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Research Article

Drug and Toxin-Induced Cerebellar Ataxias

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Abstract

Ataxia is the inability to coordinate voluntary movement and can present with a variety of symptoms involving dyscoordination of gait and extremity movement, slurred speech, and abnormal eye movements. Ataxia can be divided into either cerebellar or sensory. Cerebellar ataxia originates from damage to the cerebellum or its connecting tracts, while sensory ataxia is a result of damage to the afferent sensory pathways such as the dorsal column and large myelinated proprioceptive fibers.

Keywords: Antiepileptics; Diplopia; Dysdiadochokinesia

Introduction

The cerebellum is particularly susceptible to toxic insults due to its complex and highly metabolic nature. Purkinje and granule cells are the most frequently damaged cerebellar cells due to toxic agents upon pathologic evaluation [1]. The purkinje cells are the sole output fibers from the cerebellar cortex and provide inhibitory input to the cerebellar nuclei [2]. The granule cells are the only excitatory cell in the cerebellar cortex and help to form the complex network of connections intrinsic to the cerebellum. The cerebellum is a complex structure containing up to half of the neurons in the central nervous system [3-5].Although cerebellar findings are commonly encountered by the practicing neurologist, when acute and lesional causes of ataxia are ruled out, toxin-induced ataxia should be highly suspected. Toxic cerebellar syndromes can be separated into three major categories: prescribed medications, drugs of abuse, and environmental exposures. Many medications can produce ataxic syndromes, including antiepileptics, antiarrhythmics, antineoplastics and antibiotics, which form the highest risk agents. The risk of developing ataxia from these agents is dependent on the dose and rate of increase. Furthermore, age, renal function, and drug—drug interactions can predispose-drug-induced ataxia. Those with prior cerebellar damage are also more likely to have symptomatic worsening following new drug administration or uptitration. The neurologic examination is important in confirming a cerebellar origin of ataxia and can also be useful in determining underlying etiology. Neurologic examination will often reveal an ataxic gait with truncal titubation, saccadic abnormalities, dysmetria, intention tremor and dysdiadochokinesia. Speech can also be involved with an ataxic dysarthria comprised of disturbances of speech prosody and articulation [6,7]. Tone is frequently reduced, often with pendular reflexes following cerebellar insult [8]. Sensory ataxia will usually present with predominant gait disturbance worsened with the loss of vision and a positive Romberg's sign. Particular drugs or toxins will often have a predisposition to preferentially affect only a portion of the cerebellum and thus produce unique clinical cerebellar symptoms. Although the differential for acute cerebellar ataxia is broad and includes etiologies such as ischemic and inflammatory insults, this review will focus on acute toxin-induced cerebellar ataxia.

Antiepileptics

Phenytoin

The antiepileptic medication with the highest risk of producing ataxia and cerebellar dysfunction is phenytoin [9]. The risk is dose dependent with a tendency for patients at a lower dose to develop nystagmus and truncal ataxia, whereas appendicular ataxia becomes more prominent at higher dosing [10]. Toxicity is dependent upon the unbound plasma concentration of phenytoin and drug levels are sensitive to physiologic changes such as hypoalbuminemia, malnutrition, and kidney injury [11]. Furthermore, serum phenytoin levelsneeds to be corrected if the serum albumin level is low because of its binding characteristics11. Up to 37% of patients on chronic phenytoin developataxia [9]. The presence of mild nystagmus is frequent and occasionally can be used as an indicator of compliance with medication. Most patients on phenytoin at a therapeutic level have nystagmus and this tends to become increasingly prominent as the serum level exceeds 20 mg/mL10. Other adverse events due to chronicexposure include gingival hyperplasia and drug reaction with eosinophilia and systemic symptoms (DRESS). Dangerous skin manifestations of acute intravenous use include purple hand syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis and ischemia of the skin [12]. CYP2C9 and CYP2C19 are both involved in phenytoin metabolism and genetic polymorphisms increase the risk of ataxia in this subset of the population [13]. CYP2C9 mutations can lead to a reduction of the phenytoin metabolic rate by 25-54%13. Due to their alterations in drug metabolism, these patients show reduced volumes of cerebellar white matter and trends towards reduced cerebellar gray matter compared to normal phenytoin metabolizers14. Although somewhat conflicting

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in studies, duration and dose of phenytoin use are likely related to the degree of cerebellar atrophy [14].Management of phenytoin toxicity involves withdrawal of the agent. It is important to recognize thatwith cessation of treatment, some patients recover completely with resolution of the cerebellar dysfunction, whereas some may suffer from permanent cerebellar impairment [15]. Neuropathologic examinations of these patients have demonstrated widespread loss of Purkinje cells, a decline in the population of granule cells, and Bergmann gliosis with relative sparing of basket cell axons [16].

Carbamazepine, Oxcarbazepine, Eslicarbazepine

Carbamazepine, oxcarbazepine, and eslicarbazepine all pose significant risks of producing cerebellar ataxia9. Toxicity of these agents produces nystagmus, ataxia, disequilibrium, headache and potentially alterations in mental status [12]. In a review of randomized placebo-controlled trials, oxcarbazepine had the highest absolute risk increase of producing ataxia, with patients being at 23 times higher risk of developing ataxia compared to placebo9.In the same study, thenumber needed to harm was less than ten [9]. In a systematic review of cohort studies, carbamazepine more frequently produced ataxia and dizziness than oxcarbazepine. Likely both agents are higher risk for this side effect than eslicarbazepine. All three agents appear to produce a largely dose-dependent level of nystagmus, action tremor and gait ataxia [10]. These side effects may be more common in the elderly or those with prior cerebellar insults [10,12]. Carbamazepine is a medication that may be combined with lithium, another cerebellotoxic agent, for mood control. The combination of these drugs can produce symptoms even when both medications are within therapeutic levels10. Clinicians should also be aware that certain medicines that are CYP3A4 inhibitors suppress carbamazepine metabolism and increase its serum concentration [13,14]. Some of the more common agents include clarithromycin, fluoxetine, verapamil, oxybutynin, valproic acid, and loratadinec [15,16]. Severe carbamazepine toxicity can be deadly and lead to coma. If ataxia develops, free drug levels should be checked, and the medication reduced or discontinued. Persistent ataxia after medication discontinuation is rare and there should not be underlying damage to the cerebellum after cessation of the medication.

Lacosamide

In a randomized placebo-controlled trial of adjuvant lacosamide, with doses ranging from 200mg to 600mg per day, patients demonstrated a largely dose dependent increase in dizziness, headache, nausea, ataxia, nystagmus and diplopia [17].

The prevalence of ataxia was 23% among patients taking lacosamide 600mg per day, 13% in those taking 400 mg per day, 4% in those taking 200 mg per day and only 3% in those receiving placebo [17]. These effects led to higher patient discontinuation of lacosamide, particularly at higher doses, as compared to placebo. In this study lacosamide had minimal effects on other concurrent antiepileptic concentrations compared to placebo.

In a phase III long term follow up trial of adjuvant lacosamide therapy for partial onset seizures, 10.7% of patients withdrew due to adverse effects, with the most common being dizziness (in 1.6% of patients) [18]. This study was conducted in a population who had previously tolerated the medication at variable doses during a prior double blinded placebo-controlled trial. Lacosamide induced ataxia is most likely to occur with medication initiation or dose adjustment and management often requires a dose reduction [17,18].

Lamotrigine

Lamotrigine is a medication that inhibits voltage-gated sodium channels, thereby stabilizing neuronal membranes and reducing glutamate release. Lamotrigine has been associated with severe dermatologic reactions, often requiring slow titration of the medication.However, cerebellar symptoms are more common. In a review of prior randomized controlled drug trials, the most frequent adverse events related to lamotrigine use were ataxia, nausea, diplopia and dizziness. The relative risk of diplopia was the highest amongthe adverse events at 3.79, while the relative risk of ataxia was 3.34 [19]. In this review, ataxia developed in 15% of patients as compared to only 4.5% in placebo groups [19].

Valproic Acid

Valproic acid rarely causes ataxia as a direct adverse effect.However, its effects on the metabolism of other medications and the risk of encephalopathy from hyperammonemia have be known to produce ataxia [9,20]. Valproic acid can produce encephalopathy either byaffecting hepatic function or precipitation of hyperammonemia. When hyperammonemic encephalopathy due to valproic acid occurs with normal hepatic function it is known as valproate-induced non-hepatic hyperammonemic encephalopathy (VNHE) [21]. The features of this form of encephalopathy include irritability, drowsiness and coma, with movement symptoms of asterixis and cerebellar ataxia. Management of valproate induced hyperammonemia includes dose reduction or potential L-carnitine supplementation [22].

Benzodiazepines and Barbiturates

Benzodiazepines function by increasing the frequency of opening of chloride channels on GABA-A receptors, thereby reducing neuronal hyperexcitability. These medications, especially at high doses, produce ataxia to varying degrees depending upon the specific agent used9. This is more common in children, who present with a mild and reversible ataxia.Benzodiazepines do not appear to have a direct toxic effect on the cerebellum.

Barbiturates decrease cellular excitability by prolonging the opening of chloride channels on GABA-A receptors. Toxicity isdose-dependent and produces a neurologic syndrome mainly manifesting with central nervous system depression.Other potential symptoms includeintention tremor, gaze-evoked nystagmus and gait ataxia due to cerebellar involvement [10,12,23].Up to 5% of epileptic patients receiving phenobarbital will develop cerebellar signs. Thiopental is another barbiturate with a high prevalence of ataxia, occurring in up to 12.7% in one review study [9].

Other Antiepileptics

A variety of other antiepileptic agents have been known to produce ataxia as a prominent side effect. Gabapentin functions on calcium channels to enhance GABAergic inhibition of neuronal firing. It commonly produces a reversible ataxic syndrome with one study demonstrating ataxia in 7.7% of patients taking adjuvant gabapentin for epilepsy23,24. Other common side effects included somnolence (29.3%), vertigo (7.2%) and asthenia (14.6%) [24]. Ataxia was not strongly dose dependent, with the majority of patients experiencing this symptom at doses less than 1200mg daily. Paradoxically, gabapentin is occasionally used totry to reduce ataxia due to cortical cerebellar atrophy from a variety of inherited conditions [25]. It is believed that there is a relative deficiency of GABAergic activity that

occurs with Purkinje cell loss, producing ataxia that responds to gabapentin or pregabalin administration25. Other medications altering GABAergic effects such as vigabatrin and tiagabine appear to cause similar degrees of ataxia9.Talampanel and zonisamide also have a high risk of producing cerebellar ataxia, with the absolute risk increase being 23.53 and 8.33 respectively [9].

Antineoplastics

5-Fluorouracil

Over the last several decades, 5- fluorouracil (5-FU), a pyrimidine analog, has been used as a chemotherapeutic agent for the treatment of various solid tumors such as gastrointestinal and pancreatic cancers, head and neck cancer, and breast cancers [26,27]. 5-FU is an antimetabolite that inhibits thymidylate synthase and blocks thymidine formation by interfering with DNA synthesis28. Typically, 5-FU is used with other chemotherapy as part of a combination regimen [26,28].The most common side effects include bone marrow suppression, gastrointestinal side effects (diarrhea and stomatitis), alopecia, and hand-foot syndrome26,28. Cardiotoxicity has been described and is less common [29,30] while neurotoxicity is rare (occurring in less than 1% of patients treated with 5-FU) [31].

In a study conducted with 1240 patients who were treated with 5-FU either alone or in combination with other agents, only two patients had side effects of neurotoxicity [26]. There are several case reports of patients developing cerebellar ataxia, which is one of the most common forms of neurotoxicity noted [26,31-33]. Another described neurological adverse effect is cerebellar syndrome, which can include cerebellar ataxia, dysphagia, and dysmetria, among other symptoms33. Peripheral neuropathy and even seizures can also be observed after treatment with 5-FU [32,33]. Acute neurotoxicity is dose related and can be self-limiting. However, there are some reports of residual neurological symptoms even after several weeks of discontinuing 5-FU33. Using 5-FU in high doses (more than 2200 mg/m2/week) or using it in combination with interferon alpha can increase the incidence of neurotoxicity [28,34]. Although it is not very lipid-soluble, it can easily cross the blood-brain barrier28. A proposed mechanism of neurotoxicity hypothesizes that fluoroacetate, which is a byproduct of 5-FU catabolism, accumulates in nerve cells, causing impairment of the urea cycle and increasing ammonia levels28,34. Another possible mechanism proposes that 5-FU increases thiamine metabolism, causing thiamine deficiency [34-37].

Capecitabine

Capecitabine is a prodrug of 5-FU that is converted preferentially in tumor tissue by thymidylate phophorylase, which is expressed in higher levels in tumor tissue38. It has been shown to have the adverse effect of cerebellar syndrome, much like 5-FU, with ataxia, nystagmus, slurred speech, and encephalopathy [38,39]. The mechanism is unclear, but there have been reports of severe neurotoxicity in patients with reduced levels of dihydropyrimidine dehydrogenase (DPD), which is the rate-limiting enzyme in 5-FU catabolism [38-40]. Other possible mechanisms may be similar to the processes that cause cerebellar ataxia in patients receiving 5-FU [39]. This may impair the clearance of 5-FU, leading to higher concentrations of the drug for prolonged periods of time in the plasma and CSF, contributing to the toxicity38. However, there are case reports that argue that DPD deficiency may not always play a role, as some patients experience marked cerebellar ataxiawithout any other toxicities to suggest DPD deficiency41. Symptoms of ataxia and other forms of neurotoxicity have been seen 6-19 weeks after the medication is administered38. Many cases note that the symptoms resolve with discontinuation of the drug [41,42].

Cytarabine

Cytarabine is a chemotherapeutic agent that is used alone and in combination to treat a variety of leukemias and lymphomas. It is a structural analog of deoxycytidine and is converted to uracil arabinoside by cytidine deaminase [43]. Uracil arabinoside is then converted to the active form of the drug (ara-C triphosphate) and can diffuse into cells. Once intracellular, it competitively inhibits deoxycytidyl-triphosphate to inhibit DNA polymerase, DNA repair and RNA synthesis and DNA synthesis [43-45]. Neurotoxic manifestations with intrathecal cytarabine include headaches, meningismus, seizures and myelopathy 43,46. With systemic therapy, toxicity can present as seizures and cerebellar dysfunction. Acute cerebellar syndrome is the most common of the various neurotoxic profiles of cytarabine and is typically seen with use of high doses of the drug43. Signs and symptoms of cerebellar toxicity typically present three to eight days after starting high dose cytarabine (HIDAC), and can occur either during the first or subsequent cycles43. Patients present with truncal and/or limb ataxia, nystagmus, dysmetria, dysdiadochokinesia, and dysarthria, as well as headaches, changes in mental status, and seizures [43,47-50].

Cerebellar toxicity is dose related, and more dependent on the cumulative dose of cytarbine, as opposed to the duration of therapy [48-51]. Patients who are older than age 50, have prior neurologic dysfunction, renal or hepatic impairment are at higher risk of developing an acute cerebellar syndrome [43,49,52,53]. There is decreased clearance of cytarabine and its metabolites in patients with renal and hepatic dysfunction, leading to a longer duration of exposure [9,47]. The mainstay of treatment of cerebellar toxicity is discontinuation of cytarabine, and symptoms typically improve over the course of weeks to months [48,49]. However, in some patients, there may be residual symptoms even after discontinuation, with irreversible ataxia seen in 16.7% of patients in one study [48,49,53]. Some patients were treated with dexamethasone for its anti-inflammatory effects, with improvement in symptoms [47]. In many cases, work up of cerebellar symptoms, including CT scans, EEG, lumbar puncture, and MRI can be largely unrevealing [47]. In one case study, brain MRI did show diffuse cerebellar high intensity lesions on T2 and hypointensity on T1, without gadolinium enhancement. Some brain MRI findings can be consistent with diffuse cerebellar atrophy [54]. In another case study, a PET scan showed decrease in the 18-FDG uptake in the frontal, parietal and temporal lobes, as well as in the cerebellum [12].

In post-mortem analysis of patients who experienced cerebellar toxicity, there was noted to be degeneration of purkinje cells in the cerebellar hemispheres and the vermis [47,50]. Pathologic changes revealed reactive proliferation of glial cells, with patchy loss in the molecular and granular layers of the cerebellum [47,50]. One study showed the loss of purkinje cells in the deeper areas of the cortical sulci, with comparative preservation to purkinje cells at the folial crests and in the posterior inferior cerebellum [53].

Immunosuppresants

Cyclosporine

Cyclosporine and other calcineurin inhibitors are used to prevent rejection of organ transplants and in immunological diseases. Most commonly, a fine tremor can be noted as a side effect [23]. Cerebellar toxicity can be seen, along with aphasia, seizures, and paresthesias [23,55,56]. Cyclosporine produces a cerebellar syndrome with predominant nystagmus and postural instability [9]. It is hypothesized that the cerebellar toxicity is not associated with plasma concentrations of the medication. Cyclosporine may expose silent cerebellar lesions or infarcts, causing ataxia and other cerebellar signs and symptoms [23]. These may occur months after cyclosporine is started, and may be worsened by hypomagnesemia. In a study of 12 bone marrow transplant patients that developed neurotoxicity with cyclosporine, 25% had cerebellar ataxia [56]. Patients can be at higher risk if they are liver transplant recipients [23,57]. In many patients, brain MRI will show evidence of subcortical white matter lesions, consistent with a leukoencephalopathy [58-60]. Symptoms can begin a few days to months after initiation of therapy [23,58].

Tacrolimus

Tacrolimus is an immunosuppressant that is used widely after transplantation to prevent rejection. Similar tocyclosporine, it has been reported to cause neurotoxicity that can present as cerebellar ataxia [23,58,61]. Symptoms are typically mild and transient, resolving with discontinuation of the drug.

Antiarrhythmics

Amiodarone

Amiodarone is a commonly used antiarrhythmic in the treatment of supraventricular and ventricular arrhythmias. Amiodarone has many well-known toxicities, including thyroid toxicity, pulmonary fibrosis, dermatological side effects, corneal deposits, and hepatotoxicity [62,63]. Amiodarone can also be neurotoxic in 20-54% of patients and can cause a postural tremor, parkinsonism, peripheral neuropathy and cerebellar deficits [23,62,64]. Cerebellar deficits can include truncal or limb ataxia, wide-based gait, axial hypotonia, nystagmus, vertigo, dysdiadochokinesia, dysmetria, dysarthria, and dysphagia [62-64]. Neurological workup including head CT, brain MRI, and EMG may be unrevealing 63,64. Approximately 5-7% of patients treated with amiodarone develop cerebellar toxicity [10,23,64]. In one study of 54 patients treated with amiodarone for ventricular arrhythmias, 54% had neurotoxicity [65]. Among those who develop cerebellar toxicity, 52% will develop cerebellar symptoms within one month of therapy initiation, and in another 26% symptoms develop in 1-4 months [64-65].

Symptoms may improve with discontinuation of amiodarone over months to years, while in some cases residual symptoms do not resolve [62,64,65]. In one case report, symptoms improved with reduction amiodarone dosing by 50%, and resolved once the medication was stopped. Another case report showed that intravenous amiodarone can cause an acute cerebellar toxicity, which resolved quickly after the discontinuation of the drug [66]. In older patients, it may be safer to use lower doses of amiodarone to prevent toxicity62. Patients are at increased risk with advancing age, diabetes, renal failure, and alcoholism [62-68]. The mechanism of cerebellar toxicity is unclear, but may be due to amiodarone penetrating nerve tissue and accumulating in lysosomal structures, creating lipid inclusion bodies in nerve cells. The mechanism of peripheral neurotoxicity of amiodarone has been thought to be due to axonal demyelination of peripheral nerves [69-70] and due to lysosomal lipid deposits that can be caused by the action of amiodarone on lysosomal metabolism [71,72].

Procainamide

Procainamide, which is used to treat cardiac arrhythmias, can cause cerebellar toxicity with acute cerebellar ataxia when used in high doses23,73. Onset of symptoms can be acute, appearing when serum concentration of the medication rises rapidly [73]. These symptoms typically resolve when procainamide is discontinued [23,73]. Other well-known side effects of procainamide include drug-induced lupus, agranulocytosis, rash, Raynaud's disease, induction of arrhythmias, and QRS and QT prolongation [73,74]. In one case study, symptoms of ataxia began 10 days after initiation of procainamideand resolved 3 days after discontinuation [73].

Propafenone

Propafenone is anantiarrhythmic associated with dose dependent ataxia. Symptoms often resolve with lowering of the dose or cessation of the mediation [75].

Antimicrobials

Metronidazole

Metronidazole can cause cerebellar toxicity when used for a prolonged duration of treatment, typically over 6 weeks to several months [76,77]. Symptoms can include ataxia, paresthesias, slurred speech, hypotonia, seizures, and nystagmus [76,77]. Brain MRI can show evidence of toxicity with hyperintensities on T2 and FLAIR in the dentate nuclei, nodularity in the cerebellar parenchyma on T2, or cerebellar edema with increased diffusion coefficients [76-80]. Other brain MRI findings can include abnormalities in the Guillian-Mollaret triangle, inferior olivary nuclei, central tegmental tracts, dorsal medulla and dorsal pons [81,82]. In one study, brain SPECT showed lower perfusion of the left cerebellar hemisphere, in addition to T2 abnormalities in the dentate nuclei on brain MRI [83]. However, some patients may not have any abnormalities on brain imaging [84].

There is increased risk of toxicity with higher cumulative doses of 25 to 1080 grams [78]. In a study of 793 cancer patients who received metronidazole, two developed cerebellar dysfunction [85]. In patients that received a cumulative dose of more than 30 grams, 8.6% developed metronidazole neurotoxicity [85]. In patients with alcoholic liver disease, serum concentrations of metronidazole may be higher and contribute to neurotoxicity86. Both the symptoms and MRI abnormalities are reversible after discontinuation of metronidazole. Symptoms resolve in 24 hours to 2 weeks after stopping the drug [78,81,87]. Methylprednisolone has been used to promote neurological improvement [88].

While the mechanism of cerebellar toxicity is unclear, one hypothesis suggests that metronidazole causes an acute toxic insult leading to localized vasogenic edema and axonal swelling [78,80]. In rat models, high doses of metronidazole cause cerebellar lesions78,80. In dogs, metronidazole administration for prolonged periods was associated with Purkinje cell damage.

Mefloquine

Mefloquine is used for malaria prophylaxis and treatment. In an acute intoxication, patients may develop fevers, headaches, dizziness, nausea, gait instability and other neuropsychiatric symptoms [89]. Female patients and those with lower BMI may be at higher risk [89-91]. Proposed mechanisms of toxicity include interfering with calcium homeostasis in neurons, inhibiting acetylcholinesterase, and inhibiting potassium ATP channels [89,92,93]. Treatment is to discontinue the drug and refrain from future use [23].

Isoniazid

Isoniazid is used as part of a treatment regimen for tuberculosis. Common side effects are caused by its interaction with vitamin B6 and include peripheral neuropathy. Some reports describe the onset of tremors, vertigo, slurred speech, nystagmus and limb and truncal ataxia weeks to months after initiation of treatment with isoniazid [94,95]. These symptoms improve with stopping the medication and treating with pyridoxine [94,95]. At doses higher than 6 mg/kg, ataxia, seizures, dizziness, and slurred speech have been seen, but it is unclear if this is due to cerebellar toxicity [23]. In one case report, brain MRI showed evidence of bilateral dentate nuclei lesions [96]. Chronic kidney disease may be a risk factor to developing neurotoxicity [96].

Lindane

Overuse of lindane, which is used in the treatment of scabies and lice, can cause hyperreflexia, hypertonia, limb and truncal ataxia and seizures [23,97]. Toxicity may be due to its interaction with GABA-B receptors in the cerebellum [98].

Other Medications

Lithium

The neurotoxic effects of lithium were known long before its use for mood disorders [99,100]. After its introduction for the management of psychiatric disorders in 1949, cases of both chronic and acute lithium induced neurotoxicity were described and some cases of toxicity have led to permanent ataxia despite medication removal [101-103]. Lithium toxicity often manifests with tremor and ataxia and may occur acutely, subacutely or with chronic medication use. Most commonly, ataxia will present subacutely and correlate with supratherapeutic concentrations of lithium9. Even at therapeutic levels, toxicity can occur due to cerebellar neuronal tissue retention of lithium [100]. Acute lithium toxicity may also be associated with other neurologic manifestations including altered mental status, seizures, parkinsonism and enhanced reflexes10. Acute or chronic toxicity can lead to the syndrome of irreversible lithium-effectuated neurotoxicity or SILENT [100]. Cases of SILENT often have predominant cerebellar symptoms however cognitive impairment and extrapyramidal symptoms may be present. In a review of cases of SILENT, the average dose at which toxicity occurred was 1403mg/day, although toxicity could be seen in doses as low as 438mg/day. Patient age does not appear to correlate to the risk of permanent neurologic injury following lithium toxicity [104]. The mean serum concentration at which SILENT occurred in one study was 2.29mM/L [100,104]. Long lasting neurotoxicity may be more likely when used in combination with other drugs such as haloperidol, thioridazine, phenytoin, and chlorpromazine. Persistent neurologic symptoms are highly variable but commonly include ataxia, nystagmus, dysarthria and extrapyramidal symptoms. Subcortical dementia, hyperreflexia, choreoathetoid movements and extensor plantar responses may also be present. Rare cases of optic neuritis and osmotic demyelination have been described following lithium toxicity [105,106]. Acute intoxication will often present with leukocytosis without clear infection and altered mental status. As cognitive status improves, cerebellar ataxia becomes apparent. An irregular coarse limb tremor can also be useful in identifying the lithium toxidrome. The majority of cases of acute lithium toxicity will improve with dose reduction or cessation of the medication. Toxic metabolic insults can alter previously well controlled lithium levels and should be evaluated when a new lithium toxidrome develops without dose change.

Cases of SILENT can be very prolonged however most patients have at least partial improvement with time. Although the mechanism of neurologic injury is unclear, pathologic reviews of SILENT have demonstrated cerebellar atrophy, Purkinje cell loss, cerebellar gliosis, and demyelination at other central and peripheral nervous system sites [107-109]. Lithium toxicity is best avoided by strict monitoring and regular dose adjustments. Toxicity treated with early hemodialysis may reduce the risk of long-term neurologic sequelae.

Bismuth

Bismuth has been used in various formulations to treat skin and gastrointestinal disorders, especially in the treatment of Helicobacter pylori infections. Rare cases of chronic daily bismuth use have presented with ataxia, cognitive changes, tremors, myoclonus and seizures [23,110]. Prior high dose formulations in Australia and France increased the frequency of this syndrome. Regular and excessive use of over-the-counter bismuth formulations, such as peptobismol, can rarely present with toxicity [111]. This syndrome can mimic Creutzfeld-Jacob disease due to the severity of spontaneous, reflexive and movement-induced myoclonus. The mechanism of toxicity is not clear. Bismuth-induced ataxia is often preceded by a subacute progressive encephalopathy. Symptoms improve slowly with cessation of bismuth however permanent deficits in cognition may remain. Those with chronic kidney disease are at higher risk for toxic effects [112]. Cerebellar toxicity can be worsened in setting of hypoxia, causing Purkinje cell loss [113].

Drugs of Abuse

Alcohol

Alcohol adversely effects GABAergic transmission, producing cerebellar ataxia due to its effects of granule cells in the cerebellum [10]. Alcohol may increase GABA release from the Golgi cells of the cerebellum producing increased GABAergic inhibition of granule cells. Increased granule cell tonic inhibition produces motor incoordination. The exact mechanism is complex and currently being investigated [2,10]. Ethanol may further disrupt the mossy fiber-granule cell-Golgi cell synaptic site leading to ataxia [2]. Alcohol intoxication produces a rostral vermis cerebellar syndrome characterized by wide based ataxic gait with truncal titubation and relative sparing of extremity coordination. Dysarthric speech is often present, but hypotonia may be lacking [114]. Motor coordination issues develop at doses as low as 0.08g/L due to early cerebellar effects [115]. Older age correlates with earlier cerebellar coordination dysfunction at lower serum alcohol concentrations, allowing young adults to be able to consume larger amounts of alcohol before ataxia becomes apparent [115].

Frontal lobes and the cerebellum are particularly susceptible to damage from chronic alcohol use. Decreased myelination may be apparent on pathologic studies of these areas, particularly in the white matter [12]. Chronic alcohol toxicity will lead to loss of granule cells and atrophy of the cerebellum with the greatest effect in the superior anterior vermis. Intrauterine exposure to alcohol is alsodamaging to the development of the cerebellum and will produce long term neurobehavioral abnormalities. Interestingly, recent animal studies of choline supplementation prior to alcohol exposure in pregnant mice ameliorated the level of cerebellar dysfunction of the pups [116]. Choline may be beneficial in the prevention of the toxic effects on the cerebellum if given prior to exposure [116,117]. Alcohol is often associated with thiamine deficiency or Wernicke's encephalopathy which can produce both a sensory and cerebellar gait ataxia.

Phencyclidine

Phencyclidine (PCP) is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that can present with cerebellar ataxia, tremor and nystagmus.PCP can be inhaled, ingested or injected either intravenously or subcutaneously. It has a rapid onset of action over 2-5 minutes when inhaled or smoked [118]. PCP is lipid, water, and alcohol soluble and therefore can have a very large volume of distribution with varying effects depending on body habitus and blood alcohol concentration. It has greatest affinity for the NMDA receptor complexes in the hippocampus, neocortex, basal ganglia, and limbic system [119]. At moderate doses PCP also inhibits the reuptake of dopamine, serotonin, and norepinephrine while simultaneously stimulating production of dopamine and norepinephrine through tyrosine hydroxylase activity [118,119] .Given the wide pharmacologic effects of this drug, the clinical manifestations are extremely variable with the most common findings of nystagmus and hypertension being found in 57% of patients [120].

Intoxicated patients will often present with violent behavior, analgesia, hypertension, nystagmus and tachycardia. Rapidly waxing and waning agitation and sedation with slurred speech, nystagmus and ataxia will be present. Decreased pain perception, pinpoint pupils, sympathomimetic effects, and bizarre horizontal, vertical, rotary nystagmus can help differentiate an ataxic PCP intoxication from other toxidromes. PCP may also lead to increased tone with hyperreflexia, myoclonus, choreoathetoidor dystonic movements such as opisthotonos and torticollis [120]. High doses of PCP can lead to coma, hyperthermia and death. Although cerebellar effects are present in the majority of patients with PCP, overt ataxia is less common with about 10% having this manifestation to a significant degree [118,120,121]. PCP intoxication is diagnosed with urine toxicologic screen, which will remain positive for 2-4 days following drug use. However, diphenhydramine, dextromethorphan and venlafaxine can produce false positives with some screening urine drug tests [120,121]. Management of intoxication is largely supportive. Use of benzodiazepines may be warranted in patients without psychosis, given the risk of exacerbating hyperthermia and dystonic movements with antipsychotic use [118]. In patients without hyperthermia, atypical antipsychotics are beneficial in controlling psychosis, and require close cardiac monitoring.Diphenhydramine can be useful to treat dystonic movements brought on by this drug. Although intoxication syndromes usually resolve over 4-8 hours, large ingestions may take weeks to fully recover [120]. PCP has been shown to be toxic to Purkinje cells in rat studies, leading to permanent cerebellar damage [122]. The mechanism of this injury was felt to be due to excessive excitatory activity from climbing fibers originating in the inferior olive [122].

Marijuana

The predominant psychoactive constituent of marijuana is tetrahydrocannabinol (THC).Cannabinol and cannabidiol present in marijuana plants can also produce less potent psychoactive responses [123]. There are two specific cannabinoid receptors: CB1 receptors present in the basal ganglia, substantia nigra, cerebellum, hippocampus and frontal cortex, and CB2 receptors which are not present in the central nervous system [124]. Neurologic signs of marijuana use are highly dose dependent. In dogs high doses of marijuana exposure were associated with ataxia, depression, disorientation, and tremors. Non-neurologic signs included hypersalivation, hypothermia, and mydriasis [125].

Recreational use of low or moderate doses leads to euphoria, lack of inhibition, mydriasis, hypersalivation, conjunctival injection, increased appetite, and elevated heart rate [126]. High doses produce vomiting, hypertension, tremor, ataxia, hallucinations and stupor [126,127].

Children are more susceptible to the depressive effects of cannabis and toxicity can produce rapid onset ataxia, sedation, tachycardia, respiratory depression and coma [128]. Management of toxicity is generally supportive however in severe cases in children can be treated with benzodiazepines with close monitoring of respiratory status [128].

Cocaine

Cocaine is a psychostimulant that may present with acute ataxia due to its risk of producing ischemic and hemorrhagic strokes, including in the cerebellum [10,129]. In rat models, cocaine has been shown to alter the immunoreactivity to serotonin in the cerebellum, affecting the development of Purkinje cells [130].

Heroin

Heroin use can lead to changes in cognition, personality, ataxia, dementia, coma and death. Chronic use has been shown to lead to loss of the cerebellar purkinje cell layer and proliferation of Bergman glia [131]. In chronic heroin users, the loss of Purkinje cells has been observed [23].

Methadone

Ingesting methadone can cause an acute toxic encephalopathy with changes in the level of consciousness due to cerebellar edema causing obstructive hydrocephalus [132,133]. Cerebellar edema may also lead to watershed infarcts and can appear to be similar to an infectious cerebellitis on brain MRI133. Treatment includes methylprednisolone and drainage of CSF, with possible need for a decompressive craniotomy [23,132].

Nicotine

Nicotine is toxic to the cerebellum and can cause depletion of purkinje cells [23,134]. Chronic toxicity in rat models demonstrated decreased purkinje cells in the cerebellar vermis and loss of cerebellar white matter [135,136]. Nicotine can exacerbate ataxia in patients with pre-existing ataxia, such as in patients with multiple system atrophy or spinocerebellar ataxia [137,138].

Toxins And Heavy Metals

Bromide

Methyl bromide is a colorless gas and has versatile uses. It can be used as an insecticide, solvent, refrigerant, methylating agent and in fire extinguishers [139]. It has been shown to be toxic to both the central and peripheral nervous systems in multiple studies [23,139,140]. Case reports of bromide intoxication (through occupational exposure from insecticides or bromide-containing compounds that are part of over-the-counter sleep aids) had a constellation of symptoms including cerebellar deficits with slurred speech and gait ataxia, as well as pyramidal and extrapyramidal signs [139,140]. Cerebellar atrophy and sometimes pontine tegmental atrophy can be seen on brain MRI [23]. Other findings on brain MRI include lesions in the cerebellar dentate nuclei, periaqueductal region, dorsal midbrain and pons139. Lesions can also be seen in the posterior putamen, subthalamic nuclei, dorsal medulla oblongata, inferior cerebellar peduncles and areas of the midbrain [141]. Avoidance of bromides after acute insult is imperative. In one case, an acute intoxication was treated with hemoperfusion, which is a procedure similar to hemodialysis [142].

Mercury

There are several major formulations of mercury that pose a risk of exposure tohumans [143].

Although modern use of mercury in industrial products is rare, in the past it was commonly found in thermometers, batteries, light bulbs, and electrodes. Some prior dental amalgams contained mercury and produced a risk for mercury vapor inhalation, which cancause multiorgan dysfunction with renal, pulmonary and gastrointestinal effects. The absolute amount of mercury vapor produced by a dental filling is low and toxicity requires chronic exposure to multiple dental amalgam fillings. While modern fillings no longer contain mercury, exposure to liquid mercury from antiques can produce vapor toxicity [143]. Neurologically,vapor exposurecauses a peripheral neuropathy and erethism (severe behavioral, mood, and cognitive change). Methyl mercury or organic mercury is present in some fish and predominantly affects the central nervous system, producing perioral and distal extremity parasthesias, ataxia, and optic atrophy with early visual field constriction and hearing loss. On pathologic evaluation, methyl mercury preferentially damages neurons of the visual cortex and granule cells in the cerebellum143.A regional decrease in blood flow may be present in the cerebellum on single photon computed tomography following mercury exposure [144].Methyl mercury toxicity can cause cerebellar atrophy in 27% of intoxicated patients144.Ethyl mercury was previously found in some parenteral vaccines in the form of thimerosal, a component used as a preservative to prevent fungal growth. Although only present in low levels and non-toxic in adults, there is concern for toxic levels in infants receiving frequent vaccinations, prompting discontinuation of this preservative [145]. Currently thimerosal is no longer a component of vaccines in the United States. Organic mercury toxicity from sources such as fish responds poorly to chelation.On the other hand, inorganic mercury toxicity can be managed with early chelator therapy such as dimercaprol, in addition to supportive measures [143,144].

Lead

Lead intoxication can occur due to ingesting paintsand can be worse in children[23]. Symptoms and signs include abdominal pain, anemia, central and peripheral neurotoxicity and cerebellar ataxia [23]. MRI brain findings include cerebral calcifications and hyperintense lesions23. Lead intoxication is treated with chelating agents.

Toluene

Toluene is an industrial solvent found is gasoline, paints, glues and rubber manufacturing. Toluene preferentially affects areas of the CNS with high lipid content such as myelin [12]. Although the exact mechanismof CNS damage is unknown,toluene intoxicationcan produce lightheadedness, altered cognition, and ataxia. Tremor may be present in the head and extremities and severe toxicity can cause anosmia, hearing loss, personality changes, spasticity and hyperreflexia. White matter damage can produce a clinical picture similar to leukoencephalopathy with dementia. Non-neurologic affects include eye and respiratory irritation and hepatorenal damageb [146]. Cerebellar toxicity can occur with either acute or chronic exposure. Diagnosis can be made with either serum toluene levels or urine hippuric acid levels. MRI can be useful and may show both cerebral and cerebellar atrophy with T2 white matter hyperintensities within the deep structures of the brain including the periventricular area, internal capsular, and brainstem pyramidal regions [12]. Management is supportive with avoidance of further toxic exposures.

Carbon Monoxide

Purkinje cells require high levels of oxygen and are susceptible to hypoxia [10]. Carbon monoxide (CO) produces hypoxia by binding hemoglobin and limiting oxygen saturation of red blood cells. Severe acute CO toxicity can damage Purkinje cells and lead to irreversible cerebellar symptoms in addition to behavioral changes, cognitive impairment and parkinsonism.

Discussion

Initial evaluation of either acute or subacute ataxia requires neuroimaging to rule out lesional causes such as stroke, tumor, hemorrhage, or inflammatory insult. When no clear cause is discovered with neuroimaging, a close review of a patient's medication list for drugs commonly associated with ataxia is warranted in addition to a urine drug screen. Although medicationinduced ataxia often develops after the initiation of a new drug or a change in dose, it is important to remember that some medications such as phenytoin, valproate, and lithium can lead to ataxia without a clear dose change. Initiation of a drug that does not normally cause ataxia but may alter the metabolism of one that does should be considered. Furthermore, an acute metabolic or infectious insult can cause ataxia and cerebellar symptoms to develop in a patientwho previously tolerated high risk medications without issues. The elderly, those with abnormal renal function, and patient's with significant polypharmacy are at high risk of drug induced ataxia and close monitoring after the initiation of a medication with the risk of ataxia as an adverse effect is required. Illicit drug induced ataxia should also be considered when no clear medication appears to be leading to a new acute ataxia. Additionally, when thorough evaluation for an acute or subacute toxicity is unrevealing consideration of environmental exposures to toxic substances such as solvents, heavy metals, and toluene should be considered. Management of possible medication induced ataxia should entail removal of a single agent at a time and monitoring for improvement. The majority of drug induced ataxias completely resolve with cessation of the offending agent. However, many may take days to months to see improvement. Some medications can lead to permanent cerebellar damage despite cessation,including phenytoin, lithium and cytara

bine. Antiepileptics represent an important and common cause of new ataxia and warrant close monitoring of patients on these medications for signs of cerebellar dysfunction. Although nearly all antiepileptics can produce ataxia to some degree, medications that have their primary mechanism of action on sodium ion channels represent the highest risk. Purkinje cells are susceptible to medications that alter ion channel conductance as they contain a high proportion of small conductance calcium activated potassium channels important for regulation of purkinje cell firing patterns [147].

It is important to have a broad differential with new ataxia and to determine if new medications, toxins, or drugs may be contributing to a patient's presentation.

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