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Thyroid and Parathyroid Diseases and Psychiatric Disturbance

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1. Introduction

Different factors have stimulated the interest on the relationships between psychiatric conditions and endocrine disturbances in general and thyroid disease in particular (Lishman, 1998). Historically, several authors have speculated about the role of hormones and endocrine disorders in relation to psychiatric conditions, and important attention has been devoted to the role of hormones in relation to control and feedback processes in neural structures (Carroll et al. 1981). Psychiatric syndromes have consistently been described or documented in endocrine diseases (Lishman, 1998; Kathol, 2002) and may pose a real clinical challenge for psychiatrists working in general hospitals (liaison or psychosomatic psychiatrists), but the evidence in the literature to support his or her intervention is limited, according to modern criteria. The purpose of this chapter is primarily to review available data in relation to the characteristics and frequency of specific psychiatric syndromes in primary thyroid and parathyroid disturbances; issues of diagnosis and differential diagnosis; mechanisms of production of psychiatric symptomatology; and treatment issues, including response of psychiatric syndromes to treatment of the endocrinopathy and to psychotropic medication.

2. General clinical and epidemiological aspects

The most severe psychiatric syndromes in endocrine diseases are not as frequent as in the past, due to improvements in diagnosis and treatment of the hormonal disorders (Kathol, 2002). Still, a high prevalence of psychiatric disturbances has been reported in most endocrine conditions, including thyroid and parathyroid diseases. Depression and anxiety together with cognitive disorders are the most common presentations (Table 1). As expected, lifetime prevalence is even higher in several reports (Eiber et al. 1997). Cognitive impairment is rather frequent in conditions such as hyperparathyroidism, particularly among the elderly, and dementia can also be found; delirium, but also psychosis in clear consciousness, including paranoid psychosis and mania may be seen in severe endocrine

diseases. Methodological issues limit the value of the available data: case studies and case reports abound in this literature, research diagnostic criteria have rarely been used and comparison between studies is difficult due to wide differences in the samples selected and methods used. However, standardized research interviews were used in some studies reviewed here and standardized instruments in most. The emerging general picture suggests the clinical relevance of the documented psychopathology, including the depressive and anxiety syndromes, which may be very severe in diseases such as hyperthyroidism (Table 2).

	Hyperthyroidism	Hypothyroidism	Hyperpara-thyroidism	Hypopara-thyroidism
Any Disorder	53%-100%		23%-66%	
Depression	++ 30%-70%	++	++ 16%-36%	+
Apathy	"Apathetic hyperthyroidism"	+	+	
Delirium	+	+	++ 2%-5%	++
Impaired cognition	++	+++ Cretinism	++ 3%-12%	+
Dementia	Risk Factor DAT?	++	+	+/-
Others	• Overactivity • Irritability • Organic personality in the elderly	• Slowing/Lethargy • Mania (Treatment induced)	• Fatigue • Violent behaviour?	• Social withdrawl • "Neurotic" behaviour

DAT: Dementia, Alzheimer Type.
+/+++: Clinical relevance.
Brown et al., 1987; Bunevicius et al.; Casella et al., 2008; Eiber et al., 1997; Espiritu et al., 2010; Joborn et al., 1986; Kathol & Delahunt, 1986; Mooradian, 2008; Pérez- Echeverria, 1985; Velasco et al., 1999; Solin et al., 2009

Table 1. Psychiatric syndromes in thyroid and parathyroid disorders: prevalence and clinical relevance.

It was in this context that we completed a study in 100 consecutive patients admitted to the Endocrine Unit in our University hospital (Pérez-Echeverría, 1985; Lobo et al., 1988). Patients hospitalized in the Internal Medicine ward were used as a comparison group, as well as outpatient groups of both the internal medicine and the endocrine Departments. Standardized instruments, including the Clinical Interview Schedule (CIS) and the General Health Questionnaire-28 items (GHQ-28), were used throughout the study. In support of the relevance of psychiatric syndromes in these patients and specifically in hyperthyroid

patients, the prevalence of disorder at the time of admission (first three days) was significantly higher than in all the comparison groups (Table 2). Similarly, according to standardized criteria, the severity of disorder was significantly higher in the endocrine inpatients (68% had "moderate" or "severe" syndromes) than in the control groups (26,6%, 16% and 40%, respectively).

	Prevalence of any Disorder		Comments
	Admission	Discharge	Severity of psychiatric disorders is significantly higher in endocrine in-patients (++); and decreases significantly at discharge (+++)
All patients (n=100)	91%	54%	
Controls I.M. in-patients (n=30) I.M out-patients (n=100) Endocrine out-patients (n=100)	53,3% 38% 70%		
Hyperthyroidism	100%	86%	Correlations biochemical variables (any)/ Irrtability, Psychastenia.

+ Significance p< 0,05; ++ p<0,01; +++ p<0,001.
* Pérez-Echeverría, 1985; Lobo et al., 1988.

Table 2. Psychiatric disorders in endocrine in-patients and in hyperthyroidism in- patients. Prevalence and correlation with biochemical variables.*

This epidemiological documentation may be important to identify the individuals at risk for specific psychiatric syndromes in liaison programs with endocrine departments; or to search for the syndromes when the psychiatrist consults in specific endocrine patients such as the individuals with thyroid or parathyroid conditions. Screening instruments such as the Hospital Anxiety and Depression Scale (HADS) (Lloyd et al., 2000) or the General Health Questionnaire-28 Items (Lobo et al., 1988) are considered to be appropriate in endocrine patients. The sections dedicated to specific endocrine diseases suggest when the search may be mandatory, such as in cases of hyperthyroidism, where anxiety, but also depressive syndromes may be severe or in cases of cognitive deficits in hypothyroid disease. Table 1 also summarizes the authors' judgement about the clinical relevance (+ to +++) of the psychiatric syndromes in these specific endocrine conditions, according to their frequency, severity and/or special characteristics.

Non-biological hypotheses have been formulated to explain depressive or anxiety syndromes when there is considerable stress and psychosocial difficulties associated with conditions such as hyperthyroidism. However, the authors suggest that the "organic", endocrine origin of the psychiatric syndromes in these patients is most important. The following data support this contention: studies documenting a higher prevalence of psychiatric disturbance than in comparable general population samples (Mayou et al., 1991) and, in particular, in medical samples of comparable severity of the medical disorder (Pérez-Echeverría, 1985); both clinical practice and studies documenting that the prevalence of psychiatric disorder and/or its severity decreases after successful treatment of the endocrine condition (Pérez-Echeverría, 1985). Although some reports are discrepant (Joborn et al., 1988), special support comes from studies documenting statistically significant correlations

between severity of psychiatric symptoms/syndromes and hormonal levels or biological parameters (Table 2) (Pérez-Echeverría, 1985; Lobo et al., 1988; Linder et al., 1988).

In relation to diagnosis the dictum of experienced, anonymous liaison psychiatrists seem to be quite appropriate here: "In the general hospital, every psychiatric symptom is "organic"…unless you can document otherwise". In taking the history of rather atypical psychiatric presentations, the clinical psychiatrist should include questions related to the thyroid or parathyroid disorder, particularly when there are signs and /or symptoms suggesting the endocrine abnormality (table 3). If the suggestions are well founded, he or she should also perform at least focal physical examinations to document the presence or absence of endocrine signs. In these cases, but not routinely, he or she should also indicate tests of endocrine function.

Endocrinopathy	Symptoms	Signs
Hyperthyroidism	Diaphoresis Heat intolerance Oligomenorrhea	Exophthalmos Tachycardia Arrytmia (in elderly) Tremor
Hypothyroidism	Cold intolerance Menorrhagia	Goiter Slow relaxing reflexes Myxedema
Hyperparathyroidism	Nausea Muscular weakness (proximal) Abdominal pain	Hypertension
Hypoparathyroidism	Muscle spams Paresthesias	Choreiform movements Chvostek´s sign Trousseau´s sign

Table 3. Somatic symptoms and signs suggesting a thyroid disease.

According to the International Classification of Diseases (10th edition or ICD-10), the diagnosis of an "organic" psychiatric syndrome of thyroid or parathyroid origin in a given patient should be considered when the presenting syndrome is known to be associated with the specific endocrine disease, and is supported by the absence of suggestive evidence of an alternative cause of the mental syndrome. Specifically, the "organic" psychiatric syndrome in cases of thyroid or parathyroid disease is supported when: a) the psychiatric symptoms, the course of illness and/or the age of presentation are atypical for a primary psychiatric disorder; b) there is no family or personal history of the psychiatric condition; c) no precipitating stress is known; d) there is a temporal relationship between the onset of the psychiatric and the endocrine symptoms. The challenge for the consulting psychiatrist is to make explicit the diagnosis of the endocrine origin of the psychiatric syndrome early in the procedure, before his or her diagnosis is confirmed after observing that the syndrome disappears following the removal or improvement of the underlying endocrine disorder.

Most psychiatric syndromes in endocrine patients resolve with standard treatment of the endocrine disease, and this applies to thyroid and parathyroid disorders. However, when symptoms are particularly severe or life-threatening; or when they last longer than reasonably expected (table 4), good clinical sense suggests the importance of psychiatric

treatment. Well-controlled studies are lacking, but syndrome specific medication is usually recommended, as well as supportive psychotherapy and, recently, cognitive-behavioural psychotherapy in cases of abnormal illness behaviour. Relevant clinical factors, and exceptions to these general norms will now be discussed for the specific endocrine diseases.

Endocrinophaty	**Psychiatric syndromes**	**Treat if psychiatric syndromes persist after adequate endocrine treatment***
Hyperthyroidism	Anxiety (Depression)	>4 weeks or extreme severity
Hypothyroidism	Depression/ Anxiety	>4 weeks
Hyperparathyroidism		>4 weeks
Hypoparathyroidism	Depression	?

*Treatment should also be recommended when syndromes are very severe or life threatening.
Lobo et al., 2007.

Table 4. Treatment of psychiatric syndromes with psychotropic medications in endocrine patients.

3. Thyroid disease and the "clustering" of somatic and psychiatric morbidity

In relation to epidemiology, we have recently studied the role of thyroid disease in the clustering of somatic and psychiatric morbidity in the elderly population. Pioneer studies by authors such as Eastwood and Trevelyan found that psychiatric and somatic illnesses tend to "cluster" in a limited group of individuals in the general population. The first author speculated about vulnerability to illness, and research in this area was considered "the main task for epidemiology in the field of psychosomatic medicine". Since then, a considerable number of studies have approached this subject, and some authors argued that the association between somatic and psychiatric morbidity is well established. However, previous research was conducted primarily in clinical samples, and not in representative, general population samples (Scott et al., 2007). Furthermore, Eastwood's statement (Eastwood, 1989) suggesting that the association of general psychiatric and somatic morbidity has not been convincingly shown in the elderly population is still valid. Given the relationships between comorbidity and frailty described in the elderly, as well as the negative consequences (Slaets, 2006), studies in the older population were considered to be a research priority.

The study we conducted was part of the ZARADEMP Project, an epidemiological enquiry to document in the elderly community the prevalence, incidence and risk factors of dementia, depression and psychiatric morbidity, as well as their association with somatic morbidity (Lobo et al., 2005). The main objective in this specific study was to try to confirm in the elderly population the tendency of general psychiatric morbidity to cluster with general

somatic morbidity. In view of the considerable prevalence of thyroid disease in the elderly and the documented association between thyroid disturbances and psychopathology, we also set as an objective to study the role of thyroid disease in the clustering.

The site of the study was Zaragoza, a capital concentrating 622,371 inhabitants (fifth city in Spain) or 51% the population of the historical kingdom of Aragón. The objectives and general methodology of the ZARADEMP Project have been previously described (Lobo et al., 2005). It is a longitudinal, epidemiological study with four waves, and Wave I (*ZARADEMP I*) was relevant for this report (Figure 1). It was the baseline, cross-sectional study, intended to document the prevalence and distribution of somatic and psychiatric morbidity and of comorbidity. Participating individuals have been followed up in Waves II, III and IV (or *ZARADEMP II, III* and *IV*) to eventually study the influence of hypothesized risk factors for incident cases.

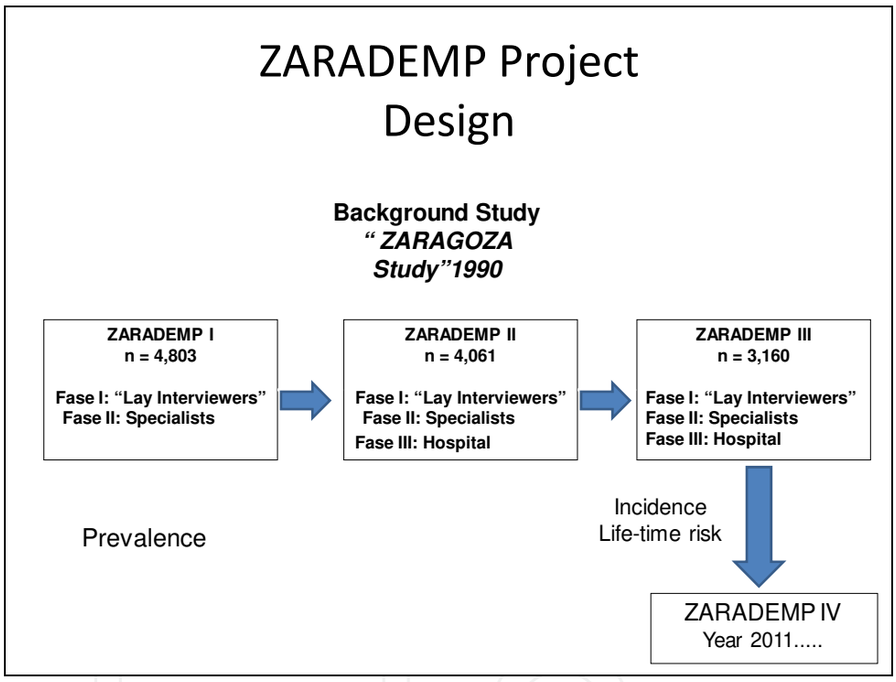


Fig. 1.

A stratified, random sample of 4,803 individuals aged 55 and over was selected for the baseline study. The elderly were assessed with standardized, Spanish versions of instruments, including the Geriatric Mental State (GMS)-AGECAT (Lobo et al, 2005). The GMS is a semistructured standardized clinical interview used for assessing the mental state of elderly people. A computerized diagnostic program, *AGECAT* is available to be applied to it. This interview is also a syndrome case finding instrument, the *GMS-B* threshold scores discriminating between "non-cases", "subcases" and "cases". We also used the *History and Aetiology Schedule (HAS)*, a standardized method of collecting history and etiology data from an informant, or directly from the respondent when he or she was judged to be reliable. Psychiatric cases were diagnosed according to GMS-AGECAT criteria, and somatic morbidity, and specifically thyroid disease was documented with the EURODEM Risk Factors Questionnaire.

	Cases (*n*)	Prevalence (%)	95% CI
55 – 64 years (*n*=1088)	29	2,7	1.8 – 3,8
65 – 74 years (*n*=1702)	66	3,9	3.0 – 4,9
75 – 84 years (*n*=1097)	34	3,1	2.2 – 4,3
≥85 years	21	2,3	1,4 – 3,5

Table 5. Prevalence of thyroid disease in community-dwelling individuals aged ≥ 55 years (distribution by age group).

The relevant results for this chapter may be summarized as follows. As expected, the prevalence of somatic disease tended to increase with age in most categories (Table 4). However, it decreased after the age of 84 in several categories, including thyroid disease. General comorbidity clustered in 19.9% of the elderly when hypertension was removed from the somatic conditions category, 33.5% of the sample remaining free of both somatic and psychiatric illness. General comorbidity was associated with age, female sex and limited education, but did not increase systematically with age. The frequency of psychiatric illness was higher among the somatic cases than among non-cases, and the frequency of somatic morbidity among the psychiatric cases was higher than among non-cases. This association between somatic and psychiatric morbidity remained statistically significant after controlling for age, sex and education (OR= 1.61, IC 1.38-1.88). Most somatic categories were associated with psychiatric illness but, adjusting for demographic variables and individual somatic illnesses, the association remained statistically significant only for cerebro-vascular accidents, CVA's (OR= 1,47, CI 1,09-1,98) and thyroid disease OR= 1,67, CI 1,10-2,54).

	Without psychiatric morbidity (*n*=2211)		
	Cases (*n*)	**Prevalence (%)**	**95% CI**
Thyroid disease	46	2,1	1,5 – 2,8
	Psychiatric morbidity (*n*=2592)		
Thyroid disease	**Cases (*n*)**	**Prevalence (%)**	**95% CI**
	104	4.0	3,3 – 4,8

Table 6. Prevalence of thyroid disease in patients with or without psychiatric morbidity in community-dwelling individuals aged ≥ 55 years.

This was the first study documenting in the (predominantly) elderly population that there is a positive and statistically significant association of general somatic and general psychiatric morbidity. Furthermore, in support of the initial hypothesis our results suggest that thyroid disease may have more weight in this association.

4. Hyperthyroidism

Hyperthyroidism is usually accompanied by physiological symptoms such as sweating, heat intolerance and muscle weakness. However, also common symptoms such as nervousness, fatigue or weight lost may be confounded for primary psychiatric symptoms. Graves´ disease, an autosomal disorder, is the most frequent cause of hyperthyroidism or thyrotoxicosis. While proponents of psychosomatic theories suggested in the last century that an important etiological factor for hyperthyroidism was the presence of psychological conflicts, there is very slight evidence to support the theory. Clinicians in Europe, certainly do not support this conjecture, as shown in the E.C.L.W. study (Huyse et al, 2000). No cases of this endocrine condition were referred for psychiatric consult among 15,000 medical inpatients seen in psychosomatic psychiatry services because of psychopathological reasons (Lobo et al , 1992). However, there is some evidence to support the idea that stress can precipitate the hyperthyroidism (Santos et al, 2002) or complicate the clinical course (Fukao et al , 2003).

The study by Pérez- Echeverría was one of the early investigations reporting the prevalence of psychiatric disturbance among hyperthyroid patients. Only few more studies have reported prevalence data since then. (Trzepacz et al., 1988; Bunevicius et al., 2005). The study by Stern conducted in members of a patients` foundation documented, as expected, that anxiety (72%) and irritability (78%) were the commonest symptoms (Stern et al., 1996).

Psychological disturbance of some degree is universal in Graves` disease (Pérez-Echeverría et al., 1986; Stern et al., 1996), and may delay the diagnosis of the hormonal disorder. Anxiety is most frequently reported, but also depressive syndromes. Rather unusual symptoms may accompany these psychopathological syndromes such as overactivity and restlessness or hyperacuity of perception and increased reaction to noise stimulus. It is the unusual presentation of anxiety (or depression) that may help the physician to differentiate the endocrine disorder from primary affective disturbance. Emotional lability may also be apparent, and both anxiety and irritability may be quite severe and stimulate relatively understandable behavior such as impatience and intolerance of frustration. While depression is not so common, it may be quite prominent and be accompanied by weakness, fatigue and other somatic symptoms. Psychomotor retardation is rare, the exception being the subgroup of elderly patients. "Apathetic hyperthyroidism" has been described in this age group (Mooradian & Arshg, 2008), and some of these cases may progress to stupor and coma.

Classical studies suggested that up to 20% of Graves` disease patients might have some kind of psychosis. However, as discussed by Lishman , there was probably a selection bias (Lishman, 1998). Delirium-type, acute organic syndromes are now rare because of advances in medical treatment. However, delirium in such cases may be a medical emergency. Affective psychoses have been described (Brownlie et al., 2000; Marian et al, 2009), but also schizophrenia-type psychoses, most commonly with paranoid ideation. Organic personality disorder has been described, particularly among the apathetic elderly. Distraibility and over-arousal have also been reported, sometimes leading to persistent cognitive impairment, which may continue even after the patient is euthyroid (Stern et al, 1996). Specific cognitive difficulties in hyperthyroid patient have been described, such as deterioration of memory, concentration or visuomotor speed (MacCrimmon et al., 1979; Álvarez et al., 1983).

The possibility that subclinical hyperthyroidism in the elderly increases the risk of Alzheimer´s disease has been suggested (Kalmijn, 2001) and we are now involved in a large longitudinal study to assess specific risks of dementia, including thyroid disease, in a 15-year follow-up study ingrained in the ZARADEMP project. (Lobo, 2005).

The initial symptoms in hyperthyroidism may be quite similar to anxiety disorders, but the described, unusual symptoms of anxiety may alert the clinicians (Kathol et al., 1986). Other symptoms that should alert the physicians are the preference for cold and intolerance to heat, or loss of weight coupled with increased appetite. A careful medical history and examination are mandatory in such cases and the laboratory test would usually give unequivocal answers to the diagnostic difficulties. An accelerated pulse during sleep or cognitive difficulties are also considered to suggest the diagnosis of hyperthyroidism in such cases (Hall et al., 1979; Mackenzie,1988). To help in the differential diagnosis some specific scales have been developed (Iacovides et al, 2000). Transient thyroid hormone elevations, usually mild, may occur in approximately 10% of psychiatric inpatients, but should not be diagnosed of hyperthyroidism. Thyroid abnormalities have also been documented in some studies in primary affective disorders (Oomen et al., 1996). However, later studies did not replicate the findings (Engum et al., 2002) and the possibility of factors of confusion such as the use of psychotropic medication has been considered. Other clinical situations may mimic the thyroid condition before the laboratory results are available, such as abuse of stimulants or drug intoxications. However, the nervousness and emotional lability in hyperthyroid patients may be wrongly diagnosed as alcohol abuse or abstinence.

Subclinical hyperthyroidism has also stirred interest in recent studies. The clinical interest derives from the fact that it has been associated with cognitive deterioration and dementia in the elderly (Kalmijn,2000;Ceresini,2009), both in cross-sectional and longitudinal studies.

While the clinical and epidemiological studies reviewed support the association of hyperthyroid function with psychopathological disturbance, the causal mechanisms are not clear (Bunevicius et al., 2006). One study suggested that the active thyroid hormone (T3) influenced mental performance in healthy subjects (Kathmann et al., 1994). The individuals overestimated time intervals and increased their word fluency, but no other cognitive problems were detected. Pérez-Echeverría (1985) and Lobo et al (1988) documented direct, convincing correlations between abnormal levels of thyroid hormones and psychopathology. The abnormal psychological phenomenon seemed to be directly related to the endocrine disturbance, since non-endocrine medical patients in the same ward, and with similar levels of illness severity had lower levels of psychopathology. Furthermore, in support of the direct effect of thyroid hormones elevation on the psychopathology, anxiety, depression and related phenomenon improved with "treatment as usual", when hormonal levels returned to normal, at the time of hospital discharge.

In general, there is a good resolution of anxiety and depression with antithyroid treatment alone, unless there is previous psychiatric history (Kathol et al., 1986). Beta-blockers such as propanolol are also considered to be effective in cases of anxiety (Trzepacz et al, 1988). However, recovery may be slow and reduced psychological well-being has been reported in a considerable proportion of "remitted" hyperthyroidism (Pérez-Echeverría, 1985). Bunevicius also reported persistent mood and anxiety symptoms in treated hyperthyroidism (Bunevicius et al., 2005). Psychosis may occur or be exacerbated by antithyroid medication. Low potency

neuroleptics such as haloperidol and perphenazine have been reported, including symptoms resembling thyroid storm and malignant neuroleptic syndrome. There is a limited clinical experience with the new generation of neuroleptics. Finally, treatment of depression is recommended if psychopathological symptoms are severe or persistent.

5. Hypothyroidism

Classical symptoms of hypothyroidism include fatigue and weakness, somnolence, weight gain, constipation and cold intolerance. However, other common symptoms may suggest primary psychiatric disease and include lethargy, progressive slowing, diminished initiative and impaired concentration and memory. (Kornstein et al., 2000).

Congenital hypothyroidism is also well known, and usually occurs as the consequence of thyroid dysgenesis, and more rarely as the result of inherited defects in the synthesis of thyroid hormone. The cretinism syndrome emerges if hypothyroidism is untreated. This syndrome is characterized by mental retardation, aside from the classical somatic and neurological signs. Screening programs for hypothyroidism at birth are now mandatory to prevent this severe condition. (American Academy of Pediatrics, 2006), since early treatment should lead to normal intellectual development. The most frequent cause of adult hypothyroidism is Hashimoto´s thyroiditis or autoimmune thyroiditis. Treatment of Grave´s disease with radioactive iodine may also lead to hypothyroidism, but an important iatrogenic cause in psychiatric patients is the side effect of lithium, particularly in vulnerable individuals such as women or rapid cyclers.

There are no good prevalence studies of psychiatric disturbance in hypothyroid patients, but the main psychiatric syndromes have been described in case reports and/or clinical samples. Depression and, to a lesser extent anxiety (Sait Gönen et al., 2004), occur rather frequently, even with moderate hormonal deficits, and could be observed as early as few weeks after the onset of the condition. Previous history of affective disorder is considered to increase the risk. The depressive syndromes may mimic primary affective disorder, particularly in old women, and may need the checking of hormonal levels for the differential diagnosis. The initial symptoms of hypothyroidism mimic the somatic symptoms of depression, and may include low energy, fatigue, apathy, low appetite and sleep disturbance. Marked irritability and labiliy of mood may alert to the presence of atypical syndromes, suggesting an organic condition. Thyroid replacement is required in such cases and is usually effective, although depression persists in a proportion of patients

A special emphasis should be placed in subclinical hypothyroidism. In this controversial condition, which is sometimes classified as grade 2 and grade 3 hypothyroidism, there may be minimal clinical, traditional symptoms, and thyroid levels may be normal, but with increased TSH. The relevance of subclinical hypothyroidism is derived from the fact that depression is common and may severely affect quality of life. (Haggerty et al., 1993; Dermatini et al., 2010). In the study by Chueire et al. (2003), using standardized instruments and psychiatric diagnostic citeria, they found depression among 49% of subclinical hypothyroid, elderly patients. The same authors have recently reported that depression in such patients is more frequent than among patients with overt hyperthyroidism (Chueire et al., 2007). Furthermore, they conclude that subclinical hypothyroidism increases more than four times the risk of depression, and highlight the relevance of thyroid screening tests in

the elderly. Treatment of depression in such cases is recommended (Carvalho et al., 2009), but may be frustrating (Hendrick et al., 1998). It has been suggested that subclinical hypothyroidism is rather common in the general population, particularly in the adult and elderly women, but may go undetected and untreated. Screening tests of hormonal levels may be crucial in doubtful cases.

Delirium has been observed in approximately 10% of severe cases of hypothyroidism, and organic delusional syndromes have been documented in some case reports. "Mixedema madness", a psychosis in untreated cases of hypothyroidism was described before the standard use of thyroid function tests (Kudrjavcev, 1978), but is quite rare now. Some authors have called "Hashimoto`s encephalopathy" the clinical picture of delirium with focal neurological signs and seizures. It has been considered to be associated with high levels of serum antithyroid antibodies, but the psychopathological symptoms probably overlap with delirium of different etiologies (Schiess & Pardo, 2008).

Longstanding hypothyroidism may end up in a marked dementia syndrome. Before, cognitive disturbance may be apparent (Samuels et al, 2008). Memory deterioration is common, but may be accompanied by impairment of other cognitive functions. While some cognitive difficulties may be associated with the depressive syndromes, some authors have reported independent, cognitive difficulties (Burmeister et al.,2001). Mild hypothyroidism has also been associated with mild cognitive difficulties (Bunevicius et al, 1999; Miller et al, 2007). While most cases of cognitive disturbance improve with hormonal treatment, some studies reported negative results (Walsh et al., 2003). Hypothyroidism used to be considered one example of reversible dementia with appropriate hormonal treatment (Cummings et al., 1980). However, most authors doubt about its effectiveness in well established cases of dementia (Clarnette & Patterson, 1994; Lobo et al., 2010).

Present knowledge about the effects of thyroid hormones in the central nervous system suggests the critical influence in brain development, and probably a direct role in adult brain homeostasis. Multiple isolated effects have been described, including a modulation of noradrenergic, serotonergic, and dopaminergic receptor function, and an influence on second messenger, calcium homeostasis, axonal transport mechanisms, and morphology. However, both the biochemical mechanisms and the physiological relevance are poorly understood.

Even minor changes in thyroid hormone may induce important affective changes (Bauer et al., 1990). However, the connections between this hormone and primary affective disorder remain controversial .Some authors conclude that depressed patients are basically euthyroid (Baumgartner, 1993). Thyroid autoimmunity has been reported in bipolar disorder (Kupka et al., 2002) but the finding needs replication. Special consideration merit the cases of hypothyroidism seen in 10% of patients treated with lithium. Disregulation in the hypothalamic-pituitary-thyroid axis is commonly linked to primary affective disorders (Hendrick, 1998; Engum et al., 2002). Close to 50% of depressive patients with major depression have a positive, blunted TSH response to TRH. While these findings support the connection between thyroid disorder and primary affective disorder (Stipcevic et al., 2008), other authors conclude that depressed patients are basically euthyroid (Baumgartner et al., 1993). New studies are considered to be needed to clarify this relationship.

The neuropsychiatric symptoms of hypothyroidism maybe the first to recover, probably in few days, with adequate hormonal replacement. Slow correction is usually recommended,

particularly in the elderly, because the risk of cardiac or psychiatric dysfunction. Short periods of mania or hypomania may occur during the treatment, but will typically subside during the replacement. Moderate doses of neuroleptics are usually well tolerated in cases of psychosis, but these cases may not recover totally.

6. Hyperparathyroidism

Primary hyperparathyroidism is often caused by parathyroid adenomas (Bresler et al., 2002). It is characterized by the presence of elevated parathyroid hormone, elevated calcium and hypophosphatemia. Hyperparathyroidism may lead to renal calculus and bone disease. Classical symptoms of hypercalcemia, such as anorexia, lethargy or fatigue, may be attributed to primary psychiatric disease. The symptoms may be insidious, but gradually increase and may lead to coma. The early recognition of hyperparathyroidism is now more common, due to the use of routine biochemical screening.

The prevalence of hyperparathyroidism is considered to be around 0.1%, and increases both in women and with age. Radiation of head and neck may produce this condition, but is also a known consequence of lithium therapy in psychiatric patients (Kingsbury & Salzman, 1993). The common use of lithium in long term treatment of affective disorders should alert physicians about side effects, since hyperparathyroidism symptoms may be confounded for affective psychopathology. The determination of serum calcium levels may be considered in the protocol of atypical psychiatric presentations of cognitive difficulties or affective symptoms, particularly depression. Calcium levels may also be monitored in patients in lithium treatment, since hypercalcemia as a secondary affect has been reported and may be confounded with the relapse of affective symptoms (Pieri-Balandraud et al., 2001).The EEG is an important diagnostic tool in such cases, since the slow activity accompanied by frontal delta paroxysms are quite suggestive of hypercalcemia.

Lithium is considered to alter the feedback inhibition, and the set point of the parathyroid gland. It also stimulates hormone secretion. The lower incidence of stones in lithium-induced hypercalcemia, contrary to what is observed in primary hyperparathyroidism, has been considered to be the effect of interference of lithium in cAMP production (Kingsburg et al 1993). Hypercalcemia should be considered in the differential diagnosis of bipolar, lithium-treated patients with unusual psychopathological symptoms and/or resistance to treatment. Mild calcium elevations may be managed medically. However, cessation of lithium frequently does not correct the hyperparathyrodism and the parathyroidectomy may be necessary.

Psychopathological symptoms are considered to be quite common in hyperparathyroidism (Brown et al 1987). However, most studies are derived from case reports or were completed in short samples and standardized methods of assessment were rarely used (White et al 1996). Depressive and anxiety syndromes have been most frequently described (Joborn et al., 1986; Birder, 1988). Nevertheless, the preponderance of symptoms such as apathy, fatigue, irritability or neuro-vegetative symptoms should alert the physician. Cognitive symptoms of depression are usually not as severe as in primary affective disorder, the exception being the elderly patients (Linder et al 1988). Overt delirium has frequently been observed when hypercalcemia is high (above 16 mg/dl), and coma has been reported with serum levels above 19 mg/dl (Petersen 1968). In the elderly, cognitive disorders and eventually dementing syndromes may occur if the endocrine disorder persists (Joborn et al.,

1986). Psychosis has rarely been described, but Joborn et al reported paranoid ideas and hallucinations in their study and Bresler et al (2000) reported violent behavior, included attempted mass murder in a case of paranoid ideation in clear consciousness. More chronic cases, aside from cognitive disorder, have been associated with personality changes leading to withdrawn behavior and seclusion.

The pathogenesis of psychiatric syndromes in hyperparathyroidism may be explained by the hipercalcemia itself, since similar symptoms have been reported in different etiologies. The calcium ions are considered to be crucial in normal neurotransmission. High calcium levels have been associated with abnormal CSF concentrations of monoamine metabolites, such as 5-hydroxy-indoleacetic acid (5-HIAA) found in primary hyperparathyroid patients. Calcium levels correlated with depressive symptoms and returned to normal after parathyroid surgery (Joborn et al 1988). Affective symptoms in primary hyperparathyroidism have also been reported to correlate with abnormal levels of both cortisol and melatonin, which improve after successful surgery (Linder et al 1988). Nevertheless, other studies did not find a correlation of psychopathology and calcium levels. (Joborn et al 1988; White et al., 1996). The influence of hypomagnesemia and hypophosphoremia, as well as the parathormone itself and vitamin B have also been hypothesized to influence the pathogenesis of psychiatric symptoms in hyperparathyroidism.

Most studies suggest that psychiatric symptoms in hyperparathyroidism significantly improve or disappear after successful surgical treatment, unless the endocrine disorder is chronic. (Roman and Sosa 2007, Casella et al., 2008, Espiritu, 2010). Joborn reported that improvement may be observed in few days, and the same authors have shown that approximately half the patients significantly improved in a follow-up period of several years (Joborn et al., 1988). Wilheim et al 2004 observed that both depression and quality of life improved in a similar proportion of patients. However, Chiang (Chiang et al .,2005), did not find significant differences in neuropsychological performance between patients undergoing parathyroidectomy and the controls. On the basis of significant improvement in depressive symptoms and quality of life in patients with mild hypercalcemia, parathyroidectomy has been suggested in the management of asymptomatic hyperparathyroidism (Wilheim et al., 2004). However, in view of rather conflicting results, we have previously recommended a conservative treatment in asymptomatic cases or cases with mild symptoms (Lobo et al.,1992).

7. Hypoparathyroidism

Hypoparathyroidism can occur as a primary form with inadequate parathyroid hormone secretion, but the commonest cause is the removal of, or interference with blood supply in the parathyroid gland during neck surgery. The affected patients present with hypocalcemia, which causes neuromuscular irritability.

Muscle cramps and paresthesias are typical symptoms, but facial grimacing and seizures may occur, suggesting a neuro-psychiatric condition. In a classical study, Denko & Kaelbing (1962) and similarly other authors (Velasco et al., 1999), reported a high frequency of cognitive disorder, but a considerable proportion of patients had psychotic symptoms, including hallucinations and catatonic stupor. However, the systematic study of psychiatric symptoms in hyperparathyroid patients is sparse. Reviews of this subject have concluded

that approximately half the cases due to surgery had psychopathological symptoms, and the frequency might be even higher in idiopathic cases (Lishman 1998). Delirium has been commonly reported in the post-surgery period, as might be expected in relation to abrupt biochemical disturbances.

In non-acute idiopathic hypoparathyroidism, emotional lability and anxious syndromes have been described, and also depressive syndromes. Cognitive difficulties and even dementia syndromes have also been reported in these patients. The emotional lability may coincide with fluctuating, neurotic kind of minor symptoms and behavior. Irritability, nervousness and socially inadequate behavior are among the symptoms most often described. On the contrary the reviews suggest that psychotic syndromes in clear conscientious are uncommon. Chronic cases of hypoparathyroidism may eventually lead to neurological and cognitive deficits. They are considered to be related to intracranial calcification, and in such cases they are irreversible (Kowdley et al., 1999).

Hypoparathyroidism is also frequent in the velocardiofacial syndrome (22q.11.2 deletion syndrome), in wich attentional and behavioral disorders are common among children, and schizophreniform and bipolar disorders are common in adults. (Jolin et al., 2009). In the pathogenesis of this condition, the hypocalcemia itself is considered to be the main agent. Patients with calcium levels in the lower limit of normal may be relatively asymptomatic ("partial parathyroid insufficiency"), but psychopathological symptoms such as depression and anxiety may appear episodically, precipitated by calcium deprivation. In an early study, Fourman et al (1967) reported the efficacy of calcium versus placebo in a double blind clinical trial to improve the psychopathological symptoms.

An important issue, similarly to other endocrine disorders, is the failure to detect and diagnose this condition. This is particularly relevant in cases of anxiety resistant to treatment. Since anxiety can provoke hyperventilation, tetany in hypoparathyroid patients may be precipitated (Fourman et al., 1967). In doubtful cases, calcium and phosphorus levels should be monitored, especially in patients operated in the neck. The presenting signs of hypoparathyroidism may be an epileptic crisis or an abnormal EEG.

Psychiatric syndromes in non-chronic hypoparathyroidism patients are treatable with calcium supplements and vitamin D. (Velasco et al., 1999). Depressive and anxiety syndromes have a good response, unless they are severe. The benzodiazepines are considered to be effective in cases of anxiety. Improvement in cognitive syndromes has also been reported in a considerable proportion of patients, the exception being the severe cases and the dementia syndromes. There is some report about the susceptibility of these patients to the parkinsonian side effects of neuroleptics. However, Pratty et al (1986) did not confirm this unwanted side effect.

8. Conclusions

This chapter reviews available data in relation to the characteristics and frequency of psychiatric syndromes in primary thyroid and parathyroid disturbances, including the contributions of the authors. It also reviews issues of diagnosis and differential diagnosis; mechanisms of production of psychiatric symptomatology; and treatment issues, including response of psychiatric syndromes to treatment of the endocrinopathy and to psychotropic medication. The most severe psychiatric syndromes in endocrine diseases are not as

frequent as in the past, due to improvements in diagnosis and treatment of the hormonal disorders, but still, a high prevalence of psychiatric disturbances has been reported in both thyroid and parathyroid diseases. Depression and anxiety together with cognitive disorders are the most common presentations. Cognitive impairment is frequent among the elderly, and dementia can also be found; delirium, but also psychosis in clear consciousness, including paranoid psychosis and mania may be seen in severe endocrinopaties. Methodological issues limit the value of the available data. However, standardized research interviews were used in some studies reviewed here and standardized instruments in most. The emerging general picture suggests the clinical relevance of the documented psychopathology, which may be very severe in some cases. The authors review their contribution in two relevant, epidemiological type of studies. In the first one, neat correlations were documented between hormonal disturbances and psychopathology in patients hospitalized because of hyperthyroid conditions. In the second study, during the ZARADEMP project, the clustering of somatic and psychiatric morbidity was documented in a large, community sample of individuals aged 55 years or more, and thyroid disease was considered to have specific weight in this association.

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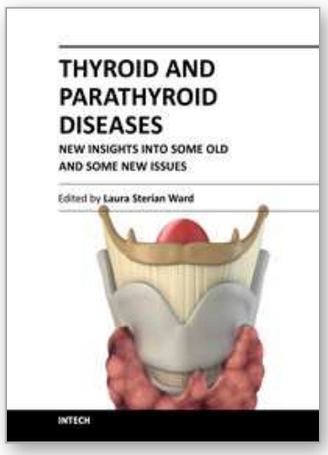
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This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

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