

Pellagra encephalopathy as a differential diagnosis for Creutzfeldt-Jakob disease

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Abstract In the present study we evaluated cases referred as suspected Creutzfeldt-Jakob disease (CJD). Five out of 59 without prion disease showed neuropathological features of pellagra encephalopathy with widespread chromatolytic neurons (age range 40–48 years at death; one woman). These patients presented with a progressive neuropsychiatric disorder lasting for 2 to 24 months. Common symptoms included gait disorder, para- or tetraspasticity, extrapyramidal symptoms, incontinence, and myoclonus. Protein 14-3-3 in the cerebrospinal fluid was examined in a single patient and was positive, allowing the clinical classification as probable sporadic CJD. Pellagra encephalopathy may be considered as a differential diagnosis of CJD including detection of protein 14-3-3.

Keywords Chromatolysis · Creutzfeldt-Jakob disease · Dementia · Pellagra · Prion · Surveillance

Introduction

Dementia is an umbrella term that implies the presence of cognitive decline with or without behavioural impairment that significantly affects one's daily activities. There are

many etiological factors leading to dementia. When it progresses within 12 months, prion disease is suspected (Josephs et al. 2009).

Human prion diseases (transmissible spongiform encephalopathies) are fatal illnesses characterized by the accumulation of abnormally folded, disease-associated isoform of the normal cellular prion protein in the central nervous system. Etiologically, human prion diseases may be sporadic, genetic, or acquired (Kovacs and Budka 2009). The most frequent is sporadic Creutzfeldt-Jakob disease (sCJD). According to Surveillance criteria (WHO), definite diagnosis of sCJD relies on neuropathological examination, while probable and possible diagnosis on the constellation of clinical symptoms (dementia plus two further from visual disturbance, cerebellar ataxia, myoclonus, extrapyramidal or pyramidal signs) supported by the presence of 14-3-3 protein in the cerebrospinal fluid (CSF), and/or periodic sharp wave complexes in EEG and/or high signal intensity in the basal ganglia in MRI (Quadrio et al. 2011; Zerr et al. 2009).

In the present study we evaluated cases referred to the Hungarian CJD Surveillance unit as clinically suspected CJD. Unexpectedly, five patients showed features of pellagra encephalopathy, hence here we provide clinicopathological characterization of these cases.

Material and methods

Selection of cases

Patients with rapidly progressive dementia (defined by the presence of cognitive decline within a period of less than 36 months from the first symptoms to death) who were referred to our CJD Surveillance Unit between 1998 and 2009 were included in our study. Clinical symptoms were retrospectively analysed using clinical files.

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Neuropathology

Formalin fixed, paraffin-embedded tissue blocks (2.5 × 2.0 cm) were evaluated. We followed sampling and diagnostic criteria as recently published (Kovacs and Budka 2010). In addition to routine stainings, the following monoclonal antibodies were used for immunohistochemistry: anti-tau AT8 (pS202, 1:200; Pierce Biotechnology, Rockford, IL, USA), anti-prion-protein (12F10, 1:1,000, Cayman Chemical, Ann Arbor, MI, USA), anti-phospho-TDP-43 (pS409/410, 1:2,000, Cosmobio, Tokyo, Japan), anti-ubiquitin (1:50,000, Millipore, Temecula, CA, USA), anti- α -synuclein (1:10,000, clone 4D6, Signet, Dedham, MA, USA), anti-A β (1:50, clone 6F/3D, Dako, Glostrup, Denmark), alpha-B-crystallin (1:500, Leica Biosystems Newcastle Ltd., Newcastle, UK).

Results

Summary of cases

In sum 230 cases were referred based on the clinical suspicion of prion disease. CSF 14-3-3 protein was examined

since 2005 and was not carried out in all. Neuropathological investigation was performed in 223 (97 %). In 164 cases we confirmed prion disease (definitive). Seven cases were classified as probable sCJD according to the Surveillance criteria. In the present study we included the remaining 59 cases (27 women and 32 men); where we excluded prion disease after neuropathological examination.

Diagnostic grouping of cases with rapid dementia where prion disease was excluded

Mean age at death (\pm standard deviation) was 65.3 \pm 8.7 years (range: 38 to 87). The mean duration of illness after the first symptoms was 9.3 \pm 8.7 (range: 0.5 to 36 months). According to the neuropathological diagnoses (Table 1), the following groups were distinguished: the most frequent were neurodegenerative diseases ($n=20$, 33.8 % of cases; mean age at death: 67.1 \pm 5.9 years; mean duration of illness: 13.7 \pm 10.2 months), followed by cerebrovascular disease ($n=8$, 13.5 %; 66.4 \pm 7.7; 3.6 \pm 2.3), metabolic disorder ($n=6$, 10.1 %; 49.6 \pm 7.3; 7.1 \pm 6.7), encephalitis ($n=7$, 11.8 %; 70.1 \pm 6.4; 3.5 \pm 2.6), and neoplasia ($n=6$, 10.1 %; 59.5 \pm 17.5; 6.9 \pm 5.7). In 12 cases (20.3 %; 67.9 \pm 6.2; 8.6 \pm 8.3)

Table 1 Summary of diagnostic groups, diagnoses and the number of cases classified as possible or probable Creutzfeldt-Jakob disease according to Surveillance criteria. Abbreviations: *NDD* neurodegenerative disease; *TU* tumour; *MET* metabolic disease; *VASC* cerebrovascular disease; *ENC* encephalitis; *MIX* mixed pathology; *Poss* possible, *Prob* probable; *FTLD-TDP* frontotemporal lobar degeneration with TDP-43 immunoreactive neuronal inclusions

Group	Diagnoses	Total	CJD criteria	
			Poss	Prob
NDD	Alzheimer disease	11	5	0
	Lewy body disease	6	4	0
	Multiple system atrophy	1	0	0
	Progressive supranuclear palsy	1	0	0
	FTLD-TDP	1	0	0
TU	Primary brain tumour	3	3	0
	Meningeal carcinomatosis	2	0	1
	Multiple micrometastases	1	0	0
MET	Pellagra encephalopathy (+ vermis atrophy)	5	4	1
	Wernicke encephalopathy	1	0	0
VASC	Vascular leukoencephalopathy (including Binswanger)	2	2	0
	Multiple brain infarctions	6	3	0
ENC	Striatal encephalitis (paraneoplastic)	1	1	0
	Meningoencephalitis (Viral or tuberculosis)	5	1	0
	Limbic encephalitis (paraneoplastic)	1	0	1
MIX	Alzheimer disease + Lewy body disease	1	1	0
	Alzheimer disease + Multiple infarctions	4	4	0
	Alzheimer disease + Vascular leukoencephalopathy	1	1	0
	Alzheimer disease + Meningeal carcinomatosis	1	1	0
	Alzheimer disease + Metabolic gliosis	1	0	0
	Alzheimer disease + Encephalitis	2	1	0
	Cerebellar (vermis) degeneration + Multiple infarctions	1	0	0
	Metabolic gliosis + Lacunes + Senile changes Braak & Braak II	1	1	0
Summary	59	31	3	

mixed neuropathological alterations were documented. Interestingly, according to the surveillance criteria (WHO), three cases could be classified as probable (single cases with mixed neurodegenerative disorder, meningeal carcinomatosis, and pellagra encephalopathy), and 31 as possible sCJD (Table 1) when only the clinical data were considered. In 27 cases, due to the lack of EEG, MRI, or examination of CSF 14-3-3, this classification could not be performed.

Clinicopathological description of cases with pellagra encephalopathy

Five cases (out of 59 with rapid dementia without histological evidence of prion disease) were diagnosed neuropathologically as pellagra encephalopathy (Table 2). These

patients were significantly younger as compared to the other cases, and presented with a progressive neuropsychiatric disorder lasting for 2 to 24 months. Common symptoms included cognitive decline, behavioural change and gait disorder. Para- or tetraparesis together with extrapyramidal symptoms, and incontinence were also noted in three. Two patients showed convulsions. Myoclonus was observed in another two patients, while sensory disturbance, and aphasia was only in single patients as well as untreatable diarrhoea. EEG revealed diffuse slowing without periodic sharp wave complexes. Protein 14-3-3 in the cerebrospinal fluid was examined and was positive in a single patient, while routine parameters were in a normal range for the five patients. Together with the complex clinical symptoms this allowed us to classify this single case as probable sCJD prior

Table 2 Clinicopathological observations on five patients with pellagra encephalopathy. *PSWC* periodic sharp wave complex; *BGG* basal ganglia. *n.d.* not done

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at death (years)	40	48	45	47	45
Year of death	2002	2003	2005	2009	2009
Sex	m	m	m	m	w
Duration (months)	4	24	4	2	24
Duration of alcohol abuse	> 5 y	> 5 y	10 y	> 15 y	> 2 y
Progressive dementia	+	+	+	+	+
Tetra-, or paraparesis	+	–	+	+	–
Ataxia	–	+	+	+	+
Dysarthria/dysphagia	+	+	–	–	–
Myoclonus	+	–	–	+	–
Rigor	+	–	–	–	–
Pyramidal signs	+	–	+	+	–
Incontinence	–	+	+	–	+
Hallucinations	–	–	+	+	–
Anxiety	–	–	+	–	–
Convulsions	–	–	+	–	+
Unconsciousness	–	+	+	+	–
EEG: PSWC/triphasic wave	–	–	–	–	–
MRI high signal in BGG	–	n.d.	–	n.d.	–
CSF 14-3-3	n.d.	n.d.	n.d.	+	n.d.
Liver pathology	Steatosis	Steatosis	Steatosis	Steatosis	Steatosis
Chromatolytic neurons	+	+	+	+	+
<i>Frontal Cx</i>	+	+	+	+	+
<i>Anterior cingular Cx</i>	–	+	+	+	+
<i>Parietal Cx</i>	+	+	+	+	+
<i>Motor Cx</i>	+	+	+	+	+
<i>Occipital Cx</i>	–	–	–	–	–
<i>Temporal Cx</i>	–	–	–	–	–
<i>Thalamus</i>	–	+	+	+	+
<i>Pontine nuclei</i>	+	+	+	+	+
<i>Locus coeruleus</i>	+	+	–	+	+
<i>Raphe nuclei</i>	+	+	–	+	+
<i>Dentate nucleus</i>	–	+	–	+	–

to the neuropathological examination. Cranial MRI was performed in three; high signal intensity was not seen in the striatum or thalamus.

Neuropathological examination revealed a uniform picture in all patients with chromatolytic alpha-B-crystallin negative neurons, showing excentric nucleus (Fig. 1). These neurons were mainly seen in neocortical regions, thalamus, and brain-stem nuclei (Table 2). There was a lack of argyrophilic or ubiquitin immunoreactive inclusions. None of the examined neurodegeneration-related proteins (i.e. alpha-synuclein, tau, TDP-43, amyloid-beta, prion protein) showed depositions, moreover there was a lack of inflammatory infiltrates, spongiform change of the neuropil, or vascular lesions. In these patients we did not observe histopathological signs of Wernicke encephalopathy. Purkinje cell loss and atrophy in the anterior vermis was significant in three.

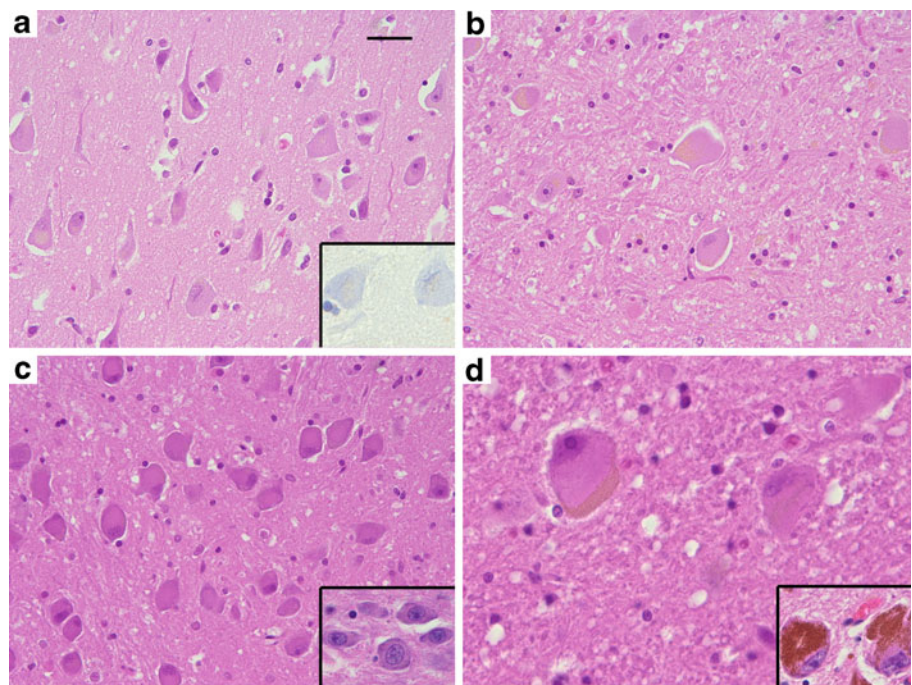
Discussion

In the present study we show that pellagra encephalopathy is an important differential diagnosis for rapidly progressive dementia in alcoholic patients and may occasionally mimic sCJD, a transmissible prion disorder. We detected five cases in the frame of a comprehensive surveillance for prion diseases, referred primarily due to the clinical observation of rapidly progressive dementia. Other diagnoses in our cohort included neurodegenerative diseases, as well as neoplastic and cerebrovascular disorders, compatible with recent neuropathology-based studies (Chitravas et al. 2011; Gelpi et al. 2008; Heinemann et al. 2007; Josephs et al. 2009; Van Everbroeck et al. 2004).

Pellagra encephalopathy is clinically characterised by rapidly progressive dementia, fluctuating disturbances, liberation signs, and startle myoclonus. It has been suggested that it may be more frequent as actually diagnosed (Hauw et al. 1988). Evaluation of its frequency is hindered by the low rate of autopsy. In addition, the lack of classical symptoms, such as dermatitis and diarrhoea, makes the correct diagnosis more difficult. All of our cases showed rapid dementia and gait disorder predominantly with cerebellar symptoms (4), and pyramidal signs (3), while the duration of illness varied between 2 and 24 months. This is similar to observations of another study, which reported vigility disorder, ‘gegenhalten’, myoclonus, ataxia, cerebellar symptoms, accelerated reflexes, neuropathy, autonomic dysfunction, and cranial-nerve symptoms (Ishii and Nishihara 1981; Ishii and Nishihara 1985; Serdaru et al. 1988). A single case was classified as probable sCJD according to surveillance criteria before the neuropathological examination was performed. This underpins the importance of brain autopsy in rapidly progressive dementia, in particular in the surveillance of prion diseases.

The fact that pellagra encephalopathy occurred in such a number in our cohort of clinically suspected CJD cases, indicates that evaluation of rapidly progressive neurological symptoms may be difficult in patients with known alcohol abuse. In the clinical practice these patients receive prompt thiamine therapy whenever progressive neurological symptoms are observed. This strategy is useful to avoid Wernicke encephalopathy, which was not observed in our patients. However, during thiamine (and pyridoxine) treatment there is an increased need for pyridine coenzymes, and this leads

Fig. 1 Histological images of the anterior cingulate cortex (a), ventrolateral thalamic nucleus (b), pontine base nuclei (c), and locus coeruleus (d) from a representative case (patient 4 in Table 2) with pellagra encephalopathy. Right lower inset in a indicates lack of alpha-B-crystallin immunoreactivity of the same neurons; inset in c and d indicates representative image of non-diseased pontine base nuclei and locus coeruleus neurons, respectively, in an age-matched individual. Bar in a represents 25 μ m for a–c and 40 μ m for d



to further clinical deterioration before the typical triad (i.e. dermatitis and diarrhoea in addition to dementia) of pellagra could be recognized (Serdaru et al. 1988). Niacin deficiency may lead to neuropsychiatric symptoms due to relative serotonin deficiency, moreover, the decreased kynurenic acid synthesis also contributes to neurotoxicity (Brown 2010). In addition, the microstructural alterations of the corpus callosum in chronic alcoholism may influence the clinical presentation (Pfefferbaum et al. 2006). From a clinical point of view, supplementation of niacin in addition to B vitamins is recommended in alcoholic patients, not only due to the therapeutic advantage but it helps the diagnostic procedure in rapidly progressive dementia (Brown 2010).

From a neuropathological aspect chromatolytic neurons in pellagra encephalopathy can be distinguished from ballooned neurons, frequently seen in neurodegenerative diseases in the limbic system, based on the lack of alpha-B-crystallin (stress-response protein) and ubiquitin immunopositivity. Indeed, none of the neurodegeneration-related proteins showed any deposits in our cases.

In summary, our and previous studies indicate that pellagra encephalopathy should be suspected in patients with alcohol intake presenting with rapidly progressive dementia combined with para- or tetraparesis, neuropathy, visual disturbance, and myoclonus (Ishii and Nishihara 1981; Ishii and Nishihara 1985; Serdaru et al. 1988). We suggest that pellagra encephalopathy may be considered as a differential diagnosis also of sCJD, including detection of protein 14-3-3 in CSF. Evaluation of niacin metabolites together with the detection of isolated anterior vermis atrophy in MRI without high signal abnormalities suggestive of sCJD (Zerr et al. 2009) could help the diagnostic procedure. Indeed, EEG and MRI did not support the suspicion of sCJD in our case. Whether the frequency of pellagra encephalopathy shows geographic differences associated with nutritional supplementation merits further studies.

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