Methylphenidate Reversal of Executive Dysfunction in a Patient with Bi-Frontal Lobe Glioblastoma

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ABSTRACT

An elderly man with advanced glioblastoma developed neuro-cognitive deficits that were reversed by methylphenidate. After tumor resection from the right frontal lobe, he received cranial irradiation, temozolomide and Tumor Treating Fields (TTFields). MRI afterwards showed enhancements near the resection cavity and the contralateral frontal lobe. The patient experienced mild executive dysfunction that was not limiting his activities. Adjuvant temozolomide was started along with TTFields. After 2 cycles, his brain MRI showed stable disease, but he exhibited significant executive dysfunction. Methylphenidate improved his neuro-cognitive slowing in cycles 3 and 4. His disease eventually progressed during the 5th cycle, and he experienced a marked decline in activities. Repeat head MRI revealed tumor progression and cerebral edema. Treatments were discontinued while dexamethasone improved his neurological functions and bevacizumab biosimilar was later added. This case demonstrates the activity of methylphenidate for managing executive dysfunction in patients with glioblastoma while minimizing the use of dexamethasone.

KEYWORDS: executive function; glioblastoma; methylphenidate

INTRODUCTION

Glioblastoma is a devastating malignancy in the central nervous system and the median overall survival of patients is only 24 months despite aggressive standard-of-care treatment consisting of external beam radiotherapy and concomitant daily temozolomide, followed by adjuvant temozolomide and Tumor Treating Fields therapy.[1] At the time of recurrence, patients are typically enrolled in clinical trials, received lomustine, treated with bevacizumab, or placed in hospice, and they usually live for another 6 months before second progression or death. Although survival benchmarks have improved in the past decade, glioblastoma remains incurable, and the disease eventually progresses in an unrelenting fashion during recurrence. The rate of clinical trial participation is low, however, in the order of 8–11%.[2] This is likely due to a large number of patients deemed ineligible because of their deficits arising from locations that significantly impair neurologic performance status. The neuro-oncologist's ability to recognize and manage specific neurologic syndromes will help improve patient eligibility for clinical trials and potentially their treatment outcome.

The prefrontal cortex is responsible for anticipation, planning and execution of a task or an activity. We describe an elderly patient with dysfunction of the prefrontal cortex secondary to glioblastoma, with wild-type IDH-1 on immunohistochemistry and unmethylated *MGMT* promoter on molecular profiling. After radiation and daily temozolomide, the patient experienced neurocognitive slowing, imbalance, and urinary incontinence. These symptoms were attributed to bi-frontal lobe dysfunction. Methylphenidate was able to reverse his neurologic deficits and improve his quality of life. The medication also kept him on treatment to control his glioblastoma for a longer period.

CASE REPORT

The patient is a 74-year-old right-handed man, with no significant past medical history other than prostatic hyperplasia, who experienced confusion, communication difficulties, head bobbing, and a grand mal seizure in November 2021. A non-contrast head CT and a gadolinium-enhanced MRI revealed a heterogeneously enhancing mass measuring 3.6 x 4.0 x 4.6 cm in the right frontal brain with adjacent cerebral edema (**Figure 1**). He received levetiracetam and dexamethasone to control his seizure and brain swelling respectively, and later underwent a craniotomy for partial resection of the mass (**Figure 1).** Pathology was consistent with a glioblastoma with wild-type IDH-1 R132H by immunohistochemistry and unmethylated *MGMT* promoter by molecular profiling. The Ki-67 proliferation index was 40%, indicating a high growth rate. He developed hyperglycemia but it quickly resolved when dexamethasone was rapidly weaned off 10 days after surgery.

After the diagnosis was established, the patient was enrolled in a prospective phase III clinical trial and received involved-field cranial irradiation for 6 weeks concurrent with daily oral temozolomide and Tumor Treating Fields therapy (NCT04471844). Sulfamethoxazole-trimethoprim was started for prophylaxis against Pneumocystis pneumonia because of lymphopenia that developed one month into treatment. Lymphopenia was transient and the medication

Figure 1. MR images before and after gross total resection of glioblastoma. **(A)** Post-gadolinium-enhanced T1-weight MP RAGE image showed a heterogeneously enhancing tumor in the right frontal lobe. (**B**) There was significant cerebral edema in the surrounding brain parenchyma on the right as well as the left frontal white matter. **(C)** Post-gadolinium-enhanced T1-weight MP RAGE image demonstrated gross total resection of the tumor. (**D**) The cerebral edema was also decreased on the right side while the edema in the left frontal white matter became more prominent.

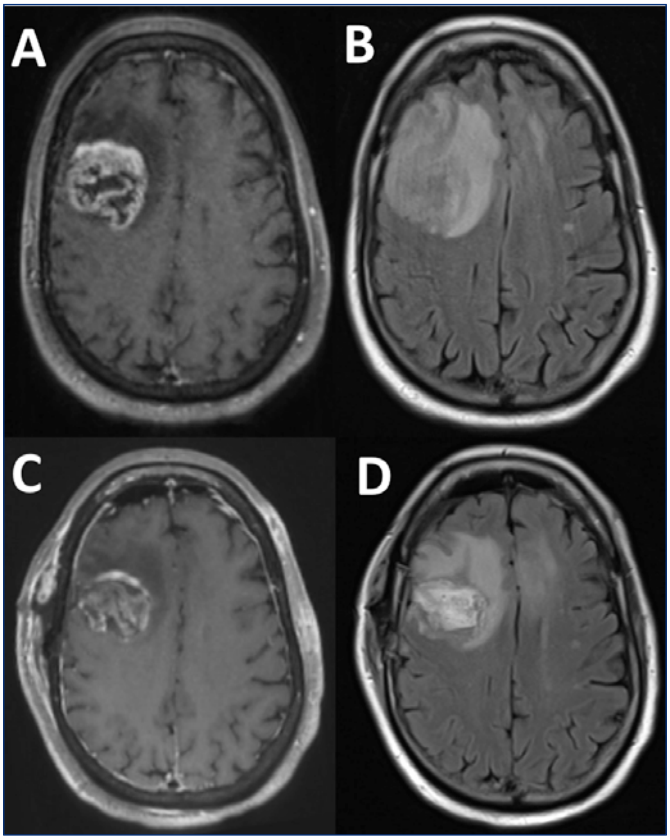
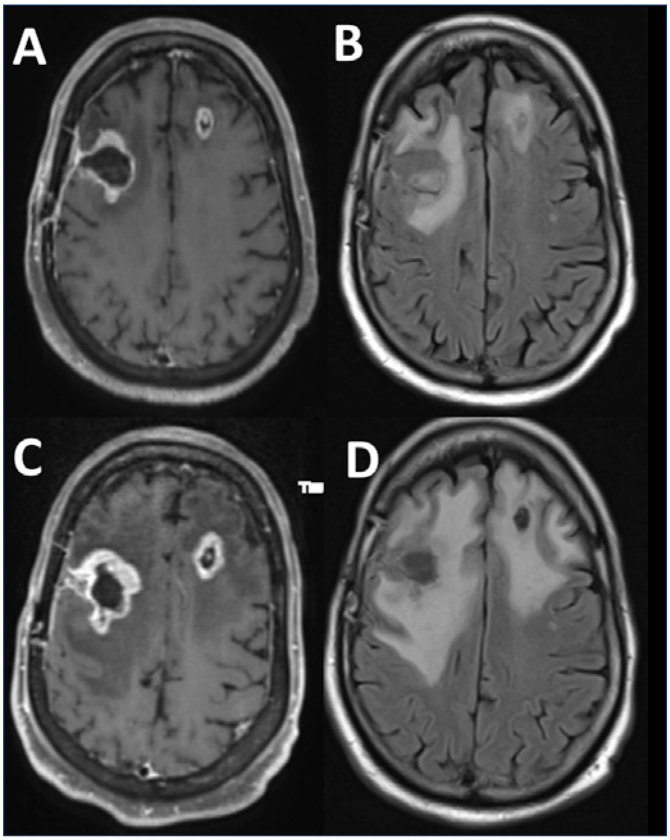


Figure 2. MR images after initial cranial irradiation and after 5 cycles of adjuvant treatment. (**A**) Post-gadolinium-enhanced T1-weight MP RAGE image showed a slight increase in enhancement near the surgical cavity and the contralateral left frontal white matter. (**B**) There was noticeable but mild cerebral edema in the right and left frontal white matter. (**C**) Post-gadolinium-enhanced T1-weight MP RAGE image demonstrated tumor progression in both right and left frontal lobes. **(D)** There was a marked increase in cerebral edema in the white matter of both frontal lobes.



was discontinued after just 4 weeks. Tumor Treating Fields therapy was maintained throughout the entire course of radiation. A post-radiotherapy gadolinium-enhanced MRI showed prominent enhancements in the brain parenchyma anterior and posterior to the surgical cavity, as well as a new 1.4 cm enhancement in the left frontal white matter (**Figure 2**). The patient developed mild neurocognitive dysfunction impairing his ability to perform daily tasks. He also stumbled while walking and once fell forward when hiking on an uneven trail. These symptoms were thought to be a result of executive dysfunction due to bi-frontal lobe pathology exacerbated by radiotherapy.

The patient then proceeded to the adjuvant phase of treatment, consisting of monthly temozolomide at a dose of 150–200 mg/m2/day for five days in monthly cycles and continuation of Tumor Treating Fields therapy. After the first two cycles of treatment, his neurologic symptoms worsened but his repeat gadolinium-enhanced head MRI showed stable disease. Therefore, methylphenidate 5 mg twice daily was added to treat his executive dysfunction, and it was escalated gradually to 10 and then 15 mg twice daily with marked improvement of his symptoms. After two more cycles of adjuvant temozolomide, the patient was still functioning at a high level neurologically and his gadolinium-enhanced head MRI showed stable enhancement patterns. However, during his fifth cycle of treatment, the patient exhibited worsening of neurocognitive slowing accompanied by decreased interaction with his family. He was unable to put on his socks and use utensils to eat his meals. He also stumbled more frequently than before, and developed urinary incontinence and an episode of bowel incontinence. A repeat head MRI revealed increased gadolinium enhancements in both frontal lobes indicating tumor progression (**Figure 2).** Temozolomide and Tumor Treating

Fields were discontinued. He then received dexamethasone 4 mg twice daily, together with omeprazole 20 mg daily, with symptomatic improvement. Metformin 500 mg twice daily was also started due to his pre-diabetes and susceptibility to steroid-induced hyperglycemia. The patient then proceeded to treatment with bevacizumab biosimilar (a monoclonal antibody that has similar biological activity as the bevacizumab originally approved by the United States Food and Drug Administration) for glioblastoma recurrence, and his executive function was maintained while dexamethasone was being weaned.

DISCUSSION

Methylphenidate is a psychostimulant that can modulate cognition.[3,4] Its primary physiological action is to facilitate neural transmission by preventing the reuptake of monoamine neurotransmitters dopamine and norepinephrine, at neuronal synapses.[3] Specifically, pyramidal neurons in layer III of the prefrontal cortex receive dopaminergic and norepinephrinergic afferent fibers from (1) the ventral tegmental area and medial-dorsal thalamic nuclei, and (2) the locus coeruleus, respectively.[5] Increased dopamine and norepinephrine at these synapses result in the potentiation of excitatory activities on these pyramidal neurons. Furthermore, both D1 and D2 receptors mediate the afferent modulation and the D1 receptor definitely has a greater effect than the D2 receptor, and specifically pharmacological blockade of D1 resulted in slower neural processing speed to a greater extent than D2 in mice and primates.[5]

The human prefrontal cortex is essential for functions such as anticipation, planning and execution of a task or an idea.[6] A brain tumor in this location can affect the adjacent neural substrates, either directly by mass effect, cerebral edema, or both, or indirectly by treatment effects or altered cerebral blood flow pattern. Indeed, our patient exhibited neurocognitive slowing impairing his daily functions and he also has bi-frontal lobe impairment characterized by imbalance and incontinence. It has been shown in a prospective clinical trial that methylphenidate improves attention, mood, and behavior in patients with malignant gliomas.[7] Increasing the dose of methylphenidate improves the function of the prefrontal cortex but only up to a maximum, after which the benefit attenuates and side effects emerge. This attenuation of benefit from monoamine neurotransmitters may be a result of desensitization due to their persistent presence at the synapse and continuous stimulation of the D1 and D2 receptors on pyramidal neurons.[8] Therefore, gradual dose escalation of methylphenidate and repeat neurocognitive evaluations are important to determine the minimum dose needed in the patient. Although methylphenidate may attenuate imbalance and risk of falling due to improvement in attention, it does not typically reverse incontinence in the patient.

Modafinil and armodafinil (R-enantiomer of modafinil) are stimulants that are used to treat excessive daytime sleepiness and narcolepsy. They are also monoamine reuptake inhibitors but their effect on the dopamine and norepinephrine neurotransmitter systems is weaker than that of methylphenidate.[9,10] Both drugs also prompt the release of orexin and histamine in the hypothalamus, causing heightened arousal and wakefulness.[9,10] However, in randomized clinical trials, neither modafinil nor armodafinil showed efficacy in improving cognition of brain tumor patients.[11,12] This failure may be foreseeable because methylphenidate is more potent than modafinil or armodafinil in modulating dopamine and norepinephrine reuptake at the synapses. Furthermore, activation of the pre-frontal cortex by hypothalamus-originated orexin and histamine may be attenuated due to their indirect influence on only a subset of dopaminergic and norepinephrinergic neurons from the ventral tegmental and locus coeruleus areas.[13]

Patients treated with cranial radiotherapy often have neurologic syndrome attributable to treatment effects. In patients with small cell lung cancer who received prophylactic whole brain irradiation, hypometabolism manifesting as low FDG uptake on PET scan can be found in the frontal lobes.[14] Compared to prophylactic radiotherapy at 2,500 or 3,000 cGy in 10 fractions, the biological equivalent for our patient's radiation treatment for glioblastoma (6,000 cGy in 30 fractions) is substantially higher and most of it is directed at the bi-frontal brain.[15,16] It is likely that, for a period of 4 months after radiation during which pseudo-progression can cause clinical deterioration, our patient experienced impaired executive dysfunction secondary to subacute radiation-induced encephalopathy and not from tumor progression. Indeed, on his head MRI, there was no change in the extent of gadolinium enhancements or FLAIR signal changes. The addition of methylphenidate greatly improved his neurocognitive processing speed, imbalance, and urinary incontinence. But his glioblastoma eventually progressed when his head MRI showed increased gadolinium enhancements. Therefore, prompt recognition of executive dysfunction and treatment with methylphenidate prevented the premature declaration of neurologic progression in our patient during his participation in a clinical trial.

In summary, this case illustrates the importance of methylphenidate for managing executive dysfunction, which is a modifier of treatment outcome in our glioblastoma patient. Future clinical trial testing will be needed to evaluate the efficacy of methylphenidate combined with other neurocognitive enhancement drugs.

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