Central Hypothyroidism Associated with Oxcarbazepine in Pediatric Patients: Case Series and Literature Review

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ABSTRACT

Central hypothyroidism, a hypothyroid state resulting from insufficient stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland, is a rare under-recognized side effect of oxcarbazepine. We describe four young patients diagnosed with central hypothyroidism likely due to oxcarbazepine and conducted a literature review for previously published cases. Four patients ranging in age from 11-20 years were treated with oxcarbazepine and were subsequently found to have low free thyroxine (FT4) levels and inappropriately normal thyroid stimulating hormone (TSH) concentrations. All had normal thyroid examinations and normal morning cortisol. The two patients who were still growing had normal growth hormone markers. Magnetic resonance imaging (MRI) of the brain was normal in all. Three of the patients experienced symptoms consistent with hypothyroidism; treatment with levothyroxine led to resolution of symptoms. Three of the patients discontinued oxcarbazepine; subsequently all had normalization of thyroid function. Oxcarbazepine can lead to low FT4 concentrations with normal TSH values. Assessment of TSH and FT4 could be included in the periodic screening of patients taking oxcarbazepine. A limited number of reported cases have suggested that monitoring of thyroid function studies may be indicated in patients taking oxcarbazepine, to monitor for development of CH.

KEYWORDS: Central hypothyroidism; oxcarbazepine; child; youth

INTRODUCTION

Central hypothyroidism (CH) is a hypothyroid state resulting from insufficient stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland.[1] Medications including glucocorticoids, dopamine, and bromocriptine can lead to central hypothyroidism (CH) by suppressing thyroid stimulating hormone (TSH) through their action at the hypothalamus or pituitary.[2] Oxcarbazepine has also been reported to cause CH.[1,3,4] Oxcarbazepine, a structural analogue of carbamazepine, was developed for the treatment of focal seizures among children and adolescents and has been used in the United States since 2000.[1] Here we describe the evaluation and management of four youth with CH secondary to oxcarbazepine in our institution and compare them with the clinical course of six previously described adolescents who developed CH following oxcarbazepine use.[1,4]

CASE PRESENTATIONS

Patient 1

A 16-year 10-month-old girl with Townes Brocks syndrome (TBS) was found to have abnormal thyroid function tests (TFTs) during evaluation of menorrhagia. TBS is a rare autosomal dominant malformation characterized by a triad of imperforate anus, malformed ears (commonly associated with sensorineural or conductive hearing loss), and thumb anomalies and is not typically associated with CH.[5] She reported constipation and tiredness. She had been treated with oxcarbazepine for focal seizures for the past 8 years. She had normal vital signs and a history of normal growth and development. Her thyroid examination was normal. Laboratory evaluation showed CH [**Table 1**] and she was started on levothyroxine 100 mcg daily (1.14 mcg/kg/day). The oral dose for levothyroxine for adolescents with growth and puberty complete is around 1.6 mcg/kg/dose once daily.[6] The patient was lost to follow up, discontinued the levothyroxine on her own, and continued to take oxcarbazepine. Repeat laboratory tests 16 months later showed persistent CH: inappropriately normal TSH 2.567 uIU/mL in the setting of a low free T4 (FT4) 0.69 ng/dL concentration. She reported fatigue, constipation, and weight gain. She restarted levothyroxine and was biochemically euthyroid on follow-up. Subsequently she discontinued the oxcarbazepine, after which the levothyroxine was stopped as well. Repeat thyroid function studies subsequently normalized.

Patient 2

An 11-year 9-month-old girl with Phelan McDermid syndrome was found to have a low FT4 and normal TSH as part of the evaluation for developmental delay. Phelan–McDermid syndrome is a disorder of neurological development resulting from deletion of the distal long arm of chromosome 22 (22q13.3) which is not typically associated with CH.[7] She had been treated with oxcarbazepine for focal seizures over the past 7 months. She had baseline constipation

Table 1. Clinical and laboratory parameters of our patients

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4
At presentation				
Age and gender	16y 10mo, F	11y 9mo, F	20y 8mo, M	11y 10mo, M
BMI, Kg/m2 (percentile)	37.8 (99)	20.76 (81)	21.56	17.27 (38)
Height in cm (percentile)	152.1 (5)	135 (3)	169	155.7 (76)
GV (cm/year)	—	6	—	6.9
PMH	TBS, seizures, depression, tethered cord, IIH	PMD, focal seizures, ADHD, developmental delay	ALL, BMT, GVHD on steroids, depression, asthma, seizures	Benign Rolandic epilepsy
TFT prior to OXZ use	Normal at 11mo	Normal at 8y 5mo	—	—
Age at starting OXZ	8y	11y 2mo	17y 6mo	10y 4mo
OXZ dose at presentation	600 mg twice daily	750 mg twice daily	900 mg twice daily	300 mg am, 450 mg pm
Age at abnormal TFT	16y 10mo	11y 9mo	20y 8mo	11y 4mo
Medications other than OXZ	OCP, sertraline, acetazolamide	FP inhaler	HC, sertraline, olanzapine, MT, FP inhaler	Vitamin D
Laboratory studies at diagnosis				
TSH (0.35 -5.5 uIU/mL)	1.822	0.617	3.239	1.246
FT4 (0.80-1.80 ng/dL)	0.65	0.77	0.63	0.72
Morning cortisol (5.5-20 ug/dL)	14.4	9.9	16.1	17.6
IGF1 (ng/mL)	—	454 (90–581)	—	430 (76–549)
IGF BP3 (ng/mL)	—	5380 (2838–6846)	—	
MRI brain	Normal	Normal	Normal	Normal
Levothyroxine (LT4)	0.67–1.1 mcg/kg/day	Not started	0.4–0.8 mcg/kg/day	0.6 mcg/kg/day
Follow-up details				
Age at D/c of OXZ	17y 8mo	12y 8mo	20y 8mo	Not discontinued
Age at D/c of LT4	18y 3mo	Not started	continuing	continuing
Thyroid function studies post initiation of LT4				
TSH (0.35 -5.5 uIU/mL)	0.008	—	0.90	1.41
FT4 (0.80-1.80 ng/dL)	1.48	—	1.15	0.81
Follow-up thyroid function studies				
TSH (0.35-5.5 uIU/mL)	[1]2.52, [2]2.28	[3]2.085, [4]2.386	—	—
Free T4 (0.8-1.8 ng/dL)	[1]1.00, [2]1.00	[3]0.75, [4]0.89		—

[1] One month post discontinuation of levothyroxine; [2] 3.5 months post discontinuation of levothyroxine; [3] One month post discontinuation of oxcarbazepine; [4] Three months post discontinuation of oxcarbazepine. D/c- discontinuation, BMI- body mass index, FT4-Free T4, FP- Fluticasone propionate, GV – growth velocity, HC- hydrocortisone, IGF1- insulin like growth factor 1, IGF BP3- IGF binding protein 3, mo- months, MT- montelukast, MRI – magnetic resonance imaging, OXZ- oxcarbazepine, TSH- thyroid stimulating hormone, y-year

attributed to Phelan-McDermid syndrome and did not have other symptoms of hypothyroidism. Her growth pattern was consistent with her genetic potential, and she had Tanner 2 breast development. She had a normal thyroid gland on examination. Further evaluation did not reveal any other pituitary dysfunction. Repeat TFTs were consistent with CH. After discussion with her neurologist, she was weaned from oxcarbazepine and transitioned to valproic acid. Her TFTs normalized 3 months after stopping oxcarbazepine.

Patient 3

A 20-year-old male with a complex medical history and focal seizures treated with oxcarbazepine for 3 years was diagnosed with syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the setting of severe fatigue, dizziness and nausea. Further work up revealed isolated CH. Examination showed a normal thyroid gland. Both SIADH and CH were attributed to oxcarbazepine use. The oxcarbazepine was discontinued, and he was started on topiramate. He was treated with levothyroxine 50 mcg daily, with plans to discontinue within a few months of stopping the oxcarbazepine. Three months after discontinuation of oxcarbazepine,

he had normal TFTs, and levothyroxine dose was decreased to 25 mcg daily. Plans were made to discontinue levothyroxine, but he transitioned to an adult endocrinologist for ongoing care and further information was not available.

Patient 4

An 11-year 10-month-old girl with seizure disorder treated with oxcarbazepine for benign Rolandic epilepsy was referred to endocrine clinic for CH based upon low FT4 and normal TSH, detected on screening laboratory studies ordered by her neurologist. Rolandic epilepsy, also known as benign childhood epilepsy with central-temporal spikes is the most common pediatric epilepsy.[8] She reported recent fatigue, cold intolerance, and poor concentration. The patient had a normal thyroid gland and unremarkable systemic examination. She was growing along her genetic potential. She was started on levothyroxine 25 mcg daily (0.6 mcg/kg/day) and continued to take oxcarbazepine. Oxcarbazepine dose was increased, and free T4 was at low end of reference range. The levothyroxine dose was increased to 37.5 mcg daily. Two years later she began an oxcarbazepine wean, with plans for a trial off of levothyroxine once she was off of the oxcarbazepine.

DISCUSSION

We describe four young patients who developed CH in the setting of oxcarbazepine therapy. Oxcarbazepine was replaced with other antiseizure medications in 3 of the patients, with normalization of TFTs off of levothyroxine therapy in two of them while the third patient was on a tapering dose of levothyroxine. One patient continued on oxcarbazepine and levothyroxine at the time of publication.

CH refers to thyroid hormone deficiency owing to a functional or anatomical disorder of the pituitary, hypothalamus or hypothalamic-pituitary-portal circulation causing decreased TSH, thyrotropin releasing hormone or both.[9] The diagnosis of CH should be considered in any patient with low FT4 and a low or inappropriately normal TSH level, as was seen in the four patients described in this report. The FT4 by equilibrium dialysis, the most accurate method for the determination of FT4 levels was low in all three patients who had thyroid hormone analyzed by this assay, ruling out possible interference in measurement.[9]

Isolated CH is rare, as CH usually presents along with other pituitary hormone deficiencies.[9] All the patients had normal morning cortisol and the younger patients (patients 2 and 4) had normal growth hormone markers. An MRI brain scan was normal in all, ruling out anatomical problems of the hypothalamic pituitary axis.

Older antiepileptics, such as phenytoin, carbamazepine, phenobarbital and valproic acid, may cause subclinical hypothyroidism due to hepatic microsomal P450 enzyme induction and hence increased thyroid hormone metabolism.[1] Oxcarbazepine, the 10-keto analogue of carbamazepine, has minimal effect on P450 enzyme system and is associated with fewer side effects than carbamazepine.[3] The mechanism of oxcarbazepine induced CH is unclear and might be due to disruption of the hypothalamic pituitary axis.[10] Oxcarbazepine may change pituitary or hypothalamic responsiveness to feedback by thyroid hormones.[1] While the United States Food and Drug Administration (FDA) recommends monitoring serum sodium levels in patients on oxcarbazepine with symptoms suggestive of hyponatremia such as nausea, malaise, headache, lethargy, confusion, or increase in seizure frequency or severity because oxcarbazepine can cause SIADH,[11] routine screening for CH is not part of standard guidelines.

A small number of international studies have reported on the effects of oxcarbazepine on thyroid function among youth with normal thyroid function.[3,10,12-17] Some studies reported decreased thyroxine (T4) and FT4 levels without change in TSH.[3,10,12] One study reported a decrease in FT4 levels and increase in TSH levels compared to baseline TFTs,[16] while another described a decrease in FT4 levels without change in T4, triiodothyronine (T3), or TSH levels.[13] Two other studies observed no changes in TFTs after 1 year of oxcarbazepine treatment.[14,17]

Table 2 summarizes the four patients identified in our study and the six previously reported pediatric cases of CH associated with oxcarbazepine.[1,4] The mean age (± standard deviation) of the four patients in our cohort was 183.2 ± 51.7 months, similar to 145.5 ± 26 months in the six previously reported cases. The majority of patients were female: 75% in our cohort compared to 83.3% in the prior cases. The mean dose of the oxcarbazepine at presentation with abnormal TFTs was 1312.5 ± 447.9 mg daily in our cohort compared to 1155 ± 473.9 mg daily in the previously reported cohort. The duration of oxcarbazepine treatment prior to abnormal TFT detection was available for six patients (of 10) and ranged widely from 7 to 106 months (median 32.5 months). Nine (of 10) patients treated with oxcarbazepine had at least one symptom suggestive of hypothyroidism: lethargy, fatigue, decreased energy level or increased sleepiness were present in eight patients, weight gain was reported in five patients, and cold intolerance was noted in four patients. Menstrual irregularities, constipation, dry skin/hair and poor linear growth were each reported by three patients.

CONCLUSIONS

The majority of patients with CH associated with oxcarbazepine, both in our cohort and those previously described, reported symptoms of hypothyroidism which developed at a wide range of treatment duration and dosing range. The majority (80%) of patients with CH associated with oxcarbazepine were female; given the small numbers of patients described, further work is needed to identify if there is any

Table 2. Characteristics of cases of central hypothyroidism associated with oxcarbazepine use

Case Number (ref)	Age	Sex	OXZ		Symptoms of hypothyroidism	Levothyroxine (LT4)	Outcome
			Daily dose (mg)	Duration (mo)			
1[1]	15y	Female	750	—	Menstrual irregularities, cold intolerance, constipation, PTM	50 ug/d	Euthyroid
2[1]	14y	Female	900	—	Menstrual irregularities, cold intolerance, constipation, PTM	50 ug/d	Euthyroid
3[3]	10.9y	Male	600	27	Poor GV, short stature, decreased exercise tolerance and energy level	—	Replaced OXZ with valproic acid Improved GV.
4[4]	10y	Female	1380	—	Rapid weight gain, constipation, poor GV	25 ug/d	Euthyroid, Tapered off OXZ and started on lacosamide
5[4]	13y	Female	1500	72	Weight gain, fatigue and dry skin, poor GV	37.5–100 ug/d over 2½y	Euthyroid
6[4]	10y	Female	1800	—	Fatigue, joint pain and butterfly rash on the face	25 ug/d	Resolution of joint pain & facial rash, fatigue persisted. Replaced OXZ with lamotrigine, weaned off LT4. Euthyroid.
7 (PC-1)	16y 10mo	Female	1200	106	Menstrual irregularities, fatigue, cold intolerance, weight gain	100 ug/d, subsequent reduction to 75 ug 5d a week	Replaced OXZ with levetiracetam and weaned off LT4. Clinically and biochemically euthyroid.
8 (PC-2)	11y 9mo	Female	1500	7	None	—	Replaced OXZ with valproic acid with normalization of TFT
9 (PC-3)	20y 8mo	Male	1800	38	Severe fatigue, SIADH	50 ug/d x 3 mo, then 25 ug/d x 1 mo	Replaced OXZ with topiramate with a plan to stop LT4 after 1 mo
10 (PC-4)	11y 10mo	Female	750	12	Cold intolerance, increased sleepiness, poor concentration	25 ug/d	Remains on OXZ

d-day, GV- growth velocity, mo- months, OXZ-oxcarbazepine, PC- present case, PTM- pretibial myxedema, SIADH-syndrome of inappropriate antidiuretic hormone secretion, y-year

association between sex and risk of CH. Given the importance of thyroid function in normal growth, pubertal progression, and metabolism, monitoring for thyroid dysfunction with clinical and laboratory assessments could be considered prior to and during oxcarbazepine treatment. Thyroid function studies should include both FT4 and TSH to assess for CH. Prospective studies are needed to determine optimal timing and frequency of thyroid function screening in youth treated with oxcarbazepine.

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Disclosures

The authors have no conflicts of interest or sources of support including grants, fellowships, and gifts of materials (e.g., chemicals, experimental diets) to disclose.

Acknowledgment: We thank patient and the family for giving consent for publication.

Data Availability Statement : Original data generated and analyzed during this study are included in this published article.

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