CNS Toxicities: Pharmaceuticals

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Central nervous system (CNS) toxicity from pharmacological agents is on the increase with the explosion of novel therapeutics for the treatment of autoimmune and neoplastic disorders. It is important for neurologists to be able to recognize such toxicities and distinguish them from neurological complications of the underlying disease being treated. The aim of this course will be to familiarize the practicing neurologist with the CNS medication toxicities most commonly encountered via a case based presentation.

CNS Toxicity associated with Medications for CNS Demyelinating Diseases

The number of FDA approved medications for relapsing remitting multiple sclerosis (MS) has increased rapidly over the last 5 years and these novel medications have interesting interactions with the immune system. A variety of immunosuppressant medications are used to treat neuromyelitis optica spectrum disorders (NMOSD), although no medications have yet been FDA approved. The use of these medications has led to a number of infectious CNS adverse effects that can be difficult to distinguish from the underlying CNS demyelinating disease. Thus, infectious complications should thus always be considered among the differential diagnosis of a new neurologic episode in those with CNS demyelinating disease on immunosuppressant medications.

Natalizumab is monoclonal antibody against α4 integrin that has strong efficacy in relapsing remitting MS. However, it has been recognized to be associated with a small but important risk of progressive multifocal leukoencephalopathy (PML) an infectious disorder of the white matter caused by reactivation of the John Cunningham (JC) virus. There are three major risk factors for the development of PML: 1) JC virus exposure in the past based on serum serology results; 2) Use of natalizumab for greater than 2 years; 3) Prior use of immunosuppressant medications. In those with all three risk factors the risk of developing PML is less than 1/100 while in those with none of these risk factors the risk is 2/100,000. A careful calculation of the risk-benefit ratio is needed when considering natalizumab treatment for MS. A few cases of PML have been reported with some of the other recently FDA approved medications for multiple sclerosis including dimethyl fumarate and fingolimod, although the risk appears to be less than with natalizumab. Alemtuzumab and rituximab have also been reported to be associated with PML when used for other diseases; although widely used, rituximab has not yet been FDA approved for MS treatment. PML has also been reported in a NMOSD in a patient on long-term immunosuppressant medication although the coexisting lupus (also a risk factor for PML) may have contributed to PML risk. Herpes viruses have also been reported with some new MS medications, most notably fingolimod and alemtuzumab; vaccination for varicella zoster virus prior to their use is generally recommended.

CNS toxiciy associated with Treatment of Rheumatologic Disorders

Traditional non-biologic agents (e.g., methotrexate) can be associated with CNS neurotoxicity. A number of novel ‘biologics’ used in rheumatologic disorders are known to cause CNS toxicity from autoimmune, infectious or neoplastic complications. Tumor necrosis factor inhibitors may be associated with an increased risk of developing CNS demyelinating disease.

CNS Toxicity with Immunosuppressant’s used in Organ Transplantation

Most transplant centers use a triple immunosuppression approach with 1) a calcineurin inhibitor (e.g., tacrolimus); 2) an antimetabolite (e.g., mycophenolate); and 3) prednisone. The calcineurin inhibitors are commonly associated with tremor and less frequently with posterior reversible encephalopathy syndrome (PRES [discussed below]) or a toxic leukoencephalopathy.

CNS Toxicity with Anti-Neoplastics

Mild cognitive dysfunction is a common accompaniment of chemotherapy and has led to the term ‘chemo-brain’. However, an acute severe encephalopathy can occur as a direct complication (e.g., ifosfamide encephalopathy which is treated with methylene blue), from a toxic leukoencephalopathy (e.g., methotrexate) or in association with PRES (discussed below). Cerebellar ataxia can accompany cytarabine use while intrathecal use of antineoplastics can cause an aseptic meningoencephalitis or myelopathy. Accelerated atherosclerosis and resulting in cerebral infarcts has been reported with tyrosine kinase inhibitors (e.g., nilotinib). The immune checkpoint inhibitors which inhibit either Cytotoxic lymphocyte-associated protein 4 (CTLA-4) (e.g., ipilimumab) or programmed cell death-1 (PD-1) (e.g., nivolumab or pembrolizumab) are utilized for melanoma and other cancers and work by activating the immune system to help destroy cancer cells. Check point inhibitors can tip the delicate balance between tolerance and autoimmunity towards the latter and result in autoimmune disorders of the CNS including myelitis and encephalitis.

CNS Toxicity with Antimicrobials

Hospitalized patients, particularly those in the intensive care unit are frequently placed on antibiotics for confirmed or suspected infection. Encephalopathy or delirium is a common complication in this patient population from the hospitalization, sleep deprivation, medication toxicity, multiple medical comorbidities (e.g., renal failure) and direct (CNS metastases) or indirect (septic encephalopathy) neurological complications. The β-lactam ring common to penicillin’s, cephalosporins and carbapenems decrease release of the neurotransmitter GABA which may explain their potential to cause seizures; other antibiotics (e.g., fluoroquinolones) may also predispose to seizures. The cephalosporin cefepime is an under-appreciated cause of encephalopathy in those with renal failure and may be accompanied by myoclonus or seizures. Metronidazole may cause encephalopathy accompanied by ataxia often with accompanying MRI lesions in the dentate nucleus. Discontinuation of the offending antibiotic will usually result in resolution of symptoms within days.

CNS Toxicity with Analgesics and Anesthetics

The epidemic in opioid use for chronic noncancer pain in the USA has received much attention. The AAN has produced a position paper in 2014 with recommendations for neurologists about prescribing practices. Neurologists may encounter such patients in the inpatient setting when admitted for overdose or when they develop encephalopathy precipitated by the initiation of opioids particularly in those predisposed (e.g., hepatic failure). Miosis is typical along with respiratory depression. The hypoventilation may lead to respiratory acidosis and secondary increased intracranial pressure from increased pCO2 in those with underlying brain disorder. Thus extreme caution is advised with opiate use in those with increased intracranial pressure as cerebral herniation has been reported from increased intracranial pressure worsened by opioids. Neurologists are often consulted to evaluate patients not awakening, confused or with apparent neurologic abnormalities after undergoing anesthesia. Those with neurodegenerative disorders may be particularly predisposed. However, it is essential to look beyond just delayed awakening from anesthesia as the cause because hypoxic ischemic brain injury, seizures, medication toxicity (e.g., perioperative benzodiazepines), systemic disorders (e.g., septic encephalopathy) or a direct neurologic complication in those undergoing neurosurgery (e.g., iatrogenic intracranial hemorrhage) are all potential etiologies in this setting. Propofol can cause myoclonus and other abnormal movements during its induction and withdrawal. These are a benign phenomenon with no long lasting effect, recognition of which prevents misdiagnosis as seizures.

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