Toxic-Metabolic, Nutritional, and Medicinal-Induced Disorders of Cerebellum

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KEY POINTS
- A number of toxic, metabolic, nutritional, and medicinal insults may affect the cerebellum.
- Acute alcohol intoxication, chronic alcoholism, anticonvulsant therapy, and thiamine deficiency are among the more common causes of cerebellar dysfunction.
- Metabolic explanations for cerebellar dysfunction can include hypoglycemia and hypothyroidism, as well as pronounced electrolyte disturbance.
- Illicit drugs such as cocaine, heroin, and phencyclidine can result in cerebellar damage.
- Poisoning with a number of agents, including carbon monoxide and insecticides, can affect the cerebellum.
- Rapid assessment and management of patients with toxin- and metabolic-induced disorders of the cerebellum can have an important impact on outcome.

INTRODUCTION

The human cerebellum is situated behind the pons and medulla within the posterior cranial fossa and is composed of 2 vastly convoluted hemispheres and a narrow medial section known as the vermis. The cerebellar vermis (derived from Latin word for worm) is situated in the corticonuclear zone of the cerebellum (Fig. 1). Three pairs of dense fiber bundles known as peduncles connect the cerebellum to the brain. Despite extensive research into the role of the cerebellum in human...
motor control and cognition, the exact mechanisms of its activities are only marginally understood. The cerebellum receives significant input from cerebral cortical and subcortical regions as well as the spinal cord. Such circuitry allows the cerebellum to have extensive information from the somesthetic, vestibular, visual, and auditory sensory systems, as well as from motor and nonmotor regions of the cerebral cortex.

Although the afferent connections are more substantial the efferent projections, the cerebellum possesses widespread outgoing connections to many regions of the brainstem, midbrain, and cerebral cortex. The cerebellum does not initiate motor activity; however, it does interact with many regions of the brain where movements are initiated to ensure that such motor activity is performed in a coordinated fashion. Like other components of the human brain, the cerebellum is sensitive and vulnerable to a wide gamut of pathologic processes that can lead to cerebellar dysfunction. In addition, a number of pathologies specifically affect the cerebellum. Insult to the cerebellum can result in a constellation of neurologic deficits, including:

- Ataxia (truncal, limb, and gait);
- Hypotonia;
- Dysarthria; and
- Ocular motility problems (including nystagmus and tremor).

The cerebellum is particularly susceptible to the toxic effects of metabolic and medicinal insults; the cerebellar cortex and Purkinje neurons are particularly vulnerable. In susceptible individuals, the most frequent etiology for a toxic abnormality of the cerebellar function stems from acute alcohol poisoning as well as alcoholism. The cerebellum is potentially sensitive to drug exposure, such as anticonvulsants, antineoplastics, lithium salts, and calcineurin inhibitors; to illicit drugs, such as cocaine, heroin, phencyclidine; and to environmental poisons, such as mercury, lead, manganese, and toluene/benzene derivatives. Thus, the astute clinician must be aware of the multiple potential factors that can adversely affect cerebellar function. This will obviously guide timely and effective management with efforts to prevent long-standing disability or even death.
Alcohol (ethanol) can promote toxic effects on both the central and peripheral nervous systems. The damaging effects of alcohol on the nervous system stem from acute intoxication and withdrawal syndrome owing to abrupt cessation of alcohol intake. Acute and subacute disorders that can affect the cerebellum include nutritional deficiencies. A direct toxic effect on the components of the brain affects the vermis of the cerebellum and the mamillary bodies. Indirect effects can be from a brain injury-related propensity to falling.

After ingestion, alcohol rapidly crosses the blood–brain barrier. It directly interacts with a number of neurochemical receptors. Clinically, depending on the amount ingested, as well as the buildup of tolerance, the patient can present with behavioral effects of ethanol such as euphoria, social disinhibition, and drowsiness, as well as aggression in combination with slurred speech and gait ataxia. At particularly high serum concentrations of ethanol, subjects can develop progressive lethargy that can evolve into stupor and coma with the potential for death related to respiratory depression or cardiovascular collapse.

Ethanol, by itself or in combination with thiamine deficiency, can exert deleterious effects on the cerebellum. Ethanol-induced changes in cerebellar activity causes impairment of motor coordination and ataxia. In addition, alcohol-related cerebellar dysfunction may play a role in cognitive deficits associated with alcoholism.

Pathophysiology

The exact pathophysiology of the deleterious impact of ethanol on the human cerebellum remains marginally understood. As a psychoactive drug, ethanol diffusely affects the γ-aminobutyric acid (GABA)ergic transmission in brain via the facilitation of presynaptic interneuron firing. Recent scientific observations show that alcohol consumption impairs motor coordination by increasing the tonic inhibition of granule cells, which are mediated by a specific extrasynaptic GABA A receptor subtype. The excitability of the cerebellar granule cells is in part modulated by the GABAergic output from the Golgi cells. GABAergic input is received from the granule cells in tonic currents mediated by extrasynaptic receptors, as well as from phasic currents. These phasic currents are mediated by synaptic receptors. The input received from both type of currents results in a filtering effect of the mossy fibers, which represent the most significant input to the cerebellum. This suppressive input profoundly alters cerebellar information and storage capacity.

This specific combination of α-6 and δ extrasynaptic subunit in this specific combination of α-6 and δ extrasynaptic subunits in the GABA A receptor is only found in these types of cerebellar granule cells, and the unique combination seems to direct the firing power of these cells by producing tonic inhibition. Studies have demonstrated that alcohol indirectly enhances GABAergic transmission to the cerebellar granule cells via an increase in GABA release from the Golgi cells. Concentrations of alcohol in the blood high enough to produce behavioral changes have been shown to enhance the tonic inhibition of cerebellar granule cells mediated by the extrasynaptic GABA receptors. The greatest effect of this increased GABA inhibition is impaired motor coordination.

Neuropathologically, direct adverse effects of ethanol on the human central nervous system include both cerebral atrophy and cerebellar degeneration. Alcoholic cerebellar degeneration is recognized by atrophy and loss of granule cells, mainly in the anterior superior section of the vermis.
**Metabolic Disorders**

A number of metabolic disorders, such as metachromatic leukodystrophy, Refsum disease, and mitochondrial disorders such as Leigh syndrome and Kearns–Sayre syndrome, affect the cerebellum and result in ataxia and other neurologic manifestations of cerebellar dysfunction. A detailed discussion of these disorders is beyond the scope of this article.

In patients with epilepsy, anticonvulsants, particularly diphenylhydantoin, carbamazepine, and primidone, can cause ataxia. In children, a constellation of ataxia, papilledema, and drowsiness can be seen with lead poisoning. Rare metabolic causes of cerebellar ataxia include Maple syrup urine disease, Hartnup disease, and ataxia–telangiectasia.

**CARBON MONOXIDE AND HYPERTHERMIA**

The cerebellar cortex is susceptible to oxygen deprivation and, at its resting state, consumes one of the highest amounts of the oxygen within the human central nervous system. In the human central nervous system, the cerebellar Purkinje cells and the hippocampal neurons are the most vulnerable groups to the adverse effects of hypoxia. In postanoxic animals, there is loss of Purkinje cells with resultant ataxia.6 In humans, such vulnerability is even more pronounced and in many cases the postanoxic neurologic syndrome manifests with clinical features of cortical, pyramidal, extrapyramidal abnormalities as well as cerebellar ataxia.7,8

**Carbon Monoxide Poisoning**

Carbon monoxide (CO) poisoning as well as severe hyperthermia can have a profound effect on cerebellar function. CO has a high affinity for the oxygen-binding site of hemoglobin and can promote cardiopulmonary arrest. Because CO results in hypoxia, most of the clinical manifestations of CO poisoning stem from this hypoxic insult, which primarily affects the nervous system and heart. CO poisoning can be acute or chronic. The most common neurologic presentations of acute CO poisoning include headache, dizziness, and visual impairment. Severe CO poisoning may result in seizures and coma as well as respiratory impairment. Long-term residual neurologic deficits stemming from CO poisoning include behavioral disturbance with cognitive impairment, parkinsonism, and cerebellar abnormalities.9,10

**Hyperthermia**

Hyperthermia is associated with insufficient or inappropriate reactions of heat-regulating circuits. Hyperthermia can be seen during heat waves, resulting in heat stroke. Older individuals who have a limited ability to adjust to the temperature, athletes having inappropriate exposure to temperature extremes, and children left in cars during the summer months seem to be the most susceptible. Illicit drug use (especially amphetamines and cocaine) and the use of agents that can be associated with neuroleptic malignant syndrome identify other populations at greater risk. Neurologic manifestations can include cerebellar dysarthria, gait ataxia or a pan-cerebellar syndrome.11 Symptoms may resolve within 3 to 10 days in those individuals with a reversible injury. Cerebellar deficits may also be part of a diffuse encephalopathy, which includes seizure, disorientation, dizziness, and severe fatigue.12 Up to 20% of patients affected with heat stroke experience residual neurologic deficits and neuroimaging of brain has shown cerebellar atrophy may follow months after the initial event of hyperpyrexia.13
Purkinje cells are for the most part susceptible to heat-induced pathology. Neuro-pathologic studies have demonstrated significant and widespread loss of Purkinje cells along with expression of heat shock protein 70 by Bergmann glia. Based on the findings of the study by Bazille and colleagues, loss of Purkinje cell axons leads to appearance of myelin pallor of the white matter of the folia and the hilum of the dentate nuclei. DNA internucleosomal breakages were observed by utilizing in situ end-labeling in the dentate nuclei and centromedian nuclei of the thalamus. This observation was associated with degeneration of the cerebellar efferent pathways, including the superior cerebellar peduncles, and decussation of the superior cerebellar peduncles and dentatothalamic tract. According to these investigators, Ammon’s horn and other areas that are vulnerable to the deleterious effects of hypoxia were not affected.

NUTRITIONAL DEFICIENCIES

It is well recognized that a balanced and adequate diet is necessary for the development and normal functioning of the human nervous system. Nutritional inadequacies, particularly vitamin deficiency states, can exert adverse effects on central and peripheral components of the nervous system, resulting in a spectrum of neurologic presentations that can include mental retardation, altered sensorium, psychosis, seizures, cerebellar ataxias, and peripheral neuropathies. A number of nutritional inadequacies that cause cerebellar disorders are discussed herein.

THIAMINE DEFICIENCY

Neurologic disorders associated with thiamine deficiency include beriberi, Wernicke encephalopathy, and Korsakoff syndrome. Potential causes of thiamine dietary insufficiency can include recurrent vomiting, gastric surgery, alcoholism, severe dieting, and elevated demand with insignificant nutritional intake. Thiamine deficiency associated with alcoholism is more common in males, whereas thiamine deficiency stemming from gastric–bariatric surgery is more frequent in females. Wernicke encephalopathy manifests with subacute onset of ocular abnormalities, gait ataxia, and alteration of mental status. Ocular abnormalities consist of horizontal and vertical nystagmus, ophthalmoparesis, and conjugate gaze palsy. Gait and trunk ataxia originate from cerebellar and vestibular dysfunction. Cerebellar involvement also presents with dysarthria. Patients with Wernicke encephalopathy can progress to develop Korsakoff syndrome, which is characterized by severe anterograde and retrograde amnesia as well as confabulation.

MEDICINES

A number of medications at toxic levels can result in neurologic abnormalities. Cerebellar dysfunction may stem from the direct impact of toxic levels of these medications or may be part of a more global phenomenon, such as toxic encephalopathy. Once a clinician encounters medicinal-induced cerebellar syndromes, certain features in the patient’s clinical picture should be carefully sought. The development of medicinal-induced cerebellar disorders usually initially affects the patient’s gait, and this may or may not be followed by involvement of the extremities. The cerebellar involvement, particularly ataxia with nystagmus, may occur with either acute or chronic use of the offending medicine and can occur when the serum levels of the medicine are “subtherapeutic, therapeutic, or toxic.” In general, the cerebellar disorder usually improves with cessation of the offending medicine; however, certain cerebellar findings may persist.
An interesting practical concept is that patients who chronically take a particular medication may develop acute cerebellar deficits with no alteration of their dosage.

**Antiepileptics**

Antiepileptics, as a family, are well recognized for their potential for toxicity and causing cerebellar ataxia. Certain antiepileptics, such as phenytoin, carbamazepin, and barbiturates, are well known for causing ataxia, whereas benzodiazepines are most often associated with excessive sedation before patients develops ataxia. Valproic acid is commonly associated with the onset of a tremor that closely imitates intention tremor of the cerebellar origin.

**Phenytoin**

Patients with epilepsy who take relatively higher doses of phenytoin may develop permanent ataxia and cerebellar atrophy. This has impacted on the decision-making process in the choice of older versus newer anticonvulsant agents. Of interest, there is a correlation between the dose of phenytoin and development of ataxic symptoms with a tendency for patients at a lower dose to develop nystagmus and truncal ataxia, whereas appendicular ataxia becomes more prominent at higher dosing. These clinical manifestations can slowly progress, but may improve by lowering the dose or cessation of phenytoin. In clinical practice, certain patients tolerate high doses without developing any ataxia. Such patients do not necessarily have to be switched from phenytoin to an alternative agent, at least in the shorter run, if expense and tolerability, along with the ready ability to check blood levels to ensure compliance, make this a reasonable choice.

Patients with epilepsy who have a CYP2C mutation (*2 or *3) show a reduction in phenytoin metabolism that in turn is associated with cerebellar atrophy with mainly loss of cerebellar white matter. Of note, cerebellar abnormalities may develop a number of years after initiation of treatment despite therapeutic blood levels. 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 μg/mL. It is important to recognize that, with cessation of treatment with phenytoin, some patients recover completely with resolution of the cerebellar dysfunction, whereas some may suffer from permanent cerebellar impairment. It is also important to recognize that the serum phenytoin level, because of its binding characteristics, needs to be corrected if the serum albumin level is low.

Certain patients with previous, clinically asymptomatic cerebellar injury or with myoclonic-type epilepsy may be more prone to phenytoin toxicity. An important clinical point is that certain medicines may increase the half-life of phenytoin and increase the chance of toxicity. These drug–drug interactions are not necessarily uncommon with phenytoin and have impacted on its attractiveness as a choice for anticonvulsant therapy. Neuroimaging studies may demonstrate various degrees of cerebellar atrophy in patients with permanent cerebellar dysfunction after chronic exposure to phenytoin (see Fig. 1).

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. Urgent admission and treatment of patients with acute intoxication with phenytoin and ataxia is necessary to avoid possible long-term neurologic deficits.

**Carbamazepine**

Carbamazepine, another still commonly used antiepileptic, can be associated with dose-dependent ataxic manifestations. Affected patients manifest gaze-evoked
nystagmus, action tremor, and gait ataxia.\textsuperscript{1,11,20} Elderly patients and those with pre-existing cerebellar atrophy are at greater risk for developing cerebellar damage at lesser serum concentrations. Of clinical pertinence is that carbamazepine is also used in the treatment of painful entities such as trigeminal neuralgia and may also be used to stabilize the mood in patients with bipolar (manic–depressive) disorder. In the latter scenario, the combination of carbamazepine and lithium salt—2 toxic agents for the cerebellum—requires familiarity with this issue and close observation.\textsuperscript{21} Treatment of psychiatric patients suffering from mood disorders with a combination of lithium compounds and carbamazepine may cause cerebellar toxicity even when serum concentrations of both medicines are within therapeutic range. Clinicians should also be aware that certain medicines that are CYP 3A4 inhibitors suppress carbamazepine metabolism and increase its serum concentration. Some of the more common agents include clarithromycin, fluoxetine, verapamil, oxybutynin, valproic acid, and loratadine. Toxicity with carbamazepine is a potential medical emergency, because it can lead to a decrease in the level of consciousness and coma. It is significant to recognize that in certain patients the total serum concentration of carbamazepine is therapeutic; however, the free drug level is actually elevated. Patients with clinical manifestations of severe carbamazepine toxicity need to be admitted and treated in monitored units because toxicity with carbamazepine may cause coma and death.

**Phenobarbital**

Phenobarbital is another commonly used antiepileptic that can cause ataxic signs, including gaze-evoked nystagmus, tremor, and gait ataxia. Based on our own observations of epileptic patients, a significant number of them suffer from cerebellar abnormalities.

**Gabapentin**

Gabapentin (Neurontin, Pfizer, New York, NY) augments GABAergic suppression and can cause ataxia. This ataxic side effect is generally readily treated with either reduction in the dose or, if necessary, discontinuation. Of interest, gabapentin may ameliorate ataxia in patients with isolated cerebellar atrophy.\textsuperscript{22} Vigabatrin suppresses GABA transaminase and may cause ataxia when it is used for treatment of drug-resistant epilepsy. This potential side effect tends to be observed during initiation of the therapy.\textsuperscript{23}

**NICOTINE**

Nicotine is a well-recognized cerebellar toxin\textsuperscript{24,25} and, in the adult rat, chronic exposure to nicotine causes a decrease in the number of Purkinje cells in the cerebellar vermis.\textsuperscript{26} Clinical reports indicate that nicotine may at least temporarily worsen ataxia in patients with multiple system atrophy\textsuperscript{27} and in patients with spinocerebellar ataxia, cigarette smoking can transiently aggravate dysarthria, limb ataxia, and truncal titubation.\textsuperscript{28}

Although a number of scientific observations have assessed the deleterious effects of chronic nicotine exposure on the various cells and layers of cerebellum, 1 particular study concentrated on the effects of long-term nicotine exposure on cerebellar white matter.\textsuperscript{29} The investigators administered oral nicotine via cannula for 60 days, using dose rates of 5 and 10 mg/d to male Drukrey rats. At the conclusion of the study, the cerebellum was removed and neuropathologic study demonstrated that long-term nicotine exposure had caused significant loss of the white core of cerebellum.
ANTINEOPLASTIC MEDICINES

Treatment of cancer patients with a number of antineoplastic medicines such as 5-fluorouracil, methotrexate, cytarabine, cisplatin, oxaliplatin, paclitaxel, capecitabine, and epothilone D can be associated with neurologic side effects, particularly ataxia. At high doses, 5-fluorouracil may induce a pancerebellar syndrome. Intrathecal administration of methotrexate may cause damage to cerebellar structures and induce ataxia. Administration of cytarabine at doses greater than 3 g/m² may cause intoxication, which presents with nystagmus and other cerebellar deficits. Cisplatin, oxaliplatin, and paclitaxel, which are used in the treatment of cancer, may induce polyneuropathy with a significant component of sensory ataxia. Capecitabine, an antimetabolic agent, is utilized for the treatment of metastatic colorectal and breast cancers and may cause widespread toxic encephalopathy as well as diffuse white matter lesions that affect both supratentorial and infratentorial structures. Epothilone D, which is used for treatment of prostate cancer, may demonstrate neurologic toxic effects including ataxia.

AMIODARONE

Amiodarone is an antiarrhythmic medicine with a thyroxinelike structure, and is used for treatment of both atrial and cardiac arrhythmias. As a class III antiarrhythmic medicine, amiodarone prolongs phase 3 of the cardiac action potential. Amiodarone can have a number of unfavorable side effects, such as interstitial lung disease, skin rash, hypothyroidism or hyperthyroidism, corneal microdeposits, ataxia (particularly gait ataxia), tremor, dizziness, cognitive impairment, and peripheral neuropathy. Up to 5% to 7% of patients treated with amiodarone manifest a cerebellar disorder. The neurologic side effects of amiodarone, particularly cerebellar ataxia, may improve once the patient stops taking the medication, but may continue for a number of years, perhaps reflective of the long half-life of elimination of amiodarone.

Procainamide hydrochloride is another antiarrhythmic medicine used for treatment of ventricular tachycardia that may induce cerebellar ataxia at high doses with a significant increase in serum level. The ataxia resolves after cessation of the medicine.

Bismuth preparations are used for treatment of gastrointestinal and skin disorders. Bismuth can induce a progressive toxic neurologic syndrome that is recognized by encephalopathic features, such as confusion, seizures, delirium, myoclonus, and cerebellar deficits, including tremor and gait ataxia.

Lithium salts, which are still used extensively for the treatment of acute mania and prophylaxis of recurrent bipolar and unipolar affective disorders, may cause toxicity during maintenance treatment or acutely. Such neurologic toxicity manifests with tremor and ataxia. The hypothyroidism induced by lithium salts may intensify the ataxia. Acute lithium intoxication can be associated with a constellation of neurologic symptoms, including altered sensorium, seizures, hypokinesia, tremor, and enhanced deep tendon reflexes; it can also include coma in severe cases. Although these neurologic deficits associated with acute lithium toxicity resolve, some patients may demonstrate a cerebellar disorder with dysarthria, tremor, and gait ataxia.

ILlicit Drugs

Use of illicit drugs such as phencyclidine, cocaine, and heroin can cause neurologic damage with a predilection for cerebellar ataxia.
Phencyclidine

Phencyclidine (also known as PCP or angel dust), is a member of the dissociative anesthetics and primarily functions as a noncompetitive N-methyl-D-aspartate receptor antagonists. Utilization of this illicit drug at toxic doses may cause cerebellar ataxia, tremor, and nystagmus. It has been shown that phencyclidine in rats is toxic to the cerebellar Purkinje cells. Näkki and colleagues assessed the expression of Fos protein in the cerebellum and functionally related nuclei of the brainstem. These investigators observed that PCP induced Fos immunostaining in neurons of the inferior olive, cerebellar granule cell layer, and deep cerebellar and vestibular nuclei. They concluded that high doses of PCP cause toxicity to the Purkinje cells at least partially via excessive activity of climbing fibers, which represent the excitatory neural input that arises from the inferior olive and synapses on Purkinje cell dendrites.

Cocaine

Cocaine use can cause seizures, delirium, altered mental status, and cerebellar ataxia. As a psychomotor stimulant, cocaine is particularly notorious for causing both ischemic and hemorrhagic strokes and the ischemic stroke may leave the patient with cerebellar ataxia. The proposed underlying pathophysiologic mechanisms for cocaine-induced strokes include hypertension, embolism, vasospasm, and vasculitis.

Heroin

Another illicit, often dangerous, agent is heroin, which can result in serious neurologic complications. Inhalation or ingestion of heroin can uncommonly be associated with a toxic spongiform leukoencephalopathy. Clinically, patients may present with lethargy, inattention, forgetfulness, and personality changes as well as dysarthria, ataxia, dementia, coma, and even death. Neuropathologic study of the brains of chronic heroin addicts has demonstrated loss of Purkinje cell layer along with a reactive proliferation of Bergman glia.

SUMMARY

A large number of toxic and metabolic insults, nutritional deficiencies, and commonly used medications can have toxic and injurious effects on cerebellum. Clinicians’ familiarity with this subject and search for the insulting agent can have a significant on patients’ lives.

REFERENCES


