Neurol Sci (2011) 32 (Suppl 2):S229–S231
DOI 10.1007/s10072-011-0793-z

Metabolic, electrolytes disorders and tromboembolic risk in malignant glioma patients

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Published online: 13 October 2011

Abstract In malignant gliomas, the management of symptoms and minimization of side effects assume major importance. Corticosteroids provide transient relief from neurological symptoms. However, treatment with steroids is also commonly associated with considerable side-effects including: hyperglycemia, osteoporosis, myopathy, lymphopenia and others. Sometimes, antiepileptic drugs may contribute to clinical decline of neuro-oncological patients in stable disease not only by neuropsychological impairment but also by metabolic interations. Several studies have demonstrated a high frequency of hyponatremia among patients treated with carbamazepine and particularly with oxacarbamazepine. Venous thromboembolism is a common complication in patients with cancer and it is particularly high in malignant gliomas, occurring in approximately 20–30% of such patients. Prophylactic treatment in patients with glioblastoma is a key topic. The role of prophylaxis has not yet been established with certainty. Overall the data show a clear reduction of venous thromboembolic events in patients treated with intermittent pneumatic compression (IPC). The addition of enoxaparin dose of 6.000 UI, starting in the perioperative period, induces an increase of major bleeding events. In the absence of availability of IPC, the use of enoxaparin 4.000 UI in addition to graduated compression stockings, reduces thromboembolic events without major bleeding events.

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Keywords Glioblastoma · Steroids · Side effects · Venous thromboembolism

Brain tumors are rare diseases and the survival for brain tumor patients is not substantially changed over the last 20 years. In this disease, the management of symptoms and minimization of side effects assume major importance. Corticosteroids are extensively employed in brain tumors. They provide transient relief from neurological symptoms caused by increased intracranial pressure and edema associated with brain tumors [1]. However, treatment with steroids is also commonly associated with considerable side-effects including: hyperglycemia, osteoporosis, myopathy, lymphopenia and others. Hyperglycemia is a troubling consequence of chronic steroid therapy, an excess of steroids impairs the suppression of glucose production and stimulation of glucose utilization, which might cause diabetes mellitus or aggravate preexistent diabetes. The risk of developing diabetes is more frequent in elderly patients. Concerning hyperglycemia management, the ideal goal would be to maintain stable blood glucose without significant fluctuations during the steroid treatment period. A realistic goal would be to aim for fasting blood glucose between 120 and 140 mg/dL to prevent hyperosmolar or ketotic events, while minimizing the risk of precipitating a hypoglycemic episode. A reasonable goal for postprandial blood glucose is <200 mg/dL [2]. The first steps in the management of steroid diabetes are diet and exercise. The role of oral agents in the cancer patient with steroid diabetes is limited because of potential side effects, slow onset of action, and some lack of flexibility, because of these reasons for most patients, insulin will be a more appropriate therapy than oral agents. For many patients, a basal insulin in the morning and then a standard dose of short-acting insulin before meals will offer for the best result.

Glucocorticoid-induced osteoporosis (GIO) is the most common cause of secondary osteoporosis. As a consequence, patients exposed to glucocorticoids are at an increased risk of fractures sometimes with dramatic clinical features [3]. Several guidelines advocate the following measures for the prevention and treatment of GIO: general health awareness, the administration of calcium and vitamin D, reduction of the dose of corticosteroids to a minimum, and therapeutic intervention with bisphosphonates or alternate agents.

The exact incidence of steroid myopathy is unknown; moreover, sensitivity to steroids varies among patients [4]. Usually, it occurs after prolonged use of corticosteroids. Steroid myopathy is typically an insidious disease process that causes weakness mainly to the proximal muscles of the upper and lower limbs and to the neck flexors. Patients typically complain of a progressive inability to rise from chairs, climb stairs, and perform overhead activities. Some authors have shown involvement of the respiratory muscles thus, pulmonary symptoms could be identified [5]. The main treatment recommendations for steroid myopathy are a decrease in the dose of steroid below a threshold level or the discontinuation of the corticosteroid's use. Alternate-day dosing could also be considered.

Sometimes, antiepileptic drugs may contribute to clinical decline of neuro-oncological patients in stable disease not only by neuropsychological impairment but also by metabolic interations. Several studies have demonstrated a high frequency of hyponatremia among patients treated with carbamazepine (CBZ) and particularly with oxacarbamazepine (OXC) [6]. Approximately 60% of persons older than 40 years receiving OXC had hyponatremia compared to about 20% of those in the same age range receiving CBZ. Moreover, increasing the number of combination antiepileptic drugs increased the risk of hyponatremia. If any patient taking OXC or CBZ presents with symptoms, such as headache, general malaise, gait disturbance, and somnolence, the serum sodium should be measured promptly, and if hyponatremia is confirmed, the antiepileptic (OXC or CBZ) should be reduced or replaced.

Hematologic toxicities as thrombocytopenia and leukopenia of valproate are common, vary in onset and severity, usually are dose dependent and combination with chemotherapeutic agents increased the risk of these toxicities. Caution for elective surgery is advised for the increase of von Willebrand factor levels and impairment of platelets function [7]. Moreover, carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid were found to interact most frequently with anticancer drugs. Clinicians should be cautious when antiepileptic drugs are prescribed concurrently with anticancer drugs. In general, the use of enzyme-inducing antiepileptic drugs (EIAEDS) is discouraged.

The hypothalamic–pituitary unit is particularly a radiosensitive region in the central nervous system [8]. As a consequence, hypopituitarism (RIH) commonly develops after radiation treatments not only for sellar and parasellar neoplasms but also for extrasellar brain tumors. In adult patients the most common symptoms are: anorexia, weight loss, fatigue, tiredness, weakness, dizziness and postural hypotension, gastrointestinal symptoms, arthralgia and myalgia, intolerance to stress and infection. While hypothalamic–pituitary sparing techniques are being developed, strategies for risk assessment and early recognition of RIH and other adverse effects should be initiated at completion of radiation treatments.

Venous thromboembolism (VTE) is a common complication in patients with cancer and it is particularly high in malignant gliomas, occurring in approximately 20–30% of such patients. Most attention has focused on the postoperative period, but evidence suggests that the incidence remains high in all perioperative period. The mechanism of development of VTE is unclear, but the risk factors include histologic diagnosis of glioblastoma multiform, larger tumor size, paresis, older age, longer time surgery, chemotherapy, and steroids [9].

Prophylactic treatment in patients with glioblastoma is a key topic. The role of prophylaxis has not yet been established with certainty, and in various neurosurgery and intensive care units the practice is inconsistent. To prevent these complications, there are pharmacological methods, which include the use of heparin and low molecular weight heparin, and mechanical methods like intermittent pneumatic compression device and graduated elastic compression stockings. But it is unclear when treatment should start, which is the most beneficial for glioblastoma patients, and the benefits of prophylactic treatment. We performed a systematic review of the literature in Medline (since 1970), from which we identified eight randomized controlled trials in which physical methods and/or drugs were evaluated in the perioperative prophylaxis of neurological patients. The active treatment was represented by IPC (intermittent pneumatic compression) of lower limbs, heparin calcium, heparin chloride, enoxaparin, nadroparin, or by dalteparin.

Overall the data show a clear reduction of venous thromboembolic events in patients treated with IPC; IPC should be initiated preoperatively and continued until discharge or longer in case of persistence of risk factors (paresis). The addition of enoxaparin dose of 6.000 UI, starting in the perioperative period, induces an increase of major bleeding events. In the absence of availability of IPC, the use of enoxaparin 4.000 UI in addition to GCS (graduated compression stockings), starting the day after surgery, reduces clinically manifest thromboembolic events without major bleeding events.

Conflict of interest The authors certify that they have no conflict of interest related to the publication of this article.

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