Disruption of Hypothalamic Regulation of Appetite Associated with Proton Beam Therapy

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Introduction

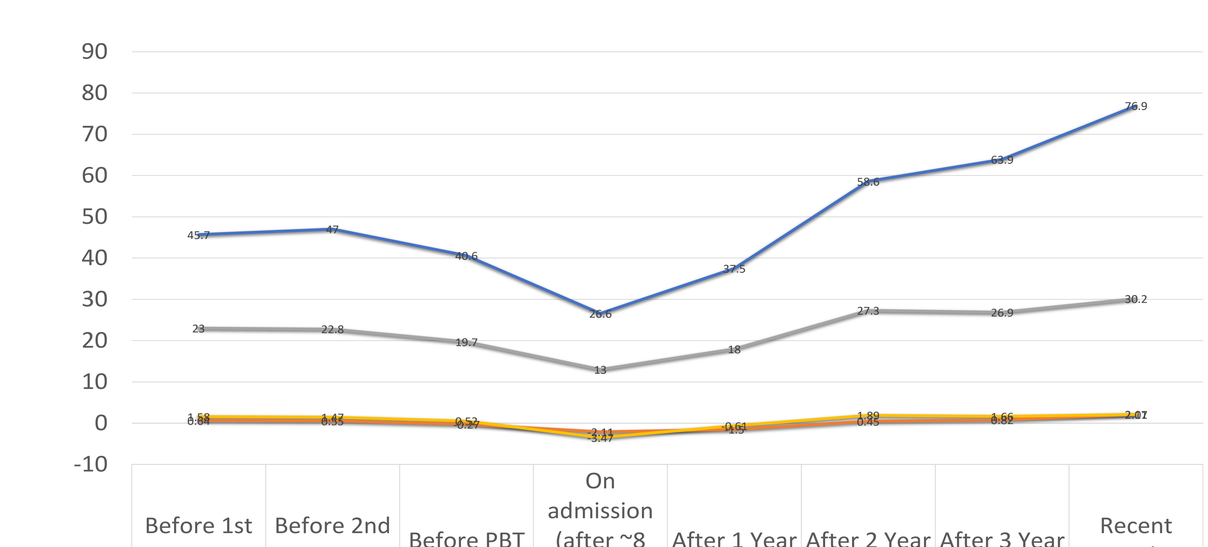
- Proton beam therapy (PBT) is being used increasingly for the treatment of craniopharyngioma[1] because radiation dose to the temporal lobe, the hypothalamus and the optic apparatus is reduced. This is perceived as a major benefit; however its real therapeutic gain has yet to be established[2].
- We are report two patients diagnosed with craniopharyngioma, treated with PBT, who and presented with profound anorexia and weight loss following irradiation.

Case 1

- A 12 year old girl presented with history of headache, generalised tonic-clonic seizure
- MRI revealed obstructive hydrocephalus and posterior fossa tumor
- Hydrocephalus was drained and an ommaya reservoir was inserted
- A near total resection of the craniopharyngioma was performed leaving minimal tumor adherent to the posterior cerebral artery and hypothalamus.
- Assessment of pituitary function following surgery demonstrated panhypopituitarism, including diabetes insipidus.
- 4 months following surgery, she received PBT (50.44CGE in 28 daily fractions)
- She became anorexic with weight loss (BMI SDS decrease by 1.84) (Figure 1).
- After vigorous monitoring and continuous active intervention she gained weight
- Over period of years developed excessive eating and obesity requiring intervention.

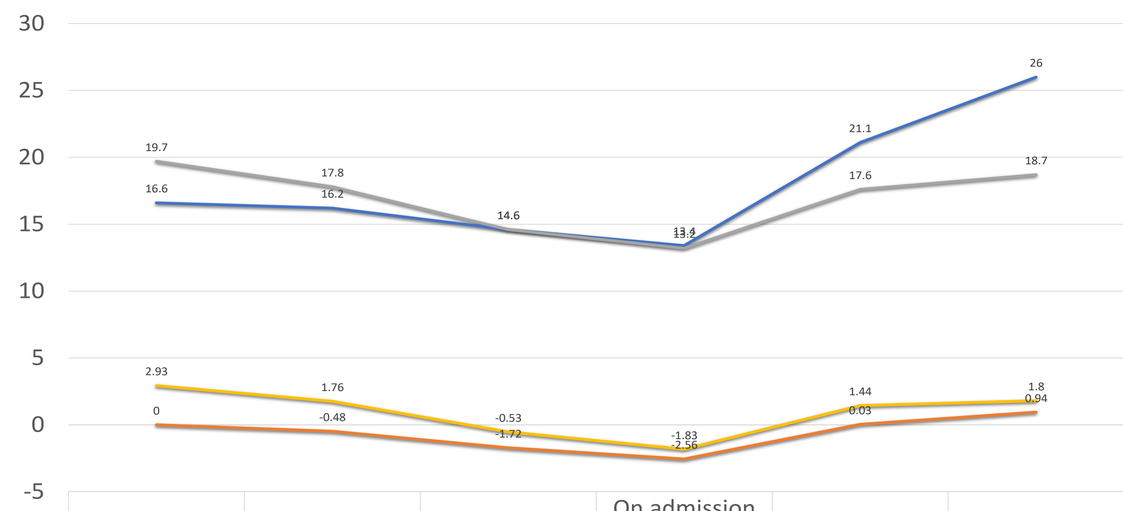
Case 2

- A 4 year old boy with short stature was diagnosed with growth hormone deficiency.
- MRI revealed a suprasellar tumour.
- A subtotal resection removed all tumor except small layer at pituitary stalk and base of hypothalamus. Histology confirmed craniopharyngioma
- Assessment of pituitary function following surgery demonstrated panhypopituitarism, including diabetes insipidus.
- Four months following surgery MRI revealed a moderate-size cyst, which was fenestrated and an ommaya reservoir was inserted
- Eleven months later he received PBT (54 CGE in 30 daily fractions)
- Following PBT there was an abrupt onset of anorexia.
- and BMI decreased ≃ 2SD, requiring supported nutrition by gastrostomy.
- One year following PBT, appetite recovered and gastrostomy was removed.



	Before 1st Surgery	Before 2nd Surgery	Before PBT	On admission (after ~8 weeks of PBT)	After 1 Year	After 2 Year	After 3 Year	Recent weight
Weight (Kg)	45.7	47	40.6	26.6	37.5	58.6	63.9	76.9
Weight (SD)	0.64	0.55	-0.27	-2.11	-1.5	0.45	0.82	2.07
BMI(Kg/m2)	23	22.8	19.7	13	18	27.3	26.9	30.2
BMI (SD)	1.58	1.47	0.52	-3.47	-0.61	1.89	1.66	2.11

Figure 1: Serial weight and BMI of case 1



	Before 1st Surgery	Before 2nd Surgery	Before PBT	On admission (after ~8 weeks of PBT)	After 1 Year	Recent weight
Weight (Kg)	16.6	16.2	14.6	13.4	21.1	26
Weight (SD)	0	-0.48	-1.72	-2.56	0.03	0.94
BMI(Kg/m2)	19.7	17.8	14.6	13.2	17.6	18.7
BMI (SD)	2.93	1.76	-0.53	-1.83	1.44	1.8

Figure 2: Serial weight and BMI of case 2

Discussion

- The most recent advances in the treatment of craniopharyngioma, including precision radiotherapy, focus on minimizing treatment-related toxicity.
- Cranial irradiation is a leading cause of hypothalamic and pituitary injury. The hypothalamus has a critical role in energy homeostasis, which is regulated by a complex neuroendocrine system. Injury to the hypothalamus can lead to anorexia, weight loss or obesity[3].
- A proton has a defined maximum penetration depth, called the Bragg peak, at which the majority of its energy is released over a few millimeters beyond which it has no energy[4] and early clinical results report good favorable clinical outcomes.
- A relative low rate of hypothalamic dysfunction has been described associated with PBT as compare to conventional radiotherapy. However, a recent study shows an association of radiation dose with hypothalamic and pituitary damage[5].

Conclusion

- Although PBT is generally well-tolerated for the treatment for craniopharyngioma, long-term follow up and larger cohort studies are necessary to establish whether dosimetric advantages of PBT translates to clinical benefits in in reducing long-term toxicity
- Hypothalamic involvement of craniopharyngioma and treatment-related lesions of hypothalamic areas are major risk factors for impaired survival, neuropsychological deficits.
- Any patient receiving PBT/conventional radiotherapy should be followed up for acute and long term sequalae of radiation.
- Until further data regarding the long term outcomes of PBT treated patients are available, we suggest surveillance should be based on radiation dose, rather than the modality of radiation delivery.

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