NEUROLOGIC COMPLICATIONS OF DRUG THERAPIES

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Introduction

This talk provides a brief overview of neurologic complications of drug therapies encountered in the routine care of inpatients, with a focus on those most commonly observed. Also included are less common complications which (a) may be overlooked in the differential diagnosis, (b) are a frequent question from consulting services, (c) may be discounted as a “zebra” as opposed to a common thoroughbred, or (d) may produce devastating or permanent consequences such that prompt diagnosis may change prognosis. As a general principle, cessation of the offending agent is advised. In some instances specific therapies may be necessary to reverse or inhibit the neurologic adverse effect. Selected neurologic complications of the drug therapies reviewed below will be highlighted in the course.

Antimicrobial Drugs

Antimicrobials are given in nearly every hospital setting. A brief review of their capacity to produce neurologic sequelae follows. Antibiotics are an under-recognized class of medications associated with acute neurologic complications in the hospital. Cephalosporins and penicillin have been associated with encephalopathy, often associated with seizures and/or myoclonus, while quinolones, macrolides, and procaine penicillin have been linked to encephalopathy and psychosis, typically arising within days after antibiotic administration. Metronidazole may result in encephalopathy accompanied by cerebellar signs and MRI abnormalities emerging weeks after initiation of the drug. The clinician should maintain a high index of suspicion as confusion, lethargy, or disorientation may be attributed to delirium secondary to infection or metabolic derangements and a medication effect may be easily overlooked.

Elderly patients are at unique risk for specific neurologic effects associated with a number of classes of antimicrobials as detailed in a recent comprehensive literature review. In this review focusing on the geriatric population, the authors found associations between fluoroquinolones and mania, insomnia, acute psychosis, and delirium. Macrolides were associated with dizziness, insomnia, light-headedness, and confusion. Intravenous infusion of sulfonamides, including trimethoprim-sulfamethoxazole (TMP-SMX), was implicated in the development of acute psychosis. TMP-SMX may also cause both resting and postural tremor. The tremor starts within a few days of initiation and typically resolves within several days of stopping the drug.

Aminoglycosides are classically associated with ototoxicity, but may also cause peripheral neuropathy, encephalopathy, or acute weakness. Weakness develops as a result of neuromuscular transmission blockade. For this reason aminoglycosides are best avoided in patients with myasthenia gravis or Lambert-Eaton myasthenic syndrome.

Among the azoles, voriconazole is the member most reported to produce adverse neurologic effects. It has been documented to produce visual disturbances (altered or enhanced visual perception, blurred vision, color vision change, photophobia, and hallucinations) in 20-30% of patients as well as painful peripheral neuropathy, agitation, insomnia, and anxiety.

The shared β-lactam ring structure amongst the penicillins, cephalosporins, and carbapenems are believed to decrease release of the neurotransmitter, GABA, from nerve terminals and lower the threshold for seizure generation. The known neurotoxic effects of β-lactam antibiotics include slurred speech, tremor, encephalopathy, and seizures, and reported risk factors include significant renal injury, damage to the blood-brain barrier, pre-existing CNS disease, and old age. All penicillins can produce an encephalopathy, myoclonus, and seizures if given in high enough doses or in the setting of renal failure. Carbapenems may lower the seizure threshold by inhibition of the GABA-A receptors, producing seizures with an estimated incidence of 3%. Carbapenems have also been associated with hallucinations and delusions. Compared with imipenem, meropenem, and, ertapenem, the newer carbapenem, doripenem, appears to interact less with the GABA receptors, reducing the neurotoxic potential. All four generations of cephalosporins have been associated with neurologic complications. Truncal asterixis, or negative myoclonus involving the trunk and lower extremities, has been reported in a patient with

chronic renal failure treated with ceftazidime for cellulitis. Cephalosporin toxicity is often associated with renal failure. The fourth-generation cephalosporin, cefepime, has been increasingly recognized as a cause of reversible encephalopathy, myoclonus, and sometimes seizures in the setting of concomitant renal disease. Additional clinical features include hallucinations, agitation and coma. Hemodialysis may be effective if urgent clearance is necessary as may be the case when non-convulsive status epilepticus secondary to cefepime neurotoxicity is refractory to antiepileptic drug therapy.

Neurologic complications associated with fluoroquinolones include seizures, confusion/encephalopathy, myoclonus, and psychosis. Ofloxacin and ciprofloxacin have been reported to produce orofacial dyskinesias and extrapyramidal signs including gait disturbance, dysarthria, and choreiform movements. Levofloxacin is the most commonly administered drug in the hospital that results in breakthrough seizures in patients with epilepsy.

Beginning with the use of highly active antiretroviral therapy (HAART) in 1996, mortality rates in human immunodeficiency virus type-1 HIV-1 infected individuals have fallen dramatically. As a consequence of its widespread use, our understanding of the neurologic complications related to HAART has improved. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, has the greatest frequency of neurologic side effects among newer antiretroviral regimens. Over 50% of patients will experience a constellation of neuropsychiatric symptoms variably including vivid dreams, headaches anxiety, depression, paranoia, or psychosis by day seven of therapy which will typically abate within one month of treatment.

Polymixins have been associated with dizziness, weakness, facial and peripheral paresthesias, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, ataxia, and neuromuscular blockade. The paresthesias are the most common side effect with reported incidences of 27% and 7.3% with patients receiving colistimethate sodium IV and IM, respectively. The neurotoxic effects of polymixins have been reported to begin within four days of treatment onset but are typically mild and resolve upon discontinuation of the drug.

The tetracyclines produce predominantly vestibular symptoms including blurred vision, light-headedness, loss of balance, vertigo, and tinnitus. In some cases symptoms evolve after receiving only one or two doses of the drug.

Weakness from use of the lincosamide, clindamycin, has been attributed to neuromuscular blockade. Use of the reversible anticholinesterase inhibitor, neostigmine, produces partial reversal of weakness.

Metronidazole has been implicated in the development of characteristic bilateral lesions at the dentate nuclei. Patients may present clinically with dizziness, nausea, sensory neuropathy, dysarthria, and ataxia. On brain MRI, hyperintense T2 lesions typically present within the supratentorial white matter and deep cerebellar nuclei, typically the dentate nuclei. Management of the acute cerebellar symptoms requires cessation of metronidazole.

Chemotherapy and Immunosuppressant Drugs

A detailed discussion of neurologic complications of biologic chemotherapeutic agents will not be discussed here, but it is important for the clinician to be aware that these agents, including the interferons (α, β, and γ), interleukin-2 (IL-2), tumor necrosis factor (TNF), and the monoclonal antibodies are capable of producing neurologic side effects, including most prominently neuropsychiatric symptoms with interferons and interleukins. In selected monoclonal antibodies, peripheral neuropathy, posterior reversible encephalopathy syndrome (PRES), and PML have been reported. PRES is a syndrome of variably manifesting as acute onset of headache, encephalopathy, focal neurologic deficits and seizures. Characteristic MRI findings include bilateral asymmetric predominantly subcortical vasogenic edema, classically in the parietal and occipital lobes. PRES is typically reversible but can result in permanent morbidity when hemorrhages or infarcts occur and it has rarely been associated with a rare fatal phenomenon known as subacute diencephalic angioencephalopathy (SDAE). Bevacizumab appears to be associated with a higher incidence of ICH only combined with anticoagulation. Rituximab, a monoclonal antibody directed against the CD20 antigen of B-lymphocytes, warrants specific mention amongst the monoclonal antibodies for its widespread use. Rituximab has been associated with development of PML at a rate of 2 cases per 8000 uses. Median symptom onset from first dose is 16.0 (range, 1 – 90) months and from last rituximab dose 5.5 (range, 0 .3 – 66.0) months. PML is a rare demyelinating disease of the CNS in which patients often present with confusion/disorientation, weakness/hemiparesis, impaired motor coordination, speech changes, and vision changes. Unfortunately, fatality rates can approach 90%. Rituximab has also been reported in association with the posterior reversible encephalopathy syndrome PRES.

Cyclosporine and tacrolimus are associated with numerous neurologic side effects. These agents work by inhibiting both production of IL-2 and their ability to activate T-lymphocytes. These deserve special mention because of their known association with PRES. When PRES develops in a patient taking either tacrolimus or cyclosporine, the drug should, in most cases, be held at least temporarily. This often requires an increase or addition of alternative immunosuppressant agents, in order to reduce the risk of transplant rejection. These decisions should be made in conjunction with a transplant specialist. Following liver transplantation, cyclosporine toxicity may develop as early as three days following surgery in up to 10% of patients. An acute confusional state with paranoia, tremor, and speech abnormalities may develop. Some patients may become mute, and coma is a rare complication if toxicity remains unrecognized. Cyclosporin and tacrolimus are also reported to produce postural and intention tremors. Cyclosporin-induced tremor has been reported in up to 40% of treated patients. The tremor is usually begins shortly after treatment initiation and is generalized with mild to moderate intensity. Following liver transplantation, tremor was observed in 10 of 44 consecutive patients within the first weeks following surgery. Reduction of the dose resulted in improved symptoms, although fine tremors persisted in three patients.

Corticosteroids can produce a myopathy resulting in variable degrees of weakness. The presentation is typically proximal muscle weakness and atrophy. Significant myopathy has been demonstrated at doses of 40 mg/day with prednisone. Steroids may also cause mood disorders, psychosis or tremor, particularly upon initiation of steroids or administration of high doses.

Cytarabine may cause nystagmus, dysarthria, ataxia, and intention tremors due to damage to the cerebellar Purkinje cells in lateral hemispheres. Toxic effects occur in 8-23% of patients and may be associated with higher doses in the elderly, prior neurologic deficits, and hepatic disease. In children with leukemia treated with cytarabine, effects have been reported to last as long as two years.

Methotrexate may cause aseptic meningitis, transverse myelitis, acute or subacute encephalopathy, and leukoencephalopathy. Aseptic meningitis is typically associated with intrathecal administration and occurs two to four hours after drug injection and may last up to 72 hours. Symptoms are usually self-limited without need for additional treatment. Transverse myelopathy is a rare complication of intrathecal use. Symptoms typically begin within 30 minutes to 48 hours but have been reported to occur within two weeks. Clinical recovery is variable and future use of intrathecal methotrexate is contraindicated. The encephalopathy may present with somnolence, confusion, or seizures within 24 hours of use. The encephalopathy is usually self-limited and retreatment is possible. Methotrexate leukoencephalopathy typically develops after six months of use.

The chemotherapy agents most commonly associated with peripheral neuropathy are platinum compounds (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine), proteasome inhibitors (bortezomib), and antiangiogenic compounds (thalidomide). Chemotherapy-induced peripheral neuropathy is typically dose dependent and may produce persistent symptoms despite discontinuing the medication. When symptoms persist despite discontinuation, this is referred to as the coasting phenomenon. A study of oxaliplatin showed that symptoms partly resolve in 80% of patients and completely resolve in 40% of patients within six to eight months of drug discontinuation.

The mammalian target of rapamycin inhibitors (mTORis) sirolimus and its metabolite everolimus are relatively newer agents in oncology and transplant medicine and are becoming more widely used in transplant medicine due to a significantly reduced neurotoxic profile in comparison with the calcineurin inhibitors. A retrospective review of 202 patients receiving sirolimus after kidney or liver transplants did not suggest any neurotoxicity was attributable to sirolimus. Cases of PRES associated with sirolimus are rare and neurologic disease is rarely associated with everolimus.

The taxols may act either through dissociation or aggregation of intracellular microtubules. Sensorimotor neuropathy has been reported to develop after a single dose, and is more likely to occur in combination with cisplatin and with doses exceeding 250 mg/m^2. Cases of pure proximal weakness and myopathy have been reported with evidence of myopathic changes on EMG. The course of neuropathy following taxol use is, unfortunately, unpredictable. Limited follow-up of subjects following treatment identified patients who developed a moderate or severe neuropathy weeks following cessation of therapy.

Thalidomide may produce a length-dependent sensory peripheral neuropathy or less likely a ganglionopathy with clinical signs of large and small fiber damage. In a report of thalidomide therapy (median dose, 373 mg/d), 41% of

patients developed neuropathy during treatment. The median time of onset was 24 weeks (range, 2 to 60 weeks). Cessation of thalidomide may result in partial reversibility of symptoms. The long-term prognosis is not well known. Thalidomide is also associated with tremor which is typically mild to moderate and reversible in most cases.

The vinca alkaloids induce edema within the fast and slow conducting axons as a consequence of altering the cellular microtubule structure. Most patients treated with vincristine develop a sensory-predominant polyneuropathy. When given in the setting of a hereditary polyneuropathy, vincristine may acutely produce tetraplegia, which may be misdiagnosed as acute inflammatory demyelinating polyradiculoneuropathy. Cases have been reported with onset after only two doses or as soon as 10 days after onset of chemotherapy manifesting as severe weakness and sensory loss. Gradual improvement began as early as two months after cessation and may continue over a 12-month period.

Sedative and Analgesic Drugs

Patients may be admitted with a history of chronic pain or may have acute pain in the setting of a new illness or a procedure. Patients are at higher risk for CNS complications with concomitant hepatic, renal, or hematologic disease as the pharmacokinetics and pharmacodynamics of most drugs are influenced by metabolism, clearance, and protein binding through these organ systems.

Expect the opiates to produce miosis, depressed levels of consciousness, depressed respiratory drive, and seizures in severe cases. Respiratory acidosis resulting from hypoventilation may pose additional secondary injury in the setting of primary brain disease as it may lead to increased ICP. Pethidine (meperidine) has a potentially toxic metabolite, norpethidine, known to potentially result in anxiety, tremors, or seizures. In addition to lowering the seizure threshold, many opiates' inherent serotonergic activity may produce or exacerbate the reversible cerebral vasoconstriction syndrome (RCVS) or lead to serotonin syndrome when combined with other serotonergic medications. Among the opiates, fentanyl has the highest serotonergic activity. Naloxone is the reversal agent of choice for opiates. With successful opiate reversal, continued monitoring of vital signs until the expected duration of action has passed is essential, as the half-life of naloxone is less than two hours.

Neuropathic pain is frequently treated with gabapentin or carbamazepine. Toxicity of these drugs may produce sedation, imbalance, ataxia, tremors, and myoclonus. Disabling asterixis and myoclonus of the face, trunk, and extremities have also been described with the use of gabapentin, particularly in the setting of renal insufficiency.

Among the sedatives, propofol is known for its anxiolytic and amnestic effects as well as short duration. It acts through centrally active alpha-2 agonist activity and does not have analgesic properties. Due to highly lipophilic properties, prolonged use can lead to delayed emergence. Other abnormal movements have been reported with propofol, typically with induction or withdrawal of the drug. These include dystonia, choreiform movements, opisthotonus, and "seizure-like phenomena," with tonic-clonic movements reported up to six days after discontinuation. These are not ictal as evidenced by electroencephalography recording during the movements. It is hypothesized that propofol inhibits subcortical or spinal inhibitory pathways thereby allowing excitatory movements to appear. The movements are self-limited and do not require specific treatment but can lead to over-treatment and iatrogenic complications if their cause and benign nature is not appreciated.

Malignant hyperthermia is a potentially fatal complication of succinylcholine and all inhaled anesthetic agents except nitrous oxide. The reaction occurs within an hour of drug use. The neurologic signs include hyperthermia, masseter rigidity, and generalized rigidity. Other frequent initial signs include hypercarbia refractory to increased minute ventilation and sinus tachycardia. The treatment of choice is dantrolene.

Elderly patients, those with impaired hepatic or renal function, and patients with pre-existing neurodegenerative or intracranial disease may take longer than expected to return to baseline cognitive function after discontinuing anesthetic agents in the ICU or operating rooms.

Psychotropic Drugs

Anticholinergic syndromes could result from use of tricyclic antidepressants, antihistamines, antiparkinsonian medications such as trihexyphenidyl or benztropine, antipsychotics such as clozapine or olanzapine or belladonna alkaloids. Clinical features may include delirium with hallucinations, mydriasis, hypertension, tachycardia, urinary

retention, warm, dry, erythematous skin, tongue and mucosae, and seizures in the most severe cases. The clinician should assess for the presence or absence of diaphoresis to distinguish between the toxicity of sympathetic stimulants and anticholinergics, respectively. In the setting of a latent or previously known neurocognitive disorder, the use of anticholinergics may also worsen cognition. For patients on an anticholinergic agent for management of “urinary incontinence,” the use of anticholinergics with quaternary amines such as darifenacin or trospium may be preferable as there are animal models that suggest they have significantly less permeability across the blood-brain barrier.

Benzodiazepines are effective for their anxiolytic, amnestic, and sedating qualities. As with opiates, similar risks with CNS depression and increased ICP exist. Delayed emergence from sedation may be more likely to occur with lorazepam or diazepam due to their greater potency, slower clearance and prolonged duration of action and saturation of peripheral tissues, respectively. Reversal of benzodiazepine effect is accomplished with flumazenil. Vigilance following its use is indicated as well as the risk for seizure increases flumazenil administration, and its duration of action is less than one hour.

Although many drugs may cause or exacerbate delirium, benzodiazepines have the highest association with delirium. Delirium is a disturbance in attention and awareness that develops over a short period of time (usually hours to a few days), represent a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day. There is a disturbance in other aspects of cognition such as memory, disorientation, language, visuospatial ability, or perception and these disturbances are not better explained by another preexisting, established, or evolving neurocognitive disorder nor are they in the context of a severely reduced level of arousal.

Antipsychotics (neuroleptics) are commonly used in the inpatient setting for management of symptoms resulting from the development of hospital acquired delirium, decompensated dementia, and acute psychosis. Antidepressants are sometimes initiated during prolonged hospitalizations for situational depression and perhaps more commonly following acute ischemic stroke where there is evidence for their early initiation. Both antidepressants and antipsychotic agents are also frequently continued as part of an outpatient regimen for treatment of primary psychiatric disorders upon admission to the hospital. Neurologic complications relating to these drugs primarily arise when doses are increased or when other dopaminergic or serotonergic agents are added to the medication regimen in hospital.

A well-recognized complication of antipsychotic use is the neuroleptic malignant syndrome (NMS). NMS is typically characterized by a tetrad of mental status changes, fever, rigidity, and autonomic instability. As no specific diagnostic test exists, diagnosis is purely clinical. NMS must be recognized because of its potential to result in death. Published cases of NMS have suggested mortality rates as high as 25%, but with timely diagnosis and appropriate treatment survival rates can exceed 90%. Monitoring the serum creatine kinase may provide supportive evidence of the diagnosis and assess the risk of renal injury and response to therapy. Myoglobinemia and renal failure have been reported as strong predictors of mortality. Treatment involves discontinuation of anti-dopaminergic medications, IV hydration to protect against rhabdomyolysis, maintenance of normothermia, administration of dantrolene and/or bromocriptine, and supportive care. NMS is widely attributed to the overuse of certain medications however; an NMS-like syndrome can also develop after abrupt discontinuation of medications with dopamine agonist activity. Reported cases have involved patients previously treated for idiopathic Parkinson’s Disease whose medications were abruptly stopped or reduced. The approach to treatment is similar to NMS with immediate reintroduction of the patient’s dopaminergic medications. This phenomenon highlights the importance of medication reconciliation at the time admission. A study performed at a large institution in the US reported that greater than one-third of patient admissions had medication errors, nearly half of errors were admission errors, and antidepressants and neurological agents were two classes among the top five most common classes involved in errors.

Extrapyramidal symptoms (EPS) are most often associated with neuroleptics. Medications with dopamine-antagonist activity used for other systemic complications including antiemetics and gastrointestinal pro-motility agents are other potential culprits. Antidepressants with serotonergic activity have also been associated with EPS. EPS may be classified according to speed of onset as acute (akathisia, dystonia, and parkinsonism) or tardive (tardive dyskinesia and dystonia). A general strategy for management of EPS is cessation of the medication or reduction of the dosage when cessation is not feasible. When EPS is due to a neuroleptic, substituting one neuroleptic for another neuroleptic with a higher D2 receptor dissociation constant or a lower D2

receptor percent occupancy may guide the selection of an alternative neuroleptic. In cases where a neuroleptic is indicated because of agitation refractory to non-pharmacologic measures, quetiapine is generally well tolerated.

Akathisia is described as a subjective feeling of motoric restlessness with typical onset within hours to days. This subjective sensation can often be disconcerting to the patient and may be described as nervousness, anxiety, or tension. After proper recognition, treatment of akathisia involves reduction or cessation of the inciting medication. If reduction or cessation is not feasible, benzodiazepines may be tried as first-line therapy. If benzodiazepines are not effective or clinically appropriate, propranolol or benztropine may also be effective.

Dystonias are sustained muscular contractions with abnormal, twisting, often repetitive movements, postures, or both, typically with onset within hours to days. As in akathisia, these movements may be uncomfortable or painful to the patient. Partial relief may be found from a tactile or proprioceptive trick (*geste antagoniste*) that reduces the dystonia; for instance, a patient with head tilt due to cervical dystonia might touch the chin to keep the head straight. Acute dystonia may be treated with either IV benzatropine or diphenhydramine. For patients who require IV administration of a neuroleptic with minimal or no prior exposure to neuroleptics, such as the adolescent presenting to the emergency department with acute psychosis, pretreatment with benzatropine or diphenhydramine is reasonable.

Parkinsonism refers to the cardinal features of idiopathic Parkinson's Disease – rest tremor, rigidity, bradykinesia, and postural instability – in the absence of idiopathic Parkinson's Disease. A key differentiating feature is the lack of asymmetry in medication induced parkinsonism which is characteristic of idiopathic Parkinson's Disease. Elements of medication-induced parkinsonism typically present over a period of days to weeks. As in akathisia and acute dystonia, treatment with an anticholinergic or antihistamine may be effective. If avoidance of the adverse effect of anticholinergics or antihistamines is desired, amantadine has shown similar efficacy in treating EPS in comparison to both trihexyphenidyl and benzatropine.

The serotonin syndrome is a potentially life-threatening drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs. Excessive stimulation of serotonin-5-hydroxytryptamine (5HT)-1a or 5HT-2 receptors in the central nervous system is hypothesized to mediate these reactions, which may be mild to severe. A number of medication classes including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products can cause serotonin syndrome. The syndrome is a constellation of symptoms including encephalopathy, mydriasis, clonus, tremor, hypertonicity (legs>arms), fever and hyperactive bowel sounds. Often, only a few of the features are present. In the hospital, serotonin syndrome is most likely to occur when an opiate (most commonly fentanyl) or antiemetic is initiated in the setting of SSRI or SNRI use. Antidepressants taken in the outpatient setting are often overlooked when they are not continued in hospital. The majority of these agents have long half-lives, and continue to be biologically active for days to weeks.

Other

Various drugs of abuse can produce a toxidrome caused by modulation of central and peripheral catecholamine neurotransmitter function. These drugs include, but are not limited to cocaine, amphetamines and related substances including methamphetamine, "bath salts," methylphenidate, cathinone ("khat"), and MDMA ("ecstasy"). The typical clinical picture is one of adrenergic overdrive with increased sympathetic activity manifesting as tachycardia, tachypnea, diaphoresis, hypertension, hyperthermia, mydriasis, hyperreflexia, and tremor. Medical sequelae include acute coronary syndrome, heart failure, renal failure, and hepatotoxicity and electrolyte abnormalities. Rhabdomyolysis has been reported. Neurologic sequelae include acute encephalopathy, seizures, stroke and coma. Serotonergic amphetamines can produce clinical manifestations of serotonin toxicity.

Several agents including baclofen, cyclobenzaprine, diazepam, methocarbamol, and tizanidine are used as muscle relaxants. They are well known to cause CNS depression. Cyclobenzaprine is pharmacologically related to the tricyclic antidepressants. As such, its associated anticholinergic properties may depress cognitive performance in the setting of a neurocognitive disorder, and its serotonergic activity may increase the risk for serotonin syndrome or RCVS.

Valproic sodium is an antiepileptic widely used for the treatment of epilepsy and bipolar spectrum disorders. Hyperammonemia may occur in the presence or absence of clinical or laboratory evidence of liver injury. Elevated ammonia may cause encephalopathy including features of lethargy, emesis, cognitive slowing, incoordination, and coma in severe cases. Cases may be associated with carnitine deficiency due to malnutrition or inborn errors of metabolism. Treatment involves discontinuation of the drug, with potential use of L-carnitine, lactulose, or neomycin. Time to recovery ranges from 1 to 30 days.

Neurologists are occasionally consulted urgently for evaluation of a 'blown pupil' and on examination the patient is found to be otherwise normal. A cursory discussion with the patient will often disclose a long-standing history of benign anisocoria, prior cataract surgery, or a poorly tolerated facemask used to deliver recent aerosolized anticholinergics (i.e. ipratropium).

Conclusions

The nervous system is susceptible to an expansive range of disease, extending from hyperacute disease to chronic illness. The well-prepared clinician will have a sound foundation in the potential adverse effects resulting from commonly used drugs. Ubiquitous use of antimicrobials requires awareness of their potential to produce encephalopathy which must be differentiated from septic encephalopathy. Recent advances in the use of biologic chemotherapies will be of continued interest as research actively continues to translate research at the bench to the bedside for these increasingly common medications. The high prevalence of psychiatric and neurodegenerative disease requires careful reconciliation of home medications with newly added drugs in the hospital in order to avoid toxicity or withdrawal from centrally acting agents. As the population ages, clinicians are likely to see an increase in neurologic complications of drugs used in the hospital setting as the elderly seem to be particularly prone.

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