CNS Toxicities: Syndromes

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The number of drugs associated with syndromic neurologic presentations (e.g., posterior reversible encephalopathy syndrome) is on the increase with the introduction of novel treatments for a wide range of diseases. Recognition of these syndromes and discontinuation of the offending medication is essential and failure to recognize these disorders can result in morbidity and mortality. Specific treatments may be available targeted at that distinct syndrome but supportive care and discontinuing the implicated medication is the mainstay. When recognized early and treated appropriately the prognosis is generally excellent.

Posterior Reversible Encephalopathy Syndrome (PRES)

A large list of medications have been associated with PRES including immunosuppressant's used post organ transplant (e.g., tacrolimus, cyclosporine), anti-angiogenic monoclonal antibodies (e.g., bevacizumab) and other novel monoclonal antibodies used for a variety of autoimmune disorders (e.g., the IL-12 and IL-23 blocker ustekinumab used in psoriasis). The pathophysiology is thought to relate to endothelial dysfunction and disturbance of cerebral autoregulation. Other predisposing conditions which may coexist or be the major contributor in their own right include pre-eclampsia, eclampsia, autoimmune disorders and renal impairment. Onset is within hours to days and clinical features include headache, encephalopathy and seizures occur in approximately two thirds. Examination may reveal visual deficits that range from minor visual field abnormalities to cortical blindness. Hypertension is typical and MRI shows FLAIR hyperintensities in the posterior regions from vasogenic edema. Treatment is supportive and the offending medications should be discontinued. Prognosis is excellent and most will recover back to baseline.

Reversible Cerebral Vasoconstriction Syndrome (RCVS)

At least half of RCVS cases occur secondary to vasoactive medications including illicit drugs (e.g., cannabis, cocaine, amphetamines), antidepressants (e.g., selective serotonin or selective norepinephrine reuptake inhibitors), sympathomimetics (e.g., pseudoephedrine), triptans, ergot alkaloid (e.g., bromocriptine), or blood product medications (e.g., IVIg). Women are more predisposed. The classic presentation is that of recurrent thunderclap headaches that last a few hours. Transient focal neurologic deficits may also occur. MRI head may be normal but sulcal subarachnoid hemorrhage is a characteristic finding. MR or CT angiography are preferred for diagnosis as catheter based angiogram can result in worsening. Cerebrospinal fluid is typically non-inflammatory, in contrast to the inflammatory CSF that usually accompanies primary CNS vasculitis. Steroids worsen RCVS and should be avoided. Management includes discontinuation of offending medications and supportive treatment. Some have advocated vasodilators such as calcium channel blockers but data supporting this approach is limited.

Serotonin Syndrome

A variety of medication classes have prominent serotonergic activity that alone, or much more often in combination, can result in serotonin syndrome. Classes of medication with prominent serotonergic activity include: selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, opiates or related drugs (including fentanyl, tramadol, and meperidine), triptans and ergotamine, over the counter cough medicine and antiemetics. Patients present with agitation, restlessness and confusion. Examination reveals tremors, myoclonus, hyperactive reflexes, increased tone and clonus. Temperature is elevated (>38C) and autonomic hyperactivity is common (mydriasis, diaphoresis, tachycardia, hypertension). Treatment is with discontinuation of the offending agent, sedation with benzodiazepines, serotonin antagonists (cyproheptadine) and supportive care.

Neuroleptic Malignant Syndrome

This is a severe life-threatening disorder associated with dopamine blocking medications and can be seen with typical (e.g., haloperidol) or atypical (e.g., risperidone) neuroleptics and with antiemetic's (e.g., metoclopramide). It is characterized by confusion, rigidity, hyperthermia and autonomic dysfunction; catatonia may also occur. An markedly elevated creatine kinase (>1000 IU/L) and leukocytosis is typical. Treatment involves discontinuation of the implicated medication and supportive care. Dantrolene (a muscle relaxant) or bromocriptine (a dopamine agonist) are often also used but supporting data for the use of those agents is limited.

Drug Induced Parkinsonism

Chronic use of the aforementioned typical or atypical neuroleptics may result in the development of parkinsonism. A rigorous evaluation of the medication list is necessary in all patients with parkinsonism. Anti-emetics and non-neuroleptic medications (e.g., valproic acid) are underappreciated causes of drug induced parkinsonism and the elderly seem to be most at risk. Discontinuation of the medication leads to resolution of symptoms.

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