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Poisoning of neurons in the brainstem that help control balance.

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Neurotoxic Central Vestibulopathy

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WHAT IS CENTRAL NEUROTOXIC VESTIBULOPATHY?

Central neurotoxic vestibulopathy is a poisoning of certain cells called neurons that help control balance by receiving and processing information from the inner ear vestibular sense organs (the semicircular canals, utricle, and saccule).

Central neurotoxic vestibulopathy is distinguished from peripheral vestibular otoxicity in affecting neurons of the central nervous system (CNS), rather than neurons of the peripheral nervous system.

Substances such as lead or mercury that result in CNS neurotoxicity are well-known examples of central neurotoxicants. Various central neurotoxicants may predominantly affect different areas of the CNS. The drugs known as quinolines are central neurotoxicants which may more commonly affect the vestibular nuclei and adjacent areas of the brainstem.[1]

In part owing to their CNS neurotoxicity, the use of many quinoline drugs, including the antiparasitic drug clioquinol, and the antimalarial drugs pamaquine and plasmocid, has been gradually phased out. [1] However, certain quinoline drugs have remained widely used. One of the more commonly used quinoline drugs that remains in use is the antimalarial drug mefloquine (also known as Lariam®). Since its introduction in the 1980s, mefloquine has been widely used for prevention and treatment of malaria among residents of malarious areas, and among civilian travelers and military personnel deployed in these locations. Other quinoline drugs which remain in use include chloroquine and hydroxychloroquine, primaquine, and a newer drug, tafenoquine.

While central neurotoxic vestibulopathy from quinoline drugs is permanent and irreversible and may be highly disabling in some users, as with other forms of acquired CNS injury, many are able to adapt or compensate to a certain degree over time.

HOW COMMON IS CENTRAL NEUROTOXIC VESTIBULOPATHY?

It is unknown how many people suffer from central neurotoxic vestibulopathy as a result of exposure to quinoline drugs.

One underpowered study among former military users of mefloquine found an elevated, but not statistically significant, hazard for subsequent hospitalization for vertiginous syndromes. [2] Case reports and post-marketing surveillance indicate that chronic vestibular symptoms, consistent with central neurotoxic vestibulopathy, are occasionally reported after use of mefloquine, [1,3,4,5] chloroquine, and hydroxychloroquine. [6,7]

The occurrence and degree of central neurotoxic vestibulopathy from quinoline drugs is believed to depend upon the specific drug used, as well as other factors including dose rate, and individual idiosyncratic susceptibility. Continued use of these drugs following the onset of psychiatric symptoms, which is considered an indication of individual susceptibility, may be a strong risk factor for the development of central neurotoxic vestibulopathy as well as other lasting neuropsychiatric effects resulting from broader CNS neurotoxicity and chronic drug-induced encephalopathy.

WHAT DAMAGE OCCURS?

Based on evidence from limited animal model and human studies, quinoline drugs are believed to exert neurotoxic effects on particular cell types in the brain and brainstem, including certain neurons within the vestibular nuclei. [1,3,8] Broader neurotoxic effects may also affect a variety of other structures within the CNS, [9] including brain and brainstem centers involved in the control of vision, proprioception, and body and eye movement, including within specific nuclei and tracts of the visual reflex, proprioceptive, extrapyramidal motor, and vestibular-cerebellar pathways [1].

SYMPTOMS	
Vestibular	• Dizziness • Imbalance • Lightheadedness • Disequalibrium • Fatigue
Psychological	• Anxiety • Parasomnias • Poor concentration • Mood swings • Memory loss • Personality disturbances
Other	• Tingling or painful sensations in hands, feel, or face • Unstable heart rate • Unstable blood pressure • Poor temperature regulation

WHAT ARE THE SYMPTOMS?

Symptoms of central neurotoxic vestibulopathy will resemble those of other forms of central vestibulopathy. [10,11] Depending on the extent and severity of related neurotoxic injury, these symptoms may be complex and highly variable or may mimic those of more common vestibular disorders. Those affected may complain primarily of disequilibrium or imbalance, a sensation of "dizziness" or "lightheadedness," a sense of motion (vertigo), and fatigue. These symptoms may make it difficult to concentrate or result in irritability.

The broader CNS neurotoxicity of quinoline drugs may also result in additional neurological symptoms, including difficulty changing focus (accommodative dysfunction), and a perception that the visual field is in motion (oscillopsia). In some patients, more complex visual illusions may occasionally occur. [12]. Neurotoxic injury to other areas of the brainstem may result in a sensation of tingling in the hands, feet, or face (paraesthesias), or painful sensations (dysesthesias), [5] instability in heart rate and blood pressure, or temperature regulation (dysautonomia), or symptoms referable to the digestive system. [9]

CNS neurotoxicity from quinoline drugs may also cause prominent mental health symptoms. For example, those reporting persistent vestibular symptoms from mefloquine typically report co-morbid psychiatric or neurocognitive symptoms, including anxiety, parasomnias, concentration difficulties, memory impairment, mood and personality disturbances. In certain cases, vestibular symptoms were preceded by an acute limbic encephalopathy during use of the drug, marked by severe amnesia, anxiety, paranoia, or psychosis. [3,9]

HOW IS CENTRAL NEUROTOXIC VESTIBULOPATHY DIAGNOSED?

Because the neurotoxic injury to affected neurons is typically microscopic and involves only focal areas of the CNS, there is as-yet no imaging modality

(e.g. MRI or CT) that can reliably identify central neurotoxic vestibulopathy. Similarly, there is no single vestibular test that can reliably identify the disorder in all cases. Historically, this form of brain injury has been conclusively identified only after death, when histopathological examination of the brain has been performed at autopsy. [1,13]

A diagnosis of central neurotoxic vestibulopathy is therefore typically a diagnosis of exclusion, and is based upon the patient's history, symptoms, and results of careful examination by appropriate vestibular specialists. The same methods that these specialists use to evaluate other causes of central dysfunction, such as VNG, CDP, VEMP, and rotatory chair testing, may be used.

The diagnosis should be considered when there are signs of central vestibulopathy accompanied by a history of exposure to quinoline drugs, in the absence of other known causes. Subsequent consultation with other specialists, including psychiatrists, neuropsychologists, and neuro-optometrists, may then identify patterns of signs and symptoms consistent with broader CNS neurotoxicity, including additional visual disturbances, focal neurocognitive deficits, seizure disorders, and mood, personality, and behavioral effects.

WHAT IS THE TREATMENT?

As with other forms of acquired CNS injury, there are no specific treatments to reverse central neurotoxic vestibulopathy. Treatments, including vestibular rehabilitation, focus instead on mitigating the effects of the injury and rehabilitating function. It is not known whether any particular drug therapies are useful for the treatment of the disorder.

PREVENTION

There is as yet no test to determine which individuals suffer increased susceptibility to the CNS neurotoxicity of quinolines. During prophylactic use of mefloquine, the onset of psychiatric symptoms may be considered prodromal, preceding the development of more serious toxicity. [14] In 2013, the U.S. Food and Drug Administration (FDA) cautioned "the occurrence of psychiatric symptoms such as acute anxiety, depression, restlessness or confusion suggest a risk for more serious psychiatric disturbances or neurologic adverse reactions. In these cases, the drug should be discontinued and an alternative medication should be substituted."

A LOOK AT THE FUTURE

Research is ongoing to better understand the complex interrelationship of physical symptoms caused by vestibular central neurotoxicity, and those of co-morbid psychiatric symptoms, such as persistent anxiety or neurocognitive impairment. Particularly in military settings, symptoms of vestibular central neurotoxicity may co-exist with those of co-morbid post-traumatic stress disorder (PTSD) or traumatic brain injury (TBI), potentially confounding the diagnosis and management of these disorders.[4,5]

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