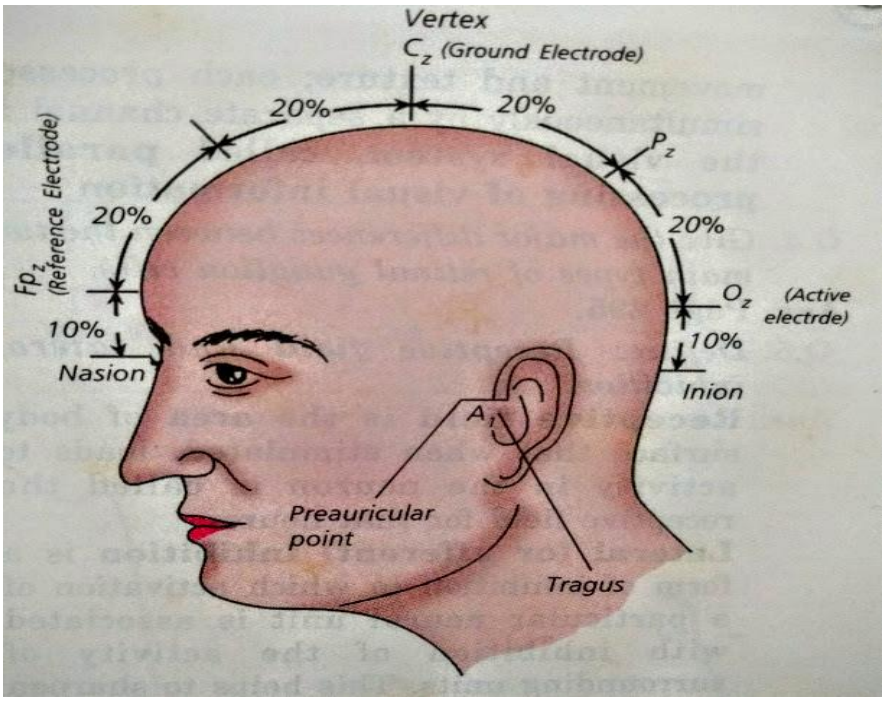


Fig.-2: Electrode placement in VEP

The electrodes were connected through the pre-amplifier to the Cathode Ray Oscilloscope.

The subject was instructed to fix gaze at the centre of the screen after covering one eye with an opaque shield. The lights were switched off. The visual stimulus was delivered by photo stimulator at a frequency of 10 flashes/sec.

The response obtained was displayed on the TV monitor and the peak latency and peak to peak amplitude of the waves were measured. The same procedure was repeated for the other eye.

BLOOD COLLECTION FOR THYROID FUNCTION TESTS:

For venous blood collection the antecubital vein of the left arm of the subjects was used and a under strict aseptic precautions 3ml of venous blood was collected in a disposable syringe transferred to vacutainer for performing blood investigations.

For thyroid function tests, serum is used. Serum is obtained by allowing the blood to clot at room temperature and then centrifuged. This separated serum was used for estimation of TSH, FT_3, FT_4.

Estimation of Thyroid hormones:

Method:

Direct solid phase enzyme immunoassay using Thyrokit.

Principle:

Enzyme linked immunosorbent assays (ELISAs) are based on the specificity of antibodies with enzyme assays. The test is done using plastic plates having micro wells. The wells are coated with an antibody specific to the hormone being evaluated. Then samples are controls are added to the micro wells. Then a second antibody which attaches to a different spot, specific for the hormone is added. Then a third antibody specific for the second antibody is added. The third antibody added has an enzyme already paired with it and has the ability to convert an appropriate substance into a product which can be recognized by fluorescent

or calorimetric optical techniques. As every molecule of the enzyme has catalytic action yielding thousands of product particles, minute quantities of hormone molecules can be easily assayed.

Procedure:

- 50 µl of sample and 50 µl of the controls were transferred to the designated wells coated with streptavidin and then 50 µl each of two monoclonal antibodies (anti TSH, anti FT3, antiFT4 pf high affinity and specificity) Horse radish peroxidase conjugate and biotin conjugate were added to the wells
- The plates were shaken for 10 seconds using an orbital shaker and then incubated for 2 hours for TSH and 1 hour for FT_3 and FT_4 at room temperature.
- The wells were washed to eliminate the nonreacted species and 100 µl of chromogen Tetra Methyl Benzidine (TMB) substrate was added to each well and then incubation was done at room temperature for 15 minutes for FT3 and FT4 and 30 minutes for TSH.
- Immunological reaction was stopped by adding 100 µl of stop solution, the sulphuric acid to each well and the developed color indicating the absorbance was measured photo metrically within 30 minutes with microtiter reader at the wavelength of 450 nm.

Fig-3:ELISA WASHER

Fig-4: ELISA READER

Calculation:

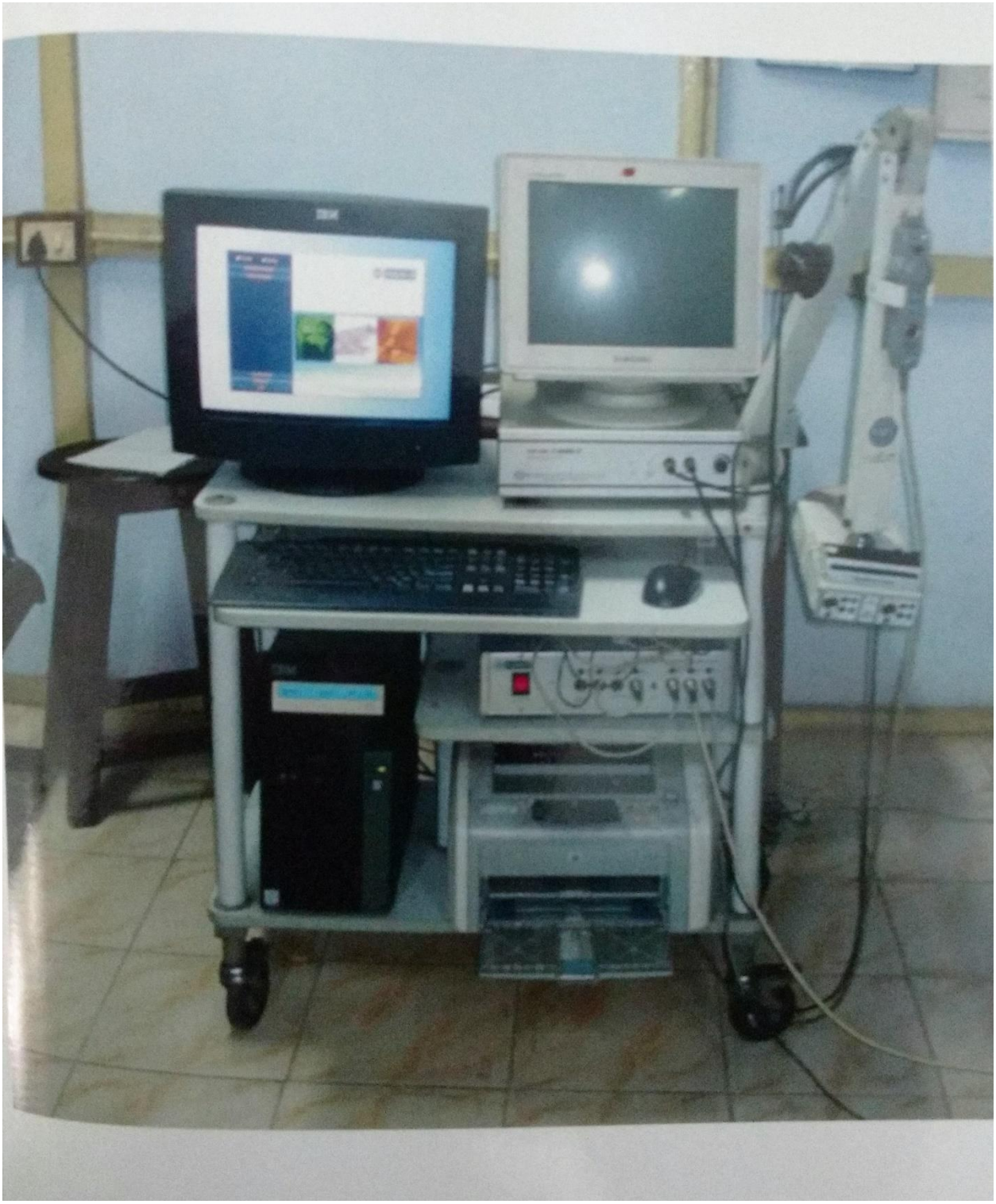
The mean optical densities of standard versus the respective hormone concentration were plotted on a semi log graph and the concentration of hormone in the sample was determined by interpolation from the calibration curve.

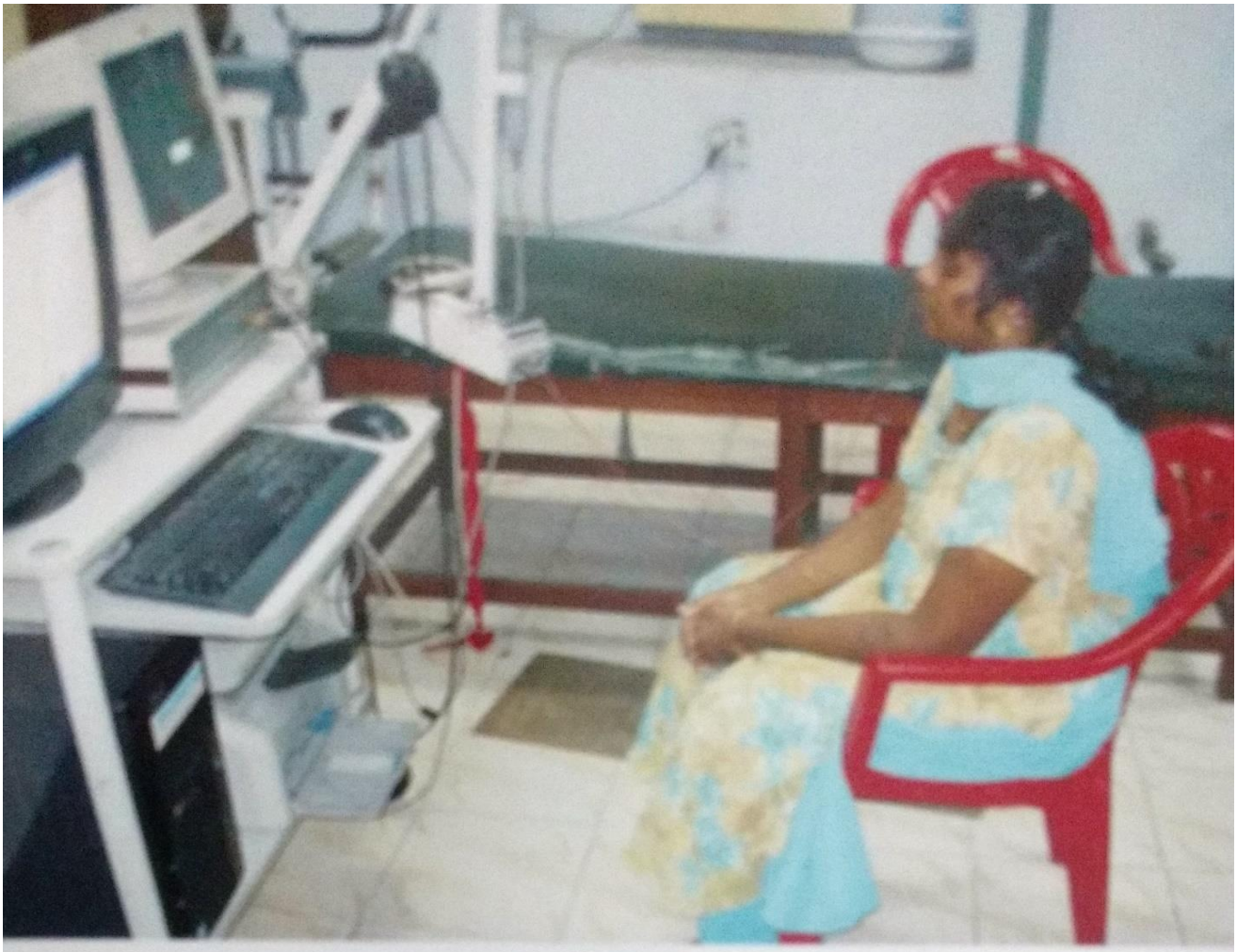
Reference value:

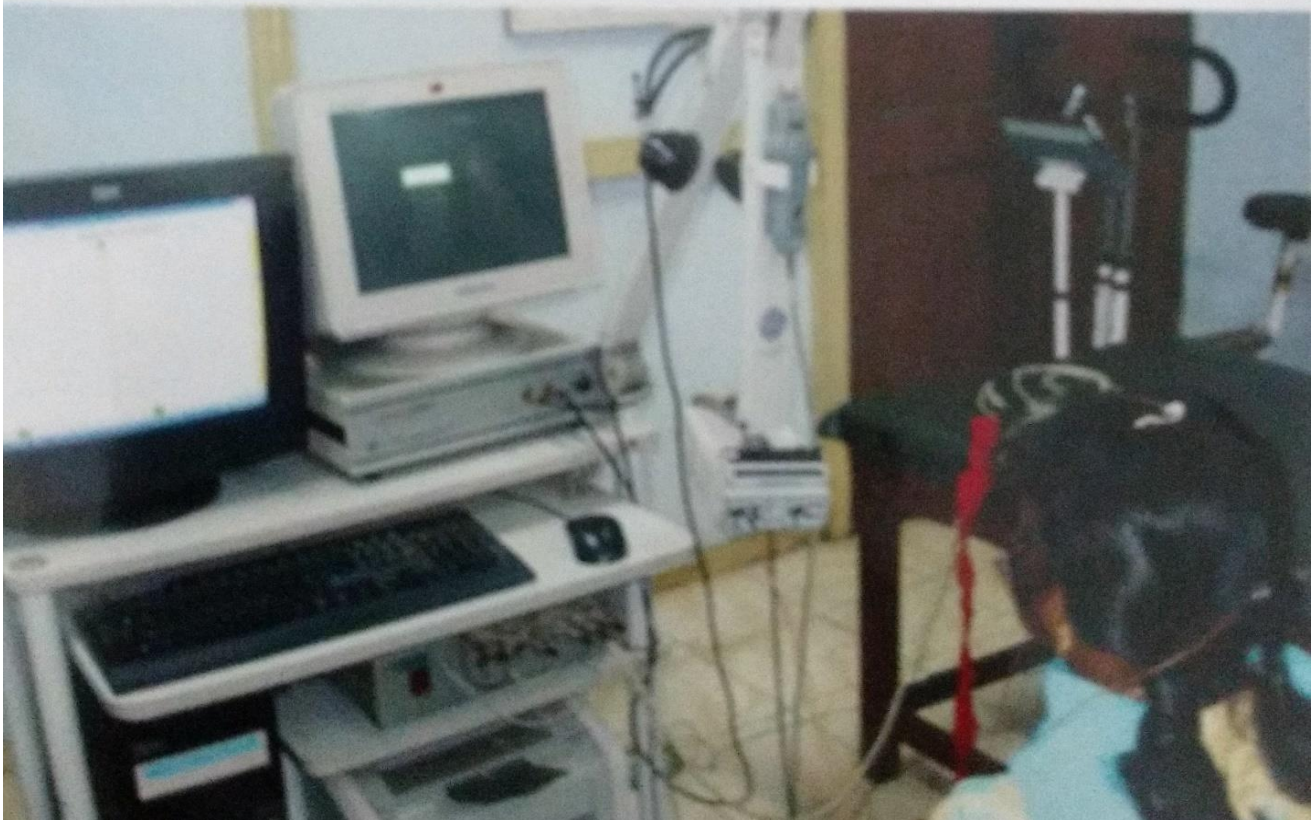
Table -1: Thyroid hormones -Normal values

Hormone	Normal value
TSH	0.30 – 5.0 mIU /ml
FT3	1.40 – 4.8 ng/ml
FT4	0.70 – 2.24 µg/ml

RMS POLYRITE







RMS ADVANCE TESTING LAB

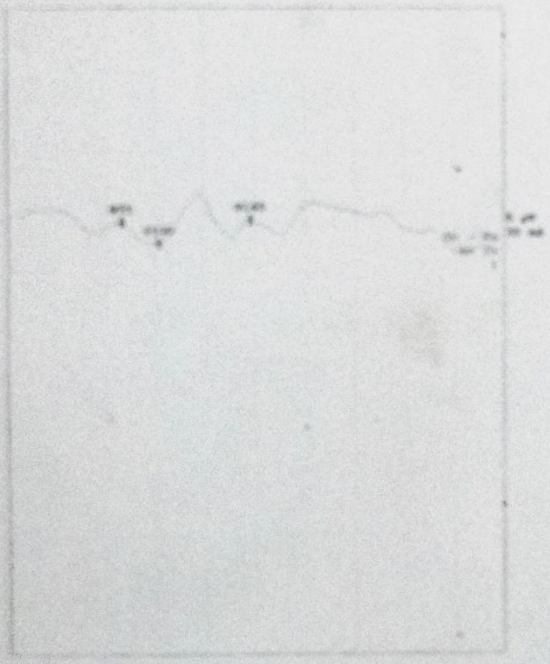
181/5 Phase I Industrial Area Chandigarh

Phones 658701-705

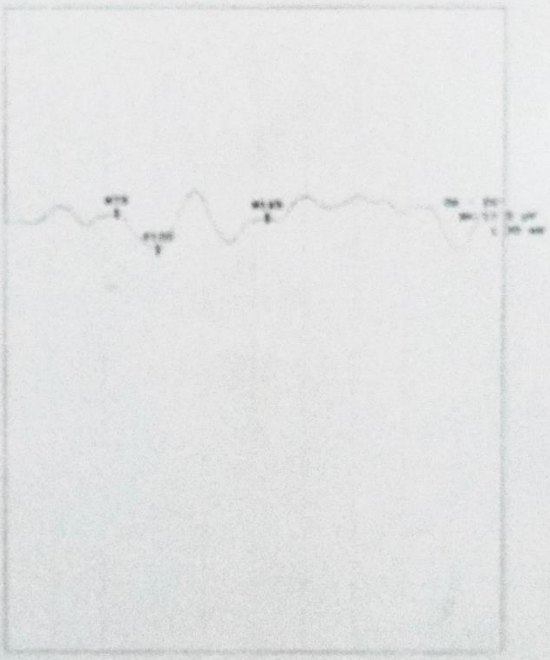
hyper 19 selvi	34/0 Yrs/Mths Male	164 Cms/59 Kg
Physician: Dr.Vengadesh Prabhu	Ref By:	Date: 03-Aug-2016

VEP RECORD

LEFT



RIGHT



LEFT

Sr	Montage	N75 (mS)	P100 (mS)	N145 (mS)	(mS)	(mS)	P100 - N75 (μV)
1	Ox - Rx	70.0	92.0	147.5			1.93
2	Ox - Rx						

RIGHT

Sr	Montage	N75 (mS)	P100 (mS)	N145 (mS)	(mS)	(mS)	N145 - N75 (μV)
1	Ox - Rx	67.5	92.5	157.5			3.39
2	Ox - Rx						

Test Comments

NOTE: THE RESULTS MAY BE CLINICALLY CORRELATED

RESULTS

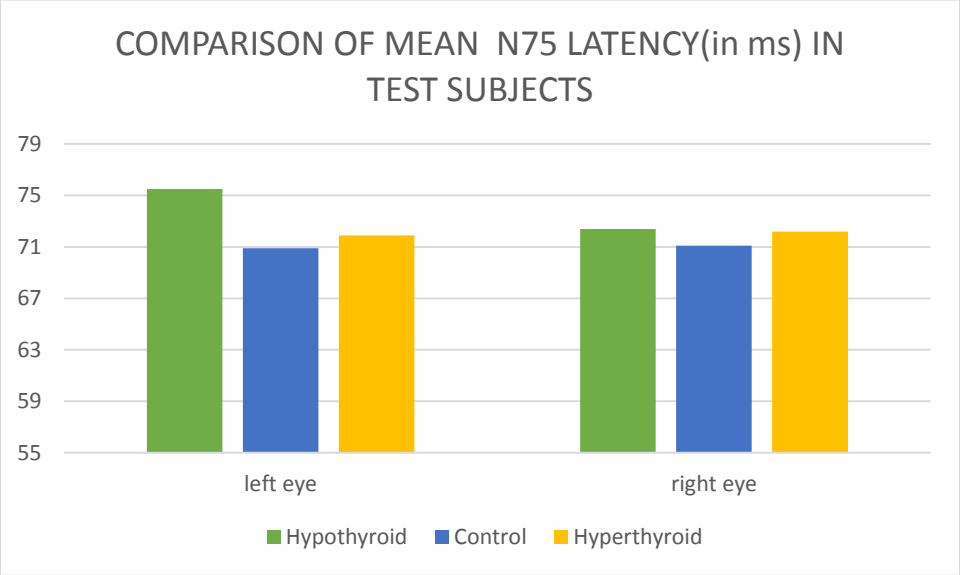
Table No.- 2: **DESCRIPTIVE STATISTICS**

PARAMETER		TOTAL	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION
Age		90	22.00	55.00	42.4667	8.30081
BMI		90	20.31	35.70	27.0612	3.39253
N75(ms)	Right eye	90	60.00	90.00	71.9522	6.47755
	Left eye	90	60.00	90.00	72.6600	8.16355
P100(ms)	Right eye	90	86.30	116.30	99.0744	5.91373
	Left eye	90	88.10	120.00	100.9756	5.99092
N145(ms)	Right eye	90	121.30	173.80	145.4900	10.00669
	Left eye	90	123.60	173.80	149.3089	11.11199
P100-N145 (µv)	Right eye	90	1.93	25.46	13.1424	5.27894
	Left eye	90	1.93	27.23	13.7193	5.92282
TSH(mIU/ml)		90	.01	16.09	4.40	3.50
FT3(ng/ml)		90	.80	6.91	3.7462	1.32
FT4(µg/ml)		90	.30	3.24	1.7536	.54

Table -3 : **GROUP STATISTICS:**

	TYPE OF SUBJECT	NUMBER OF SUBJECTS
1	HYPOTHYROID	30
2	HYPERTHYROID	30
3	CONTROLS	30
TOTAL		90

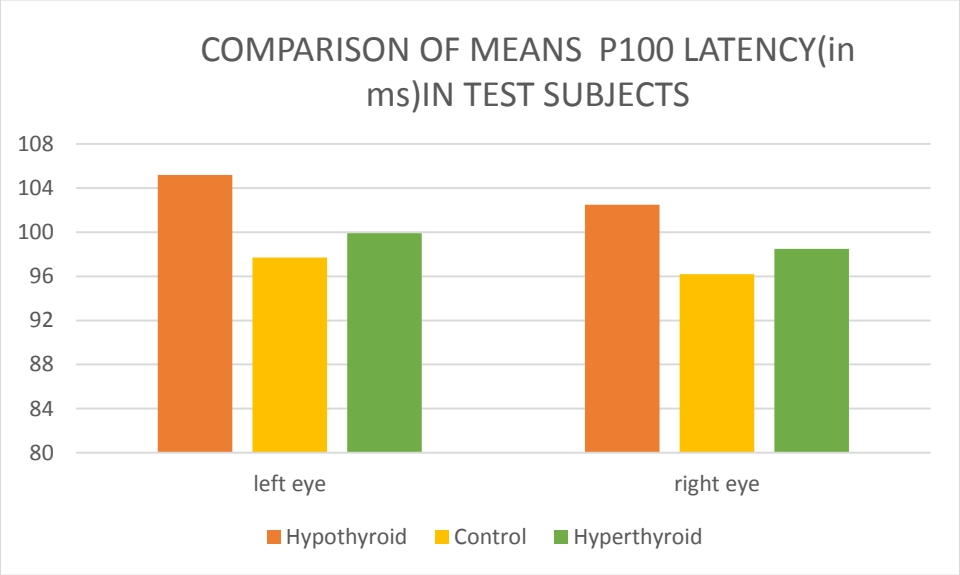
Table-4:**COMPARISON OF MEAN N75 LATENCY(in ms) IN TEST SUBJECTS**



In the above table, the Mean N75 latency of hypothyroid and hyperthyroid is more than the control in both the eyes.

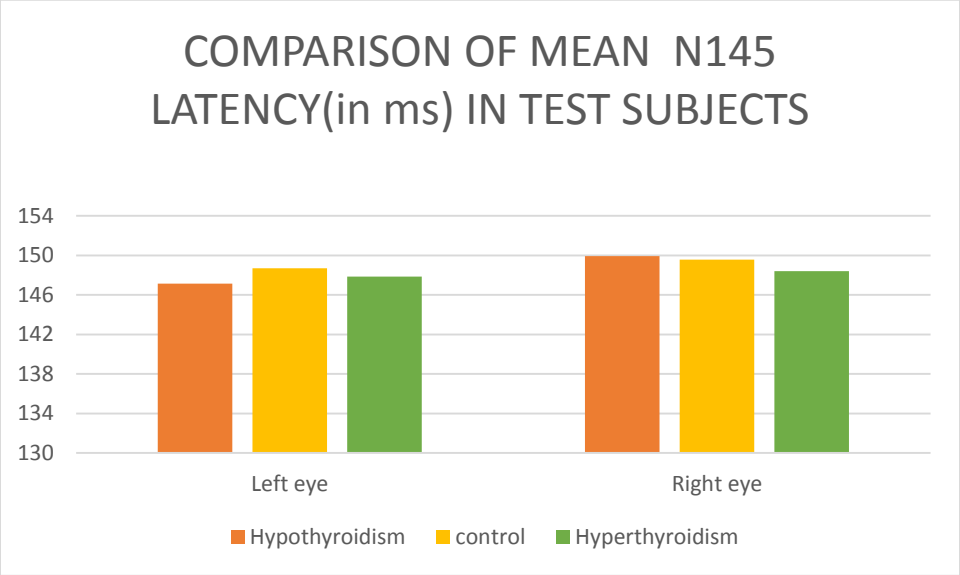
Table-5:

COMPARISON OF MEAN P100 LATENCY(in ms) IN TEST SUBJECTS



In the above table the Mean P100 latency in milliseconds is more than the controls for both hypothyroid and hyperthyroid in both the eyes

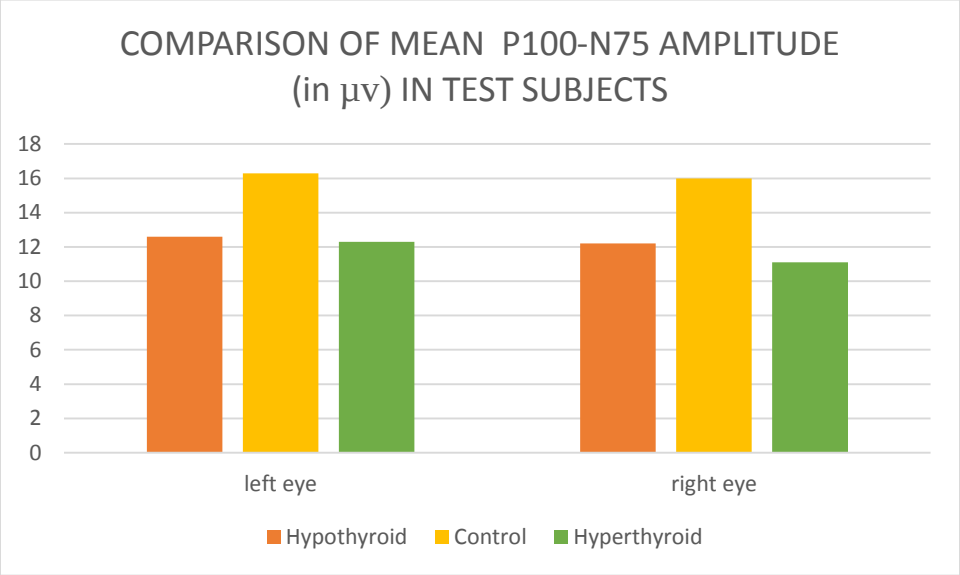
Table-6:**COMPARISON OF MEAN N145 LATENCY (in ms) IN TEST SUBJECTS**



In the above table the mean N145 latency in milliseconds is lower than that of controls for both hypothyroid and hyperthyroid subjects in the left eye. In the right eye, the hypothyroid N145 latency is lower than that of controls but in hyperthyroid the mean latency is increaed

Table-7:

COMPARISON OF MEAN P100-N75 AMPLITUDE (in μv) IN TEST SUBJECTS



In the above table the P100N75 amplitude in microvolt for hypothyroid and hyperthyroid subjects is lower than that of controls in both the eyes.

Table-8: MEAN AND DTANDARD DEVIATION OF RECORDED PARAMETERS:

S.No	GROUP		N75(ms)		P100(ms)		N145(ms)		P100-N75(ms)		TSH	FT3
			RE	LE	RE	LE	RE	LE	RE	LE	mIU/ml	ng/ml
1	HYPOTHYROID	MEAN	72.40	75.45	102.54	105.26	147.15	149.94	12.17	12.55	10.8	2.74
		SD	8.32	9.71	6.78	6.38	17.82	12.19	6.11	6.14	4.42	1.04
2	HYPERTHYROID	MEAN	71.18	70.97	98.50	99.89	148.68	149.57	11.30	11.85	1.49	4.86
		SD	4.72	8.62	5.05	4.78	11.04	12.30	4.61	5.09	1.28	1.24
3	CONTROLS	MEAN	72.27	71.96	96.18	97.78	147.84	148.42	15.96	16.31	3.73	3.63
		SD	6.02	5.15	3.80	3.99	10.13	9.40	3.77	3.02	0.48	0.64

Table-9:

COMPARISON OF VEP PARAMTERS BETWEEN NORMAL AND HYPOTHYROID SUBJECTS

S.NO	VEP PARAMETER		dF	P value	Mean difference	Std. Error difference	95% confidence interval	
							Lower	Upper
	N75	RIGHT EYE	58	0.946	-0.127	1.875	-3.881	3.627
		LEFT EYE	58	0.129	-3.09	2.007	-7.103	0.930
	P100	RIGHT EYE	58	**0.001**[x]	-6.360	1.419	-9.200	-3.520
		LEFT EYE	58	**0.001**[x]	-7.480	1.374	-10.23	-4.73
	N145	RIGHT EYE	58	0.160	7.697	5.405	-3.123	18.517
		LEFT EYE	58	0.60	-1.513	2.810	-7.138	4.112
	P100-N75	RIGHT EYE	58	**0.005**[x]	3.793	1.311	1.169	6.417
		LEFT EYE	58	**0.004**[x]	3.753	1.250	1.250	6.256

[x] – P value less than 0.05 – Significant

In the above table statistically significant change in the latency of P100 wave and P100-N75 amplitude is seen.

Table-10: **COMPARISON OF VEP PARAMTERS BETWEEN NORMAL AND HYPERTHYROID SUBJECTS**

S.NO	VEP PARAMETER		dF	P value	Mean difference	Std. Error difference	95% confidence interval	
							Lower	Upper
	N75 (jn ms)	RIGHT EYE	58	0.439	1.090	1.398	-1.708	3.888
		LEFT EYE	58	0.589	0.997	1.834	-2.674	4.667
	P100 (in ms)	RIGHT EYE	58	0.06	-2.323	1.155	-4.634	0.012
		LEFT EYE	58	0.067	-2.117	1.135	-4.389	0.156
	N145 (in ms)	RIGHT EYE	58	0.681	-1.143	2.763	-6.675	4.388
		LEFT EYE	58	0.133	4.163	2.736	-1.313	9.64
	P100-N75 (in µv)	RIGHT EYE	58	**0.001**[x]	4.658	1.088	2.480	6.835
		LEFT EYE	58	**0.006**[x]	4.009	1.408	1.190	6.828

[x]- P value less than 0.05 - Significant

In the above table statistically significant change in the amplitude of P100N75 amplitude is seen

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Table-11:**COMPARISON OF THYROID FUNCTION TEST WITH VEP OF HYPOTHYROID SUBJECTS**

THYROID FUNCTION TEST		HYPOTHYROID			
		RIGHT EYE		LEFT EYE	
		P100	P100-N75	P100	P100-N75
TSH	Pearson correlation	0.585	0.11	0.264	0.006
	p	0.001[x]	0.955	0.159	0.964
FT3	Pearson correlation	-0.278	-0.74	0.204	0.089
	p	0.137	0.698	0.280	0.641
FT4	Pearson correlation	0.060	-0.145	0.091	-0.15
	p	0.954	0.445	0.633	0.935

[x]- Pvalue less than 0.05 -significant

In the above table, TSH showed a statistically significant positive correlation with P100 latency in hypothyroid subjects.

Table-12:**COMPARISON OF THYROID FUNCTION TEST WITH VEP OF HYPERTHYROID SUBJECTS**

THYROID FUNCTION TEST		HYPERTHYROID			
		RIGHT EYE		RIGHT EYE	
		P100	P100-N75	P100	P100-N75
TSH	Pearson correlation	-0.195	0.040	-0.26	0.335
	p	0.302	0.302	0.185	0.070
FT3	Pearson correlation	0.259	0.174	0.314	-.183
	p	0.167	0.357	.091	0.330
FT4	Pearson correlation	-0.474	-0.021	0.347	-0.170
	p	0.008	0.913	0.061	0.370

In the above table there was no statistically significant correlation of thyroid function test with VEP parameters in Hyperthyroid subjects.

Table-13 :**COMPARISON OF DURATION OF THYROID DYSFUNCTION WITH VEP OF HYPOTHYROID SUBJECTS**

DURATION OF DISEASE	HYPOTHYROID			
	RIGHT EYE		LEFT EYE	
	P100	P100-N75	P100	P100-N75
Pearson correlation	-0.348	-0.113	-0.138	-0.095
P	0.569	0.553	0.469	0.619

Table-14: **COMPARISON OF DURATION OF THYROID DYSFUNCTION WITH VEP OF HYPERTHYROID SUBJECTS**

DURATION OF DISEASE	HYPERTHYROID			
	RIGHT EYE		LEFT EYE	
	P100	P100-N75	P100	P100-N75
Pearson correlation	0.115	0.160	-0.088	0.089
P	0.545	0.399	0.0655	0.640

In the above two tables there is no significant correlation between the duration of disease with P100 latency and P100N75 amplitude in both Hypothyroid and hyperthyroid subjects.

DISCUSSION

DISCUSSION:

Thyroid hormones play a very important role in the stimulation and development and differentiation of the neuromuscular system and brain in foetal and early neonatal life. Thyroid gland dysfunction causes profound symptoms which may be asymptomatic to severe life threatening such as myxedemic coma & thyroid storm

In my study visual evoked potentials was recorded with 30 hypothyroid and 30 hyperthyroid subjects on treatment and compared with controls.

In the study, the majority of the subjects were in the age group of30-40 years with mean duration of disease in the range of 2-6 years.

With regards to the nutritional status of the subjects assessed by means of Body Mass Index using height and weight of the patients, the mean BMI among the hyperthyroid subjects (Mean: 23.9) was found to be less than the controls (Mean:28.1). The mean BMI of the hypothyroid (Mean: 29.6) subjects was found to be higher than that of the control subjects which were found to be statistically significant ($P<0.5$).

With regard to the VEP parameters between the hypothyroid and hyperthyroid subjects, there was changes observed between these subjects and controls of which some were statistically significant as follows.

When the VEP parameters of hypothyroid subjects was analysed, there were changes as follows. The mean N75 of the left eye of the hypothyroid subjects showed an increased mean latency of 75.45 millisecs with a standard deviation of 9.71 millisecs compared with

that of the controls who had a mean N75 of 71.96 millisecs with a standard deviation of 5.15 millisecs. These increased latency values of N75 when analyzed using student t test showed a statically significant ($p < 0.001$). but when the mean latency N75 of the right eye of hypothyroid subjects (Mean:72.40 millisecs; Standard deviation:8.32 millisecs) were analyzed with that of the controls (Mean:72.27; Standard deviation:6.02), the results was not statistically significant ($p=0.11$).

When the P100 latency of hypothyroid subjects was analysed, it showed a mean value of 105.26 with a standard deviation of 6.38 millisecs. When it was compared with that of the controls (mean:97.78; Standard deviation :3.99), there was increase in the latency of the P100 wave which was also statistically significant($p=0.03$). similar was results was obtained with an increase in the latency of the P100 wave in the Right eye (Mean;1022.54; standard deviation:6.78) than the controls (Mean:96.18; Standard deviation:3.80). Also the increase in the latency of the P100 wave was found to be statistically significant ($p=0.02$)

When the N145 latency of the hypothyroid subjects was analysed, it was statistically insignificant between the right eye (Mean: 140.1; $p=0.29$) and the left eye (Mean:149.1 $p=0.14$) with that of the control subjects(Mean:147.8 in right eye and Mean:148.4 in the left eye).

When the N75-P100 amplitude of the hypothyroid subjects were analysed it showed a statistically significant decrease in amplitude in both the eyes (Right eye $p= 0.03$ and Left eye $P<0.00$).

Similarly, VEP parameter values of the hyperthyroid subjects was analysed with that of the control subjects and statistical significance in the difference in values was analysed using Student t test and the following results were obtained.

The N75 latency of the hyperthyroid subjects did not show a statistically significant decrease in the latency in both the eyes (Right eye p= 0.17 and left eye p=0.07) even though their mean values (right eye=71.18 and left eye=70.97) were less than that of the controls (right eye=72.27 and left eye = 71.96).

The P100 latency in hyperthyroid subjects showed an statistically insignificant increase in their latency values, even though their mean values (Right eye- 98.50 and left eye-99.89) was more than that of controls (right eye-96.18 and left eye – 97.78)

When N145 values were analysed for hyperthyroid subjects, there was an statistically insignificant association between the right (p-.0.41) and left eye (p-0.16) and the controls with the right eye showing a decreased mean latency value (143.68) than the control (147.84) and the left eye showing an increased mean latency value(149.57) than the control(148.42)

When the P100-N75 amplitude was analysed it showed a statistically insignificant (p-0.41) decrease in amplitude in the right eye and statistically significant ($p<0.01$)amplitude decrease in the left eye.

In a study by Ladenson PW, Stakes JW, Ridgway EC et al ,the pattern-shift evoked potential was measured in 19 hypothyroid patients before treatment, and after short- (one

week) and long-term (12 to 24 weeks) thyroid hormone replacement therapy. Before treatment, hypothyroid subjects had an abnormally prolonged visual evoked potential latency. After one week of therapy, the mean visual evoked potential latency for the entire group was unchanged, But after long-term therapy, significantly shortened latency of the P100 wave of visual evoked potential was observed.

In the study by Avramides A, Papamargriyis K, Mavomartis I, Saddic G, Vyzantiadis A, Milonas I (33) et al, there was similar prolongarion in the latencies of P100 with a decrease in the P100-N75 amplitude in hypothyroid subjects

In a study by Osterweil et al, similar results were obtained showing an increase in the P100 latency than the control subjects.

Similar prolongation in the latency of P100 wave has been documented by Victor R, Preedy,Gerard N,Burrow, Ross Watson et al in hypothyroid subjects.

In the study by Kristina Jameson pattern VEP showed an increase in the latency of the P100 wave with a decrease in the P100-N75 amplitude in test subjects than the controls.

In a study Salvi M, Spaggiari E, Maculuso C, Gardini E, Ferrozi F, Minelli r, Wall JR, Roti E et al, prolongation of the latency of visual evoked cortical response was observed in patients with Thyroid associated Opthalmopathy (TAO) patients without optic nerve compression

In a study by Mitchell K W, Wood C W, and Howe J W et al conducted on 16 hyperthyroid subjects before and after treatment and compared with those from a similar group of age and sex matched control subjects. No effect on latency was seen, and although larger amplitude values were noted in the thyrotoxic group these too were not significant

In the study by Abott RJ O'Malley BP, Barnett DB et al titled, " Central and peripheral nerve conduction in thyroid dysfunction", there were no change in in the latencies of the visual evoked responses and peripheral nerve conduction in the hyperthyroid subjects compared with the control group

The thyroid function tests were compared for the hypothyroid subjects with P100 latency and N75-p100 amplitude using Pearsons correlation co-efficient and the following results were obtained. When TSH levels were analysed with hypothyroid subjects, both the eyes showed appositive correlation with TSH levels and further an statistically insignificant association with the right eye (p-0.11) and a statistically significant association in the left eye (p-0.01)

Similarly, when the levels of FT_3 and FT_4 were analysed, there was a statistically insignificant association between the level of these hormones and P100 latency and N75-P100 amplitudes.

When the TSH levels were analysed with the hyperthyroid P100 latencies and N75-P100 amplitude, it showed a statistically insignificant association between TSH levels and P100 latencies and N75-P100 amplitude. TSH levels showed a statistically insignificant negative correlation with the P100 amplitudes in both the eyes. TSH levels showed a statistically insignificant positively correlation with N75-P100 amplitude.

Similarly, when the levels of FT_3& FT_4 were analysed with P100 and N75-P100 amplitudes they all showed a statistically insignificant association between them except for a statistically significant negative correlation with TSH levels and P100 amplitude.

In a study by Tamburini G, Tacconi P, Ferrigno P, Cannas A, Massa GM, Mastinu R, Velluzzi F, Loviselli A, Giagheddu M titled "Visual evoked potentials in hypothyroidism: a long-term evaluation" Visual Evoked Potentials were measured in 9 new-diagnosed hypothyroid female patients before treatment, during thyroid hormone replacement therapy and one year after having achieved and maintained euthyroidism. Their study prolonged latencies in P100 wave before treatment with lower P100-N75 amplitude than the control. After treatment the P100N75 amplitude showed no change while the latency of P100 wave decreased than that of controls. Also there was statistically significant correlation was found between the thyroid hormone levels and the P100 latency.

In a study by Khedr EM, E1 Toony LF,Tarkhan MN et al, titled “Peripheral and central nervous system alterations in hypothyroidism:electrophysiological finding”s, no significant correlation was observed between hormonal levels and different electrophysiological parameters

To summarize, hypothyroid patients showed a statistically significant increase in P100 latency and decrease in amplitude of the N75-P100 wave. In hyperthyroid subjects there were no statistically significant change5 in latencies of N75, P100 and N145 waves and N75-P100 amplitude. When the levels thyroid hormones were analysed, there was no statistically significant change with P100 latency and N75-P100 amplitude except for a statistically significant positive correlation of TSH level with P100 latency in one eye and an statistically significant negative correlation of FT4 level with P100 latency in one of the eyes.

In hypothyroidism, mentation is slow and CSF protein is elevated. They affect mitochondrial oxidative activity, synthesis and degradation of proteins and sensitivity of tissues to catecholamines. Both hypothyroidism and hyperthyroidism affect the myelin sheath of the nerves which leads to changes in the P100 latency and P100N75 amplitude. Hyponatremia is also a feature of hypothyroidism, which may also result in disorders of nerve excitability.

CONCLUSSION

CONCLUSION:

In my study on comparison of visual evoked potentials in hypothyroid and hyperthyroid, the P100 latency is increased with a decrease in P100-N75 amplitude in hypothyroidism but it was not so in hyperthyroidism. There was no statistically significant VEP changes with the duration of the disease and thyroid function tests with the VEP parameters except for a statistically insignificant positive correlation of TSH with P100 latency in one eye of hypothyroidism.

Thus, we can infer that thyroid disorders cause neuropathy. VEP can be used as a tool for early identification of subclinical neuropathy in individuals with thyroid disorders. Large scale studies of VEP in thyroid dysfunction can be undertaken to further enlighten our knowledge about neuropathy in thyroid disorders so that VEP can be used as a diagnostic tool during routine workup of thyroid patients.

SUMMARY

Summary:

Thyroid hormones have profound effects on the central nervous system. In my study " A comparison of Visual Evoked Potentials in Hypothyroid and Hyperthyroid subjects" conducted on 30 hypothyroid and 30 hyperthyroid subjects with age matched controls, the latencies of the N75, P100, N145 and P100-N75 amplitude were compared with the thyroid function test and disease duration.

In hypothyroid subjects, there was a delay in the latency of P100 wave along with a decrease in the P100-N75 amplitude while in hyperthyroids, statistically insignificant changes in the VEP parameters were also seen. Also no correlation was observed with the disease duration and thyroid function tests with the VEP parameters in my study.

From the study, it is clear that neurological changes occur in hypothyroidism and hyperthyroidism. So VEP can be used to identify subacute neurological changes in thyroid dysfunction

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PROFORMA

Date :

1. Sl. No. :

2. I.D. No. (given by investigator) : Address & Contact No.

3. Name : Ht.

4. Age : Wt.

5. Gender :

6. Religion :

7. Endocrinology OPD NO:

7. Occupation : Not working/ Housewife/ labourer – what type of

Work / Professionals/ Others (specify)

8. Per Capita Income:

Number of family members:

Net family income :

9. Educational Qualification:

10. Family History :

11. Duration of illness:

12. Social habits : H/O alcohol /smoking / Betel nut chewing /others

13. Past History :

14. Treatment History : Oral drugs / Parenteral

15. Associated Comorbidities

16.Clinical details:

14. General Examination : Alert/ Anaemia/ Jaundice/ Cyanosis/ Clubbing

Built and Nourishment

15. Vital signs : Temp.: / Pulse rate : / Blood pressure

16. Systemic Examination : Cardiovascular system :

Respiratory system :

Abdomen :

Central Nervous system :

Investigations:

Blood :

Thyroid function test: (TSH, FT_3,FT_4)

தகவல் தாள்

இந்த பரிசோதனை தைராய்டு நோய் பார்வை ஊக்கிகளைக் கொண்டு மதிப்பீடு ஈடுபடுத்துகிறது.

நோயாளிகளுக்கான தகவல் :இது ஆற்றல் மிக்கதாகவும், பாதுகாப்பாகவும் இருப்பதாக அறியப்படுகிறது. இந்த ஆய்வின் மூலம் பெறப்படும் அறிவானது உங்களைப் போன்று பல்லாயிரக்கணக்கான நோயாளிகளுக்கு நன்மை தருவதாக அமையும்.

உண்டாகக் கூடிய இடர்கள்:அனைத்து புதிய முறைகளிலும் இருப்பது போலவே இந்த முறைகளிலும் சில எதிர்பாராத இடர்கள் சம்மந்தப்பட்டுள்ளன.

ஆய்வு நடைமுறைகள்:இந்த ஆய்வில் நீங்கள் புறநோயாளியாகவே இருப்பீர்கள். இந்த சோதனை பார்வை ஊக்கிகளைக் கொண்டு. உட்கார்ந்த நிலையில் எடுக்கப்பட்டு பார்வை நரம்பு செயலிழப்பு குறித்த மதிப்பீடு அம்சங்கள் காரணிகளின் அளவு ஆராயப்படும்.

அந்தரங்கத்தன்மை:உங்கள் மருத்துவமனை பதிவேடுகள் மிகவும் அந்தரங்கமாக வைத்துக்கொள்ளப்படும்.பிற மருத்துவர்கள், விஞ்ஞானிகள் இந்த ஆய்வின் தணிக்கையாளர்கள் அல்லது ஆராய்ச்சி ஆதரவாளர்களின் பிரதிநிதிகள் ஆகியோரிடமும் அவை வெளிப்படுத்தப்படும்.இந்த ஆய்வின் முடிவுகள் அறிவியல் பத்திரிக்கைகளில் பிரசுரிக்கப்படலாம். ஆனால் பெயரை வெளியிடுவதன் மூலம் நீங்கள் அடையாளம் காட்டப்படமாட்டீர்கள்.

ஆய்வில் பங்கேற்கும் நோயாளியின் கடமை பொறுப்புகள்:உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் நீங்கள் முழுமையாக ஒத்துழைக்க வேண்டும் என்று உங்களை கேட்டுக் கொள்கிறேன். சிகிச்சையளிக்கும் மருத்துவர் கொடுக்கும் அறிவுரைகளை பின்பற்ற வேண்டும் என்றும்,என்னென்ன செய்யவேண்டும்,என்னென்ன செய்யக்கூடாது என்றும் உங்களிடம் கூறப்பட்டுள்ளவற்றில் இருந்து சற்றும் விலகக்கூடாது என்றும் நீங்கள் எதிர்பார்க்கப்படுகிறீர்கள்.

ஆய்வில் உங்கள் பங்கேற்பு மற்றும் உங்கள் உரிமைகள்:இந்த ஆய்வில் உங்கள் பங்கேற்பு தன்னிச்சையான மற்றும் காரணங்கள் எதையும் கூறாமலேயே நீங்கள் இந்த ஆய்விலிருந்து எந்த ஒரு நேரத்திலும் விலகிக் கொள்ளலாம். ஆய்வில் உங்கள் பங்கேற்பை மறுப்பது போன்ற எந்த வித அபராதமும் விதிக்கப்படமாட்டாது. உங்களை கவனித்துக்கொள்ளும் மருத்துவருடன் முழுமையாக ஒத்துழைக்க நீங்கள் சம்மதிக்க வேண்டும்.

ஆய்வில் பங்கேற்பவர் கையொப்பம்

அல்லது

பெருவிரல் பதிவு

கைபேசி எண்

ஒப்புதல் படிவம்

திரு/திருமதி/செல்வன்/செல்வி/ _____

ஆகிய நான் டாக்டர். XXXXXXXXXX, பட்டமேற்படிப்பு மாணவர் உடல் இயங்கியல் துறை, ஸ்டான்லி மருத்துவக்கல்லூரி, மருத்துவமனையில் நடத்தும் ஆராய்ச்சியில் யாருடைய வற்புறுத்தலும் இன்றி என்னுடைய முழுசம்மதத்துடன் பங்கேற்க சம்மதம் தெரிவிக்கிறேன். இந்த ஆராய்ச்சி என்னுடைய என் பார்வை நரம்பு செயல்பாடுகளை அறிந்து கொள்ள உதவியாக இருக்கும் என்பதை நான் அறிந்து கொண்டேன். ஆராய்ச்சியின் செயல்பாடுகளை ஆராய்ச்சியாளர் மூலம் அறிந்துகொண்டேன்.இந்த ஆராய்ச்சியில் எந்தவித மருந்துகளோ ஊசிகளோ அளிக்கப்படமாட்டாது எனவும் நான் இந்த ஆராய்ச்சியில் இருந்து எந்தவித முன்னறிவிப்புமின்றி விலகிக்கொள்ள எனக்கு உரிமை உண்டு எனவும் இந்த ஆராய்ச்சியின் ஏடுகள் இரகசியமாக வைக்கப்படும் என்பதையும் நான் அறிவேன்.

கையெழுத்து

CONSENT FORM

I Mr/Ms _____ understand that Dr.XXXXXXXXXXX, a postgraduate student in Stanley Medical College and Hospital, Chennai is doing the study on hypothyroid and hyperthyroid subjects and control group. I have been made to understand that these tests will assess the functioning of my optic nerve. These tests are simple, involve taking visually evoked potentials. They do not involve injections or taking any medicines and are risk free. I have been familiarized with the testing procedures. I am participating in this study willingly. I have not been forced to do so. I have also been told clearly that I could withdraw from this study without any prejudice.

Date:

Signature

MASTERCHARTS

TEST PARAMETERS IN HYPOTHYROID SUBJECTS

					LEFT EYE				RIGHT EYE						
	Age	Duration	Ht. (cms)	Wt. (kgs)	N75 (ms)	P100 (ms)	N145 (ms)	P100-N75 (µv)	N75 (ms)	P100 (ms)	N145 (ms)	P100-N75 (µv)	TSH (mIU/ml)	FT3 (ng/ml)	FT4 (µg/ml)
1	43	7	150	54	87.5	105	155	12.7	65	111	144	12	7.1	1.8	1.3
2	44	1	146	61	61.9	101	151	18.8	60	110	143	24	8.4	1.1	1.02
3	22	4	151	60	85.6	101	133	20.2	69	101	148	20	5.8	2.98	1.2
4	37	8	146	76	60	108	167	19.6	65	87	155	4	6.9	3.3	1.31
5	29	3	159	63	78.8	101	142	11.4	69	100	141	11	5	2.1	1.04
6	40	7	152	69	79.4	100	143	8.92	63	91	142	15	4	4.1	1.67
7	41	11	143	73	85	103	174	5.07	78	93	126	8.9	7.3	2.34	1.18
8	29	2	146	60	75	101	163	15.9	69	96	144	18	4	2	1.57
9	43	6	162	69	87.5	101	157	7.64	83	108	146	10	16	1.7	1.44
10	37	9	138	58	74.2	107	144	12.4	72	110	141	13	15	1.4	1.39
11	43	4	144	70	71.3	102	168	7.52	64	101	153	7.8	11	2.08	1.62
12	39	8	138	54	70.6	101	144	8.89	89	104	144	6.7	13	1.6	1.79
13	45	4	163	83	70	100	163	10	70	100	161	10	22	0.8	0.3
14	39	4	153	63	85.6	109	149	14	76	99	140	8.6	0.1	3.9	1.63
15	35	4	144	57	88.1	109	158	20.3	74	101	139	23	4.8	4.4	2.01
16	43	3	155	69	83.1	103	153	3.39	84	104	157	3.9	7	3.46	1.55
17	30	8	149	57	66.9	104	148	9.79	69	100	149	11	6	1.53	0.9
18	29	1	148	64	90	120	154	4.17	90	116	156	4.3	25	1.64	0.97
19	37	6	176	78	82.5	106	154	5.03	87	106	135	3	19	4.47	2.1
20	41	3	149	63	72.5	108	141	27.2	78	116	145	25	13	2.34	1.13
21	40	6	160	82	76.9	103	141	10.1	71	102	132	15	8.2	2.91	1.24
22	40	4	160	65	70.6	102	133	20.4	73	99	143	10	12	2.56	1.17
23	36	9	158	76	61.9	101	145	18.5	71	101	149	14	7.1	3.76	1.84
24	38	8	154	72	61.9	101	145	18.5	69	104	154	12	5.1	4.01	1.92
25	39	5	164	78	61.9	118	165	12.3	71	100	146	10	4.1	4.16	2.1
26	33	7	154	69	85.6	101	144	7.96	71	100	149	20	6.3	3	1.23
27	36	10	147	70	69	100	146	9.35	60	103	127	12	6.9	3.32	1.48
28	44	9	164	88	64.4	120	165	15	60	99	155	16	17	2.98	1.04
29	37	4	167	82	81.9	120	152	3.1	83	115	136	1.9	11	3.4	1.54
30	45	7	164	78	61.9	101	145	18.5	71	101	149	14	8	3.21	1.39

TEST PARAMETERS IN HYPERTHYROID SUBJECTS

					Left eye				Right eye						
S.No.	Age (yrs)	Duration (yrs)	Ht (cms)	Wt (kgs)	N75 (ms)	P100 (ms)	N145 (ms)	P100-N75 (µv)	N75 (ms)	P100 (ms)	N145 (ms)	P100-N75 (µv)	TSH (mIU/ml)	FT3 (ng/ml)	FT4 (µg/ml)
1	40	2	154	58	88	100	141	2.2	77	101	141	5.4	0	6	2
2	37	4	164	78	72	88.1	141	3.3	71	86	141	5.2	1.4	4	2
3	36	1	154	64	70	92.5	148	1.9	68	93	158	3.2	0.2	6	3
4	40	5	160	86	74	92.1	146	4	74	93	147	4.1	2.9	4	1
5	43	4	157	63	88	100	141	2.2	77	101	141	5.4	1.3	5	2
6	29	4	167	78	71	91.9	168	7.5	64	92	153	7.8	3.5	3	2
7	34	1	164	59	70	92.5	148	1.9	68	93	158	3.2	0.5	5	2
8	42	2	164	58	69	92.5	163	19	61	86	124	13	4.1	3	1
9	42	3	158	52	62	101	145	19	71	101	149	14	2.5	4	2
10	43	1	164	64	60	109	165	21	76	106	128	17	0.4	6	3
11	37	6	155	50	67	103	154	14	74	103	149	15	2.3	4	2
12	40	4	174	64	62	101	145	19	71	101	149	13	3.9	3	2
13	49	3	158	76	62	101	145	19	71	101	149	14	1.7	4	2
14	41	1	143	73	85	103	174	5.1	78	93	126	8.9	0.1	6	3
15	40	3	160	65	71	102	133	20	73	99	143	10	0.9	6	2
16	44	4	163	83	70	100	163	10	70	100	161	10	2.1	4	2
17	40	4	160	65	71	102	133	20	73	99	143	10	1.3	5	2
18	32	4	154	69	86	101	144	8	71	100	149	20	0.2	7	3
19	43	2	147	70	69	103	146	9.4	67	103	127	14	0.2	6	3
20	42	3	158	54	62	103	145	19	65	101	149	12	2.6	5	2
21	44	1	164	63	67	109	165	21	69	106	128	18	0.3	5	3
22	43	6	155	52	69	101	154	17	72	103	149	16	2.5	4	2
23	35	4	174	64	63	99	145	14	67	101	149	12	3.8	4	2
24	36	3	158	76	65	100	145	19	66	101	149	14	1.4	3	2
25	39	1	143	70	80	104	174	8.1	78	99	126	7.9	0.2	7	3
26	40	3	160	63	72	101	133	12	73	99	143	11	0.6	5	2
27	42	4	163	73	70	97	163	10	70	100	161	9.4	2.1	4	2
28	40	4	160	65	73	100	133	12	71	99	143	10.6	1.3	6	2
29	43	4	154	63	85	102	144	9	82	101	147	18	0.3	6	3
30	44	2	147	70	70	100	146	10.4	69	102	147	14	0.4	8	4

TEST Values for CONTROL SUBJECTS

S.No	age	Height	Weight	left eye				Right eye				TSH	FT3	FT4
	(yrs)	(cms)	(kgs)	N75 (ms)	P100 (ms)	N145 (ms)	P100-N75 (µv)	N75 (ms)	P100 (ms)	N145 (ms)	P100-N75 (µv)	(mIU/ml)	(ng/ml)	(µg/ml)
C1	32	156	61	76.3	94	164	12	73	90	121	5.8	4.2	4	2
C2	35	149	59	68.8	93	168	13	89	89	151	8.3	3.8	3	2
C3	37	168	83	75	101	131	18	68	100	174	19	4.6	5	2
C4	39	157	71	71.2	93	137	14	71	93	137	14	2.8	3	1
C5	38	152	77	70.1	97	142	12	70	97	142	12	3.8	4	2
C6	36	158	81	74.4	98	157	18	74	98	157	18	4.3	5	2
C7	42	149	71	69.3	103	161	14	69	103	161	14	3.2	3	1
C8	31	139	62	71.6	96	138	17	72	96	138	17	3.7	3	1
C9	45	167	81	75.6	102	150	19	76	102	150	19	4	3	2
C10	33	154	71	73.9	92	154	19	74	92	154	19	3.9	3	2
C11	37	147	63	69.2	93	136	15	69	93	136	15	4.1	4	2
C12	42	149	64	68.2	99	148	16	68	99	148	16	4	4	2
C13	43	152	67	70.7	100	148	13	71	95	148	13	3	3	1
C14	41	154	64	74.3	99	149	19	74	99	149	19	3.3	3	1
C15	34	149	61	69.1	98	140	17	69	98	140	17	4.3	4	2
C16	47	153	62	81.5	106	154	15	82	89	154	15	3.9	4	2
C17	37	158	61	69.3	97	155	17	69	97	155	17	4	4	2
C18	41	162	74	70.7	97	147	14	71	97	147	14	3.9	4	2
C19	39	158	68	69.2	95	140	22	69	95	140	22	4	4	2
C20	37	159	71	63.3	97	146	15	63	97	146	15	3.8	4	2
C21	32	165	79	69.1	90	144	14	69	90	144	14	3	3	1
C22	39	155	63	73.1	97	147	23	73	97	147	23	3	3	1
C23	35	164	78	83	95	151	18	83	95	151	18	3.1	3	1
C24	38	157	67	65.4	98	147	17	65	98	147	17	3	3	1
C25	38	143	52	81.2	103	164	10	81	96	164	10	4.2	4	2
C26	33	136	54	63.8	95	141	14	64	95	141	14	4	4	2
C27	35	157	72	78.3	99	142	21	78	99	142	21	3.6	3	1
C28	49	148	56	69.6	103	152	19	70	103	152	19	4.2	4	2
C29	37	154	68	64.6	97	140	16	65	97	140	16	3.8	4	2
C30	47	147	70	79.1	104	161	17	79	94	161	17	3.7	3	1