A case of drug induced liver injury secondary to Ashwagandha Root supplementation

Connor Wayman MD, Timothy Halterman MD
University of Nevada, Reno, School of Medicine. Gastroenterology Consultants, Reno NV.

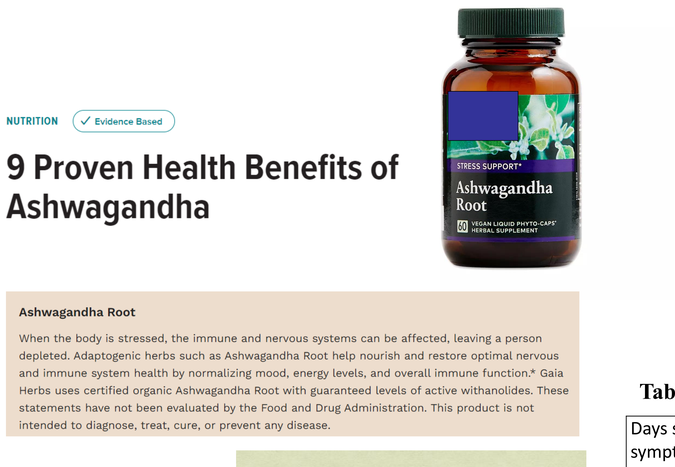
University of Nevada, Reno
School of Medicine

Introduction/Background

Ashwagandha root is an ancient Indian Ayurvedic herbal medicine sometimes referred to as “Indian Winter cherry” or “Indian Ginseng,” that is growing in popularity for its purported benefits of weight loss, muscle building and stamina benefits, and cognition promoting effects.[3,5,6] It is available in the U.S. as a pill and as a powder, with marketed benefits of “virility, stamina, stress and mental focus.” In vitro studies[3] suggest possible benefits of ashwagandha to include muscle growth, exercise stamina, weight loss, hepatocellular carcinoma targeting, and others, but overall no large scale studies have been done to test for safety or adverse effects.[3,4,5,6] Rare case reports of drug induced liver injury (DILI) related to ashwagandha have been documented.[1,2,5,7]

Here I will present a case of a young man who developed cholestatic DILI after starting ashwagandha root to supplement his workout routine.

Marketing/Sales Examples and “claims”:



Case Presentation

A 19-year-old, previously healthy male, presented to our hospital with severe pruritus and new onset jaundice after starting new weightlifting supplements including ashwagandha and creatine 1.5 months prior to admission. He denied any steroid use, alcohol use or other recreational drug use. He did vape with nicotine cartridges daily since the age of 18. Two weeks after starting creatine and ashwagandha root to supplement his previous regimen of vitamin B12 and vitamin C and whey protein, patient developed progressive pruritus without any noted rash. Five to 6 days after the onset of pruritis he noted the onset of jaundice. with mild nausea and dark urine without abdominal pain. He initially visited his outpatient primary care provider in Alabama, who sent him to Emergency department for evaluation. Initial labs showed total bilirubin 7.6, AP 149, ALT 144 and AST 74. He had additional imaging including MRI and CT scan which were unremarkable. It was thought that his liver injury was related to herbal supplements, and he was discharged with prn hydroxyzine for itching. Patient then moved across the country in the interim due to his position in the Armed Forces. Over the intervening month since discontinuing the creatine and ashwagandha supplements, his pruritus and jaundice worsened, and he returned to the hospital for subsequent evaluation. Initial evaluation showed an obviously jaundiced male with diffuse excoriations but otherwise was unremarkable. Initial laboratories showed T. bili 25 (direct>10), AP 485, ALT 53, AST 48 and INR of 1.14.

Additional serologic liver evaluation including acute viral hepatitis panel, HCV RNA, Hepatitis E IgM and IgG, HIV, EBV/CMV/HSV serologies, ANA, Actin Ab, AMA, IgG and IgG4, A1AT and ceruloplasmin, was performed and found to be normal. RUQ US showed a small sub centimeter hypoechoic tubular structure in the gallbladder of unclear significance but was otherwise normal. MRCP showed mild splenomegaly but otherwise normal bile ducts and liver. He ultimately underwent liver biopsy which showed centrizonal cholestasis with pigmented macrophages, minimal to mild portal lymphocytic inflammation without interface activity or ductular reaction, mild lymphocytic lobular inflammation with minimal hepatocellular injury. There was no significant steatosis, granulomas or viropathic changes and no fibrosis.

Patient was treated with cholestyramine, ursodiol and antihistamines for management of pruritus with mild benefit. His bilirubin slowly trended up during hospital stay but nadired at 30. He was discharged after bilirubin stabilized but was started on low dose naltrexone at discharge given persistent pruritus despite other medications.

Two days after discharge patient developed an episode of altered mental status. which lasted for about 30 mins. Patient subsequently returned to the hospital. On arrival to ED patient was at baseline mental status without asterixis. His t bili remained similar to discharge at 29 with normal INR. It was felt altered mental status was possibly due to naltrexone and this was discontinued. He was started on low dose rifampin given persistent pruritus despite other medications with mild improvement and ultimately discharged again with close follow-up. Since his discharge, patient’s bilirubin has rapidly declined on current regimen, 31.3 on day of second discharge, 3 days later down to 21.2, 6 days down to 18, and finally 9 days after second discharge value at 16.6. AST/ALT and alk phos levels with similar improvements. On follow up phone call 3 weeks after this discharge, patient mentioned visible yellowing that improved day-by-day, but the rest of his symptoms had fully resolved.

Table 1.1 Total bilirubin and symptom progression

Days since symptom onset	6 days	36 days	42 days	44 days	46 days	49 days	52 days	55 days	67 days
Total Bilirubin Level	7.6	25	30	29	31.3	21.2	18	16.6	-
Symptoms	Jaundice/ pruritis	Worsening Jaundice/pruritis/ pale stools	Mild improvement pruritis.	AMS vs. panic attack, persistent pruritis	Mild improvement pruritis	-	Pruritis improving	-	Pruritis symptoms resolved, visible jaundice improving.

Discussion

Ashwagandha root is a rare cause of cholestatic liver injury. The Drug Induced Liver Injury Network (DILIN) in combination with gastroenterologists in Iceland were able to identify five known incidences of drug induced liver injury related to ashwagandha[1,2] but reports of this are rare. Other than their report, there is one Japanese case report with a 20-year-old man,[7] with a very similar clinical course. The clinical course of our patient closely matches the six cases described in the literature so far.[1,2,7] He had a latency period of 2 weeks to the development of jaundice; similar to other reported cases. He then had prolonged course of cholestatic liver injury even after discontinuing supplements that lasted several months prior to eventual complete resolution. It seems clear that Ashwagandha-containing herbal medications can result in severe cholestatic liver injury,[1,2,5,7] which is prolonged, but ultimately self-limiting without the development of chronic DILI or progressing to acute liver failure. This case report further re-enforces the importance of careful monitoring and awareness of our patients’ supplemental health products and the importance of stressing the unknown safety profile of any herbal treatment that has not been extensively studied for safety and side effects.

References

1. Björnsson HK, Björnsson ES, Avula B, Khan IA, Jonasson JG, Ghabril M, Hayashi PH, Navarro V. “Ashwagandha-induced liver injury: A case series from Iceland and the US Drug-Induced Liver Injury Network.” *Liver Int.* 2020;40:825–829. [PMC free article] [PubMed] [Google Scholar]
2. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548536/
3. Abbas SS, Singh N. *Anti-stress Agents (Herbs) of Indian Origin - Herbal Drugs, A twenty first century perspective.* Delhi: Institute of Nuclear Medicine and Allied Sciences, Defence Research and Development Organization (DRDO), Govt. of India; 2006. pp. 578–591. [Google Scholar]
Abbas SS, Singh V, Bhalla M, Singh N. Clinical Study of Organic Ashwagandha in cases of Parkinsonism, Neuropathy, Paralysis and Uterine Tumours (Fibroids and other tumours) including Cutaneous Endodermal Carcinoma; Proc., National Seminar on “Eco-friendly Herbs of Ayurveda in Healthcare of Mankind: A Strategy for Scientific Evaluation and Uniform Standardization” - Lucknow; 2004. p. 81. [Google Scholar]
4. Singh, Narendra et al. “An overview on ashwagandha: a Rasayana (rejuvenator) of Ayurveda.” *African journal of traditional, complementary, and alternative medicines : AJTCAM* vol. 8,5 Suppl (2011): 208-13. doi:10.4314/ajtcam.v8i5S.9
5. Woo, Stephanie M et al. “Herbal and dietary supplement induced liver injury: Highlights from the recent literature.” *World journal of hepatology* vol. 13,9 (2021): 1019-1041. doi:10.4254/wjh.v13.i9.1019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8473494/
6. Wankhede, Sachin et al. “Examining the effect of Withania somnifera supplementation on muscle strength and recovery: a randomized controlled trial.” *Journal of the International Society of Sports Nutrition* vol. 12 43. 25 Nov. 2015, doi:10.1186/s12970-015-0104-9
7. Inagaki K, Mori N, Honda Y, Takaki S, Tsuji K, Chayama K. A case of drug-induced liver injury with prolonged severe intrahepatic cholestasis induced by ashwagandha. *Kanzo.* 2017;58(8). [Google Scholar]
Philips, Cyriac Abby et al. “Comprehensive review of hepatotoxicity associated with traditional Indian Ayurvedic herbs.” *World journal of hepatology* vol. 12,9 (2020): 574-595. doi:10.4254/wjh.v12.i9.574