Neurologic complications of radiation therapy and chemotherapy (*)

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Neurologic Complications of Radiation Therapy

Radiation induced toxicities are due to the effect of irradiation of normal surrounding tissue which is included in the radiation port. The mechanisms of radiation induced damage have not been completely elucidated. Hypotheses include direct damage to neural cells versus damage to the vascular endothelium with secondary effects on nervous system structures. Another hypothesis is that radiation damaged glial cells release antigens that are able to evoke an autoimmune response against the nervous system resulting in both cellular necrosis and vascular damage.

The clinical diagnosis of radiation induced neurotoxicity may be difficult especially in patients who had neurologic signs prior to treatment. It is helpful to determine if the clinical signs correlate with the irradiated site and to know the total dose received and the dose per fraction. Prior or concomitant chemotherapy may act to increase the toxicity produced by radiation. The age of the patient at the time of radiation is important as the very young and the elderly are more likely to develop toxicities. Finally, concurrent neurologic diseases such as demyelinating disorders appear to sensitize neural tissue to radiation damage.

For patients who have received cranial irradiation for a brain tumor (either metastatic or primary) the differential diagnosis of radiation toxicity includes recurrent tumor, brain abscess, or radiation necrosis. The definitive diagnosis can only be made by biopsy, although PET scanning can suggest the diagnosis (tumor is usually hypermetabolic and necrosis and abscess often hypometabolic). In the spinal cord, the differential diagnosis includes epidural spinal cord compression, intramedullary metastases, or paraneoplastic myelopathy. It is important to distinguish between compression or metastases since these are treatable conditions. There are no effective treatments for radiation myelopathy and paraneoplastic myelopathy. An MRI scan or myelogram will identify spinal cord compression and a high-resolution MRI with contrast will exclude intramedullary metastases.

When the brachial or lumbosacral plexus is involved the differential diagnosis is between recurrent tumor and radiation induced fibrosis. Lack of pain and a predominance of motor symptoms suggests radiation fibrosis whereas severe pain combined with motor and sensory symptoms suggests recurrent tumor.

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Central Nervous System Complications of Radiation

Radiation injury can occur at almost any time, from immediately after irradiation to years later. The side effects can generally be divided into those that are acute (within days), early-delayed (within 4 weeks to 4 months after treatment), and late-delayed (months to years after treatment).

Acute Effects. In general, there are few acute toxicities of whole brain irradiation when administered in standard doses. Almost all patients will develop transient alopecia and many complain of fatigue, which in a small

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number of patients can be debilitating. An acute encephalopathy with headaches, nausea, and vomiting may occur, most often in patients with increased intracranial pressure and mass effect due to tumor. In rare cases, mostly with high daily radiation fractions (>300 cGy), cerebral herniation can occur. To treat and often prevent these complications, patients should be maintained on at least 8 mg/day of dexamethasone or equivalent during whole brain irradiation, with the steroid being started 1 to 2 days prior to initiation of radiation.

Early-Delayed Effects. These disorders vary depending upon the dose and volume of irradiated tissue and the presence or absence of underlying brain disease.

Neurologic Deterioration- In patients with a primary or metastatic brain tumor, early-delayed symptoms simulate tumor progression. The patient develops headache, lethargy, and worsening or reappearance of the original neurologic symptoms. Neuro-imaging may demonstrate increased enhancement and edema which resolve spontaneously. It is important not to confuse this syndrome with radiation failure. Corticosteroids may hasten recovery and close follow-up examinations should resolve the issue.

Radiation Somnolence Syndrome- This syndrome is usually seen in children after whole brain radiation. It is characterized by the onset of somnolence, often associated with headache, nausea, vomiting, anorexia and rarely, papilledema. Symptoms start approximately 4 to 12 weeks after irradiation and may last for several days to weeks. Patients will improve spontaneously without deficits.

Focal Encephalopathy- Another early-delayed syndrome is the onset of a focal encephalopathy in patients who have received radiation to extra cranial tumors where a portion of the brain was included in the treatment port. Symptoms develop 8 to 11 weeks after treatment and depend upon the area of brain irradiated. White matter hyperintensity suggestive of demyelination can be seen on MRI scans and while most patients fully recover within 2 months, the syndrome can progress to stupor, coma, and death.

Late-Delayed Effects

Radiation Necrosis- Radiation necrosis usually develops after a total dose of 5000 cGy, but has been reported in patients who received 3000 cGy. The necrosis usually begins 1 to 2 years after radiation is completed but can become evident as early as 3 months after treatment. The longer a patients survives after irradiation, the greater the risk of radiation necrosis. The newer modalities of radiation, including high intensity brachytherapy and stereotactic radiosurgery/gamma knife result in a higher incidence of radiation necrosis than external bean radiation with 30-40% of these patients developing necrosis.

Clinically, radiation necrosis behaves as a space occupying lesion. Patients often develop signs of increased intracranial pressure with headache and lateralizing signs referable to the location of the lesion. The CT or MRI may show increased contrast enhancement with surrounding edema that cannot be indistinguished from recurrent tumor. Although necrosis is usually hypometabolic on PET scanning, many patients will have a mixture of necrosis and recurrent tumor.

The treatment of radiation necrosis may require surgery although many patients respond to corticosteroids with a decrease in edema and improvement of clinical symptoms and signs.

Cognitive Dysfunction- Delayed cognitive abnormalities start to occur in patients 1 to 2 years after cranial irradiation. This is most often seen in children receiving prophylactic cranial radiation for acute lymphocytic leukemia and adults receiving prophylaxis for small cell lung carcinoma. The changes are irreversible and there is no effective treatment. High daily fractions, age < 2 years, and the concomitant use of some chemotherapeutic (i.e. methotrexate) agents all predispose to this complication.

Some patients develop a progressive dementing illness accompanied by ataxia and urinary incontinence suggestive of normal pressure hydrocephalus. For these patients ventriculoperitoneal shunt may partially reverse the symptoms.

Radiation - Induced Neoplasms. Radiation induced neurogenic tumors may be benign or malignant and include meningiomas, gliomas, gliosarcomas, and schwannomafs. Radiation induced tumors occur in both patients who received high or low dose radiation. Risk factors include pre-existing genetic factors such as the presence of neurofibromatosis. Most of these tumors develop long after the radiation (10 to 30 years). It is not possible to conclusively identify a tumor as radiation induced but this diagnosis is supported if the tumor is of a different histology from the original neoplasm and develops within the radiated field years after treatment.

Radiation-Induced Vasculopathy. Radiation therapy can produce late-delayed effects on blood vessels of all sizes. Atherosclerotic lesions of the large intracranial vessels may become apparent 4 months to 20 years after radiation. The most commonly affect vessel is the extracranial carotid artery leading to occlusion and tran-

sient ischemic attacks or stroke. Anti-platelet agents and anticoagulants may be of use, as well as endarterectomy. Intracranial carotid artery occlusion usually develops in the supraclinoid segment and is associated with the development of a moyamoya like vasculature that can lead to hemorrhage.

Radiation Toxicity in the Spinal Cord

Early-Delayed Radiation Myelopathy- This disorder usually occurs after radiation to the cervical and upper thoracic cord. If may also occur after therapeutic radiation for Hodgkinís lymphoma, neck, and mediastinal tumors. Patients present with paresthesias or Lhermitte's sign radiating down the spine into the extremities upon flexion of the neck. Symptoms begin about 12 to 20 weeks after treatment and generally resolve within a few months to a year.

Last-Delayed Radiation Myelopathy- This myelopathy can present in one of 3 forms; a progressive myelopathy, a lower motor neuron syndrome, and hemorrhage into the cord.

Progressive myelopathy- Symptoms start about 12 to 50 months after radiation and progress subacutely or chronically. Patients may be left with a para- or quadraparesis although it some cases patients stabilize with only mild or moderate paresis. This disorder is dose dependent and older age is a risk factor. Patients present with the painless onset of numbness and paresthesias, leg weakness and sphincter dysfunction. The thoracic cord is most often affected and there is no effective treatment. Deficits are permanent.

Motor Neuron Syndrome- This characteristically follows pelvic or lumbosacral radiation. Symptoms may start as early as 3 months after treatment but have been reported as starting after more than 20 years. Patients develop the subacute onset of a flaccid lower extremity paraparesis with atrophy, fasciculations, and areflexia that is usually bilaterally symmetric but can remain restricted to one leg. There are no sensory changes and bowel and bladder function are not affected.

Hemorrhage- This is a rare complication and develops years after irradiation. It is probably due to the development of telangiectasias. Symptoms can include back pain and weakness and often resolve.

Peripheral Nervous System Complications of Radiation

Peripheral nerves are relatively radioresistant and acute and subacute complications are rarely observed. The major toxicity is the development of a plexopathy which occurs in the brachial plexus after treatment for breast or lung cancer and the lumbosacral plexus after treatment of the pelvis and lower abdomen.

The plexopathy develops as a consequence of delayed fibrosis which occurs in the surrounding soft tissues and entraps the nerves.

The interval between radiation and the development of radiation induced plexopathy is quite variable with a median time of 4 to 5 years. Occurrences as soon as 1 month after treatment and as long as 26 years after have been reported. Plexopathy is more common with doses of 5000 cGy or greater but there is individual variability.

The differential diagnosis of plexus lesions is between radiation damage and recurrent tumor. There are several signs that can help to differentiate between the two. Both tumor and radiation induced plexopathy produce weakness and sensory disturbances in a radicular distribution, however, radiation plexopathy often produces lymphedema due to sclerosis of the lymphatic channels and is usually painless. Infiltration of the plexus by tumor is typically painful and not accompanied by edema. In the brachial plexus, tumor more commonly affects the lower trunk whereas radiation damage may be limited to the upper trunk. CT and MRI are not always helpful in distinguishing between the 2 diagnosis. There is no effective treatment.

Cranial Nerves and Radiation Therapy

Damage to the cranial nerves is rare and is usually a late-delayed effect. Optic neuropathy following whole brain radiation begins 6 to 25 months after treatment and is characterized by the painless development of monocular or binocular visual loss. The likelihood of visual loss is increased if the patient received concurrent chemotherapy. Damage to the cochlea can produce tinnitus and high frequency hearing loss. The lower cranial nerves are susceptible to radiation damage after treatment of the head or neck and is often due to fibrosis of cervical soft tissues.

Endocrine Dysfunction after Radiation Treatment

Radiation induced endocrine dysfunction is not rare and when severe can produce mental status changes and other neurologic abnormalities. This may occur after treatment of nasopharyngeal carcinomas and pituitary tumors and following whole brain radiation.

The most common clinical symptoms are growth failure in children and sexual difficulties in adult males. Hypothyroidism can follow neck irradiation as well as Grave's disease with ophthalmopathy.

Toxicity Related to Combination of Radiation and Chemotherapy

The neurotoxicity of radiation is often increased by the use of chemotherapy and the reverse also holds true. For some drugs, such as methotrexate, the relative timing of the administration of radiation and chemotherapy appears important. Methotrexate given before radiation is less neurotoxic than methotrexate given after or concurrent with radiation.

Nitrosoureas are reported to be more neurotoxic in patients who have received radiation although this is not well established. Vincristine appears to enhance the neurotoxicity of spinal cord and peripheral nerve irradiation.

Neurologic Complications of Chemotherapy

Introduction

Chemotherapy induced neurotoxicity can produce significant disability, and can occur after a patient has been effectively treated or even cured of their cancer. The diagnosis of neurologic abnormalities in patients receiving treatment for cancer can be difficult. Chemotherapeutic agents may affect nervous system function in ways that are clinically indistinguishable from metastatic disease and knowledge of the neurotoxic effects of certain drugs can obviate the need for extensive diagnostic testing. Treatment modalities may also act synergistically confounding the diagnosis. For example, the combination of vincristine and corticosteroids may cause more weakness (vincristine neuropathy plus corticosteroid myopathy) than either agent alone. Finally, cancer patients take many types of medications, including those used to treat symptoms related to the cancer such as anticonvulsants, corticosteroids, and opioids and drugs to treat systemic disorders (high blood pressure, diabetes, etc). Many of these drugs, either alone or in combination can be neurotoxic. Therefore, neurotoxicity caused by medication must be strongly considered in the differential diagnosis of otherwise unexplained neurologic symptoms in cancer patients.

Central Nervous System

Acute Encephalopathy. Encephalopathy induced by chemotherapeutic agents cannot be clinically distinguished from that caused by metabolic disorders and has been reported in association with most of the commonly used chemotherapeutic agents.

Chronic Encephalopathy. A chronic encephalopathy characterized by dementia with or without seizures is most often found in adult patients who have also received radiation to the brain. Patients become quiet and withdrawn and may appear depressed. They develop moderate to severe memory loss and disorientation, particularly with respect to time. While most severe in patients who have received a combination of chemotherapy and radiation, about one third of patients who receive chemotherapy alone develop some cognitive decline with memory deficits. Some patients in this group also report gait and coordination abnormalities that progress slowly over years.

Focal Disorders. Focal disorders include acute cerebellar syndromes, acute or subacute myelopathy, visual loss, headache, and aseptic meningitis. The acute cerebellar syndrome are caused by only a few agents and may be reversible. Permanent deficits characterized pathologically by diffuse loss of Purkinje cells have been reported.

Transverse myelopathy following intrathecal therapy can be caused by methotrexate, cytarabine, and rarely, thiotepa. Visual loss is caused by several agents including a reversible retinopathy due to tamoxifen, optic neuropathy secondary to gallium nitrate, and cortical blindness secondary to high dose fludarabine and cisplatin. Headache and an aseptic meningitis have been reported in association with most chemotherapeutic agents.

Peripheral Nervous System

Diffuse Neuropathy. Diffuse toxicity to the peripheral nervous system usually produces a sensorimotor or predominantly sensory peripheral neuropathy that can be divided into three broad categories.

1.- An acute or subacutely developing sensorimotor peripheral neuropathy, often predominantly motor, which resembles the Guillain-Barré syndrome. The drugs probably cause selective demyelination and the disorder is often reversible when the drug is discontinued.

2.- A distal sensorimotor neuropathy primarily affecting axons. This disorder begins with paresthesias but motor weakness soon becomes apparent. The prototypic drug is vincristine and the symptoms may reverse with time.

3.- A pure sensory neuropathy, often painful, involving large fibers or both large and small fibers, probably originating from damage to dorsal root ganglion cells. Initial complaints are numbness and tingling in the fingers and toes, but may only affect the fingers. In cisplatin neuropathy where only large fibers are involved, there is loss of proprioception but pin prick, temperature sensation, and motor function are preserved. In contrast, the neuropathy caused by Taxol affects both large and small fibers equally.

Focal Neuropathy. Neuropathies that affect only one or a few nerves are uncommon but can complicate both vincristine and cisplatin therapy. Focal neuropathy may occur at the site of a focal injury (peroneal palsy from crossed legs in a patient receiving vincristine) or independently.

There are some findings that appear to be specific for certain agents. For example, cisplatin is the only chemotherapeutic agent that causes Lhermitteís sign. Muscle cramps appear to be more common in cisplatin neuropathy and may persist for more than a year after therapy has been discontinued. Paresthesias of the fingertips are more commonly an early sign of vincristine neuropathy.

Specific Agents and Toxicities

Alkylating Agents.

Cisplatin- Cisplatin binds to plasma proteins so it does not efficiently cross an intact blood-brain barrier. However, it does enter and accumulate in the dorsal root ganglia and peripheral nerves where concentrations may be 4 to 5 times higher than those achieved in normal brain. Consequently, as with other heavy metals, peripheral neuropathy is the major neurotoxicity.

Peripheral neuropathy can occur with cumulative doses as low as 200 mg/m2 but is more commonly seen with doses of 400 mg/m2. The degree of peripheral neuropathy correlates with both the total cumulative dose and with the dose per treatment. Focal lumbosacral plexopathies or mononeuropathies have been reported following infusion of either the internal or external iliac arteries and optic neuropathy after carotid infusion. About 6% of patients receiving common carotid intra-arterial infusion of cisplatin develop cranial nerve palsies.

The peripheral neuropathy can begin with painful tingling in the toes which then spreads proximally to affect arms and legs. Deep tendon reflexes are lost and proprioceptive loss (vibration sense first) can be so severe that patients may be unable to feed themselves or walk. Pin and temperature sensation are spared, motor power remains normal, and autonomic dysfunction is rare.

The first signs of cisplatin neuropathy may begin after the drug has been discontinued and may progress for several months before stabilizing. If the patient survives the cancer, the neuropathy usually improves and may clear entirely in months but it can take years; some patients may not have any significant recovery. Pre-existing nervous system dysfunction such as myelopathy is a risk factor for cisplatin neuropathy.

Cisplatin neuropathy may be confused with paraneoplastic sensory neuropathy. However, paraneoplastic sensory neuropathy usually affects all sensory modalities equally, does not improve after cessation of the drug, and is often associated with the presence of antineuronal antibodies in the patients serum. Once the neuropathy develops treatment is ineffective, although protection against the development of the neuropathy has been reported with several experimental drugs (not currently used in clinical practice).

Other toxic side-effects of cisplatin include the development of Lhermitteís sign during or soon after drug treatment, possibly due to transient demyelination of the posterior columns. Lhermitteís sign may also be seen after cervical irradiation. Some patients experience muscle cramps unrelated to electrolyte disturbances. Both the Lhermitteís sign and cramps usually resolve sponta-

neously.

Cisplatin can also produce ototoxicity and vestibulopathy. Risk factors for ototoxicity include concomitant ifosfamide, prior cranial irradiation, and young age. Cisplatin given prior to irradiation does not increase the risk for ototoxicity.

Vestibular toxicity characterized by vertigo, oscillopsia, and ataxia is less common than hearing loss and may be exacerbated by the previous use of aminoglycosides.

Ocular toxicity and encephalopathy are rare side effects of cisplatin and more common after intra-arterial infusion. Encephalopathy due to the drug must be differentiated from that caused by the hydration preceding cisplatin therapy or by the nephrotoxicity that can occur after treatment.

Nitrosoureas. Unlike cisplatin, these drugs (lomustine, carmustine, semustine, streptozocin, and chlorozotocin) are highly lipid soluble and readily cross the blood brain barrier. In conventional doses these drugs rarely cause neurotoxicity. Early toxic effects are bone marrow suppression appearing within 3-4 weeks of treatment and late effects are pulmonary fibrosis, renal failure, hepatotoxicity, myelofibrosis, and leukemia.

Patients with central nervous system tumors who have received previous irradiation and high doses of intravenous or intra-arterial carmustine may develop ocular toxicity and encephalopathy with or without seizures.

Mustards. The most commonly used of these drugs are ifosfamide and cyclophosphamide. Depending upon the dose and other factors, approximately 30% of patients receiving high-dose ifosfamide and Mesna (to prevent bladder toxicity) develop an encephalopathy that is characterized by cerebellar dysfunction, extrapyramidal signs, hallucinations, seizures, delirium, and sometimes coma. The disorder usually begins within 24 hours of the therapy but can be delayed for 4-6 days. Symptoms clear in 3-4 days but some patients may be left with persistent deficits and fatalities have been reported.

Antimetabolics

Methotrexate. Methotrexate can cause acute and chronic neurotoxicity after oral, intravenous or intrathecal injection. Risk factors include dose, route of administration, and concurrent treatments such as radiation.

The most common acute methotrexate neurotoxicity is aseptic meningitis that occurs in about 10% of patients who receive intrathecal drug. Patients have the sudden onset of headache, stiff neck, nausea and vomiting, lethargy and fever starting within 2-4 hours of drug instillation. The syndrome lasts about 12 to 72 hours. Examination of the CSF reveals a pleocytosis and cultures are negative. Symptoms resolve spontaneously without long-termásequelae. This syndrome can occur after any dose and its occurrence does not preclude further drug use. Patients will often not have a reoccurrence of the syndrome.

Transverse myelopathy is a rare complication of intrathecal methotrexate and usually occurs after several treatments. Patients present within 38 hours of the dose but the onset can be delayed for up to 2 weeks. Patients complain of back pain with or without radiation to the legs followed by sensory loss, paraplegia and bowel and bladder dysfunction. Recovery is variable. The pathogenesis of the disorder is unknown and it may be an idiosyncratic drug reaction.

Methotrexate can cause acute, subacute and chronic encephalopathies. The acute encephalopathy occurs after intraventricular or high-dose intravenous methotrexate. The onset is within 24-48 hours of the dosing. Patients become confused and lethargic with or without seizures. Symptoms generally clear without any deficits. Some patients develop a subacute encephalopathy following the administration of weekly high dose intravenous methotrexate with the development of multifocal deficits after the second or third treatment. Recover is within 72 hours, usually without deficits.

A diffuse leukoencephalopathy is the most devastating of the toxicities caused by methotrexate and generally occurs after repeated high intravenous doses. The leukoencephalopathy can appear months to years after treatment. Some patients recover slowly with residual mild to moderate dementia while others can progress to a severe dementia with hemi- or paraparesis.

5-Fluorouracil (5-FU). The primary neurotoxicity of 5-FU is a cerebellar syndrome that is clinically indistinguishable from paraneoplastic or ara-C-induced cerebellar disorders. Patients develop truncal and limb ataxia, dysmetria, nystagmus, and dysarthria. The signs usually reverse within a week after the drug is discontinued and can reoccur with repeat doses.

5-FU is often used in combination therapies which increases its neurotoxicity. When combined with levamisole, a few patients develop an inflammatory multifo-

cal leukoencephalopathy presenting clinically with confusion and focal signs such as ataxia or hemiparesis. Patients often improve after cessation of therapy and treatment with corticosteroids.

Plant Alkaloids

Vincristine. Vincristine is the most neurotoxic of this group and primarily affects peripheral nerves although it can cause unilateral or bilateral focal neuropathies of peripheral and cranial nerves. A dose-limiting sensorimotor neuropathy appears in virtually all patients. The earliest complaint is tingling and paresthesias of the fingertips and then the toes. Fine movements are often impaired. Muscle cramps are common and may be the first signs of neurotoxicity. Patients often do not report sensory loss but weakness is typical with patients developing foot or wrist drop. Recovery can take months after cessation of the drug.

Autonomic neuropathy characterized by abdominal pain and constipation occurs in up to one third of patients receiving vincristine. Paralytic ileus has been reported, and occurs most often in children. All patients receiving vincristine need to follow a prophylactic bowel regimen particularly if they are also receiving corticosteroids.

Paclitaxel (Taxol). Paclitaxel is another plant alkaloid that is commonly used to treat breast and ovarian cancer. More than half of patients taking Taxol at doses of greater than 200 mg/m2 develop paresthesias of the hands and feet. Both large and small nerve fibers are affected. Although symptoms may begin within a few days of the first dose most occur after multiple doses. Motor and autonomic dysfunction may also occur, especially at high doses and in patients with pre-existing neuropathies.

Corticosteroids

Steroids are among the most frequently used drugs in oncologic practice. In addition to their use to control brain and spinal cord edema they are useful chemotherapeutic agents and also act to improve appetite, elevate mood, decrease pain and restore the integrity of the blood-brain barrier. Unfortunately, steroid use is complicated by many unwanted side-effects. Low dose steroids (16 mg/24 hours) produces similar side effects as high doses (100 mg/24 hour of dexamethasone) when given for short time but there is probably a higher frequency of serious side effects from prolonged use of high doses.

The most common (and usually mild) side-effects of steroid use include insomnia, increased appetite with or without sensations of abdominal distension, visual blurring, urinary frequency and nocturia, and acne. One unusual side-effect is a sensation of anogenital burning or itching immediately after intravenous bolus injection that subsides within a few minutes. For some patients, corticosteroids diminish the senses of taste and smell and can lead to anorexia.

Non-neurologic but serious side effects of steroid use include gastrointestinal bleeding, bowel perforation, osteoporosis, avascular necrosis, glaucoma, and opportunistic infections. Pneumocystis carinii infection occurs in patients who have been on long termásteroids and are being tapered to lower doses. Prophylaxis with trimethoprim-sulfamethoxazole, one double-strength tablet (160 mg trimethoprim/800 mg sulfamethoxazole) twice a day for 3 consecutive days or once per day for 6 days is recommended. The drug is given to patients who are expected to receive steroids for more than 2 weeks and is discontinued 1 month after the steroids are stopped. Osteoporosis is a common side effect of prolonged steroid use and can cause vertebral fractures and avascular necrosis, usually of the hip. The pain from these disorders needs to be differentiated from that of cord compression or peripheral neuropathy.

Many drugs increase the metabolic clearance of steroids and may decrease its therapeutic efficacy. One study demonstrated that there was a 20% reduction in the bioavailability of dexamethasone after the addition of phenytoin.

The common neurologic side effects of steroid use include myopathy, changes in behavior, hiccoughs, tremor and visual blurring. Some patients will hallucinate when given high doses. A mild myopathy develops in most patients receiving 16 mg/24 hours of dexamethasone or equivalent for more than 2 to 3 weeks and improves after the drug is stopped.

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