

Background: The brain plays a key role in energy intake and expenditure. This includes homeostatic control of energy balance mainly through **hypothalamic neurons**, as well as **neurons in the hindbrain** in the area postrema and nucleus tractus solitarius (NTS). Both regions have a leaky blood brain barrier and that are involved in regulating hunger and satiety.

Glucagon-like peptide -1 (GLP-1) is an incretin hormone released from the enteroendocrine L-cells of the stomach. It is also produced in preproglucagon-expressing neurons in the NTS. GLP-1 and GLP-1 agonists have can promote weight loss through central anorectic effects via receptors expressed in the hypothalamus and hindbrain, and regulate glucose and lipid metabolism through humoral and neural actions, in the peripheral and central nervous systems, as shown in **Figure 1**.

While hypothalamic obesity is a well-recognized consequence of lesions such as craniopharyngiomas and other tumors in the hypothalamic region, less is known about obesity related to tumors in other brain regions. Recent studies have demonstrated beneficial effects of GLP-1 agonists in obesity due to hypothalamic damage, potentially via hindbrain signaling as this area is still intact. On the other hand, given the actions of endogenous GLP-1 in the hypothalamus on eating behaviors, GLP-1 agonists could theoretically benefit patients with obesity due to brainstem lesions.

Case: The child presented at 14 years of age with fainting episodes associated with severe obstructive sleep apnea and hypophonia. He was found to have a heterogeneous mass in the medulla extending inferiorly past the foramen of magnum into the cervical spinal cord, measuring 3.3 x 3.3 x 5.6 cm; lateral, third and fourth ventricles were diffusely enlarged. Surgical resection ensued and this was found to be a ganglioglioma, positive for a BRAF mutation. He was then started on a tyrosine kinase inhibitor, vemurafenib. In monitoring for adverse effects of vemurafenib, he was found to have glucosuria. He had a HbA1C of 6.6%, and thus was referred for endocrine evaluation.

Medical history was significant for *early onset morbid obesity*, with a normal birth weight of 3.6 kg but obese by 2 years of age. While he did not have true hyperphagia except for the brief period that he was on dexamethasone just after tumor diagnosis, he described **long-standing issues of obsession with food and nighttime food cravings**. He maintained a high level of physical activity, 1 hour per day at least 5 days/week. He denied polyuria or nocturia but did have polydipsia. On examination, his BMI was 44 kg/m², blood pressure 136/73. General appearance was that of a severely obese young man. Pertinent findings include severe acanthosis nigricans, mid-puberty. His growth curve is shown in **Figure 2**.

Diabetes autoantibodies were negative; random insulin level was 195 mIU/ml. **Brain imaging revealed the site of the tumor and subsequent resection bed involved the area encompassing the nucleus tractus solitarius (NTS)** (**Figure 3**). **Figure 4** demonstrates the site of the NTS and its actions.

He was started on metformin, with improvement in his HbA1C but no change in weight or appetite. **He was then started on once-weekly long-acting exenatide, (Bydureon), a GLP-1 agonist; HbA1C became normal at 5.0%, BMI z-score decreased by 0.12 within 3 months (as shown in Figure 4), and food preoccupation has resolved.**

Conclusion: This case represents obesity and diabetes in a child with a brainstem lesion involving the region of the NTS, a site known to be involved in body weight regulation. Treatment with a GLP-1 agonist was effective for diabetes as well as eating behaviors, and weight stabilized. Consideration of the multiple central nervous system sites involved in appetite and weight regulation may allow for effective treatment of children with brain tumors, beyond those affecting the hypothalamus.

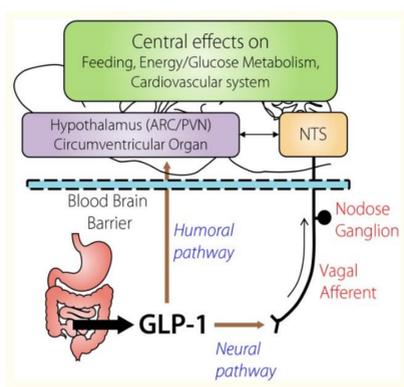


Figure 1: Central and peripheral, humoral and neural actions of GLP-1

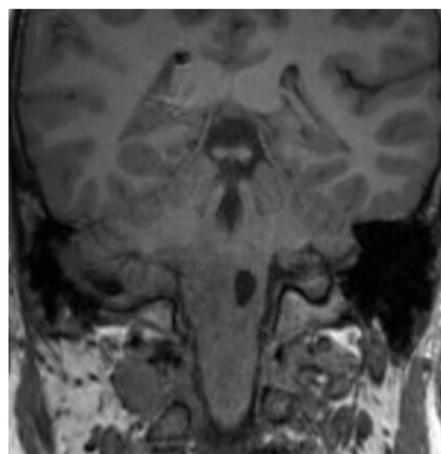
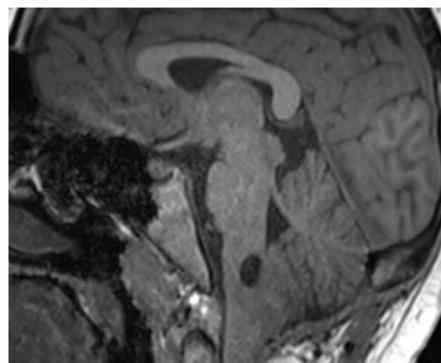


Figure 2: Sagittal and coronal brain MRI of this child

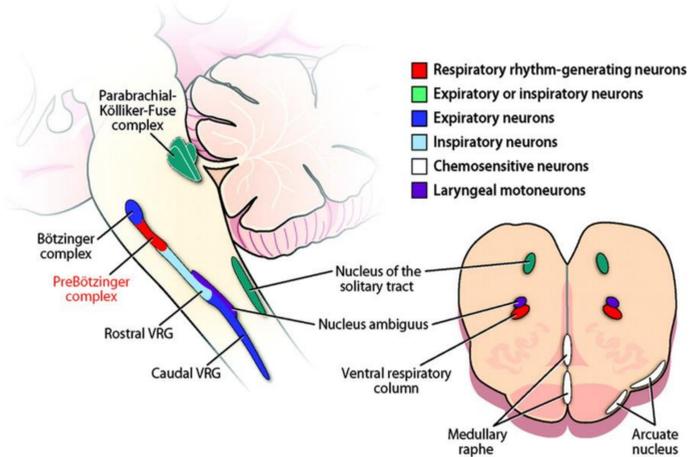


Figure 3: Brainstem regions involved in key functions

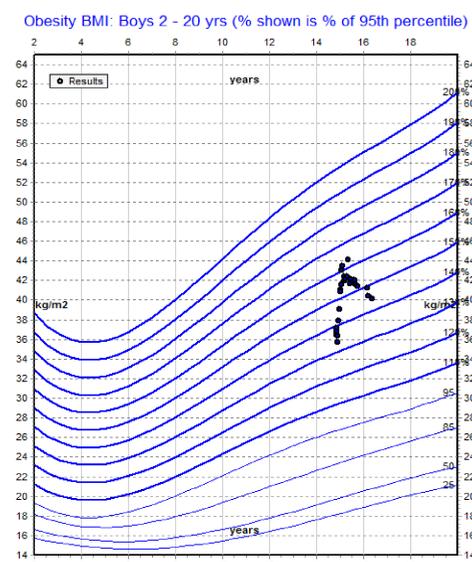


Figure 4: Growth chart of case