

RESEARCH

Central hypothyroidism related to antipsychotic and antidepressant medications: an observational study and literature review

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Abstract

Objective: To investigate the final diagnosis and clinical outcome of patients referred to endocrinology in our district general hospital with biochemical isolated central hypothyroidism (CeH), and whether there is an association between this biochemical picture and treatment with antidepressant and antipsychotic medications.

Methods: We performed a retrospective observational study of patients referred to endocrinology with unexplained biochemical isolated CeH over a 5-year period.

Results: Of the 29 patients included in the study, 4 were found to have a partially empty or empty sella and 1 to have a bulky pituitary gland which was deemed to be an incidental radiological finding. No patients had any clinically significant pathology. On reviewing their medications, 18/29 (62%) were found to be on psychotropic medications.

Conclusions: Our study suggests a relationship between patients on psychotropic medications and biochemical isolated CeH, an association only described in a very limited amount of literature prior to this. The mechanism behind this may be suppression of TSH secretion via antagonism of the dopamine-serotonergic pathway. Determining a correlation between psychotropic medications and isolated CeH could lead to the avoidance of further radiological investigations and unnecessary anxiety for patients. However, a larger observational study is needed to provide further evidence to support/refute our finding.

Key Words

- ▶ central hypothyroidism
- ▶ antipsychotics
- ▶ antidepressants
- ▶ psychotropic medication

Introduction

Central hypothyroidism (CeH) is a heterogeneous disorder characterised by reduced thyroid hormone (TH) secretion due to pituitary and/or hypothalamic disorders. There is insufficient stimulation of TH secretion from an otherwise normal thyroid gland due to impaired thyrotropin (TSH) levels. In contrast to primary hypothyroidism (which remains one of the most common endocrine disorders in clinical practice), CeH remains relatively rare, with an

estimated prevalence of 1 in 16,000 to 1 in 100,000 (1, 2). The signs and symptoms associated with CeH are generally milder, compared to primary hypothyroidism, often leading to a delay in diagnosis. The typical biochemical picture observed in CeH is of a low free thyroxine (FT4) level, along with an inappropriately normal or low-normal TSH level.

CeH can be broadly divided into two sub-types (congenital or sporadic) based on the underlying

disease process. In the majority of patients, sporadic CeH manifests as part of multiple pituitary hormone deficiencies (e.g. pituitary adenoma, craniopharyngioma, post-cranial radiotherapy, traumatic brain injury, and autoimmune hypophysitis (AH)) (3). Isolated CeH remains extremely rare and is mostly seen as cases of congenital hypothyroidism or occasionally secondary to iatrogenic factors (e.g. immune checkpoint inhibitors). Although antidepressant and antipsychotic medications have been reported to influence TH levels by a variety of mechanisms (4), to our knowledge there are no previous case series or reports which have conclusively linked these medications with the development of isolated CeH.

A collaboration between biochemistry and the adult endocrinology department at our university health board has led to an increased number of referrals of patients with biochemically confirmed CeH. The majority of these patients were subjected to further clinical, biochemical, and radiological evaluation to assess the functional and structural integrity of the hypothalamic–pituitary–thyroid (HPT) axis. A significant proportion of such patients had biochemical evidence of isolated CeH (confirmed over a period of time, with more than one thyroid function test and after excluding assay interference) with radiological investigations excluding a structural pituitary lesion. Interestingly, observational evidence suggested that the majority of such patients with isolated biochemical CeH were on antidepressant or antipsychotic medications.

As a result, we have conducted a retrospective observational study on a cohort of patients referred to the endocrinology clinic (since January 2016) with biochemical CeH. We have also done an extensive review of the literature exploring the possible impact of antidepressant or antipsychotic medication on the HPT axis.

Objectives

The primary objective of this retrospective observational study was to evaluate the final diagnosis and clinical outcome of patients referred to endocrinology with biochemical evidence of isolated CeH.

The secondary objective was to assess the possible contribution of iatrogenic factors (antidepressant and antipsychotic medications) on our cohort of patients with biochemically proven CeH.

Materials and methodology

Participants

The Cwm Taf University health board biochemistry department database of all the thyroid function tests (TFTs) carried out in the adult population (aged >16 years) was screened for possible CeH. This covered a period of 5 years (January 2016 to March 2021).

The inclusion criteria for identifying patients with biochemical evidence of CeH are shown in Table 1.

The exclusion criteria for the study are as shown in Table 2.

Roche Elecsys FT4 III assay and Roche Elecsys TSH assay were used for the assessment of thyroid function tests.

Table 1 Inclusion criteria.

Age >16 years
A low free T4 <11.0 pmol/L (reference range: 11–25)
A low-normal or low TSH
Referred to endocrinology for investigation

Table 2 Exclusion criteria.

Patients with a past medical history of thyroid or pituitary disease
If the clinical or biochemical evaluation confirmed pre-existing pituitary hormone dysfunction (apart from CeH)
Multiple pituitary hormone derangements
Recent non-thyroidal illness (on review of case notes)
Patients on medications such as amiodarone, steroids, lithium, and immune check point inhibitors

Analysis

The clinical and biochemical data for each patient were analysed using Welsh Clinical Portal (WCP) online, which provides access to primary care (general practice) notes, secondary care specialty clinic letters, and biochemical and radiological investigations.

We identified the patients with a biochemical picture of isolated CeH and excluded the patients with known pituitary and/or thyroid dysfunction as well as those on medications already known to affect thyroid function (see Table 1). Patients' medication history was accessed using the records available on WCP. The biochemistry and radiological investigation results were systematically analysed to evaluate possible HPT axis dysfunction.

Results

A total of 151 TFTs results were identified using the pre-determined biochemical cut-off (low FT4 and low-normal or normal TSH) to diagnose CeH; 33 of these were duplicate test results (from patients already counted once in the list), so these were excluded from the study.

Out of the remaining 118 patients with biochemical evidence of CeH, a further 89 patients were excluded from the final analysis as they fell into one or more of the exclusion criteria (see Table 2). The final list comprised 29 patients ($n = 29$) who fulfilled the selection criteria for this retrospective observational study (Fig. 1).

The TSH of these patients ranged from 0.06 to 3.81 mU/L and the T4 ranged from 6.9 to 10.9 pmol/L.

Of the 29 patients who were included in the analysis, 17 ($n = 17$) subsequently went on to have an MRI of their pituitary gland (59%). Most of the patients who did not receive imaging (8/12 patients) had normalisation of their TFTs on repeat testing, while the other four patients did not undergo an MRI scan due to patient refusal or not attending appointments.

Of the 17 patients with isolated CeH who underwent pituitary MRI, 12 were reported to have a normal scan (71%). Four patients had an empty or partially empty sella (24%). These patients' TSH ranged from 0.75 to 2.31 mU/L and T4 from 6.9 to 10.1 pmol/L. All the patients were deemed clinically and biochemically euthyroid

on subsequent out-patient clinic evaluation. One of the patients was reported to have a bulky pituitary gland on radiological imaging. This was subsequently observed to be an incidental radiological finding, with the rest of their pituitary hormone profile being within the normal range. The only medication she was on was amlodipine.

Of the 29 patients who were included in the final analysis, 18 (62%) were observed to be on antidepressant or antipsychotic medication. Of note, three of the four patients with an empty or partially empty sella were on at least one of these medications. Of the other patients, statins were being taken by six, gabapentin and metformin by two, and amlodipine by one. The pie chart below (Fig. 2) sums up the breakdown of psychotropic medications being taken by this cohort of patients with biochemical evidence of sporadic CeH (note: some of the patients were taking more than one of these medications).

Of these 18 patients, the most prescribed medication was citalopram (5 patients).

All but one of the 29 patients in our study had their TFTs repeated since these results and subsequent investigations. Nineteen out of 28 patients' (68%) TFTs subsequently normalised, though often only in one test before the same picture of biochemical CeH returned. In 9/28 (32%) the biochemical picture of CeH persisted.

The patients found to have a partially empty or empty sella in our retrospective review were subjected to a trial of levothyroxine (25 µg once daily) to assess if they had any symptomatic improvement with thyroxine replacement. However, only one of these patients noticed any symptomatic improvement. This patient had a persistently low T4 level ranging between 7.9 and 10.8 pmol/L. This normalised to 12.7 with thyroxine replacement.

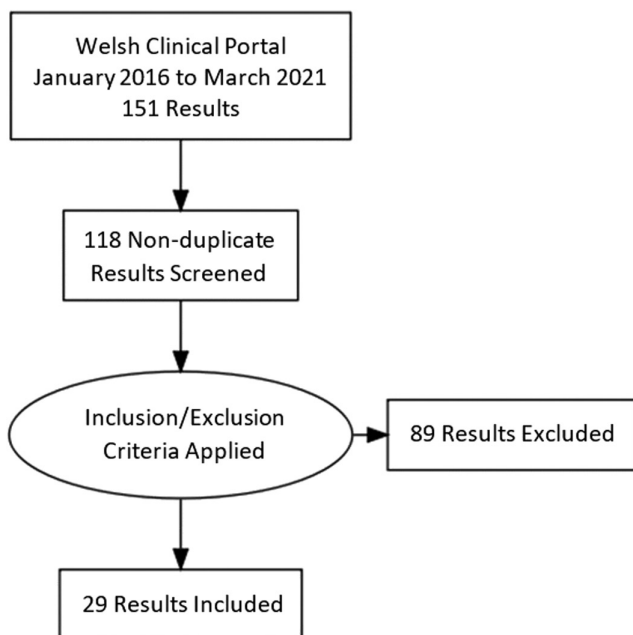


Figure 1
Flow diagram of study inclusion and exclusion.

Medications taken by Patients with Biochemical Isolated Central Hypothyroidism

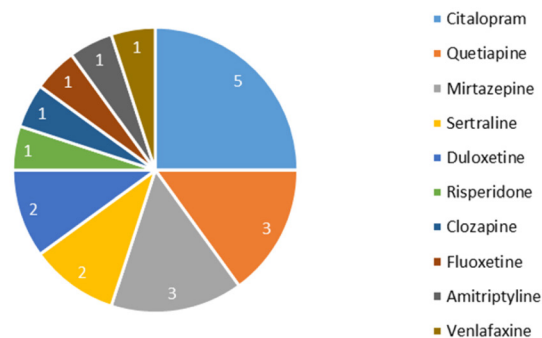


Figure 2
Medications taken by patients with biochemical isolated central hypothyroidism.

None of the other three patients had any symptomatic benefit, however.

Discussion

CeH is rare, with an estimated prevalence of 1:16,000 to 1:100,000 in the general population (2). It is generally diagnosed on a background of hypothalamic-pituitary pathologies, such as pituitary adenoma, craniopharyngioma, post-cranial radiotherapy, and AH as part of multiple pituitary hormones defects. Isolated CeH manifesting in adult life remains extremely uncommon in clinical practice.

Thyrotrophs are localised in the antero-medial region of the anterior pituitary gland and make up the least (<5%) of the total anterior pituitary cell population (5). Growth hormone (somatotrophs) and sex steroids (gonadotrophs) are typically the first hormones affected in cases of hypopituitarism caused by pituitary adenomas, with thyrotrophic and corticotrophic involvement manifesting at a later stage of the disease. Similarly, post-cranial radiotherapy or in the chronic phase of a traumatic brain injury, growth hormone, and gonadotrophin hormone deficiency is far more prevalent than TSH deficiency. In contrast, TSH deficiency is more common, and seen earlier in the disease course, in patients with AH. Patients with AH though characteristically also have adrenocorticotrophic hormone deficiency, leading to secondary adrenal insufficiency, and may have cranial diabetes insipidus due to impaired secretion of vasopressin (3).

The use of glucocorticoids, somatostatin analogues, and anti-epileptic medications have all been linked to suppression of TSH secretion (6), leading to transient or permanent CeH. To our knowledge, antidepressant or antipsychotic medication use had not previously been reported as a causative factor in CeH. An article by Burch (7) in the *New England Journal of Medicine* comprehensively evaluated the different ways various drugs can affect the thyroid gland with no mention of antidepressants or antipsychotic medication leading to CeH.

In some literature, the use of psychotropic medication has been reported to lead to reduced T4 levels, with TSH levels remaining unchanged. This is believed to be the impact of this class of agents on the HPT axis via suppression of catecholaminergic or serotonergic systems (8). A meta-analysis observed a decrease in T4, free T4, and triiodothyronine (T3) levels with serotonin-noradrenaline reuptake inhibitors (SSRI) treatment, with no appropriate compensatory response in TSH (9). However, this was not

statistically significant, and the authors acknowledged this is preliminary low-quality evidence. However, this same response is described in a review article by Bou Khalil *et al.* (4), who also notes that non-SSRIs such as mirtazapine can also affect TFTs in a less predictable manner. These too were found to sometimes cause this picture of CeH; however, the mechanism behind this is not discussed. They also note that tricyclic antidepressants have been found in some trials to significantly reduce T4 and TSH levels.

Joffe and Sokolov (10) and Baumgartner (11) have also discussed the lowering of serum T4 levels with antidepressant treatment in humans. Baumgartner hypothesises that falls in the serum levels of T4 are due to an enhanced conversion of T4 to T3 in the CNS by iodothyronine deiodinase type 2 enzyme, citing studies that have found increased levels of T3 in the mitochondria of the amygdala. Another theory is that depression itself influences the HPT axis, and many studies reference that those patients with a lower baseline TSH respond better to antidepressant treatment (12). Why this is the case though remains to be identified.

In terms of antipsychotics, typical antipsychotics like phenothiazines are noted to decrease TSH response to TRH by inhibiting alpha-adrenergic receptors (13). This is also the case with clozapine. Cases of CeH with quetiapine treatment have also been reported and, in fact, the investigation of this in our health board in an unpublished paper partly inspired this research (A Chalishazar and A Kalhan, unpublished observations). Poutanen *et al.* (14) describe three cases of quetiapine-induced hypothyroidism, one case of which had a normal TSH and low T4 level. A case in a 12-year old is also described by Zenno and Leschek (15) which resolved after withdrawal of quetiapine treatment. In fact, the product information for quetiapine (Seroquel by Astra-Zeneca) acknowledges the potential for clinically significant changes in TH levels, particularly in the first 6 weeks of treatment (16). A large study comparing the thyroid function of healthy individuals and patients taking antipsychotics for schizophrenia or bipolar disorder found that patients taking quetiapine and olanzapine had significantly lower T4 levels, again without a change in TSH (17).

All in all, the methods by which different medications can affect the HPT axis are only partially understood and require further research and study to understand. Regarding our patients not on antidepressant or antipsychotic medication, a review of the literature showed no known relationship between statins and TFTs.

Table 3 below shows the mechanism of action of antidepressant and antipsychotic medication linked with isolated CeH in our observational study.

An alternative explanation for our observations could be sick euthyroid disease, which can mimic CeH with transiently low TSH levels and/or T_4 levels due to an underlying illness. Thus, if isolated biochemical CeH is present, it is recommended to repeat the TFTs before further investigating with imaging. In these cases, a detailed clinical history and repeat TFTs indicated that sick euthyroid was not likely to be the cause of the erroneous low FT4 results. It is also worth considering that antidepressants are among the most prescribed medications worldwide. In the Organisation for Economic Co-operation and Development countries, of which there are 38, antidepressant use ranges between 12.3 and 129.6 per 1000 people daily (9). Therefore, due to the high prevalence of these medications, it could be a coincidence that a large number of patients in our study were found to be taking them. However, we feel this is unlikely, as other commonly prescribed medications were not found to be implicated by our study.

It is also important to rule out the possibility of analytical error as a cause of erroneous results. TSH is routinely measured by non-competitive sandwich assays, but these can be susceptible to interference. Heterophilic antibodies in a patient's serum blood sample can interfere with the measurement of TSH and can cause both negative and positive interferences (18). Most manufacturers, however, have introduced mechanisms to reduce interference, such as nonspecific animal immunoglobulins and heat aggregated, nonspecific, murine monoclonal antibodies within the reagents. Interference can also be a consequence of macro-TSH, which is an inactive circulating form of TSH composed of monomeric TSH complexed with autoimmune anti-TSH antibodies. This is not cleared from the circulation by the kidneys due to its size. Dietary supplemental biotin can also cause interference if taken

in high doses, due to the biotin–streptavidin interactions which are utilised in certain manufacturer assays.

Free T4 is measured by competitive immunoassay and may also be affected by interference. Heterophilic antibodies can also cause assay interference in these free hormone assays, and high-dose supplementary dietary biotin can again affect these. In addition, variant TH-binding proteins and anti-iodothyronine antibodies present in the serum can also cause interference (19). Interference in the free hormone assays is typically positive, so the likelihood of assay interference causing mildly low FT4 levels is low, albeit impossible to be fully excluded at this time.

We believe the strength of our work is that it is a thorough evaluation of all patients who were referred to our endocrinology department with biochemically confirmed CeH over the last 5 years. We have investigated a novel and hitherto unreported association of CeH with psychotropic medications, and our findings correlate with the literature quoted on how these drugs can affect THs. We believe our study opens the door to exploring this link further.

The limitation is that our study is of a retrospective observational nature which can be prone to bias. Although results were collected over a 5-year period, it is still unfortunately a small study which limits its statistical power to infer a definitive conclusion. Going forward, we plan to collect and analyse a larger set of biochemically proven CeH results nationally and work collaboratively across different health boards.

Conclusion

Prior to our study, the relationship between psychotropic medication and deranged TFTs has only been described in a limited amount of literature. Medications such as lithium have long been known to affect thyroid function, but our study suggests that antidepressant and antipsychotic medications can induce a transient biochemical CeH state.

Table 3 Mechanism of action of psychotropic medications.

Medication	Mechanism of action
Citalopram, sertraline, fluoxetine	SSRI
Quetiapine	Dopamine, serotonin, and adrenergic antagonist
Mirtazapine	NASSA
Risperidone	Decreases dopaminergic and serotonergic pathway activity
Duloxetine	SNRI
Clozapine	Dopamine and serotonin antagonist
Amitriptyline	TCA

NASSA, noradrenaline and specific serotonergic antidepressants; SNRI, serotonin-noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

The underlying mechanism for this remains uncertain, although our theory is that it is most likely to be mediated via catecholaminergic and serotonergic pathways inducing TSH suppression.

The cohort of patients on psychotropic medications with isolated CeH (who were clinically and biochemically eupituitary) had no structural abnormality on further radiological imaging. However, due to the limited size of our study and the risks of missing important pituitary pathology, it is not yet possible to recommend against the radiological screening of this group of patients.

Key messages

- Our retrospective observational study suggests a relationship between patients on antidepressant or antipsychotic medications and isolated CeH.
- The suppression of TSH secretion via antagonism of the dopamine-serotonergic pathway seems to be the likely mechanism for these medications to induce CeH.
- Determining a correlation between psychotropic medications and isolated CeH could lead to alleviating anxiety in patients (related to the possibility of organic/structural pituitary lesions) and the avoidance of further radiological investigations.
- A larger observational study is needed to provide further evidence to support/refute our finding.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Consent

Consent was deemed not to be required as this is an evaluative data analysis study using routinely available medical data. Those involved in the project would have routine access to this data for evaluative purposes, without the need of patient consent. This was agreed by the local Research and Development Department as above (Ref: CT/1567.21).

Ethical approval

This study was registered and approved locally via the Research and Development Department (Ref: CT/1567.21) as an evaluative data analysis study – accessing routinely available medical data along with a literature

review. The primary objective of this retrospective data analysis study was to evaluate the final diagnosis and clinical outcome of patients referred to endocrinology with biochemical evidence of isolated CeH.

Author contribution statement

F K performed the data analysis and wrote the manuscript. A C wrote the unpublished study that was the precursor to this paper. K M provided specialist biochemistry input in the discussion and reviewed the final manuscript. A D collected the biochemistry data. A K conceived the study, provided specialty endocrinology input to the paper, and reviewed the final manuscript.

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