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## Cognitive Function in Elderly with Subclinical Hypothyroidism

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### 1. Introduction

Overt thyroid disease often involves mood disorders and cognitive impairment in adults. But at the subclinical level a relationship has been difficult to establish. Some authors regard thyroid stimulant hormone small elevation in the elderly as part of aging. However, there is a body of studies that demonstrate the impact of SH in target tissues; vg, ejection fraction and lipid profile alterations; thus many experts recommend comprehensive treatment, adjusting it to the patient's specific context, age, comorbidities etc. However, regarding cognitive and mood problems there is still controversy. There are studies concluding no association between SH, cognition or depression but these used insensitive instruments to measure cognition and depression, or they had some other methodological bias. There are also cross-sectional and case studies showing an association with newly-developed more sensitive instruments. Subclinical hypothyroidism, cognitive impairment and depression occur more often in old age. Population aging increases SH, cognitive impairment, and depression prevalence and this will be a health burthen for patients, their families, and society; thus measures to minimize it is urgent in developing countries, where a high increase in the elderly population is expected. Indeed Healthcare polices everywhere must strive for mind and physical well-being. We will review instruments to screen and score different spheres of cognitive function in the geriatric or general practitioner's office, and assess the available evidence, and aspects that need further investigation.

### 2. Definitions

1. Subclinical hypothyroidism (SH) is defined as an elevated serum thyroid stimulant hormone (TSH) level  $\geq 4.0$  mUI/L with free thyroxine (FT4) within normal range, with or without symptoms.
2. Cognition impairment: refers to decrease ability in mental activities to acquire, store, retrieve and use information. People with mild cognitive impairment are able to perform basic everyday activities, but present mental decline (forgetfulness, confusion, inattention etc) noticeable by themselves, their relatives, or test. While in dementia the performing of everyday activities are also deteriorated.

- 3. Depression is a long lasting sadness accompanied by loss of interest in activities; even activities the subject finds enjoyable. It can affect mental activity, behavior, and general well-being.

3. Subclinical hypothyroidism

3.1 Prevalence and risk factors for SH

SH comprises the largest fraction of TSH elevation. SH predominates in women, and its prevalence increases with age. In the United States, the percent of individuals with TSH over 4.5 mIU/L raises to 14% after 70 years of age [Hollowell et al 2002]. But a study [Hoogendoorn et al 2006] in Netherlands reported 4.4% of adult population with TSH over 4.0 mU/L; it also reported a decrease in the mean TSH by age (Figure 1). In Spain, a study reported a prevalence of hypothyroidism (TSH >6.7 mUI/L) of 11% in 60-69 age group population [Sender Palacios et al, 2004]. In Cuba, [Hernandez-Perera et al 2005] reported that 5.3% of population older than 59 years had a serum TSH >5.6 mU/L. The prevalence estimates have varied depending on the population studied and the criteria used to define it.

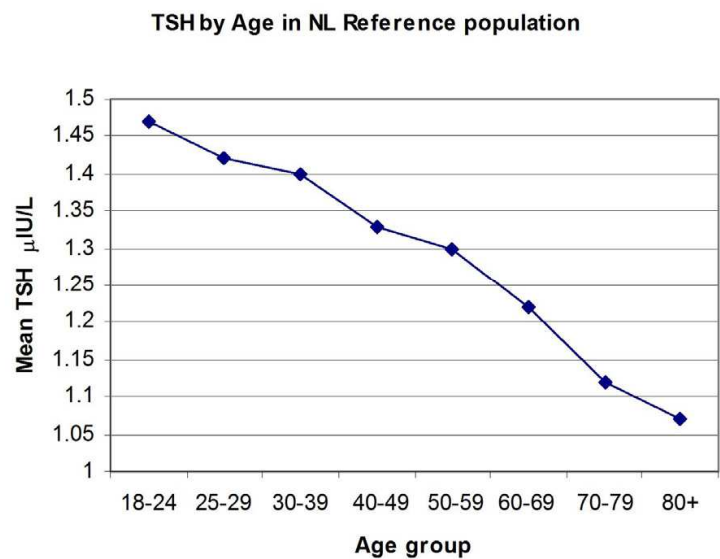


Fig. 1. TSH  $\mu$ IU/L by Age Adapted from Hoogendoorn et al 2006

Besides age and gender, genetics is among the population factors that inflict variation to prevalence estimates, accounting for almost 65% thyroidal phenotype [Samollow et al 2004, Peeters RP 2009]. Also, the amount of dietary iodine has to be considered. Its deficiency translates into endemic goiter, congenital hypothyroidism and other thyroidal dysfunction [Jameson & Weetman, 2005]. Sustained implementation of iodinated salt has been successful in abating simple goiter and cretinism [Basil S Hetzel 2004]. In Mexico City, Martinez et al [1999] reported 11% of subjects 55 and older with TSH higher than 5.6  $\mu$ IU/L; however, in Monterrey Mexico, a region formally known for endemic goiter, 27.3% of geriatric outpatients had TSH >4.5  $\mu$ IU/L [Cárdenas-Ibarra et al 2008]. The unexpectedly high frequency was confirmed by a population study [Cárdenas-Ibarra et al 2011a]. Another interesting observation of this study was a non significant difference of prevalence by gender, suggesting that advancing age decreases the gender gap of SH prevalence. The inhabitants of this region tend to ingest rather

large quantities of iodinated salt (the only one available for a half century now) owing to the very hot weather that characterized this region. According with iodine sufficiency is the region low goiter prevalence (Cárdenas-Ibarra et al 2011a) and that 93.4% of congenital hypothyroidism is due to thyroid dysgenesis and 6% dyshormogenesis (Vela-Amieva et al 2003). Albeit, urinary iodine excretion was not measured. NHANES III [Hollowell et al 2002] reported an increase in mean TSH with age (see Figure 2) and also significantly higher TSH concentrations in persons with high iodine excretion (>500 µg/g creatinine) than in persons with normal iodine excretion (50–500 µg/g creatinine) ( $P < .02$ ). Moreover, in a borderline sufficient iodine intake prevalence of overt hypothyroidism was 0.4% and subclinical 4.0%. In this study decreasing TSH serum levels with age were also observed [Hoogendoorn et al 2006] (Fig 1). Thyroid malfunction may come from an excess of iodine intake by a direct inhibitory effect to the thyroidal gland or by eliciting autoimmunity [Teng et al 2006]. Impairment in thyroid function changes directly with thyroid autoimmunity; but high urinary iodine excretion predicted an increase of TSH and antithyroperoxidase antibodies one month later [Karmisholt & Laurberg 2008]. Surveillance of dietary iodine is recommended.

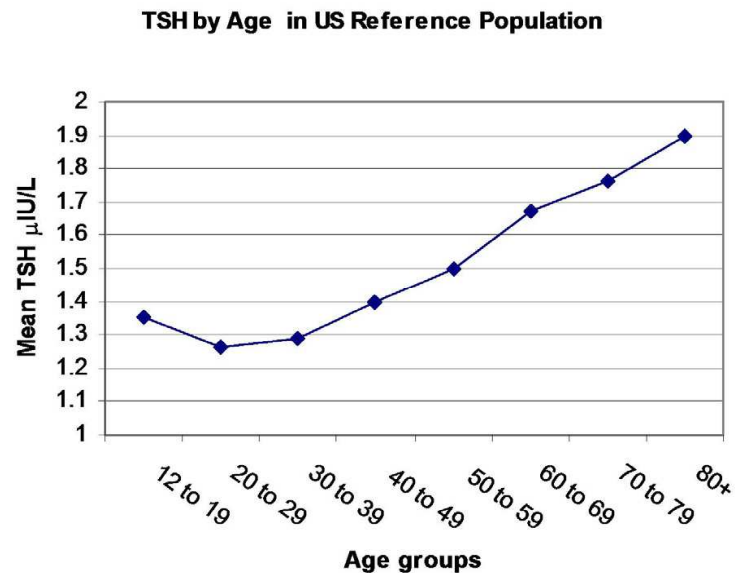


Fig. 2. TSH µIU/L by Age Adapted from Hollowell et al 2002

**3.2 Clinical aspects of SH in the old**

Thyroxine regulates the metabolism of all cells, rendering multisystem unspecific symptoms. Diagnosis of hypothyroidism in the elderly is specially challenging, since it develops very insidiously and symptoms usually go unnoticed [VermaA & Hasan 2009]. Even when symptoms are noted, they are confused with other health problems or are disregarded because they are thought to be part of aging. A questionnaire assessing hypothyroidism somatic symptoms was not able to predict abnormal TSH levels [Cárdenas-Ibarra et al 2011a]. See Table 1. In general, in symptom comparison among groups [Canaris et al 2004], subclinical hypothyroidism versus euthyroidism can show significant differences. These researchers reported a positive but weak association between the proportion of symptoms reported by the patients and progression of thyroid failure. Single or grouped symptoms are of little value at the individual level in just one consultation; thus most often SH is regarded as asymptomatic.

It is not until the patient is on levothyroxine that he/she notices improvement, such as less body aches, and not running out of energy. However, other symptoms such as weight change, puffy eyes, or hoarse voice take longer too reverse, if they do. Other functions such as cognition and mood symptoms can be reliably measured through validated instruments, but memory and depression complaints can not discriminate SH from euthyroidism. Mental slowing and depression are among the early hypothyroidism symptoms. Screening thyroid function in the elderly can save a lot of time, permit the implementation of appropriate measures, and avoid anguish to the patients and their families.

Symptom	Sensitivity	Especificity
Doesn't sweat	0.28	0.76
Deep voice	0.31	0.70
Paresthesia	0.64	0.47
Dry skin	0.56	0.59
Constipation	0.51	0.65
Can't lose weight	0.49	0.76
Slow to move	0.36	0.76
Rough skin	0.35	0.74
Puffy eyes	0.47	0.78
Cold intolerance	0.31	0.78

Cárdenas-Ibarra et al 2011a

Table 1. Symptoms on subjects with and without SH

3.3 Brain and thyroidal hormones

The availability of active thyroid hormone in adult brain results from the balance of its activation and inactivation [Kester et al 2004]. The selenoenzyme, type 2 iodothyronine deiodinase, removes an outer ring iodine atom from the thyroxine to generate triiodothyronine, the active hormone. The type 3 iodothyronine deiodinase removes an inner ring iodine to inactivate the hormone. Brain protection from triiodothyronine swings is attained by coordinating the expression of type 2 and 3 deiodinases. This is, expression of type 2 increases while type 3 decreases in low thyroxine; the opposite occurs with excess thyroxine. The monocarboxylate transporter-8 is a thyroid hormone specific transporter protein that crosses the blood-brain barrier. It is expressed in all brain locations involved in negative thyrotrophic releasing hormone feedback.

The hypothalamus-pituitary-thyroid axis is controlled by thyroid receptor beta 2 isoform, which is expressed solely in the hypothalamus and anterior pituitary, and is specific for triiodothyronine [Abel et al 1999]. Low level of hypothalamic triiodothyronine elevates TSH. Thyroid hormone receptor studies on mutant mice report that the behavior of mice, lacking receptor beta, brings to mind the attention-deficit-hyperactivity disorder. The mice lacking TR alpha respond poorly to fear conditioning, showing poor memory, high anxiety, and inhibition of exploratory behavior. [Williams 2008]

Triiodothyronine deficiency prevents proper glucose uptake in neurons and decreases brain perfusion impairing processes of cognition and mood [Kinuya et al 1999]. Functional Magnetic resonance imaging revealed load effect of blood oxygen level dependent on the response in regions of interest in the frontal cortex (working memory), absent in subjects with SH, but present after six months of levothyroxine and improved performance in n-back task [Zhu et al 2006]. Hage & Azar 2011 review concluded that thyroid hormone supplements might help in the clinical response to antidepressive drugs. It seems sensible to screen for thyroidal problems in patients with depression that do not respond to treatment.

### 3.4 Normal thyroidal aging changes

Morphologic changes are reduction of follicle and colloidal content; but the individual remains clinical healthy. In iodine plentiful regions, age and thyroid stimulant hormone are positively related, while free thyroxine does not show a significant change with age. Anti-thyroperoxidase antibodies increase with age 8.5% in the 20-29 year age group to 22.3% in the 70-79 year age group; but antibodies are related to disease rather than senescence. [Hollowell et al 2002]. In borderline sufficient iodine, TSH decreases while free thyroxine increases with age and antithyroperoxidase antibodies show insignificant changes. Atzmon et al [2009] reported that remarkably old individuals had high serum TSH levels, and that their offspring also had higher TSH values than age-matched controls, but this might not be extrapolable to other populations.

There is decreased production and release of TSH which produces 25% less production of thyroxine, but the serum level of thyroxine does not decrease due to underactive peripheral diiodinase type 2 function; also, the level of rT3 is positively age-related [Mariotti et al 1993]. Hence the level of free Triiodothyronine decreases, but free thyroxine remains unchanged [Latrofa & Pinchera 2005]. There is no data of hypothalamic Triiodothyronine turnover to maintain adequate glucose uptake and brain perfusion in old age.

## 4. Cognition

Cognition comes from the Latin word *cognoscere*, meaning “to know”. Cognition refers to mental activities to acquire, store, retrieve and use information. The mental processes most tested to evaluate cognition decline are: orientation (time, place, person), memory (code and retrieval), visuospatial (perception and memory), attention (speed and discrimination), language (denomination, fluency, comprehension, read & write), and executive function (concept, association, praxis) [Albert et al 1988].

### 4.1 Instruments to measure cognition and mood

The screening instruments most used to measure one or more of the above cognitive processes in general or geriatric clinical settings are:

- Mood: “Geriatric Depression Scale” (GDS) Yesavage validated for screening; it is widely use in English and Spanish-speaking population [Yesavage 1986]. The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale for English speaking educated outpatients. [Zigmond & Snaith 1983]; Beck Depression Inventory is a self-administrated 21 close-ended questionnaire [Beck 1961 in Jorde et al 2006].



- Mini-Mental-State-Examination (MMSE); low sensitivity in mild cognitive impairment; low specificity in subjects with less than middle schooling [Crum et al 1993].
- Katz's "Activities of daily-living" (Katz) useful for detecting dependence [Katz et al 1970].
- Lawton's "Instrumental activities of daily-living" (LW) tests subject's functionality. It has been used to screen for dementia [Lawton et al 1969].
- Dementia Rating Scale (DRS). Its application requires specialized personnel [APA 1994].
- Brief Neuropsychological Batteries; best options for screening (a paramedic can be trained to apply them):
  - ADAS-COG, (Alzheimer's Disease Assessment Scale-Cognitive) developed in educated Anglo population. Assesses orientation, memory, language, praxis, and executive function [Kolibas E et al 2000].
  - NEUROPSI: it assesses orientation, attention, memory: coding (verbal and visuospatial) delayed memory (verbal and visuo-spatial), language, and executive function. It was validated and standardized in Latin-American population; it is also useful in illiterate subjects [Ostrosky et al 1999].
- Evaluation of just one mental process saves times but the partial information can be misleading and many still need specialized personnel to apply it. [Begin et al 2008] For attention: paced auditory serial addition task, Stroop test, concept shifting, digit spans backward; for memory: Wechsler memory scale, facial memory test, selective reminding test, word learning task. Praxis clock drawing, Rey-Osterrieth complex figure, etc.

#### 4.2 Cognitive function in elderly

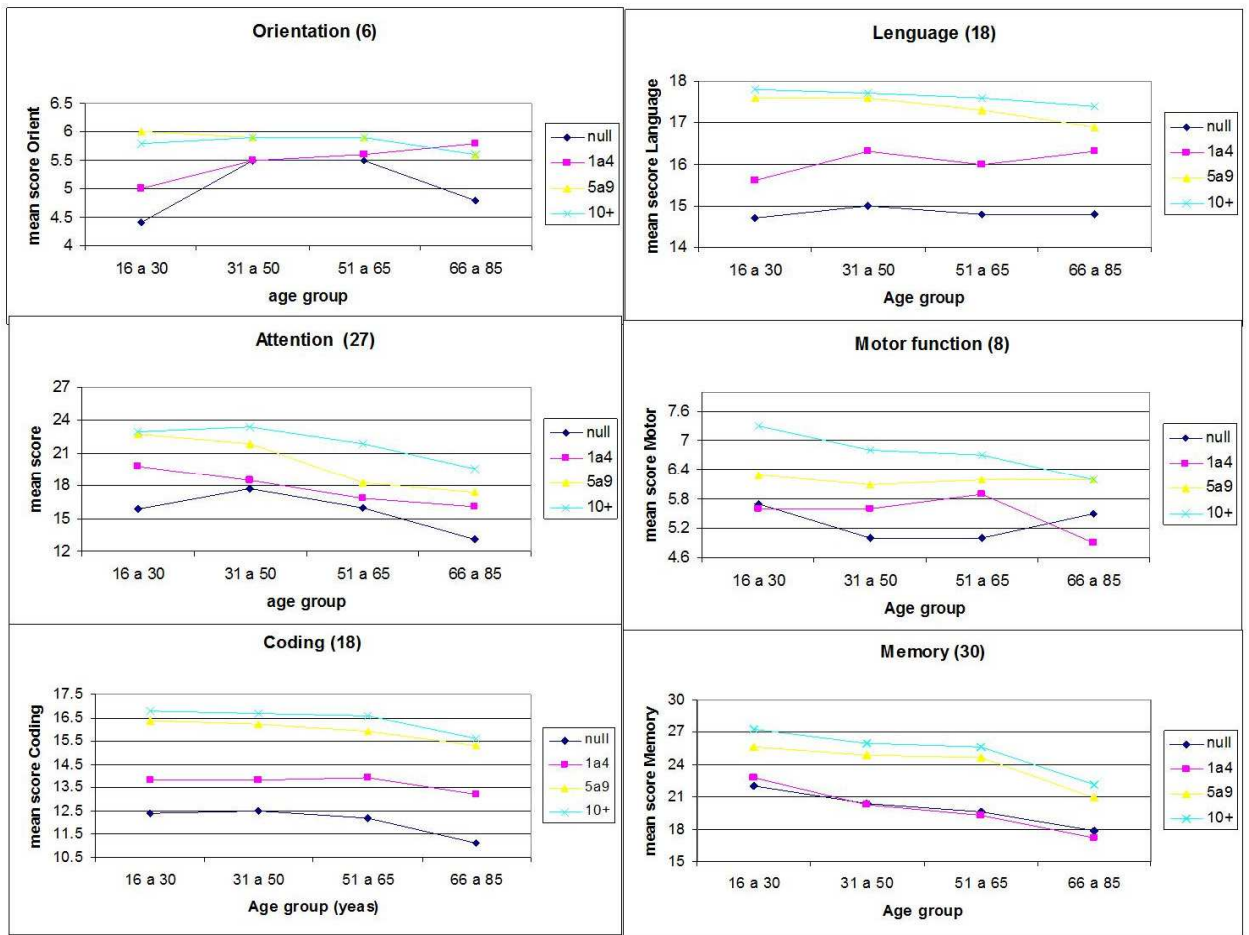
Advancing age is the first risk factor for dementia, although dementia is not part of normal aging. There is a cognitive continuum disease that can be differentiated from normal although mild cognitive impairment overlaps with both normal and disease [Petersen 2004]. Mood disorders are also overrepresented in the elderly, mainly depression: a long lasting feeling of sadness, hopeless, helpless, worthless, and aversion. Depression can affect mental activity, behavior and physical well-being. Cognitive function is affected by depression through interference in attention, memory (coding and retrieval), and decision taking.

In absence of overt disease, a decline of cognitive performance is seen in aging. The decline is associated to brain age changes: less glucose utilization, long-term potentiation and paired-pulse facilitation, protein expression, neurotransmitter levels and trophic changes. But it is not known if the above changes produce or are a product of alterations in the old brain. Freeman et al 2009 in a proteomic study in an animal model demonstrated that changes in hippocampal proteome were related to cognitive performance. They also indicated the relevance of comparing old subjects sub grouped by cognitive level; they found that 9 hippocampal proteins were related with cognitive status. Only one was detected when comparing old with young animals.

A study [Cárdenas-Ibarra et al 2006] in a randomly selected sample of 142 geriatric outpatients to determine the frequency of impaired cognition by Mini-mental test examination found that 74.5% of subjects did not completed basic schooling, thus MMSE scores above 20 instead of 26 were considered normal. Still, impaired cognition was found in 59% vs 20% of those with partial vs full basic schooling ( $X^2=4.52$ ,  $gl=1$ ,  $p<0.05$ ). The

proportion of subjects with normal cognition decreased by age; in the over 80 y/o than in the 60-69 y/o, 27.3% vs 66.6% respectively ( $X^2=15.3$ ,  $gl=6$ ,  $p<0.05$ ). Disadvantaged scores for GDS and LW were among CI and dementia ( $p<0.05$ , ANOVA); and Katz only to dementia ( $p<0.05$ , ANOVA) concluded that 31.7% were known dementia cases; another 24% had a new diagnosis of impaired cognition.

Ostrosky et al [Ardila et al 2000] used NEUROPSI in elderly urban population to describe normal cognitive decline in relation to education. They measured cognition in 806 subjects, of these 56.8% were over 50 years old. They reported different relationship patterns among education and specific cognitive domain; for example parallelism for copying a figure task, protection for word recall, confluence upwards for digits backwards, confluence downwards for semantic verbal fluency. they also found that healthy illiterate subjects showed no significant age decline in the domains of orientation, digits backward, language (repetition, naming, comprehension), and motor functions (hand position imitation, and alternating movement). Age changes are affected by education. Among the illiterate, peak performance is reached at an older age than subjects with formal education. Performance by age group and schooling on orientation, attention, coding, language motor function and memory subscales are shown in figure 3.



Adapted from ref Ardila et al 2000

Max. Score in brackets

Fig. 3. Mean scores of Six Mental Processes by Age and Schooling



In agreement with cognitive preservation notion, a study in open elderly rural population found that about 12% of the subjects scored higher than normal ranges for age and schooling supplied in the NEUROPSI manual (Figure 4), confirming that lucidity can be present in advancing age with little or no formal education [Cárdenas-Ibarra et al 2011].

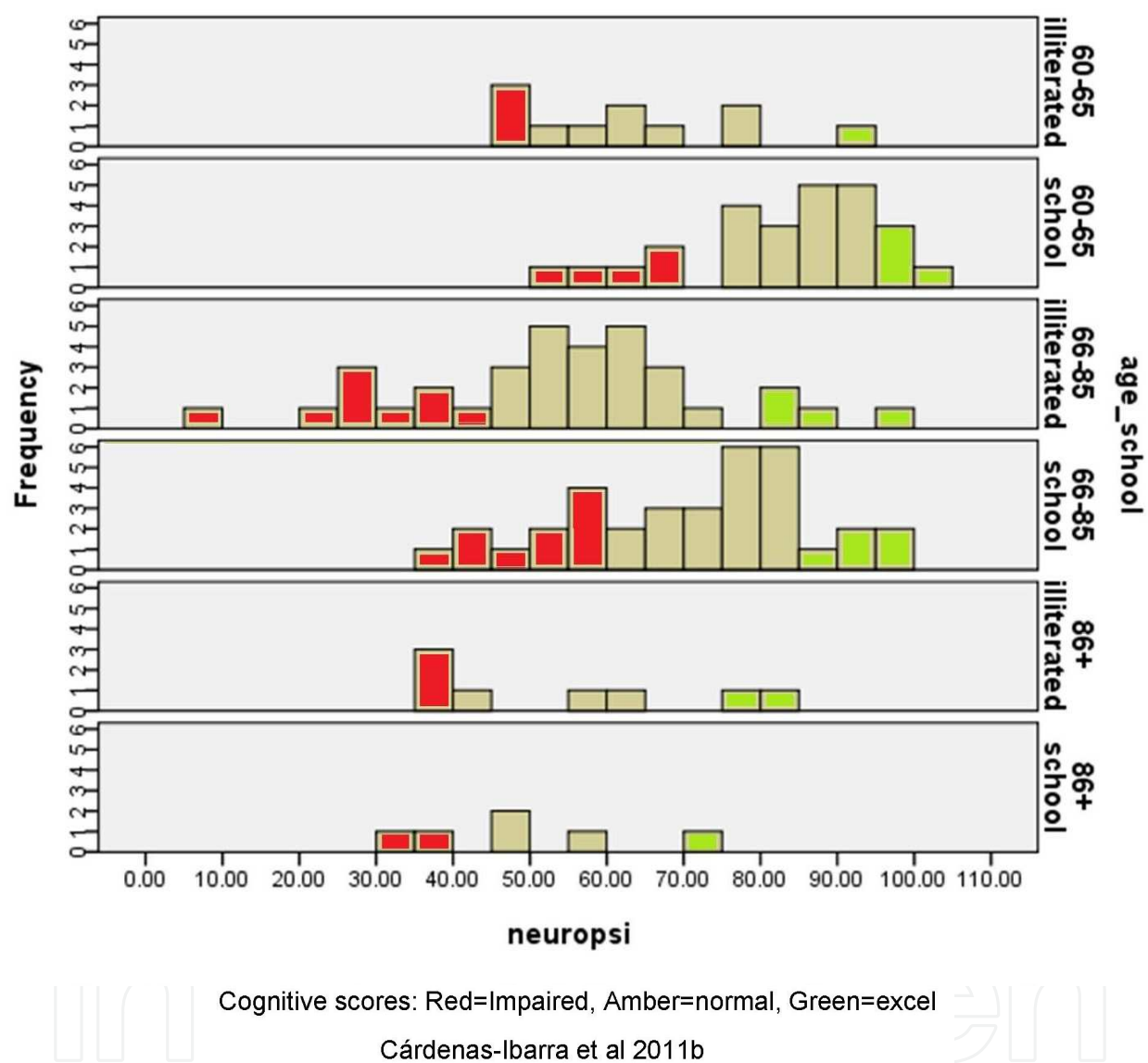


Fig. 4. Distribution of Rural Eldery's Neuropsi Score

5. Thyroidal status and cognitive function

Elderly people have the highest risk for thyroidal dysfunction as well as cognitive and mood disorders. Depression and memory complaints are excessively often in old age. In fact, depression is among the early symptoms of hypothyroidism; and memory loss relates to the level and length of thyroidal deficiency. Overall intellect is irreversibly affected in the developing brain as seen in congenital hypothyroidism.

The importance of thyroxine in the developing brain is well documented; the inability to focus and mood disturbances in the hyperthyroidal state. Also in overt hypothyroidism lack of concentration, slow thinking and depression are described. In fact, it has been identified among the reversible causes of dementia [Jamerson & Weetman 2005]. But, Roberts et al [Roberts et al 2006] did not find association; neither did Gussekloo et al [Gussekloo et al 2004] in a cohort of aging subjects. But the cognitive assessment instrument they used was the Mini-Mental-State-Examination, which is not sensible for mildly impaired cognitive function; including LW and Katz in the cognitive assessment did not increase sensitivity for dysfunction not reaching dementia. However, Gussekloo et al also reported that low free T3 was associated with rapid cognitive decline. These conflicting results demand studies with adequate assessments and well defined study groups.

A cross-sectional study [Cárdenas-Ibarra et al 2008] was set to compare the frequency of thyroid stimulating hormone (TSH)  $>4.5$  mUI/L level in 33 randomly selected geriatric outpatients without dementia versus 101 dementia cases (DSM-IV-R). High TSH was found in nine (27.3%, CI: 12.1- 42.5%) and thirty (29.7%, CI: 20.8-38.6%), respectively. It is worth mentioning that 76.7% were subclinical hypothyroidism; i.e., free thyroxine was in normal range. However, average free thyroxine levels in patients with a high TSH were significantly lower than those with a normal TSH; the free thyroxine level of most of the subclinical hypothyroidism cases were in the lower half in contrast with the Gaussian distribution of free thyroxine in those with TSH in normal range. McDermott et al [McDermott & Ridway 2001] conclude that many of subclinical hypothyroidism cases require treatment. Monzani et al [Monzani et al 1993] and Lauberg et al [Laurberg et al 2005] point out that in the presence of depression and/or cognitive decline, thyroid supplementation will improve symptoms. From the perspective of quality of life and patient care; even a modest cognitive improvement is highly desirable [Steverson 1990].

Treatment is only being recommended for patients with low range thyroxine levels; while the presence of cognitive decline, not reaching level of dementia, in subclinical hypothyroidism must be addressed in other studies to assess its potential benefit.

To circumvent MMSE sensibility, specificity, language and cultural bias, we turn to NEUROPSI, an abovementioned instrument. We found it easy to apply and calculated a Cronbach's alpha of 0.86 denoting it as a reliable instrument [Cardenas-Ibarra et al 2011b and 2011c]. NEUROPSI was used to describe the cognitive function of the elderly in a rural open population study. These results are being submitted for publication. Our team is committed to a project with an open population to determine the local overt and subclinical hypothyroidism prevalence in urban elderly. To identify enough elderly subjects with SH, besides the population section, additionally a convenient sample of elderly visiting hospital patients with unknown thyroidal status were invited to be tested. Subjects with known thyroidal problems were excluded, subjects with known dementia, arrhythmia, kidney, lung, heart severe dysfunction or cancer were also excluded. Thus, subjects identified as having subclinical hypothyroidism were invited to a clinical trial [Cárdenas-Ibarra et al 2008b] with parallel control random assignment to test thyroxine versus placebo; which has not ended yet. Meanwhile, with the baseline data comparison was made between 37 subjects with SH and 39 controls (normal thyroid function) who were age and schooling matched. Impaired cognition in subjects with SH was almost double of that found in controls, in who

the prevalence of impaired cognition was as expected. These results have only been discussed in a congress [Cárdenas-Ibarra et al 2011d]

A lower global cognitive status has been reported in hypothyroidism, specifically: attention, memory, word fluency, and psychomotor and visuospatial processes. Mixed results are reported for specific domains even in those with positive association. Moreover, improvement of cognitive impairment after levothyroxine replacement in elderly with SH has been reported. Bono et al [Bono et al 2004] reported better verbal fluency after 6 months with levothyroxine treatment. Enhanced elevating memory was reported by Monzani et al [Monzani et al 1993]. Enhanced working memory was noted after six months of thyroxine supplementation [Zhu et al 2006]. Improved response to antidepressants with levothyroxine has been documented in subjects with SH [Hage&Azar 2011]

Data on the extent of dysfunction reversibility for cognitive processes is lacking. Much work needs to be done to standardize cognitive results for comparison and uniform protocols to get homogenous groups on thyroidal function (including and excluding criteria). Long survival without cognitive enjoyment of being is pointless. The goal now is quality of life. Since the cognitive processes are central to well-being, its preservation is as important as a healthy body.

Cognitive labeling must be avoided; nevertheless timely repeated cognitive evaluation must be pursued to detect early decline and risks. Along with protocols to overcome cardiovascular risk and other preventable health problems, cognitive assessment by trained personnel to apply a neuropsychologically validated, reliable, and culturally compatible instrument must be performed. Interpretation and recommendations should be made by neuropsychologist or gerontologist consultants.

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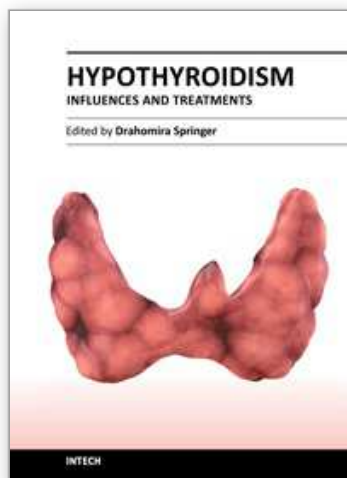
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## **Hypothyroidism - Influences and Treatments**

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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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