Pellagra Encephalopathy in the Context of Alcoholism: Review and Case Report

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Abstract — Aims: The aim of the study was to review and describe the Alcoholic Pellagra Encephalopathy, a severe neuropsychiatric condition caused by a combination of niacin (vitamin B3) deficiency and alcohol abuse. Methods: PsychInfo, Medline and Embase databases were searched for peer-reviewed studies addressing this illness. Results: A historical and conceptual review of the psychopathological aspects of this condition is offered, followed by the report of a patient with a history of chronic alcohol consumption showing signs of pellagra, delusions and visual hallucinations, which was treated successfully with niacin. Conclusion: Pellagra encephalopathy should still be considered in the differential diagnosis of acute psychotic disorders seen in the context of chronic alcoholism.

INTRODUCTION

The clinical syndrome named ‘Pellagra’ by Frapolli (1771) was first described in 1735 by Gaspar Casal (1680–1759) but only published in a posthumous work (1762). Known as ‘mal de la rosa’ (since a large synonymy has accrued), the condition was characterized by a typical reddish and glossy rash on the dorsum of hands and feet and around the neck (sign since called ‘Casal’s necklace’). Casal also drew attention to the digestive complaints and to the seasonal changes in mood and behaviour exhibited by those affected (more on this later). The history of the pellagra syndrome illustrates well how the description and explanation of a medical disorder can be deeply affected by their socio-political context (Roe, 1973; Etheridge, 1993).

Considered now as a vitamin deficiency state, pellagra has been linked to a chronic lack of niacin (vitamin B3 or nicotinic acid), an important constituent of coenzyme I and coenzyme II. Its clinical map is believed to include the classic 3 Ds: Dermatitis, Dementia and Diarrhoea (Hegyi et al., 2004). The order of appearance and severity of these three sub-syndromes varies and some may not show at all. From a relic of the nineteenth century, the concept of ‘Dementia’ associated with pellagra includes a gamut of complaints ranging from organic confusion and related cognitive dysfunctions to affective disorder, psychotic symptoms (such as delusions, hallucinations and paranoid responses) and general behavioural disorganization (Berrios, 1987). To contextualize the clinical report included below, the construction of pellagra, its psychiatric sub-syndrome and the role of alcohol in its development ought to be discussed separately.

THE CONSTRUCTION OF PELLAGRA

In the large (and polyglottal) historical literature on Pellagra, three periods are thrown into relief: the earlier eighteenth century reports; the acme of interest during the following century—when its clinical profile, psychiatric aspects and aetiology were discussed in detail, and the twentieth century workable vitamin deficiency accounts and successful therapies leading to the disappearance of its endemic presentation. From then on, the clinical literature has dealt with sporadic cases.

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THE PSYCHIATRIC COMPLICATIONS OF PELLAGRA

In 1735 Casal (1762) noticed: ‘Est & alia metastasis, seu transitus morbi hujus fatis frequent, nec minus miserandus, qui non indiscriminatim quolibet tempore accidit, sed aestivali praefertim, dum solis calor majorem efficaciam habet, tunc enim multi eorum, qui morbo de la rosa penitùs contaminati sunt, in maniam, suo potius melancholiam degenerant: atque ea mutatione, misserrimi ægri, non tàm furoris, quàm angoris insuperabilis vi coacti, in varias nugarum species, seu ideas insuperabilis vi coacti, in varias nugarum species, seu ideas

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semel accedit) transire folent...' (p. 338) (‘There is also another frequent change in the disease, not less wretched, which does not occur in any Season but in Summer, when the sun is at its strongest. Then many cases of ‘mal de la rosa’ will become complicated by mania, which may become melancholia. Affected less by anger than by insupportable anguish, patients experience all kinds of fears and ideas, and abandoning their homes they wonder off in solitary fields and thickets and as occasionally happens, die of desperation...' (authors’ translation).

In order to understand Casal’s description (transcribed in its original Latin, for as far as the authors know, it has not been included in its entirety in an English publication before), it must be remembered that in the eighteenth century the terms mania and melancholia meant ‘furious madness’ and ‘monodelusional madness’, respectively, and have little to do with the disorders currently travelling under such names (Berrios, 1988a,b).

Ever since, writers have paid attention to the psychiatric complications of Pellagra. Early in the nineteenth century, descriptions were rather rudimentary but as psychopathology developed later in the century, a number of remarkable monographs appeared carrying detailed clinical descriptions (Briere de Boismont, 1834; Billod, 1860, 1865; Landouzy, 1860; Bouchard, 1862; Roussel, 1866; Typaldos, 1866; Tuczek, 1888). After the 1850s, and in view of the high prevalence of pellagra in mental asylums, alienists also became interested in finding out whether diet remained the main factor or whether the mentally ill had a propensity to developing the condition.

**LLOPIS’ 1946 MONOGRAPH**

On account of its psychopathological finesse and the poignancy of the historical moment in which it was written, the monograph by Llopis (1946) is worth mentioning amongst publications on the psychiatry of Pellagra up to the division of the twentieth century. Llopis was the head of the Psychiatric Services for the Spanish Republic during the Civil War (1936–1939) and hence a direct witness of its unfolding tragedy (Colodrón, 1991). The result of the severe starvation to which Republicans civilians were exposed, Llopis’s sample of 83 cases (75 females, 8 males) had a social and demographic structure different from the conventional endemic type (associated with exclusive maize consumption) repeatedly studied before. The masterly clinical descriptions included in the text (indeed, based on them, Llopis developed a new model for the organic psychosis) are good enough for retrospective statistical analysis. Llopis proposed that the sample could be divided into four psychiatric sub-syndromes: neuroslothia, pseudodementia, confusional-psychosis and chronic confusional stupor.

For reasons of space this paper will only be able to report the results of an exploratory principal component analysis of the 75 female cases (SPSS, Version 17) (to avoid a gender-related confounder, the small number of males was excluded from the analysis). Three factors were identified: ‘Stuporous-Confusional’ (Variance 23%), ‘Hallucinatory-confusional’ (17%) and ‘Psychotic’ (13%) (for variable loadings, see Table 1). Alcoholism was not a significant variable in the sample.

**Table 1. Results and factors identified in Llopis’s analysis (75 female patients)**

<table>
<thead>
<tr>
<th>Factor 1 ‘Stupor-confusion’ (after rotation) variance 23%</th>
<th>Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotionalism</td>
<td>0.644</td>
</tr>
<tr>
<td>Depression</td>
<td>0.710</td>
</tr>
<tr>
<td>Confusion</td>
<td>0.600</td>
</tr>
<tr>
<td>Delusions</td>
<td>0.800</td>
</tr>
<tr>
<td>Stupor</td>
<td>0.724</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor 2 ‘Hallucinatory-confused’ (after rotation) variance 17%</th>
<th>Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0.680</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0.702</td>
</tr>
<tr>
<td>Confusion</td>
<td>0.563</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor 3 ‘Psychotic’ (after rotation) Variance 13%</th>
<th>Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoia</td>
<td>0.851</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0.428</td>
</tr>
<tr>
<td>Strangeness</td>
<td>0.552</td>
</tr>
</tbody>
</table>

**PELLAGRA AND ALCOHOL**

Given that the case reported in this paper concerns a patient with chronic alcoholism, it is important that the history of the association between pellagra psychosis and alcohol abuse is sketched in some detail. Without documentary support it has been claimed by Cook et al. (1998) that ‘Alcoholic pellagra encephalopathy’ was first recognized in 1869 (p. 323).

The relationship between alcohol and pellagra was discussed during the nineteenth century only in two contexts: (a) the role that its absence might play in the aetiology of pellagra. Indeed, as a result of these debates it was claimed that drinking some wine might be therapeutic (Holland, 1817) (p. 345); (Briere de Boismont, 1834) (pp. 85–86) and (b) differential diagnosis. In this regard, the term ‘pseudo-pellagra’ was coined to name cases of chronic alcoholism that exhibited features redolent of pellagra (Roussel, 1866) (pp. 125–135). The earliest evidence these authors have found of a debate on the role of alcohol in the actual production of pellagra is from the early twentieth century when Carrière (1907) discussed the distinct possibility that alcohol might contribute to the development of the disease (see p. 38).

It is likely that alcoholic pellagra encephalopathy is currently underdiagnosed (Serdaru et al., 1888). Its rapid onset is characterized by stupor or delirium, cogwheel rigidity and sucking reflexes and grip. Glossitis, estomatitis and gastrointestinal symptoms (diarrhoea, constipation or vomiting) can be associated. There can be oppositional hypertonia, myoclonus and ataxia, catatonic symptoms, echopraxia and waxy flexibility; and irritability, poor concentration, anxiety, apathy, psychomotor restlessness, fatigue and depression. A full-blown psychosis rarely occurs but in advanced cases delusions and alterations of sensation and perception have been reported (Greenberg et al., 2001; Sakai et al., 2006). The concomitant presence of the neurological signs of alcoholic encephalopathy may blur the differential diagnosis (WHO, 2000).

**CASE REPORT**

Male, aged 48, brought to the Meixoeiro Hospital Emergency Room (Spain) by his family who reported that the previous week he had become delusional and started walking naked on the road, always facing the sun. The patient justified his behaviour by saying that he had been ordered by Christ, his cousin,
to ‘move the moon’. His case notes stated that he had abused alcohol heavily since adolescence. His average consumption was of about 96 g of ethanol/day. In 2006 he had been hospitalized on account of alcoholic liver and hypochromic macrocytic anaemia. There was no previous history of psychiatric illness.

On examination he was untidy in appearance, conscious, orientated and uncooperative. Immediate, recent and remote memory and concentration were impaired. He showed dysphoric and expansive affect. Speech was appropriate. No alterations of formal thought were found. He showed restlessness but not marked psychomotor agitation. He exhibited fantastic, mystic and megalomaniac delusions and visual hallucinations and insightlessness. His behaviour was chaotic and he paced up and down. On a few occasions, he assaulted staff when prevented from leaving the ward. There was terminal insomnia. Physical examination revealed erythematous-scaly skin injuries in sun-exposed areas. He showed a dystonic posture.

Blood count, liver function tests and kidney, ions, glucose, ammonium, study of anaemia, folate, vitamin B12, CPK, thyroid function tests, coagulation, Treponema pallidum serology, Hepatitis B and C, HIV ELISA, non-contrast head CT and chest radiography were performed. Relevant findings were: haemoglobin 11.1 g/dl, MCV (mean corpuscular volume) 111.4 fl, transferrin saturation 12%, transferrin 173 mg/dl, iron 28 μg/dl and folate 4.1 ng/ml. GOT 72 IU/l, GPT 17 IU/l, GGT 125 IU/l. No other alterations, including CT and RX, were found.

A provisional diagnosis of ‘psychotic disorder induced by alcohol’ DSM-IV-TR was made (American Psychiatric Association, 2000). He was prescribed chlorothiazide 1152 mg/day (Majumdar, 1991), Olanzapine 10 mg/day, folic acid 15 mg/day and vitamin complex B1, B6, B12.

Upon admission he had been drowsy but after 48 h he became confused, more dystonic and delusional. There were no signs of alcohol withdrawal. Vital constants were in range, except slight hypotension on account of which Olanzapine was reduced to 5 mg/day. Four days later, the fluctuating confusional state was still present. The skin lesions were treated with emollients as they were thought to be sunburns. The skin had rough and rugged, lichenified, pigmented and cracked. Given the poor outcome and the nature of the skin lesions, Pellagra was suspected. Niacin was added to treatment (150 mg/day). Twenty-four hours later, the alteration of consciousness began to improve and the hypertonia disappeared. In seven days all psychiatric symptoms, including delusions, and the skin lesions disappeared.

**DISCUSSION**

Niacin deficiency has been associated with schizophreniform and manic-depressive symptoms and with anxiety. In this case the patient presented fantastic, mystic and megalomaniac delusions and visual hallucinations. Alcoholic pellagra encephalopathy may cause neurological symptoms and confusion, decreased consciousness, oppositional hypertonia and myoclonus. After 48 h of drowsiness the patient developed confusion interspersed with fluctuating delusional occupational episodes. Skin lesions were also a key diagnostic feature. Ab

initio misinterpreted as sunburns (because of the patient continued exposure to the August sun) they were re-evaluated and the presence of a ‘Casal necklace’ and the fact that they showed ‘redness, roughness, crust and erysipelas’ led to the diagnosis of pellagra.

It is likely that the vitamin deficiency was secondary to chronic malnutrition related to alcohol abuse. This makes difficult the differential diagnosis with other neuropsychiatric syndromes associated with alcohol abuse such as Alcoholic Hallucinosis and Delirium Tremens.

Common vitamin replacement (usually B1, B6 and B12) therapy may aggravate or precipitate alcoholic pellagra encephalopathy, as it happened in the case reported here. Both his confusion and dystonia were exacerbated by vitamin B1, B6 and B12. He improved only after the addition of nicotinic acid treatment. The whole B complex seems necessary in these cases, as in addition to treating the pellagra the development of a Wernicke encephalopathy can be prevented.

The treatment of pellagra consists in the administration of 100–300 mg daily of niacinamide in three doses. In uncooperative patients, it can be administered subcutaneously. The use of adjunctive therapy of B-complex vitamin preparations and a diet rich in protein is recommended (Lampton and Goldberger, 2005).

The exact relationship between niacin deficiency and the pathogenesis of psychotic symptoms is unclear. It has been speculated that it is due to a neuronal insult: a direct cytotoxic damage or secondary axonal change (Serdaru et al., 1988). Post-mortem examination has revealed chromatolysis notably in the pons (Ishii and Nishihara, 1981). Indirect evidence has also suggested that niacin antagonism is associated with glial degeneration thereby interfering with signal transmission across neurons (Penkowa et al., 2002). Another study has showed that in schizophrenia there was a reduced sensitivity to the vasodilator effecting of Niacin. Since this effect depends upon the release of prostaglandins, this study suggested that schizophrenia may be associated with abnormalities in enzymes, receptors or signal transduction mechanisms affecting the synthesis, release or response to vasodilating prostaglandins (Messamore et al., 2003). A recent study has also suggested that the non-invasive Niacin skin-flush test can be used to show impaired arachidonic acid-related signal transduction in schizophrenia, suggesting that this test could be useful in the diagnosis of schizophrenia (Puri et al., 2001). It has also been claimed that nicotinic acid could improve schizophrenia by reducing CNS transmethylation (Himwich, 1971, pp. 198–226). Some studies have used niacin as an augmenting agent for the treatment of schizophrenia but with mixed results (Petrie et al., 1981).

In the case under consideration there was an improvement, not only of the neurological and dermatological injuries, but also of the psychotic symptoms. However, the patient was also taking Olanzapine 5 mg/day so the contribution of niacin treatment in this respect cannot be fully ascertained. Be that as it may, Pellagra should be considered in the differential diagnosis of patients with psychosis and chronic and excessive consumption of alcohol.

**Conflict of interest statement.** None declared.