Alcohol and Alcoholism, 2019, 1–5
doi: 10.1093/alcalc/agz004
Article

Article

Pellagra and Alcohol Dependence Syndrome: Findings From a Tertiary Care Addiction Treatment Centre in India

Venkata Lakshmi Narasimha[1], Suhas Ganesh[2], Sarath Reddy[1], Lekhansh Shukla[3], Diptadhi Mukherjee[1], Arun Kandasamy[1,*], Prabhat K. Chand[1], Vivek Benegal[1], and Pratima Murthy[1]

[1]Centre for Addiction Medicine, Department of Psychiatry National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bengaluru 560029, India, [2]Schizophrenia Neuropharmacology Research Group at Yale (SNRGY), Department of Psychiatry, Yale University, New Haven, CT, USA, and [3]Department of Psychiatry, AIIMS Bhopal, India

*Corresponding author: Centre for Addiction Medicine, Department of Psychiatry National Institute of Mental Health and Neurosciences (NIMHANS), Hosur road, Bengaluru 560029, India. Tel.: +91-9008977699; E-mail: arunnimhans05@gmail.com

Received 24 September 2018; Revised 12 December 2018; Editorial Decision 8 January 2019; Accepted 9 January 2019

Abstract

Aim: To define the prevalence and clinical presentation of pellagra, a multi-systemic disease caused by the deficiency of niacin, in patients admitted to a tertiary addiction treatment centre in southern India, with alcohol dependence syndrome (ADS)—(ICD10).

Methods: Review of the health records of 2947 patients who received inpatient care for ADS between 2015 and 2017.

Results: Out of 2947, 31 (1%) were diagnosed with pellagra. Nearly two-thirds (64.5%) of those with pellagra were from a low-income group. Of the clinical-triad of pellagra, all patients had dermatitis, more than half (58%) had delirium, a minority (19%) had diarrhoea. Nearly two-thirds (61%) had presented in a complicated-withdrawal state. Associated conditions included peripheral neuropathy (32%); Wernicke's encephalopathy (26%); seizures (16%).

Seventeen (54%) had BMI $<18.5\,kg/m^2$. Treatment was a high dose of parenteral vitamins including niacin (mean dose: 1500 mg/day) for an average of 7.5 days followed by oral multivitamin supplements. All had complete resolution of pellagrous symptoms by the end of the three weeks of inpatient care.

Conclusions: Pellagra is an acute medical condition, frequently encountered in the context of alcohol dependence and poverty. It often presents with other disabling and life-threatening comorbidities like delirium tremens and Wernicke's encephalopathy. The classical triad of pellagra is only seen in a minority of cases. Thus a high index of suspicion is required lest pellagra may remain undiagnosed. Prompt identification and treatment with a high dose of niacin in combination with other vitamins result in complete recovery.

INTRODUCTION

Pellagra is a disease caused by the deficiency of niacin and/or its precursor tryptophan and is compounded by other vitamin-B deficiencies. Painstaking documentation of symptoms in eighteenth-century European asylums, where patients were available for frequent assessment christened pellagra as 'disease with four D's'—sun-sensitive Dermatitis, Diarrhoea, Dementia, and ominously Death (Bryan and Mull, 2015). However, these classic symptoms rarely occur

together or follow a predictable pattern. Moreover, they are modified by environmental factors like climate (sun-exposure), the presence of other vitamin deficiencies and stage of illness (Kirkland, 2013). Alleviation of extreme poverty and food fortification has decreased the prevalence of pellagra in developed countries; modern clinicians rarely see this disease during their training. It is likely that except in the most dramatic cases, pellagra is frequently underdiagnosed (Brown, 2010; Bryan and Mull, 2015).

Excessive alcohol consumption is a known risk factor for pellagra. Badawy (2014) reviewed the mechanisms by which excessive alcohol use can lead to absolute niacin deficiency. Pellagrous encephalopathy can also occur in combination with Wernicke's encephalopathy (López *et al.*, 2014). It may be difficult to diagnose pellagra in an alcohol dependent patient who presents with inanition, confusion, agitation, diarrhoea as all these symptoms are also seen in alcohol withdrawal states complicated with Wernicke's encephalopathy. Also, there are no gold-standard biochemical tests to diagnose niacin deficiency. 'Niacin-number' is a sensitive and specific test but it requires a multi-step process which is not standardized for routine clinical use (Shah *et al.*, 2005; Kirkland, 2013).

The objectives of this report are to summarize the common clinical presentations of pellagra in persons with alcohol dependence, associated comorbidities and clinical management as seen in our centre where a high index of suspicion is maintained for the presence of pellagrous skin lesions during the evaluation of persons seeking treatment for alcohol dependence.

METHODS

We carried out a review of the electronic health record database of patients admitted to a tertiary care addiction treatment centre in south India, during the years 2015–2017. The data were collected by two investigators who reviewed each case-record independently. Patients who received inpatient care, diagnosed with alcohol dependence syndrome (ADS) as per the 10th edition of the International Classification of Diseases (ICD10) (WHO, 1992) along with pellagra during the specified period, were included in the study. A clinical diagnosis of pellagra was reached if there was a classical skin lesion suggestive of pellagra with typical distribution and zone of demarcation, along with a preceding history suggestive of poor dietary intake and rapid improvement with niacin supplementation (Hegyi *et al.*, 2004). All these cases have been seen by at least one of the authors and in most cases by two authors of this report, before being diagnosed with pellagra. Sociodemographic data, clinical measures of alcohol use pattern, clinical presentation and treatment details were collected from the case records. A body mass index (BMI) <18.5 kg/m^2 is defined as undernutrition and haemoglobin concentration less than 12.5 gm/dL is defined as anaemia. Figure 1 describes the process of patient identification from the clinical records.

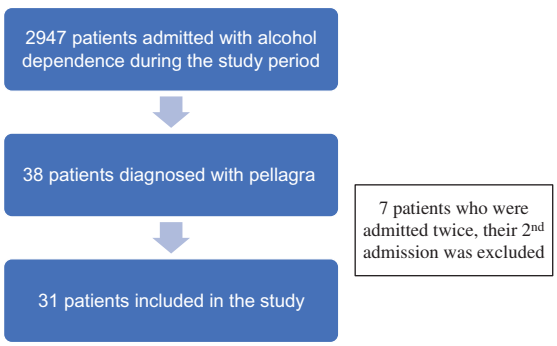

Fig. 1. Flow diagram of patient identification.

RESULTS

Sociodemographic details

A total of 2947 patients were admitted to the addiction treatment centre during the study period (2015–2017) for treatment of ADS (ICD10, F10.2). Among them, 31 (1% of total admissions) were diagnosed as having pellagra. Twenty-one (68%) were from an urban background, 20 (65%) were from a low-income group [defined as an annual income of <15,000 INR]. Only 4 (13%) had 10 or more years of formal education. Mean age at admission was 41.5 years (SD = 8.4 years).

Clinical measures

Mean duration of regular alcohol use in the pellagra group was 20.6 years (SD = 9.2 years). Average daily intake of alcohol was 20 units/day (SD = 8 units) where one unit is approximately equal to 13 g of pure ethanol. Height measurements of six subjects were missing in the records; for the remaining group ($N = 25$) mean BMI was 18.3 kg/m^2 (SD = 2.1 kg). Seventeen patients (54%) had BMI <18.5 kg/m^2, and 14 had haemoglobin <12.5 g/dL. Twenty patients (61%) had complicated withdrawal which included delirium tremens, withdrawal seizures or alcoholic hallucinosis. Mean duration of delirium was 6.2 days.

Due to the inclusion criteria all patients had characteristic dermatitis (100%), 18 (58%) had delirium and 6 (19.5%) had diarrhoea. Only 3 (10%) cases had all three symptoms of the triad; 21 (68%) had at least 2 symptoms; while, 7 (22.5%) had only a single symptom, i.e. dermatitis. While 548 (18.5%) of the 2916 non-pellagra patients had delirium, the prevalence of delirium in patients with a diagnosis of pellagra was significantly higher ($p1 = 0.185$, $n1 = 2916$, $p2 = 0.58$, $n2 = 31$, $P = 0.192$, $z = -5.6$, $P < 0.0001$).

Among the comorbidities, 8 (25.8%) of patients had Wernicke's encephalopathy, and 10 (32.3%) had peripheral neuropathy. The prevalence of Wernicke's encephalopathy in patients with pellagra was significantly higher compared to the prevalence of this condition in the total number of admissions ($p_1 = 0.033$, $n_1 = 2916$, $p_2 = 0.258$, $n_2 = 31$, $P = 0.04$, $z = -6.7$, $P < 0.001$).

Management

All the patients received detoxification with benzodiazepines and a regimen of multivitamin infusions. This regime provides 1500 mg of thiamine, 1500 mg of nicotinamide, 75 mg of riboflavin, 1500 mg of pyridoxine, 750 mg of pantothenol and 15 mg of cyanocobalamin given in three divided doses in a day, given as an intravenous infusion each diluted in 100 mL normal saline over 45 min. Patients in simple withdrawal received multivitamin infusions for an average of 5 days as compared to those in complicated withdrawal who received multivitamin infusions for 7 days. Following this, all patients received multivitamin tablets to ensure at least 300 mg of nicotinamide is supplemented every day. All the patients recovered completely by the end of 3 weeks of admission. None of the patients developed allergies or adverse reactions to parenteral multivitamins. Figure 2 shows resolution of dermatitis with treatment in one of the patients with pellagra.

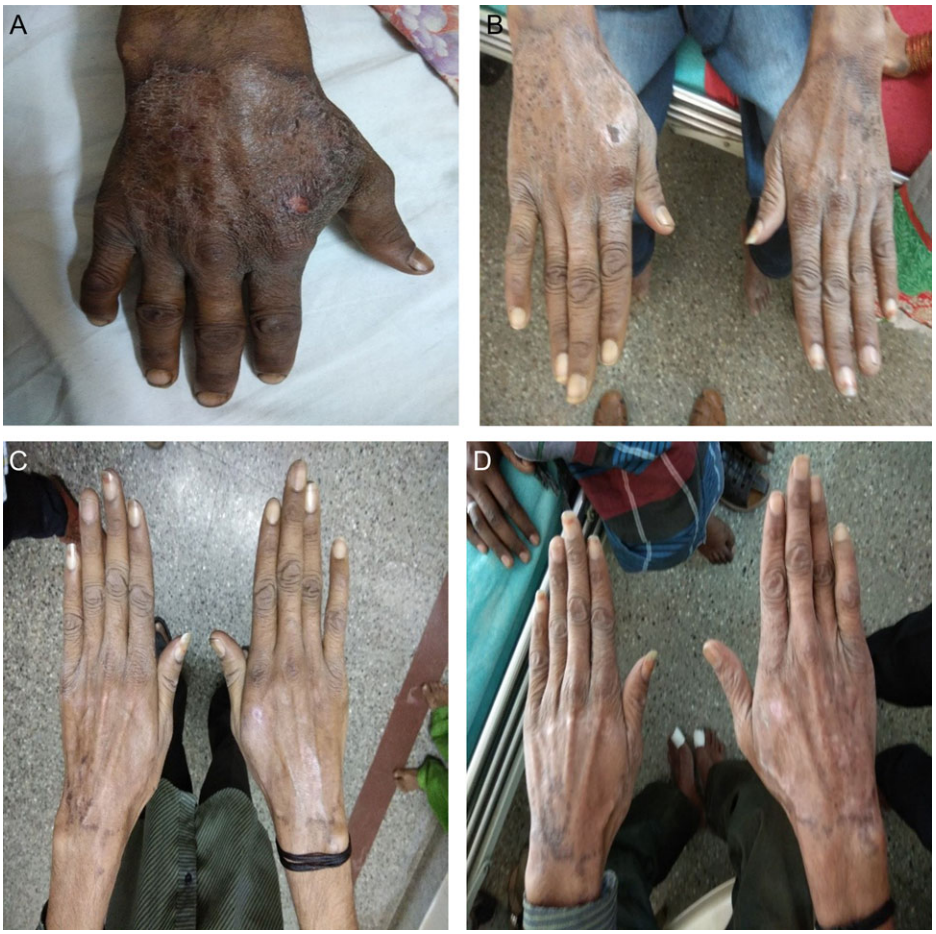

Fig. 2. Images clinical presentation of pellagrous dermatitis in a patient and course of resolution with multivitamin supplementation. Images A, B, C and D corresponds to the lesions on the Days 2, 8, 13 and 20 of the treatment. Note the rapid resolution of pigmentation.

DISCUSSION

Our study shows that clinically diagnosed pellagra (based on skin lesions and response to niacin) is present in at least 1% of ADS inpatients attending an Indian alcohol treatment centre and frequently coexists with other severe neuropsychiatric syndromes like delirium tremens, seizures and peripheral neuropathy. The findings of our study have important implications for the evaluation and treatment of patients with alcohol dependence.

Between the years 1980 and 2000, outbreaks of pellagra have been reported in food-aid dependent populations in the context of emergencies and refugee programs (WHO, 2000) in Zimbabwe, Mozambique, Malawi, Nepal and Angola (Matapandeu *et al.*, 2017). The mean age of presentation in the Malawi refugee data is 31 years which is 10 years younger than the mean age at presentation noted in the ADS sample in our study. The population prevalence of pellagra in India is not known. Nevertheless, similar to developed countries cases of pellagra are supposed to be rare enough to merit publication as case reports (Gupta *et al.*, 2014).

It is important to consider the catchment area of our centre to understand the generalizability of these findings. Our centre is located in a metropolitan city in India and caters to a mixed urban and rural population of a southern Indian state. The staple diet of the population in this state is rice and wheat. Among the alternate cereals, finger millet (*Eleusine coracana)* is commonly used while maize is rarely used for subsistence. Interestingly, finger-millet is particularly rich in bioavailable niacin and tryptophan unlike other alternate cereals (Kumar *et al.*, 2016). However, ours is a referral centre for complicated substance use disorders and has the provision of highly subsidized treatment for lower-income patients. Thus, it is possible that the prevalence of pellagra in other treatment settings may be much lower. On the other hand, multiple reports show that ADS is now an important risk factor for pellagra since extreme undernutrition is largely alleviated elsewhere (López *et al.*, 2014). Ishii and Nishihara conducted a neuropathological study and reported that signs of pellagra in ADS patients are frequently missed ante-mortem (Ishii and Nishihara, 1981). This underdiagnosis could be due to various reasons. Firstly, the physicians may be unfamiliar with the characteristic pellagrous skin lesion as the population prevalence of pellagra is low. Secondly, it is difficult to delineate signs of pellagra from complicated alcohol withdrawal, Wernicke's encephalopathy and general inanition. Thirdly, pellagra can be present in patients who otherwise do not have signs of undernutrition. For example, in our study, only half of the patients had low BMI or anaemia. Lastly, a physician looking for the classical triad of signs may miss the diagnosis as seen in our report where only 10% of cases had all the three signs.

Manifestations of inadequate niacin intake are modified by multiple factors. First, the human body can synthesize niacin from tryptophan, but this process is inefficient and depends on other B complex vitamins. Second, at least the cutaneous manifestations depend on exposure to sunlight. Thus the skin lesions may become apparent only in summer or spring (Wan *et al.*, 2011).

We found that alcohol-dependent patients with pellagra were more likely also to have delirium or/and Wernicke's encephalopathy as compared to those without pellagra. This is a preliminary finding and may be explained by confounding variables like the amount of alcohol consumed or overall undernutrition. However, it also indicates that the presence of one vitamin deficiency syndrome should alert the clinician to look for other known syndromes. It is all the more important as replacement of other vitamins without replacing niacin can worsen the course of pellagrous encephalopathy (López *et al.*, 2014). The combination of Wernicke's encephalopathy and pellagra can be a diagnostic challenge. Consider this: a patient with pellagrous skin lesions also develops global confusion, there may be no definitive way of telling if it is a manifestation of Wernicke's encephalopathy or pellagrous encephalopathy. In our experience, we did not observe myoclonus which is supposedly specific for pellagrous encephalopathy. It is possible that benzodiazepines used for alcohol withdrawal suppress myoclonus.

In our centre, ADS patients receive a combination of B-complex vitamins including thiamine, nicotinamide, vitamin B_{12}, folic acid, pyridoxine, riboflavin and pantothenate. We replaced niacin and thiamine each at doses of 1500 mg/day for a period of 5–7 days followed by oral replacement which resulted in complete resolution of symptoms within 3 weeks. While most treatment guidelines recommend prophylactic treatment with thiamine in complicated alcohol withdrawal, similar recommendations are not made for niacin replacement (NICE, 2010) Usually recommended treatment of pellagra includes nicotinamide 100 mg orally every sixth hourly or thrice daily for 3–4 weeks or till resolution of symptoms. However, patients undergoing severe alcohol withdrawal may not be amenable for oral medication, and intravenous infusion of 1 gm thrice daily is recommended (Hegyi *et al.*, 2004).

Our study has multiple limitations; we have already discussed the concerns regarding generalizability. Another important limitation is that we have used photosensitive dermatitis to ascertain caseness. As a result, we may have missed some cases as dermatitis is not a *sine qua non* of pellagra (Ishii and Nishihara, 1981). Also, a detailed dietary history could have revealed why some patients with seemingly good nourishment developed pellagra. Nevertheless, we show a substantial prevalence of pellagra in alcohol-dependent patients and thus urge health-care providers who work in this field to refresh their knowledge about this condition. Treatment of alcohol-dependent patients who are undergoing a complicated withdrawal or have undernourishment should thus include a combination of B-complex vitamins, to avoid worsening of the deficiency of other vitamins and related conditions.

SUMMARY

- Pellagra is a known complication in patients with chronic severe alcohol use from low socio-economic status.
- All the three components of the classical triad may not be evident in all patients.
- Pellagra may present with a complicated withdrawal state more often than a simple withdrawal state.
- Most of the patients have significant medical comorbidities in the form of Wernicke's encephalopathy, peripheral neuropathy and seizures.
- Treatment should be a combination of B-complex in high doses through an intravenous route in severe cases.
- Prevention of pellagra, focusing on nutritional aspects should become part of the routine intervention in persons with chronic alcohol use.

ACKNOWLEDGEMENTS

Centre for Addiction Medicine, Department of Psychiatry, NIMHANS.

CONFLICT OF INTEREST STATEMENT

None declared.

DISCLOSURE

No conflict of interest.

REFERENCES

Badawy AAB. (2014) Pellagra and alcoholism: a biochemical perspective. *Alcohol Alcohol* **49**:238–50.

Brown TM. (2010) Pellagra: an old enemy of timeless importance. *Psychosomatics* **51**:93–7.

Bryan CS, Mull SR. (2015) Pellagra Pre-Goldberger: Rupert Blue, Fleming Sandwith, and The 'Vitamine Hypothesis'. *Trans Am Clin Climatol Assoc* **126**:20–45.

Gupta SK, Arora AK, Sood N, *et al.* (2014) Pellagra revisited. *Indian Dermatol Online J* **5**:525–6.

Hegyi J, Schwartz RA, Hegyi V. (2004) Pellagra: dermatitis, dementia, and diarrhea. *Int J Dermatol* **43**:1–5.

Ishii N, Nishihara Y. (1981) Pellagra among chronic alcoholics: clinical and pathological study of 20 necropsy cases. *J Neurol Neurosurg Psychiatry* **44**:209–15.

Kirkland JB. (2013) Niacin. In Janos Zempleni JWS, Gregory JF, Stover PJ (eds). *Handbook of Vitamins*, 5th edn. vol. 1. Boca Raton: CRC Press, 149–90.

Kumar A, Metwal M, Kaur S, *et al.* (2016) Nutraceutical value of finger millet [Eleusine coracana (L.) Gaertn.], and their improvement using omics approaches. *Front Plant Sci* **7**:934.

López M, Olivares JM, Berrios GE. (2014) Pellagra encephalopathy in the context of alcoholism: review and case report. *Alcohol Alcohol* **49**:38–41.

Matapandeu G, Dunn SH, Pagels P. (2017) An outbreak of Pellagra in the Kasese Catchment Area, Dowa, Malawi. *Am J Trop Med Hyg* **96**:1244–7.

NICE. 2010. *Alcohol-Use Disorders: Diagnosis and Management of Physical Complications*. National Institute for Health and Care Excellence, London, UK. https://www.nice.org.uk/guidance/cg100/chapter/Recommendations#wernickes-encephalopathy.

Shah GM, Shah RG, Veillette H, *et al.* (2005) Biochemical assessment of niacin deficiency among carcinoid cancer patients. *Am J Gastroenterol* **100**:2307–14.

Wan P, Moat S, Anstey A. (2011) Pellagra: a review with emphasis on photosensitivity. *Br J Dermatol* **164**:1188–1200.

WHO. (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.

WHO. (2000) *Pellagra and its Prevention and Control in Major Emergencies*. Geneva: World Health Organisation, https://www.who.int/nutrition/publications/en/pellagra_prevention_control.pdf.