DISORDERS

NEUROTOXICITY

Substances which cause damage in the brain can lead to vestibular dysfunction

ARTICLE

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Neurotoxic Vestibulopathy

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Antimalarial Drugs That Can Cause Vestibular Dysfunction

WHAT IS NEUROTOXIC VESTIBULOPATHY?

Neurotoxic vestibulopathy is a poisoning of certain cells called neurons in the areas of the brain that help control balance by receiving and processing information from the inner ear and other sense organs.

Vestibular neurotoxicity is distinguished from peripheral vestibular otoxicity in affecting neurons of the central nervous system (CNS).

Substances such as lead or mercury that result in neurotoxicity are called neurotoxicants. The synthetic drugs known as quinolines are well-known examples of vestibular neurotoxicants[1].

Owing to their harmful effects, efforts are generally made to minimize exposure to neurotoxic compounds. Historical examples of quinolines which have been gradually phased out, in part owing to their neurotoxicity, include the antiparasitic drug clioquinol, and the antimalarial drugs pamaquine and plasmocid[1]. However, certain quinolines have remained widely used owing to their medicinal properties. One of the more commonly used vestibular neurotoxicants that remains in use is the quinoline 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.

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

HOW COMMON IS NEUROTOXIC VESTIBULOPATHY?

It is unknown how many people suffer from neurotoxic vestibulopathy as a result of prior exposure to synthetic quinolines.

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 also indicate that chronic vestibular symptoms are not uncommonly reported after use of the drug.[1,3] However, despite the drug's widespread use, there are as yet no published studies that adequately describe evaluation of vestibular function during long-term follow-up of former mefloquine users.

The occurrence and degree of vestibular neurotoxicity from quinoline drugs such as mefloquine is believed to depend upon the specific drug used, as well as other factors including dose rate, and individual idiosyncratic susceptibility factors including genetic factors, some of which are currently being investigated.

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 DAMAGE OCCURS?

Based on evidence from limited animal model and human studies, the synthetic quinolines are believed to exert neurotoxic effects on particular cell types in the brain and brainstem, including certain neurons within the vestibular nuclei.[1,3,4] Related neurotoxic effects may also affect related 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] Additional neurotoxic effects may also affect a variety of other structures within the hindbrain, midbrain, and limbic system.[5]

WHAT ARE THE SYMPTOMS?

Symptoms of neurotoxic vestibulopathy will resemble those of other forms of central vestibulopathy.[6,7] Depending on the extent and severity of 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. Additional visual symptoms may occur, including a 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.[8]

Quinoline neurotoxicity may also result in additional neurological symptoms, including a sensation of tingling in the hands, feet, or face (paraesthesias), or painful sensations (dysesthesias). Neurotoxic injury to other areas of the brainstem may result in instability in heart rate and blood pressure, or temperature regulation (dysautonomia), or symptoms referable to the digestive system.[5]

Quinoline neurotoxicity 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.[5]

HOW IS NEUROTOXIC VESTIBULOPATHY DIAGNOSED?

Because the neurotoxic injury to affected neurons is microscopic and involves only certain specific cell types of the CNS, there is as yet no imaging modality (e.g. MRI, CT) that can reliably identify 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.[1,9]

A diagnosis of neurotoxic vestibulopathy is therefore typically a diagnosis of exclusion, and is based upon:

- The patient's history
- Symptoms
- Results of careful examination by appropriate vestibular specialists

The same methods that specialists use to evaluate other causes of central vestibulopathy may be used.

Additionally, consultation with other specialists, including psychiatrists, neuropsychologists, and neuro-optometrists, may identify patterns of signs and symptoms consistent with broader neurotoxicity, including additional visual disturbances, focal neurocognitive deficits, mood, personality, and behavioral effects.

WHAT IS THE TREATMENT?

As with other forms of acquired brain injury, there are no specific treatments to reverse neurotoxic vestibulopathy. Treatments 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 neurotoxic effects of synthetic quinolines. During prophylactic use of mefloquine, the onset of psychiatric symptoms may be considered prodromal, preceding the development of more serious toxicity.[10] 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 neurotoxicity, and those of co-morbid psychiatric symptoms, such as persistent anxiety or neurocognitive impairment. Particularly in military settings, symptoms of vestibular 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.[11]

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