

Toxicant-associated steatohepatitis: à propos a case of benzene exposure

Daniel Benharroch¹
Boris Talalay²

¹Department of Pathology,

²Department of Family Medicine, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Abstract: An attempted interpretation of recurrent episodes of hepatitis in a girl at ages 6 and 13 years, which were followed by an interval of 35 years of apparent good health, is reported. A subsequent transient incidence of a halothane hypersensitivity reaction at age 48 years led to the disclosure of negative hepatitis A, B and C antigenicity. A tentative diagnosis may be reached if we accept, at its face value, the statement that a toy that the child played with before each hepatitis episode carried a very high benzene content. The toy was a “pate-à-ballon” or “magic balloon,” and it can carry a benzene content that is seven to nine times higher than the traditionally authorized concentration.

Keywords: toxic hepatitis, volatile organic compound

Introduction

Recurrent jaundice was the primary symptom of hepatitis in a female child, and it raised widely differing diagnoses, including viral, toxic, drug-induced, metabolic and autoimmune hepatitis.¹ In 1956, a biochemical workup was not performed, given that the child's condition did not necessitate hospitalization. A second episode with a more severe clinical picture may have convinced the physician and family to perform a more intensive workup, probably in a clinic or a hospital, but this option was not selected.

A retrospective study of the case highlighted the once unobtrusive anamnestic details about the child during her first and second bouts of jaundice. It also addresses features that were released much later, when the patient was middle aged. The suggestion of a cautious diagnosis is herewith sanctioned.

Case report

A 6-year-old Caucasian girl from Morocco who had experienced a normal birth and development showed evidence of jaundice. Icterus was evident in the sclera, and her mother noticed that her urine was dark. The general practitioner (GP) established a diagnosis of hepatitis, apparently in the absence of biochemistry and serology tests, and he ordered rest and a light regimen. The circumstances of this first episode were blurred in the recollection of the patient and her family.

In 1963, at the age of 13 years, the patient developed a second bout of jaundice, which appeared to have been more severe than the first. Abdominal pain, nausea, fatigue and weakness were noted. The patient was not sure about the presence of a fever. The physician was strict with bed confinement, and he prescribed corticosteroids. The patient was bedridden for a month, after which she resumed a completely normal life.

Correspondence: Daniel Benharroch
Department of Pathology, Soroka
University Medical Center and Faculty of
Health Sciences, Ben-Gurion University
of the Negev, 1, Itshak Rager Boulevard,
PO Box 151, Beer-Sheva 84101, Israel
Tel +972 5 0757 9140
Email dbenharroch@yahoo.com

As a young woman and still in perfect health except for having well-balanced thoracolumbar scoliosis, she emigrated to Israel. She got married and had three children, and at the age of 48 years, she was given halothane as part of a surgery for the stripping of a varicose vein. When she woke from the anesthesia, she experienced severe malaise, nausea and vomiting. Liver function test results, including those for transaminases, were slightly elevated.

Because of her history of jaundice in childhood, her GP required a study of her hepatitis B virus (HBV), hepatitis C virus (HCV) and later hepatitis A virus (HAV) antigens at that stage. The results were found to be negative.

An analysis of hepatitis virus antigens was repeated, at the age of 65 years, in view of this case report. The results for the HBV antigen, HBV antibody and HCV antibody were negative, but that for the HAV immunoglobulin G was positive.

The patient has provided written informed consent to publish this case report.

Discussion

The first jaundice episode in a child at age 6 years would be most consistent with hepatitis A, and the apparently mild course of this disease may support the diagnosis.² However, the occurrence of a second bout (although it was more severe) in the absence of a report on the use of needles or blood components, or of hepatitis B in the family or at school, makes the occurrence of hepatitis A at the age of 6 years followed by hepatitis B at the age of 13 years seem unlikely. In addition, the normal follow-up results until the age of 65 years and the normal serology results, except for mildly increased alkaline phosphatase, which was probably attributable to statin therapy, also make this diagnosis seem unlikely.³ Non-alcoholic steatohepatitis (ASH) is not rare in children. However, none of the major risk factors, such as diabetes and obesity, prevailed.⁴ Having a normal medical history until the age of 65 years does not contribute to this possible diagnosis.

These findings point to toxic hepatitis or, as it has been renamed, toxicant-associated steatohepatitis (TASH).⁵ The direct questioning of the patient and her mother highlighted this option, and a specific toxicant was more probable in this difficult case. More often than expected, steatohepatitis is associated with normal serum aminotransferases.

During the period that included both episodes of hepatitis, the child's father was in charge of a large service station. Although he was not directly involved with handling gasoline and did not return home with dirty clothes, he most likely adsorbed some of the gasoline vapor onto his clothing, hair

and skin. Thus, he may have exposed his family, chronically and at tiny daily doses, to petrol vapor. Moreover, the child paid frequent visits to the service station.⁶

However, the second type of exposure to the toxicant, acute exposure, is more exotic. This trend was clarified only recently because previously it was not considered toxic. Before both hepatitis occurrences, the child had been playing with a game that has been distributed and sold worldwide over the last 65 years. She blew up balloons with a toy called "pate-à-ballon" or "magic balloon".⁷

The toy consists of a tube or tubes and a pipette; the tube contains a paste with a strong, acrid smell. A fragment of the paste is applied to one end of the pipette. By blowing through the other end, the child obtains a soft balloon, which may sustain a game, presumably for hours.

The use of the paste is not recommended by the manufacturers for children younger than 3–5 years, nor is it advised to hold the balloon with bare hands for more than a few seconds. The substance in the paste consisted of polyvinyl acetate dissolved in acetone, to which ethyl acetate plastic fortifiers were added. It is now understood beyond doubt that, at least in certain toy companies and over a certain time period, the paste of this toy contained seven to nine times more benzene than the authorized amount (37.6–45.6 mg/kg; Nb. 76/789/EEC).

Thus, the child was reportedly exposed to two sources of benzene. One was a chronic low dose from her father's clothes, hair and skin, and the other was a heavy, acute source from the "pate-à-ballon". In fact, gasoline vapor toxicants primarily include benzene, in addition to toluene and xylene (BTX-volatile organic compound [VOC]).⁶ Exposure to these toxicants is highest in service station attendants, but a direct and indirect environmental exposure prevails to an unknown degree.

The global distribution of the "pate-à-ballons" has been described since the 1950s. There are questions, then, as to why this contamination has not been curbed before and why more cases of TASH were not brought to the attention of the medical authorities to impede its spread. In fact, "pate-à-ballons" were withdrawn from the German toy market by November 2008. However, other countries have not followed this example.⁸

One possible reason may be due to ignorance. It is generally believed that benzene's effect is dose dependent.^{9,10} Others did not find evidence of benzene hepatotoxicity.¹¹ However, the idea that benzene toxicity may also be human leukocyte antigens (HLA) related cannot be excluded because some cytochrome P450 isoenzymes, more specifically, a missing *CYP_{4F}₃* gene, may lead to much more serious ben-

zene poisoning. Thus, idiosyncratic effects from this organic solvent are expected.^{12,13} Exposure to benzene in the home seems to provide a share of the total risk from this VOC.¹⁴

Hepatotoxicity may develop as a consequence of exposure to this VOC, and it will present either as toxicant-associated fatty liver disease (TAFLD) with milder, if any, symptoms or as TASH with a more severe and chronic clinical picture. A liver biopsy has never been performed in this patient to confirm the suggested diagnosis. As a rule, the speculative morphological picture should resemble that of ASH, with fatty change, chronic and focal acute inflammation and with or without hepatocytes bearing Mallory bodies. Evolution to fatty cirrhosis has been described.⁵

Had the clinical features justified this attitude at any stage, the patient would have undergone a liver biopsy. It is strongly suggested that at least during the jaundice episode at age 13 years, the patient may have shown evidence of TASH.

The limitations to this case report are numerous and include the absence of a liver biopsy or imaging and evidence of recall bias. In addition, our interpretation of the data, the suggested diagnosis and the indication that the deletion of CYP_{4F₃} may have occurred are all highly speculative.

Acknowledgment

The authors thank the members of Kibbutz Sde Boker for their help.

Disclosure

The authors have declared that no conflicts of interest exist.

References

- White FV, Dehner LP. Viral diseases of the liver in children: diagnostic and differential diagnostic considerations. *Pediatr Dev Pathol.* 2004;7(6):552–567.
- Leung AK, Kellner JD, Davies HD. Hepatitis A: a preventable threat. *Adv Ther.* 2005;22(6):578–586.
- Srivastava A, Mathias A, Yachha SK, Aggarwal R. Occult hepatitis B infection in children with chronic liver disease. *Eur J Gastroenterol Hepatol.* 2015;27(4):375–377.
- Temple JL, Cordero P, Li J, Nguyen V, Oben JA. A guide to non-alcoholic fatty liver disease in childhood and adolescence. *Int J Mol Sci.* 2016;17(6):E947.
- Wahlang B, Beier JJ, Clair HB, et al. Toxicant-associated steatohepatitis. *Toxicol Pathol.* 2013;41(2):343–360.
- Periago JF, Prado C. Evolution of occupational exposure to environmental levels of aromatic hydrocarbons in service stations. *Ann Occup Hyg.* 2005;49(3):233–240.
- Balloon Magic [webpage on the Internet]. Balloon Magic, A Toy for Children with Toxic Content. Available from: <http://www.balloonmagic.com/bmthemag.php>. Accessed September 12, 2016.
- Lasecuritedesjouets [webpage on the Internet]. Toys Security. Available from: <http://lasecuritedesjouets.blogspot.co.il/2008/11/pate-ballons-retrait-du-march-en.html>. Accessed September 12, 2016.
- D'Andrea MA, Reddy GK. Adverse health effects of benzene exposure among children following a flaring incident at the British petroleum refinery in Texas City. *Clin Pediatr (Phila).* 2016;55(3):219–227.
- Hetal R. Evaluation of benzene induced histopathological alterations in the rat. *Int J Adv Res.* 2016;4:563–567.
- Bahadar H, Mostafalou S, Abdollahi M. Current understandings and perspectives on non-cancer health effects of benzene: a global concern. *Toxicol Appl Pharmacol.* 2014;276(2):83–94.
- Watkins PB. Role of cytochrome P450 in drug metabolism and hepatotoxicity. *Sem Liver Dis.* 1990;10(4):235–250.
- Zaho Z, Bi Y, Xia Y, et al. Elevated expression of CYP4F3 associated with occupational benzene-induced hepatotoxicity and induction of CYP4F3 by benzene metabolites in HL60 cells. *FASEB J.* 2008;22(3):921–924.
- Kim YM, Harrad S, Harrison RM. Levels and sources of personal inhalation exposure to volatile organic compounds. *Environ Sci Technol.* 2002;36(24):5405–5410.

International Medical Case Reports Journal

Publish your work in this journal

The International Medical Case Reports Journal is an international, peer-reviewed open-access journal publishing original case reports from all medical specialties. Previously unpublished medical posters are also accepted relating to any area of clinical or preclinical science. Submissions should not normally exceed 2,000 words or

Submit your manuscript here: <https://www.dovepress.com/international-medical-case-reports-journal-journal>

4 published pages including figures, diagrams and references. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.