



Central Nervous System Adverse Effects of Doxycycline: Clinical Spectrum, Mechanisms, and Management

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ABSTRACT:

Doctors prescribe doxycycline, a tetracycline antibiotic, to people with both infectious and non-infectious diseases. Most people can handle it, but it can cause serious adverse effects on the brain and spinal cord (CNS) that are rare. This review compiles contemporary literature on the neurological spectrum of doxycycline-induced CNS toxicity, including severe headaches, pseudotumor cerebri, epilepsy, and behavioural disturbances. The text discusses possible pathophysiological mechanisms, such as mitochondrial dysfunction and alterations in neurotransmitter modulation, as well as evidence-based approaches to diagnose and treat the problem. To keep patients safe while they are on doxycycline for a long time, it is important to know about these rare side effects.

Keywords: doxycycline, mechanism, toxicity, CNS, CSF, GABA receptor, side effects

1. INTRODUCTION

Doxycycline, a semisynthetic derivative of tetracycline, is an important medicine for treating infections caused by bacteria like Lyme illness, acne vulgaris, and infections of the respiratory tract [1]. Part of the reason it is so popular. It has good pharmacokinetics, including high tissue penetration and a single daily dose [2]. There are still some safety concerns, though. Gastrointestinal disturbances and photosensitivity are the most common adverse events. Central nervous system (CNS) toxicity also presents a unique clinical challenge [3].

Central nervous system (CNS) side effects from doxycycline are often underrecognized or underreported due to their rarity and nonspecific symptoms [4]. Recognizing these effects is essential, as they may vary from mild migraines to serious complications like pseudotumor cerebri (PTC) or epilepsy [5]. This review looks at the symptoms, causes, and treatments for CNS side effects that can occur when you take doxycycline.

2. Clinical Spectrum of CNS Adverse Effects

2.1 Headache and Dizziness

Headaches are the most prevalent central nervous system adverse effects of doxycycline, affecting a small yet clinically significant group of patients [6]. People often call these tension-type headaches, and they may resolve on their own or when the dose is reduced [7]. Dizziness and vertigo have also been reported, which could make people less likely to stick to their treatment or make them more likely to get hurt while doing things that require them to be alert [8]. These symptoms are usually mild, but they can get worse if you take CNS-active drugs at the same time [9].

2.2 Pseudotumor Cerebri (Idiopathic Intracranial Hypertension)

Doxycycline is usually safe and works well, but sometimes it can cause central nervous system side effects, from headaches to more serious problems like pseudotumor cerebri or seizures. Some symptoms include a very severe headache, difficulty seeing, pulsatile tinnitus, and inflammation of the optic nerve (papilledema) [13]. If left untreated, IIH can lead to permanent vision loss [14].



2.3 Seizures and Neurotoxicity

Doxycycline can make you have seizures, but this doesn't happen very often. People who currently have problems with their minds or kidneys are more likely to get it [15]. Tetracyclines, as a group, may increase the risk of seizures by either directly impacting the brain or disrupting metabolic balance [16]. Some cases exist where people experienced tonic-clonic seizures after taking large amounts of doxycycline [17]. This may be due to the drug blocking mitochondrial protein production in nerve cells, leading to energy problems [18].

2.4 Psychiatric and Behavioral Effects

Doxycycline has been linked to psychiatric manifestations, including anxiety and insomnia [19]. People sometimes think that these moderate impacts are caused by other mental health problems [20]. Doxycycline can sometimes lead to delirium and hallucinations, mostly in older people or those with liver problems [21]. Because there aren't many large studies, it's still unclear how often these side effects occur [22].

3. Pathophysiological Mechanisms

3.1 Mitochondrial Toxicity

Tetracyclines, such as doxycycline, inhibit bacterial protein synthesis by attaching to the 30S ribosomal subunit, thereby preventing aminoacyl-tRNA binding [23]. Because the ribosomes in human mitochondria are similar to those in bacteria, tetracyclines can also block protein production in mitochondria [24]. This reduces energy production (ATP) and can cause problems in nerve cells [25]. These effects are particularly important in cells that require a lot of energy, such as those in the brain [26].

3.2 Modulation of Neurotransmitters

Doxycycline may affect the central nervous system by altering neurotransmitter levels, including those that act on GABA receptors. These changes can make nerve cells more excitable, which might lead to seizures or anxiety in some people [27, 28]. Doxycycline also inhibits matrix metalloproteinases (MMPs), enzymes that help maintain the blood-brain barrier [29]. If these enzymes are blocked, the barrier may weaken, letting more harmful substances enter the brain [30].

3.3 Fluid Retention and Intracranial Pressure

Pseudotumor cerebri may occur when the body retains fluid, and the flow of cerebrospinal fluid (CSF) is blocked, causing pressure inside the skull to rise [31]. Tetracyclines can cause problems with the kidneys, such as renal tubular acidosis or changes in how the kidneys handle electrolytes, leading to fluid shifts in the body [32]. These changes can increase pressure in the brain. This risk is higher with more fat-soluble tetracyclines, but doxycycline can also cause it [33].

3.4 Direct Neurotoxicity

Direct neurotoxicity can happen if doxycycline or its breakdown products build up in the central nervous system. This is more likely in people whose kidneys or liver do not work well, since these organs help remove the drug and its metabolites. Most doxycycline is excreted in the feces, but the kidneys also help clear its metabolites [34,35]. If the drug builds up, it can damage nerve cells and may cause encephalopathy or seizures [36]. (Fig 1)

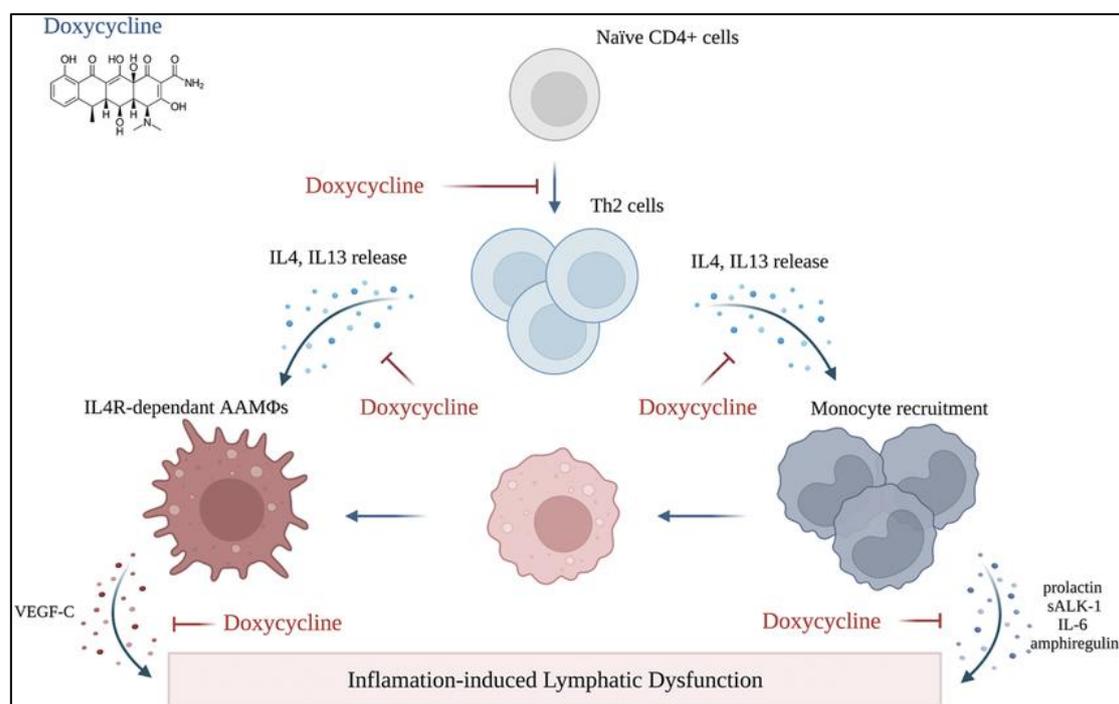


Figure: 1 Immunomodulatory Effects of Doxycycline on Th2-Mediated Inflammation and Lymphatic Dysfunction

4. Risk Factors and Drug Interactions

4.1 Patient Demographics

Young women have a higher risk of developing pseudotumor cerebri when taking tetracyclines [37]. Age also matters. Older adults are more likely to have psychiatric or delirium-related side effects because their bodies clear the drug more slowly [38].

4.2 Concomitant Medications

Taking other drugs that affect the central nervous system along with doxycycline increases the risk of CNS side effects [39]. Combining doxycycline with isotretinoin increases the risk of pseudotumor cerebri [40]. Taking other neurotoxic antibiotics, such as fluoroquinolones, can also increase these risks [41].

4.3 Renal and Hepatic Impairment

Patients with kidney or liver problems are at risk for drug buildup and toxicity [42]. Doxycycline depends less on the kidneys for removal than other tetracyclines, but serious kidney or liver issues can still change how the drug is processed [43]. For long-term treatment, it is important to monitor liver function tests [44].

5. Diagnosis and Management

A clinical diagnosis of central nervous system toxicity from doxycycline needs thorough assessment and the ruling out of other possible causes [45]. A complete medication list is key. If doctors think someone might have pseudotumor cerebri, they should get brain scans, like an MRI or CT, to check for other problems. After that, a spinal tap is needed to measure the pressure of the cerebrospinal fluid [46].

5.2 Management Strategies

The first thing to do to deal with these adverse reactions is to stop taking doxycycline right away [47]. If pseudotumor cerebri occurs, acetazolamide may be given to lower cerebrospinal fluid pressure [48]. Analgesics and rest can help with headaches and dizziness [49]. Brief use of antiseizure medications may be necessary in the presence of seizures [50].



5.3 Alternative Therapies

If doxycycline needs to be discontinued due to central nervous system side effects, select other antibiotics based on the infection type [51]. For instance, macrolides or fluoroquinolones could treat respiratory infections, but they might also pose risks to the central nervous system [52]. Acne can be treated with topical medicines or hormone treatments [53].

5.4 Monitoring and Prevention

To reduce risk, patients at high risk should undergo a brain checkup before starting treatment [54]. It's important to teach patients about the signs of increased intracranial pressure and to tell them to report any vision changes right away [55]. People who are on long-term doxycycline should have regular check-ups [56].

6. Conclusion

Doxycycline is usually safe and works well, but sometimes it can cause central nervous system side effects, from headaches to more serious problems like pseudotumor cerebri or seizures.

A better understanding of how processes like mitochondrial toxicity and fluid movement in the body work can help doctors identify patients at greater risk. If problems pop up, keeping a close watch on those at risk, stopping the drug quickly, and giving the right care is key.

Further research is still required to better establish the true incidence of these uncommon complications and to define optimal management strategies when they arise.

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CONFLICT OF INTEREST: None

Abbreviations

CNS – Central Nervous System

CSF – Cerebrospinal Fluid

ATP – Adenosine Triphosphate

MRI – Magnetic Resonance Imaging

CT scan – Computed Tomography Scan

PTC – Pseudotumor Cerebri

MMPs - Matrix Metalloproteinases

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