Pellagra among chronic alcoholics: clinical and pathological study of 20 necropsy cases

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SUMMARY Twenty cases of pellagra, diagnosed on neuropathological grounds, were found among 74 necropsy cases of chronic alcoholism. Although these patients had presented with various mental, neurological and gastrointestinal symptoms, the diagnosis of pellagra had not been established clinically because, in the majority, there were no skin lesions. It is emphasised that whenever chronic alcoholics exhibit certain mental, neurological or gastrointestinal symptoms, one should strongly suspect pellagra even in the absence of skin lesions (pellagra sine pelle agra).

Pellagra is a disease caused primarily by niacin deficiency. It is characterised by the classical triad of dermatitis, diarrhoea and dementia. If untreated, patients eventually die. Some people therefore add "death" to the triad, thus making "4 D's". Nowadays, the disease has virtually disappeared in developed countries, except in association with chronic alcoholism. The conspicuous association between severe alcoholism and pellagra has been commented upon clinically by many previous workers.1-4

We found 20 cases showing neuropathological features of pellagra among 74 chronic alcoholics who came to necropsy. The pellagra had not been suspected clinically, because of the absence of characteristic skin manifestations. The aim of this paper is to show the clinical and pathological findings of these cases of niacin-deficiency encephalopathy and to call attention to "pellagra sine pelle agra" among chronic alcoholics.

Cases and methods

Between 1965 to 1979, 758 chronic alcoholics were admitted to our hospital. Of these, 81 died and 74 underwent complete postmortem examination. All organs including the brain were kept in 10% formalin for two weeks and sections were taken from each organ. Recently 14 to 20 additional sections were prepared from the brain in each case and stained with haematoxylin and eosin, Nissl, periodic-acid-Schiff, luxol fast blue and Bodian stains. Sections examined were frontal lobe (areas 4, 6, 8, 11, 12, 24), parietal lobe (areas 1–3, 7), temporal lobe (areas 20, 21, 38), occipital lobe (areas 17, 18), insula, Ammon's horn, hippocampal gyrus, amygdala, caudate, putamen, thalamus, hypothalamus, midbrain, upper and lower medulla, cerebellum (vermis, hemisphere, dentate nucleus) and upper cervical cord. In two cases the brain was postfixed with 2% osmium tetroxide, dehydrated and embedded in Epon 812 and examined with an electron microscope. Clinical data were obtained from the charts. A representative case is described below.

A 39 year-old man (case 12) was admitted because of mental confusion. He was a severe alcoholic and had been admitted eight times during the previous 10 years. Ten days prior to admission, he was found to be speaking incoherently. He had lost his appetite, and become unable to take even alcoholic beverages. He was emaciated, confused, disoriented and agitated on account of hallucinations. He mumbled unintelligible words and did not answer questions. He was tremulous and markedly ataxic. After admission his delirium tremens persisted, and the level of consciousness fluctuated. Profuse sweating, insomnia, visual and auditory hallucinations persisted until his death. On the 14th hospital day he developed severe diarrhoea. This could not be controlled despite the administration of vitamin B₁, B₆, B₁₂, C, various antibiotics and anti diarrhoeal agents. He developed a spastic paraparesis and was confined to bed with incontinence of
both urine and faeces. He expired of bronchopneumonia six weeks after admission.

Necropsy revealed bilateral aspiration bronchopneumonia and severe decubitus ulcers. There were no other significant findings in the viscera and no liver diseases. The brain weighed 1280 grams. Grossly the cerebrum showed no abnormalities. The superior vermis was atrophic with narrow cerebellar folia and widened sulci. Histologically, the most significant finding was central chromatolysis of neurons occurring in wide areas. The Betz cells and other relatively large pyramidal cells of the cortex, as well as the neurons of the pontine nuclei, dorsal vagal nuclei, gracile and cuneate nuclei, vestibular nuclei and anterior horn cells of the spinal cord showed severe chromatolytic changes (figs 1 and 2). A section of the atrophic cerebellar vermis revealed complete disappearance of Purkinje cells with Bergmann's astrogliosis and depopulation of the granular cell layer.

The clinical and pathological findings of the 20 cases are summarised in the table.

### Fig 1
Central chromatolysis in neurons of pontine nuclei. Nissl ×200, case 12.

### Fig 2
Central chromatolysis in Betz cells (a) and anterior horn cells (b). Nissl ×200, case 12.

**Summary of the clinical findings** All the patients were male alcoholics. Their age ranged from 38 to 89 years with a mean of 52 years. The average drinking history extended over 19 years. The mean duration of the terminal illness was 13.5 weeks. In 19 of the 20 cases, the clinical diagnosis on admission had been delirium tremens. Neuropsychiatric symptoms observed were confusion (20/20), hallucination (18/19), insomnia (16/17), tremor (14/17), gait disturbance (19/20), extrapyramidal rigidity of the limbs (16/17), incontinence of urine and faeces (19/20), polyneuropathy (7/16) and seizures (3/20). Anxiety, depression, excitement and neurasthenia were also observed in from one-third to one-half of the cases. Deep tendon reflex was increased bilaterally in the majority of cases, except for those patients who also had peripheral neuropathy. The disturbance of tone was more pronounced in the legs than in the arms in all 16 cases showing rigidity. This was severe enough to cause paraparesis, confining the patients to bed, particularly in the terminal stages of their illness. In one case (case 19) the clinical diagnosis was Wernicke's encephalopathy and this was later confirmed by pathological examination.

Gastrointestinal symptoms observed in the patients were anorexia (12/20), diarrhoea (9/20), vomiting (5/20) and constipation (3/20). Glossitis was noted in 13 cases. Seven patients had relatively good appetite during hospitalisation. Diarrhoea was seen at the beginning of the illness in some cases, but in others, it only appeared in later stages. One patient (case 1) had severe diarrhoea at the onset, but later became constipated. In most cases the diarrhoea did not respond to various medications.

Skin lesions were only observed in six cases. The lesions were described as vesicles or bullae over the extremities, eczema-like lesion around the mouth and nose, desquamation and roughened skin over the hands, and reddish discoloration of the scrotum. None of these lesions was considered to be typical of pellagrous dermatitis. Pellagra was not suspected by the physicians in charge.

Laboratory data indicated malnutrition in approximately half the cases. Anaemia (red cell counts of less than 3.5×10¹²/l or a haemoglobin below 70%) was seen in nine cases. There were 11 cases with hypoproteinaemia (serum proteins less than 6.0 g/l). In five cases, liver function tests showed moderate elevations of SGOT and SGPT. Jaundice was not noted in any of the 20 cases.

Treatment comprised intravenous administration of glucose, electrolytes, vitamin B₁, B₆, B₁₂ and various antibiotics for associated bronchopneumonia, decubitus ulcers and diarrhoea. Niacin was not prescribed in any of the cases.

The clinical features and evolution of the disease in 18 cases (excluding cases 11 and 19) were surprisingly similar. The chronic alcoholics were hospitalised because of delirium tremens. They subsequently developed neurological signs and symptoms, such as extrapyramidal rigidity, gait disturbance, double
Table  Clinical and pathological findings of 20 cases of alcoholic pellagra

| Case No | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| Autopsy No | 51 | 123 | 179 | 282 | 290 | 292 | 320 | 337 | 405 | 466 | 471 | 515 | 530 | 565 | 567 | 633 | 688 | 768 | 890 | 896 |
| Age of patients (years) | 38 | 58 | 48 | 45 | 58 | 51 | 48 | 43 | 45 | 44 | 40 | 39 | 39 | 66 | 56 | 43 | 69 | 68 | 89 | 48 |
| Total course (weeks) | 6 | 13 | 6 | 13 | 18 | 13 | 9 | 17 | 8 | 30 | 8 | 8 | 17 | 17 | 5 | 4 | 20 | 43 | 1 | 13 |
| Clinical diagnosis | DT | DT | DT | DT | DT | DT | DT | DT | DT | DT | DT | DT | DT | DT | DT* | DT | Wern† | DT |
| Clinical manifestations | | | | | | | | | | | | | | | | | | | |
| Confusion | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hallucination | + | + | + | + | + | + | ? | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Insomnia | + | + | ? | + | + | + | ? | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tremor | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + |
| Gait disturbance | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Extrapyramidal rigidity | ? | + | + | + | + | + | + | ? | + | + | + | + | + | + | + | + | + | + | + | + |
| Incontinence | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyneuropathy | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Seizure | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Anorexia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Vomiting | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Diarrhoea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Constipation | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Glossitis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin lesions | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Decubitus ulcers | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Brain weight (grams) | 1500 | 1350 | 1270 | 1470 | 1330 | 1370 | 1230 | 1280 | 1220 | 1450 | 1280 | 1070 | 1250 | 1250 | 1200 | 1280 | 1200 | 1080 | 1150 |
| Central chromatolysis in Betz cells | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| large cortical neurons | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| pontine nucl | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| dorsal vagal nucl | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| gracile and cuneate nucl | ? | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| descending trigeminal nucl | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| vestibular nucl | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| nucl ambiguous | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| parahypoglossal nucl | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

DT: Delirium tremens; *Case 14 also had Korsakoff's psychosis; †Wernicke's disease; ?: Not certain or not examined.
incontinence, polyneuropathy, seizures and gastrointestinal symptoms. They deteriorated progressively, developing terminal bronchopneumonia, and expiring within several weeks to a few months from the onset of symptoms.

**Summary of the necropsy findings** Malnutrition was obvious in most cases. Body weights at necropsy ranged from 33 kg to 72 kg, with an average of 45.2 kg. The mean weight of the brain was 1279 grams. This is less than the average brain weight of Japanese males (1363 grams) of the same age. On macroscopic examination 11 cases showed slight to moderate cerebrall gyral atrophy and 12 cases showed ventricular dilatation. The blood vessels at the base of the brain including the circle of Willis showed minimal atherosclerotic changes in most cases. Two cases (2 and 19) had small infarcts in the basal ganglia and in the white matter of the frontal lobe. No other vascular lesions were noted. There were no subdural haematomas.

Histologically the most striking finding was central chromatolysis of neurons. This chromatolytic change was constantly observed in Betz cells and in the neurons of the pontine nuclei. The neurons were rounded, and showed peripheral displacement of the nuclei and Nissl substance. The same changes were noted in the relatively large cortical neurons (18/20), dorsal vagal nuclei (19/20), gracile and cuneate nuclei (15/15), descending trigeminal nuclei (19/20), vestibular nuclei (19/20), parahypoglossal nuclei (nuclei of Roller) (17/20), in the nuclei ambigu (10/20), arcuate nuclei (12/18), dentate nuclei (10/14), oculomotor nuclei (8/16), and anterior horn cells (3/4). A few neurons in the basal ganglia, thalami and mamillary bodies exhibited similar changes in some cases. The Purkinje cells, and the neurons of the substantia nigra and Ammon's horn never showed chromatolysis.

Electron microscopy revealed that, in the chromatolytic neurons, RNA granules and lipofuscin pigment deposits were pushed to the periphery of the cytoplasm. The central portion of the cytoplasm was occupied by mitochondria, lysosomes and dilated vesicles. Neurofilaments were not increased in number (fig 3).

The entire length of the spinal cord was available for histological examination in only two cases. There were no degenerative changes in the long tracts. Cases 18 and 19 showed changes of Wernicke's encephalopathy. Cases 10, 12 and 18 exhibited pictures of alcoholic cerebellar degeneration. Case 19 also showed demyelinating lesion in the pons, consistent with central pontine myelinolysis.

Histological examination of the tongue was carried out in all 20 cases. In 13 there was histological evidence of glossitis, such as parakeratosis, acanthosis, elongation of the rete ridges and chronic inflammatory cell infiltration of the submucosa (fig 4). There were no morphologically significant lesions in the gastrointestinal tract, except for chronic atrophic gastritis seen in 10 cases. The neurons of the Auerbach's plexus revealed chromatolysis in five cases. The heart weighed 150 to 310 grams, with an average of 240 grams. There were no right ventricular dilatation suggestive of beriberi heart disease. Other associated findings included cirrhosis of the liver in two cases, fatty liver in three cases, and hepatic fibrosis in three cases. Bronchopneumonia was observed in 16 cases and was thought to be the most frequent cause of death. Other causes of death included oedema of the lungs in three cases and asphyxia due to tracheal obstruction in one case.
**Discussion**

None of these 20 patients exhibited the classical cutaneous features of pellagra and none had the diagnosis confirmed by biochemical methods (excretion of N' -methylnicotinamide etc). However, we believe these 20 cases had "pellagra" on neuropathological and clinical grounds. The most consistent neuropathological abnormality in pellagra is said to be central chromatolysis of the neurons in various areas: Betz cells, pontine nuclei, dorsal vagal nuclei, gracile and cuneate nuclei, nucleus ambiguous, descending trigeminal nuclei, arcuate nuclei and anterior horn cells. The Purkinje cells, neurons in Ammon's horn and hypoglossal nuclei, although among the largest neurons, are not affected. The distribution of chromatolytic neurons in our 20 cases mirrored the distribution reported in pellagra by many authors. Myelopathy closely resembling subacute combined degeneration of \( B_{12} \) deficiency has also been reported. The spinal cords in the two cases examined did not show these myelopathic lesions. They are infrequent and their absence cannot be taken to invalidate the diagnosis of pellagra.

The presence of glossitis in 13 out of 20 cases is also in favour of the diagnosis, although the histological picture of pellagous glossitis (as of pellagous dermatitis) is non-specific. Only six patients developed skin lesions, usually in their terminal stages. One of the reasons for the rarity of the cutaneous manifestations of pellagra among chronic alcoholics may be that pellagous dermatitis develops in the exposed parts of the body, namely the face, neck, dorsum of hands, arms and feet, whereas our alcoholics generally have little occasion to be exposed to the sun. They were usually kept in darkened side rooms while they had severe mental symptoms.

Although gastrointestinal symptoms such as diarrhoea, constipation and vomiting were observed in 12 cases, much attention was not paid to these symptoms. The patients with severe diarrhoea were treated with antibiotics and anti-diarrhoeal agents without obtaining any benefit. Gillmann and Gillmann\(^{10}\) stated that pellagrins exhibited no remarkable pathological findings in the intestine. In our cases too, there were no significant changes in the gastrointestinal mucosa. However, careful examination revealed that neurons of the dorsal vagal nuclei demonstrated marked chromatolytic changes in almost all cases (fig 5). Similar changes were also noted in the Auerbach plexus of the intestinal wall. In contrast, neurons of the dorsal vagal nuclei and the gastrointestinal wall in 10 non-alcoholic control cases showed no such chromatolytic changes. The autonomic nervous system controls gastrointestinal peristalsis, and both nausea and vomiting may be caused by stimulation of the medullary tegmentum where the dorsal vagal nuclei are located. We believe that the gastrointestinal symptoms in pellagrins may be due to an abnormality of the autonomic nervous system, namely the central chromatolysis of its neurons.

The mental symptoms shown by our 20 cases varied greatly. They included confusion, hallucinations, insomnia, delirium, anxiety, depression, excitement and neurasthenia. All of these symptoms may occur in non-alcoholic, endemic pellagrins.\(^{11-14}\) However, the mental symptoms in our cases were considered to be those of delirium tremens, because all the patients were severe alcoholics and because pellagra was not suspected clinically.

Klauder and Winkelman\(^{1}\) reported 100 patients with cutaneous features of pellagra, the majority of whom were chronic alcoholics. They divided the patients into three groups. Group 1 consisted of those cases in whom the dermatitis was a conspicuous, apparently initial symptom. There was a paucity or entire absence of somatic symptoms, such as diarrhoea. The patients in group 2 presented pellagrous dermatitis and frank somatic symptoms, characteristic of pellagra (diarrhoea, mouth and tongue lesions, in addition, some had mental or neurologic symptoms). In group 3, severe cutaneous and somatic symptoms of pellagra developed suddenly after a prolonged debauch. In addition, there was an acute delirium with increased psychomotor activity (necessitating restraint), complete disorientation and auditory and visual hallucinations. On admission, the diagnosis...
had been delirium tremens. They stated that it was not always possible to differentiate mental symptoms of pellagra from those of alcoholism.

Spies et al. also reported 60 cases of pellagra. The mental symptoms were acute, consisting of disorientation, confusion, excitement, mania, depression, delirium etc. The authors gave a detailed description of a 55-year-old non-alcoholic pellagriner who had visual and auditory hallucinations. It seems impossible to differentiate pellagrous psychosis from alcoholic delirium tremens on the ground of the mental symptoms alone.

There seem to be differences, however, in the neurological symptoms. Jollife et al. observed 150 cases of what they called nicotinic acid deficiency encephalopathy. About half their 150 patients had clinical evidence of pellagra. Their symptoms were characterised by clouding of consciousness, cogwheel rigidity and uncontrollable grasping and sucking reflexes. Leigh collected 14 necropsy cases of non-alcoholic pellagra, among whom spastic paraplegia was observed in three cases. In almost all of our 20 cases, extrapyramidal rigidity of the extremities with gait disturbance, incontinence and hyperreflexia were observed. In our experience, these neurological symptoms are not seen in ordinary alcoholics with delirium tremens. Of 758 chronic alcoholics admitted to our institution during the 14 year period, there were 158 cases who were diagnosed as delirium tremens or transient hallucinosis. In 138 patients (other than our 20 cases of pellagra), the mental symptoms subsided within a few days to two weeks of admission and the aforementioned neurological symptoms and signs were not observed. Therefore, when an alcoholic shows neurological signs, particularly extrapyramidal rigidity, in addition to various mental and gastrointestinal symptoms, one should strongly suspect pellagra, a curable disorder. The relevant treatment (niacin) should not be delayed until the appearance of skin manifestations.

Diarrhoea, vomiting and the elimination of niacin-synthesising bacteria (by antibiotics) may have played a part in the enhancement of the deficiency state of our patients. However, we are convinced that our 20 cases are not instances of pellagra superimposed on the terminal stage of other conditions. We believe that the mental symptoms in our cases had been those of pellagra psychosis from the onset. Case 11 provides good evidence on this point. The patient was a 40 year old man who expired rather suddenly of pulmonary oedema. He had mental symptoms without any neurological signs or progressive disability. Neuro-pathologically typical pellagrous changes were identified in wide areas of the nervous system, as in the other cases.

Pellagrins are not only deficient in niacin but also in other vitamins. Some of the clinical features seen in pellagrins (polyneuropathy for example) are believed to be caused by associated thiamine deficiency. Seven of our 20 patients developed polyneuropathy with severe paresthesiae and burning pains of the extremities, loss of deep tendon reflexes and muscle weakness when confined to bed. Five of these seven patients had been taking thiamine (50–75 mg/day) either by mouth or intravenously, when they developed polyneuropathy. We are not certain whether thiamine deficiency alone is responsible for pellagrous neuropathy or whether deficiency of niacin and other vitamins group B should be incriminated.

Pellagra is now believed to be a disappearing disease. Figueroa et al. found only two pellagrins among 451 newly admitted alcoholics in Chicago. They attributed this unexpectedly low incidence of pellagra to the fortification of bread with niacin. More recently, however, Spivak and Jackson were able to collect 18 pellagrins with characteristic skin lesions during a four year period. Fifteen of these were chronic alcoholics. Sporadic case reports of alcoholic pellagra with autopsy confirmation have been published in Japan.

The clinical diagnosis of florid pellagra is easy. It is rare, however, to see a typical pellagra, presenting with the classical triad. It is important to recognise the neurologic and mental manifestations of the disease when it occurs without dermatitis or gastrointestinal symptoms. It was unfortunate that neither clinical nor pathological diagnoses of pellagra were made in our 20 cases for over a decade, because of the absence of skin lesions and, because the brains were not examined by a neuropathologist. Recently four further alcoholics have come to us with severe mental, neurological and gastrointestinal symptoms. They showed a dramatic response to the administration of niacin and other vitamins. Still mentioned that “pellagra sine pelle agra” still lies hidden and unsuspected in the mortality data of mental hospitals. We whole-heartedly agree with this statement.

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