Hypopituitarism Following Ophthalmic Intra-Arterial Chemotherapy for Retinoblastoma

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INTRODUCTION

- Ophthalmic intra-arterial chemotherapy (OIAC) and intravitreal chemotherapy (iVitC) are being increasingly used over systemic chemotherapy for retinoblastoma (RB) to deliver high doses directly to the tumor while minimizing exposure to adjacent tissues, limiting side effects.
- Extra-ocular complications are believed to be rare and mainly linked to the procedure itself.
- No endocrine effects have been described with OIAC.

CASE

- 1-year old male with right eye RB underwent 4 cycles of OIAC with carboplatin, melphalan and topotecan and adjuvant iVitC with melphalan and topotecan, delivering a cyclophosphamide equivalent dose of 1.3 g/m2.
- He had transient occlusion of ophthalmic artery and 3rd cranial nerve palsy after the third session, but no other complications.
- Brain MRI pre-therapy and 6 months post-therapy showed normal Hypothalamic-Pituitary (HP) structures.
- He had normal thyroid function at baseline, but 5 months post-therapy he had low free thyroxine (FT4) with normal thyroid stimulating hormone (TSH), which was not followed.
- At age 4 (2.8 years post-therapy) he complained of headache, abdominal pain and fatigue, prompting an evaluation which showed abnormal thyroid function testing, later confirmed to be consistent with diagnosis of central hypothyroidism (Table 1).
- Other pituitary functions were normal, except for low morning cortisol of 4.7 ug/dL (RR: 4.8-19.5 ug/dL) consistent with central adrenal insufficiency.
- Treatment with hydrocortisone and levothyroxine led to resolution of his symptoms.

Timeline	TSH Values (in mIU/L) Ref Range: 0.50-4.30 mIU/L	Free T4 Values (in ng/dL) Ref Range: 0.9-1.8 ng/dL
Baseline	2.87	1.21
5 months post chemotherapy	3.01	0.7
2.8 years post chemotherapy	1.88 (TSH untreated)	0.7
2.8 years post chemotherapy	1.95 (TSH treated with HAMA)	0.7 (FT4 done by equilibrium dialysis)
3 months post thyroxine replacement	-	1.35

Table 1: Timeline of laboratory values

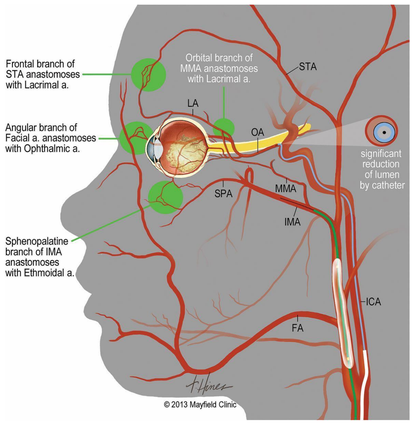

Figure 1 (on left): Ophthalmic artery (OA) is selectively infused with chemotherapy while external carotid artery (ECA) is blocked temporarily with a balloon catheter which promotes strong anterograde flow in OA and it's anastomoses (shown in green circles) to allow chemotherapeutic agents to reach the eye[(3)]. However sometimes there can be a retrograde flow during this procedure which can lead to spilling of chemotherapy into the internal carotid artery (ICA) and its branches that supply the HP structures, which could lead to exposure of the hypothalamic pituitary axis to toxic chemotherapeutic agents.

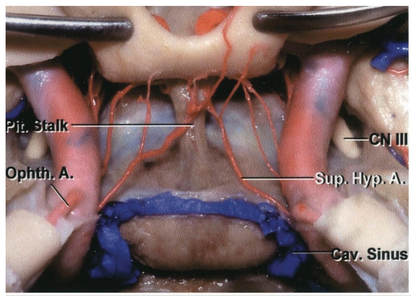

Figure 2 (on right): Shows the branches of ICA including OA that supplies the eye and superior hypophyseal artery that supplies to hypothalamic and pituitary regions [(4)].

DISCUSSION

- Unlike radiotherapy induced HP injury, the risk conferred by chemotherapy is unclear.
- HP dysfunction is seen in intrathecal chemotherapy, and there appears to be a increased risk with high dose systemic alkylating agents as well [(1)].
- During OIAC, orbital blood flow temporarily changes, which can sometimes result in a retrograde flow through intracranial arteries [(2)], this retrograde flow may cause exposure of HP structures to very high doses of chemotherapy drugs.
- Our case denotes an acquired HP dysfunction, with no other precipitating factor, suggesting it may have been due to HP exposure to high dose chemotherapy following OIAC and iVitC.

CONCLUSION

- Our case highlights the possibility of HP injury following localized high dose chemotherapy through OIAC and iVitC.
- As these therapies gain notoriety in RB treatment, understanding their endocrine effects is crucial.
- Further studies are needed to assess the risk of HP dysfunction in patients receiving similar therapies, and determine appropriate screening.

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