Side Effects of Therapies for Brain Tumours

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7.1 Introduction

The brain is the most complex organ in the body and although there are some areas of the brain that are more "eloquent" (e.g., the speech centre, motor and sensory strips, dominant temporal lobe and optic radiations) than others (frontal lobes, non-dominant temporal lobe), all are important. Where tests are not sophisticated enough to show a problem, this does not mean that the person will be free from problems affecting day-to-day abilities.

Focal therapies such as surgery, focal radiotherapy or intra-tumoural chemotherapy and local gene therapy may produce either immediate, sub-acute or late side effects in many patients, some of which will be evident and others which will go unnoticed, if not checked for systematically.

Systemic therapies aimed at symptomatic control of oedema (e.g., dexamethasone), the effect of the tumour on cortical neurones (anti-epileptic drugs [AEDs]) or the tumour (e.g., systemic chemotherapy; immunotherapy), will largely produce similar multi-system allergic or toxic side effects profiles. There may be some specific organs or structures that are more susceptible to toxicity. Largely, side effects will fall into the categories of early allergic or dose-dependent toxicity – which will be reversible by drug withdrawal or dose reduction – or late cumulative toxicity, which largely will be irreversible and may even progress despite drug withdrawal, e.g., nitrosourea-related pulmonary fibrosis and cisplatin-related neuropathy.

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7.2 Symptomatic Medication Complications

Avoidance of side effects starts with consideration of whether a therapy is really required. Symptomatic management with dexamethasone in the perioperative period is only required where there is headache suggestive of raised intracranial pressure or where there is a focal neurological deficit that is causing distress. The dose of dexamethsone should be in line with the severity of the symptoms and requirement for a fast symptomatic response. Dexamethasone is not required for tumour-associated epilepsy. Similarly, the prescription of AEDs in patients who have never had a seizure is increasing and is now often included in perioperative protocols in some centres, without acknowledgement that there is inadequate evidence for the efficacy of prophylactic AEDs and in the certain knowledge that 10–15% of patients are likely to experience side effects. These may be difficult to distinguish from the effect of the tumour or surgery, e.g., fatigue and neurocognitive, personality and mood-related effects. Prophylactic proton pump inhibitors (PPIs) or H2 receptor antagonists are inadvertently continued in >6% of hospital discharges without any evidence of a requirement to be on these drugs, when dexamethasone is discontinued [1].

(a) *Dexamethasone*

Dexamethasone is the most common steroid used. The benefit of steroids, when used at the appropriate doses and timings, are obvious and almost always outweigh the risk of side effects. However, dexamethasone should be used cautiously in the elderly, especially if there is heart, liver or renal failure; diabetes; hypertension; glaucoma or a past history of severe psychosis. Early side effects include sleep disturbance, emotional lability and psychiatric, gastrointestinal and endocrine symptoms. Insomnia is very common, particularly if the drug is prescribed after 12 midday. Neuropsychiatric effects, such as euphoria, anxiety, acute confusion and psychosis, usually occur early and are dose related. Gastrointestinal symptoms include dyspepsia, abdominal distension and, rarely, gastrointestinal ulceration or acute pancreatitis. Gastrointestinal side effects can be minimised by keeping the steroid dose as low as possible and giving an H2 receptor antagonist or a PPI (e.g., omeprazole, lansoprazole). Endocrine effects of dexamethasone, such as increased appetite, unmasked diabetes, and increased susceptibility to infection, e.g., candida, occur early, within the first few weeks, while weight gain is a late effect as a result of the increased appetite, reduced mobility and the effect of dexamethasone on metabolism and body deposition of fat. Ankle oedema, skin atrophy, bruising, striae, and acne can occur after a few weeks at high dosage (e.g., 4 mg twice daily). Rarely, an acute myopathy can come on within a week of a patient starting high-dose corticosteroids, but more commonly, a proximal myopathy starts after a few weeks; this is painless and mainly affects the proximal lower limb muscles and proximal upper limbs to a lesser extent. It is twice as common in women than in men. Recovery after withdrawal can take weeks or months. With long-term usage, elevation in blood

sugar occurs in 47–72% of patients, peripheral oedema in 11%, anxiety or psychiatric disorders in 10%, oro-pharyngeal candidiasis in 6–8%, Cushing's syndrome in 15% and muscular weakness in 60%. Osteoporosis with vertebral fractures, avascular necrosis of the hip and tendon rupture are the result of long-term high-dose usage, as is psychological dependence and fatigue associated with adrenal suppression. Ophthalmological complications such as worsening of glaucoma are a rare, but serious, early complication, while cataract and scleral thinning occur commonly with prolonged use.

Withdrawal of dexamethasone after usage for some months should be done slowly. It may be associated with changes in mood, the development of myalgia/muscle cramps, arthropathy, or headaches. Dexamethasone withdrawal headache is non-specific and may lead to the reinstatement of higher doses due to concerns of raised intracranial pressure. Imaging evidence of reduced tumour mass effect and patient re-assurance and education that dexamethasone withdrawal can cause headache, may aid eventual withdrawal and limit psychological dependence. Dexamethasone-induced adrenal insufficiency from long-term dexamethasone may persist for 6–12 months after the withdrawal of dexamethasone.

(b) *Anti-epileptic drugs (AEDs)*

Early allergic responses that necessitate the withdrawal of AEDs include hypersensitivity syndrome, which is characterized by multi-system involvement, fever, lymphadenopathy, rash, abnormal liver function and eosinophilia. More commonly, a less severe rash occurs in 5–10% of patients within the first 2 months of taking enzyme-inducing AEDs (phenytoin, phenobarbital, carbamazepine) or lamotrigine. There is cross-reactivity between these AEDs. Accompanying steroids may lessen or delay the appearance of allergic rash, which might only subsequently appear on steroid withdrawal. Levetiracetam, valproate, topiramate, or tiagabine are moderately safe alternative choices of AEDs with a lower risk of rash. All AEDs (especially valproate) can cause serious hepatic toxicity and liver failure. Although this is rare, it is advisable to monitor liver function during the introduction of AEDs and for the following 6 months. The incidence of haematological toxicity is low, but valproate may cause dose-dependent thrombocytopenia (Table 7.1). Carbamazepine can cause a mild neutropenia and hyponatraemia that may influence the later use of chemotherapy. Valproate is often associated with weight gain, especially if the patient is also taking dexamethasone. Valproate can also inhibit platelet aggregation and the coagulation cascade, which may lead to a higher tendency to haemorrhage when used with heparins, warfarin or non-steroidal anti-inflammatory drugs. Valproate can also cause fine tremor, which is often more noticeable in the hemiparetic limb. Toxicity from any of the AEDs may lead to dysarthria, diplopia, ataxia with nystagmus, lethargy and weakness, and can be easily mistaken for tumour progression, although the presence of nystagmus and intermittent diplopia and the absence of papilloedema or focal neurological deficits are helpful pointers to the likely diagnosis of AED toxicity. Idiosyncratic side effects of AEDs include headache; cognitive, speech or

Table 7.1 Cautions, toxicity and side effects of anti-epileptic drugs commonly used in tumour-associated epilepsy

Carbamazepine	Cautions	Hepatic, renal, cardiac disease. Glaucoma
	Toxicity	Diplopia, dizziness; confusion, ataxia, tremor
	Side effects	Early severe blood disorders and leucopenia. Rash, hypersensitivity reaction, agitation; jaundice, renal failure, depression, psychosis, alopecia, hyponatraemia, oedema, osteomalacia
Lamotrigine	Cautions	Hepatic, renal disease
	Toxicity	Diplopia, dizziness; confusion and ataxia
	Side effects	Early severe blood disorders and aplastic anaemia and leucopenia. Rash, hypersensitivity reaction, flu-like illness, worsening seizures; dizziness, drowsiness, insomnia, headache, agitation
Levetiracetam	Cautions	Hepatic, renal disease
	Toxicity	Drowsiness, tiredness and dizziness
	Side effects	Drowsiness, tiredness and dizziness. Rarely, amnesia, psychiatric symptoms (e.g., aggression), insomnia, headache, rash, anaemia (folate deficiency)
Phenytoin	Cautions	Hepatic disease
	Toxicity	Diplopia, dizziness; confusion, ataxia, tremor
	Side effects	Early severe blood disorders and leucopenia. Rash, agitation, jaundice, systemic lupus erythematosus, hypersensitivity reaction, depression, psychosis, gum hypertrophy, peripheral neuropathy, megaloblastic anaemia, osteomalacia
Topiramate	Cautions	Hepatic and renal disease. May cause secondary acute angle closure glaucoma in myopes in first month
	Toxicity	Diplopia, dizziness; confusion, ataxia, tremor
	Side effects	Rash, agitation; leucopenia, jaundice, weight loss, paraesthesia, memory problems, fatigue, speech problems, depression, psychosis
Valproate	Cautions	Hepatic disease, clotting disorders. Pancreatitis
	Toxicity	Tremor. Diplopia, dizziness; confusion, ataxia
	Side effects	Leucopenia, alopecia, weight gain, gastrointestinal side effects, memory problems, dementia, gynaecomastia

memory problems; or psychiatric symptoms. Patients with cognitive problems may be best suited to using agents, e.g., levetiracetam, lamotrigine, tiagabine or oxcarbazepine by extrapolation from studies in people with non-tumour-associated epilepsy. Obese patients may benefit from topiramate or zonisamide, as these have a tendency to produce weight loss, but topiramate may cause memory, concentration and speech problems and acute angle closure glaucoma. These phenomena reverse when the drug is withdrawn. Levetiracetam, commonly used as a first-line AED in brain tumour patients, can cause fatigue, or personality change with anger and irritability or low mood in 10–15% of cases and causation may be difficult to separate from the effect of radiotherapy or tumour or psychiatric issues related to the diagnosis.

(c) *Gastric acid suppressants* (H2 receptor antagonists and proton pump inhibitors)
These agents should only be prescribed if patients are symptomatic or at risk (e.g., on anti-inflammatory drugs or dexamethasone). They can cause headache, dizziness, rash and tiredness and, rarely, confusion, depression and hallucinations. Leucopenia, thrombocytopenia, rash and disturbance of hepatic enzymes are possible. It may be difficult to distinguish the side effects of these agents from those related to AEDs or chemotherapy. Omeprazole and lansoprazole can, rarely, be associated with hyponatraemia, confusion and agitation.

7.3 Surgical Complications

Patients with tumours present with: *progressive focal neurological deficits,* e.g., unilateral motor or sensory symptoms, dysphasia, and visual field defect; *progressive cognitive changes*, e.g., subacute confusion or memory loss; *headache alone or associated with change in personality, mood and memory or associated with papilloedema* and lastly with *late-onset seizures*. Twenty-five percent of an unselected series of people with a brain tumour lacked capacity to give informed consent for surgery when more formally assessed [2]. This is the background from which to determine the side effects profile of surgical procedures.

Specific risks of brain tumour surgery include: seizures, weakness, balance and coordination difficulties, memory and cognitive problems, spinal fluid leakage, meningitis, brain swelling and stroke. General risks include infection, bleeding, blood clots, pneumonia and blood pressure instability. The overall major complication rate is between 27 and 36%, with neurological complications being the most frequently encountered. Infra-tentorial tumour location, age over 60 years, eloquent area, severe pre-operative deficit and severe concomitant disease were risk factors for systemic complications [3]. Previous radiotherapy and re-operations are factors strongly related to the incidence of complications. While most surgical complications are obvious immediately after surgery, some – such as posterior fossa syndrome/cerebellar mutism and supplementary motor area syndrome – may only appear hours or days after surgery and can appear devastating, although both improve significantly in 4–6 weeks [4, 5].

7.4 Radiotherapy Complications

The side effects of radiotherapy are related to demographic, radiation and tumour factors. Age; past medical history (e.g., vascular disease/hypertension); pre-existing brain heath (e.g., stroke, dementia); tumour size and grade; and radiation volume, total dose and fraction size should all be taken into account when considering the likelihood of developing complications from radiotherapy.

1. *Acute reaction*
   If the tumour has not been adequately resected, or steroids are not continued in an appropriately high dose, there is a risk of developing an acute radiation reaction during radiotherapy, with worsening of focal signs or headache and somnolence. This may require an increase in dexamethasone dosage or even consideration of a further debulking. Somnolence usually improves by 6–8 weeks. Hair loss, nausea, anorexia and fatigue can occur within the first 4–6 weeks of treatment.
2. *Early delayed reaction*
   In about one-third of patients, "early delayed" radiation reaction/"pseudo-progression" will occur in the first 3 months after completion of radiation. This presents as tiredness, subtle difficulty in thinking clearly and with memory loss and sometimes confusion or worsening of focal symptoms, possibly with headaches. There may be a need to restart or increase steroids for a few weeks to manage symptoms. Magnetic resonance imaging (MRI) might suggest tumour progression. "Pseudo-progression" is related to demyelination/inflammation and will settle down. Pseudoprogression is more common in glioblastoma with high levels of methylguanine methyl transferase (MGMT) promotor methylation.

   Fatigue is the most common symptom post-treatment. The prevalence of fatigue ranges between 25% and 90% and occurs at all stages of care. The fatigue may be related to primary causes affecting the brain (tumour, irradiation, injury), secondary causes (psychological; sleep disturbance; pain; comorbid conditions [underactive pituitary, infection, malnutrition]), or medication [6]. Medications to treat epilepsy, pain, nausea may contribute to fatigue. Endocrine dysfunction may also contribute to fatigue. Management of fatigue should include the removal of drugs that may be associated with fatigue; advice about sleep and healthy living, diet, and physical exercise; and, if anxiety or depression is present, the management of these through talking therapies, cognitive behavioural therapy, mindfulness, or antidepressants. A Cochrane review of studies on the management of fatigue in adult brain tumour patients [7] found only one randomised controlled trial [8] that included solely patients with high levels of fatigue. The other studies were looking at prevention of fatigue and recruited patients who may or may not have had fatigue at entry. Fatigue is complex and the evidence that a specific drug will significantly help fatigue in everyone is lacking.
3. *Late effects*
   Late effects of radiotherapy are usually degenerative or vascular in nature [9]. The target tissue may be brain, pituitary gland, cranial nerve/end organ and second tumours.

   In the brain, white matter damage, leuco-encephalopathy with ex-vacuo hydrocephalus (Fig. 7.1), is associated with a slow continuous subtle drop-off in memory, attention and executive function. This is particularly the case when the radiotherapy includes the hippocampus. The effect on the developing brain is more pronounced than the effect in adults. Damage to oligodendrocyte 0-2A progenitor cells may result in failure to replace myelin, and damage to astrocytes

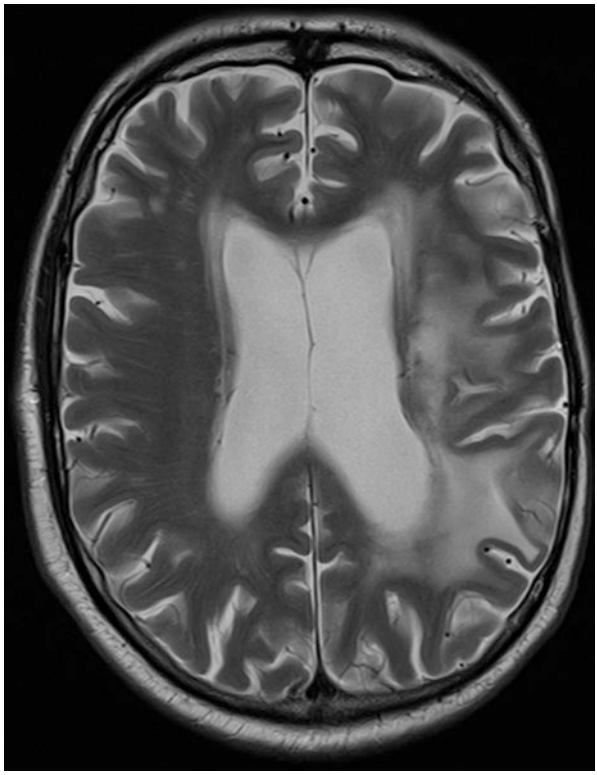

Fig. 7.1 T2-weighted image showing brain atrophy and radiation-related leucoencephalopathic changes

may influence growth factors, with the development of "reactive" astrocytes that express glial fibrillary acidic protein, which releases pro-inflammatory cytokines [10]. Activated microglia may also produce cytokines that mediate a chronic inflammation within the brain [11]. The neuro-pathological correlates show vascular abnormalities, e.g., endothelial cell nuclei damage, capillary loss, and vascular thickening and dilatation [12], breakdown of the blood brain barrier and radiation necrosis with blockage of small blood vessels. These changes are dose and volume related.

(a) *Radiation-induced dementia*

Some identifiable radiation-induced cognitive impairment can be found on neurocognitive testing in up to 90% of adult brain tumour patients who survive for >6 months post-irradiation [13]. Cognitive areas affected early are verbal memory, spatial memory, attention, and problem-solving ability. This is often associated with fatigue and changes in mood. By 2 years about 50% of patients will be aware of cognitive decline and by 5 years after radiotherapy this has increased to between 70–80% [14]. With time either a solely profound memory and cognitive disturbance is found or sometimes a "normal pressure hydrocephalus" like clinical picture will develop with progressive gait apraxia, subcortical dementia and urinary incontinence.

(b) *Radionecrosis*

Radionecrosis is a delayed effect of the radiotherapy that occurs in patients who have survived radiotherapy or radiosurgery. It can occur from 6 months to several years after the radiation treatment, but it usually occurs within the first 1 to 2 years [15]. Clinically it produces subacute progressive focal neurological problems that are difficult to distinguish from tumour recurrence in the irradiated brain. MRI perfusion studies can sometimes be helpful, or MR spectroscopy, which typically shows low choline and creatine and *N*-acetylaspartate (NAA) in radiation necrosis, whereas with tumour recurrence choline, lipids and lactates are increased. Pathologically, radiation necrosis primarily affects the smaller arterioles and arteries, causing coagulative, fibrinoid necrosis of the vascular walls with endothelial thickening and infiltration of lymphocytes and macrophages, resulting in occlusion and infarction. A randomised trial in 200 adult patients with low-grade glioma who received either 50.4 Gy or 64.8 Gy at 1.8 Gy per fraction demonstrated that the 5-year incidence of radiation necrosis was 10% in patients receiving 64.8 Gy versus 5% for those given 50.4 Gy [16].

(c) *Vascular disorders*.

Stroke-like migraine after radiotherapy (SMART)

Stroke-like migraine after radiotherapy (SMART) is a late complication [17]. SMART attacks are more common in patients treated for brain tumours in childhood or in patients living with low-grade glioma. The symptoms come on over minutes or hours with a spread of "negative" phenomena (e.g., numbness, weakness, dysphasia or visual aura) which may help distinguish from stroke which presents with sudden onset, or seizures which produce "positive" phenomena (jerking, tingling) that spreads over seconds. Cases generally also have headache with migrainous features. Occasionally, seizures do occur during an attack and then the differential diagnosis of SMART attack will have to include seizures with prolonged Todd's paresis. Symptoms may take several days or weeks to recover. Diagnosis is based on medical history, clinical characteristics, and radiological investigations. Attacks can start as early as 1 year after treatment or as late as 35 years, but most frequently occur between 1 and 5 years after treatment. Attacks are more frequent in males. Diagnosis requires: (a) a history of cranial irradiation without evidence of recurrent neoplasm and (b) prolonged, reversible signs and symptoms referable to a unilateral cortical region. These may include: "negative" phenomena, such as visuo-spatial deficits, confusion, hemisensory deficits, hemiparesis, and aphasia, or "positive" phenomena, such as seizures. There is often an antecedent migraine headache, with or without aura. Imaging shows transient, diffuse, unilateral cortical gadolinium enhancement of the cerebral gyri, sparing the white matter, within the previous radiation field. Lastly, the condition must not be attributed to tumour recurrence or another identifiable disorder, e.g. posterior reversible encephalopathy syndrome (PRES) related to immunosuppressant drugs or hypertension, where neuroradiological changes involve both hemispheres, usually in the occipital lobes and the MR changes involve the white matter. The MRI abnormalities in SMART demonstrate cortical enhancement on T1-weighted images and T2-weighted images are suggestive of parenchymal hyperperfusion in the

underlying brain. These changes settle. Fluorodeoxyglucose positron emission tomography (FDG PET) has demonstrated hypermetabolism in the involved areas. Electroencephalograms (EEGs) may show slowing over the affected area and a few may demonstrate seizures [18], but epileptiform activity should not put one off the clinical diagnosis of SMART where seizures do not explain the clinical and radiological features.

Stroke

Late ischaemic complications, including transient ischaemic attacks (TIAs) or established ischaemic stroke, can occur as a late effect of cranial radiation on cerebral vessels many years after radiotherapy. TIAs are focal, sudden-onset phenomena with unilateral weakness, numbness, dysphasia, homonymous visual field loss or visual loss in one eye, lasting less than 24 h, whereas stroke will persist and be accompanied by MRI changes to support infarction. Management is as with any new stroke—correction of any risk factors, e.g., smoking, hypercholesterolaemia and hypertension and secondary prevention with anti-platelets, a statin and anti-hypertensives.

Cavernomas and microhaemorrhages

Cavernomas are thin-walled dilated capillary spaces within the brain, found in up to one in 200 people. Cavernomas are thought to be congenital but can be acquired after radiotherapy (Fig. 7.2a, b). Cavernomas have been hypothesized to result from a proliferative vasculopathy that begins with the development of capillary telangiectasias triggered by radiation injury to the cerebral microcirculation [19]. An alternative explanation is that radiation may cause direct DNA damage, which leads to the formation of cavernomas. Cavernomas have been correlated with radiation dose. At doses >30 Gy, there is a shorter latency to the development of cavernomas [20]. Cavernomas can sometimes be misdiagnosed as tumour progression, especially if they are associated with symptomatic haemorrhage or seizures. Intervention is not usually required, as these are low-pressure bleeds from the capillary structures. Multiple micro-haemorrhages may also be found on scans and are often asymptomatic (Fig. 7.2c, d).

(d) *Hypopituitarism*

Disturbances in pituitary hormone secretion are common following radiotherapy to the hypothalamicpituitary axis. Hormonal deficiencies may affect body image, growth, sexual function, skeletal health and quality of life. It is important that cancer survivors are tested regularly, e.g., annually, to screen for pituitary insufficiency and timely treatment with hormone replacement is offered. The severity and frequency of pituitary disturbance correlates with the total radiation dose and length of follow-up. It is possible that concomitant chemotherapy may potentiate the action of radiotherapy. Children are most seriously at risk, as the first hormone to be affected is growth hormone (GH) resulting in slow growth, poor bone development, increased subcutaneous fat and fatigue. Loss of GH in adults is not such a serious matter although has been associated with fatigue. Isolated GH deficiency can occur after doses as low as 18 Gy. GH deficiency occurs within 5 years in 30% of patients given <30 Gy and within 3–5 years in 50–100% of patients treated with 30–50 Gy. Multiple hormonal deficiencies occur by 10 years of follow-up in patients given doses >30 Gy of

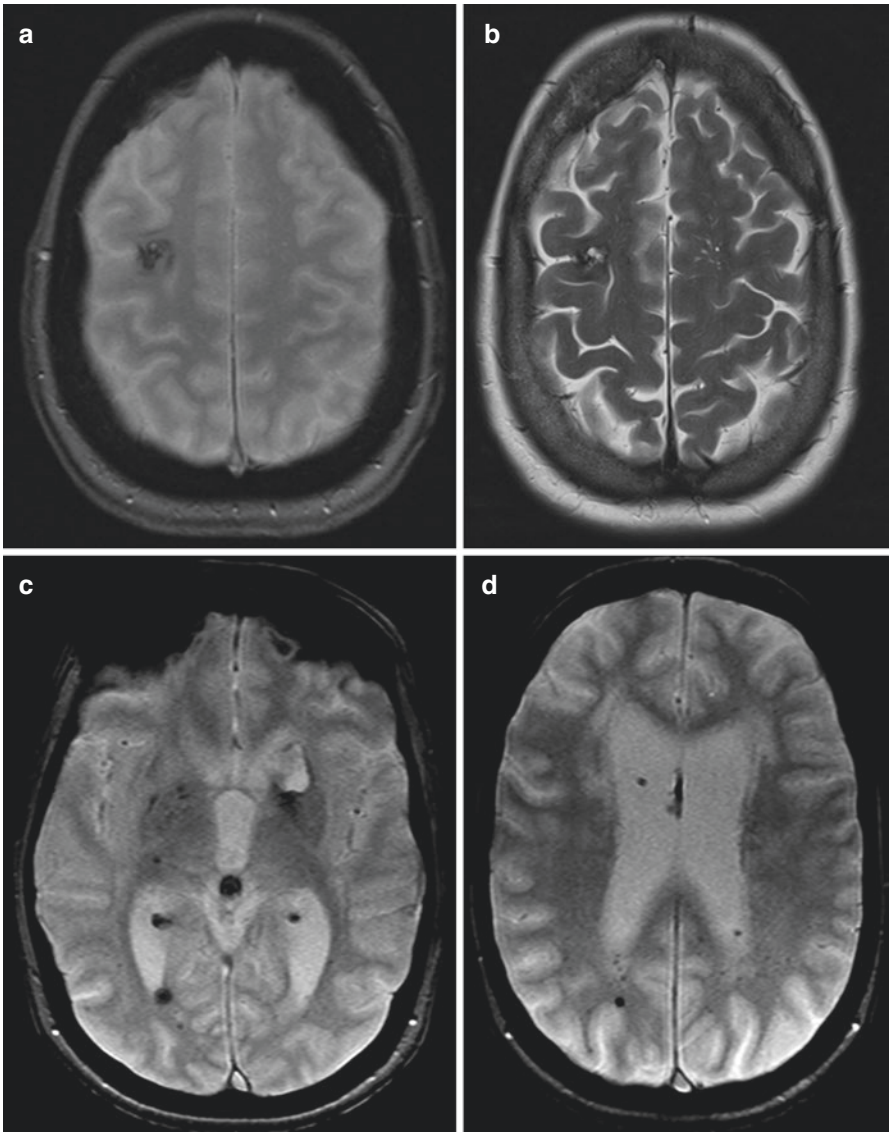

Fig. 7.2 (**a**, **b**) Radiation-induced right frontal cavernoma. (**c**, **d**) Radiation-induced multiple microhaemorrhages

radiation include deficiencies in GH (30–60%), sex hormone (20–30%), thyroid-stimulating hormone (TSH; 3–9%) and adrenocorticotropic hormone (ACTH; 3–6%) [21].

In children, injection of GH-releasing hormone (GHRH) analog therapy (e.g., Genotropin [somatotropin, Pfizer Inc. New York, New York) helps. Replacement can be associated with injection-site reactions, such as pain, redness/swelling, inflammation, bleeding, scarring, lumps, or rash.

Gonadotropin deficiency will affect secondary sex characteristics, fertility and bone and muscle mass. Diagnosis is confirmed by normal or low normal basal luteinizing hormone (LH)/follicle-stimulating hormone (FSH) with low circulating sex hormone concentrations in the blood. In children, because of the influence on bone age, treatment with sex steroids is required to aid the development of secondary sex characteristics. In adults, amenorrhoea, sweating and flushes may occur in women and in men there may be reduced libido, erectile dysfunction, reduced shaving frequency, fatigue and mood changes. Sex steroid replacement improves quality of life generally.

Hyperprolactinaemia predominantly occurs in young women; it is usually subclinical, but can affect 20–50% of women who have had cranial irradiation. Prolactin levels can be assessed using blood tests. If hyperprolactinaemia is high enough to impair gonadotropin release it can cause galactorrhoea and ovarian dysfunction in females or affect libido and cause impotence in males. If symptomatic, hyperprolactinaemia can be treated with dopamine agonists such as cabergoline. Low serum testosterone can be replaced.

TSH deficiency usually requires radiation doses of >40 Gy to be associated with a high risk of involvement. Hypothyroidism will cause hair loss, dry skin, weight gain, cold intolerance, bowel change, fatigue and memory problems, and muscle weakness and is easily treated with thyroxine replacement.

Cortisol deficiency secondary to ACTH deficiency, similarly, is seen at higher treatment doses. IIt causes fatigue and memory problems, muscle weakness, nausea, and dizziness, but with weight loss and hypoglycemia. Both cortisol defiiency and thyroid hormone deficiencies are more commonly seen in children treated for central nervous system (CNS) malignancies, where the pituitary is within the radiation field, but these features can occur years after the treatment of brain tumours adjacent to the pituitary gland where the pituitary is within the treatment field. Cortisol deficiency is treated with oral hydrocortisone twice daily.

(e) *Cranial nerve/end organ radiation damage*

Cranial and peripheral nerves are generally considered to be radio-resistant; however, radiation also commonly damages end organs, e.g., the cochlea – leading to sensorineural hearing loss – or it damages the lens, retina and optic nerve – leading to multifactorial visual loss.

Deafness is very common in survivors of medulloblastoma, ependymoma or astrocytoma within the posterior fossa. The rate of deafness appears to increase with age >50 years. The mean total dose to the cochlea during fractionated raditherapy appears to be an important factor in predicting deafness in those treated in childhood. The effect of dose per fraction ($\leq$ or > 2.0 Gy) is probably also relevant. Chemotherapy combined with radiotherapy may have a synergistic effect, especially if the chemotherapy is ototoxic in its own right.

The optic nerve and eye are generally shielded where possible when treating intracranial tumours. However, where it is not possible to shield the eye, a variety of complications are possible, from an early increase in intraocular pressure during treatment, to the development of late complications of cataract, dry eye from lacrimal gland damage, and retinopathy or optic neuropathy.

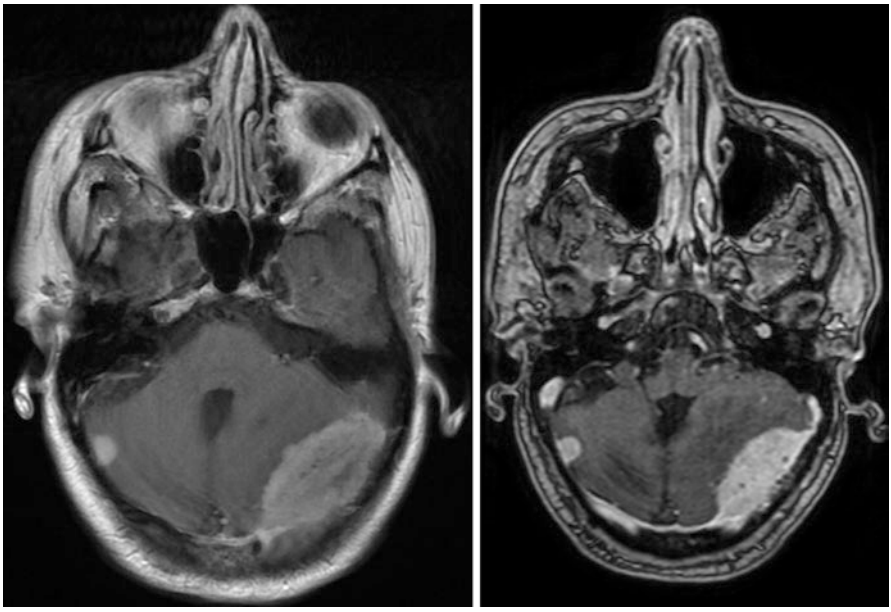

Fig. 7.3 T1-weighted gadolinium enhanced magnetic resonance image showing radiation-induced meningiomas 15 years after treatment of medulloblastoma

(f) *Second tumours*
Radiation to the central nervous system may be required for different tumour types e.g. acute lymphoblastic leukaemia (ALL), childhood medulloblastoma, ependymoma or astrocytoma, head and neck soft tissue sarcoma, and retinoblastoma. A late complication is development of a different tumour type within the radiation field. Second neoplasms are infrequent but with higher doses of radiation used for brain tumours, and where survival from the primary tumour is excellent, there is an increased risk for meningiomas (Fig. 7.3) and glial tumours [22].

7.5 Chemotherapy Complications

Chemotherapy that crosses the blood brain barrier is most likely to be effective. Drugs such as alkylating agents (temozolomide, procarbazine,) and nitrosoureas (e.g., 1-(2-chloroethyl)-cyclo-hexyl-1-nitrosourea—CCNU [lomustine]) are most commonly used, alone or in combination (e.g., procarbazine, CCNU, vincristine [PCV]).

Patients being prescribed chemotherapy should avoid aspirin and not receive immunisation or vaccination, nor should they become pregnant and they should therefore use barrier contraception. Nursing mothers should not breastfeed. Patients should avoid sun exposure and keep well hydrated, eat in small amounts and frequently and get plenty of rest. Avoid things that may worsen the symptoms of nausea, such as heavy or greasy/fatty, spicy or acidic foods (lemons, tomatoes, oranges). Brush teeth with a soft bristle toothbrush.

Patients should report signs of infection, e.g., fever, to their GP early and will get regular blood tests between treatments. Hair may appear thin and brittle and fall out 2–3 weeks after the starting of many chemotherapy drugs.

7.5.1 Temozolomide

Temozolomide is an alkylating agent and the first-line chemotherapy for patients with glioblastoma. It is most commonly given along with radiotherapy (concomitantly) and after completion of radiotherapy for 5 days every 4 weeks, for six courses. Temozolomide causes haematological toxicity (lymphopenia, neutropenia, thrombocytopenia) in >10% of patients. Elderly patients and women have a higher risk of developing haematological toxicities or myelodysplastic syndrome. Pneumocystis pneumonia (PCP) is a risk, especially in patients requiring high-dose steroids or those who have lymphocyte counts <500 cells/μm. PCP prophylaxis is required for "high-risk" patients who are receiving concomitant temozolomide and radiotherapy. All patients, particularly those receiving steroids, should be observed closely for the development of lymphopenia and PCP. Care should be given when treating patients with severe renal or hepatic impairment. Severe hepatotoxicity can be fatal. Temozolomide may interact with valproate, an anti-epileptic drug (AED), to reduce the excretion of temozolomide, other AEDs, steroids and sulpha drugs. Forty-nine percent of patients treated with temozolomide report one or more severe reactions, most commonly fatigue (13%), convulsions (6%), headache (5%) or thrombocytopenia (5%). The common side effects (>10%) are: gastrointestinal (e.g., nausea and vomiting – clinical toxicity criteria (CTC) grade 3/4 in 6–10%), anorexia, constipation or diarrhoea; muco-cutaneous (rash, mouth ulcers); neurological (headache, dizziness, abnormal taste); or generalized, e.g., sleep disturbance, fatigue (16%). To reduce nausea and vomiting, temozolomide should be given on an empty stomach and an anti-emetic may be advised before treatment. Immunosuppression can be associated with new infections or the reactivation of infections e.g. cytomegalovirus (CMV); hepatitis B infections and herpes simplex encephalitis, including cases with fatal outcomes. Sixty to seventy percent of patients with glioblastoma (grade 4) derive no survival benefit and for the recurrent anaplastic gliomas (grade 3), more than 50% of patients have tumour progression at 6 months [23]. Selection of patients for treatment is important with those who have highly methylated MGMT obtaining more benefit from chemotherapy.

7.5.2 Procarbazine

Procarbazine is usually given in conjunction with CCNU and vincristine as PCV. It is the first-line combination for patients with oligodendroglioma and is also commonly given after the failure of temozolomide. Procarbazine is an alkylating agent.

Patients taking procarbazine should avoid several food types that are high in tyramine, including: avocados, bananas, figs, papaya, raisins, and sauerkraut; beef or chicken liver; meats prepared with tenderizer; bologna, pepperoni, summer

sausage, game meat, and meat extracts; pickled or smoked fish, anchovies, dried fish, herring, caviar, and shrimp paste; beer (alcoholic and nonalcoholic); wine (especially red wine), champagne, sherry, vermouth, and other distilled spirits; caffeine (including coffee, tea, cola), ginseng; cheese; chocolate; yogurt; soy sauce, miso soup, and bean curd; and fava beans.

As with all chemotherapy, haematological side effects are dose-limiting and recovery may be delayed. Leukopenia, anaemia, and thrombocytopenia have been reported frequently. Pancytopenia, eosinophilia, hemolytic anaemia, and bleeding tendencies, including petechiae, purpura, epistaxis, hematuria and hemoptysis, have also been reported. Gastrointestinal side effects, including nausea and vomiting, are the most commonly reported. Hepatic dysfunction, jaundice, stomatitis, hematemesis, melena, diarrhoea, dysphagia, anorexia, abdominal pain, constipation, and dry mouth are also reported. Peripheral neuropathy with paraesthesia of the extremities and depressed deep tendon reflexes have been reported to occur in 17% of patients, but usually when procarbazine is given in combination with vincristine. Nervous system side effects, including leucoencephalopathy, coma, convulsions, neuropathy, ataxia, paraesthesia, nystagmus, diminished reflexes, falling, foot drop, headache, dizziness, chills, weakness, fatigue, hallucinations and unsteadiness have also been reported. Psychiatric side effects, including hallucinations, depression, apprehension, agitation, psychosis, nervousness, confusion, mania and nightmares can occur. Hypotension, tachycardia, and syncope also occur, as can pneumonitis, pleural effusion, retinal haemorrhage, papilloedema, photophobia and diplopia.

7.5.3 CCNU

1-(2-Chloroethyl)-cyclo-hexyl-1-nitrosourea (CCNU, lomustine) is an alkylating agent given by mouth in capsule form. It is often given in combination with procarbazine and vincristine. Other alkylating agents such as 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU, carmustine) are frequently given intravenously. As with all chemotherapy there is a range of side effects that can affect all systems. Haematological toxicity increases with the number of courses, with a nadir in platelet count at 4–5 weeks with recovery at 5–6 weeks and white cell count nadir at 5–6 weeks and recovery by 6–8 weeks.

Poor appetite and nausea occur within 5–6 h after taking the medication and can be helped by taking prophylactic anti-nauseant agents, while neurocutaneous symptoms such as hair loss and mouth ulcers occur in >10% of patients. Pulmonary and renal toxicity is cumulative with dosage and may be delayed for years after diagnosis. Pulmonary infiltrates and fibrosis can occur.

7.5.4 Vincristine

Vincristine is a plant vinca alkaloid that is given intravenously. It is a vesicant and care must be given when it is given intravenously. Partial or complete hair loss is common and the nadir in blood count occurs at 7–10 days, with recovery by 21 days.

Side effects include gastrointestinal symptoms and peripheral neuropathy, generally with paraesthesia and numbness in the feet and, less commonly, the hands.

7.6 Targeted and Immunotherapy Agent Complications

Targeted and immunotherapy agents have been used alone, in combination, or along with other types of therapy. Targeted therapies aimed at growth factor receptors, e.g., *epidermal growth factor receptor* (EGFR), e.g., cetuximab, gefitinib; *vascular endothelial growth factor receptor* (VEGFR), e.g., bevacizumab, cediranib; *platelet-derived growth factor receptor* (PDGFR), e.g., temsirolimus, have all been tried in brain tumours with very limited success. Complications are similar between agents and bevacuzimab and ipilimumab will be used as examples.

Immunotherapy has a different mechanistic approach compared with that of chemotherapy, radiation and surgery. Most of the current immunologic treatments are antibody-based therapies, but some, more recently, have been cell-based therapies and there are several tumour vaccine strategies. Immunotherapy can be passive or active. In passive immunotherapy, a patient is given immune cells or antibodies that target the tumour cell and this does not require activation of the patient's own immune system. Active immunotherapy boosts the patient's own immune system. Passive immunotherapy can be divided into three types: therapies in which there is direct injection of monoclonal antibodies, e.g., bevacizumab, a humanized IgG1 monoclonal antibody that binds to and neutralizes VEGF; therapies in which there is cytokine stimulation, e.g., interleukin 2 (IL2); and therapies in which there are stimulated immune effector cells (adoptive or cell-based immunotherapy), e.g., lymphocyte-activated killer cells (LAKs) and cytotoxic T-lymphocytes (CTLs). Active immunotherapy boosts the patient's immune system by priming it with antigen exposure. There is a relatively high frequency of immune-related adverse effects from immunotherapies, ranging from endocrine, hepatic, gastrointestinal, and dermatological toxicities. The side effects are due to the aberrant infiltration of stimulated $CD4^+$ and $CD8^+$ T-cells into normal tissues, along with elevated levels of pro-inflammatory cytokines [24]. The stimulated immune response can overshoot its target and attack healthy tissues and organs, similarly to an autoimmune disorder.

7.6.1 Bevacizumab

Bevacizumab is the most commonly used targeted agent. It is given by infusion once every 2 weeks. It can lead to improvements on scanning by its influence on the blood brain barrier and can reduce the need for dexamethasone. The most common side effects are high blood pressure (18%), proteinuria (7%), infusion reactions (3%), bleeding (nose/rectum), back pain, headache, taste disturbance, diarrhoea and loss of appetite or skin problems (dryness or inflammation), watery eyes or jaw pain, and swelling or numbness. The most serious side effects may be gastrointestinal perforation, poor wound healing and serious bleeding. Bevacizumab should not be used for 28 days before or after surgery and until surgical wounds are fully

healed; it should not be used before or during pregnancy or breastfeeding. It is often given with chemotherapy, where it amplifies the risk of toxicities.

7.6.2 Ipilimumab

Ipilimumab (CTLA-4 checkpoint inhibitor) may be associated with pneumonitis, colitis, bowel perforation, hepatitis, pancreatitis, skin rash and mouth ulcers. It may also cause neurological complications including paralysis (acute inflammatory demyelinating neuropathy; Guillain-Barre); chronic inflammatory demyelinating polyneuropathy (CIDP); transverse myelitis; myositis; myasthenia gravis. Hormonal upset of thyroid, pituitary and adrenal glands and eye problems with blurred vision and eye pain and redness may occur. Side effects are best managed by steroids and antihistamines.

7.7 Conclusion

Early side effects of brain tumour treatment usually resolve with steroids to treat brain oedema, demyelination or immunotherapy reactions. Drug withdrawal or dose reduction may be necessary to manage acute toxic effects of chemotherapy or targeted immunotherapy. Late effects are becoming an increasing problem as survival improves and depend on factors that are often not reversible – e.g., radiotherapy dose and volume. There is no good evidence that there are effective treatments to prevent, delay or reverse late cognitive effects, stroke like complications and fatigue, but more high quality clinical research is required. Prevention of late effects by increasing fractionation schemes, reducing dose per fraction or total dose of radiation and hippocampal sparing techniques are a balance between effectively treating the tumour and preventing long-term brain injury. It seems likely that technologies such as proton beam treatments may play an increasing role by more selectively targeting the tumour, although their value has yet to be proven in good randomised clinical trials or long-term prognostic studies. As aggressive primary brain tumours are often highly resistant to chemotherapy and targeted and immunotherapy, care must be taken to choose those most likely to respond to these potentially toxic treatments and advise against active treatment where they may just accentuate acute toxicities for no discernible benefit. Supportive and palliative care should be advocated in parallel, rather than leaving such care until it is too late to be helpful.

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