ACTA ONCOLOGICA
2022, VOL. 61, NO. 12, 1477–1480
https://doi.org/10.1080/0284186X.2022.2156812

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Central hypothyroidism after chemotherapy in childhood cancer survivors: a single centre series

Amy L. Wanaguru[a,b], Daniel J. Tait[c,d], Richard J. Cohn[b,e], Karen A. Johnston[e] and Kristen A. Neville[a,b]

[a]Department of Endocrinology, Sydney Children's Hospital, Randwick, Australia; [b]School of Paediatrics and Child Health, UNSW Sydney, Kensington, Australia; [c]Department of Paediatrics, Shoalhaven District Memorial Hospital, Nowra, Australia; [d]Graduate School of Medicine, University of Wollongong, Wollongong, Australia; [e]Kids Cancer Centre, Sydney Children's Hospital, Randwick, Australia

ARTICLE HISTORY Received 27 September 2022; Accepted 5 December 2022

Introduction

Endocrinopathies are a common late effect in childhood cancer survivors (CCS) (those alive 5 years after diagnosis), with studies stating cumulative risk being around 45% of all survivors. A study of the Childhood Cancer Survivor Study cohort showed 44% had at least one endocrinopathy, 17% had 2 and 7% had 3 or more [1], which included patients with exposure to radiation.

Central (secondary) hypothyroidism refers to thyroid hormone deficiency secondary to pituitary or hypothalamic dysfunction, resulting in inadequate thyroid hormone secretion. In the general population, isolated central hypothyroidism is reported as very rare (approximately 1:20,000–80,000) [2], but more common (approximately 1:2200) in association with other anterior pituitary hormone deficiencies [3].

Central hypothyroidism and other pituitary hormone deficiencies are most commonly associated with exposure to cranial irradiation, after neurosurgery or in association with raised intracranial pressure [4–6]. Thyroid dysfunction (primary and secondary) after chemotherapy alone remains controversial, however has been reported, particularly in association with haematopoietic stem cell transplant (HSCT) conditioning [7–10]. Several studies with small patient numbers have described central hypothyroidism after chemotherapy alone [7,11–13].

The diagnosis of central hypothyroidism is usually based on clinical features (fatigue, cold intolerance, weight gain, slow growth velocity) combined with biochemical evidence; low/normal/slightly elevated thyroid stimulating hormone (TSH) and either low free T4 (fT4) on 2 occasions, or declining fT4 (>20%) on longitudinal testing [6].

The objective of this case series is to describe one centre's experience of central hypothyroidism in CCS exposed only to chemotherapy as a novel pathophysiology.

Material and methods

This is a retrospective medical record review of seven patients with central hypothyroidism from oncology long term follow up clinic at Sydney Children's Hospital, Randwick, Australia.

Case description

Patient 1 underwent standard treatment at age 3 years for acute lymphoblastic leukaemia (ALL) which was complicated by simple partial seizures treated with carbamazepine (Table 1). Thyroid function tests (TFT) were first performed at 12 years old to investigate rapid weight gain with acanthosis nigricans. TFT were repeated on 4 occasions over an 8-month period and consistently demonstrated low fT4 and normal range TSH. She was started on thyroxine and had 3 kg of weight loss.

Patient 2 underwent standard treatment for ALL at age 12 years that required modification due to extensive complications and a lengthy intensive care admission. He presented at 16 years of age with delayed puberty, lethargy and weight gain. TFT showed low fT4 with low-normal TSH, which were repeated on two occasions. Subsequently he was diagnosed with partial growth hormone (GH) deficiency, hypogonadotropic hypogonadism and suboptimal cortisol response. He was started on thyroxine and testosterone replacement with improvement in mood, energy levels and 3 kg of weight loss.

Patient 3 underwent standard treatment for ALL at 4 years of age. She presented at 14.6 years old with poor energy levels and obesity. TFT showed low fT4 and normal range TSH which were confirmed on two occasions prior to starting thyroxine.

Patient 4 was diagnosed at 3 months of age with a primitive neuroectodermal tumour (PNET) in the right cervical thoracic paravertebral region. She underwent standard chemotherapy treatment with focal radiotherapy to the neck. She had TFT done at 5 years of age due to history of constipation and low energy levels which showed low fT4 and normal range TSH. TFT were repeated on several occasions over a period of 8 months before starting thyroxine.

Patient 5 was diagnosed with stage 4 neuroblastoma at 18 months of age and underwent chemotherapy, surgery, focal radiotherapy to the liver and right adrenal, followed by

CONTACT Amy L. Wanaguru amy.wanaguru@health.nsw.gov.au Endocrine Department, Sydney Children's Hospital, High St, Randwick, 2031 Australia

Table 1. Patient characteristics and results.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Female	Male	Female	Female	Female	Female	Female
Diagnosis	ALL	ALL	ALL	PNET cervical	Stage IV Neuroblastoma. Secondary AML	Pilocytic astrocytoma	Stage IV neuroblastoma
Age at cancer diagnosis (years)	3.3	12.7	4.8	0.3	1.3	3.9	Antenatal
Cancer treatment	CPM, VCR, DAU, CYT, ASP, DEX, PRED, TGN, 6MP, DOX, IV/IT MTX	CPM, VCR, DAU, CYT, ASP, DEX, PRED, TGN, 6MP, DOX, IV/IT MTX, DOX	CPM, VCR, DAU, CYT, ASP, DEX, PRED, TGN, 6MP, DOX, IV/IT MTX, DOX	CPM, VCR, IFO ETO, ADR, ACTD RTX − 6.5 Gy (neck only)	CPM, VCR, ETO, ADR, ACTD, CIS, RTA, CAR, MEL, FLU, CYT, IDA, BUS, ATG RTX − 21 Gy (right adrenal and liver)	TGN, PCB, CCNU, VCR	CPM, DOX, VCR, CIS, ETO, CAR, MEL
TSH pre-treatment with thyroxine (mIU/L)	1.3 (0.7–5.7)	1.3 (0.7–5.7)	1.3 (0.5–4.3)	4.3 (0.7–5.7)	1.6 (0.7–4.6)	13.3 (0.6–4.8)	2.5 (0.51–4.3)
fT4 pre-treatment with thyroxine (pmol/L)	6.0 (10.3–25.4)	10.1 (10.3–25.4)	10.9 (12.6–21.0)	10.3 (12.9–27.0)	11.8 (12.6–21.0)	6.2 (12.5–21.5)	11.5 (12.6–21)
Time to develop central hypothyroidism (years)	9.3	3.4	9.8	7.0	9.1	5.85	16
Other pituitary hormone results	IGF-1/cortisol/ACTH/ oestradiol/FSH/LH/ prolactin—normal	Partial GHD. Suboptimal cortisol response. Hypogonadotropic hypogonadism.	IGF-1/cortisol/ACTH/ oestradiol/FSH/LH/ prolactin—normal	GH testing normal.	GH testing normal. Hypergonadotropic hypogonadism.	IGF-1/oestradiol/FSH/LH/ prolactin—normal	IGF-1/cortisol/ACTH/ oestradiol/FSH/LH/ prolactin—normal
MRI pituitary result	Normal	Normal	Normal at age 6 years	Normal	Normal	Normal	Normal
Current age (years)	28	25.4	20.8	15.9	17.5	16.9	19.5
Current height (cm, centile)	165 (60th)	179.8 (65th)	161.9 (45th)	143.5 (<1st)	162.9 (50th)	152 (5th)	145 (<1st)
Current weight (kg, centile)	65 (75th)	74.3 (65th)	76.1 (93rd)	41.15 (3rd)	47.8 (20th)	56.9 (60th)	36.6 (<1st)
Current BMI (kg/ m^2, centile)	23.9 (65th)	26.5 (80th)	29 (95th)	20 (45th)	18 (15th)	24.6 (80th)	17.4 (3rd)
Current thyroxine dose (mcg/per day)	100	142	120	75	0 (ceased at 14.4 years)	90	75

ALL: acute lymphoblastic leukaemia; PNET: primitive neuroectodermal tumour; AML: acute myeloid leukaemia; CPM: Cyclophosphamide; VCR: Vincristine; DAU: Daunomycin; CYT: Cytarabine; ASP: Asparaginase; DEX: Dexamethasone; PRED: Prednisolone; TGN: Thioguanine; 6MP: 6 Mercaptopurine; DOX: Doxorubicin; IV/IT MTX: Intravenous/Intrathecal Methotrexate; IFO: Ifosphamide; ETO: Etoposide; ADR: Adriamycin; ACTD: Actinomycin D; CIS: Cisplatinum; RTA: Retinoic Acid; CAR: Carboplatin; MEL: Melphalan; FLU: Fludarabine; CYT: Cytarabine; IDA: Idarubicin; BUS: Busulphan; ATG: Atgam; RTX: Radiotherapy; PCB: Procarbazine; CCNU: Lomustine; GHD: growth hormone deficiency.

autologous HSCT with chemotherapy-only conditioning. She then developed acute myeloid leukaemia (AML) at 5.8 years old which was treated with chemotherapy and allogeneic HSCT with chemotherapy-only conditioning. She developed seizures at 8 years of age treated with carbamazepine. TFT showed low fT4 and normal range TSH on repeated measures over 12 months before starting thyroxine. Subsequently carbamazepine was ceased and after completion of growth a successful trial off thyroxine was completed.

Patient 6 was diagnosed at 4 years of age with a pilocytic astrocytoma at the cerebellar vermis with spinal metastases and underwent surgical resection followed by standard chemotherapy. TFT done at 9 years of age showed low fT4 with slightly high TSH with negative thyroid antibodies, which were repeated several times prior to starting thyroxine. TSH normalised immediately after starting thyroxine with ongoing low fT4 until dose was optimised.

Patient 7 was diagnosed with stage 4 neuroblastoma antenatally and underwent treatment with surgery, chemotherapy and autologous HSCT with chemotherapy-only conditioning. She was known to the endocrine clinic for short stature with normal IGF-1 and then had rapid pubertal progression resulting in an adult height <1st centile. TFT done to investigate menorrhagia at 16 years showed low fT4 with normal range TSH, which were repeated several times prior to starting thyroxine.

Discussion

The seven cases discussed are CCS who had no prior exposure to cranial irradiation and who developed central hypothyroidism, diagnosed on serial TFT, as a late effect. These cases highlight the importance of considering hypothalamic pituitary axis (HPA) dysfunction in survivors with chemotherapy-only exposure. They also demonstrate that central hypothyroidism can be an isolated condition, as all except one case had normal HPA screening.

The literature reports risk factors for developing central hypothyroidism in CCS are; pituitary radiation of >30 Gy, suprasellar tumours, raised intracranial pressure, cranial nervous system surgery and other pituitary hormone deficiencies [1,14–16]. Whether central hypothyroidism occurs after chemotherapy alone remains controversial, as clinical presentation can be non-specific and biochemical markers difficult to interpret [17]. Central hypothyroidism has recently been reported 5.5% of the St. Jude Lifetime cohort ($n = 3141$), with a median time since cancer diagnosis of 24 years [16]. This was predominately observed in those that had been exposed to cranial irradiation or those with a tumour involving the HPA region, but was also reported in 0.7% of those with neither risk factor, supporting our findings [16]. We note that a history of seizures increased the risk of central hypothyroidism, and we hypothesise that anti-epileptic drugs may have contributed, as seen in our series [16].

Widely suggested diagnostic criteria for central hypothyroidism are low fT4 with low/normal/slightly elevated TSH [6,14]. However, often only a TSH level is measured and the diagnosis of central hypothyroidism can thus be easily missed [14]. TRH stimulation test is thought to be useful in cases of mild central hypothyroidism, but is unavailable in Australia and many other countries [6]. Diminished nocturnal TSH surge has also been reported as a marker of dysfunction of the hypothalamic control of the thyroid axis but does not necessarily indicate or predict central hypothyroidism [14,15,17].

Several studies, with small patient numbers, have reported central hypothyroidism in CCS exposed to chemotherapy only, but diagnostic criteria were broader than generally accepted, including blunted nocturnal TSH surge or abnormal TRH stimulation test in asymptomatic patients with normal fT4 levels [7,11–13]. Baronio et al. reviewed 31 ALL survivors treated with chemotherapy only and found 6 (19%) had slightly high TSH [7]. Three of the 6 patients went on to have TRH stimulation testing which was abnormal in all three, however only 1/6 had a low fT4 [7]. Rose et al. reviewed 208 CCS who had symptoms of hypothyroidism and underwent nocturnal TSH surge and TRH stimulation testing [12]. Sixty-two (30%) met the criteria for central hypothyroidism, however we note that only 8% had a low fT4. Ten of the 62 patients with central hypothyroidism had exposure to chemotherapy-only [12]. A second study by Rose et al. reviewed 31 CCS treated with chemotherapy-only who had slow growth or altered pubertal timing [13]. Sixteen (52%) were diagnosed with central hypothyroidism based on fT4 in lowest third of normal range with blunted nocturnal TSH surge or abnormal TRH stimulation test [13].

Only one of our patients had additional anterior pituitary hormone deficits, highlighting that central hypothyroidism can be isolated in nature. Rose et al. reports central hypothyroidism with other endocrine deficits in 50–75% of patients [12,13]. Multiple pituitary hormone deficits after chemotherapy-only have been described by others but it remains controversial if chemotherapy is causal [15].

We hypothesise the aetiology of central hypothyroidism after chemotherapy-based cancer treatments in childhood is likely multifactorial, including direct chemotherapy effects, sequalae of critical illness, and complications of other treatments such as antiepileptic drugs (AEDs). Evidence of direct chemotherapy effects is reported in the literature:

- Transient central hypothyroidism reported in the immediate period following chemotherapy, most notably L-asparaginase [9].
- Direct toxic effects of chemotherapeutic agents that may cross the blood brain barrier, such as vincristine [9], or injected intrathecal chemotherapy such as methotrexate [16].

Cerebral insults are known risk factors outside of cancer diagnoses and we speculate could be causative in those with critical illness like Patient 2 [6]. Abnormal TFT in association with AEDs is a well-recognized phenomenon in the literature [18,19]. Carbamazepine was used by two of the patients in this series and the most common TFT pattern described is low fT4/fT3 with normal TSH [18,19]. There is conflicting evidence as to whether these changes in TFT are consistent

with clinical hypothyroidism [19,20], however symptomatic central hypothyroidism has been reported [21].

We can only postulate what caused central hypothyroidism in our patients, but in light of the potential morbidities of hypothyroidism including metabolic consequences, reduced physical performance and impact on growth, this is important to be aware of, identify and treat [6]. The implications from this case series are:

- Further research is necessary to assess prevalence of central hypothyroidism and risk factors in CCS.
- Oncologists and endocrinologists should have a low threshold for performing TFT in all CCS regardless of treatment history.
- When ordering TFT always request TSH and fT4 to allow detection of central hypothyroidism.
- Consider monitoring TFT in CCS on antiepileptics, as thyroid dysfunction can also be seen in this cohort.

Consent statement

Informed consent has been obtained from each patient (or patient's guardian) for publication of this case report.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Amy L. Wanaguru received funding through the Australian Government Research Training Program Scholarship. The sponsor was not involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

ORCID

Amy L. Wanaguru http://orcid.org/0000-0002-1784-1119

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

References

[1] Mostoufi-Moab S, Seidel K, Leisenring WM, et al. Endocrine abnormalities in aging survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2016;34(27):3240–3247.

[2] Persani L. Clinical review: central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J Clin Endocrinol Metab. 2012;97(9):3068–3078.

[3] Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, et al. Hypopituitarism. Lancet. 2007;369(9571):1461–1470.

[4] Chemaitilly W, Sklar CA. Childhood cancer treatments and associated endocrine late effects: a concise guide for the pediatric endocrinologist. Horm Res Paediatr. 2019;91(2):74–82.

[5] Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer. 2010;17(3):R141–59.

[6] Persani L, Brabant G, Dattani M, et al. European thyroid association (ETA) guidelines on the diagnosis and management of Central hypothyroidism. Eur Thyroid J. 2018;7(5):225–237.

[7] Baronio F, Battisti L, Radetti G. Central hypothyroidism following chemotherapy for acute lymphoblastic leukemia. J Pediatric Endocrinol Metab JPEM. 2011;24(11–12):903–906.

[8] Izaki S, Goto H, Okuda K, et al. Long-term follow-up of busulfan, etoposide, and nimustine hydrochloride (ACNU) or melphalan as conditioning regimens for childhood acute leukemia and lymphoma. Int J Hematol. 2007;86(3):253–260.

[9] Yeung SC, Chiu AC, Vassilopoulou-Sellin R, et al. The endocrine effects of nonhormonal antineoplastic therapy. Endocrine Reviews. 1998;19(2):144–172.

[10] Armstrong AE, Danner-Koptik K, Golden S, et al. Late effects in pediatric high-risk neuroblastoma survivors after intensive induction chemotherapy followed by myeloablative consolidation chemotherapy and triple autologous stem cell transplants. J Pediatric Hematol Oncol. 2018;40(1):31–35.

[11] Ansari S, Rostami T, Kiumarsi A. Central hypothyroidism: a rare complication in a child undergoing chemotherapy for acute lymphoblastic leukaemia. Iranian J Blood Cancer. 2014;7(1):49–52.

[12] Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden Central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab. 1999;84(12):4472–4479.

[13] Rose SR, Schreiber RE, Kearney NS, et al. Hypothalamic dysfunction after chemotherapy. J Pediatric Endocrinol Metab JPEM. 2004;17(1):55–66.

[14] Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and growth disorders in survivors of childhood cancer: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(8):2761–2784.

[15] Gebauer J, Higham C, Langer T, et al. Long-Term endocrine and metabolic consequences of cancer treatment: a systematic review. Endocr Rev. 2019;40(3):711–767.

[16] van Iersel L, Li Z, Srivastava DK, et al. Hypothalamic-Pituitary disorders in childhood cancer survivors: prevalence, risk factors and long-term health outcomes. J Clin Endocrinol Metab. 2019;104(12):6101–6115.

[17] Seejore K, Kyriakakis N, Murray RD. Is chemotherapy implicated in the development of hypopituitarism in childhood cancer survivors? J Clin Endocrinol Metab. 2020;105(4):61.

[18] Zhang Y-X, Shen C-H, Lai Q-L, et al. Effects of antiepileptic drug on thyroid hormones in patients with epilepsy: a meta-analysis. Seizure. 2016;35:72–79.

[19] Hamed SA. The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. Expert Rev Clin Pharmacol. 2015;8(6):741–750.

[20] Yılmaz Ü, Yılmaz TS, Akıncı G, et al. The effect of antiepileptic drugs on thyroid function in children. Seizure. 2014;23(1):29–35.

[21] Miller J, Carney P. Central hypothyroidism with oxcarbazepine therapy. Pediatr Neurol. 2006;34(3):242–244.