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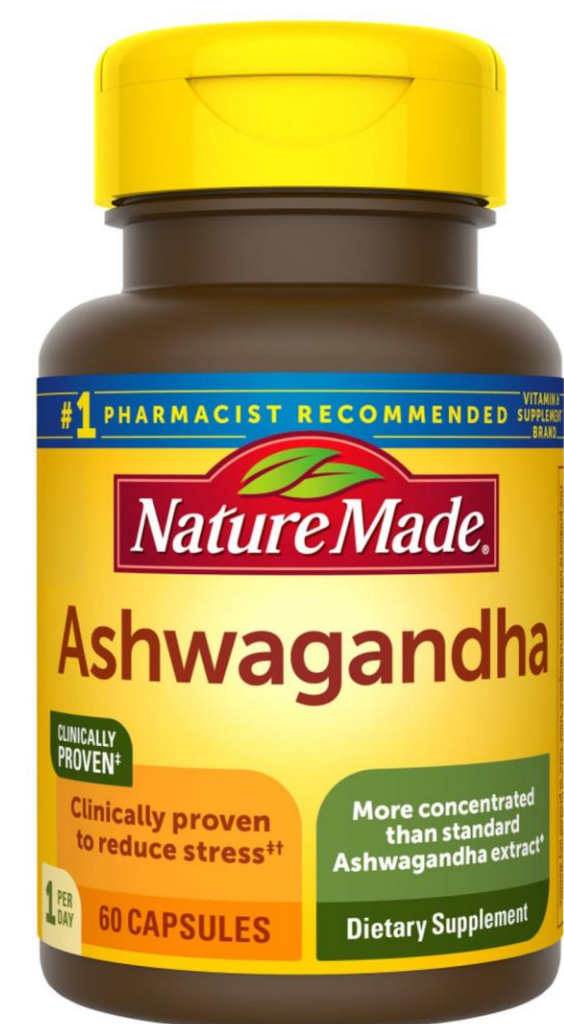
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AN HERBAL LIVER EFFECT: ASHWAGANDHA-INDUCED HEPATOTOXICITY

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Introduction:

Ashwagandha is a popular Ayurvedic herb that is derived from the extracts of the roots of *Withania somnifera*, an evergreen shrub endemic to India and Southeast Asia. It is generally utilized as a tonic to increase one's energy and reduce stress levels. Often referred to as "Indian ginseng", it provides neuroprotective and anti-inflammatory properties that address stress, pain, and fatigue. Additionally, it may assist in dealing with rashes, diabetes, and arthritis. It has also been shown to counteract the effects of aging. Though these properties have not been shown in prospective studies, it has become a popular product among western countries. Extracts of the herb are often supplied as tablets without few, if any, adverse reactions. Several case reports however have brought to light that taking ashwagandha may induce liver injury in patients taking commercial products that contain this extract.

Case Presentation:

We present the case of a 44-year-old Caucasian female with a past medical history of irritable bowel syndrome, anxiety, ADHD, herniated disc status post motor vehicle collision presenting to the emergency department for complaint of a one-month history of painless jaundice and pruritus. She states that she takes Xanax for anxiety and has been taking an herbal supplement for her stress relief. She notes that she was also evaluated in Florida and hospitalized with a negative ultrasound, MRCP, and hepatitis screening. She was notified that she would require a liver biopsy. She noted worsening jaundice, prompting her evaluation in the emergency department again. She also reported nonspecific abdominal discomfort. She stated that the herbal supplement she was taking composed of Ashwagandha and stopped taking the supplement since she noted her symptoms. She denied any nausea, vomiting, chest pain, shortness of breath, fever, chills, edema, tick bites, or recent illnesses.

Her vital signs during evaluation were blood pressure 111/67, temperature 98.3, pulse 82, respiratory rate 15, SpO2 99%. She was well appearing, normocephalic/atraumatic, with normal rate and regular rhythm. She had no respiratory distress, rales, rhonchi, wheezing. Her abdomen was soft and nontender however there was significant jaundice, including scleral icterus. She was alert and oriented to person, place, and time. With regard to evaluation of her lab work, she exhibited transaminitis and hyperbilirubinemia. Her lab work revealed a total bilirubin 10.5, direct 6.0, ALP 106, AST 62, ALT 55. Her basic metabolic panel revealed no significant electrolyte abnormalities. Her urinalysis revealed 3+ bilirubin however without concern for urinary tract infection. Her complete blood count had no leukocytosis, and her hemoglobin and hematocrit were stable at 12.3/36.1 with normocytic MCV.

She had an abdominal ultrasound and CT abdominopelvic imaging without concern for gallbladder pathology or any abdominopelvic concern. She noted that she had prior extensive workup, including a negative hepatitis panel and MRCP during her evaluation in Florida. A call was placed to the gastroenterologist on call, and it was recommended that the patient be prescribed cholestyramine for her itching and was provided strict follow up with a gastroenterologist on an outpatient setting. She was informed to discontinue taking any herbal supplement, such as Ashwagandha as this may have precipitated her underlying jaundice and liver disease.

Discussion:

Indian Ginseng, Winter Cherry, Poison Gooseberry are all other names that contain *Withania somnifera*, the herb used in Ayurvedic medicine notable for its anti-inflammatory, anti-oxidant, anti-tumor, and anti-stress properties based on studies performed in animals, revealing no adverse effects [1]. There is evidence that Ashwagandha may be effective in chemoprevention based on in vivo studies of apoptosis, angiogenesis, stress response, however, this has only been studied in animals [2]. It is also notable that among 50 adults treated with 300mg Ashwagandha vs placebo for 8 weeks, the measures of memory, attention, and information-processing improved more with use of the herb [3]. Among 52 adults treated for chronic stress, it was perceived with decreased stress levels associated with the herbal extract [4]. One case discussed a 23-year old woman who developed thyrotoxicosis after use of an herbal preparation of Ashwagandha [5]. Another discussed a 20-year old male who developed jaundice a month after increasing the dose of Ashwagandha and labwork revealed a bilirubin 20.7, with jaundice persisting for months, which ultimately resolved [6]. One report from Japan discusses the case of a 20-year old man who developed cholestatic drug-induced liver injury with jaundice after use of Ashwagandha in combination with multiple anxiolytic drugs [6].

The mechanism by which hepatotoxicity occurs is unclear; few cases have been associated with mild to moderate illness and without acute liver failure or underlying chronic liver damage. In any case, rechallenge should be avoided. According to an Iceland study, five cases of liver injury were attributed to Ashwagandha-containing supplements. Two were extracted from the Drug-Induced Liver Injury Network (DLIN) in 2016 and another three from case presenting to the hospital in Iceland during 2017-2018. All patients in this study developed jaundice, nausea, lethargy, pruritus and abdominal pain after a latency period of 2-12 weeks. The liver injury was associated with cholestatic pattern or mixed. No patient developed any hepatic failure. Follow-up liver testing normalized in 1-5 months. Chemical analysis confirmed Ashwagandha in available supplements [7].

Most reported cases of DILI secondary to supplements contain multiple ingredients; thus, finding the precipitating agent can be difficult [8]. Approximately half of the U.S. population uses dietary supplements [9] and a population survey showed that Ayurvedic medicine was used by only 0.1% of the adult U.S. population in 2012 [10]. However, Ashwagandha is not limited to Ayurvedic medicine; in fact, many dietary supplements containing Ashwagandha are marketed in the U.S.

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Overall, herbal supplement adverse events are estimated to cause 23,000 emergency department visits annually in the U.S. [11] Ashwagandha was marketed as the predominant ingredient, and chemical analysis did not identify other hepatotoxic substances. Clinicians should be aware that Ashwagandha is a component of herbal supplements that may be obtained over the counter. Interestingly, commercial herbal preparations are found to be mixtures of herbs and nutritional products that are often mislabeled. Drug-induced injury associated with herbal and dietary supplements is an important cause of liver injury and failure, and the prevalence of this data has led to an increase in the awareness of hepatotoxic agents secondary to have led to an increasing appreciation of hepatotoxicity as well as other adverse events.

Conclusions:

Ashwagandha is commonly found in herbal supplements that patients have access to over the counter. In rare occurrences, it may precipitate a jaundice concerning for liver failure without concern for obstruction on imaging. Patients can be reassured that the jaundice will resolve without intervention. We present a case of a 44-year-old female who presented with painless jaundice after recently starting Ashwagandha supplementation. Her lab work was significant for transaminitis and hyperbilirubinemia, however she had normal imaging. She presented well-appearing to the emergency department however with significant jaundice. This is the key for the emergency physician evaluating a patient with transaminitis and hyperbilirubinemia with negative imaging: a thorough history to determine if any medications can be inducing the liver injury, including herbal medications, is important. The emergency physician should obtain a thorough medical history however also an important medication history, including any herbal medications, such as reviewing medications containing products that may be unfamiliar to physicians.